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Predicting long-term mortality after Fontan procedures: A risk score based on 6707 patients from 28 studies

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Abstract

Background: Reported long-term outcome measures vary greatly between studies in Fontan patients making comprehensive appraisal of mortality hazard challenging. We sought to create a clinical risk score to assist monitoring of Fontan patients in the outpatient setting.

Methods: A systematic review was conducted to evaluate risk factors for long-term (beyond the first postoperative year) mortality in Fontan patients. Studies were eligible for inclusion if ≥90 patients were included or ≥20 long-term mortalities we reported. Risk factors for long-term mortality were determined. The pooled hazard ratios were used to create components of a clinical score for long-term mortality using meta-analysis techniques.

Results: Twenty-eight studies were included. The total number of patients was 6707 with an average follow-up of 8.23 ± 5.42 years. There were 1000 deaths. Thirty-five risk factors for late mortality were identified and classified into 9 categories and their relative hazards were used to derive the initial components of a weighted, practical and clinically based Fontan risk score (ranging from 0 to 100). The final score included 8 risk factors: anatomic risk factors, elevated preoperative pulmonary artery pressure, atriopulmonary Fontan, heart failure symptoms, arrhythmia, moderate/severe ventricular dysfunction or atrioventricular valve regurgitation, protein losing enteropathy, and end organ disease (cirrhosis or renal insufficiency).

Conclusion: In patients with Fontan circulation, the influence of readily available risk factors can be quantified in an integer score to predict long-term mortality. Prospective validation and refinement of this risk score will be undertaken.

KEYWORDS
Fontan physiology, quality and outcomes of care, systematic review

1 | INTRODUCTION

The Fontan procedure has transformed the lives of patients with single ventricle physiology and offered them the potential for long-term survival with good quality of life.[1,2] Since it was first performed in 1968, surgical techniques have evolved substantially.[2] The perioperative landscape including intensive care and cardiac catheter based interventions, have also advanced resulting in improved postoperative survival. As this patient population is aging, multiple morbidities are encountered which lead to premature death. Given the large number of patients with Fontan circulation reaching adulthood, we sought to inform surveillance strategies in the outpatient setting by creating a risk score that can be used to risk stratify this patient population.

Abbreviations: AV, atrioventricular; BNP, brain natriuretic peptide; CI, confidence interval; HR, hazard ratio; OR, odds ratio; PLE, protein losing enteropathy.

TABLE 1 Hazard ratios for the factors associated with mortality with confidence interval (CI)

