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DISSERTATION

Risk factors for mortality after the Norwood procedure in hypoplastic left heart syndrome

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TECHNISCHE UNIVERSITÄT MÜNCHEN

Fakultät für Medizin

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LIST OF ABBREVIATIONS

AA	aortic atresia
APVC	anomalous pulmonary vein connection
AS	aortic stenosis
ASD	atrial septal defect
ARDS	adult respiratory distress syndrome
AUC	area under curve
BIF	bootstrap inclusion fraction
CPR	cardiopulmonary resuscitation
DHCA	deep hypothermic circulatory arrest
HLHS	hypoplastic left heart syndrome
PLSVC	persistent left superior vena cava
MA	mitral atresia
mBT(s)	modified Blalock-Taussig (shunt)
MS	mitral stenosis
neo-AI	neo-aortic valve insufficiency
PA	pulmonary artery
PI	pulmonary valve insufficiency
PVR	pulmonary vascular resistance
Q_p	pulmonary blood flow
Q_s	systemic blood flow
RV	right ventricle
RVEDP	right ventricular end-diastolic pressure
RV-PA (conduit)	right ventricle-to-pulmonary artery (conduit)
SVC	superior vena cava
SVR (trial)	Single Ventricle Reconstruction (trial)

TI	tricuspid valve insufficiency
TV	tricuspid valve
VSD	ventricular septal defect

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CHAPTER I: INTRODUCTION

The hypoplastic left heart syndrome (HLHS) is a congenital heart defect, which is defined as "a spectrum of cardiac malformations with normally aligned great arteries without a common atrioventricular junction, characterized by underdevelopment of the left heart with significant hypoplasia of the left ventricle including atresia, stenosis, or hypoplasia of the aortic or mitral valve, or both valves, and hypoplasia of the ascending aorta and aortic arch" (Tchervenkov *et al.*, 2006). Once considered a uniformly fatal condition, the prognosis of patients born with HLHS has improved considerably over the last few decades.

Anatomic relations between the underdeveloped left heart structures and the ascending aorta were described at the end of the 19th century (Dilg, 1883; Shattock, 1891), but it was Lev who first used the term "hypoplasia of the aortic tract complex" for the inflow and outflow tract obstructions of the left side of the heart (Lev, 1952). Noonan and Nadas subsequently proposed the term "hypoplastic left heart syndrome" in the late 1950s to describe cardiac anomalies with hypoplastic left ventricle, obstructive lesions of the left side of the heart, and right ventricular hypertrophy (Noonan *et al.*, 1958). Despite the broad spectrum of anatomic variations in this category, HLHS is considered a single diagnosis due to a similar circulation pathophysiology and similar treatment options.

Theoretical research on the surgical correction of HLHS emerged during 1960s and 1970s (Sinha *et al.*, 1968; Deely *et al.*, 1971). Several unsuccessful surgeries based on this research were carried out in the late 1970s (Doty *et al.*, 1977; Mohri *et al.*, 1979), so comfort care remained the only option until Norwood and colleagues successfully performed reconstructive surgery in the early 1980s (Norwood *et al.*, 1980; Norwood *et al.*, 1981; Norwood *et al.*, 1983). Since then, therapeutic options for children with HLHS have increased with the introduction of neonatal heart transplantation (Bailey *et al.*, 1986), ductus stenting as a bridge to transplantation (Ruiz *et al.*, 1993), as well as ductus stenting with pulmonary artery banding and atrial septectomy as an alternative to the Norwood procedure (Gibbs *et al.*, 1993).

Parallel progress in neonatal perioperative and postoperative management of children with HLHS, including the introduction of prostaglandins to maintain the ductal patency prior to the surgery, developing interstage home surveillance programs (Ghanayem *et al.*, 2003), as well as advances in technical performance of the surgery has dramatically improved survival in this critically ill population.

1 Hypoplastic left heart syndrome

1.1 *Preclinical and clinical background to HLHS*

1.1.1 Epidemiology

Hypoplastic left heart syndrome is the most common form of a functional single ventricle. Its birth prevalence of 0.016% per 10 000 live births accounts for 7.5% of all congenital heart defects according to The New England Regional Infant Cardiac Program report of 1980 (Fyler *et al.*, 1980). The Baltimore-Washington Infant Study reported a birth prevalence of 0.018% per 10 000 live births that accounted for 3.8% of all congenital heart defects (Perry *et al.*, 1993). Taking into account other large epidemiological studies (Samanek *et al.*, 1989; Morris *et al.*, 1990; Reller *et al.*, 2008), HLHS has a reported birth prevalence of 0.016% - 0.026% per 10 000 live births, accounting for 2 - 7% of all congenital heart defects.

1.1.2 Etiology

Hypoplastic left heart syndrome is phenotypically a heterogeneous disease, and several studies suggest a genetic etiology with a multifactorial mode of inheritance and a possible contribution from environmental factors during pregnancy.

The sibling recurrence risk for congenital heart defects has been reported 1 - 3%, but there are variations in risk in individual subgroups of cardiac malformations (Nora *et al.*, 1988; Burn *et al.*, 1998). Pedigree analyses have shown that among first-degree relatives the recurrence risk ratio for left ventricular outflow tract obstruction is 13-fold that of the population prevalence, and 16% of first-degree relatives have anomalies of the aorta, aortic valve, left ventricle, or mitral valve (Lewin *et al.*, 2004; Øyen *et al.*, 2009). Consistent with these findings, the sibling recurrence risk for HLHS has been reported 8 - 13% (Boughman *et al.*, 1987; Hinton *et al.*, 2007), which is markedly higher than the reported frequency of 1 - 3% for all congenital heart defects. Moreover, genetic disorders and/or major extracardiac anomalies were reported in up to 30% of patients with HLHS (Natowitz *et al.*, 1988).

Using the data from the Baltimore-Washington Infant Study, Kuehl and colleagues suggested that environmental factors may influence the development of HLHS; a hypoplastic left heart cluster was identified in patients from a region of Baltimore where solvents, dioxin and polychlorinated biphenyl had been released in the air (Kuehl *et al.*, 2006). Maternal occupational exposure to pesticides and herbicides was also found to be associated with a higher risk for HLHS (Rocheleau *et al.*, 2015). Furthermore, the seasonal pattern of HLHS, with a preponderance of diagnoses in children born in the summer months, also suggests a possible environmental contribution to the development of HLHS (Eghtesady *et al.*, 2011).

1.1.3 Anatomy and morphology

The usual anatomic arrangement is levocardia and visceroatrial situs solitus with atrioventricular and ventriculoarterial concordance. Dextrocardia in the settings of situs

solitus, or as a part of situs inversus totalis, is very rare but has been described (Oppido *et al.*, 2004; Alves, 2005; Szczechowicz *et al.*, 2014).

The ascending aorta is hypoplastic, and its size usually depends on the patency of the aortic valve. Typically, mean aortic diameter is 2.5 mm or less in the case of aortic atresia and 4 - 5 mm for aortic valve stenosis (Jonas, 2014). The narrowest parts of the ascending aorta are usually at the sinotubular junction or the junction with the aortic arch (Jonas, 2014). The aortic root is frequently prominent, and the coronary arteries arise from the aortic sinuses.

The aortic arch is hypoplastic to varying degrees; its diameter is usually between 3 - 5 mm and may be interrupted (Jonas, 2014). Additionally, a localized coarctation of the aorta is relatively common, and the degree of obstruction varies considerably (Elzenga *et al.*, 1985). Typically, the coarctation is found at a preductal or paraductal location and contains ductal tissue; however, a medial thickening of the aortic wall without ductal tissue has also been reported (Machii *et al.*, 1995; Smith *et al.*, 2005).

The main pulmonary artery is usually larger than normal, measuring approximately 10 - 15 mm in diameter (Jonas, 2014). The left and right pulmonary arteries arise from main pulmonary artery as usual, but they can originate at different levels from each other and at different distances from the pulmonary valve. The ductus arteriosus arises directly from the main pulmonary artery and has a diameter of approximately 10 mm (Jonas, 2014).

As usual, the major epicardial coronary arteries occupy the atrioventricular and interventricular grooves. Coronary abnormalities are common in HLHS; ventricle-coronary fistulas are most frequent and are associated with the anatomic subtype aortic atresia and mitral stenosis or hypoplasia (Baffa *et al.*, 1992; Nathan *et al.*, 2012). Other coronary abnormalities that may be present include distal tortuosity of major coronary arteries and a single right or single left coronary artery (Baffa *et al.*, 1992). An anomalous left coronary artery arising from the pulmonary artery is rare but has been described (Nathan *et al.*, 2011).

In patients with HLHS, the left atrium is usually small and frequently hypertrophied. The endocardium may be thickened and analogous to that seen in endocardial fibroelastosis. The left atrium usually receives all four pulmonary veins (Jonas, 2014).

Depending on anatomic variations of the disease, the left ventricular cavity ranges from well recognizable, in the milder form, to almost unidentifiable in the most severe form. The left cardiac valves are hypoplastic, stenotic, or atretic, and various degrees of valve dysplasia may be present if the patency of valves is preserved (Smith *et al.*, 2005). A histological examination shows that myocyte differentiation of the left ventricle is preserved, but regions of myofibril disarray with abundant connective tissue and dilated, thin-walled vessels are present (Bohlmeyer *et al.*, 2003).

Although a ventricular septal defect is not an integral part of HLHS, it can be present at a perimembranous location or affect the muscular part of the interventricular septum (Smith *et al.*, 2005). With respect to the size of the defect and transseptal pressure gradient, the blood flow across the septum can be restrictive or non-restrictive.

Endocardial fibroelastosis is relatively common, and its greater incidence was reported in fetuses with left ventricular patent inflow and obstructed outflow tract (O'Connor *et al.*, 1982; Axt-Fliedner *et al.*, 2014). These findings are supported by Shimada and colleagues, who showed that the distention of the immature left ventricle in combination with the stagnant flow triggers development of endocardial fibroelastosis in animal models (Shimada *et al.*, 2015).

Right-sided cardiac structures are enlarged and hypertrophic, most notably the right ventricle which comprises most of the ventricular mass. The right atrium is connected to the superior and inferior vena cava as usual. The persistent left superior vena cava may drain to the right atrium via the coronary sinus (Smith *et al.*, 2005).

Malalignment of the interatrial septum is frequent in HLHS patients, and leftward displacement of the superior attachment of the septum primum is also typical of HLHS (Park *et al.*, 2013). The foramen ovale may be smaller than normal, the limbus of the foramen ovale may be abnormally oriented, and the eustachian valve may be underdeveloped (Feit *et al.*, 1991; Remmel-Dow *et al.*, 1995). The valve of the fossa ovalis may be thickened and may restrict the blood flow at the atrial level. An intact atrial septum was reported in about one-tenth of autopsies (Smith *et al.*, 2005).

The tricuspid valve is as usual composed of anterior, posterior and septal leaflets, which are supported by the subvalvular apparatus, consisting of a prominent anterior papillary muscle, variable numbers of inferior papillary muscles, and the medial papillary muscle arising from the supraventricular crest (Smith *et al.*, 2005). Dysplastic abnormalities of the tricuspid valve were reported in up to one third of patients with HLHS and were more prevalent in the anatomic subtypes with a patent mitral valve. A bileaflet valve was identified in up to 12% of patients; quadricuspid valve, cleft of leaflets, or accessory orifices of the tricuspid valve were less common (Stamm *et al.*, 1997). The size of the tricuspid annulus is usually within or above the upper range of normal (Smith *et al.*, 2005).

The right ventricular cavity dimensions are enlarged, and the walls of the ventricle can be hypertrophic. Myocardial necrotic, fibrotic or ischemic changes of various degrees may be present (Baffa *et al.*, 1992). Similar regions of myofibril disarray, as in the left ventricle, have been identified in the right ventricle (Bohlmeyer *et al.*, 2003). The level of remodeling of the right ventricle, including re-positioning of septomarginal trabeculation that affects the chordal attachments of the anterior portion of the septal leaflet, depends on the severity of the disease (Smith *et al.*, 2005).

In HLHS patients, the pulmonary valve is usually larger than normal, and the leaflets can sometimes be thickened and rolled (Smith *et al.*, 2005). Pulmonary valve stenosis in HLHS patients is very rare but has been described (Farra *et al.*, 2005; Cantinotti *et al.*, 2010).

The anatomy of HLHS is shown in Figure 1.

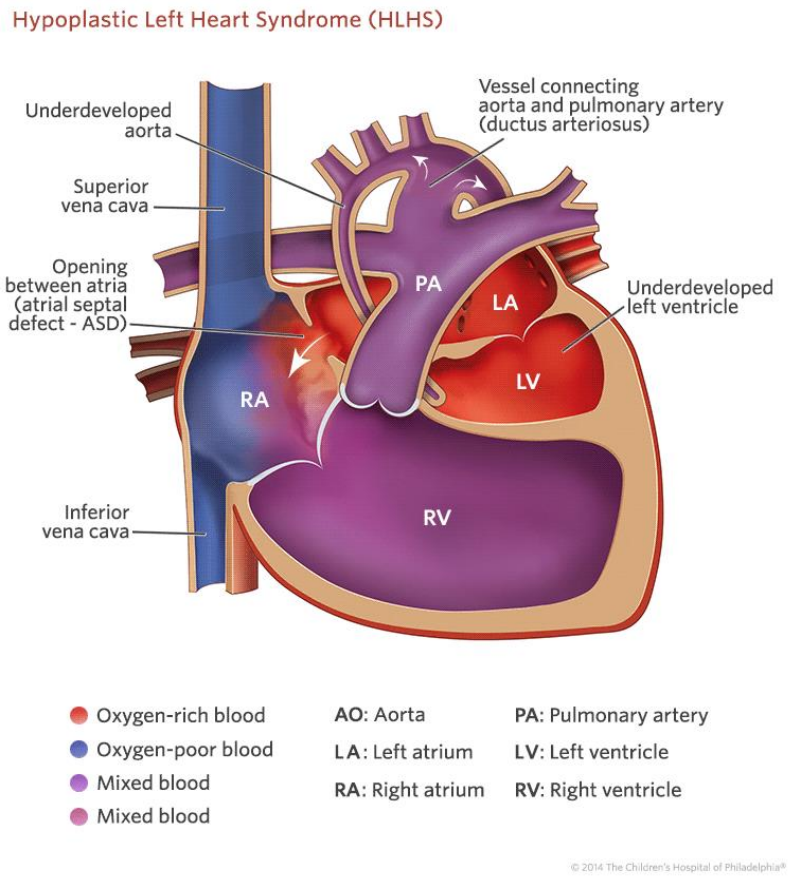


FIGURE 1. Hypoplastic left heart syndrome. Reproduced with permission, © 2014 Children's Hospital of Philadelphia.

1.2 *Treatment strategies*

The following three primary treatment strategies for patients with HLHS have evolved over the last few decades: 1) a multi-stage surgical approach ending ultimately in Fontan circulation, 2) a biventricular repair in the milder form of the disease if the left ventricle is well developed and capable of supporting the systemic circulation, and 3) orthotopic heart transplantation.

1.2.1 Multi-stage surgical approach

Since Norwood and colleagues first successfully performed reconstructive surgery for HLHS in the early 1980s, the multi-stage surgical approach has become a gold standard for this once fatal condition. Ultimately resulting in the total separation of the pulmonary and systemic circulation, the multi-stage surgical approach takes the patient through a series of three consecutive operations.

Stage I: Norwood procedure and hybrid approach

The goals of the stage I surgery are to maintain the systemic and coronary perfusion, to establish an optimal pulmonary blood flow, to allow the growth of the pulmonary arteries, and to prevent the development of postcapillary pulmonary hypertension due to the

restriction of the pulmonary venous return at the atrial level. This can be accomplished either using the Norwood procedure or the hybrid approach.

The timing of the Norwood or hybrid procedures depends on the clinical presentation. If the patient is in a stable condition, an early elective surgery can be performed. If there are signs of hemodynamic instability or impending cardiogenic shock, the surgery must be performed immediately. Although the optimal timing for Norwood or hybrid procedures has not been determined, an older age at the time of surgery was associated with adverse outcomes in some studies, and the surgery should probably not be delayed beyond the first two to three weeks of life (Alsoufi *et al.*, 2011; Sames-Dolzer *et al.*, 2015).

Norwood procedure

Preoperative considerations

The Norwood procedure is performed in hypothermia with the use of a cardiopulmonary bypass; either deep hypothermic circulatory arrest or regional cerebral perfusion is employed. A modified Blalock-Taussig shunt or right ventricle-to-pulmonary artery conduit is commonly used for pulmonary perfusion.

Deep hypothermia allows controlled, time-limited, safe circulatory arrest. Although the deep hypothermic circulatory arrest is relatively safe, the impact of its duration on later neurodevelopmental outcomes seems to be nonlinear, with little influence at shorter durations and with steadily worsening outcomes after longer durations (Wypij *et al.*, 2003). Regional cerebral perfusion allows antegrade cerebral perfusion through the brachiocephalic artery and seems to produce fewer central nervous system perturbations in the early postoperative period than the deep hypothermic circulatory arrest (Newburger *et al.*, 1993). However, the use of the deep hypothermic circulatory arrest for the correction of single ventricle anomalies was not shown to be predictive of worse neurodevelopmental outcomes in early childhood (Fuller *et al.*, 2010).

A modified Blalock-Taussig shunt directs the blood from the brachiocephalic artery to the pulmonary artery. Increased systemic vascular resistance relative to the pulmonary vascular resistance leads to continuous systolic and diastolic blood flow into the shunt that occurs during the systole as well as during the diastole. Continuous diastolic blood flow can result in the "coronary steal phenomenon" and consequently in decreased myocardial perfusion (Ohye *et al.*, 2004). A right ventricle-to-pulmonary artery conduit, which connects the right ventricle directly to the pulmonary artery, eliminates the diastolic run-off seen in the modified Blalock-Taussig shunt, thus avoiding the "coronary steal phenomenon" and potential ischemic myocardial injury (Ohye *et al.*, 2004). However, the ventriculotomy scar associated with the right ventricle-to-pulmonary artery conduit raises concerns about the function of the right ventricle and the increased potential for ventricular arrhythmias in the future (Tateno *et al.*, 2006).

Surgical technique at the German Heart Center Munich

The approach is through a median sternotomy. The thymus is partially excised to obtain optimal access to the upper mediastinum. An arterial cannula is inserted in the pulmonary artery and venous cannulas are placed in the superior and inferior vena cava through the

right atrium. After the cardiopulmonary bypass is established, the right and the left pulmonary arteries are temporarily snared to exclude the pulmonary circulation.

Deep hypothermic circulatory arrest is performed after a minimum of 20 minutes cooling to 18-20°C. The brachiocephalic vessels are occluded, and cardioplegia is administered through a side arm on the arterial cannula after clamping the descending aorta. Alternatively, if regional cerebral perfusion is used, the arterial cannula is either advanced into the previously implanted shunt, in the case of the modified Blalock-Taussig shunt, or inserted directly into the brachiocephalic artery.

The main pulmonary artery is transected above the pulmonary valve, and the ductus is resected. Ductal tissue is then excised from the distal aorta. The resulting opening of the aorta is extended distally into the descending aorta and proximally over the aortic arch and the hypoplastic ascending aorta to the level of the transected main pulmonary artery. The ascending aorta is sutured to the root of the main pulmonary artery (Damus-Kaye-Stensel anastomosis). The rest of the hypoplastic aorta is augmented with the biological patch.

Next, the atrial septum is excised through an atriotomy. Following reconstruction of the aorta, the arterial cannula is inserted into the neo-aorta. After a de-airing procedure, the cardiopulmonary bypass is started, and the rewarming phase begins. During the rewarming phase, the distal main pulmonary artery is closed with a patch or, in rare cases, with a direct suture. Then the pulmonary circulation is reestablished by implanting aorto-pulmonary shunts: for the modified Blalock-Taussig shunt, between the brachiocephalic artery and central pulmonary arteries; for the right ventricle-to-pulmonary artery conduit, between the infundibulum of the right ventricle, avoiding injury to the coronary artery branches, and the pulmonary artery.

After rewarming, weaning the patient from the cardiopulmonary bypass is begun and self-sustaining circulation is established. The sternum is routinely left open and delayed sternal closure is performed on the following day or as soon as the hemodynamics of the patient are stable.

The surgical anatomy after the Norwood stage I procedure using a modified Blalock-Taussig shunt is shown in Figure 2.

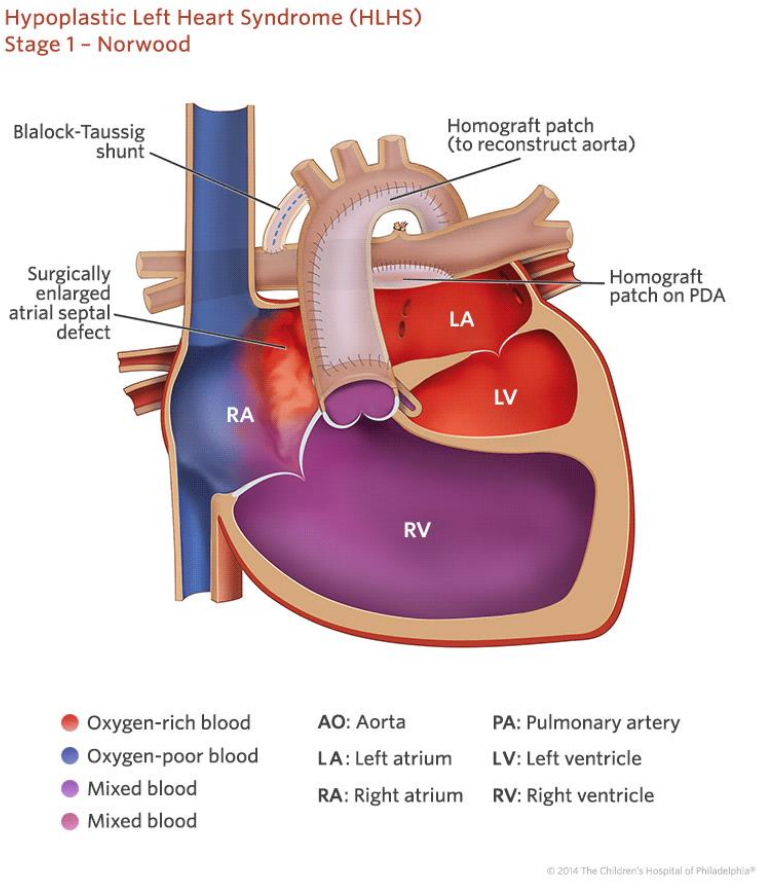


FIGURE 2. Stage I: Norwood procedure. Reproduced with permission, © 2014 Children's Hospital of Philadelphia.

Hybrid approach

The hybrid procedure, as an initial palliation in children with HLHS, was introduced in the early 1990s (Ruiz *et al.*, 1993; Gibbs *et al.*, 1993), but use of this technique only became widespread after early successes were reported in the 2000s (Akintuerk *et al.*, 2002; Akintuerk *et al.*, 2007; Galantowicz *et al.*, 2005; Galantowicz *et al.*, 2008). It combines a surgical approach with catheterization and consists of placing pulmonary artery bands through a median sternotomy and interventional ductal stenting (Akintuerk *et al.*, 2002; Galantowicz *et al.*, 2005).

The potential advantage of the hybrid procedure over the Norwood procedure is that a cardiopulmonary bypass, cardioplegic cardiac arrest and deep hypothermic circulatory arrest are not employed, thus minimizing the extent of the stage I surgery. However, potential disadvantages include increased risk of coronary malperfusion due to the unrepaired hypoplastic ascending aorta and aortic arch, possible restriction at the atrial level, and the requirement for extensive surgery during the stage II procedure (Honjo *et al.*, 2010).

Stage II: Superior cavopulmonary anastomosis and hemi-Fontan procedure

The goals of the stage II surgery are to reduce volume overload of the right ventricle, to provide sufficient "low pressure" pulmonary perfusion, and to improve circulatory system efficiency. This can be accomplished with either Glenn bidirectional cavopulmonary anastomosis or the hemi-Fontan procedure.

