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REVIEW ARTICLE

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Five decades of the Fontan operation: A systematic review of international reports on outcomes after univentricular palliation

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Abstract

Almost fifty years after its first clinical application, the modified Fontan operation is among the most frequently performed procedures in congenital heart disease surgery in children today. The objective of this review is to systematically summarize the international evolution of outcomes in regard to morbidity and mortality of patients with Fontan palliation. All studies published over the past five decades with more than 100 Fontan patients included were screened. In eligible studies, information concerning preoperative patients' characteristics, Fontan modifications employed, early mortality, long-term survival and frequency of relevant complications was extracted. Ultimately, thirty-one studies published by the largest surgical centers with an overall number of 9390 patients were included in this review. The extracardiac total cavopulmonary anastomosis is the most frequently used Fontan modification. Hemodynamic data demonstrate a rigorous overall adherence to suggested Fontan selection criteria. The analysis showed a clear trend toward improved early and long-term survival over the time period covered. Although inconsistently reported, severe complications such as arrhythmias, thromboembolic events and protein-losing enteropathy as well as reoperations and reinterventions were frequent. In conclusion, patients palliated for complex univentricular heart malformations nowadays benefit from the experience and technical developments of the past decades and have a significantly improved long-term prognosis. However, important issues concerning postoperative long-term morbidity and mortality are still unsolved and clear intrinsic limitations of the Fontan circulation are becoming evident as the population of Fontan patients ages.

KEYWORDS

Fontan procedure, long-term outcome, single ventricle, univentricular heart disease

1 | INTRODUCTION

The introduction of the Fontan operation in 1971 marked a turning point in the treatment and prognosis of the most complex congenital heart diseases: the univentricular heart malformations.[1]

The original approach, described for patients with tricuspid atresia and performed for the first time in 1968 by Fontan and colleagues, consisted of a classical Glenn shunt, in which the superior vena cava is connected to the right pulmonary artery, followed by connection of the right atrium to the left pulmonary artery with the interposition of a homograft.[1,2] Several modifications have since been introduced. Only shortly after Fontan, Kreutzer et al. described their modified atriopulmonary connection techniques.[3] In 1979, a right atrial-right ventricular connection was reported by Björk et al.[4] More recently and still widely applied, the total cavopulmonary connection (TCPC) or lateral tunnel Fontan was established by de Laval et al. in 1988. Venous blood flow of the inferior vena cava (IVC) was directed to the pulmonary artery by an intraatrial tunnel consisting of a prosthetic baffle incorporating the atrial wall.[5] The most recent approach, the extracardiac TCPC, was introduced by the groups of Puga and Marceletti and is now the most frequently applied modification. Systemic venous blood is entirely redirected extracardially by interposing an extracardiac conduit connecting the IVC with the pulmonary artery.[6,7]

Owing to the continuous improvements in surgical techniques and perioperative care, the development of preoperative selection criteria and innovations in medical and interventional treatment strategies, early and late mortality rates have been constantly declining and the

Fontan operation is now performed in virtually all kinds of cardiac malformations not amenable to biventricular repair.[8–14]

However, it has become evident that the profoundly unphysiological character of the Fontan circulation does not remain without consequences. Passive pulmonary blood is largely dependent on pulmonary vascular resistance as well as preserved systolic and diastolic ventricular function. The Fontan circulation physiology results in venous congestion with elevated venous pressures and reduced ventricular preload with a chronic low output state. This may lead to reduced exercise tolerance, end organ damage and consequently numerous complications, including ventricular failure, Fontan-associated liver disease, renal failure, arrhythmias, thromboembolic events, plastic bronchitis and protein-losing enteropathy. Several authors have expressed their concern about the obviously inevitable decline of the Fontan pathway function leading to irreversible Fontan failure and premature death.[15–18]

Now, almost 50 years after the first clinical application of the original procedure, the modified Fontan operation is among the most frequently performed procedures in congenital heart disease surgery in children.[19–21] It is regularly performed in large cardiothoracic surgical centers with an ever-growing number of studies reporting institutional and multi-institutional outcomes. The objective of this review is to systematically summarize the international evolution of outcomes in regard to morbidity and mortality of Fontan patients by analyzing the collective data published over the past five decades.

2 | METHODS

To identify relevant studies concerning outcome after Fontan procedure published to date, a systematic literature search via PubMed database was conducted. The following search terms were used: (Title:) "Fontan" OR "univentricular heart" OR "single ventricle" OR "cavopulmonary connection" OR "Fontan circulation" OR "Fontan-circulation," (Abstract:) AND "follow up" OR "follow-up" OR "outcome" AND "survival" OR "mortality" OR "morbidity" OR "complications" OR "failure." Additional studies were identified through hand search of bibliographies in relevant publications retrieved.

All retrieved abstracts of studies published between 1971 and 2016 were screened. Follow-up studies with $\geq$100 Fontan patients were taken into consideration and further reviewed. Exclusion criteria applied were: articles not published in the English language, articles that neither presented early nor late mortality after Fontan operation and articles that did not specify the period of Fontan operations performed or only examined a certain subgroup of patients with univentricular heart malformations. If a given institution had published more than one article with overlapping study periods and patient cohorts, we chose the study with the largest cohort that best fit the selection criteria.

