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Review Article

Long-term survival and complications of Fontan patients: where do we stand?

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Abstract: Single ventricle disease (SVD) is a rare but severe form of congenital heart disease (CHD) which requires surgical palliation through the Fontan procedure. This operation, which was pioneered in 1971, has become the final part of a surgical pathway after the Norwood and Glenn procedures. The pathway aims to reduce the load on the functional ventricle whilst improving systemic blood oxygenation. Advances in surgical technique and the modern era have shifted the approach from addressing mortality concerns to offering a lifeline to patients in need. With improved survival, the Fontan population grows which requires an emphasis on the lifelong complications that these individuals face along with specific risk factors that predispose them to these issues allowing for risk stratification and systematic monitoring. This narrative review aims to summarize the recent cohort studies on Fontan patients to identify long-term outcomes of the procedure along with their associated risk factors. The literature review was conducted till December 2025 using PubMed, Scopus, and Google Scholar, the procedure itself is not curative. I has numerous morbidities including arrhythmia, heart failure, neurocognitive delays, protein-losing enteropathy, renal dysfunction, and Fontan-associated liver disease (FALD). FALD specifically may affect over half of Fontan patients within 35 years and the seriousness of FALD sequelae including cirrhosis and hepatocellular carcinoma underscores the need to prioritize early and systematic monitoring. Preoperatively, demographic, surgical, and biomarker risk factors have been shown to be predictors of postoperative complications/mortality. Overall, Fontan patients tend to have excellent survival rates over both the short and long terms compared to prior surgical eras. As postoperative concerns now shift from early mortality to long-term complications, our healthcare system must adapt to ensure lifelong follow-up and a systematic approach for early detection.

Keywords: Fontan, single ventricle disease, congenital heart disease, palliation, survival, complications, Fontan-associated liver disease

Introduction

Congenital heart diseases (CHDs) are a form of cardiovascular diseases (CVDs) that have been present since birth [1]. The most common types of CHDs include ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA) [2]. Rarer entities include Ebstein's anomaly, double outlet right ventricle (DORV), cor triatriatum, and total anomalous pulmonary venous return (TAPVR) [3-6]. In general, CHD remains the most prevalent birth defect accounting for one third of all congenital malformations [7]. There has been a rise in the number of children under 5 years old living with CHD globally reaching 4.18 million in 2021 [8] which emphasizes its role as a significant global health burden. Management of CHD depends on the subtype present.

While less prevalent than the four main subtypes of CHD mentioned above [9], single ventricle diseases (SVDs) represent a disproportionately significant cause of morbidity and mortality. SVDs are a group of CHDs characterized by a functionally univentricular heart where one ventricle cannot sufficiently perfuse the pulmonary or systemic circulation [10]. Some of the most common SVDs include hypoplastic left heart syndrome (HLHS), tricuspid atresia, Ebstein anomaly, DORV, double inlet left ventricle, and some atrioventricular canal defect

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[11]. These patients are at risk of increased long-term morbidity such as heart failure, neurological deficits, and increased mortality mainly if left untreated [12].

Such patients are typically managed with a staged surgical pathway approach consisting of the Norwood, Glenn, and Fontan procedures [13]. The Fontan procedure comes as the natural endpoint of the surgical pathway where the Norwood and Glenn operations are designed as hemodynamic optimization prior to Fontan [13]. The Fontan operation is the cornerstone of the management of single-ventricle physiology cardiovascular diseases [14]. This procedure was pioneered by Francis Fontan in 1971 for a patient with tricuspid atresia [15]. It has now become a commonly performed cardiac operation with an estimated 1062 operations per year being performed in the United States from 2001 to 2014 [16]. Moreover, an epidemiological model by Plappert et al. [17] has estimated the number of people living with Fontan circulation in 2020 to be 66 people per million (ppm) across 11 countries with an expected increase to 79 ppm in 2030.

The Fontan procedure is indicated for complex single-ventricle physiology in which biventricular repair is not feasible [14]. Suitable candidates typically have preserved ventricular function, low pulmonary vascular resistance (PVR), and competent atrioventricular valves (AVVs). Fontan surgery is typically performed following successful superior cavopulmonary connection once pulmonary artery development and pulmonary vascular resistance are adequate for passive pulmonary blood flow [14, 18]. By directing systemic venous return to the pulmonary arteries without a subpulmonary pump, Fontan circulation achieves a full separation of the pulmonary and systemic circuits which improves systemic oxygen delivery [19]. Surgical advances have led to improved survival with contemporary 10-year survival rates now exceeding 90% [20]. However, circulation remains inherently non-physiological relying on passive pulmonary blood flow and chronically elevated venous pressures [19, 21]. This physiology predisposes survivors to progressive multiorgan complications including heart failure, arrhythmias, thromboembolism, and end-organ dysfunction [21, 22].

This increase in the prevalence of the Fontan population as well as the importance of this procedure for SVD patients necessitates a better understanding of the long-term outcomes and multisystem complications of this operation. This review synthesizes recent evidence on Fontan morbidity and highlights its progressive multisystem implications. We place a particular emphasis on Fontan-associated liver disease (FALD), which has emerged as an important determinant of long-term morbidity requiring prolonged surveillance. In addition, we also summarize key demographic, surgical, and physiological factors that consistently predict adverse outcomes providing a basis for risk-based monitoring in modern Fontan care. By doing so, we highlight the broader shift in Fontan management where excellent early surgical survival has created a growing adult population and introduced the challenge of managing progressive multisystem morbidity.

Methods

The literature review was conducted until December 2025 providing an overview of SVDs and the Fontan procedure along with relevant cohort studies. The utilized databases were PubMed, Scopus, and Google Scholar. The results were retrieved using the following key words: “Fontan procedure”, “Palliation”, “Single Ventricle Diseases”, “Congenital Heart Disease”, “Outcomes”, and “hepatic complications” along with their relevant MeSH terms.

Articles were selected based on their relevance to this review. The inclusion criteria encompassed studies without restrictions on their type or country of origin, provided they were written in or translated into English. In addition to primary research articles, relevant reviews were added to provide a comprehensive overview of the topic. References from selected articles were also examined to identify significant studies.

Single ventricle diseases

SVDs entail a single functioning ventricular chamber often incapable of adequately sustaining both systemic and pulmonary circulation [10]. In these conditions, the contralateral ventricle may be anatomically absent, hypoplastic, or structurally incapable of sustaining

effective hemodynamic output [23, 24]. These defects hinder the normal in-series biventricular circulation which forces the heart to rely on a single ventricle to support both circuits in parallel. As a result, oxygenated and deoxygenated blood mix within the heart leading to chronic volume overload and systemic arterial desaturation which are significant contributors to long-term morbidity [25, 26].