Stage II surgery is usually performed at four to six months of age. Earlier age at the time of the surgery was more frequently associated with adverse outcomes in some studies (Jaquiss *et al.*, 2004; Cnota *et al.*, 2012); however, a clinical equivalence in patients who underwent an early stage II surgery was reported at the time of the Fontan completion (Jaquiss *et al.*, 2006). Although the timing for second stage surgery differs significantly among centers, it should probably be performed between three to six months after the Norwood procedure (Meza *et al.*, 2017).

Glenn bidirectional cavopulmonary anastomosis

Preoperative considerations

Glenn bidirectional cavopulmonary anastomosis is usually performed in normothermia or mild hypothermia and with the use of a cardiopulmonary bypass; however, the surgery can be performed safely without the bypass (Hussain *et al.*, 2007). Leaving an additional source of pulmonary perfusion during the Glenn procedure remains controversial. Patients with preserved antegrade pulmonary blood flow after the Glenn procedure were reported to have increased pulmonary artery growth and arterial oxygenation (Yoshida *et al.*, 2005; Gray *et al.*, 2007). In addition, decreased collateral vessel formation was observed in patients with preserved pulmonary perfusion (Gray *et al.*, 2007). Although outcomes after the bidirectional cavopulmonary anastomosis do not seem to be affected by the presence or absence of antegrade pulmonary blood flow (Berdat *et al.*, 2005; Gray *et al.*, 2007), some studies suggest that the elimination of antegrade pulmonary blood perfusion at the time of the Glenn procedure may confer a long-term advantage (Mainwaring *et al.*, 1995; Mainwaring *et al.*, 1999).

Surgical technique at the German Heart Center Munich

The surgical approach is a median sternotomy. The superior vena cava is fully mobilized. The azygos vein is divided between ligatures or clips (except in cases of azygos continuation). The right and the proximal part of the left pulmonary artery, as well as the arterio-pulmonary shunt, are dissected free. The arterial cannula is placed in the neo-aorta, and venous return is secured through the cannulas placed in the right atrium and in the distal part of the superior vena cava.

After initiating a cardiopulmonary bypass, the systemic to pulmonary artery shunt is closed and divided. The operation is performed on a beating heart with normothermia. The superior vena cava is then temporarily occluded with a snare proximal to the venous cannula. After that, a vascular clamp is applied directly above the cavoatrial junction. The superior vena cava is divided above the clamp, and the cardiac end of the superior vena

cava is oversewn. The mobilization of the superior vena cava, the right pulmonary artery and its branches is then completed. The right pulmonary artery is snared distally, and the left pulmonary artery is cross clamped, when possible. An incision is made on the superior aspect of the right pulmonary artery. If present, distal anastomosis of the modified Blalock-Taussig shunt is taken down and the incision is extended. The connection between the superior vena cava and the right pulmonary artery is created with a running suture.

After that, the snares and clamps are removed, and the patient is slowly weaned from the cardiopulmonary bypass. After modified ultrafiltration, the cannulas are removed. Following hemostasis and placement of a pericardial membrane, the sternum is closed.

The surgical anatomy after Glenn bidirectional cavopulmonary anastomosis is shown in Figure 3.

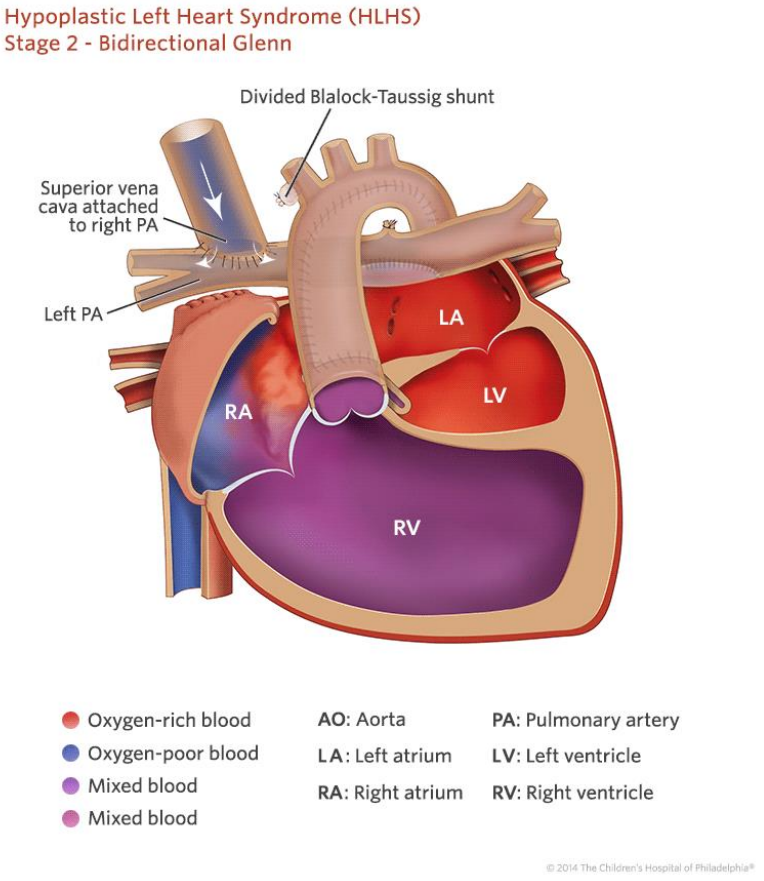


FIGURE 3. Stage II: Glenn procedure. Reproduced with permission, © 2014 Children's Hospital of Philadelphia.

Hemi-Fontan procedure

The hemi-Fontan procedure is an alternative to the bidirectional Glenn procedure as a second stage surgery. It is technically more difficult than the Glenn procedure and it is performed with the use of a cardiopulmonary bypass. After initiating the bypass, atriopulmonary and superior cavopulmonary anastomoses are performed. A homograft or a patch is then used to augment these anastomoses and to create a baffle that will redirect

blood from the vena cava superior to the pulmonary arteries. A second patch is then placed in the right atrium to isolate the venous return from the vena cava superior.

The three-dimensional models showed that the hemi-Fontan procedure achieves a hemodynamic performance similar to the Glenn procedure, with nearly equal power loss and flow distribution to each lung; however, significant differences in the flow distribution were found after the completion of the Fontan circulation (Bove *et al.*, 2003). Despite extensive surgery at the atriocaval junction and in the area close to the sinoatrial node during the hemi-Fontan procedure, no differences in the rate of sinus node dysfunction at the time of hospital discharge were reported compared to the Glenn procedure (Cohen *et al.*, 2000).

Stage III: Total cavopulmonary anastomosis

The goals of the stage III surgery are to further reduce the volume overload of the right ventricle, to improve the circulatory system efficiency, and to increase arterial oxygen saturation. Stage III surgery can be performed using several different techniques, but the most commonly used are the total cavopulmonary anastomosis using the extracardiac conduit or the lateral tunnel technique.

Stage III surgery is usually performed when children are two to five years of age. Although surgery at a younger age was associated with better exercise performance in adolescents (Madan *et al.*, 2013), some authors reported higher rates of Fontan failures in younger patients (Gentles *et al.*, 1997). The stage III procedure can also be safely performed on older patients (Pace *et al.*, 2010; Deraz *et al.*, 2014).

Total cavopulmonary anastomosis with extracardiac conduit

Preoperative considerations

If the bidirectional Glenn procedure was performed as a stage II surgery, a total cavopulmonary anastomosis with an extracardiac conduit is used to complete the Fontan circulation. The total cavopulmonary anastomosis with an extracardiac conduit is usually performed using a cardiopulmonary bypass; however, it can be safely performed without the bypass (Tireli *et al.*, 2006).

Although the extracardiac conduit has theoretical advantages over the lateral tunnel technique, including avoidance of extensive surgery close to the sinoatrial node, lower probability of thrombogenic and arrhythmogenic events, and the avoidance of cardioplegic cardiac arrest, the evidence of the benefits remains inconclusive (Khairy *et al.*, 2012). Fenestration is usually performed on high risk patients, but improved short-term outcomes were also reported for standard-risk patients (Lemler *et al.*, 2002). No differences in late outcomes have been observed between the fenestrated and non-fenestrated Fontan procedure with an extracardiac conduit (Thompson *et al.*, 1999; Fiore *et al.*, 2014).

Surgical technique at the German Heart Center Munich

Surgical approach is a median sternotomy. The superior vena cava, the right and proximal part of the left pulmonary artery, the right atrium and the inferior vena cava are dissected

free. An arterial cannula is placed in the neo-aorta, and venous return is secured through cannulas placed in the distal parts of the superior and inferior vena cava.

A cardiopulmonary bypass is initiated and the operation is performed on a beating heart with normothermia. The superior vena cava is then temporarily occluded with a snare proximal to the venous cannula. If possible, the right and left pulmonary arteries are cross clamped. Next, an incision is made on the inferior aspect of the right pulmonary artery. The top end of the 18 mm Gore-Tex conduit is anastomosed end-to-side to the undersurface of the pulmonary artery using a continuous running suture. The snares and clamps can now be removed from the vessels, and the conduit is temporarily occluded with a vascular clamp. The inferior vena cava is then temporarily occluded with a snare proximal to the venous cannula, and a vascular clamp is placed across the cavoatrial junction. Afterwards, the cavoatrial junction is transected while clamped, and the cardiac end is oversewn and the clamp is removed. The inferior end of the Gore-Tex conduit is anastomosed end-to-end to the transected inferior vena cava with a running suture. After de-airing the conduit, the clamp and the snare are removed, and the patient is slowly weaned from the cardiopulmonary bypass.

Fenestration is performed only on very high-risk patients. In these cases, a 4 mm fenestration is created between the conduit and the right atrium using two vascular clamps, usually without restarting the cardiopulmonary bypass. After modified ultrafiltration, the cannulas are removed. Following hemostasis and the placement of a pericardial membrane, the sternum is closed.

The surgical anatomy after the total cavopulmonary anastomosis with an extracardiac conduit is shown in Figure 4.

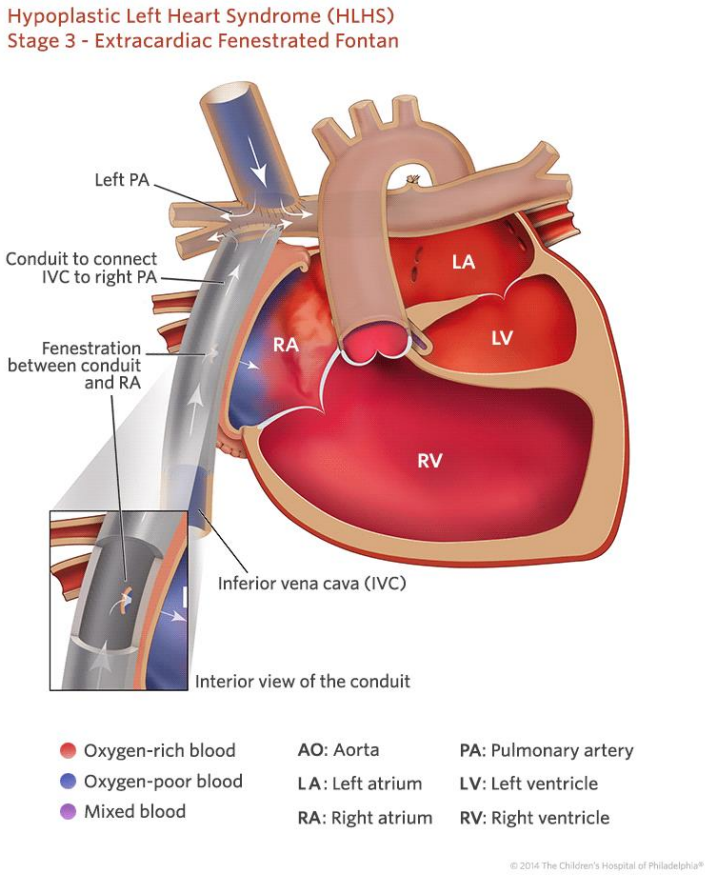


FIGURE 4. Stage III: Extracardiac Fontan procedure. Reproduced with permission, © 2014 Children's Hospital of Philadelphia.

Total cavopulmonary anastomosis with lateral tunnel technique

If the hemi-Fontan procedure was performed as the stage II surgery, the lateral tunnel technique is used to complete the Fontan circulation. After the cardiopulmonary bypass is initiated, the right atrium is opened and the internal patch separating the blood flow from the superior and inferior vena cava is removed. A Gore-Tex patch is then placed to redirect blood from the inferior vena cava to the pulmonary arteries. A small opening is created in the Gore-Tex patch if fenestration is performed.

The lateral tunnel technique and the technique employing an extracardiac conduit have comparable results, including operative morbidity and mortality, the postoperative hemodynamic, and the functional status (Azakie *et al.*, 2001; Kumar *et al.*, 2003; Fiore *et al.*, 2007; Lee *et al.*, 2007; Robbers-Visser *et al.*, 2010). Some studies have found the extracardiac conduit superior to the lateral tunnel approach due to fewer arrhythmias, but the evidence is inconclusive (Azakie *et al.*, 2001; Hakacova *et al.*, 2008; Robbers-Visser *et al.*, 2010). The controversy around these techniques regarding the rate of nodal dysfunction persists (Kumar *et al.*, 2003; Fiore *et al.*, 2007; Lee *et al.*, 2007).

1.2.2 Biventricular repair

Biventricular repair represents an alternative to the multi-stage reconstructive surgery and can be attempted in patients with hypoplastic left heart complex, a subset of patients with

HLHS (Tchervenkov *et al.*, 1998). It allows a normal, two-ventricle arrangement in the patient's heart, and the feasibility of the repair depends on the ability of the left ventricle to support the systemic circulation and on the patency of the left cardiac valves.

The theoretical advantage of biventricular repair is the potential growth of the left ventricle, which was noted in some patients after the surgery (Tchervenkov *et al.*, 1998; Serraf *et al.*, 1999). In addition, in-series connected pulmonary and systemic circulation supported by both ventricles provides circulatory efficiency superior to a parallel connection supported only by the right ventricle. However, the reoperation rate after biventricular repair was reportedly high, reaching 54% five years after the surgery (Serraf *et al.*, 1999). The need for a left ventricle morphologically capable of supporting the systemic circulation and the high reoperation and mortality rates limit the use of biventricular repair in the surgical management of HLHS.

1.2.3 Heart transplantation

Orthotopic heart transplantation as a primary management strategy constitutes an alternative to the multi-stage surgical approach. A multicenter study conducted by Chrisant and colleagues reported 72% post-transplant 5-year actuarial survival in children with non-palliated HLHS; most of the deaths occurred within three months of the surgery. While awaiting a transplant, 25% of children died, and overall survival, taking into account mortality after being placed on the list and after transplantation, was 68% at three months and 54% at five years (Chrisant *et al.*, 2005). A more recent report using the Pediatric Heart Transplant Study database compared outcomes of 388 infants with non-palliated HLHS and infants with other congenital heart diseases (non-HLHS) or cardiomyopathy in the periods 1993 to 1999 and 2000 to 2006. In the earlier period, the authors reported 1-year survival for the HLHS-group, 55% after listing and 77% after the transplantation, indicating a significant waitlist mortality. In the more recent period, there was a considerable improvement in the 1-year waitlist mortality, with a survival rate to transplant for the HLHS-group of 82% (Guleserian *et al.*, 2011).

Although these results are encouraging and correspond with an improvement in survival rates after pediatric heart transplantation over time (Dipchand *et al.*, 2013; Thrush *et al.*, 2014), the continuing limited number of available donor hearts as well as improved survival rates of patients who undergo multi-stage surgical reconstruction limit the use of heart transplantation in children with HLHS (Canter *et al.*, 2007).

1.2.4 Palliative care approach

Decades ago, palliative care was the only option available for children with HLHS. As perioperative management and outcomes have significantly improved over the last few decades, palliative care has become a less preferred alternative. A survey among pediatric cardiologists reported that non-interventional palliative care for uncomplicated HLHS was the preferred choice of only 1.5% respondents, whereas nearly 90% preferred the surgical reconstruction (Yates *et al.*, 2011).

An ethical controversy persists about whether the palliative care approach should be offered and discussed with parents. Some argue that non-intervention should no longer be offered

as an option because outcomes have improved markedly over time and because other life-threating pediatric cardiac conditions, with prognoses comparable or worse than HLHS, are being treated without offering a palliative care option (Wernovsky, 2008). Proponents of offering palliative care claim that parents can only make well-informed decisions when each alternative, including palliative care, is discussed and when potential ramifications for each alternative are well explained (Kon, 2008).

When offering palliative care, comprehensive evaluations and individual risk assessments should be performed to obtain an accurate prognosis. For patients with additional risk factors, including chromosomal and major organ abnormalities, the palliative care approach may be the preferred option. However, for patients without any risk factors and with a good chance of early survival, intervention may provide the greatest benefit and outweigh the risks.

2 General considerations

2.1 *Mortality*

Mortality after the Norwood procedure has decreased markedly during the last few decades, which can primarily be attributed to improvements in perioperative and postoperative care. Secondarily, outcomes have improved significantly over time among centers that care for children with HLHS, suggesting a positive learning curve for the Norwood procedure. Centers with higher volume of surgeries employing Norwood procedures show higher survival rates than low-volume centers (Checchia *et al.*, 2005; Hirsch *et al.*, 2008; Welke *et al.*, 2009).

Despite an ongoing increase in the survival rate over the last few decades, the mortality rate after the Norwood procedure remains one of the highest in pediatric cardiac surgery (Jacobs *et al.*, 2005). The mortality peaks between the Norwood stage I and stage II procedures, with the highest rate during the hospitalization following the Norwood procedure (Feinstein et al., 2012; Tabbutt *et al.*, 2012). Mortality after the stage II procedure is significantly lower than after the Norwood procedure, and early postoperative results after completion of the Fontan circulation are excellent, approaching survival rates of 95 – 100% (Feinstein *et al.*, 2012).

2.2 *Resource utilization*

Surgical treatment of patients with HLHS, irrespective of the preferred treatment strategy, is extremely resource-consuming compared to the average pediatric cardiac surgery (Faraoni *et al.*, 2016). Despite ongoing efforts to optimize resource utilization in patients with HLHS, many resources are being allocated to patients who do not survive hospitalization. The mortality related resource utilization fraction, i.e. the percentage of inpatient investment spent on hospitalizations that have a fatal outcome, was reported to be high in the period corresponding with the Norwood procedure. These findings suggest that resources invested in inpatient care for HLHS are disproportional for patients who will not survive hospitalization (Danford *et al.*, 2015). As the mortality of patients with HLHS decreases, the total admission rate in later life increases (Czosek *et al.*, 2013). Patients who

underwent multi-stage surgery in childhood require increased medical attention as they become adults, and the costs of this population can be expected to increase (Danford *et al.*, 2015; Thomas *et al.*, 2016).

A more effective allocation of resources from high-risk patients with limited chances of survival after the Norwood procedure to patients who underwent multi-stage reconstructive surgery in childhood, and require increased medical attention, could at least to some extent offset the increase in costs expected in HLHS population.

2.3 *Risk models for mortality*

Many studies published in the last few decades have analyzed potential risk factors associated with higher mortality rates during the multi-stage reconstructive surgery. The following categories include most of the factors analyzed: demographic, clinical, anatomic/echocardiographic, catheterization and surgical parameters.

The most commonly analyzed demographic parameters were gender (Stasik *et al.*, 2006; Hehir *et al.*, 2008; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015), birth weight (Simsic e*t al.*, 2005; Stasik *et al.*, 2006; Hehir *et al.*, 2008; Carlo *et al.*, 2011; Tabbutt *et al.*, 2012; Alsoufi *et al.*, 2015), and prematurity (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Hehir *et al.*, 2008; Ghanayem *et al.*, 2012; Cross *et al.*, 2014; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015).

The clinical parameters included the presence of genetic disorders and/or major extracardiac anomalies (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Hehir *et al.*, 2008; Tabbutt *et al.*, 2012; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015), mechanical ventilation in the preoperative period (Simsic *et al.*, 2005; Shamszad *et al.*, 2014), and the delayed sternal closure (Hehir *et al.*, 2008; Tabbutt *et al.*, 2012).

The anatomic/echocardiographic parameters included the specific anatomic subtype of HLHS (Vida *et al.*, 2008; Sathanandam *et al.*, 2010; Polimenakos *et al.*, 2011; Ghanayem *et al.*, 2012; Cross *et al.*, 2014), the presence of a restrictive atrial septal defect in the preoperative period (Hehir *et al.*, 2008; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015; Sata *et al.*, 2015), the presence of a significant tricuspid valve insufficiency (Hehir *et al.*, 2008; Carlo *et al.*, 2011; Hansen *et al.*, 2011; Lee *et al.*, 2012; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015), a right ventricular function (Simsic *et al.*, 2005; Hehir *et al.*, 2008; Carlo *et al.*, 2011; Ghanayem *et al.*, 2012; Alsoufi *et al.*, 2015), and the diameter of the ascending aorta (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Alsoufi *et al.*, 2015).

The most commonly analyzed parameters drawn from the catheterization examination before the stage II surgery were right ventricular end-diastolic pressure (Carlo *et al.*, 2011; Schwartz *et al.*, 2014), pulmonary to systemic blood flow ratio (Carlo *et al.*, 2011; Friedman *et al.*, 2011), pulmonary vascular resistance (Carlo *et al.*, 2011; Friedman *et al.*, 2011; Alsoufi *et al.*, 2012), and arterial or caval oxygen saturations (Friedman *et al.*, 2011; Lee *et al.*, 2012).

The surgical parameters most often included were age at the surgery (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Alsoufi *et al.*, 2011; Hansen *et al.*, 2011; Sames-Dolzer *et al.*, 2015; Alsoufi *et al.*, 2015), a shunt type implanted during the Norwood procedure (Lai *et al.*,

2007; Hehir *et al.*, 2008; Tabbutt *et al.*, 2012), concomitant cardiac surgery (Carlo *et al.*, 2011; Schwartz *et al.*, 2014; Alsoufi *et al.*, 2015), the duration of the cardiopulmonary bypass (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Hehir *et al.*, 2008), and the duration of the deep hypothermic circulatory arrest (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Hehir *et al.*, 2008; Tabbutt *et al.*, 2012).

These and many other potential risk factors for mortality during the multi-stage reconstructive surgery have been analyzed independently, but the results remain inconsistent. The majority of studies included mixed groups of patients with a single right and left ventricle, and various techniques were employed to perform stage II and stage III procedures.

Systematic reviews of studies from other medical fields have shown that the majority of published medical studies do not adhere to current methodological recommendations for construction of prediction risk models. Poor reporting of model performance along with use of inappropriate methods for developing multivariate models limit the reliability of the results (Mallett *et al.*, 2010; Bouwmeester *et al.*, 2012). Violations of methodological recommendations for construction of prediction models, diverse technical modifications, as well as intra- and inter-center variability may partially explain the conflicting risk factors reported.

Because mortality after the Norwood procedure in children with HLHS remains one of the highest in pediatric cardiac surgery and multi-stage surgical correction is extremely resource-consuming, attempts to identify risk factors for adverse outcomes and to address the high mortality rates continue.

3 Dissertation objectives

The objectives of this dissertation are to analyze potential risk factors for mortality in patients with HLHS and to conduct a survival risk analysis.

The primary objective is to develop a predictive risk model for mortality between the Norwood stage I and stage II procedures in patients with HLHS.

The secondary objective is to identify risk factors associated with mortality between the stage II and stage III procedures in patients with HLHS.

The tertiary objective is to conduct a survival analysis in patients with HLHS and to evaluate mortality rates following the reconstructive stages.

CHAPTER II: METHODS

4 Study design

This dissertation was performed as a single center retrospective study. The objectives of the dissertation were defined in Chapter I, Section 3.