In studies eligible for inclusion, the following data were extracted: general information (center, number of Fontan patients, follow-up time), preoperative patient characteristics (morphology of systemic ventricle, age, weight, mean pulmonary artery pressure, systemic ventricular end-diastolic pressure, transpulmonary pressure gradient), frequency of Fontan modifications, early mortality, long-term survival estimates, frequency of relevant complications as well as frequencies of reoperations, reinterventions and cardiac transplantations.

Data were collected and analyzed using Microsoft Office Excel 2011 for Mac OS X (Microsoft, Redmond, WA, USA). Results are given in numbers and percentages. For comparability reasons, if figures were not presented in the studies, we calculated or recalculated given figures as follows: percentages for late mortality as well as reoperations, reinterventions and cardiac transplantations were calculated or recalculated based on the entire cohorts of Fontan patients in the respective studies. Percentages for late complications, such as arrhythmias, thromboembolic events and protein-losing enteropathy were calculated or recalculated based on the number of early survivors of the Fontan operation, excluding early mortality. Calculated figures not provided in the original manuscripts are marked in the tables. Furthermore, the corresponding authors of 30/31 studies included were contacted via email with a request to provide missing data not reported in the original manuscripts. By this, additional data was obtained from 1 study. If patient cohorts were subdivided into several groups, the collective was summarized if possible.

Graphs were created with GraphPad Prism Version 6.0 2014 for Mac OS X (GraphPad, La Jolla, CA, USA).

3 | RESULTS

Overall, 650 potentially eligible studies were identified through the systematic PubMed search and further hand search. Of these, 392 were excluded because the study title reflected a nonmatching topic. A further 155 articles were excluded after screening of the abstract (review, case-report, editorial comment, particularly specific research question or examination of only a subgroup of patients with univentricular malformations, not written in the English language, limited patient cohort size). After comprehensive examination of the remaining 103 studies, 72 studies were excluded because they did not meet the selection criteria (limited patient cohort sizes, missing data on early or late mortality, period of Fontan operations performed not specified, no extractable data with regard to our research focus, studies from the same center with overlapping study periods). A total of 31 studies were then included in this review.

3.1 | General information: Follow-up period after Fontan, number of patients and geographic distribution of patients

The study periods of the analyzed reports comprised 47 years of Fontan operations (1968–2015), covering the eras of the original Fontan procedure and modified atriopulmonary connections as well as the more recent modifications of the lateral tunnel and extracardiac TCPC, which were introduced in the late 1980s and early 1990s. Postoperative follow-up intervals varied substantially, ranging from a mean of 2.0 years to up to 18.4 years.[22,23] Study periods, authors, centers, number of patients and duration of follow-up of the studies included are listed in Table 1.

The individual sample sizes of included studies varied from a minimum of 100 patients to a maximum of 1052 patients, resulting in an overall number of 9390 patients.[26,48] Studies were published by more than 40

TABLE 1 List of included studies

Study period, first author	Center	Patients (n)	Follow-up (years)
2009–2013, Zhu[24]	Children's Medical Center, Shanghai	101	2.4*
2002–2008, Salazar[22]	Texas Children's Hospital, Houston	226	2.0*
1997–2008, O'Brien[25]	The Children's Mercy Hospitals and Clinics, Kansas City	145	3.3*
1997–2003, Ocello[26]	Ospedale Civico, Palermo	100	3.3*
1996–2006, Kim[27]	Sejong General Hospital, Sejong	200	4.4*
1995–2011, Ovroutski[28]	Deutsches Herzzentrum Berlin, Berlin	140	
1995–2006, Lee[29]	Seoul National University Children's Hospital, Seoul	165	6.2/2.7*
1994–2015, Ono[30]	German Heart Center Munich, Munich	434	6.6*
1994–2014, Nakano[31]	Fukuoka Children's Hospital, Fukuoka	500	6.7**
1994–2009, Hasaniya[32]	Children's Hospital, Loma Linda	160	6.5*
1994–2007, Tweddell[33]	Children's Hospital of Wisconsin, Wisconsin	256	4.4*
1994–1998, Azakie[34]	Hospital for Sick Children, Toronto	107	2.8/2.5*
1992–2009, Rogers[35]	The Children's Hospital of Philadelphia, Philadelphia	771	
1992–2008, Brown[36]	James Whitcomb Riley Hospital, Indianapolis	220	6.7*
1992–2007, Hirsch[37]	University of Michigan, Ann Arbor	636	4.2**
1991–2002, Alphonso[38]	Guy's and St. Thomas Hospitals, London	122	4.5**
1990–1994, Sharma[39]	All India Institute of Medical Sciences, New Delhi	202	
1988–2011, Dabal[40]	University of Alabama, Birmingham	207	5.4**
1988–2008, Robbers-Visser[41]	Sophia Children's Hospital, Rotterdam	209	4.3**
1988–2004, Hosein[9]	Birmingham Children's Hospital, Birmingham	406	6.1*
1988–2003, Giannico[42]	Bambino Gesu Hospital, Rome	221	4.2**
1987–2007, Chungsomprasong[43]	Siriraj Hospital, Bangkok	139	4.8**
1984–2004, Ono[44]	Hannover Medical School, Hannover	121	10.9*
1983–1995, Podzolkov[45]	Scientific Center of Cardiovascular Surgery, Moscow	150	3.7*
1981–2009, Idorn[46]	Rigshospitalet, Copenhagen	235	8.3*
1979–2010, Ohuchi[23]	National Cerebral and Cardiovascular Center, Osaka	201	18.4*
1978–2000, Cazzaniga[47]	Hospital Ramón y Cajal, Madrid	124	8.4*
1975–2010, D'Udekem[14]	Fontan Registry, Australia and New Zealand	1006	
1973–2012, Pundi[48]	Mayo Clinic, Rochester	1052	15.3*
1973–1991, Gentles[49]	Children's Hospital, Boston	500	
1968–1988, Fontan[50]	Hopital Cardiologique du Haute-Leveque, Bordeaux	334	5.0**