Other than the immediate hemodynamic burden, SVDs share a pathogenesis characterized by loss of biventricular mechanics leading to intrinsic myocardial, mechanical, and molecular defects [23]. In healthy individuals, there is adequate left ventricular torsion and architecture which allows efficient ejection with minimal myocyte shortening. A single ventricle, whether morphologically right or left, must sustain both pulmonary and systemic preload with reduced torsion efficiency resulting in volume overload, elevated wall stress, and reduced mechanical reserve [27]. Moreover, several studies show that the single ventricle (especially when morphologically right sided) lacks longitudinal fiber orientation and exhibits a substantial reduction of torsion [28]. This limits its ability to adapt to afterload making it structurally and energetically less suited for systemic pressures [28]. This mechanical inefficacy is amplified by metabolic insufficiency as the systemic right ventricle has a limited ability to satisfy increased oxygenation demand under stress [29]. At the molecular level, the single ventricle undergoes maladaptive remodeling characterized by a shift towards slower, energy-conserving contractile proteins. There is an upregulation of fetal proteins such as the β-myosin heavy chain (β-MHC), brain natriuretic peptide (BNP), and atrial natriuretic peptide (ANP) as well as the downregulation of contractile proteins such as the α-myosin heavy chain (α-MHC), sarcoplasmic reticulum calcium-adenosine triphosphatase 2a (SERCA) leading to impaired calcium handling, and diminished β1-adrenergic signaling. This remodeling is often referred to as the activation of the “fetal gene program” [23]. In addition, abnormal cyclic nucleotide signaling occurs through phosphodiesterase PDE3B and PDE5A upregulation, adenylyl cyclase AC5/AC7 dysregulation, and increased calcium/calmodulin-dependent protein kinase II (CaMKII) activity further depressing contractility and stress responsiveness. Moreover, increased class I/II histone deacetylase signaling promotes maladaptive remodeling reducing contractility and [30].

Although the exact etiology of SVDs remains poorly understood, it has been shown to be influenced by a combination of genetic and environmental factors that disrupt normal cardiac development during embryogenesis [23]. Understanding these risk factors is crucial to identify at-risk pregnancies and implementing appropriate monitoring and intervention strategies. Among genetic factors, mutations in transcription factors critical to cardiac morphogenesis have been strongly implicated in SVD development [23]. Variations in NKX2-5 and GATA4 have been associated with left-sided obstructive lesions, including HLHS, by disrupting normal cardiac looping and chamber specification [31]. Similarly, NOTCH1 mutations contribute to the development of single-ventricle (SV) lesions due to their role in regulating endocardial differentiation and ventricular development [32]. Additional transcription factors such as HAND1 also play an essential role in early cardiac formation [33]. Loss-of-function mutations in HAND1 have been implicated in HLHS pathogenesis due to its critical involvement in left ventricular specification and outflow tract formation [34]. Recently, WDFY3 has been reported as a novel candidate gene associated with CHD in humans with emerging evidence linking it to HLHS and SV physiology [31].

In addition to genetic considerations, a range of maternal factors have been implicated as contributors to the development of SV physiology. Maternal and perinatal health factors such as gestational weight gain have been shown to influence outcomes in SVDs. Abnormal maternal weight, whether excessive or insufficient, appears to be independently linked with an elevated risk of mortality or heart transplantation among newborns with SV and CHD [35]. Furthermore, maternal comorbidities such as diabetes, chronic hypertension, pre-eclampsia, and obesity have been shown to affect neonatal outcomes by impairing placental perfusion and fetal cardiovascular development [36]. These maternal metabolic conditions have been associated with abnormal fetal brain hemodynamics in fetuses with CHD including HLHS and tricuspid atresia [37]. A recent meta-analysis further identified maternal obesity

as a significant risk factor for congenital cardiac malformations like outflow tract defects which can progress to SVD [38]. Viral infections during pregnancy have also been linked to an increased risk of outflow tract anomalies and conotruncal defects which are frequently involved in fetal CHD and SV physiology [39].

Given the anomalies described above, clinical manifestations of SVDs appear early in the neonatal period or infancy and can often be severe. Affected neonates commonly present with cyanosis, tachypnea, poor feeding, lethargy, and failure to thrive reflecting the heart's limited capacity to maintain adequate oxygen delivery and circulatory stability [23]. Physical examination or imaging may reveal signs such as hepatomegaly, cardiomegaly, or elevated central venous pressure indicating early volume overload of the single functioning ventricle [26]. These episodes may be exacerbated by exertion, such as during feeding, resulting in transient desaturation. Over time, signs of chronic heart failure may develop especially in patients with a dominant right ventricle such as peripheral edema [40]. Furthermore, prolonged hospitalizations and medical interventions during early life are prevalent reflecting the high clinical burden and complex care required in these patients [41].

Each SVD condition presents a unique structural physiology but entails a single functional ventricle [42]. For instance, HLHS involves the underdevelopment of left-sided structures including the left ventricle, mitral valve, aortic valve, and ascending aorta [43]. Tricuspid atresia features an absent tricuspid valve leading to an underdeveloped right ventricle [44]. In double-inlet left ventricle, both atria connect to the left ventricle resulting in an underdeveloped ventricle [45]. In unbalanced atrioventricular septal defect, one ventricle is underdeveloped and cannot support circulation [46]. With a functional single ventricle, both the systemic and pulmonary blood flow circulations operate in parallel, as opposed to being in series, causing oxygenated and deoxygenated blood to mix [10]. Consequently, there is obligate arterial desaturation due to blood mixing and chronic overload of the single ventricle that receives and ejects both circulations [25]. A visual representation of relevant examples of SVDs can be found in **Figure 1**.

Epidemiology

SVDs are rare but serious forms of CHD accounting for approximately 7.7% of childhood CHD cases with a birth incidence of 4-8 per 10,000 live births [47]. HLHS is the most frequent with a birth incidence of 2-3 per 10,000 live births predominantly affecting male infants, and tricuspid atresia occurs in 1 per 10,000 [11]. However, accurate global estimates remain challenging due to regional diagnostic disparities and reporting [48]. In high-income countries, standardized neonatal screening has led to more consistent incidence data and earlier interventions. Conversely, in low- and middle-income countries, SV lesions are frequently underdiagnosed or diagnosed late due to limited access to echocardiography and perinatal care leading to poorer outcomes and the underestimation of disease burden [49]. Geographic variation in incidence may also reflect environmental or genetic risk factors, but differences in healthcare infrastructure likely play a larger role [50]. For instance, population-based studies in Europe show higher detection rates compared to African or South Asian countries which may reflect both epidemiological variation and systemic inequities [49].

Management and treatment

Pharmacological interventions in SVDs aim to manage the physiological complications resulting from the underlying cardiac defect [51]. Supplemental oxygen may be used to alleviate hypoxemia [52]. The administration of nitric oxide may reduce PVR, increasing oxygenation by enhancing pulmonary blood flow [53]. In cases of cardiac strain, inotropic agents may be administered to support ventricular contraction; however, catecholamines should be avoided due to the risk of arrhythmogenesis [54]. Prostaglandin E1 may be administered to maintain ductal patency to maintain collateral flow as a temporary measure until definitive interventions are performed [55]. Non-steroidal anti-inflammatory drugs should be avoided to prevent premature PDA closure [55].