First author/year	Factors associated with mortality and the corresponding confidence intervals
Pundi (2015)[5]	Diuretic use (HR = 1.58) CI = 1.22–2.04 Elevated pulmonary artery pressure >15 (HR = 1.42) CI = 1.15–1.77 Preoperative sinus rhythm (HR = 0.38) CI = 0.26–0.57 Longer cardiopulmonary bypass time (HR = 1.12) CI = 1.07–1.22 Fontan opearation after 2001 (HR = 0.12) CI = 0.02–0.84 Atrioventricular valve (AVV) replacement with Fontan operation (HR = 4.02) CI = 2.07–7.80 Elevated Fontan pressure (>20 mm Hg) (HR = 2.29) CI = 1.72–3.05 Atrial (>13 mm Hg) pressures (HR = 1.85) CI = 1.39–2.47 Prolonged chest tube drainage (>21 days) (HR = 1.15) CI = 1.05–1.26 Postoperative ventricular arrhythmias (HR = 1.79) CI = 1.18–2.72 Renal insufficiency (HR = 2.49) CI = 1.74–3.58 Protein-losing enteropathy (HR = 1.97) CI = 1.48–2.63 Asplenia (HR = 1.55) CI = 1.07–2.25
Assenza (2013)[6]	Lack of thromboprophylactic therapy (HR = 4.76) CI = 1.2–20 Diuretic use (HR = 9.16) CI = 1.19–70.36 Renal insufficiency (creatinine above 2) (HR = 8.21) CI = 2.84–23.78 Liver insufficiency (MELDXI > 18) (HR = 7.76) CI = 2.05–29.33
Burkhart (2003)[7]	Elevated pulmonary artery pressure >15 (HR = 3.5) CI = 1.5–8.1 Male gender (HR = 3.4) CI = 1.2–10.1 Age >30 years at the time of Fontan (HR = 2.9) CI = 1.2–6.7
Diller (2010)[8]	Heart rate reserve on exercise test per 10 BPM (HR = 0.828) CI = 0.710–0.965 Atriopulmonary Fontan (HR = 3.7) CI = (1.388–9.643) Arrhythmia (HR = 6) CI = (2.382–13.158)
D'Udekem (2014)[9]	Atriopulmonary Fontan (HR = 6.2) CI = 2.4–16.0 Older age >7 years (HR = 2.7) CI = 1.2–5.7 Male gender (HR = 2.5) CI = 1.3–4.6 Prolonged pleural effusion (HR = 2.9) CI = 1.1–7.4
Elder (2013)[10]	Liver insufficiency (odd ratio [OR] 19.0) CI = 4.70–77.28 Presence of a pacemaker (OR 13.4) CI = 2.59–69.84 Systemic oxygen desaturation (OR 0.86) CI = 0.75–0.98
Fernandes (2011)[11]	Low peak VO_2 on exercise test (<16.6 mL/kg/min) (HR = 7.5) CI = 2.6–21.6 Lower Ventilatory anaerobic threshold (<9) (HR = 5.5) CI = 2.1–14.8 Lower heart rate at peak exercise (peak-exercise heart rates of <122.5) (HR = 10.6) CI = 3.0–37.1
Hosein (2007)[12]	Preoperative impaired ventricular function (HR = 7.17) CI = 2.30–22.31 Elevated pulmonary artery pressure >15 (HR = 1.14) CI = 1.04–1.26 Earlier date of Fontan operation 0.85/year CI = 0.76–0.94
Iyengar (2014)[13]	Hypoplastic left heart syndrome (HR = 2.8) CI = 1.1–7.5
Johnson (2013)[14]	Thrombosis (OR = 1.35) CI (not mentioned) Protein losing enteropathy (OR = 5.2) CI (not mentioned) High altitude (not mentioned) pulmonary artery pressure (pre-Fontan) (not mentioned) Resting O_2 saturation (not mentioned) Elevated Fontan pressure (not mentioned)
Khairy (2008)[15]	Protein-losing enteropathy (HR = 2.5) CI = 1.1–5.3 Hypoplastic left heart syndrome (HR = 10.1) CI = 1.0–98.3 Atrial pressure on follow-up per mm Hg (HR = 1.2) CI = 1.07–1.36 Diuretic use (HR = 8.7) CI = 1.9–40.7
Kim (2008)[16]	Severe infection post Fontan (HR = 12.4) Elevated pulmonary artery pressure >15 (HR = 3.445)
Ohuchi (2011)[17]	Atriopulmonary Fontan (HR = 3.95) CI = 0.75–20.75
Ohuchi (2015)[18]	Peak VO_2 on exercise test (HR = 0.95) CI = 0.76–0.98 Heterotaxy (HR = 12.7) CI = 1.68–150 Earlier date of Fontan operation (HR=0.8) CI = 0.61–1.00
Ohuchi (2014)[19]	Elevated BNP (HR = 1.13 per 10 pg/ml) CI = 1.02–1.25 Elevated norepinephrine (HR = 1.93) CI = 1.16–4.07 Low forced expiratory volume 1 per 5% (HR = 0.33) CI = 0.10–0.81
Wolff (2014)[20]	Heterotaxy (HR = 3.17) CI = 1.23–8.14

(Continues)

TABLE 1 (Continued)

First author/year	Factors associated with mortality and the corresponding confidence intervals
Rathod (2014)[21]	Protein-losing enteropathy (HR = 8.5) CI 1.9–38.2 Ventricular indexed end-diastolic volume >125 mL/body surface area (HR = 1.12 per 10 mL/BSA1.3 increase) CI 1.05–1.19
Ghelani (2015)[22]	Protein-losing enteropathy (HR = 5.1) CI = 1.4–18.8 Ventricular indexed end-diastolic volume (HR = 1.04 per 10 mL/BSA1.3 increase) CI = 1.02–1.06 Global circumferential strain on echocardiogam (HR 1.3 per unit decrease) CI = 1.1–1.5

The hazard ratios for the most common risk factors for used to create the Fontan risk score.

2 | METHODS

A systematic review of published studies that evaluated long-term mortality in Fontan circulation was performed. Two independent investigators conducted the search for studies. Randomized, prospective, and retrospective nonrandomized studies were considered eligible for inclusion, provided that the study population included at least 90 patients with a Fontan circulation or at least 20 mortalities to maintain statistical power. We excluded studies that focused on mortality within the first year of the Fontan procedure.

PubMed and the Cochrane Library were used to search for studies published in English with no restriction on date of publication. The following search terms were used: Fontan procedure, Fontan, univentricular heart, single ventricle, cavopulmonary, survival, mortality, death, prognosis, outcome, and heart transplantation. We identified 2314 studies using our search strategy. We excluded nonhuman studies, studies without long-term mortality, letters to the editor, editorials, and case reports after screening through the abstracts. After full-text evaluation of 57 studies, we excluded studies identified as substudies from already included papers, studies with short-term mortality up to 1 year after Fontan, studies with small sample size or wrong population or primary outcome. No additional studies were identified through screening reference lists.