List of studies included in this review sorted by reported time period of Fontan operations. Duration of follow-up after Fontan operation is given as reported (*mean or **median).
/, study cohort discriminated between Fontan modifications intracardiac and extracardiac total cavopulmonary connection; blank space, information not available.

surgical centers, predominantly from developed economies. The geographical distribution of patient numbers is depicted in Figure 1.

3.2 | Preoperative patient characteristics

Reported ventricular morphology of palliated univentricular heart malformations showed a larger proportion of malformations with a systemic left ventricle in most of the studies included. A few more recent studies, though, included a majority of patients with systemic right ventricles, ranging from 51.0% to 64.0% of the respective cohorts.[33,37] Presence of heterotaxy varied considerably with proportions between 3.1% and 39.8% of the patient populations.[23,37] The reason for this variability remains unclear; none of the studies specified how the diagnosis of heterotaxy was established. Preoperative

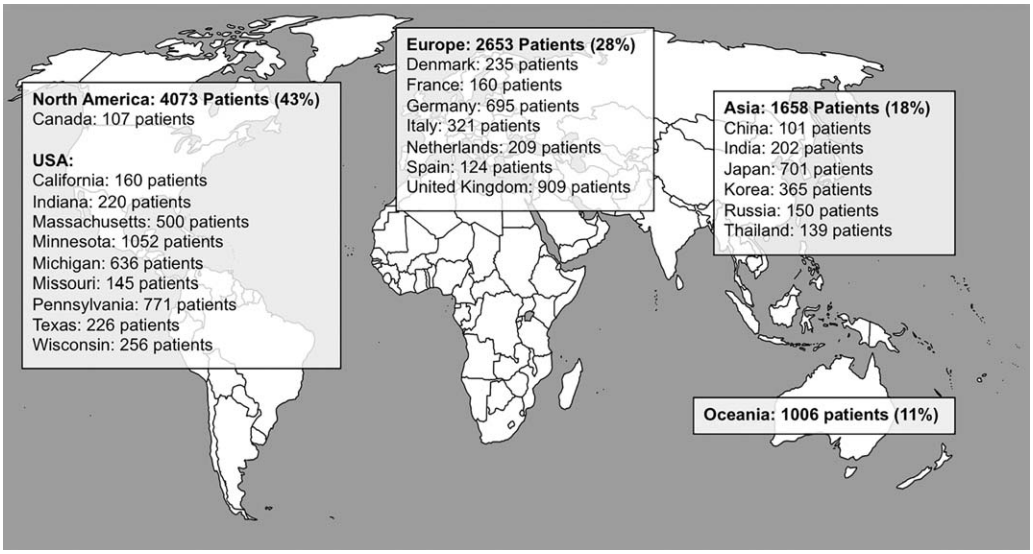

FIGURE 1 Overview of Fontan patient numbers and geographical distribution. Depiction of patient numbers and their geographical distribution from reports included in this review. Figures are absolute numbers and percentages of total patient number from the reports included

demographic data showed a clear trend toward younger age and consequently lower body weight at the time of Fontan procedure. Age at Fontan operation varied between 4.6 (median) and 9.8 (mean) years until 1990 and between 2.0 (median) and 5.6 (mean) years in the most recent surgical era.[26,37,40,50]

Reported hemodynamic data prior to Fontan operation illustrated a nearly homogeneous distribution of mean pulmonary artery pressure (mPAP), systemic ventricular end-diastolic pressure (EDP) and transpulmonary pressure gradient (TPG) with only a marginal tendency to lower mPAP and EDP over time. In the majority of univentricular heart malformation patients in the studies reviewed, the "commandments" suggested by Choussat et al. considering the preoperative hemodynamic prerequisites have been respected.[8] Reported preoperative patients' characteristics are shown in Table 2.

3.3 | Modifications of the Fontan operation

Distribution of the surgical modifications of the Fontan procedure displayed a continuous sequential replacement of the atriopulmonary connections by the lateral tunnel TCPC and the extracardiac TCPC over time. In the entire combined patient cohort, the extracardiac TCPC was the most frequent modification, performed in 3704 patients (44.0%), followed by the lateral tunnel TCPC in 2760 patients (32.8%) and atriopulmonary connection modifications in 1949 patients (23.2%). The relative proportions of Fontan modifications in the individual studies are depicted in Figure 2.