As mentioned previously, the long-term treatment of SVD patients is a staged surgical pathway approach consisting of the Norwood, Glenn, and Fontan procedures [13]. The Norwood procedure aims to establish the single

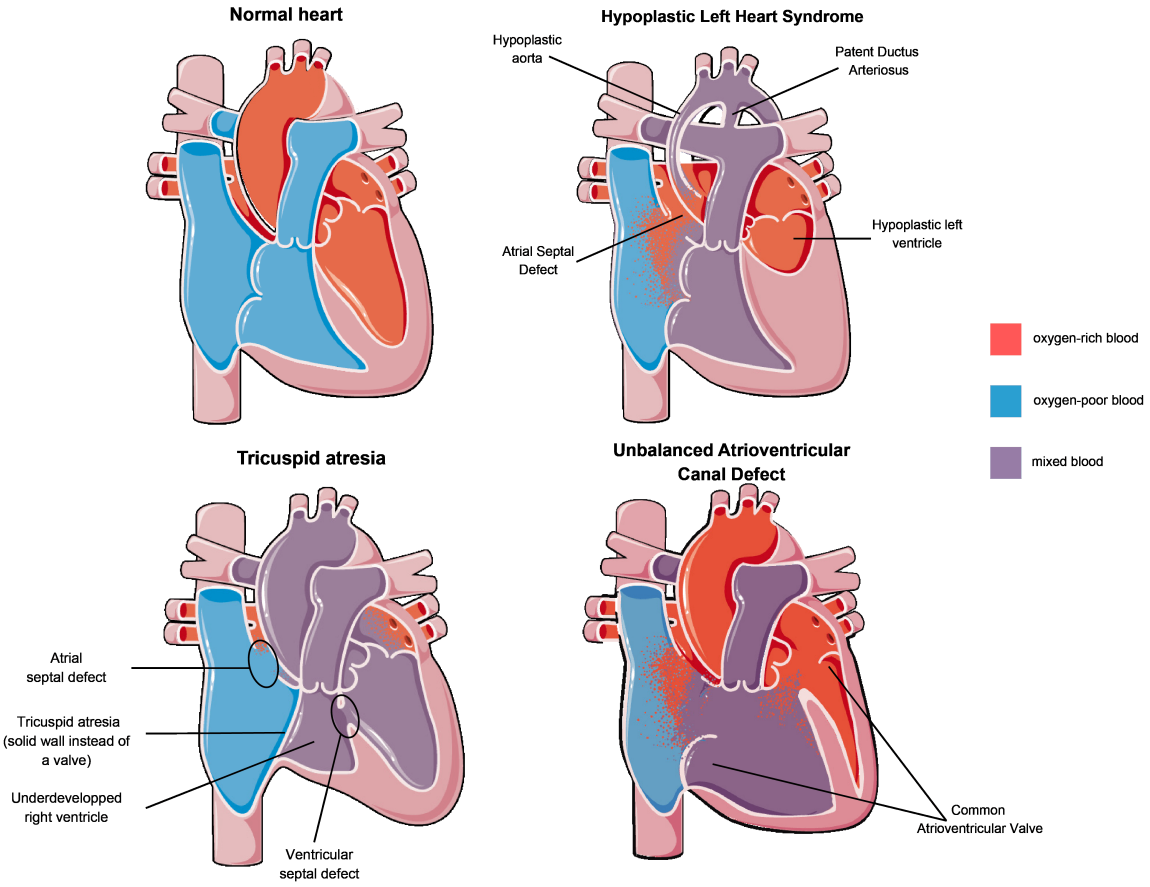

Figure 1. This figure illustrates the differences between common forms of SVDs.

functioning ventricle as the supplier of both pulmonary and systemic circulation [56]. This consists of three key surgical steps. Initially, an atrial septectomy is performed through a cannulation site into the right atrium while under deep hypothermic circulatory arrest to ensure later atrial mixing of oxygenated and deoxygenated blood [57]. Moreover, the aortic arch is reconstructed to become the outflow of the functional ventricle, likely the right ventricle in cases like HLHS, followed by shunt placement from the systemic circulation to the pulmonary artery [58]. The classic shunt involved is the Modified Blalock-Taussig (MBT) shunt which is a tube graft connecting the subclavian or innominate artery to the pulmonary artery trunk [59]. An alternative shunt called the right ventricle-pulmonary artery (RV-PA) or Sano shunt was also introduced which could address the theoretical coronary steal phenomenon occurring with the MBT shunt [60].

The Glenn procedure is the second step of the surgical pathway aiming to reduce the load on the functional ventricle by diverting venous blood from the upper half of the body [61]. This is first done by ligating the MBT or RV-PA systemic-to-pulmonary shunt placed in the first procedure [62]. The superior vena cava (SVC) is then ligated, and an anastomosis is created by connecting it to the pulmonary arteries [63]. Modern techniques entail a bidirectional Glenn (BDG) where an end-to-side anastomosis is performed on the pulmonary trunk proximal to the PA bifurcation compared to the classical Glenn procedure where the anastomosis was performed to the side of the right PA [64]. BDG unloads the functional ventricle whilst ensuring bilateral pulmonary perfusion, improved oxygenation, and less pulmonary AVM formation compared to the classical Glenn [64, 65]. While Glenn circulation is usually an intermediate till Fontan completion, it remains the ultimate

long-term palliative strategy for some SVD patients with contraindications for the Fontan procedure [65]. Absolute contraindications include having pulmonary hypertension, PA hypoplasia or obstruction, severe ventricular dysfunction, AVV regurgitation, severe cyanosis or hypoxemia, or end-stage hepatic or renal disease [14].

For patients with no such contraindications, Fontan surgery represents the ultimate palliative step for improving circulation and oxygenation [66]. The selection criteria for favorable Fontan completion include having low PVR, no PA obstruction or hypoplasia, well-functioning single ventricle, no significant AVV regurgitation, and no uncontrolled arrhythmias [14]. Moreover, patients should be between 4-15 years old, have a low PA pressure less than 15 mmHg, have a PA-to-aorta ratio of greater than 0.75, and have a ventricular ejection fraction greater than 55% [14].

After hemodynamic optimization through the two preceding steps, Fontan completes the rerouting of deoxygenated blood to the pulmonary circulation through either the lateral tunnel (LT) intracardiac approach or the more widely used extracardiac conduit (EC) method [67]. The LT method consists of connecting inferior vena cava (IVC) directly to the PA through an intracardiac baffle [68]. However, the EC method, which involves ligating the IVC entry point to the right atrium (RA) and connecting its distal end directly to the PA, has been associated with shorter bypass times, less early and intermediate risk of atrial arrythmias, and preservation of ventricular and pulmonary vascular function [14, 69]. Fontan fenestration has been shown to improve early postoperative physiology by reducing pulmonary artery pressures and the need for prolonged pleural drainage, without increasing early mortality or Fontan failure [69]. With the EC method, opinions differ on whether to electively fenestrate the conduit, fenestrate with later closure, or not to fenestrate at all [70].