The risk of bias was assessed using the Cochrane risk of bias tool for randomized controlled trials[3] and the modified Newcastle Ottawa scale for nonrandomized studies.[4] When more than one study included the same patients, only the most recent study that included these patients was used in the final analysis.

The factors associated with long-term mortality were divided into nine categories as follows: era of operation, preoperative, operative, and postoperative risk factors, long-term cardiac complications, long-term noncardiac complications, factors detected on cardiac imaging, cardiopulmonary exercise testing, and laboratory results.

Each article was assigned to one or more category, depending on the mortality risk factors reported in the study. Each category of predictors was summarized by one or two researchers depending on their area of expertize and experience.

The hazard ratios (HRs) for 8 significant risk factors that were thought obtainable in the outpatient setting were pooled from the different papers. Each of the 8 factors included in the risk score was found to be a significant predictor of long-term mortality in at least 2 studies. A meta-analysis was conducted using a random-effect model to calculate a pooled HR for each different factor. A computerized model was used. Under this model, weights were assigned to each risk factor based on the HRs and the corresponding confidence intervals for that risk factor in each study (Table 1). Based on the pooled HRs a total mortality score was created. A higher risk is associated with increased risk of mortality. The risk scores were calibrated to give a maximum risk score of a 100. The final score was rescaled to 100 for easy implementation by multiplying by a constant. The score is additive, that is, a patient with more risk factors will have a higher risk.

3 | RESULTS

Our search identified 28 studies eligible for inclusion, of which 15 were published after 2010 (Figure 1). These encompassed 6707 patients with