3.4 | Early mortality and long-term survival

There was a clear decrease in early mortality rates after Fontan procedure over time. While the first studies reported early mortality rates of up to 20.1%, it is as low as 0.5% in recent publications.[36,50] Early mortality rates according to the era of Fontan operations performed are plotted in Figure 3.

A total of 24 (77.4%) studies reported long-term survival rates. Kaplan-Meier survival estimates, sorted by surgical eras, are depicted in Figure 4. The graph illustrates a clear trend of improved long-term survival in the more recent studies. While 15-year survival rates in the earlier reports ranged from 52% to 82%, they reached up to 95% in the most recent surgical era.[9,36,43,50] The studies with the longest follow-up periods have reported survival rates of 83% after 25 years and 43% after 30 years, respectively.[14,48]

Only 16 (51.6%) of the studies specified causes of late mortality. The most common cause of late mortality was related to Fontan failure due to systemic ventricular failure.[9,23,24,30–32,36,44,45,48] Other frequent causes of late death included sudden death and death after reoperation, especially after cardiac transplantation.[22,24,34,38,42,44,50]

3.5 | Long-term morbidity

Complications during long-term follow-up have not been consistently reported. Most frequently, studies focused on the most common complications such as arrhythmias and thromboembolic events, but also less common complications such as protein-losing enteropathy. Further complications such as Fontan-associated liver disease, plastic bronchitis, varicosis, hemorrhage, chronic effusions, renal failure and others were only mentioned occasionally. Arrhythmias comprised the most frequently reported complication with incidences varying from 3.0% to up to 41%, followed by thromboembolic events and protein-losing enteropathy with incidences of 0.6%-10.2% and 0.9%–10.2%, respectively (Table 3).[38,42,44,48,51] During long-term follow-up, reoperations and reinterventions were frequent, with relative proportions in the individual studies ranging from 0.0%-26.6% and 0.0%-28.1%, respectively.[24,44,47] However, only 14 (45.2%) studies reported reoperation rates after Fontan

TABLE 2 Preoperative patients' characteristics

Study period, first author	Systemic ventricle (%)		Heterotaxy (%)	Age at Fontan (years)	Weight at Fontan (kg)	PAP (mm Hg)	EDP (mm Hg)	TPG (mm Hg)
	LV	RV						
2009–2013, Zhu			20.1	3.7**	15.0**			
2002–2008, Salazar	38.9	34.5	18.1	4.3*	17.2*			4.1*
1997–2008, O'Brien			12.4	3.0**	13.6**	12.0**	9.0**	
1997–2003, Ocello			23.0	5.6*	19.8*	11.0*	7.0*	
1996–2006, Kim			32.0	3.4**		12.4*	10.0*	4.9*
1995–2011, Ovroutski		36.4	17.9	3.8**	14.3**	10.0**	7.0**	4.0**
1995–2006, Lee				4.0/4.3*	15.8/16.7*			7.1/5.5*
1994–2015, Ono		51.0	7.8	2.3**	12.0**			
1994–2014, Nakano			24.6	3.4**	12.0*			
1994–2009, Hasaniya			12.5	3.3**	15.5**	12.0**		
1994–2007, Tweddell	44.1	55.5	7.0	3.0**	13.0**	13.0**	9.0**	
1994–1998, Azakie	58.9	41.1	12.1	3.8/4.0*	14.9/15.9*	11.0/10.0*	7.0/7.0*	5.0/5.0*
1992–2009, Rogers	30.1	18.8	8.6	2.3**	12.0**	11.3*	7.5*	
1992–2008, Brown			11.8	2.5*				
1992–2007, Hirsch	36.0	64.0	3.1	2.0**	11.1**	12.0**	8.0**	
1991–2002, Alphonso	57.0	41.0	15.6	5.6*	18.5**	13.5*		
1990–1994, Sharma						11.1*	10.7*	
1988–2011, Dabal			5.8	4.6**				
1988–2008, Robbers-Visser	54.6	44.0		3.0/3.2**	14.0/14.0**	11.2/11.0**	9.0/9.4**	
1988–2004, Hosein	59.0	40.0	11.1	4,7**	16.8**	12.0**	8.0**	5.0**
1988–2003, Giannico			12.0	6.0*				
1987–2007, Chungsomprasong	55.3	28.2	12.9	8.7**		13.0**	10.0**	
1984–2004, Ono	67.8	32.2	10.7	5.8*				
1983–1995, Podzolkov				8.6/10.0*		14.3/13.3*		
1981–2009, Idorn		31.1		3.1–12.4*				
1979–2010, Ohuchi	40.0	46.3	39.8	5.7*			6.9*	
1978–2000, Cazzaniga	70.0	12.0	4.8	7.3*	22.0**			
1975–2010, D'Udekem	61.0	31.0	6.6	4.6**		12.0*		
1973–2012, Pundi	*68.0*	*29.0*	12.8	9.4*	*29.9***	*16.0***	*11.0***	
1973–1991, Gentles	69.4		8.2	6.8*				
1968–1988, Fontan				9.8*				

Overview of reported preoperative patients' characteristics before definitive univentricular palliation. Data given as reported (*mean or **median). Morphology of the dominant systemic ventricle is specified as reported. Figures given in *italics* represent data acquired through personal communication with the corresponding authors.