For the primary objective, all patients with HLHS who underwent the Norwood stage I procedure between May 2000 and May 2015 at the German Heart Center Munich were included. All patients who died during the Norwood procedure were excluded. The primary endpoint was defined as death from any cause between the Norwood stage I and stage II procedures.

For the secondary objective, all patients with HLHS who underwent the Norwood stage I procedure between May 2000 and May 2015 at the German Heart Center Munich, and who subsequently underwent the stage II procedure, were included. All patients who died during the stage II procedure were excluded. The secondary endpoint was defined as death from any cause between the stage II and stage III procedures.

For tertiary objective, all patients with HLHS who underwent the Norwood stage I procedure between May 2000 and May 2015 at the German Heart Center Munich were included. All patients who died during the Norwood procedure were excluded. The tertiary endpoint was defined as death from any cause at any point after the Norwood procedure.

The study protocol was approved by the Institutional Review Board. Because the design of this study is retrospective, the requirement for informed consent was waived.

5 Patient cohort

During the study period, 179 children with HLHS underwent the Norwood stage I procedure. Three patients who died during the Norwood procedure at the beginning of the study period were excluded. One hundred and seventy-six patients met the inclusion criteria for the primary analysis.

Of the 176 patients with HLHS who underwent the Norwood stage I procedure and proceeded to the post-Norwood period, 140 underwent the stage II procedure. No death was recorded during the stage II surgery. Thus, 140 children met the inclusion criteria for the secondary analysis.

Consistent with the tertiary objective, all patients with HLHS who underwent the Norwood stage I procedure during the study period and did not die during the stage I surgery were included. Hence, 176 children met the inclusion criteria for the tertiary analysis.

6 Data collection

6.1 *Primary analysis*

Electronic and outpatient medical records of all 176 patients who proceeded to the post-Norwood period were retrospectively reviewed. Patient- and procedure-related potential risk factors for the primary endpoint were abstracted. The factors included demographic, clinical, anatomic/echocardiographic, and operative parameters. A list of the 32 abstracted potential risk factors is shown in Table 1.

Demographic parameters

Demographic parameters were abstracted from electronic hospital medical records. Gender, birth weight, birth weight less than or equal to 2.5 kg, and gestational age were defined per se. Prematurity was defined as gestational age less than or equal to 37 weeks.

Clinical parameters

Clinical parameters were abstracted from electronic hospital medical records and outpatient medical records. Preoperative cardiopulmonary resuscitation was defined as a cardiopulmonary resuscitation performed at any point before the Norwood procedure. Preoperative catheter-based septal intervention was defined as any atrial septal intervention before the Norwood procedure, including the Rashkind atrial balloon septostomy and/or atrial septal stent implantation. Preoperative ventilation was defined as a mechanical ventilation at any point before the Norwood procedure.

Anatomic/echocardiographic parameters

Anatomic/echocardiographic parameters were abstracted from echocardiographic reports. Preoperative anatomic/echocardiographic parameters were abstracted from the last echocardiographic report before the Norwood procedure and postoperative anatomic/echocardiographic parameters were abstracted from the first echocardiographic report after the Norwood procedure. Hypoplastic left heart syndrome–forme fruste, HLHS subtype, anomalous pulmonary vein connection, ventricular septal defect, endocardial fibroelastosis, ascending aorta diameter, and ascending aorta diameter less than or equal to 2 mm were defined per se. Tricuspid valve insufficiency was classified qualitatively into one of five grades: absent (0), minimal (I), mild (II), moderate (III), or severe (IV). The grade was determined by the width and length of the insufficiency jet. Significant tricuspid valve insufficiency was defined as grades II+, III, or IV. Pulmonary valve insufficiency was classified qualitatively into one of five grades: absent (0), minimal (I), mild (II), moderate (III), or severe (IV). The grade was determined by the width and length of the insufficiency jet. The presence of pulmonary valve insufficiency was defined as grades I, II, III, or IV. The right ventricular function was assessed visually using the “eyeballing” approach and graded as normal, mildly, moderately, or severely impaired. All grades but normal were considered impaired right ventricular function. A restrictive atrial septal defect was defined as an atrial septal defect with a mean transseptal gradient greater than or equal

to 5 mmHg and/or with a maximal transseptal gradient greater than or equal to 10 mmHg and/or with a diameter less than 3 mm.

Operative parameters

Operative parameters were abstracted from the operative reports. Age at the Norwood procedure, duration of the deep hypothermic circulatory arrest, lowest temperature during the Norwood procedure, and concomitant cardiac surgery were defined per se. The shunt type at the Norwood procedure was classified either as a systemic shunt, including modified Blalock-Taussig and central aorto–pulmonary shunts, or as a right ventricle-to-pulmonary artery conduit. Shunt revision during the Norwood procedure was defined as any shunt revision during the surgery, including revision of the proximal or distal anastomosis and/or shunt exchange due to inappropriate size or hemodynamic instability. Revision of the neo-aorta during the Norwood procedure was defined as any neo-aorta revision during the surgery, including revision of the proximal or distal anastomosis or any other anastomosis necessary for the construction of the neo-aorta.

TABLE 1. Potential risk factors for primary endpoint.

Potential risk factor	Reference	Note
Demographic parameters		
Gender	male/female	-
Birth weight	kg	-
Birth weight ≤ 2.5 kg	no/yes	-
Gestational age	weeks	-
Prematurity	no/yes	gestational age ≤ 37 weeks
Clinical parameters		
Preoperative CPR	no/yes	-
Preoperative catheter-based septal intervention	no/yes	-
Preoperative mechanical ventilation	no/yes	-
Anatomic/echocardiographic parameters		
HLHS-forme fruste	no/yes	-
HLHS subtypes: AA/MA, AA/MS, AS/MA, AS/MS	no/yes	-
APVC	no/yes	-
VSD	no/yes	-
Endocardial fibroelastosis	no/yes	-
Restrictive ASD	no/yes	mean gradient ≥ 5 mmHg, max gradient ≥ 10 mmHg, or ASD diameter < 3 mm
Ascending aorta diameter	mm	-
Ascending aorta diameter ≤ 2 mm	no/yes	-
Preoperative PI grade (I – IV)	no/yes	-
Preoperative TI grade (II+ - IV)	no/yes	-
Postoperative TI grade (II+ - IV)	no/yes	-
Preoperative impaired RV function	no/yes	-
Postoperative impaired RV function	no/yes	-
Operative parameters		
Age at Norwood	days	-

TABLE 1. Potential risk factors for primary endpoint (continued).

Shunt type at Norwood	systemic/ RV-PA	systemic shunt includes mBT shunt or central aorto-pulmonary shunt
Shunt revision during Norwood	no/yes	-
Neo-aorta revision during Norwood	no/yes	-
DHCA	min	-
Lowest temperature during Norwood	ºC	-
Concomitant cardiac surgery	no/yes	-

AA, aortic atresia; *APVC*, anomalous pulmonary vein connection; *AS*, aortic stenosis; *ASD*, atrial septal defect; *CPR*, cardiopulmonary resuscitation; *DHCA*, deep hypothermic circulatory arrest; *HLHS*, hypoplastic left heart syndrome; *MA*, mitral atresia; *mBT*, modified Blalock-Taussig; *MS*, mitral stenosis; *PI*, pulmonary valve insufficiency; *RV*, right ventricle; *RV-PA*, right ventricle-to-pulmonary artery; *TI*, tricuspid valve insufficiency; *VSD*, ventricular septal defect.

6.2 *Secondary analysis*

The electronic hospital medical records and outpatient medical records of all 140 patients who proceeded to the post-stage II period were retrospectively reviewed. Patient- and procedure-related potential risk factors for the secondary endpoint were abstracted. The factors included demographic, clinical, anatomic/echocardiographic, catheterization, and operative parameters. A list of the 28 abstracted potential risk factors is shown in Table 2.

Demographic parameters

Demographic parameters were abstracted from electronic hospital medical records. Gender and weight at the stage II procedure were defined per se. Prematurity was defined as gestational age less than or equal to 37 weeks.

Clinical parameters

Clinical parameters were abstracted from electronic hospital medical records and outpatient medical records. The shunt type at the Norwood procedure was classified either as a systemic shunt, including modified Blalock-Taussig and central aorto–pulmonary shunts, or as a right ventricle-to-pulmonary artery conduit. Pulmonary artery intervention after the Norwood procedure was defined as any intervention of a pulmonary artery between the Norwood stage I and stage II procedures, including a surgical and/or catheter-based intervention. Neo-aorta intervention after the Norwood procedure was defined as any intervention of the neo-aorta between the Norwood stage I and stage II procedures, including a surgical and/or catheter-based intervention.

Anatomic/echocardiographic parameters

Anatomic/echocardiographic parameters were abstracted from echocardiographic reports. Preoperative anatomic/echocardiographic parameters were abstracted from the last echocardiographic report before the stage II procedure, and postoperative anatomic/echocardiographic parameters were abstracted from the first echocardiographic report after the stage II procedure. Hypoplastic left heart syndrome subtype, endocardial fibroelastosis, and persistent left superior vena cava were defined per se. Tricuspid valve insufficiency was classified qualitatively into one of five grades: absent (0), minimal (I),

mild (II), moderate (III), or severe (IV). The grade was determined by the width and length of the insufficiency jet. Significant tricuspid valve insufficiency was defined as grades II+, III, or IV. Neo-aortic valve insufficiency was classified qualitatively into one of five grades: absent (0), minimal (I), mild (II), moderate (III), or severe (IV). The grade was determined by the width and length of the insufficiency jet. The presence of neo-aortic valve insufficiency was defined as grades I, II, III, or IV. The right ventricular function was assessed visually using the "eyeballing" approach and graded as normal, mildly, moderately, or severely impaired. All grades but normal were considered impaired right ventricular function.

Catheterization parameters

Catheterization parameters were abstracted from the catheterization reports. The examination was usually performed shortly before the stage II surgery. If more examinations were performed between the Norwood stage I and stage II procedures, the parameters were abstracted from the last catheterization report before the stage II surgery. The right ventricular end-diastolic pressure, pulmonary artery mean pressure, pulmonary to systemic blood flow ratio, pulmonary vascular resistance, arterial oxygen saturation, and oxygen saturation in the superior vena cava were defined per se.

Operative parameters

Operative parameters were abstracted from the operative reports. Age at the stage II surgery was defined per se. Early stage II surgery was defined as a stage II surgery performed less than or equal to 90 days after birth. Pulmonary artery augmentation during the stage II surgery was defined as a patch augmentation of the pulmonary arteries during the stage II surgery. Tricuspid valve intervention during the stage II surgery was defined as any tricuspid valve intervention during the stage II surgery, including a tricuspid valve repair and/or replacement.

TABLE 2. Potential risk factors for secondary endpoint.

Potential risk factor	Reference	Note
Demographic parameters		
Gender	male/female	-
Weight at stage II	kg	-
Prematurity	no/yes	gestational age ≤ 37 weeks
Clinical parameters		
Shunt type at Norwood	systemic/ RV-PA	systemic shunt includes mBT shunt or central aorto-pulmonary shunt
PA intervention after Norwood	no/yes	-
Neo-aorta intervention after Norwood	no/yes	-
Anatomic/echocardiographic parameters		
HLHS subtypes: AA/MA, AA/MS, AS/MA, AS/MS	no/yes	-
Endocardial fibroelastosis	no/yes	-
PLSVC	no/yes	-
Preoperative neo-AI grade (I – IV)	no/yes	-
Preoperative TI grade (II+ - IV)	no/yes	-

TABLE 2. Potential risk factors for secondary endpoint (continued).

Postoperative TI grade (II+ - IV)	no/yes	-
Preoperative impaired RV function	no/yes	-
Postoperative impaired RV function	no/yes	-
Catheterization parameters		
RVEDP	mmHg	-
PA mean pressure	mmHg	-
PVR	dyn.s.cm^{-5}	-
Q_p:Q_s ratio	absolute value	-
Oxygen saturation – arterial	%	-
Oxygen saturation – SVC	%	-
Operative parameters		
Age at stage II	months	-
Early stage II	no/yes	≤ 90 days after the birth
PA augmentation during stage II	no/yes	-
TV intervention during stage II	no/yes	-

AA, aortic atresia; *AS*, aortic stenosis; *HLHS*, hypoplastic left heart syndrome; *MA*, mitral atresia; *mBT*, modified Blalock-Taussig; *MS*, mitral stenosis; *neo-AI*, neo-aortic valve insufficiency; *PA*, pulmonary artery; *PLSVC*, persistent left superior vena cava; *PVR*, pulmonary vascular resistance; Q_p, pulmonary blood flow; Q_s, systemic blood flow; *RV*, right ventricle; *RV-PA*, right ventricle-to-pulmonary artery; *RVEDP*, right ventricular end-diastolic pressure; *SVC*, superior vena cava; *TI*, tricuspid valve insufficiency; *TV*, tricuspid valve.

6.3 *Tertiary analysis*

The electronic hospital medical records, outpatient medical records and telephone inquiries were used to obtain the status (alive or dead) of all 176 patients who proceeded to the post-Norwood period.

7 Follow-up

A follow-up was undertaken in January 2016 through a review of electronic hospital medical records, outpatient medical records, or directly through telephone inquiries.

For the primary objective, all 176 patients, who underwent the Norwood procedure and proceeded to the post-Norwood period, were followed until their deaths, which occurred between the Norwood stage I and stage II procedures, or until the stage II procedure was performed.

For the secondary objective, all 140 patients, who underwent the stage II surgery and proceeded to the post-stage II period, were followed until their deaths, which occurred between the stage II and stage III procedures, or until the stage III procedure was performed. If none of these two events occurred before January 2016, patients were assigned to the "awaiting stage III" group.

For the tertiary objective, all 176 patients, who underwent the Norwood procedure and proceeded to the post-Norwood period, were followed until their deaths or until the last known outpatient follow-up visit as of January 2016.

8 Data analysis

8.1 *Missing data*

Due to the retrospective nature of the study and despite huge efforts, complete datasets could not be obtained. Little's missing completely at random (MCAR) test and pattern analysis of the data were conducted to establish whether the data were missing at random.

8.1.1 Incomplete data: Primary analysis

All 31 potential risk factors for the primary endpoint and the outcome variable were analyzed. A summary of the data relevant to the primary analysis is shown in Figure 5.

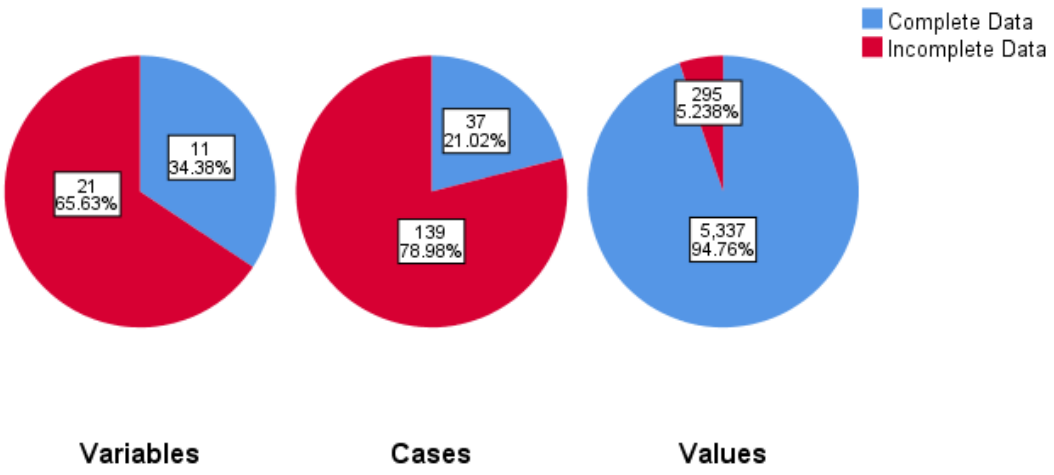


FIGURE 5. Incomplete data: primary analysis.

The analysis showed that the datasets were incomplete in the majority of the variables and patients; however, only 5% of values were missing. A summary of the data with respect to the potential risk factors for primary endpoint is shown in Table 3.

TABLE 3. Incomplete data: primary analysis.

Variable	Missing		Available
	N	Value (%)	*N*
Preoperative PI grade (I - IV)	79	44.9	97
Restrictive ASD	40	22.7	136
Gestational age	36	20.5	140
Preoperative impaired RV function	34	19.3	142
Postoperative TI grade (II+ - IV)	15	8.5	161
Postoperative impaired RV function	12	6.8	164
Endocardial fibroelastosis	11	6.3	165
Preoperative TI grade (II+ - IV)	10	5.7	166
Lowest temperature during Norwood	9	5.1	167
Ascending aorta diameter	8	4.5	168
Ascending aorta diameter ≤ 2 mm	8	4.5	168
DHCA	8	4.5	168
Prematurity	5	2.8	171

TABLE 3. Incomplete data: primary analysis (continued).

AS/MS subtype	4	2.3	172
AS/MA subtype	4	2.3	172
AA/MS subtype	4	2.3	172
AA/MA subtype	4	2.3	172
Birth weight ≤ 2.5 kg	1	0.6	175
Birth weight	1	0.6	175
VSD	1	0.6	175
Preoperative mechanical ventilation	1	0.6	175

AA, aortic atresia; *AS*, aortic stenosis; *ASD*, atrial septal defect; *DHCA*, deep hypothermic circulatory arrest; *MA*, mitral atresia; *MS*, mitral stenosis; *PI*, pulmonary valve insufficiency; *RV*, right ventricle; *TI*, tricuspid valve insufficiency; *VSD*, ventricular septal defect.

The Little's MCAR test confirmed that the data were missing completely at random, and the data analysis showed no patterns. The results of the Little's MCAR test are shown in Table 4, and the data analysis is shown in Figure 6.

TABLE 4. Little's MCAR test: primary analysis.

EM Means					
Birth weight (kg)	Gestational age (weeks)	Ascending aorta diameter (mm)	Age at Norwood (days)	DHCA (min)	Lowest temperature during Norwood (°C)
3.207	39.240	3.444	9.846	43.594	18.872

Little's MCAR test: Chi-Square = 45.340, DF = 40, *P-value* = 0.259. *DF*, degrees of freedom; *DHCA*, deep hypothermic circulatory arrest; *EM*, expectation-maximization.

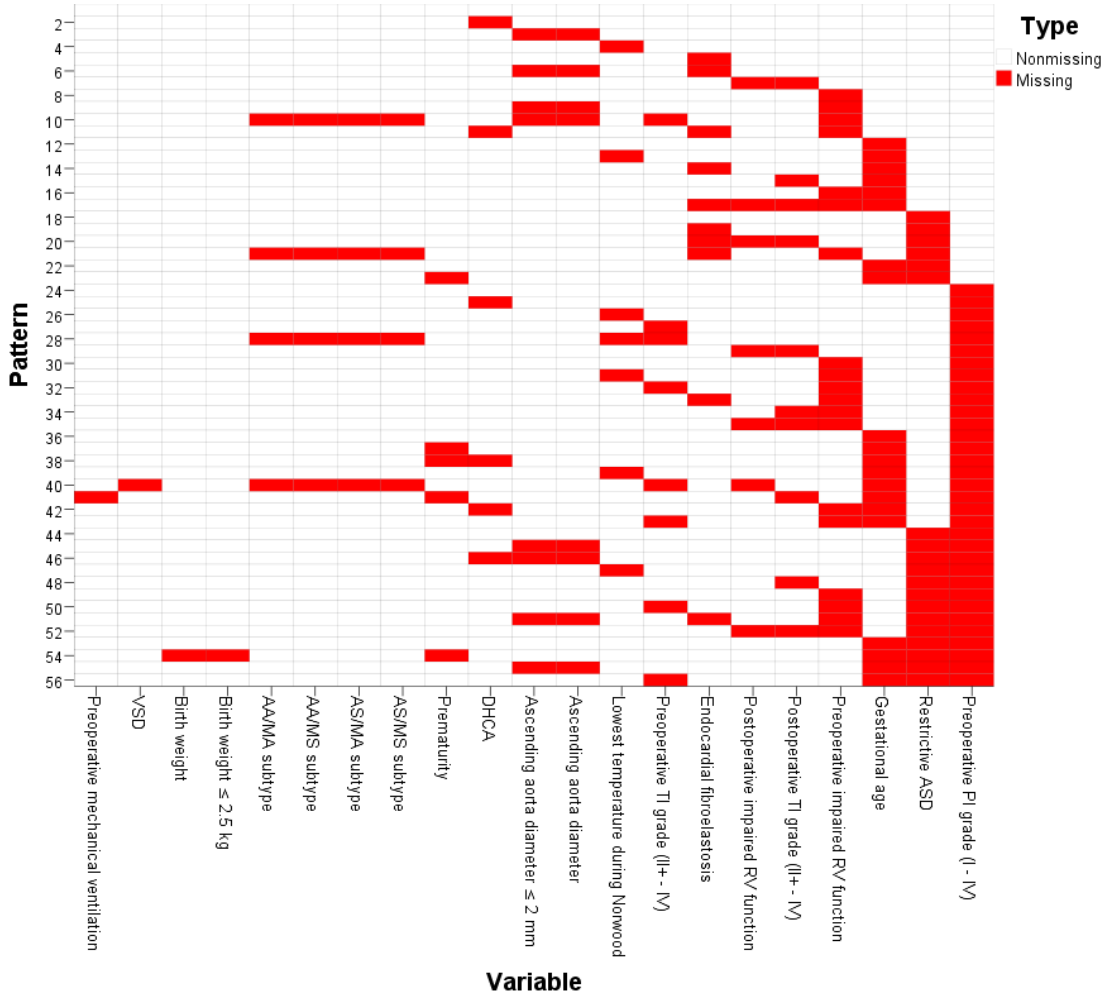


FIGURE 6. Patterns: primary analysis. *AA*, aortic atresia; *AS*, aortic stenosis; *ASD*, atrial septal defect; *DHCA*, deep hypothermic circulatory arrest; *MA*, mitral atresia; *MS*, mitral stenosis; *PI*, pulmonary valve insufficiency; *RV*, right ventricle; *TI*, tricuspid valve insufficiency; *VSD*, ventricular septal defect.

The results based on the descriptive statistics were calculated from the available data. Univariate analysis was performed with listwise deletion, and only cases with available values for the selected variable were included. Imputation using single stochastic regression method was used to complete the datasets of variables considered for the multivariate analysis. Selected variables relevant to the primary analysis, including the outcome variable, were used as predictors for imputation model. The imputation model is shown in Table 5.

TABLE 5. Imputation model: multivariate primary analysis.

Variable	Role in imputation		Model type	Missing values	Imputed values
	Dependent variable	Predictor			
Death (Norwood – stage II)	no	yes	-	0	0
Gender	no	yes	-	0	0
Birth weight	yes	yes	Linear regression	1	1

TABLE 5. Imputation model: multivariate primary analysis (continued).

Gestational age	no	yes	Linear regression	36	36*
Prematurity	yes	yes	Logistic regression	5	5
Preoperative CPR	no	yes	-	0	0
Preoperative catheter-based septal intervention	no	yes	-	0	0
Preoperative mechanical ventilation	no	yes	Logistic regression	1	1*
HLHS-forme fruste	no	yes	-	0	0
AA/MA subtype	no	yes	Logistic regression	4	4*
APVC	no	yes	-	0	0
VSD	no	yes	Logistic regression	1	1*
Endocardial fibroelastosis	no	yes	Logistic regression	11	11*
Restrictive ASD	no	yes	Logistic regression	40	40*
Ascending aorta diameter	no	yes	Linear regression	8	8*
Preoperative PI grade (I – IV)	no	yes	Logistic regression	79	79*
Preoperative TI grade (II+ - IV)	no	yes	Logistic regression	10	10*
Postoperative TI grade (II+ - IV)	no	yes	Logistic regression	15	15*
Preoperative impaired RV function	no	yes	Logistic regression	34	34*
Postoperative impaired RV function	yes	yes	Logistic regression	12	12
Age at Norwood	no	yes	-	0	0
Shunt type at Norwood	no	yes	-	0	0
Shunt revision during Norwood	no	yes	-	0	0
Neo-aorta revision during Norwood	no	yes	-	0	0
DHCA	no	yes	Linear regression	8	8*
Lowest temperature during Norwood	no	yes	Linear regression	9	9*
Concomitant cardiac surgery	no	yes	-	0	0

AA, aortic atresia; *APVC*, anomalous pulmonary vein connection; *ASD*, atrial septal defect; *CPR*, cardiopulmonary resuscitation; *DHCA*, deep hypothermic circulatory arrest; *HLHS*, hypoplastic left heart syndrome; *MA*, mitral atresia; *PI*, pulmonary valve insufficiency; *RV*, right ventricle; *TI*, tricuspid valve insufficiency; *VSD*, ventricular septal defect. *Values were imputed only for internal purposes of the imputation model.