The Fontan procedure is a life-saving operation for patients who would otherwise not survive beyond infancy. Patients with univentricular hearts rarely survived till adulthood before modern Fontan surgical techniques [71]. By establishing total cavopulmonary connection, the Fontan circulation provides proper separation of both the systemic and pulmonary circulations restoring near-normal systemic oxygen saturation and eliminating chronic volume overload. This is an important hemodynamic success of the operation that provides an acceptable functional capacity for most patients through early adulthood [72]. With modern surgical techniques, impressive long-term survival rates exceeding 90% at 20 years have been achieved. This reflects a remarkable improvement in early- and mid-term outcomes rendering SVD a survivable chronic condition compatible with adulthood [71, 73]. The extracardiac conduit approach has become the dominant technique for the total cavopulmonary connection due to its association with better long-term outcomes and lower rates of atrial tachyarrhythmias compared to the older lateral tunnel method [73]. Moreover, routine fenestration has improved early postoperative outcomes with studies showing mortality reductions from 8.6% to 1.2% following its widespread implementation [74]. These advances have transformed SVD from a fatal condition to a survivable chronic illness with an estimated 70,000 patients alive worldwide today, and this number is expected to double in the next 20 years [71].

Despite its advantages, Fontan circulation remains limited by the absence of a subpulmonary pump and a reliance on passive pulmonary blood flow. This results in chronically elevated systemic venous pressure and reduced preload limiting cardiac output both at rest and during exercise [71, 72]. This unique hemodynamic setup predisposes patients to progressive Fontan failure over time. Chronic venous congestion and weak forward flow may result in multiorgan complications. These complications include ventricular systolic and diastolic dysfunction, atrial and ventricular arrhythmias, thromboembolism, lymphatic failure with PLE and plastic bronchitis, and progressive hepatic congestion culminating in FALD [72, 75]. It is important to note that these complications can often arise despite initially preserved postoperative hemodynamics and represent a major cause of future morbidity and mortality. Indeed, the Fontan pathway imposes long-term mechanical complications. Synthetic conduits used for total cavopulmonary connection lack growth potential and are prone to stenosis, thrombosis, and flow inefficiency over time worsening venous hypertension and impairing pulmonary blood flow [71].

At present, no Fontan modification fully restores normal cardiovascular physiology. Current research focuses on addressing strategies to lower venous pressure, improve pulmonary flow, and increase ventricular preload. It also emphasizes optimizing cavopulmonary assist devices, connection geometry, pulmonary vascular modulation, and targeted lymphatic interventions [71]. Heart transplantation, sometimes combined with liver transplantation, remains the only definitive therapy of end-stage Fontan failure. However, it has inferior outcomes when compared with other transplant populations and that it has been almost phased out of practice [75].

While the Fontan procedure has changed the course of SVD management, it is not the end goal for all patients. Alternative options include permanent Glenn, biventricular conversion, mechanical support such as the ventricular assist device (VAD), and heart transplant [64]. As mentioned previously, Fontan alternatives are needed in cases of unfavorable PA anatomy, pulmonary hypertension, severe valvular disfunction, AVV regurgitation, and end-stage renal or hepatic disease [14]. When these contraindications are present with the patient undergoing previous palliation, the simplest intervention would be to maintain the patient at the permanent Glenn stage with consistent follow-up.

A subset of patients with borderline small left heart structures who have undergone previous single ventricle palliation may become candidates for biventricular conversion [76]. This includes aorticopulmonary anastomosis takedown followed by initial or staged biventricular conversion to promote blood flow through the hypoplastic left ventricle whilst relieving inflow and outflow tract obstructions [76]. After restoring the left and right ventricular outflow tracts, a cavoatrial reanastomosis is performed to reestablish the connection between the SVC and right atrium [76]. Present ASDs can be closed via fenestrated, which is the more common option, or complete repair [76]. An endocardial fibroelastosis resection is usually performed to stimulate left ventricular growth and improve its compliance for systemic circulation, and AVV repair is frequently part of the conversion [76].

The indications for biventricular repair include having two adequately sized ventricles, favorable AVV anatomy, a ventricular septum amenable to reconstruction, a large enough aortic arch and PAs, and Fontan failure with possible ventricular recruitment [77]. This alternative procedure would help avoid the progressive complications of Fontan physiology including chronic systemic venous pressure elevation and progressive FALD which would decrease long-term morbidity [77]. Biventricular repair has also been associated with improved exercise tolerance and systemic oxygenation levels compared to Fontan patients [77]. However, its limitations include its limited applicability to a small subset of Fontan candidates, increased arrhythmogenicity, risk of reconstructed valve/septum/ventricle failure, and its poor prognosis in patients with advanced end-organ disease such as FALD [77].

Patients who do not benefit from the above interventions may be given the options of mechanical support such as the ventricular assist device (VAD) and/or transplantation. Hemodynamic patterns that warrant mechanical support include systolic dysfunction, diastolic dysfunction, increased PVR, or a mixed failure [64]. Moreover, this support can be a bridging strategy till a transplant is possible, and the indications will differ based on the stage of palliation the patient is in and the degree of impairment. The main advantage of mechanical support is optimizing transplant candidacy by improving end-organ function with multiple options including extracorporeal membrane oxygenation, VAD, and total artificial heart [64]. The limitations include the numerous surgical interventions to implement the support, unique SV anatomies that may not fully fit a single supportive method, and having limited data so far [64]. When all other interventions fail, transplantation remains as a last resort. The indications include Fontan failure after most interventions were used, progressive multi-organ dysfunction, and having complications such as PLE, AVMs, or severe FALD (fibrosis/cirrhosis/hepatocellular carcinoma) where a heart-liver transplant may be offered [64]. Transplantation would offer a definitive treatment of failing Fontan, improve advanced FALD outcomes with theoretical heart-liver transplantation, and be associated with better overall outcomes if preceded with VADs [64]. However, these

patients face difficulties with transplant-list priority, high post-transplant mortality, complex anatomy due to prior surgeries, and the essential abandonment of the heart-liver transplant method [64].

Results

Numerous cohort studies have followed patients undergoing the Fontan procedure highlighting possible risk factors related to postoperative outcomes along with distinct outcomes studied in each paper. The collected studies were grouped into different categories based on similar outcome measures. The studies were either prospective or retrospective cohorts with the most common Fontan type being a fenestrated extracardiac Fontan. Sample sizes ranged from 81 to 1461 patients with their mean ages at Fontan completion ranging from 3.1 to 9.1 years. The most common type of SVD within the sample was tricuspid atresia. It is also important to note that early survival rates typically refer either to survival within 30 postoperative days or within the same hospital admission as the surgery. A comprehensive breakdown of each study can be found in **Table 1**.