/, study cohort discriminated between Fontan modifications intracardiac and extracardiac total cavopulmonary connection as well as atriopulmonary and total cavopulmonary connection; blank space, information not available.

Abbreviations: EDP, end-diastolic pressure of the systemic ventricle; LV, left ventricle; PAP, mean pulmonary artery pressure; RV, right ventricle; TPG, transpulmonary pressure gradient.

operation and only 12 (38.7%) have specified reasons for reoperations. Among the most common reoperations were pacemaker implantations, atrioventricular valve procedures and Fontan revision and conversion.[9,22,27,30,31,41,48] Cardiac transplantations were carried out in up to 3.5% of Fontan patients.[48] Reinterventions were also only sporadically mentioned; among the most common

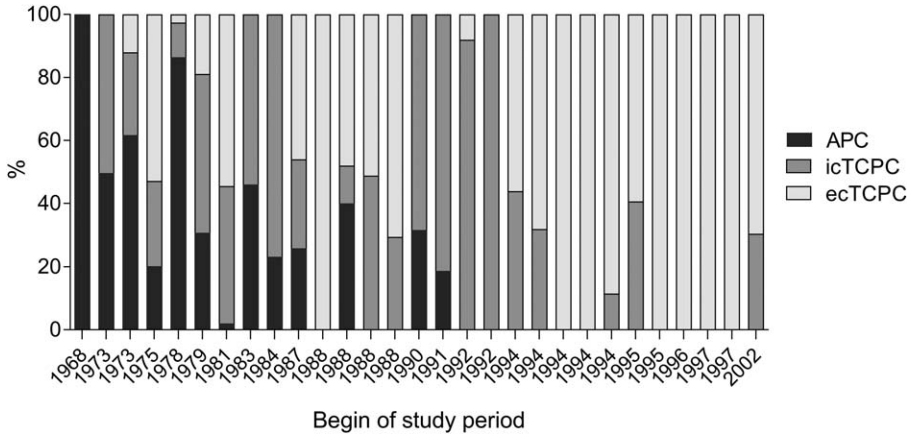

FIGURE 2 Distribution of Fontan modifications. Relative proportion of different Fontan modifications reported by the individual studies included in this review. Columns are tabulated according to the first year of study period covered by publications. Abbreviations: APC, atriopulmonary connection, ecTCPC, extracardiac total cavopulmonary connection, icTCPC, intracardiac total cavopulmonary connection

procedures were closures of fenestrations, occlusion of collaterals and balloon angioplasty of or stent implantation into the pulmonary arteries or the Fontan conduit.[9,22,30,31,44] Inconsistent reporting of reoperations or reinterventions precludes conclusions about changes in frequency across the time periods covered in this review.

Cardiopulmonary capacity during long-term follow-up was rarely reported and only 14 (45.2%) studies specified NYHA functional class at the last follow-up after Fontan operation. Overall, the majority of patients were reported to be in NYHA functional class I or II (Table 3). Data on the use of anticongestive and pulmonary anti-

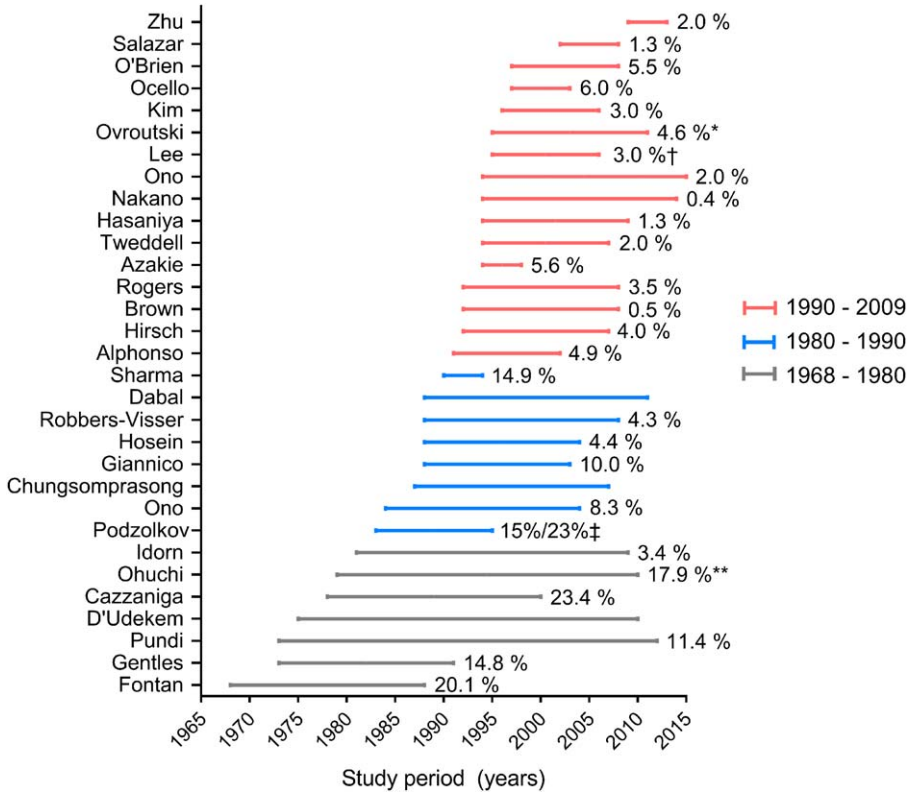

FIGURE 3 Early mortality after Fontan operation. Reported early mortality rates after definitive univentricular palliation of included studies according to study period covered. Transverse bars mark individual reports' study period; percentage value represents reported early mortality rates. Bar colors represent surgical eras according to the beginning of the study period. Early mortality was defined as 30-day mortality by 17 (54.8%) studies and in-hospital mortality by 4 (12.9%) studies. Exceptions are marked as follows: *6 weeks postoperatively, **6 months postoperatively, †operative mortality without further specification, ‡early postoperative mortality without further specification. Blank space, early mortality information not available