Of the 27 variables selected for the imputation model, 11 variables with complete datasets were used as predictors without imputation. Incomplete data in 13 variables were imputed only for the internal purpose of the imputation model and these variables were used as

predictors thereafter. The data of three variables considered for multivariate analysis were used as predictors, and the datasets of these variables were completed using imputation.

8.1.2 Incomplete data: Secondary analysis

All 27 potential risk factors for the secondary endpoint and the outcome variable were analyzed. A summary of the data relevant to the secondary analysis is shown in Figure 7.

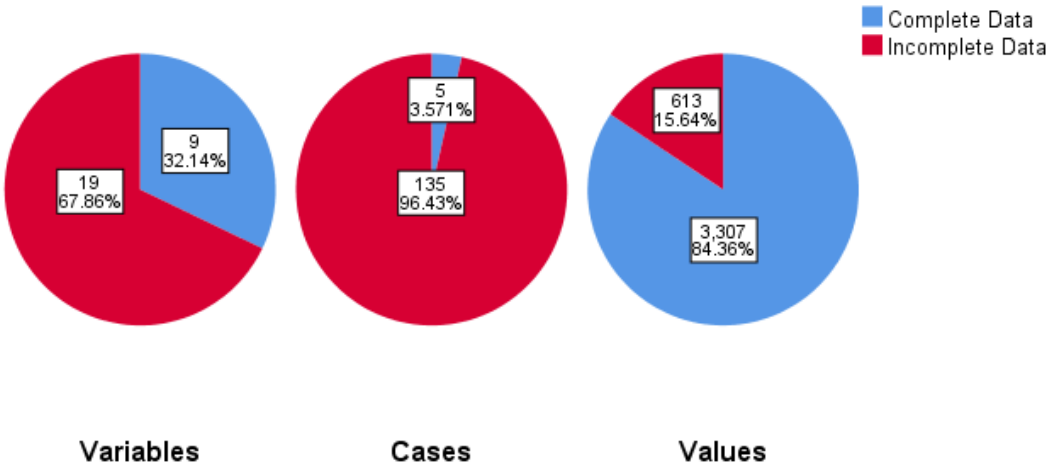


FIGURE 7. Incomplete data: secondary analysis.

The analysis showed that the datasets were incomplete in the majority of the variables and patients; however, only 15% of values were missing. A summary of the data with respect to the potential risk factors for secondary endpoint is shown in Table 6.

TABLE 6. Incomplete data: secondary analysis.

Variable	Missing		Available
	N	Value (%)	*N*
PVR	104	74.3	36
Oxygen saturation – SVC	100	71.4	40
Oxygen saturation – arterial	100	71.4	40
Q_p:Q_s ratio	99	70.7	41
PA mean pressure	74	52.9	66
Preoperative neo-AI grade (I – IV)	27	19.3	113
Death (stage II – stage III)	26	18.6	114
RVEDP	26	18.6	114
Postoperative TI grade (II+ - IV)	14	10.0	126
Postoperative impaired RV function	13	9.3	127
Endocardial fibroelastosis	9	6.4	131
Preoperative TI grade (II+ - IV)	3	2.1	137
AS/MS subtype	3	2.1	137
AS/MA subtype	3	2.1	137
AA/MS subtype	3	2.1	137
AA/MA subtype	3	2.1	137
Prematurity	3	2.1	137
Weight at stage II	2	1.4	138

TABLE 6. Incomplete data: secondary analysis (continued).

Preoperative impaired RV function	1	0.7	139

AA, aortic atresia; *AS*, aortic stenosis; *MA*, mitral atresia; *MS*, mitral stenosis; *neo-AI*, neo-aortic valve insufficiency; *PA*, pulmonary artery; *PVR*, pulmonary vascular resistance; Q_p, pulmonary blood flow; Q_s, systemic blood flow; *RV*, right ventricle; *RVEDP*, right ventricular end-diastolic pressure; *SVC*, superior vena cava; *TI*, tricuspid valve insufficiency.

The Little's MCAR test confirmed that the data were missing at random, and the data analysis showed no patterns. The results of the Little's MCAR test are shown in Table 7, and the data analysis is shown in Figure 8.

TABLE 7. Little's MCAR test: secondary analysis.

EM Means							
Weight at stage II (kg)	RVEDP (mmHg)	PA mean pressure (mmHg)	Q_p:Q_s ratio	PVR (dyn.s.cm^{-5})	Oxygen saturation – arterial (%)	Oxygen saturation – SVC (%)	Age at stage II (months)
5.187	8.632	14.682	0.97	186.412	72.033	44.410	4.261

Little's MCAR test: Chi-Square = 78.986, DF = 73, *P*-value = 0.296. *DF*, degrees of freedom; *EM*, expectation-maximization; *PA*, pulmonary artery; *PVR*, pulmonary vascular resistance; Q_p, pulmonary blood flow; Q_s, systemic blood flow; *RVEDP*, right ventricular end-diastolic pressure.

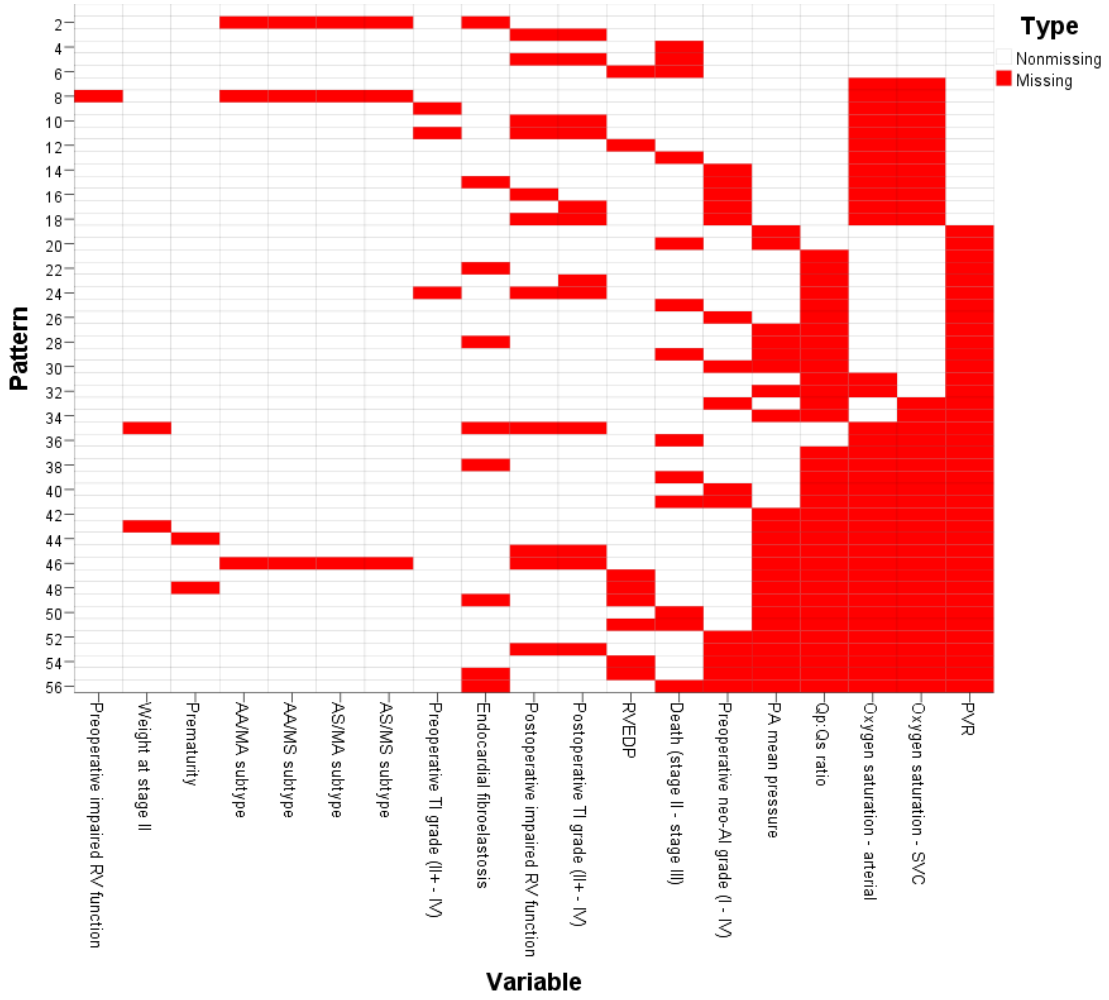


FIGURE 8. Patterns: secondary analysis. *AA*, aortic atresia; *AS*, aortic stenosis; *MA*, mitral atresia; *MS*, mitral stenosis; *neo-AI*, neo-aortic valve insufficiency; *PA*, pulmonary artery; *PVR*, pulmonary vascular resistance; Q_p, pulmonary blood flow; Q_s, systemic blood flow; *RV*, right ventricle; *RVEDP*, right ventricular end-diastolic pressure; *SVC*, superior vena cava; *TI*, tricuspid valve insufficiency.

The results based on the descriptive statistics were calculated from the available data. Univariate analysis was performed with listwise deletion, and only cases with available values for the selected variable were included. Imputation using single stochastic regression method was used to complete the datasets of variables considered for the multivariate analysis. Selected variables relevant to the secondary analysis, including the outcome variable, were used as predictors for imputation model. The imputation model is shown in Table 8.

TABLE 8. Imputation model: multivariate secondary analysis.

Variable	Role in imputation		Model type	Missing values	Imputed values
	Dependent variable	Predictor			
Death (stage II – stage III)	no	yes	Logistic regression	26	26*
Gender	no	yes	-	0	0

TABLE 8. Imputation model: multivariate secondary analysis (continued).

Prematurity	yes	yes	Logistic regression	3	3
Shunt type at Norwood	yes	yes	-	0	0
PA intervention after Norwood	no	yes	-	0	0
Neo-aorta intervention after Norwood	no	yes	-	0	0
AA/MA subtype	yes	yes	Logistic regression	3	3
Endocardial fibroelastosis	yes	yes	Logistic regression	9	9
PLSVC	no	yes	-	0	0
Postoperative TI grade (II+ - IV)	no	yes	Logistic regression	14	14*
Postoperative impaired RV function	yes	yes	Logistic regression	13	13
Age at stage II	no	yes	-	0	0
Early stage II	no	yes	-	0	0
PA augmentation during stage II	no	yes	-	0	0
TV intervention during stage II	no	yes	-	0	0

AA, aortic atresia; *MA*, mitral atresia; *PA*, pulmonary artery; *PLSVC*, persistent left superior vena cava; *RV*, right ventricle; *TI*, tricuspid valve insufficiency; *TV*, tricuspid valve. *Values were imputed only for internal purposes of the imputation model.

Of the 15 variables selected for the imputation model, nine variables with complete datasets were used as predictors without imputation. Incomplete data in two variables were imputed only for the internal purpose of the imputation model and these variables were used as predictors thereafter. The data of four variables considered for multivariate analysis were used as predictors, and the datasets of these variables were completed using imputation.

8.2 *Statistics*

Descriptive statistics were used to quantitatively summarize patients' characteristics. Univariate and multivariate inferential statistics were used to draw inferences about the entire population based on the results of the statistical tests. A survival analysis was used to analyze the survival in a time to event dependent manner. All statistical tests were two-sided whenever possible, and type I error was controlled at an α level 0.05. Analyses were performed with IBM SPSS Statistics version 23.0 (IBM, Armonk, NY, USA) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

8.2.1 Descriptive statistics

Distributions of potential risk factors were explored using histograms with box plots for continuous variables and contingency tables with pie charts for categorical variables. The data are presented as means with standard deviations for continuous variables with normal distributions, as medians with interquartile ranges for continuous variables with non-normal distributions, or as counts with percentages for categorical variables. The Shapiro-Wilk test and Q-Q plots were used to assess the normality of distributions.

8.2.2 Inferential statistics

Primary analysis: Time period between Norwood stage I and stage II procedures

A primary analysis was performed using univariate and multivariate analyses. Variables with missing data exceeding 10% or categorical variables with a frequency less than 5% were excluded from univariate and multivariate analyses to minimize the risk of model overdetermination.

A univariate analysis was performed to obtain initial estimates of the strength of the association between the primary endpoint and each variable. Continuous variables were analyzed using the non-parametric Mann-Whitney U-Test for two independent samples. Categorical variables were analyzed employing Fisher's exact test. Variables with a *P*-value ≤ 0.2 in univariate analysis or variables significantly associated with the outcome, based on the literature review, were considered for the multivariate analysis.

A multivariate analysis was performed using generalized linear models with a Bernoulli distribution. Assumptions for a binary logistic regression were tested in all variables considered for multivariate modeling, as appropriate: (1) continuous independent variables were tested for outliers setting the g-multiplier at 2.2, and the Shapiro–Wilk test and Q-Q plots were used to assess the normality of the variables' distribution; (2) multicollinearity was examined using point-biserial correlation, and Levene's test of homoscedasticity was used to assess the homogeneity of variance among the groups. Variables with a *P*-value ≤ 0.05 in the univariate analysis and variables considered for multivariate modeling based on the literature review were used to create the first model. This model was used as a core model and additional models were generated adding the other potential risk factors based on a univariate analysis (*P*-value ≤ 0.2) and their combinations, respectively; and (3) a linearity assumption between each continuous independent variable and the logit of the probability of the dependent variable was tested in each of the generated models using the Box-Tidwell transformation.

For each of the models, the accuracy of probabilistic prediction (Brier Score) and the discriminatory ability were calculated. Two models with the best Brier Score and AUC-values (*AUC*, area under the curve) were evaluated using the concordance index and Somers' D_{xy} rank correlation index. Model optimism was quantified using bootstrapping (n = 1,000 bootstrap samples) for both of the models, and calibration curves were constructed. Final model selection was based on overfitting-corrected estimates of predictive accuracy indices. Due to the limited sample size and to address the issue of separation, Firth's penalized likelihood correction was applied to the final model. Internal validation was performed using bootstrapping (n = 10,000 bootstrap samples) yielding a bootstrap inclusion fraction for each of the variables.

Secondary analysis: Time period between stage II and stage III procedures

A secondary analysis was performed using univariate and multivariate analyses. Variables with missing data exceeding 10% or categorical variables with a frequency less than 5%

were excluded from univariate and multivariate analyses to minimize the risk of model overdetermination.

A competing risk analysis was used to evaluate potential risk factors associated with mortality between the stage II and stage III procedures. After the stage II surgery, all patients were either alive and remained in this transition state, or they proceeded over time to one of the two competing and mutually exclusive end-states: death or stage III surgery. Each of the end-states was parametrically modeled using the maximum-likelihood estimates to resolve the risk distribution of time to event based on multiple overlapping phases of risk. No patient had received a heart transplantation before the time of the analysis. At any point in time, the sum of the percentages of patients in the transition state and in each of the end-states was 100%.

A univariate analysis was performed using a parametric survival regression model based on the maximum-likelihood estimates. Variables with a *P*-value ≤ 0.2 in a univariate analysis were considered for the multivariate analysis.

A multivariate analysis was performed using a parametric survival regression model based on the maximum-likelihood estimates. The effects of covariates on the probability of end-states are given as a hazard ratio with 95% confidence interval.

8.2.3 Survival analysis

Tertiary analysis: Survival analysis after the Norwood procedure

Survival analysis for the entire cohort after the Norwood procedure was performed using the non-parametric Kaplan-Meier estimator.

CHAPTER III: RESULTS

9 Time period between Norwood stage I and stage II

The stage I cohort included 176 children who underwent the Norwood stage I procedure and proceeded to the post-Norwood period. One hundred-forty children survived to the stage II procedure and 36 children died between the Norwood stage I and stage II procedures.

9.1 *Patients' characteristics: Primary analysis*

The distribution of patients' demographic, clinical, and anatomic/echocardiographic characteristics and operative details were examined in each of the three groups: (A) stage I cohort, (B) survivors to the stage II procedure, and (C) non-survivors to the stage II procedure. The values were calculated from available data.

9.1.1 Demographic parameters

Gender

The stage I cohort was comprised of 125 males and 51 females. One hundred and two males and 38 females survived to the stage II procedure, but 23 males and 13 females died between the Norwood stage I and stage II procedures. Percentages of gender distributions among these groups are shown in Figure 9.

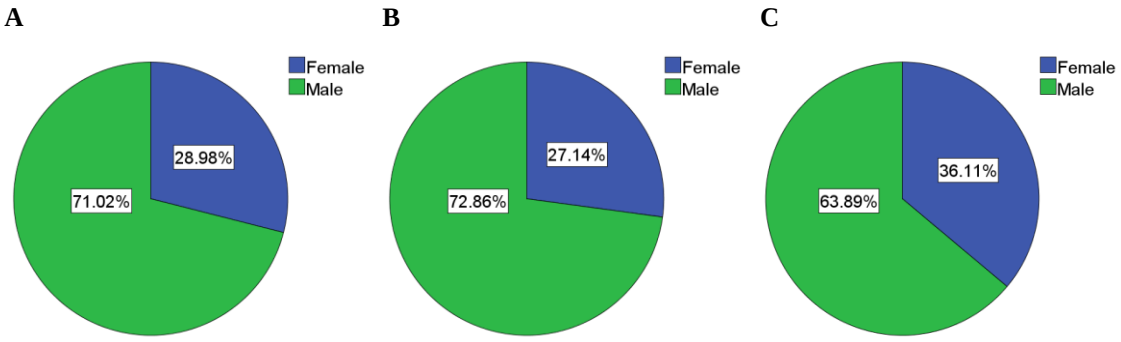


FIGURE 9. Primary analysis: Gender. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

Birth weight

The mean birth weight for the stage I cohort was 3.2 ± 0.5 kg. The mean birth weight in survivors to the stage II procedure was 3.2 ± 0.5 kg. The mean birth weight in patients who died between the Norwood stage I and stage II procedures was 3.0 ± 0.5 kg. Distributions of birth weights among these groups are shown in Figure 10.

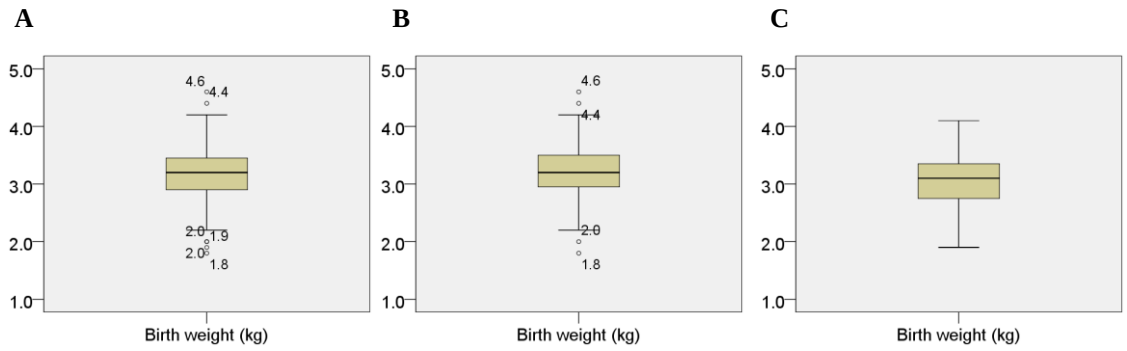


FIGURE 10. Primary analysis: Birth weight. (A) Stage I cohort (N = 175), Shapiro-Wilk test: *P*-value = 0.161. (B) Survivors to stage II (N = 139), Shapiro-Wilk test: *P*-value = 0.272. (C) Non-survivors to stage II (N = 36), Shapiro-Wilk test: *P*-value = 0.406.

Birth weight ≤ 2.5 kg

In the stage I cohort, 13 patients were born at or weighing less than 2.5 kg. Six of these patients survived to the stage II procedure, but seven patients died between the Norwood stage I and stage II procedures. Percentages of birth weights less than or equal to 2.5 kg among these groups are shown in Figure 11.

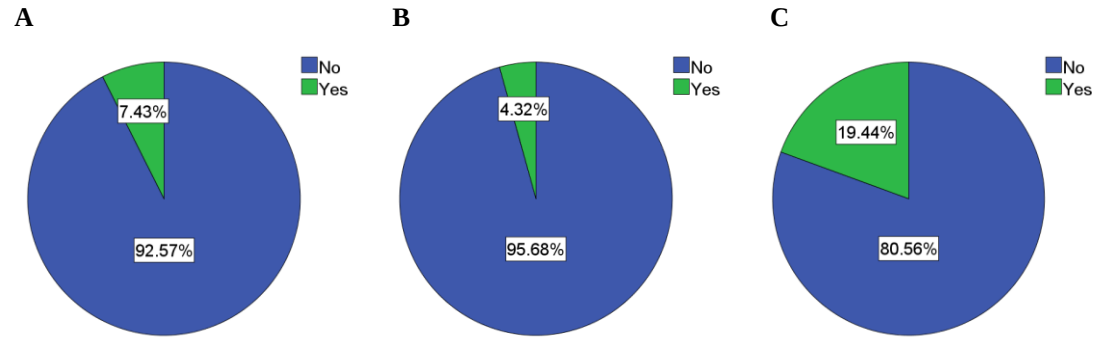


FIGURE 11. Primary analysis: Birth weight ≤ 2.5 kg. (A) Stage I cohort (N = 175). (B) Survivors to stage II (N = 139). (C) Non-survivors to stage II (N = 36).

Gestational age

The median gestational age for the stage I cohort was 39.0 ± 2.0 weeks. The median gestational age in survivors to the stage II procedure was 39.0 ± 1.3 weeks. The median gestational age in patients who died between the Norwood stage I and stage II procedures was 39.0 ± 2.3 weeks. Distributions of gestational ages among these groups are shown in Figure 12.

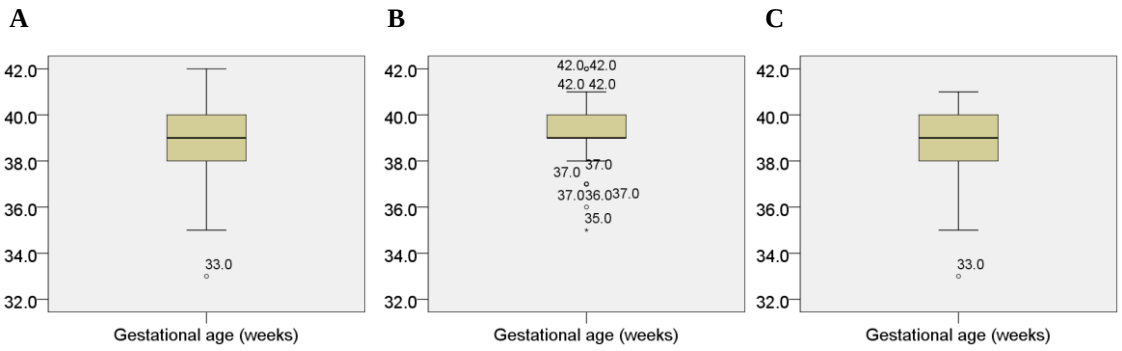


FIGURE 12. Primary analysis: Gestational age. (A) Stage I cohort (N = 140), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage II (N = 110), Shapiro-Wilk test: *P*-value < 0.001. (C) Non-survivors to stage II (N = 30), Shapiro-Wilk test: *P*-value = 0.009.