Overall survival and mortality risk factors

Most of the selected studies chose overall survival as their primary outcome with some distinguishing between short-term and long-term survival. A retrospective cohort study by Sethasathien et al. [78] reported an early survival rate of 93% and long-term survival rates of 92%, 87%, and 84% at 5-, 10-, and 15-years post-Fontan from a mostly fenestrated extracardiac Fontan cohort. Risk factors for early post-operative mortality included post-operative mean pulmonary artery pressure ≥23 mmHg and uncorrected moderate or severe AV valve regurgitation [78]. Another retrospective cohort study by Al Absi et al. [79] showed a 94% early (30-day) survival rate from a mostly fenestrated extracardiac Fontan cohort as well. Statistically significant risk factors for early mortality included heterotaxy and diminished pre-operative ventricular function [79].

Atallah et al. [80] performed a prospective multicenter cohort with consecutive recruitment of patients with HLHS who underwent the Fontan series of surgeries. 60% of these patients survived the pre-Fontan operations and 97.1% of those patients survived the Fontan stage [80]. A more complicated SVD population was studied by Arrigoni et al. [81] where they studied patients with SVD and atrioventricular septal defect. Survival rates were 71.2%, 70%, and 68.5% at 10, 15- and 20-years post-Fontan with reduced survival being linked to having moderate-to-severe or severe AVV regurgitation [81]. Moreover, the mortality rate was not significantly affected by concomitant AVV procedures which warrants their repair in SVD patients [81].

In the retrospective cohort study by Gutierrez-Gil et al. [74], early post-operative survival for mostly extracardiac Fontan SVD patients was 91.4% between 2000-2010 which increased to 98.8% from 2010 onwards following the widespread implementation of fenestration. Al Najashi et al.'s [82] retrospective cohort study revealed a predominantly extracardiac Fontan population with overall 1-, 5-, 10-, 20-, and 30-year survival rates of 96%, 94%, 93%, 89%, and 85% respectively. In the modern era from 1999 onwards, the 5-, 10-, and 15-year survival rates were 96%, 95%, and 93% respectively [82]. Univariate risk factors included hypoalbuminemia, NtProBNP >500 pg/mL, surgical era prior to 1999, lack of fenestration, and prior atriopulmonary Fontan (APF) procedure while multivariate ones included prior APF and surgical era prior to 1999 [82].

Ishigami et al.'s [83] retrospective cohort study on patients mainly with HLHS revealed overall survival rates of 96% and 86% at 10 and 20 years post-extracardiac Fontan respectively. Risk factors for Fontan failure included right ventricular dominance, aortic atresia, and elevated mean pulmonary artery pressure [83]. A prospective registry-based cohort study by Yang et al. [84] revealed a 93.5% early survival rate and an overall 30-year survival rate of 75% which has recently improved with modern methods. 59.8% of deaths were directly due to CHD, 71.7% involved CHD, 64.7% had another CVD, and 12% had no cardiac cause [84].

Constantine et al. [22] conducted a retrospective cohort study on patients receiving APF for their SVDs and monitored late outcomes after the age of 35 where 16.5% had died at follow-up mainly due to heart failure. Univariate risk factors of mortality included hypoalbuminemia,

Table 1. This table reveals cohort studies on the risk factors and outcomes of Fontan patients

Study Reference	Study Type and Location	Population Size	Most Common SVD Type	Median Age at Procedure	Most Common Fontan Type	Fenestration Rate	Outcomes
Sethasathien et al., 2020 [78]	Retrospective, single-center cohort from Thailand	117	Tricuspid Atresia	5.7 years	Extracardiac Fontan	69%	-Early survival rate of 93%. -Mortality rates were 8%, 13%, and 16% at 5-, 10-, and 15-years post-Fontan. -Early deaths linked to postoperative mean pulmonary artery pressure ≥23 mmHg and uncorrected moderate or severe AV valve regurgitation. -Early postoperative complications of renal failure (16%), arrhythmia (12%), and need for extracorporeal membrane oxygenation (6%). -Late postoperative complications of FALD (32%) and protein-losing enteropathy (4%).
Al Absi et al., 2020 [79]	Retrospective, single-center cohort from the United Arab Emirates	87	Tricuspid Atresia	4.2 years	Extracardiac Fontan	83%	-Mortality rate was 6%. -Statistically significant risk factors for 30-day survival include heterotaxy and decreased ventricular function. -No statistically significant risk factors for prolonged hospital stay (>21 days) and prolonged ICU stay.
Atallah et al., 2020 [80]	Prospective, multicenter cohort from Canada	117	Hypoplastic Left Heart Syndrome	3.5 years	Extracardiac Fontan	84%	-40% mortality rate pre-Fontan procedures and 2.9% for the Fontan stage. -Full-scale IQ, performance IQ, verbal IQ, and visual-motor integration mean values were 86.7, 86.3, 88.8, and 83.2 respectively. -Multivariable analysis deemed older age at Fontan, peri-Norwood sepsis, lower arterial partial pressure of oxygen post-bidirectional cavopulmonary anastomosis, and prior neuromotor disability as key predictors of lower scores of intelligence quotient domains. -Subgroup analysis revealed older age at Fontan and sepsis peri-Norwood as independent risk factors of poor neurocognitive outcomes.
Arrigoni et al., 2022 [81]	Retrospective, multicenter cohort from the Netherlands and Belgium	151	Unbalanced AVSD = AVSD with hypoplasia of one ventricle deemed unfit for biventricular repair	-	Extracardiac Fontan	41.1%	-Survival rates of 71.2%, 70%, and 68.5% at 10-, 15- and 20-years post-Fontan. -Reduced survival linked to moderate-severe or severe atrioventricular valve regurgitation. -Concomitant atrioventricular valve procedure had no significant effect on the mortality rate or Fontan completion. -Single ventricle with AVSD and AVV regurgitation exceeding moderate degree warrants AVV repair.
Gutierrez-Gil et al., 2023 [74]	Retrospective, single-center cohort from Colombia	81	Tricuspid Atresia	5.3 years	Extracardiac Fontan	54.3%	-Postoperative mortality in the first month was 8.6% between 2000 and 2010, which declined to 1.2% after 2010 after fenestration implementation. -Coagulopathy was the most frequent postoperative complication at 19.8%. -Less median thoracostomy days in fenestrated (9.5) than non-fenestrated (11) patients. -No marked difference in hospitalization time, days in the ICU, and oxygen therapy between fenestrated and non-fenestrated patients.
Al Najashi et al., 2021 [82]	Retrospective, single-center cohort from Saudi Arabia	458	Tricuspid Atresia	7 years	Extracardiac Fontan	52.4%	-The 1-, 5-, 10-, 20- and 30-year survival was 96%, 94%, 93%, 89%, and 85% respectively. -In the modern surgical era from 2000 onwards, the 5-, 10- and 15-year survival rates were 96%, 95%, and 93% respectively. -Univariate analysis risk factors of death/transplant include hypoalbuminemia, NtProBNP >500, surgical era prior to 1999, lack of Fontan fenestration, and prior APF procedure. -Multivariate analysis independent risk factors of death/transplant include APF and surgical era before 1999.
Ishigami et al., 2025 [83]	Retrospective, single-center cohort from Australia	398	Hypoplastic Left Heart Syndrome	5 years	Extracardiac Fontan	76.4%	-Overall survival was 96% and 86% at 10 and 20 years after extracardiac Fontan operation, respectively. -88% freedom from the failure of Fontan circulation at 10 years and 76% at 20 years. -Risk factors for the failure of Fontan circulation were right ventricular dominance, aortic atresia, and elevated mean pulmonary artery pressure.