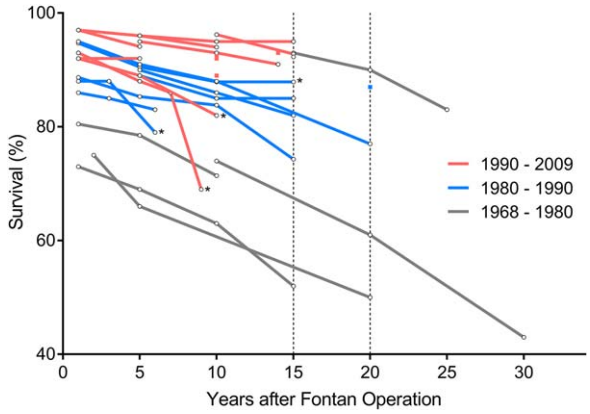

FIGURE 4 Long-term survival after Fontan. Reported late survival rates after definitive univentricular palliation of included studies according to study period covered. Only studies with specified survival rates are included in this figure. Dots represent respective reported Kaplan-Meier survival estimates at given time points. Connecting lines represent individual studies having survival estimates reported at several time points. Line/dot colors mark surgical eras, dashed vertical lines mark 15 and 20 years. *, definition by death and cardiac transplantation or revision

hypertensive medical treatments were also rarely reported and thus not analyzed.

4 | DISCUSSION

The data compiled in this systematic review outline the success story of the Fontan procedure having provided a perspective for numerous patients with complex univentricular heart malformations. They also demonstrate the continuously improving results emerging from the procedural evolution of definitive univentricular palliation and concomitant advancements in medical care throughout the past almost 50 years. Previously burdened with very poor life expectancy, a large number of these patients have entered adolescence and adulthood today.[13,14] The Fontan procedure in its contemporary modifications is now frequently performed in surgical centers in developed economies across the world. Accordingly, a large quantity of studies on early, midterm and long-term outcome has been published to date.

4.1 | Preoperative patients' characteristics

In respect to preoperative patient characteristics, different trends could be observed. More contemporary cohorts included an increasing number of patients with systemic right ventricles, were younger at Fontan operation, and had a tendency to lower mean pulmonary artery and end-diastolic pressures. These observations reflect that, together with the continuous improvement of surgical strategies as well as pre and postoperative management, the selection characteristics of patients to undergo the Fontan operation have changed fundamentally over the years. Initially created to palliate only a small subgroup of univentricular malformations, namely tricuspid atresia, the procedure is now regularly performed in the most complex malformations such as hypoplastic left heart syndrome, with satisfactory postoperative results.[11,51,52] The former relatively late timing has been revised, and, preventing long-lasting cyanosis and volume overload of the single ventricle, the Fontan operation is now generally performed between 2 and 4 years of age.[53] Low pulmonary vascular resistance and preserved systolic and diastolic ventricular function remain the most crucial prerequisites for satisfying postoperative results. Accordingly, some of the "ten commandments" for patient selection stated by Choussat et al. in 1978 have become less relevant over time. In this sense, Hosein et al. even referred to them as the "two commandments" in 2007.[8,9] Even in high-risk patients with elevated pulmonary resistance or a right systemic ventricle, formerly not considered to be Fontan candidates, good early and midterm results after Fontan completion can be achieved, for example by creation of fenestrations to minimize the risk of low cardiac output and excessive elevation of venous pressures.[54,55]

However, especially those patients with suboptimal prerequisites and multiple preoperative risk factors might pose additional challenges yet to come. Despite the advancements in extending the indication for the Fontan operation, a significant proportion of patients with univentricular heart malformations will not proceed to that stage due to interim mortality or decline as a Fontan candidate.[56,57] Several risk factors for early and late mortality are well-acknowledged but there is no universal consensus on the definite criteria for admittance or decline for the Fontan procedure. Among other factors, high pulmonary artery pressure or pulmonary vascular resistance, compromised ventricular function and significant atrioventricular valve regurgitation have consistently been associated with poor early and late outcome.[9,11,27,30,35,48,49,58,59] Consequently, a cavo-pulmonary and/or systemico-pulmonary shunt may then be considered as definitive palliation since it might represent the more appropriate approach in some high-risk Fontan candidates.