Prematurity

In the stage I cohort, 20 patients were born prematurely. Thirteen of them survived to the stage II procedure, while seven patients died between the Norwood stage I and stage II procedures. Percentages of premature births among these groups are shown in Figure 13.

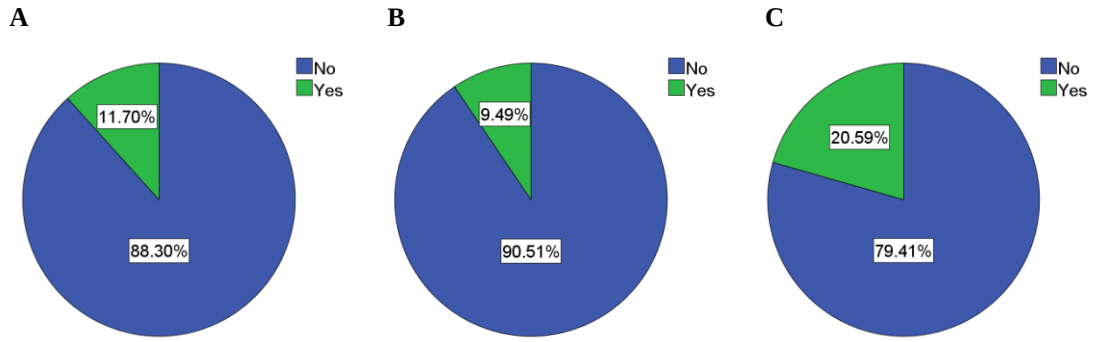


FIGURE 13. Primary analysis: Prematurity. (A) Stage I cohort (N = 171). (B) Survivors to stage II (N = 137). (C) Non-survivors to stage II (N = 34).

9.1.2 Clinical parameters

Preoperative cardiopulmonary resuscitation

Seven patients of the stage I cohort underwent cardiopulmonary resuscitation before the Norwood procedure. Five survived to the stage II procedure, but two patients died between the Norwood stage I and stage II procedures. Percentages of patients who underwent cardiopulmonary resuscitation before the Norwood procedure among these groups are shown in Figure 14.

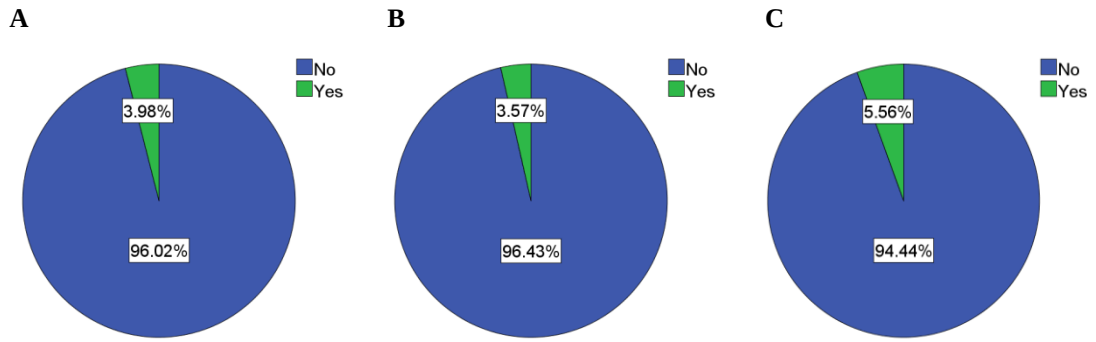


FIGURE 14. Primary analysis: Preoperative cardiopulmonary resuscitation. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

Preoperative catheter-based septal intervention

Four patients of the stage I cohort underwent catheter-based septal intervention before the Norwood procedure. One patient survived to the stage II procedure, but three patients died between the Norwood stage I and stage II procedures. Percentages of patients who underwent catheter-based septal intervention before the Norwood procedure among these groups are shown in Figure 15.

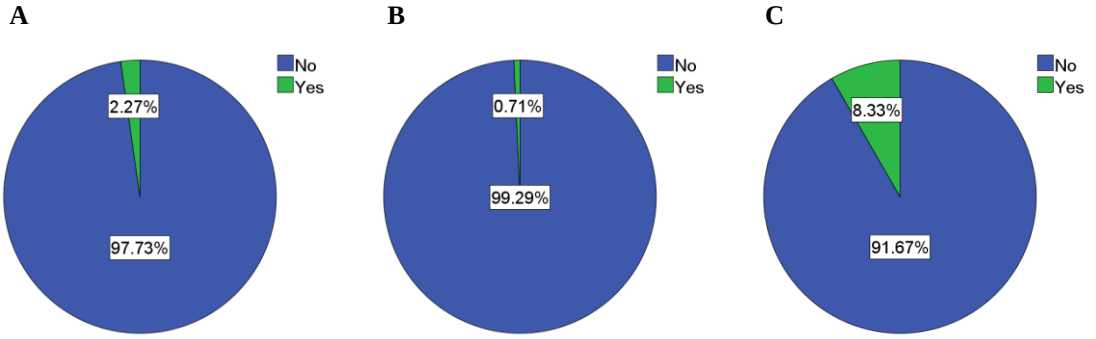


FIGURE 15. Primary analysis: Preoperative catheter-based septal intervention. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

Preoperative mechanical ventilation

Sixty-four patients of the stage I cohort required mechanical ventilation before the Norwood procedure. Fifty-one patients survived to the stage II procedure, but 13 patients died between the Norwood stage I and stage II procedures. Percentages of patients who required mechanical ventilation before the Norwood procedure among these groups are shown in Figure 16.

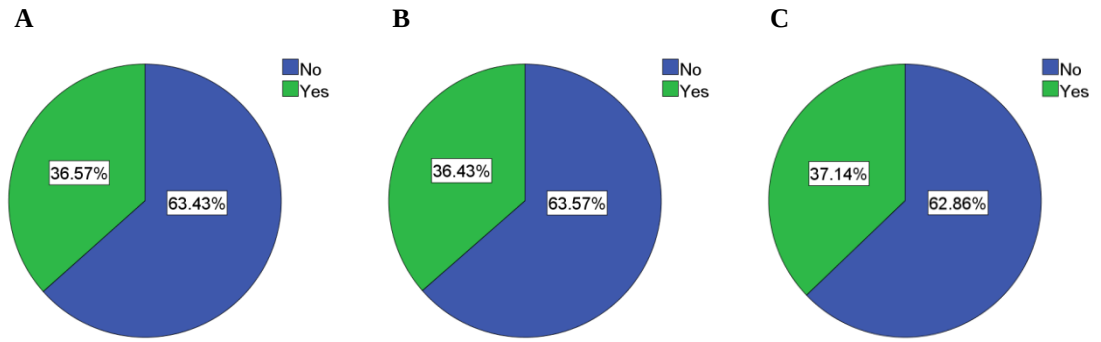


FIGURE 16. Primary analysis: Preoperative mechanical ventilation. (A) Stage I cohort (N = 175). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 35).

9.1.3 Anatomic/echocardiographic parameters

Hypoplastic left heart syndrome–forme fruste

Hypoplastic left heart syndrome-forme fruste was present in four patients of the stage I cohort. Three patients survived to the stage II procedure, but one patient died between the Norwood stage I and stage II procedures. Percentages of patients with HLHS-forme fruste among these groups are shown in Figure 17.

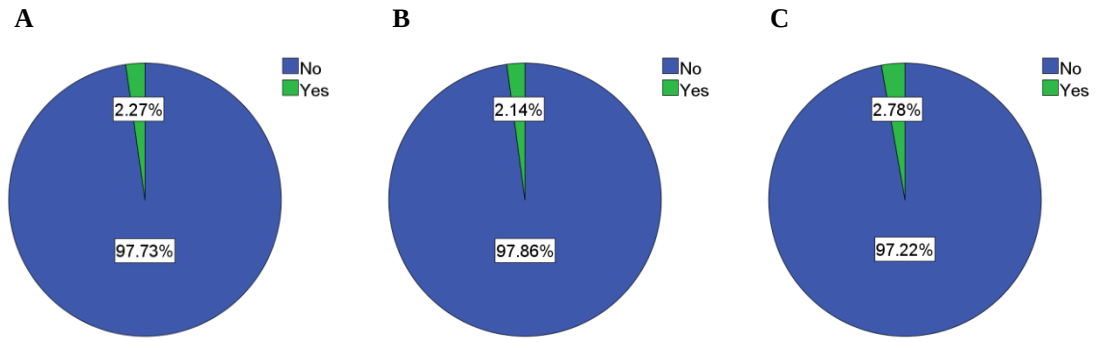


FIGURE 17. Primary analysis: Hypoplastic left heart syndrome–forme fruste. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

Hypoplastic left heart syndrome subtypes

Of the stage I cohort, aortic atresia and mitral atresia was present in 57 patients, aortic atresia and mitral stenosis in 47 patients, aortic stenosis and mitral atresia in 13 patients, and aortic stenosis and mitral stenosis in 55 patients. In survivors to the stage II procedure, aortic atresia and mitral atresia was present in 45 patients, aortic atresia and mitral stenosis was present in 37 patients, aortic stenosis and mitral atresia was present in 10 patients, and aortic stenosis and mitral stenosis was present in 45 patients. In patients who died between the Norwood stage I and stage II procedures, aortic atresia and mitral atresia was present in 12 patients, aortic atresia and mitral stenosis was present in 10 patients, aortic stenosis and mitral atresia was present in three patients, and aortic stenosis and mitral stenosis was present in 10 patients. Percentages of patients with different HLHS subtypes among these groups are shown in Figure 18.

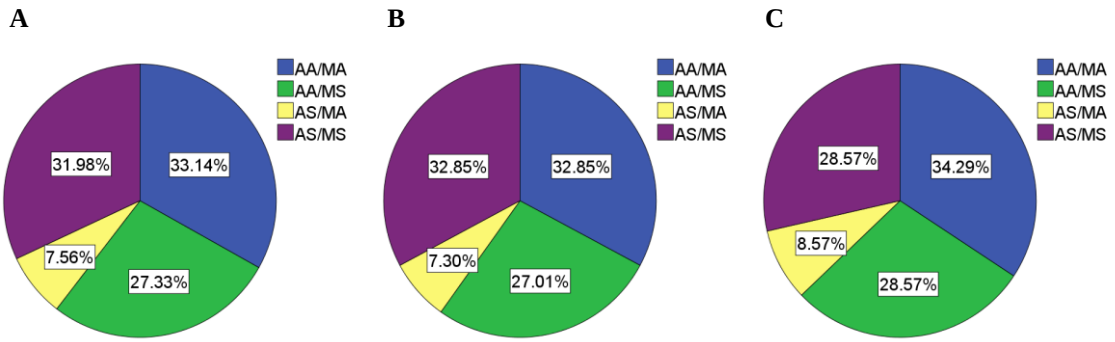


FIGURE 18. Primary analysis: Hypoplastic left heart syndrome subtypes. (A) Stage I cohort (N = 172). (B) Survivors to stage II (N = 137). (C) Non-survivors to stage II (N = 35). *AA*, aortic atresia; *AS*, aortic stenosis; *MA*, mitral atresia; *MS*, mitral stenosis.

Anomalous pulmonary vein connection

Anomalous pulmonary vein connection was present in 10 patients of the stage I cohort. Six patients survived to the stage II procedure, but four patients died between the Norwood stage I and stage II procedures. Percentages of patients with an anomalous pulmonary vein connection among these groups are shown in Figure 19.

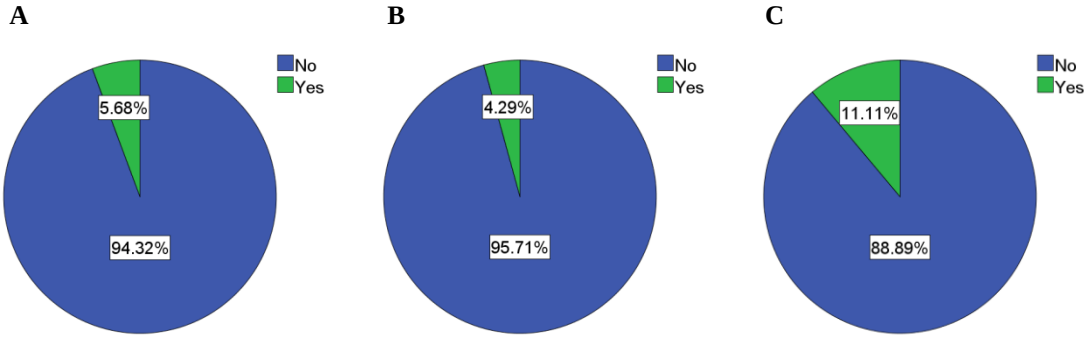


FIGURE 19. Primary analysis: Anomalous pulmonary vein connection. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

Ventricular septal defect

A ventricular septal defect was present in 34 patients of the stage I cohort. Twenty-six patients survived to the stage II procedure, but eight patients died between the Norwood stage I and stage II procedures. Percentages of patients with a ventricular septal defect among these groups are shown in Figure 20.

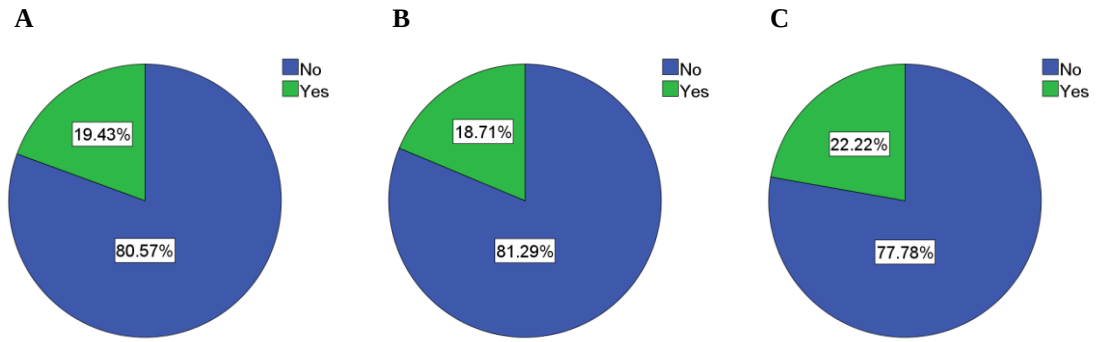


FIGURE 20. Primary analysis: Ventricular septal defect. (A) Stage I cohort (N = 175). (B) Survivors to stage II (N = 139). (C) Non-survivors to stage II (N = 36).

Endocardial fibroelastosis

Endocardial fibroelastosis of the left ventricle was present in 47 patients of the stage I cohort. Thirty-five patients survived to the stage II procedure, but 12 patients died between the Norwood stage I and stage II procedures. Percentages of patients with an endocardial fibroelastosis of the left ventricle among these groups are shown in Figure 21.

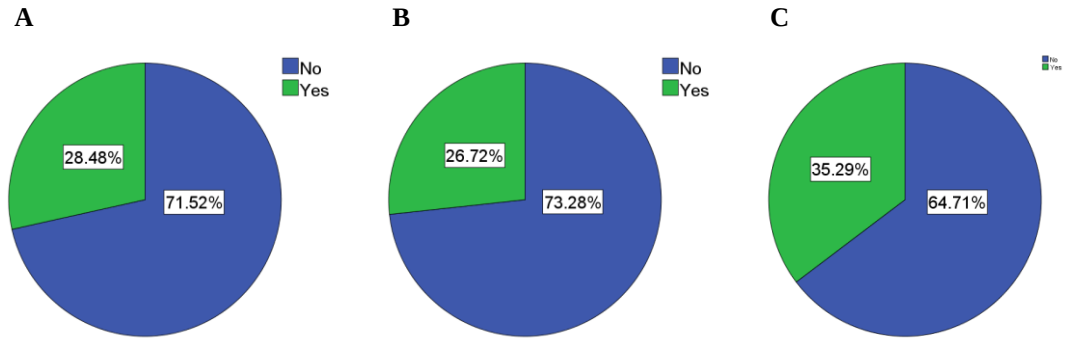


FIGURE 21. Primary analysis: Endocardial fibroelastosis. (A) Stage I cohort (N = 165). (B) Survivors to stage II (N = 131). (C) Non-survivors to stage II (N = 34).

Restrictive atrial septal defect

A restrictive atrial septal defect was present in 76 patients of the stage I cohort. Fifty-eight patients survived to the stage II procedure, but 18 patients died between the Norwood stage I and stage II procedures. Percentages of patients with a restrictive atrial septal defect among these groups are shown in Figure 22.

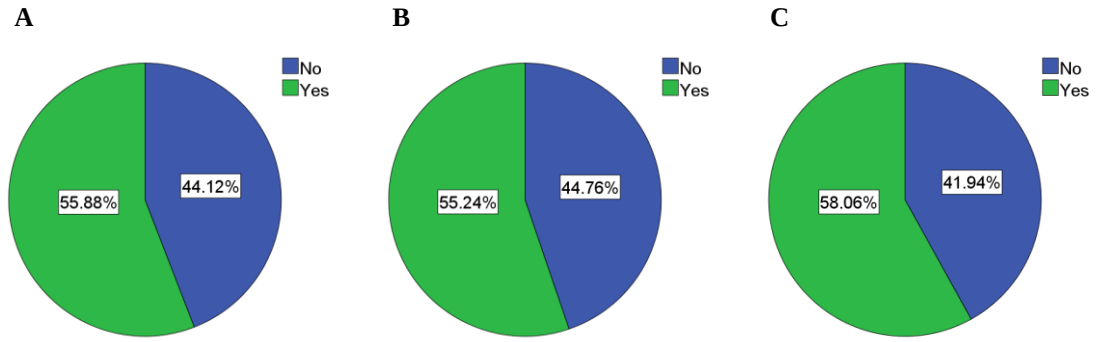


FIGURE 22. Primary analysis: Restrictive atrial septal defect. (A) Stage I cohort (N = 136). (B) Survivors to stage II (N = 105). (C) Non-survivors to stage II (N = 31).

Ascending aorta diameter

The median ascending aorta diameter for the stage I cohort was 3.0 ± 2.9 mm. The median ascending aorta diameter in survivors to the stage II procedure was 3.0 ± 2.5 mm. The median ascending aorta diameter in patients who died between the Norwood stage I and stage II procedures was 2.8 ± 4.0 mm. Distributions of ascending aorta diameters among these groups are shown in Figure 23.

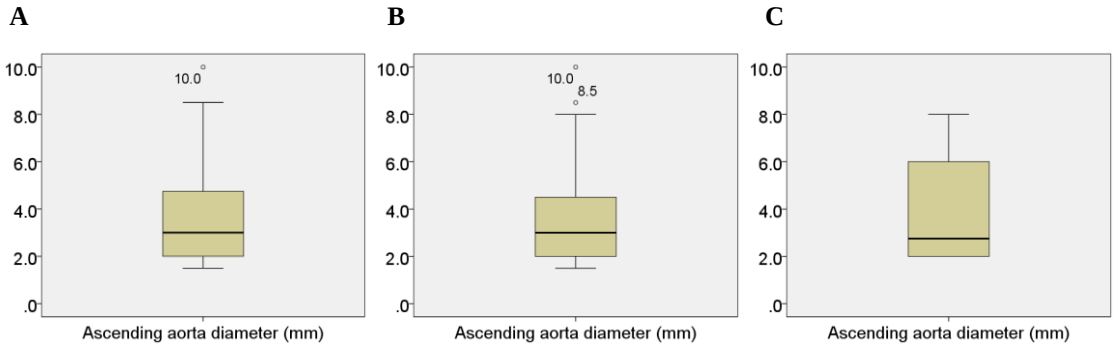


FIGURE 23. Primary analysis: Ascending aorta diameter. (A) Stage I cohort (N = 168), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage II (N = 132), Shapiro-Wilk test: *P*-value < 0.001. (C) Non-survivors to stage II (N = 36), Shapiro-Wilk test: *P*-value < 0.001.

Ascending aorta diameter ≤ 2 mm

In 47 patients of the stage I cohort, the diameter of the ascending aorta was less or equal to 2 mm. Thirty-six patients survived to the stage II procedure, but 11 patients died between the Norwood stage I and stage II procedures. Percentages of patients with ascending aorta diameter less than or equal to 2 mm among these groups are shown in Figure 24.

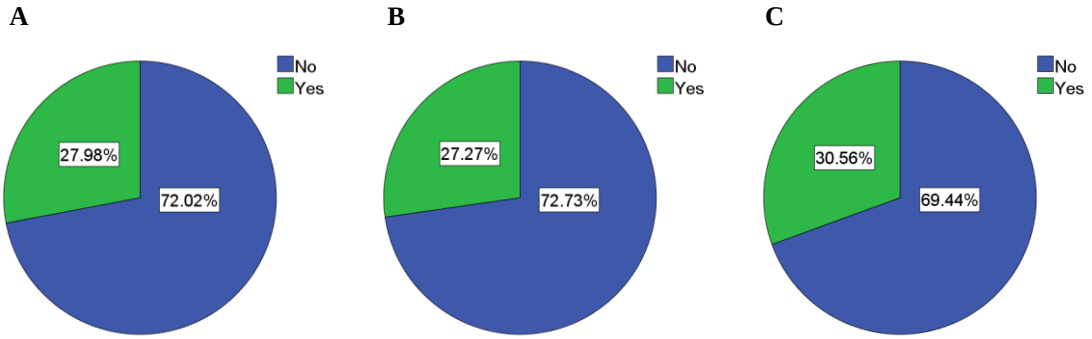


FIGURE 24. Primary analysis: Ascending aorta diameter ≤ 2 mm. (A) Stage I cohort (N = 168). (B) Survivors to stage II (N = 132). (C) Non-survivors to stage II (N = 36).

Preoperative pulmonary valve insufficiency grades I - IV

A pulmonary valve insufficiency grades I - IV was present in 19 patients of the stage I cohort before the Norwood procedure. Seventeen patients survived to the stage II procedure, but two patients died between the Norwood stage I and stage II procedures. Percentages of patients with pulmonary valve insufficiency grades I – IV before the Norwood procedure among these groups are shown in Figure 25.

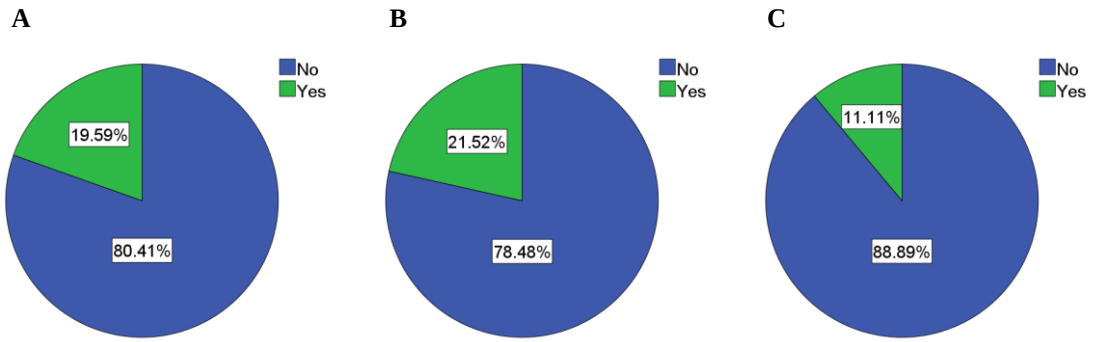


FIGURE 25. Primary analysis: Preoperative pulmonary valve insufficiency grades I – IV. (A) Stage I cohort (N = 97). (B) Survivors to stage II (N = 79). (C) Non-survivors to stage II (N = 18).

Preoperative tricuspid valve insufficiency grades II+ - IV

A tricuspid valve insufficiency grades II+ - IV was present in nine patients of the stage I cohort before the Norwood procedure. Eight patients survived to the stage II procedure, but one patient died between the Norwood stage I and stage II procedures. Percentages of patients with tricuspid valve insufficiency grades II+ - IV before the Norwood procedure among these groups are shown in Figure 26.