Yang et al., 2024 [84]	Prospective, registry-based multicenter cohort from the United States of America	1461	Tricuspid Atresia	3.1 years	Extracardiac Fontan	58.3%	-93.5% survived with Fontan circulation till discharge. -Thirty-year post-Fontan survival was 75% with higher rates for modern methods. -In Fontan patients, 59.8% of deaths were directly due to CHD, 71.7% involved CHD, 64.7% had another CVD, and 12% had no cardiac cause.
Constantine et al., 2024 [22]	Retrospective, multicenter cohort from the United Kingdom and Italy	115	Tricuspid Atresia	9.1 years	APF	20.5%	-Patients were evaluated for late outcomes of Fontan circulation at age 35 and above. -55.9% of patients were NYHA class II. -66.1% experienced arrythmia and 7.0% experienced protein-losing enteropathy. -16.5% had died at follow-up mainly from heart failure. -Univariable risk factors of death/transplantation include hypoalbuminemia, prior HF admission, prior atrial tachycardia/flutter, and baseline pulmonary vasodilator therapy. -Bivariable significant risk factors include hypoalbuminemia and prior atrial tachycardia/flutter.
Egbe et al., 2025 [85]	Retrospective, single-center cohort from the United States of America	455	Tricuspid Atresia	5 years	Extracardiac Fontan	-	-14% of the Fontan population was >40 years old defined as the middle-aged population. -Middle-aged group had more atrial arrhythmias, neurohormonal activation, and hepatorenal dysfunction. -Middle-aged group had a higher 5-year and 10-year cumulative incidence of death/transplant along with a 41% general mortality rate. -Univariable predictors of death/transplant within the middle-aged group include higher pulmonary artery wedge pressure, higher Fontan pressure, lower GFR, higher MELD-XI score, older age at baseline. -Multivariable significant risk factors include higher pulmonary artery wedge pressure and MELD-XI score.

Abbreviations: FALD: Fontan-associated liver disease; APF: Atriopulmonary Fontan; AVSD: Atrioventricular septal defect; AVV: Atrioventricular valve; NYHA: New York Heart Association; GFR: Glomerular Filtration Rate; MELD-XI: Model for End-stage Liver Disease - eXcluding INR.

prior heart failure (HF) admission, prior atrial tachycardia/flutter, and baseline pulmonary vasodilator therapy while bivariable significant risk factors included hypoalbuminemia and prior atrial tachycardia/flutter [22]. Egbe et al. [85] also focused on outcomes within the middle-aged Fontan population with 14% of their sample being >40 years old. This middle-aged group had higher 5- and 10-year cumulative mortality with a 41% mortality rate [85]. Univariate risk factors included higher pulmonary artery wedge pressure, higher Fontan pressure, lower glomerular filtration rate (GFR), higher Model for End-stage Liver Disease - eXcluding INR (MELD-XI) score, older age at baseline while multivariate risk factors included higher pulmonary artery wedge pressure and MELD-XI scores [85].

While survival has significantly improved over time, the cardiovascular sequelae of the Fontan procedure contribute to lifelong morbidity which has become the main concern following the procedure.

Cardiovascular complications

Given the toll of both SVDs and Fontan operations on the cardiovascular system, postoperative cardiovascular complications were studied in a detailed manner. Sethasathien et al. [78] reported early cardiac postoperative complications such as arrythmia in 12% of their cohort with 6% of the cohort experiencing the need for extracorporeal membrane oxygenation. Gutierrez-Gil et al. [74] reported coagulopathy as their most frequent post-Fontan complication occurring in 19.8% of the cohort. Ishigami et al. [83] addressed the freedom from failure of Fontan circulation as a cardiovascular success measure which occurred in 88% and 76% at 10 and 20 post-operative years respectively.

Constantine et al. [22] addressed New York Heart Association (NYHA) class as a measure of cardiovascular health in middle-aged patients who had undergone Fontan at a mean of 9.1 years old. Most of their cohort (55.9%) had an NYHA class II status which reflects slight limitation of their physical activity despite being comfortable at rest. Arrythmia was a prevalent cardiovascular complication noted in 66.1% of the cohort post-APF, and 16.5% of the cohort had died at long-term follow-up mostly due to heart failure [22]. Egbe et al. [85] also focused their study on middle-aged Fontan patients who had significant differences in prevalence of postoperative arrhythmia and cardiac biomarker fluctuations. The middle-aged group had an 83% prevalence of overall atrial arrythmias compared to 48% in the younger group (P<0.001) [85]. Moreover, the prevalence of atrial fibrillation was 52% in the middle-aged group compared to 20% in the younger group [85]. Median NT-proBNP was 348 pg/mL for the middle-aged group compared to 196 pg/mL for the younger one while differences in NYHA class were insignificant [85]. Of the middle-aged cohort, 11.1% died from end-stage HF and 3.2% from sudden cardiac death [85].

The Fontan circulation has a hemodynamic burden that goes beyond the cardiovascular system to trigger multiple systemic sequelae such as hepatorenal dysfunction to be discussed below.

Hepatorenal complications

As part of the broader postoperative complications, Sethasathien et al. [78] reported short-term renal failure in 16% of their sample along with long-term Fontan-associated liver disease (FALD) in 32% and protein-losing enteropathy (PLE) in 4%. Moreover, Constantine et al. [22] reported PLE in 7% adults aged 35 or above with Fontan circulation. Egbe et al. [85] utilized the MELD-XI score to assess hepatorenal dysfunction in middle-aged patients with Fontan circulation. MELD-XI is a scoring system considering bilirubin and creatinine values for hepatorenal function prognosis for Fontan patients on anticoagulation whilst excluding their INR values [86]. A higher MELD-XI score has been associated with increased sudden death, death from congestive heart failure, or heart transplant in Fontan patients compared with those with low MELD-XI scores [87]. Egbe et al.'s [85] cohort revealed a significantly (P<0.001) higher MELD-XI score of 14.6 for the middle-aged group compared 11.9 for the younger group indicating poorer hepatorenal function. Moreover, the middle-aged cohort had a mean effective GFR (eGFR) of 68 mL/min/1.73 m^2 which was significantly (P<0.001) lower than that of the younger group which was 81 mL/min/1.73 m^2 revealing a decline in renal function [85]. The middle-aged group also had a significantly (P<0.001) higher prevalence of chronic kidney

disease stage 3 or above of 37% compared to 15% of the younger group.

Beyond the hepatorenal dysfunction, an understudied subset of systemic postoperative complications includes neurocognitive deficits addressed below.