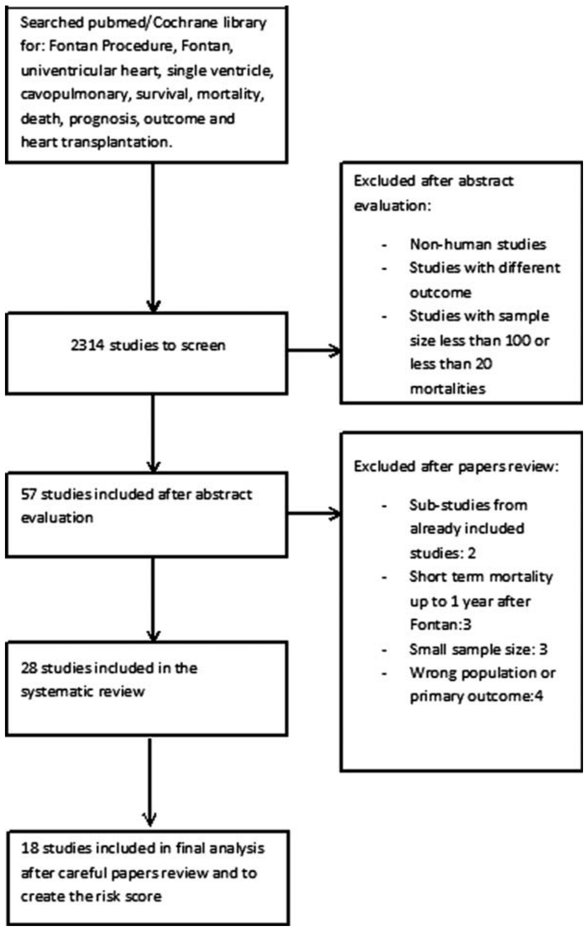

FIGURE 1 PRISMA flow diagram—study identification, selection, and exclusions

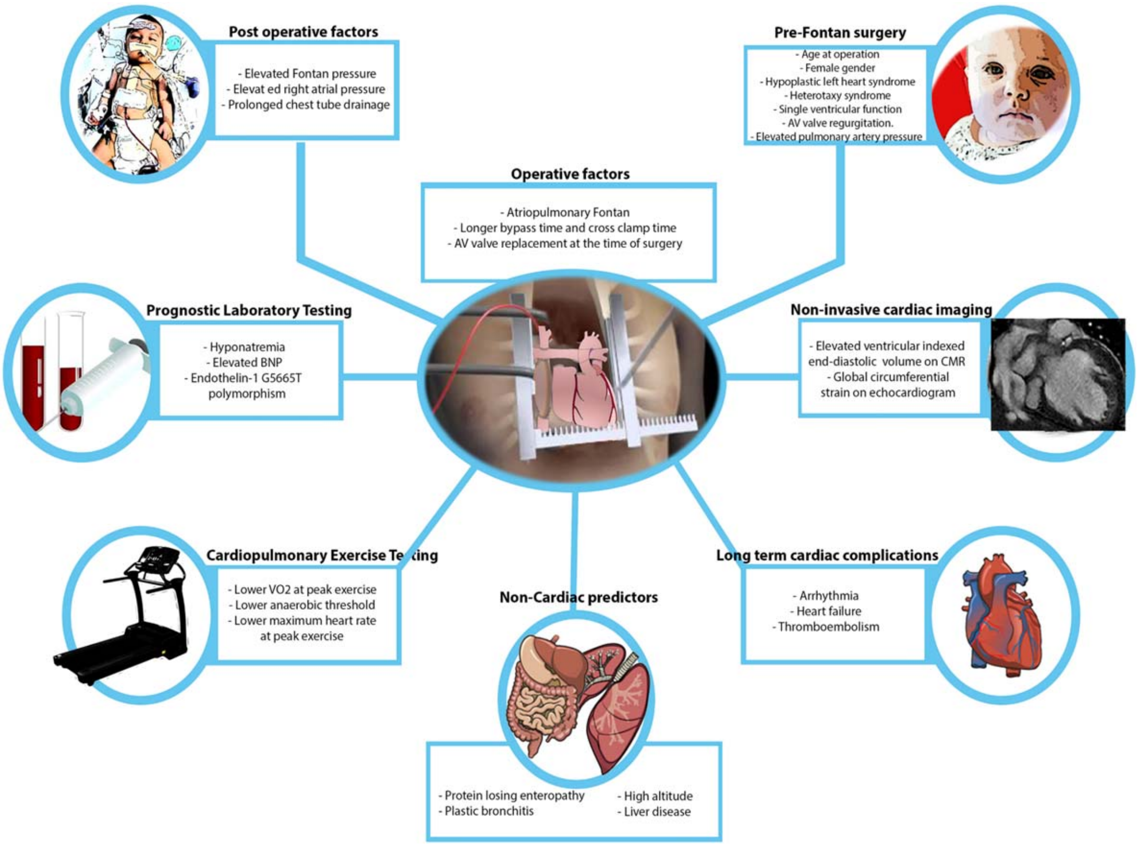

FIGURE 2 Risk factors for late mortality after Fontan procedure

an average follow-up time of 8.23 years (± 5.42 years). Risk factors for long-term mortality were reported in 18 of these studies (Table 1). Overall, there were 1000 mortalities and 138 heart transplantations.

4 | RISK FACTORS OF LONG-TERM MORTALITY

The risk factors of long-term mortality are summarized in Figure 2. The risk factors were divided into the nine different subcategories: era of operation, preoperative, operative, and postoperative risk factors, long-term cardiac complications, long-term noncardiac complications, factors detected on cardiac imaging, cardiopulmonary exercise testing, and laboratory results.

5 | THE FONTAN MORTALITY SCORE

Based on this systematic review a new Fontan risk score ranging from 0 to 100, is proposed in Table 2. The score is additive, that is, a patient with more risk factors will have a higher risk. This score will require further validation and refinement in a large registry with an appropriate number of mortality and/or transplantation outcomes.

6 | DISCUSSION

In patients undergoing the Fontan procedure, the presence of readily available risk factors can be quantified in an integer score to predict long-term mortality. For this systematic review, 28 relevant articles which described late mortality in Fontan patients were evaluated; 18 articles reported the long-term risk factors. Overall, we found considerable differences between studies in design and reported risk factors.

Patients with congenital heart disease and a Fontan circulation are at serious risk for late complications such as arrhythmias, Fontan failure and early death.[5] Theoretically, this unfavorable course may be improved by risk appropriate surveillance leading to timely intervention such as Fontan revision surgery, invasive arrhythmia management, and cardiac transplantation and this will be the purpose of creating the risk score.[23] Thus appropriate identification of high risk patients is important for improving long-term care. However, there is currently no uniform consensus on risk stratification in patients late after the Fontan procedure.