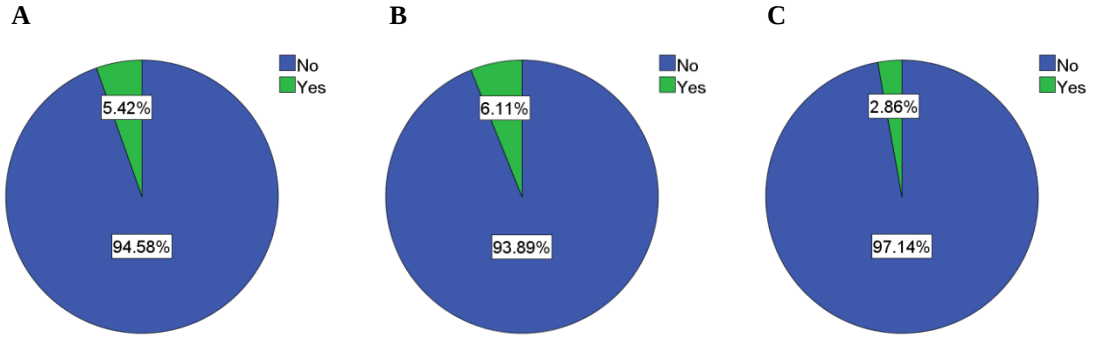


FIGURE 26. Primary analysis: Preoperative tricuspid valve insufficiency grades II+ - IV. (A) Stage I cohort (N = 166). (B) Survivors to stage II (N = 131). (C) Non-survivors to stage II (N = 35).

Postoperative tricuspid valve insufficiency grades II+ - IV

A tricuspid valve insufficiency grades II+ - IV was present in 21 patients of the stage I cohort after the Norwood procedure. Sixteen patients survived to the stage II procedure, but five patients died between the Norwood stage I and stage II procedures. Percentages of patients with tricuspid valve insufficiency grades II+ - IV after the Norwood procedure among these groups are shown in Figure 27.

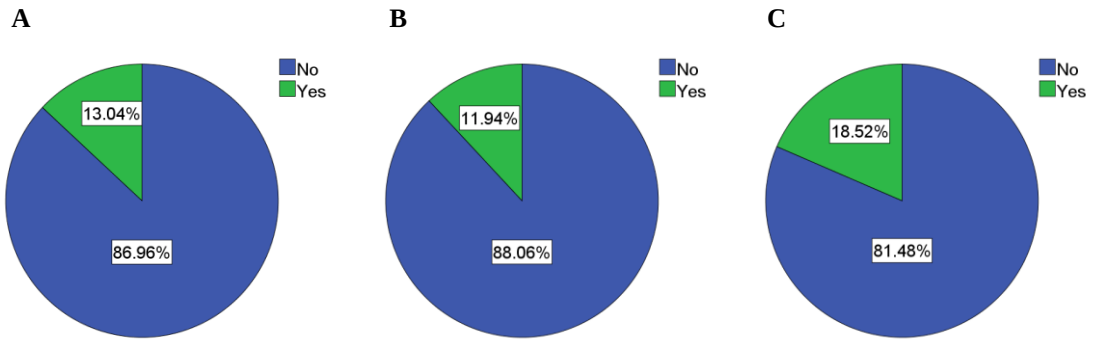


FIGURE 27. Primary analysis: Postoperative tricuspid valve insufficiency grades II+ - IV. (A) Stage I cohort (N = 161). (B) Survivors to stage II (N = 134). (C) Non-survivors to stage II (N = 27).

Preoperative impaired right ventricular function

The right ventricular function was impaired in nine patients of the stage I cohort before the Norwood procedure. All nine patients survived to the stage II procedure. Percentages of patients with an impaired right ventricular function before the Norwood procedure among these groups are shown in Figure 28.

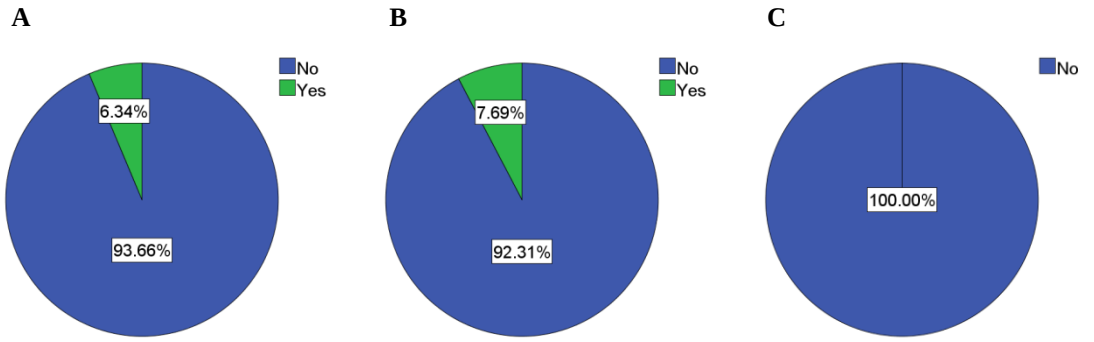


FIGURE 28. Primary analysis: Preoperative impaired right ventricular function. (A) Stage I cohort (N = 142). (B) Survivors to stage II. (N = 117). (C) Non-survivors to stage II (N = 25).

Postoperative impaired right ventricular function

The right ventricular function was impaired in 22 patients of the stage I cohort after the Norwood procedure. Fourteen patients survived to the stage II procedure, but eight patients died between the Norwood stage I and stage II procedures. Percentages of patients with an impaired right ventricular function after the Norwood procedure among these groups are shown in Figure 29.

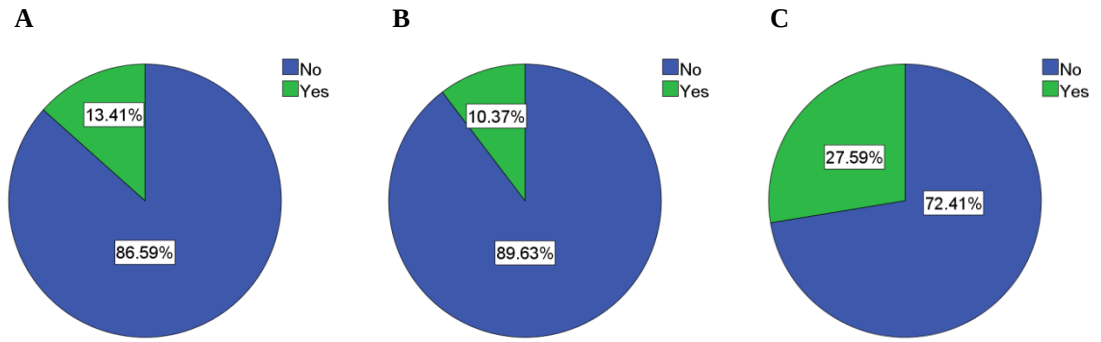


FIGURE 29. Primary analysis: Postoperative impaired right ventricular function. (A) Stage I cohort (N = 164). (B) Survivors to stage II (N = 135). (C) Non-survivors to stage II (N = 29).

9.1.4 Operative parameters

Age at the Norwood procedure

The median age at the Norwood procedure for the stage I cohort, as well as in patients who survived to the stage II procedure, was 8.0 ± 4.0 days. The median age in patients who died between the Norwood stage I and stage II procedures was 7.0 ± 5.8 days. Distributions of ages at the Norwood procedure among these groups are shown in Figure 30.

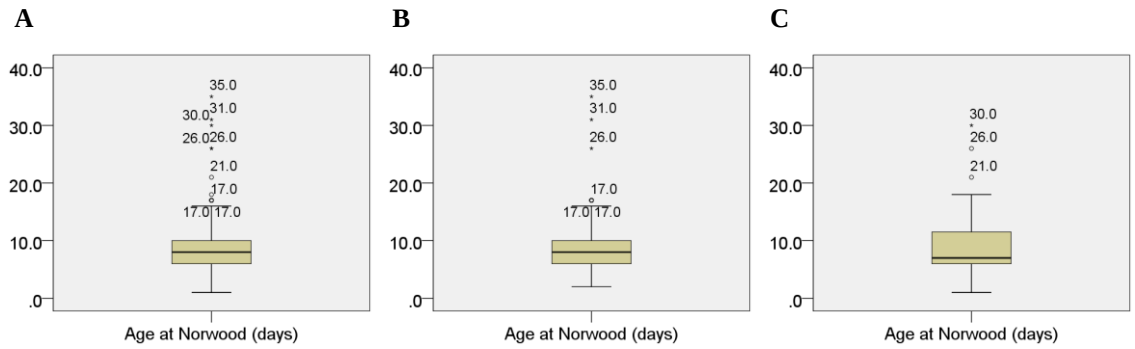


FIGURE 30. Primary analysis: Age at the Norwood procedure. (A) Stage I cohort (N = 176), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage II (N = 140), Shapiro-Wilk test: *P*-value < 0.001. (C) Non-survivors to stage II (N = 36), Shapiro-Wilk test: *P*-value < 0.001.

Shunt type at the Norwood procedure

A systemic shunt was used in 77 patients, and a right ventricle-to-pulmonary artery conduit was used in 99 patients of the stage I cohort. Fifty-six patients with a systemic shunt and 84 patients with a right ventricular-to-pulmonary conduit survived to the stage II procedure. Twenty-one patients with a systemic shunt, and 15 patients with a right ventricular-to-pulmonary artery conduit died between the Norwood stage I and stage II procedures. Percentages of patients with systemic shunts or right ventricle-to-pulmonary artery conduits among these groups are shown in Figure 31.

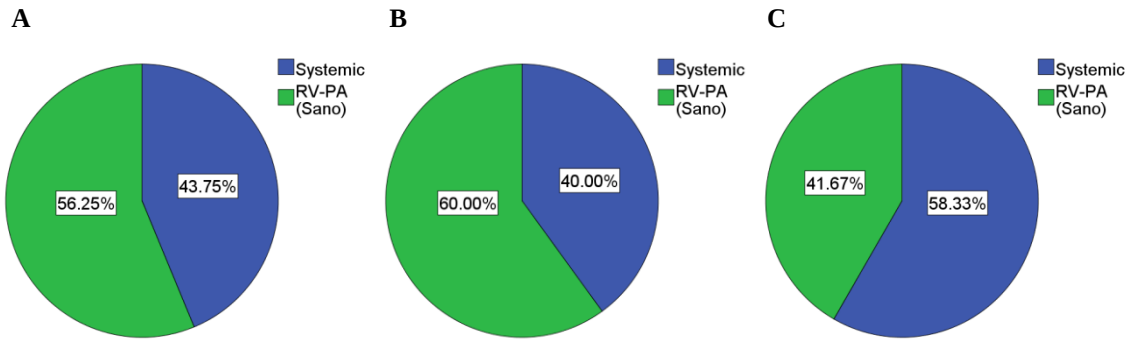


FIGURE 31. Primary analysis: Shunt type at the Norwood procedure. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36). *RV-PA*, right ventricle-to-pulmonary artery.

Shunt revision during the Norwood procedure

Fourteen patients of the stage I cohort underwent a shunt revision during the Norwood procedure. Nine patients survived to the stage II procedure, but five patients died between the Norwood stage I and stage II procedures. Percentages of patients who underwent shunt revision during the Norwood procedure among these groups are shown in Figure 32.

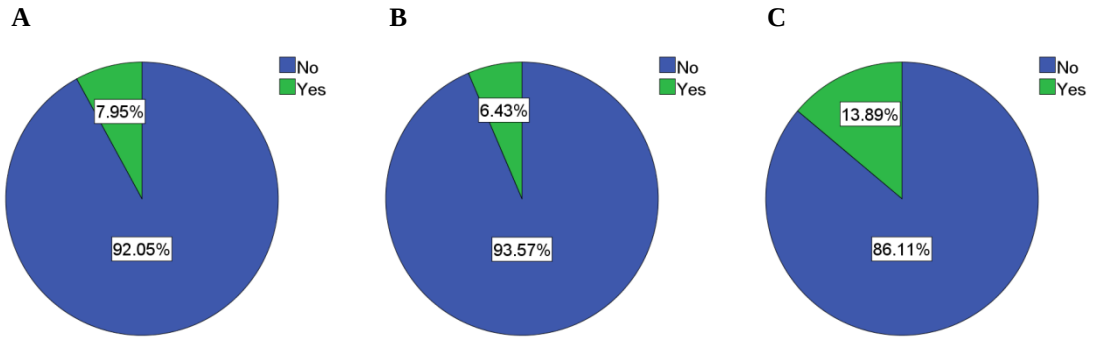


FIGURE 32. Primary analysis: Shunt revision during the Norwood procedure. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

Neo-aorta revision during the Norwood procedure

Five patients of the stage I cohort underwent a neo-aorta revision during the Norwood procedure. Four patients survived to the stage II procedure, but one patient died between the Norwood stage I and stage II procedures. Percentages of patients who underwent neo-aorta revision during the Norwood procedure among these groups are shown in Figure 33.

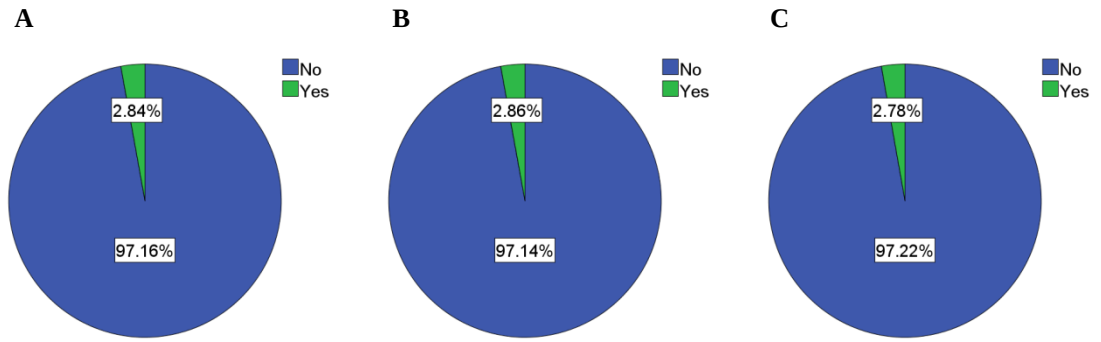


FIGURE 33. Primary analysis: Neo-aorta revision during the Norwood procedure. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

Deep hypothermic circulatory arrest

The median duration of the deep hypothermic circulatory arrest for the stage I cohort was 44.0 ± 14.8 minutes. The median duration of the deep hypothermic circulatory arrest in survivors to the stage II procedure was 42.5 ± 14.0 minutes. The mean duration of the deep hypothermic circulatory arrest in patients who died between the Norwood stage I and stage II procedures was 46.8 ± 10.5 minutes. Distributions of durations of the deep hypothermic circulatory arrest among these groups are shown in Figure 34.

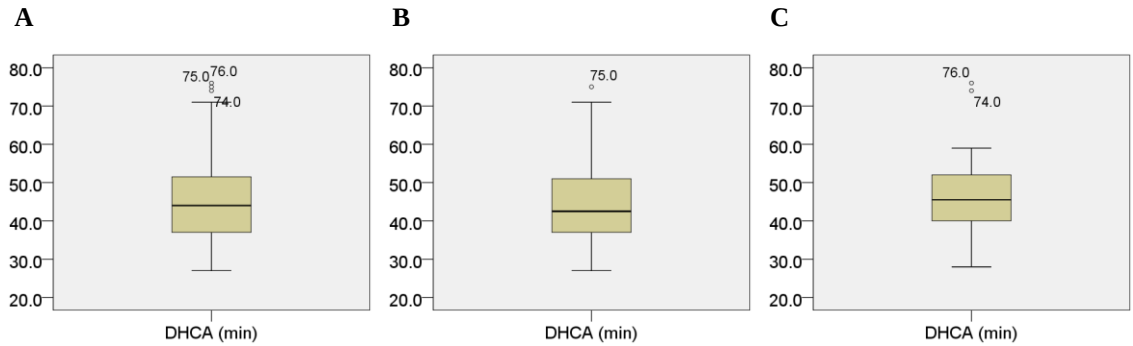


FIGURE 34. Primary analysis: Deep hypothermic circulatory arrest. (A) Stage I cohort (N = 168), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage II (N = 134), Shapiro-Wilk test: *P*-value = 0.002. (C) Non-survivors to stage II (N = 34), Shapiro-Wilk test: *P*-value = 0.071.

Lowest temperature during the Norwood procedure

The median lowest temperature during the Norwood procedure for the stage I cohort was 18.8 ± 2.0°C. The median lowest temperature during the Norwood procedure in survivors to the stage II procedure was 18.7 ± 2.0°C. The median lowest temperature during the Norwood procedure in patients who died between the Norwood stage I and stage II procedures was 19.0 ± 2.0°C. Distributions of lowest temperatures during the Norwood procedure among these groups are shown in Figure 35.

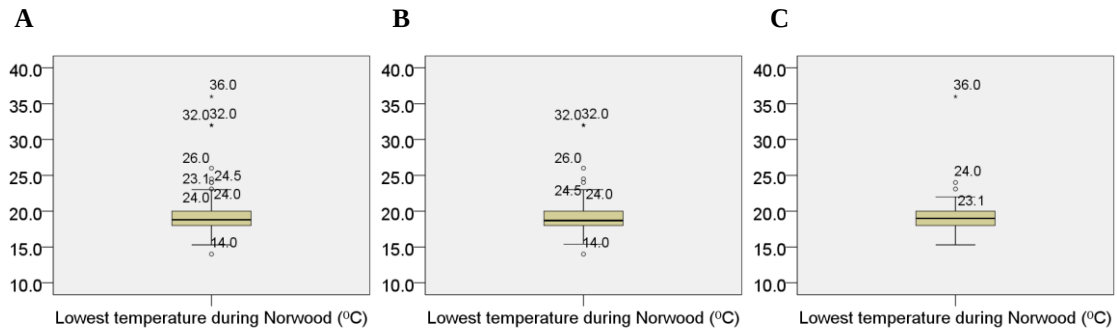


FIGURE 35. Primary analysis: Lowest temperature during the Norwood procedure. (A) Stage I cohort (N = 167), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage II (N = 132), Shapiro-Wilk test: *P*-value < 0.001. (C) Non-survivors to stage II (N = 35), Shapiro-Wilk test: *P*-value < 0.001.

Concomitant cardiac surgery

Seven patients of the stage I cohort underwent concomitant cardiac surgery during the Norwood procedure. The anomalous pulmonary vein connection was corrected in five patients, the aberrant left subclavian artery was corrected in one patient, and the anomalous left coronary artery arising from the pulmonary artery was corrected in one patient. Three patients survived to the stage II procedure, but four patients died between the Norwood stage I and stage II procedures. Percentages of patients who underwent concomitant cardiac surgery during the Norwood procedure among these groups are shown in Figure 36.

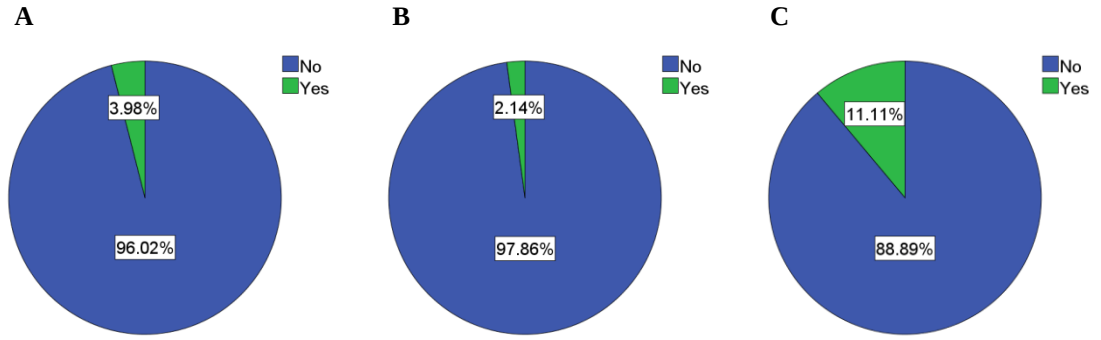


FIGURE 36. Primary analysis: Concomitant cardiac surgery. (A) Stage I cohort (N = 176). (B) Survivors to stage II (N = 140). (C) Non-survivors to stage II (N = 36).

9.2 *Mortality between Norwood stage I and stage II*

Twenty-one patients (11.9%) died in the first 30 days after the Norwood procedure. Twenty-six patients (14.8%) died during the hospitalization following the Norwood procedure. Late mortality, defined as death after 30 days but before the stage II procedure, occurred in 15 patients (8.5%). Altogether, 36 patients died between the Norwood stage I and stage II procedures, resulting in an overall mortality rate of 20.5%. Causes of death in the early and late periods between the Norwood stage I and stage II procedures are summarized in Table 9.

TABLE 9. Cause of death: Norwood - stage II.

Cause of death	Early period (≤ 30 days)	Late period (> 30 days)	Norwood – stage II (total)
Acute heart failure	18	9	27
Obstruction of the pulmonary blood flow	4	3	7
Coronary malperfusion	1	0	1
Unknown	13	6	19
Chronic heart failure	0	0	0
Cerebro-vascular event	1	0	1
ARDS	1	0	1
Sepsis	1	1	2
Unknown	0	5	5

ARDS, adult respiratory distress syndrome.

9.3 *Risk factors for mortality between Norwood stage I and stage II*

9.3.1 Univariate analysis: Primary endpoint

Seventeen potential risk factors for mortality between the Norwood stage I and stage II procedures met the inclusion criteria for a univariate analysis, consisting of 12 categorical variables and five continuous variables. Six met the screening criteria for statistical association: birth weight (*P*–value = 0.085), prematurity (*P*–value = 0.080), anomalous pulmonary vein connection (*P*–value = 0.123), postoperative impaired right ventricular function (*P*–value = 0.030), shunt type implanted during the Norwood procedure (*P*–value = 0.060), and shunt revision during the Norwood procedure (*P*–value = 0.166). The results of the univariate analysis are summarized in Table 10.

TABLE 10. Results: univariate primary analysis.

Variable	Categorical variables		Continuous variables
	χ^2 test	Fisher's exact test	Mann-Whitney U-Test
Demographic parameters			
Gender	0.308	0.308	-
Birth weight (kg)	-	-	0.085
Prematurity	0.080†	0.080	-
Clinical parameters			
Preoperative mechanical ventilation	1.000	1.000	-
Anatomic/echocardiographic parameters			
HLHS subtypes:			-
AA/MA	0.872	1.000	
AA/MS	0.853	0.835	
AS/MA	0.799†	0.729	
AS/MS	0.628	0.689	
APVC	0.217†	0.123	-
VSD	0.640	0.640	-
Endocardial fibroelastosis	0.394	0.394	-

TABLE 10. Results: univariate primary analysis (continued).

Ascending aorta diameter (mm)	-	-	0.905
Preoperative TI grade (II+ - IV)	0.686	0.686	-
Postoperative TI grade (II+ - IV)	0.532†	0.354	-
Postoperative impaired RV function	0.020†	0.030	-
Operative parameters			
Age at Norwood (days)	-	-	0.816
Shunt type at Norwood	0.060	0.060	-
Shunt revision during Norwood	0.166†	0.166	-
DHCA (min)	-	-	0.240
Lowest temperature during Norwood (°C)	-	-	0.485

AA, aortic atresia; *APVC*, anomalous pulmonary vein connection; *AS*, aortic stenosis; *DHCA*, deep hypothermic circulatory arrest; *HLHS*, hypoplastic left heart syndrome; *MA*, mitral atresia; *MS*, mitral stenosis; *RV*, right ventricle; *VSD*, ventricular septal defect; *TI*, tricuspid valve insufficiency. †1 cell (25.0%) had expected count less than 5.