Neurocognitive outcomes

Atallah et al. [80] conducted a prospective multicenter cohort study where they consecutively recruited 117 patients with HLHS who would undergo the Fontan palliation pathway with a focus on neurocognitive outcomes. The assessed intelligence quotients (IQs) were full-scale IQ, performance IQ, verbal IQ, and visual-motor integration with mean values of 86.7, 86.3, 88.8, and 83.2 respectively [80]. With the population average being 100 across these standardized measures, these values reflect mild-to-moderate neurocognitive deficits in the Fontan population. Multivariate analysis identified older age at Fontan, peri-Norwood sepsis, lower arterial partial pressure of oxygen post-bidirectional cavopulmonary anastomosis, and prior neuromotor disability as key predictors of lower scores of intelligence quotient domains [80]. Older age at Fontan and sepsis peri-Norwood were identified as independent risk factors of poor neurocognitive outcomes [80].

Fontan-associated liver disease

Although the Fontan procedure has significantly improved the survival of SVD patients, it remains associated with a spectrum of long-term complications [72]. These include ventricular dysfunction, arrhythmias, cyanosis, reduced exercise capacity, elevated PVR, PLE, plastic bronchitis, renal impairment, and most commonly hepatic complications [72]. Hemodynamic changes associated with the Fontan circulation, such as elevated central venous pressure and diminished cardiac output are responsible for the development of FALD [88].

In Fontan circulation, the liver is susceptible to the effects of the central venous hypertension via the direct discharge of the hepatic veins [89]. The elevated central venous pressure is transmitted into the hepatic sinusoids, which may further diminish portal vein in-flow [89]. Additionally, blood flow and oxygen saturation in the portal vein are expected to be reduced, causing the liver to become increasingly more reliant on the reduced buffering capacity of the hepatic arterial supply [90]. As a result, the liver will be more susceptible to the hemodynamic insults caused by impaired cardiac output [91]. The elevated central venous pressure renders the liver more vulnerable to ischemic injury [92]. The aberrant Fontan circulation also facilitates the development of intrapulmonary veno-venous or arteriovenous collaterals that further chronically aggravate hypoxia [93]. The resultant chronic hepatic injury leads to the development of liver fibrosis or cirrhosis [94]. In the more advanced stages of liver injury, there is a risk of developing hepatocellular carcinoma at a young age [90].

From a cellular perspective, the neurohormonal system plays a critical role in FALD [90]. Serum renin, aldosterone, and angiotensin are shown to be elevated in patients with Fontan physiology, with angiotensin 2 promoting the secretion of collagen 1 [95, 96]. Excessive production and deposition of collagen both contribute to liver fibrosis and various other pathologies [94, 97].

Numerous retrospective, prospective, and observational studies have underscored the impact of Fontan physiology and altered hemodynamics on the progression of various hepatic pathologies. A retrospective study by Wilson et al. demonstrated the relationship between the Fontan procedure, atrioventricular valve failure, and liver cirrhosis [98]. A total of 95 patients underwent liver assessment at a mean age of 18.2 ± 6.7 years, roughly 12 years after their Fontan operation. 15 patients were diagnosed with cirrhosis at a mean age of 22.7 ± 5.9 years. The risk factors associated with the development of liver cirrhosis included AVV repair prior to Fontan and older age at the Fontan operation. Additionally, the incidence of liver cirrhosis increased with age after the Fontan procedure. Another prospective study enrolled 76 pediatric patients with Fontan physiology, with 17 having underwent a trans-jugular liver biopsy [99]. All biopsies revealed pathological changes including clinically silent fibrosis emphasizing the need for liver surveillance for Fontan patients in early childhood. Additionally, hemodynamic data from this study revealed no association between the extent of liver pathology and PVR, emphasizing the need

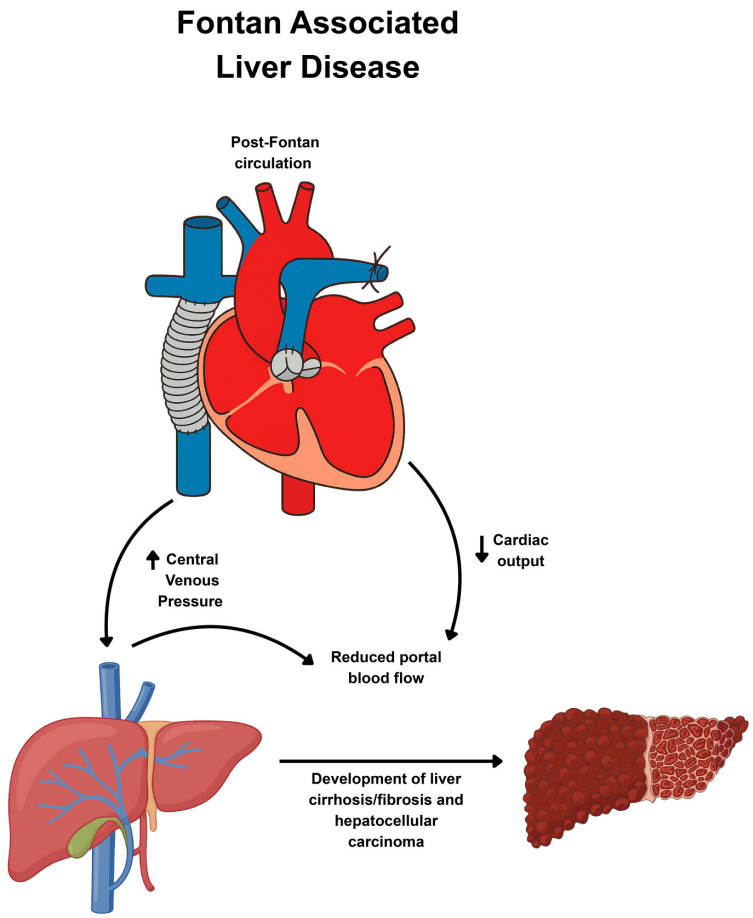

Figure 2. This figure demonstrates the physiological manifestations of FALD.

to explore alternative therapeutic strategies beyond pulmonary vasodilators to mitigate the sequelae of Fontan circulation.

A prospective observational study by Alsaied et al. recruited 25 Fontan patients with a mean age of 16.3 ± 6.8 years [100]. This study highlighted that both baseline and stress Fontan hemodynamics were significantly associated with increased extracellular volume fraction as a measure of myocardial fibrosis. Furthermore, evidence of myocardial fibrosis in these patients was associated with diastolic dysfunction, increased liver stiffness, and elevated circulating biomarkers of fibrosis. Another retrospective population-based study demonstrated a strong association between severe FALD and mortality [101]. The medical records of 512 patients who underwent the Fontan procedure were reviewed. In Fontan patients, 11.95% developed severe FALD after 10 years, and 52.24% developed severe FALD after 35 years. The 5-year mortality rate for Fontan patients with severe FALD was 12.6%. Identified risk factors for FALD development included congestive heart failure, poor hemodynamics, and supraventricular tachycardia.