4.2 | Modifications of the Fontan operation

Analysis of the Fontan modifications employed demonstrated continuous replacement of the initial surgical approaches by the more recent extracardiac conduit TCPC. Its advantages in comparison to prior modifications have been pointed out by many study groups. The extracardiac approach allows the reduction or even omission of the use of cardiopulmonary bypass, thus reducing possible perioperative complications, the laminar flow improves hemodynamic results, and the avoidance of intraatrial surgery decreases the incidence of postoperative arrhythmias.[6,34,60–62] However, it has to be considered that the patient population palliated with the extracardiac TCPC modification is currently the youngest and benefits not only from the developments in surgical techniques but also from the experience gathered concerning preoperative selection, perioperative care, medical treatment and interventional strategies. Comparability of outcome after extracardiac TCPC with previously employed Fontan modifications and older patient cohorts is, therefore, limited and long-term benefits are not yet clarified.

Research in order to further improve hemodynamic results is continuing. The recently introduced Y-shaped extracardiac baffle, which has been developed based on theoretical computational fluid-dynamic

TABLE 3 Long-term morbidity and mortality after Fontan operation

Study period, first author	Late mortality (%)	Bradyarrhythmia (%)	Tachyarrhythmia (%)	Total arrhythmias (%)	TE (%)	PLE (%)	Reoperations (%)	Reinterventions (%)	Transplantation (%)	NYHA class III or IV (%)
2009–2013, Zhu	3.0			4.0	1.0		0.0	0.0	0.0	0.0
2002–2008, Salazar	0.9						8.4	15.9	0.9	
1997–2008, O'Brien	4.1[a]			16.4		2.0			0.7	
1997–2003, Ocello	0.0			6.4[a]						3.2
1996–2006, Kim	3.5[a]			7.7	6.7[a]	2.6	12.0			0.0
1995–2011, Ovroutski										
1995–2006, Lee	5.5[a]									
1994–2015, Ono	3.0[a]	4.1[a]	3.1[a]		0.7[a]	3.6[a]	6.5[a]	15.0[a]	0.2[a]	
1994–2014, Nakano	3.4[a]	3.8[a]	2.6[a]		1.0[a]	1.6	4.4[a]	2.4[a]		
1994–2009, Hasaniya	3.8					1.9				
1994–2007, Tweddell	2.3	4.4[b]	2.8[c]		5.2[a]	2.0[a]			0.8	2.1
1994–1998, Azakie	1.9[a]			18.6[a]		1.0[a]				
1992–2009, Rogers										
1992–2008, Brown	4.6[a]			9.0[a]	2.7[a]	2.7[a]	3.2[a]		0.5[a]	4.0
1992–2007, Hirsch	2.8[a]			3.0[a]		6.0[a]			0.2[a]	2.4
1991–2002, Alphonso	5.7[a]			22.4[a]		0.9[a]				5.0
1990–1994, Sharma	3.5[a]									2.1
1988–2011, Dabal							7.2[a]		0.5[a]	<10.0
1988–2008, Robbers-Visser	8.6[a]			8.0[a]	1.5[a]		16.5[a]			
1988–2004, Hosein	5.2[a]			8.3[a]		1.3[a]	14.0[a]	27.3[a]	0.7[a]	5.1
1988–2003, Giannico	1.8[a]			11.5[a]	0.6[a]	1.2[a]	2.7[a]	4.5[a]	1.4[a]	3.0
1987–2007, Chungsomprasong	14.8			7.9	1.4					
1984–2004, Ono	4.1[a]	25.0[a]	37.0[a]		10.2[a]	2.8[a]	15.7[a]	28.1[a]		0.0
1983–1995, Podzolkov	6.7[a]			7.5[a]			7.3[a]			
1981–2009, Idorn	4.3			16.4[a]					3.4	
1979–2010, Ohuchi	12.0[a]			17.0[a,d]		2.4[a,d]	11.5[a,d]	2.5[a,d]		
1978–2000, Cazzaniga	16.1[a]					5.3[a]	26.6[a]	12.9[a]	0.8[a]	

(Continues)

TABLE 3 (Continued)

Study period, first author	Late mortality (%)	Bradyarrhythmia (%)	Tachyarrhythmia (%)	Total arrhythmias (%)	TE (%)	PLE (%)	Reoperations (%)	Reinterventions (%)	Transplantation (%)	NYHA class III or IV (%)
1975–2010, D'Udekem	5.5	5.9	10.0		5.6	1.5			1.6	1.1
1973–2012, Pundi	40.5			41.0		10.2[a]	36.0		3.5	
1973–1991, Gentles									0.2[a]	
1968–1988, Fontan	11.7[a]								1.2	2.0

Reported frequency of long-term morbidity and mortality after Fontan operation.
For comparability reasons, calculations and recalculations of given figures were made as follows: Late mortality as well as reoperations, reinterventions and cardiac transplantations were calculated referring to the entire cohorts of followed patients. Late complications such as arrhythmias, thromboembolic events and protein-losing enteropathy were calculated to exclude early mortality in the respective cohorts. Figures given in *italics* represent data acquired through personal communication with the corresponding authors.
[a]Figures calculated/recalculated from original manuscript data.
[b]Determined by patient numbers with pacemaker implantation
[c]Determined by number of patients on antiarrhythmic treatment.
[d]Complications defined by requirement of unscheduled hospitalization.
Blank space, information not available.
Abbreviations: PLE, protein-losing enteropathy; TE, thromboembolic event.

considerations to reduce energy loss, might prove hemodynamically advantageous in comparison to the original tube-shaped extracardiac TCPC.[63–65]