9.3.2 Assumptions for multivariate analysis

Outlier assumption

Birth weight, the only continuous variable considered for a multivariate analysis, was tested using the outlier labeling rule, setting g-multiplier to 2.2 (Hoaglin *et al.*, 1986). The calculated lower and upper cut-off value defined the outlier intervals: (0; 1.6} , {4.8; ∞). The minimal and maximal birth weight values were outside the intervals and thereby confirmed that outliers were not present. A normal distribution of birth weight values was confirmed (Shapiro-Wilk test, *P*-value = 0.161).

Multicollinearity assumption

Possible associations between independent variables were examined using correlation coefficients. Bivariate correlation analyses performed between birth weight and gestational age, and between birth weight and prematurity, showed positive (ρ = 0.457) and negative correlation (ρ = - 0.329), respectively. Correlations between birth weight and gestational age, and between birth weight and prematurity, are shown in Figure 37.

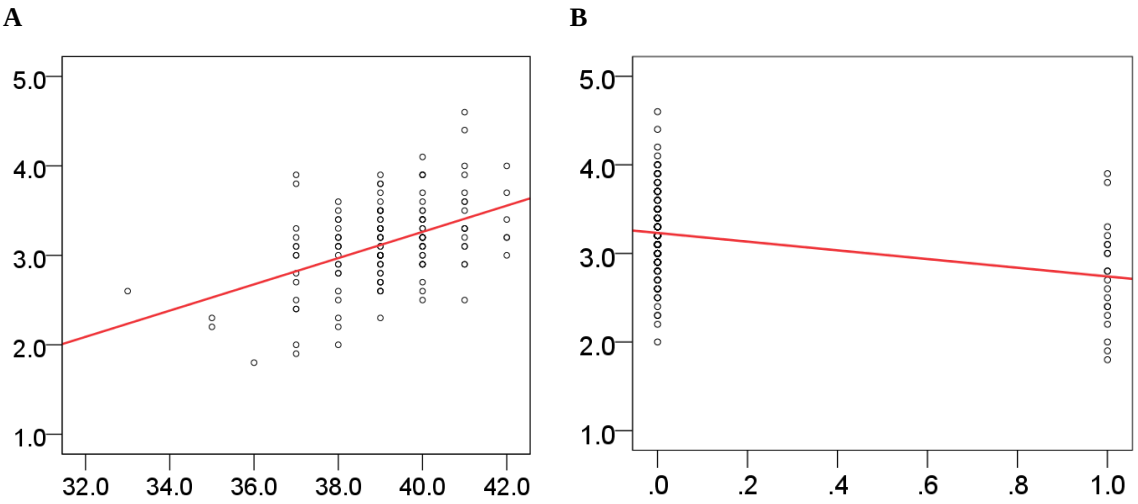


FIGURE 37. Bivariate correlations. (A) Birth weight and gestational age were positively correlated; ρ =

0.457. The *X*-axis represents gestational age (weeks); the *Y*-axis represents birth weight (kg). (B) Birth weight and prematurity were negatively correlated; ρ = - 0.329. The *X*-axis represents prematurity (0 – no, 1 – yes); the *Y*-axis represents birth weight (kg).

Because of a significant correlation between birth weight and gestational age and between birth weight and prematurity, prematurity was excluded from further analysis. The decision to exclude prematurity and not the birth weight was based on: (1) a literature review justified birth weight as a single variable to be kept in the final model, and (2) a continuous variable provides more robust data for subsequent statistical analysis than a categorical variable.

Linearity assumption

A linearity assumption was tested after the construction of multivariate models and is described in section 9.3.3.

9.3.3 Construction of multivariate models

Candidate models

Multivariate models were constructed using the variables birth weight, anomalous pulmonary vein connection, postoperative impaired right ventricular function, shunt type at the Norwood procedure and shunt revision during the Norwood procedure. The two core variables chosen to construct the first multivariate model (M-1) were birth weight, identified as a significant risk factor for mortality in most similar studies, and postoperative impaired right ventricular function, based on a *P*-value ≤ 0.05 from a univariate analysis. Seven additional models (M2 – M8) were constructed adding the variables anomalous pulmonary vein connection, shunt type at the Norwood procedure, and shunt revision during the Norwood procedure, respectively. The eight candidate multivariate models are shown in Table 11.

TABLE 11. Candidate multivariate models: primary analysis.

Candidate multivariate models	
M-1 Birth weight Postoperative impaired RV function	**M-2** Birth weight Postoperative impaired RV function Shunt type at Norwood
M-3 Birth weight APVC Postoperative impaired RV function	**M-4** Birth weight Postoperative impaired RV function Shunt revision during Norwood
M-5 Birth weight APVC Postoperative impaired RV function Shunt type at Norwood	**M-6** Birth weight Postoperative impaired RV function Shunt type at Norwood Shunt revision during Norwood

TABLE 11. Candidate multivariate models: primary analysis (continued).

M-7 Birth weight APVC Postoperative impaired RV function Shunt revision during Norwood	**M-8** Birth weight APVC Postoperative impaired RV function Shunt type at Norwood Shunt revision during Norwood

APVC, anomalous pulmonary vein connection; *RV*, right ventricle.

Linearity assumption

A Box-Tidwell transformation using crossproducts of the birth weight times its natural logarithm was used to test the linearity assumption and was added as an interaction term to each of the eight models. The interaction term of the transformed variable birth weight in each of the eight models is shown in Table 12.

TABLE 12. Linearity relation between predictors and log odds.

Model	*P*–value [birth weight*(ln birth weight)]	Significance after Bonferroni correction
M-1	0.901	*P*-value < 0.0125
M-2	0.970	*P*-value < 0.01
M-3	0.952	*P*-value < 0.01
M-4	0.956	*P*-value < 0.01
M-5	0.931	*P*-value < 0.0083
M-6	0.937	*P*-value < 0.0083
M-7	0.988	*P*-value < 0.0083
M-8	0.895	*P*-value < 0.0071

The *P*–value of the transformed birth weight was not significant in any of the eight models; thus, a linear relation in all models was confirmed.

9.3.4 Multivariate analysis: Primary endpoint

A multivariate analysis was performed using a binary logistic regression for all candidate models (M1 – M8). The Firth's penalized likelihood correction was applied to address the issue of separation in logistic regressions. The results of the multivariate analysis for models M1 - M8 are shown in Table 13.

TABLE 13. Multivariate binary logistic regression analysis with Firth's penalized likelihood correction.

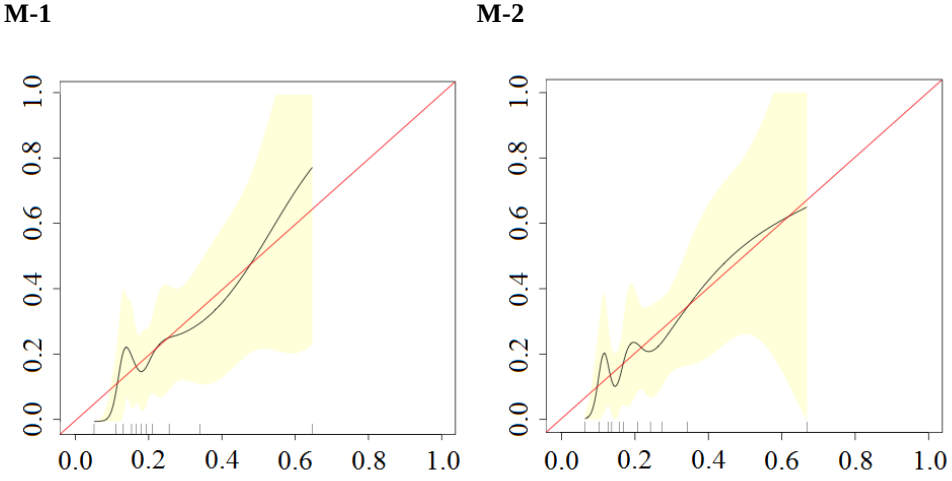
Model	Odds ratio	95% CI	*P*-value
M-1			
Birth weight (kg)	0.40	(0.18 – 0.87)	0.021
Postoperative impaired RV function	3.08	(1.18 – 7.84)	0.022
M-2			
Birth weight (kg)	0.44	(0.20 – 0.95)	0.036
Postoperative impaired RV-Function	2.77	(1.05 – 7.11)	0.039
Shunt type at Norwood	0.59	(0.27 – 1.26)	0.170

TABLE 13. Multivariate binary logistic regression analysis with Firth's penalized likelihood correction (continued).

M-3			
Birth weight (kg)	0.36	(0.16 – 0.79)	0.011
APVC	3.67	(0.93 – 13.55)	0.062
Postoperative impaired RV function	3.06	(1.17 – 7.81)	0.023
M-4			
Birth weight (kg)	0.41	(0.18 – 0.88)	0.022
Postoperative impaired RV function	3.24	(1.24 – 8.35)	0.018
Shunt revision during Norwood	2.72	(0.80 – 8.63)	0.106
M-5			
Birth weight (kg)	0.39	(0.17 – 0.86)	0.019
APVC	3.36	(0.84 – 12.44)	0.083
Postoperative impaired RV function	2.77	(1.04 – 7.14)	0.041
Shunt type at Norwood	0.62	(0.29 – 1.34)	0.226
M-6			
Birth weight (kg)	0.45	(0.20 – 0.96)	0.038
Postoperative impaired RV function	2.93	(1.11 – 7.58)	0.030
Shunt type at Norwood	0.62	(0.29 – 1.33)	0.216
Shunt revision during Norwood	2.50	(0.73 – 7.96)	0.138
M-7			
Birth weight (kg)	0.36	(0.16 – 0.79)	0.011
APVC	4.08	(1.03 – 15.24)	0.046
Postoperative impaired RV function	3.23	(1.23 – 8.37)	0.018
Shunt revision during Norwood	3.04	(0.88 – 9.85)	0.078
M-8			
Birth weight (kg)	0.39	(0.17 – 0.86)	0.019
APVC	3.74	(0.93 – 14.01)	0.062
Postoperative impaired RV function	2.95	(1.11 – 7.69)	0.031
Shunt type at Norwood	0.66	(0.30 – 1.44)	0.294
Shunt revision during Norwood	2.80	(0.81 – 9.12)	0.102

APVC, anomalous pulmonary vein connection; *RV*, right ventricle.

Calibration plots were constructed for each of the eight logistic regressions models with Firth's penalized likelihood correction to assess the match between the predicted and actual (observed) probability; these plots are shown in Figure 38.



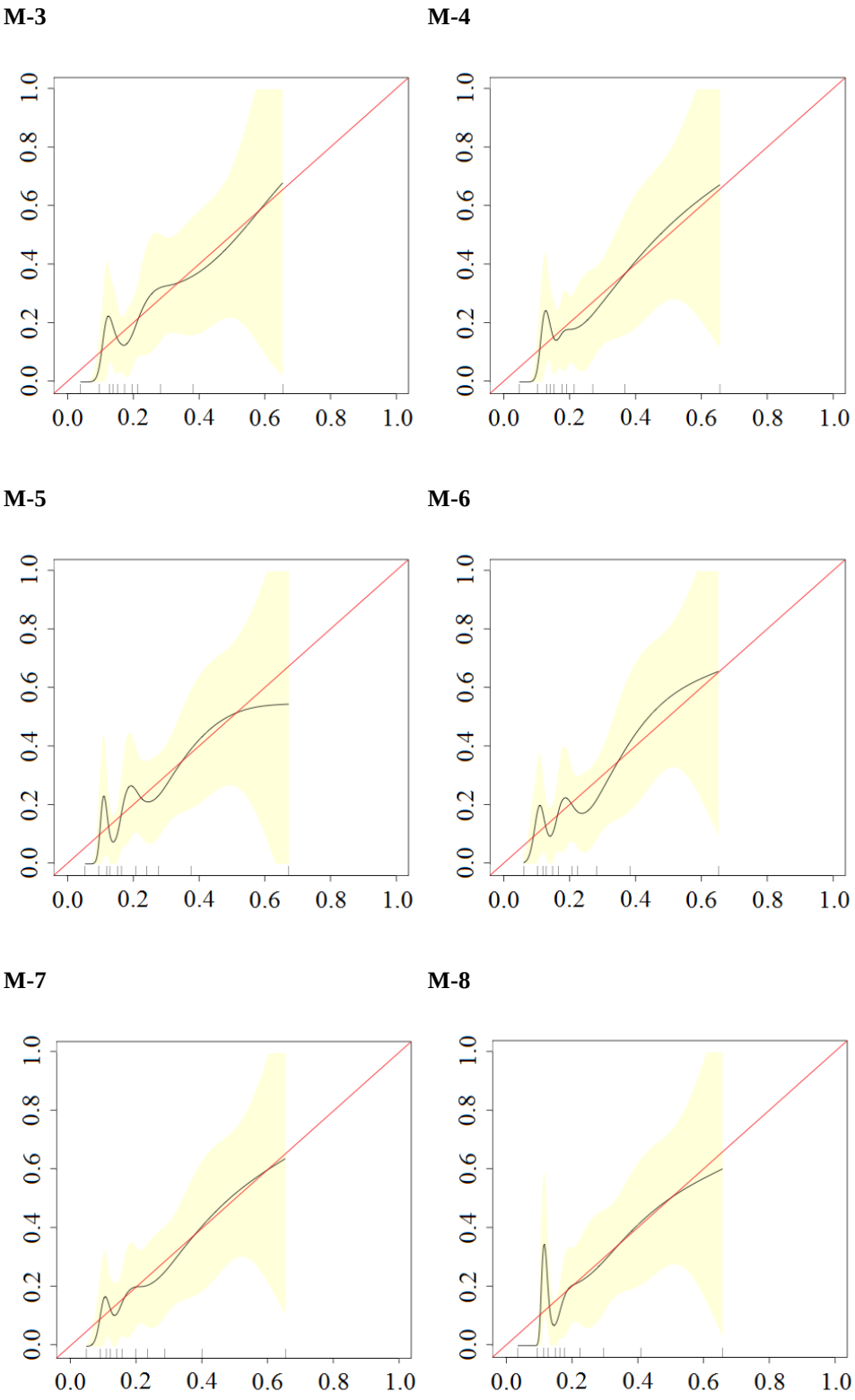


FIGURE 38. Calibration plots for logistic regression models (M1 – M8) with Firth's penalized likelihood correction. The *X*-axis represents predicted probability; the *Y*-axis represents the actual (observed) probability. The red line represents the ideal curve, when the predicted and actual probability are equal. The yellow shading shows 95% confidence intervals of the calibration curve.

9.3.5 Final model selection

For each of the eight models, the accuracy of the probabilistic prediction (Brier score) and the discriminatory ability (AUC value) were calculated. The results are shown in Table 14.

TABLE 14. Accuracy of probabilistic prediction and discriminatory ability for logistic regression models with Firth's penalized likelihood correction.

Model	Brier score	AUC
M-1	0.152	0.645
M-2	0.152	0.667
M-3	0.150	0.676
M-4	0.150	0.659
M-5	0.148	0.691
M-6	0.149	0.674
M-7	0.146	0.693
M-8	0.147	0.701

AUC, area under the curve.

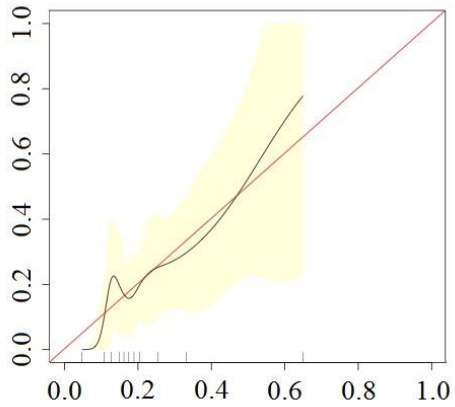
Models M-7 and M-8 yielded the best results for the Brier score and AUC-values, and were selected for the subsequent calibration. Because calibration algorithms for the Harrell's C-statistic and Somers' D_{xy} rank correlation index are based on the logistic regression without the Firth's correction, the Brier score and AUC-values of logistic regression models M1 - M8, both with and without Firth's correction, were compared; calibration plots for logistic regression models M1 – M8 without Firth's penalized likelihood correction were also constructed. The Brier score and AUC-values for logistic regression models without Firth's correction are shown in Table 15. The calibration plots for logistic regression models M1 - M8 without Firth's correction are shown in Figure 39.

TABLE 15. Accuracy of probabilistic prediction and discriminatory ability for logistic regression models without Firth's penalized likelihood correction.

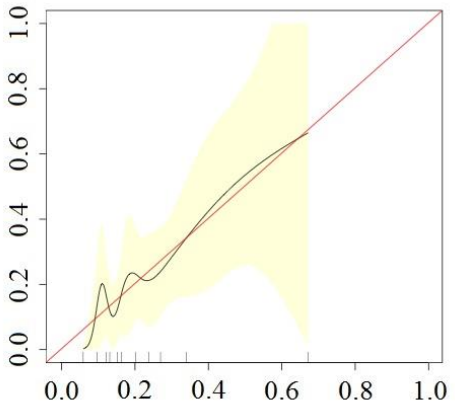
Model	Brier score	AUC
M-1	0.153	0.645
M-2	0.151	0.667
M-3	0.150	0.676
M-4	0.150	0.660
M-5	0.149	0.691
M-6	0.148	0.674
M-7	0.147	0.693
M-8	0.146	0.701

AUC, area under the curve.

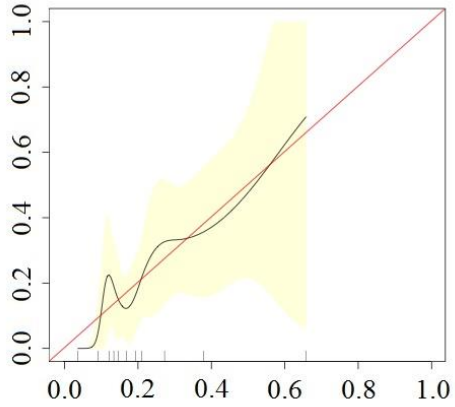
M-1



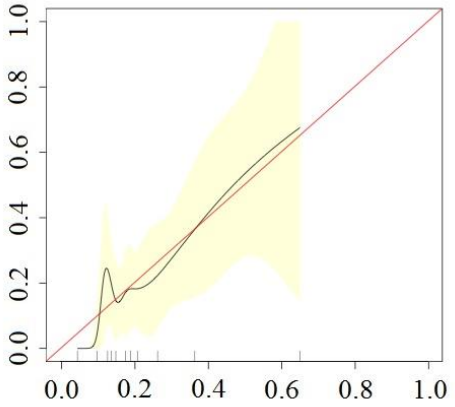
M-2



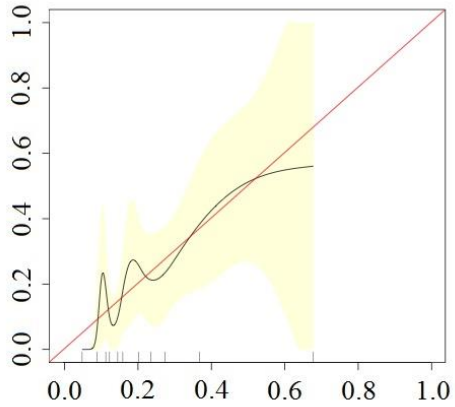
M-3



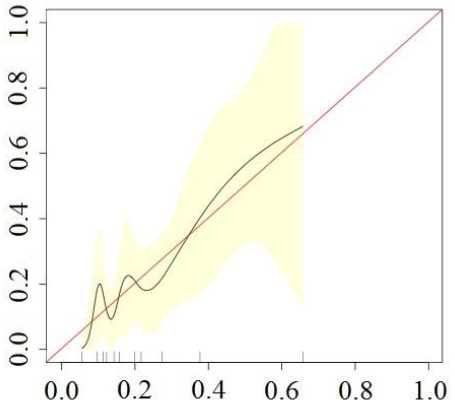
M-4



M-5



M-6



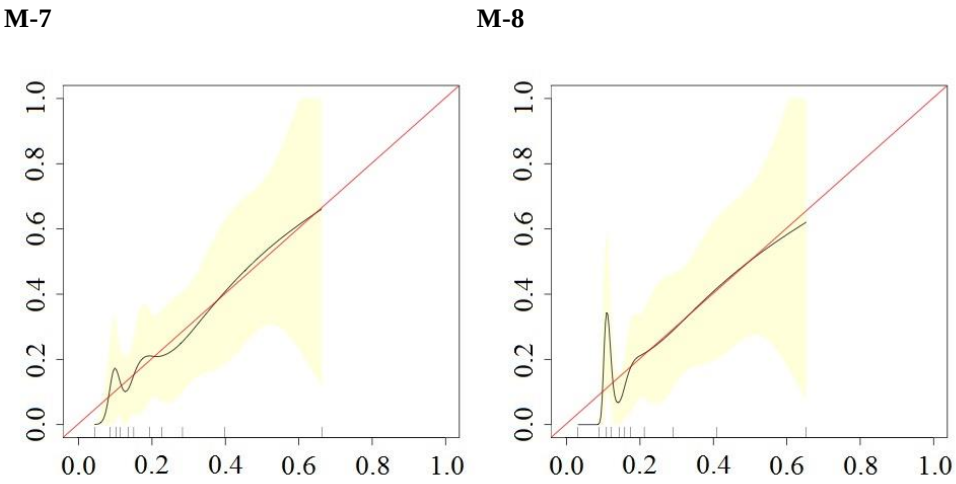


FIGURE 39. Calibration plots for logistic regression models (M1 – M8) without Firth's penalized likelihood correction. The *X*-axis represents predicted probability; the *Y*-axis represents actual (observed) probability. The red line represents the ideal curve, when the predicted and actual probability are equal. The yellow shading shows the 95% confidence interval of the calibration curve.

The discrepancies between Brier scores and AUC-values in logistic regression models M1 - M8 with and without Firth's correction were minimal, and calibration plots showed an almost equal match between the predicted and actual probability. Consequently, logistic regression models M-7 and M-8 without Firth's correction were used as precursor models for calibration using the Harrell's C-statistic and Somers' D_{xy} rank correlation index. Model optimism was quantified using bootstrapping (n = 1,000 bootstrap samples) for both models. The results are shown in Table 16.

TABLE 16. Calibration parameters: M-7 and M-8.

Parameter	M-7	M-8
Concordance index (original)	0.693	0.701
Somers' D_{xy} rank correlation index (original)	0.386	0.401
Model optimism	0.058	0.078
Concordance index (corrected)	0.664	0.662
Somers' D_{xy} rank correlation index (corrected)	0.328	0.323

After the calibration and an optimism estimation of both models, model M-7 was chosen as the final model. The discriminatory ability of this model is shown in Figure 40 and the calibration is plotted in Figure 41.

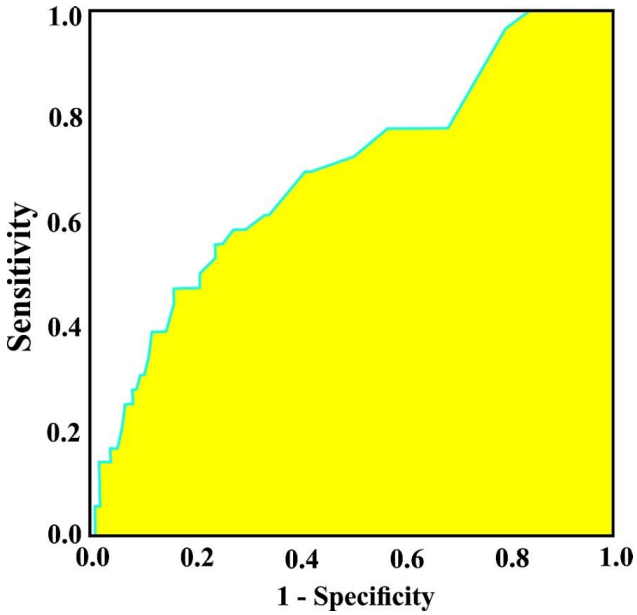


FIGURE 40. Discriminatory ability of the final model. Discriminatory ability corresponds with AUC = 0.693 (*yellow area*) before model calibration. The AUC value decreased slightly, to 0.664, after model calibration. *AUC,* area under the curve.