A retrospective observational multicenter study in a European cohort of patients reviewed the data of 2141 Fontan patients [102]. Among the cohort, 343 patients were diagnosed with FALD, with a median age of 18 years and a median follow-up of 14 years following Fontan surgery. Among these, there were 19 deaths, with 5 cases being related to advanced liver disease or cancer. Factors significantly associated with FALD included absence of Fontan fenestration, systemic ventricular dysfunction, and AVV dysfunction, whereas the type of Fontan surgery showed no significant association.

The previous studies highlight an association between Fontan physiology, altered hemodynamics, and the development of FALD. Despite its clinical significance, FALD remains insufficiently characterized with no universally accepted diagnostic criteria or surveillance guidelines. Most available data is derived from retrospective cohorts with heterogeneous follow-up durations and liver assessment methods. These limitations underscore the need for standardized, proactive monitoring strategies to enable earlier detection and timely intervention. The manifestations of FALD can be summarized in **Figure 2**.

Discussion

An important clinical variable affecting the Fontan outcome is age at the time of operation. It has been shown that earlier age at Fontan completion is associated with improved outcomes. Atallah et al. [80] reported significantly improved neurocognitive outcomes with earlier age at Fontan completion. In addition, Egbe et

al. [85] identified older age at baseline as a univariable risk factor death/transplant. The studies included in this paper are comparable in terms of early survival outcomes regardless of age at Fontan where the cohorts of Sethasathien et al. [78], Gutierrez-Gil et al. [74], and Yang et al. [84] had early survival rates above 90% with median ages between 3.1 to 5.7 years old. As for long-term survival, the 10-year survival of the Sethasathien et al. [78], Al Najashi et al. [82], and Ishigami et al. [83] cohorts were 87, 93, and 96% respectively with median ages between 5-7 years old.

Long-term outcomes in general were excellent for the procedure regardless of whether the procedure was performed from ages 3 to 7 years old. However, the lowest long-term survival rates were reported by Arrigoni et al. [81] which were 71.2, 70, and 68.5% at 10-, 15-, and 20-years post-Fontan respectively but their median age was unspecified and those patients had unbalanced AVSD as a possible confounder. As for the Yang et al. [84] cohort which had the youngest median age, they had the lowest 30-year survival but that could be attributed to records from older surgical eras being used. Al Najashi et al. [82] proved older surgical era to be an independent risk factor of death/transplant. As for the 83.5% survival rate of the Constantine et al. [22] cohort which had the oldest median age of 9.1, this could either be attributable to the older age itself or the older surgical Fontan technique of APF which was used or both. Older Fontan techniques like the APF were associated with worse outcomes whereas the majority used the extracardiac method and were associated with the best outcomes in terms of morbidity and mortality.

As for fenestration status, Gutierrez-Gil et al. [74] demonstrated a sharp decrease in mortality rate from 8.6 to 1.2% upon the introduction of fenestration into general practice in 2010. Moreover, they reported a lower thoracostomy duration of 9.5 days for fenestrated patients compared to 11 days for the unfenestrated patients [74]. Lack of fenestration was identified by Al Najashi et al. [82] as an independent risk factor of death/transplant. Moreover, the studies with the highest fenestration rates of 76.4, 83, and 84% were associated with the best survival rates of 96, 94, and 97.1% respectively [79, 80, 83].

The findings presented in this review are consistent with recent literature through several aspects. In a meta-analysis by Schwartz et al. [103], nineteen articles with a total of 5859 patients showed a 10-year survival rate of 87.2% which aligns with our findings of excellent long-term survival rates for these patients. Moreover, their study also listed APF and older age at Fontan as risk factors for mortality. Another meta-analysis by Bouhout et al. [104] compared the early outcomes of 4806 patients across 19 studies based on whether their Fontan procedure involved fenestration or not. While the fenestrated group had lower oxygen saturation rates (mean difference -3.07%, $P<0.001$), they had both significantly lower need for pleural drainage (odds ratio (OR) 0.59, $P=0.03$) and mean pulmonary arterial pressure (mean difference -0.99 mmHg, $P=0.005$) with no significant difference in stroke occurrence (OR 1.32, $P=0.65$). This proves that Fontan fenestration significantly reduces both prolonged pleural drainage and mean pulmonary artery pressure supporting the favorable outcomes of fenestration in this review.

As for the type of Fontan, a systematic review and meta-analysis by Talla et al. [105] studied the long-term outcomes of Fontan patients with an extracardiac conduit. Whilst this population exhibited an excellent 10-year survival rate of 95% favoring the extracardiac Fontan procedure, they reported that an estimated 7% of these patients will develop conduit obstruction over 10 years. Patients with Dacron polyethylene-terephthalate conduits experienced higher rates of stenosis identifying an additional risk factor for long-term morbidity and mortality.

A review by Abdulkarim et al. [106] describes pulmonary Fontan complications that were not focused on in this review such as restrictive lung disease (approximately two thirds of patients), plastic bronchitis (reported incidence of 4-14%), and pulmonary arteriovenous malformations (in up to 60% of patients with interrupted IVCs/heterotaxy following Fontan). These are mostly due to the chronic elevation of systemic venous pressure further emphasizing the importance of multi-system monitoring of these patients.

Conclusion

In conclusion, the Fontan procedure has become associated with improved survival rates

over time compared to older surgical techniques where modern techniques like the extracardiac Fontan and fenestration have dominated recent practice. Early postoperative survival rates are excellent with great improvement of long-term outcomes as well. However, long-term survival rates still drop significantly after 20-30 years possibly due to the morbidities of the Fontan circulation. This emphasizes a transition in the management of Fontan patients from managing their immediate mortality to addressing the morbidities these patients deal over a lifetime of Fontan circulation which may impact their quality of life.

The prominent morbidities of Fontan circulation include complications like arrhythmias, HF, neurocognitive delays, PLE, renal dysfunction, and FALD. FALD has become one of the most prominent long-term complications to address due to many patients experiencing severe FALD along with the serious risk of progression to cirrhosis and hepatocellular carcinoma. As such, universal diagnostic criteria and standardized surveillance protocols are essential and must be tailored to each potential complication and especially for FALD. As for risk factors for complications, demographic (older age, earlier surgical era), surgical/hemodynamic (absence of fenestration, APF, elevated PA pressure), and biochemical markers (low albumin, high NT-proBNP, high MELD-XI, reduced GFR) have been identified as the most prominent.

Lifelong multidisciplinary monitoring is essential to optimize these patients' quality of life. Early FALD monitoring potentially through hepatic biomarkers along with the integration of risk scores like the MELD-XI into clinical practice may improve hepatorenal outcomes. The availability of multicenter studies on Fontan patients with sufficient long-term follow-up is still limited which emphasizes the need for further investigation of this population. While the procedure is lifesaving, it is not a curative option but rather a palliative one which requires a lifetime of dedicated care to both prevent and address long-term complications in a timely manner. As the focus shifts to lifelong morbidity and quality of life concerns, our research ought to follow that shift and address every way to improve these patients' outcomes.

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