4.3 | Early mortality and long-term survival

Early mortality rates clearly decreased over the time period covered. In addition, long-term survival estimates were considerably higher in more recent publications compared to earlier reports. However, the growing, diverse population of aging Fontan patients is at risk of developing multiple complications eventually leading to Fontan failure and premature death.[16,66] Among the biggest concerns regarding the long-term performance of the Fontan circulation are a continuous decline of the systemic ventricular systolic and diastolic function and an increase in pulmonary vascular resistance.[67,68] In fact, in most of the studies included in this review, ventricular failure was the predominant cause for late death while Fontan failure due to increasing pulmonary vascular resistance was only occasionally reported. Several reasons, including individual preconditions originating from the cardiac malformation itself, cyanosis and volume overload prior to palliation resulting in myocardial fibrosis, permanent systemic ventricular preload restriction after Fontan palliation and multiple surgical interventions, may result in impairment of both systolic and diastolic ventricular function.[69,70] Conventional treatment strategies for heart failure employed in patients with biventricular hearts are not comparably efficient in univentricular heart malformations.[71] In the future, the establishment of evidence-based standardized treatment regimens and the implementation of innovative therapies will be decisive for these patients.[72,73]

4.4 | Long-term morbidity

A significant number of patients suffered from late complications, illustrating the palliative character of the Fontan procedure. Arrhythmia was clearly the most frequent complication (Table 3). A recent study points out that beyond the increasing incidence of tachyarrhythmias during long-term follow-up, Fontan patients also have a considerable risk of sudden cardiac death.[74] Comparative studies have shown a lower incidence in patients palliated with the extracardiac modification in which atrial scarring is prevented and the atrial wall is not incorporated into the Fontan pathway.[34,74,75] Thus, a long-term reduction of the occurrence of arrhythmias can be hoped for in contemporary patient cohorts.

Thromboembolic events and protein-losing enteropathy are both related to multifactorial causes. Reasons for thromboembolism include coagulation abnormalities, slow venous blood flow and tachyarrhythmias. The preferable antithrombotic treatment after Fontan palliation remains somewhat controversial since convincing evidence to establish standardized treatment regimens is lacking.[76–79] Protein-losing enteropathy is presumably triggered by chronic venous congestion, impaired intestinal lymphatic drainage and intestinal inflammation.[67,80,81] It is a comparably rare but nonetheless severe complication with poor prognosis. Treatment is challenging since no single proposed treatment

strategy has proven universally successful and consensus on management guidelines has not been achieved.

Catheter-based reinterventions and reoperations were relatively frequently performed; however, a considerable number of studies did not report reoperation and reintervention incidences and their actual incidence may even be underappreciated as has also been pointed out in more recent studies.[82] Moreover, indications for reinterventions were only sporadically given. The delicate Fontan hemodynamics have to be maintained under all circumstances to avoid circulatory compromise and consequent Fontan failure and, in this sense, interventions may be viewed as indispensable "maintenance work" to ensure favorable long-term outcome and minimize morbidity in Fontan patients.

As the Fontan population ages, cardiac transplantation will become increasingly important. Current indications include not only cardiac failure but also refractory hemodynamic failure, as in therapy-resistant protein-losing enteropathy. While survival after transplantation for ventricular failure shows encouraging results, reported outcome after transplantation in patients with preserved ventricular function is variable with multiple additional risk factors such as malnutrition, immunosuppression and increased pulmonary vascular resistance being discussed as reasons for increased mortality. However, while some studies found a comparably worse survival after cardiac transplantation in Fontan patients with preserved ventricular function, more recent and larger studies could not confirm these observations.[83–86]

The reported overall functional status after Fontan operation was generally good, with most of the surviving patients being in NYHA class I or II at their last follow-up. However, NYHA classification does not provide information about the overall physical capacity or quality of life of the Fontan population. One of the few studies published on this subject demonstrated significantly impaired quality of life in young Fontan patients.[87] In another report, multiple noncardiac medical problems with great impact on physical health status were observed in children and adolescents after Fontan. Psychosocial issues such as learning deficits, anxiety and depression were more prevalent in Fontan patients than in the general population.[88] These aspects of psychosocial development and quality of life are still largely underappreciated.

4.5 | Conclusions and future perspectives

Almost fifty years after the original introduction of the Fontan procedure, patients with univentricular heart malformations nowadays benefit from the experience and developments of the past decades and have a significantly improved long-term prognosis. However, important issues concerning long-term morbidity and mortality are not yet solved and clear intrinsic limitations of the Fontan circulation have become evident. Additional complex late complications such as Fontan-associated liver disease, the inevitable continuous decline of the univentricular function and increasing pulmonary vascular resistance are still deeply concerning. A comprehensive regular follow-up regime together with continuous research remains crucial for further improvements of the future perspectives after Fontan operation.

5 | LIMITATIONS

The main limitation of this review lies in the great diversity of the studies included. The studies focused on various research questions and differed in the number of Fontan patients reported, surgical strategies and follow-up duration beyond numerous other aspects. Because of the restricted number of studies and inconsistent data reports, meaningful statistical analyses cannot be performed and this review is, therefore, of descriptive character only.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

DISCLOSURES

None

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