In this systemic review, we found a large number of risk factors reported in literature. To improve the clinical use utility, the 35 factors (see Figure 2) were divided into the following predefined categories: (1) era-related, (2) preoperative factors, (3) operative factors, (4) postoperative factors, (5) long-term cardiovascular complications, (6) cardiac imaging, (7) exercise stress testing, (8) noncardiac factors, and (9) serologic factors. Preoperative anatomical factors such as hypoplastic left heart syndrome are likely disadvantageous because a morphologic RV is more likely to become dysfunctional during long-term follow-up.[24] Heterotaxy is usually associated with more complex anatomy and many other comorbidities.[5,25] High pulmonary or Fontan pressures preoperatively or postoperatively may reflect early vascular changes in the pulmonary

TABLE 2 Fontan risk score

Risk factor	Number of papers	Hazard ratio range	Final score
Anatomic risk factors (hypoplastic left heart or heterotaxy)	4	2.8–12.7	13
Elevated preoperative pulmonary artery pressure >15 or Fontan pressure >20 mm Hg postoperatively	5	1.14–3.5	6
Atriopulmonary Fontan	3	3.7–6.2	18
Heart failure symptoms or need for diuretic use	3	1.58–9.16	7
Arrhythmia	2	1.79–6	9
Moderate/severe ventricular dysfunction or moderate/severe AV valve regurgitation	2	4.02–7.17	25
Protein-losing enteropathy	5	1.97–8.5	9
End organ disease including cirrhosis or renal insufficiency	4	2.49–19	13

vasculature, which may further progress over time.[5] Atriopulmonary Fontan, which was a common place in the old era, is associated with high rates of supraventricular arrhythmias, after which further clinical deterioration is common.[26] Extra-cardiac manifestations such as protein losing enteropathy (PLE) or hepatic fibrosis can be considered a sign of Fontan failure, and increasing central venous pressures.[5] PLE had a heterogeneous definitions between the studies and while some studies depended only on hypoalbuminemia, others included clinical presentation, proof of protein loss in stool and exclusion of other causes for hypoalbuminemia as diagnostic factors.[5,27] Arrhythmia definition also varied between the studies included in the score: in one study arrhythmia was defined as postoperative ventricular arrhythmia while another study included all clinically relevant arrhythmias which were defined as associated with symptoms or required treatment.[5,8] In stress testing, reduced peak heart rate emerged as the most promising factor. This may reflect autonomic dysfunction and the inability to enhance pulmonary blood flow during exercise.[11] Although cardiac imaging and serologic testing are potentially very useful in risk stratification, only 2 papers investigated the prognostic value of these parameters and thus were not included in the risk score.[21,22] We recognize not all 35 risk factors found can be routinely evaluated in each patient, and weighing of different risk factors is highly challenging for physicians caring for these patients. For this reason, the Fontan mortality risk score was introduced to facilitate, improve, and simplify risk stratification. The next step should be to refine and validate the risk score in a cohort of Fontan patients which will be the focus of our future research. The different components of the risk score can be easily evaluated in Fontan patients in the outpatient setting, and the final score ranges from 0 to 100. As expected when evaluating such a large number of articles, not all risk factors were reported in all articles. In addition, potentially highly useful parameters such as brain natriuretic peptide (BNP), exercise testing and cardiovascular magnetic imaging were only evaluated in a limited number of articles, and therefore were not included in the final risk score.

7 | FUTURE DIRECTIONS

Large multinational collaboration will allow analysis of currently employed surveillance techniques and their utility in identifying at risk Fontan patients.[28] Ideally, our presented risk score would be validated and refined with such multinational collaboration.

8 | LIMITATIONS

Most of the studies reviewed in this systematic review, were retrospective, single-center registries. Although these studies provided valuable outcomes information, selection, or follow-up bias cannot be excluded. Importantly, across different studies, there was large variation in underlying defects, previous palliation, timing of surgery, surgical techniques used, and perioperative care. The definitions of the risk factors were heterogeneous as mentioned previously which may limit the value of grouping some of these risk factors together. Furthermore, the follow-up period varied significantly between the studies which may have created more heterogeneity in risk factors as factors associated with mortality 10 years from the Fontan operation may be different from 20 years after.

9 | CONCLUSIONS

This systematic review provides an overview of risk factors associated with late mortality across 9 different categories. To facilitate and improve decision making, the most relevant risk factors were combined into a simple risk score, based on pooled HRs. Future research may validate and further improve our proposed risk score. We believe this can be an important step toward more uniform risk stratification and improved surveillance and care for patients with Fontan circulation.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the design of the study. All authors take responsibility for the content of the manuscript. All authors have approved the manuscript and agree with submission to *Congenital Heart Disease*. The authors have no conflicts of interest to declare. Dr. Alsaied wrote the first draft of the manuscript. Dr. Alsaied, Dr. Bokma, Zuhlke, Kuijpers, Hanke and Veldtman reviewed the included studies in the systematic review. Dr. Veldtman, Bokma, Zuhlke, Kuijpers, Hanke critically revised the manuscript. Dr. Zhang and Engel provided statistical support. Dr. Veldtman is the corresponding author.

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