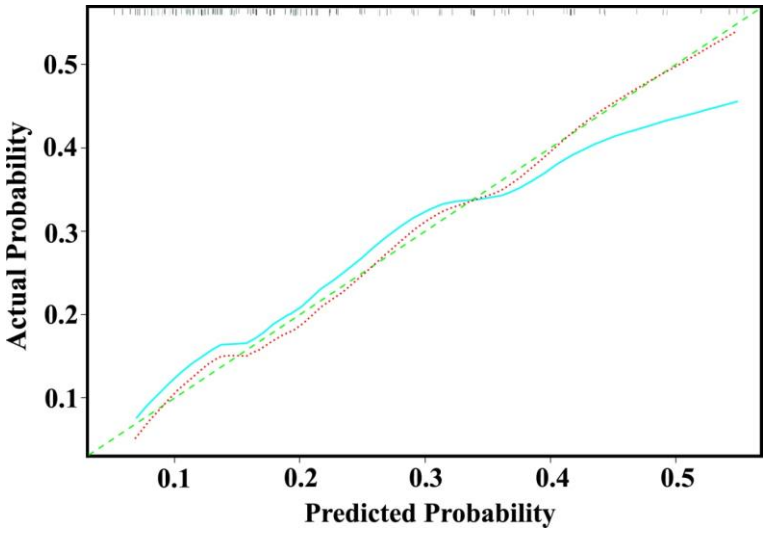


FIGURE 41. Calibration plot of the final model. The *X*-axis represents predicted probability; the *Y*-axis represents actual (observed) probability. Apparent calibration curve before (*red curve*) and bias-corrected calibration curve after (*blue curve*) model calibration. Ideal curve (*dashed green curve*) is shown as a reference line.

9.3.6 Final model validation

Internal model validation was performed using bootstrapping with 10,000 bootstrap samples. A bootstrap inclusion fraction was used to evaluate the stability of the variables in the final model. The results are shown in Table 17 and Table 18.

TABLE 17. Final multivariate binary logistic regression model with Firth's correction: bootstrap parameters.

Variable	Original	Bootstrap values			
	Odds ratio	Bias	Standard error	Odds ratio	95% CI
Birth weight (kg)	0.36	- 0.04	0.38	0.35	(0.27 – 0.45)
APVC	4.08	- 0.01	0.78	4.10	(2.51 – 6.58)
Postoperative impaired RV function	3.23	0.02	0.54	3.33	(2.34 – 4.69)
Shunt revision during Norwood	3.04	0.00	0.66	3.10	(2.02 – 4.65)

APVC, anomalous pulmonary vein connection; *RV*, right ventricle.

TABLE 18. Final multivariate binary logistic regression model with Firth's correction: *P*-values and bootstrap inclusion fraction.

Variable	BIF	*P*-values	
	(%)	Original	Bootstrap
Birth weight (kg)	74.2	0.011	0.011
APVC	49.6	0.046	0.049
Postoperative impaired RV function	63.9	0.018	0.019
Shunt revision during Norwood	41.5	0.078	0.084

APVC, anomalous pulmonary vein connection; *BIF*, bootstrap inclusion fraction; *RV*, right ventricle.

10 Time period between stage II and stage III

The stage II cohort included 140 patients who underwent the stage II procedure and proceeded to the post-stage II period. As of January 2016, 95 patients survived to the stage III procedure, and 19 patients died between the stage II and stage III procedures. Twenty-six patients were awaiting the stage III procedure.

10.1 *Patients' characteristics: Secondary analysis*

The distributions of patients' demographic, clinical, anatomic/echocardiographic, and catheterization characteristics and operative details were examined in each of the four groups: (A) stage II cohort, (B) survivors to the stage III procedure, (C) non-survivors to the stage III procedure, and (D) awaiting the stage III procedure. The values were calculated from available data.

10.1.1 Demographic parameters

Gender

The stage II cohort was comprised of 102 males and 38 females. Seventy-two males and 23 females survived to the stage III procedure, but 14 males and five females died between the stage II and stage III procedures. Sixteen males and 10 females were awaiting the stage III procedure. Percentages of gender distributions among these groups are shown in Figure 42.

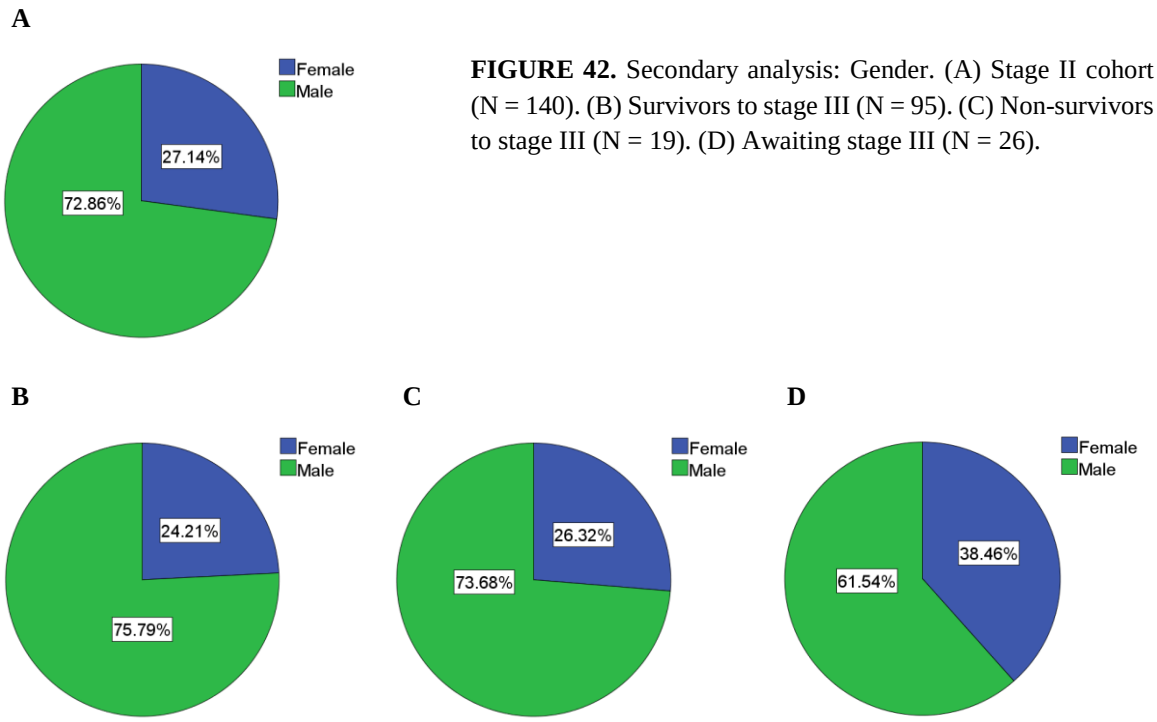


FIGURE 42. Secondary analysis: Gender. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

Weight at the stage II procedure

The median weight at the stage II procedure for the stage II cohort was 5.1 ± 1.2 kg. The mean weight at the stage II procedure in survivors to the stage III procedure was 5.2 ± 1.0 kg. The mean weight at the stage II procedure in patients who died between the stage II and stage III procedures was 5.2 ± 0.9 kg. The median weight at the stage II procedure in patients who were awaiting the stage III procedure was 4.7 ± 0.6 kg. Distributions of weights at the stage II procedure among these groups are shown in Figure 43.

FIGURE 43. Secondary analysis: Weight at the stage II procedure. (A) Stage II cohort (N = 138), Shapiro-Wilk test: *P*-value = 0.007. (B) Survivors to stage III (N = 95), Shapiro-Wilk test: *P*-value = 0.094. (C) Non-survivors to stage III (N = 17), Shapiro-Wilk test: *P*-value = 0.980. (D) Awaiting stage III (N = 26), Shapiro-Wilk test: *P*-value = 0.001.

Prematurity

In the stage II cohort, 13 patients were born prematurely. Seven patients survived to the stage III procedure, while four patients died between the stage II and stage III procedures. Two premature born patients were awaiting the stage III procedure. Percentages of premature births among these groups are shown in Figure 44.

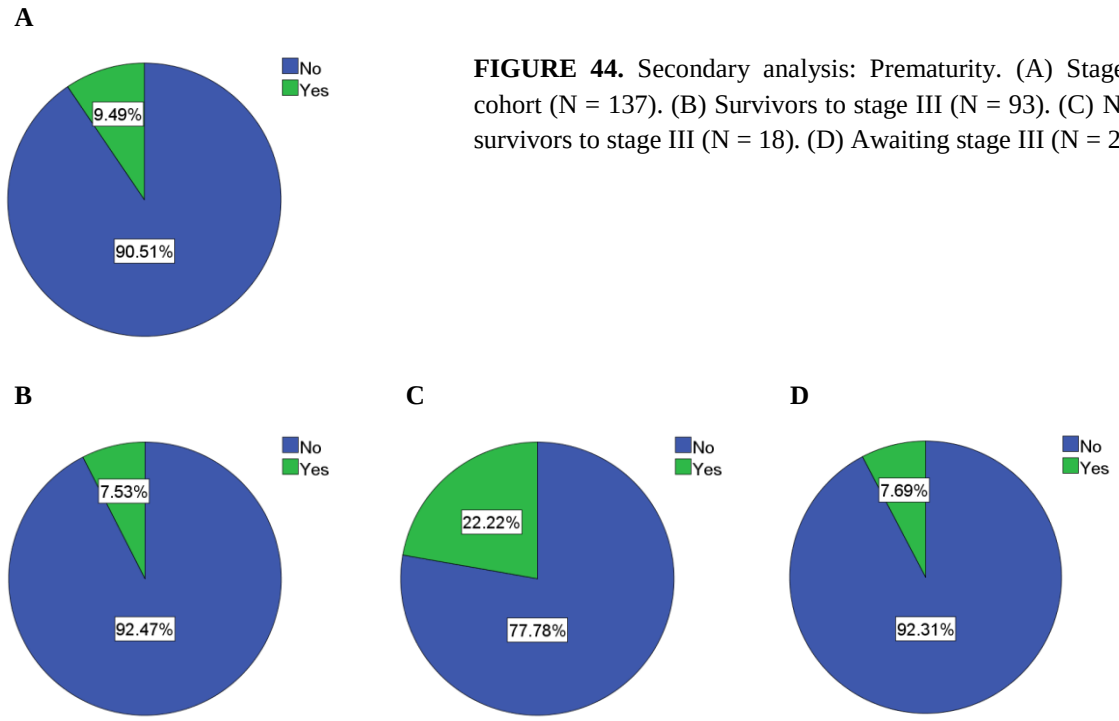


FIGURE 44. Secondary analysis: Prematurity. (A) Stage II cohort (N = 137). (B) Survivors to stage III (N = 93). (C) Non-survivors to stage III (N = 18). (D) Awaiting stage III (N = 26).

10.1.2 Clinical parameters

Shunt type at the Norwood procedure

A systemic shunt was used in 56 patients, and a right ventricle-to-pulmonary artery conduit was used in 84 patients of the stage II cohort. Thirty-three patients with a systemic shunt and 62 patients with a right ventricle-to-pulmonary artery conduit survived to the stage III procedure. Three patients with a systemic shunt, and 16 patients with a right ventricle-to-pulmonary artery conduit died between the stage II and stage III procedures. Twenty patients with a systemic shunt, and six patients with a right ventricle-to-pulmonary artery conduit were awaiting the stage III procedure. Percentages of patients with systemic shunts or right ventricle-to-pulmonary artery conduits implanted during the Norwood procedure among these groups are shown in Figure 45.

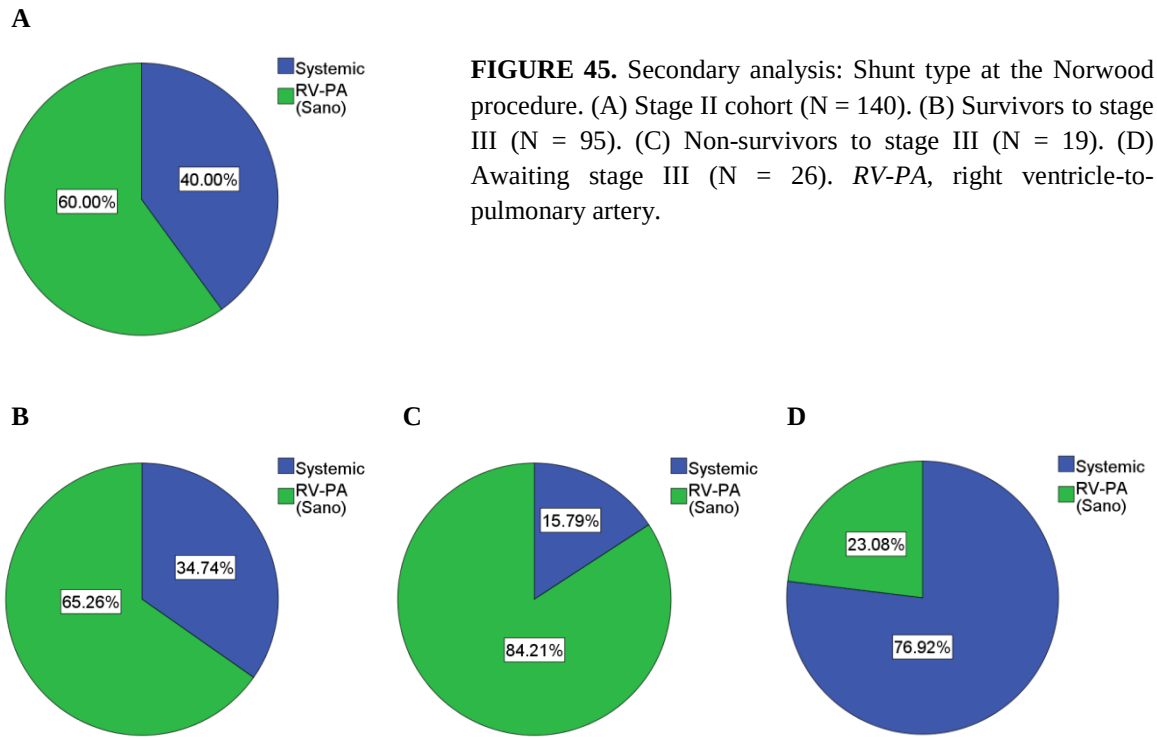


FIGURE 45. Secondary analysis: Shunt type at the Norwood procedure. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26). *RV-PA*, right ventricle-to-pulmonary artery.

Pulmonary artery intervention after the Norwood procedure

Ten patients of the stage II cohort underwent pulmonary artery intervention after the Norwood procedure. Five patients survived to the stage III procedure, but two patients died between the stage II and stage III procedures. Three patients were awaiting the stage III procedure. Percentages of patients who underwent pulmonary artery intervention after the Norwood procedure among these groups are shown in Figure 46.

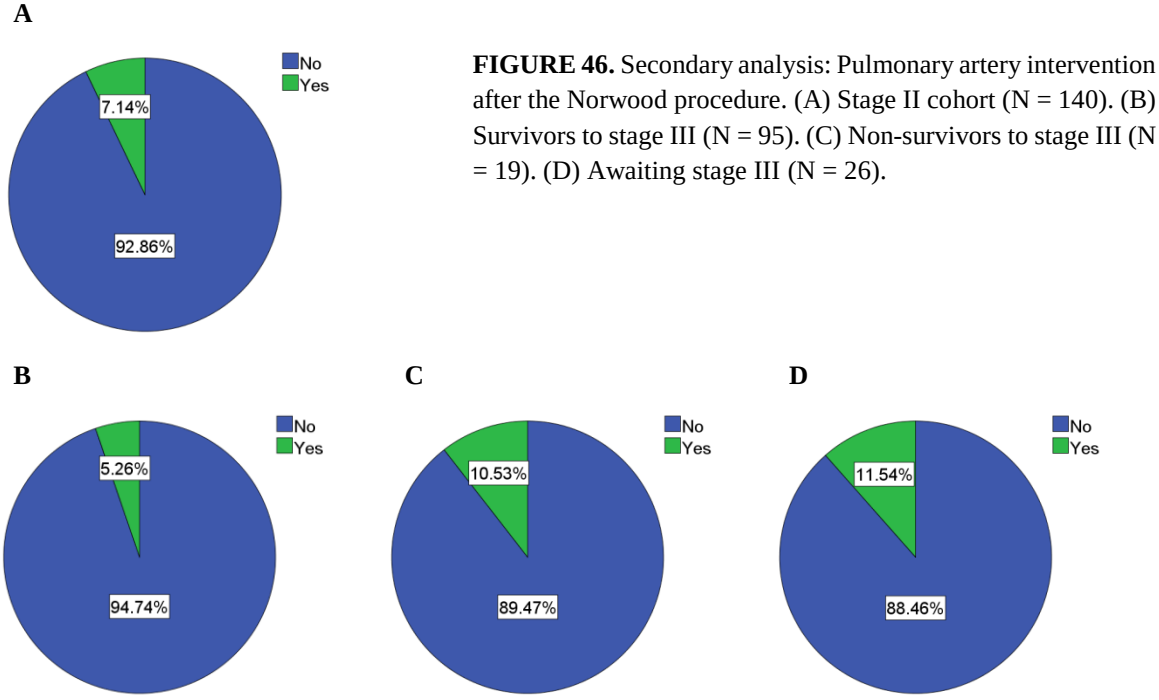


FIGURE 46. Secondary analysis: Pulmonary artery intervention after the Norwood procedure. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

Neo-aorta intervention after the Norwood procedure

Fifteen patients of the stage II cohort underwent neo-aorta intervention after the Norwood procedure. Eight patients survived to the stage III procedure, but one patient died between the stage II and stage III procedures. Six patients were awaiting the stage III procedure. Percentages of patients who underwent neo-aorta intervention after the Norwood procedure among these groups are shown in Figure 47.

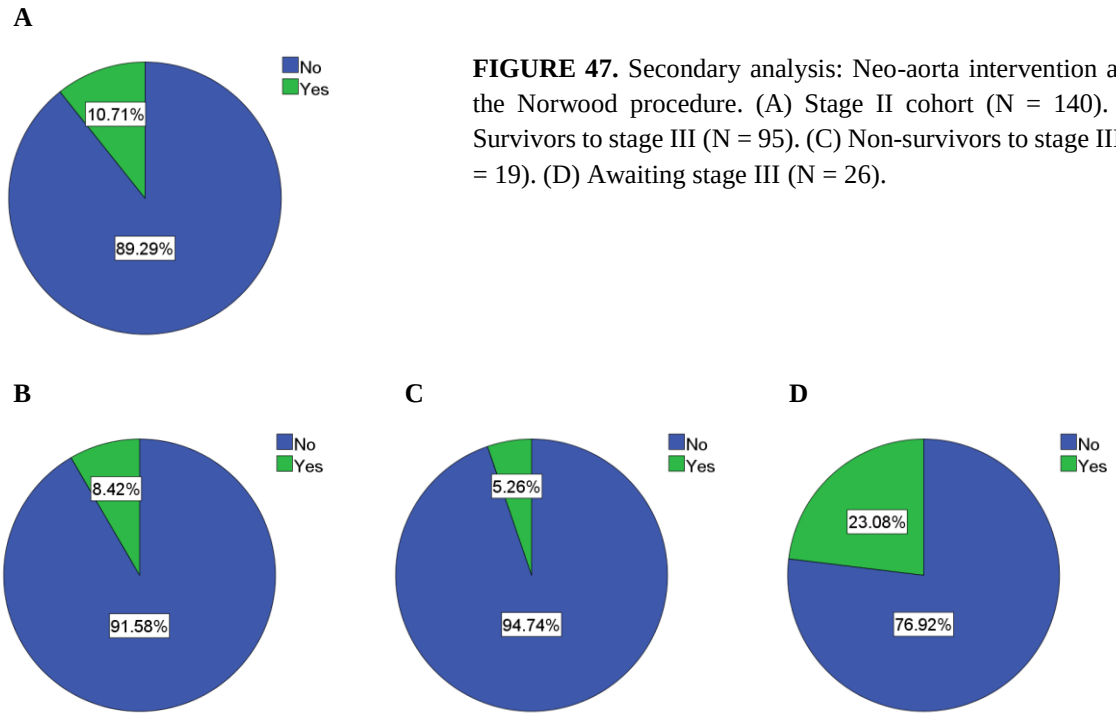


FIGURE 47. Secondary analysis: Neo-aorta intervention after the Norwood procedure. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

10.1.3 Anatomic/echocardiographic parameters

Hypoplastic left heart syndrome subtypes

Of the stage II cohort, aortic atresia and mitral atresia was present in 45 patients, aortic atresia and mitral stenosis in 37 patients, aortic stenosis and mitral atresia in 10 patients, and aortic stenosis and mitral stenosis in 45 patients. In survivors to the stage III procedure, aortic atresia and mitral atresia was present in 33 patients, aortic atresia and mitral stenosis in 25 patients, aortic stenosis and mitral atresia in six patients, and aortic stenosis and mitral stenosis in 29 patients. In patients who died between the stage II and stage III procedures, aortic atresia and mitral atresia was present in three patients, aortic atresia and mitral stenosis in six patients, aortic stenosis and mitral atresia in one patient, and aortic stenosis and mitral stenosis in eight patients. In patients who were awaiting the stage III procedure, aortic atresia and mitral atresia was present in nine patients, aortic atresia and mitral stenosis in six patients, aortic stenosis and mitral atresia in three patients, and aortic stenosis and mitral stenosis in eight patients. Percentages of patients with different HLHS subtypes among these groups are shown in Figure 48.

A

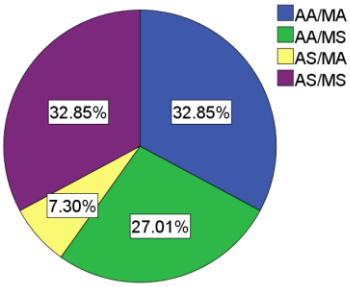
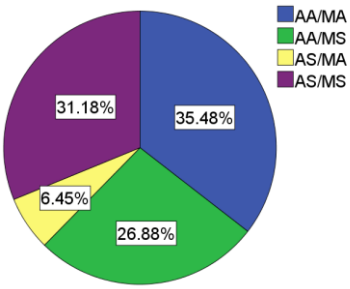


FIGURE 48. Secondary analysis: Hypoplastic left heart syndrome subtypes. (A) Stage II cohort (N = 137). (B) Survivors to stage III (N = 93). (C) Non-survivors to stage III (N = 18). (D) Awaiting stage III (N = 26). *AA*, aortic atresia; *AS*, aortic stenosis; *MA*, mitral atresia; *MS*, mitral stenosis.

B



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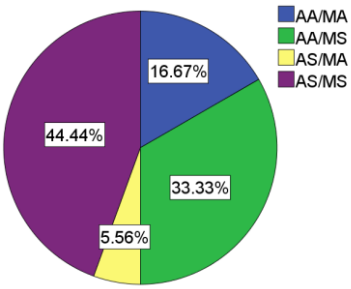

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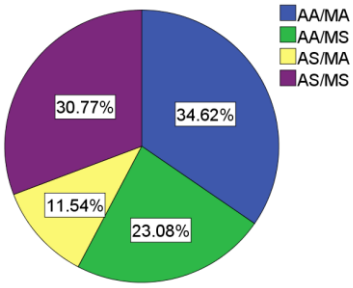


Endocardial fibroelastosis

Endocardial fibroelastosis of the left ventricle was present in 35 patients of the stage II cohort. Twenty-four patients survived to the stage III procedure, but seven patients died between the stage II and stage III procedures. Four patients were awaiting the stage III procedure. Percentages of patients with an endocardial fibroelastosis of the left ventricle among these groups are shown in Figure 49.

A

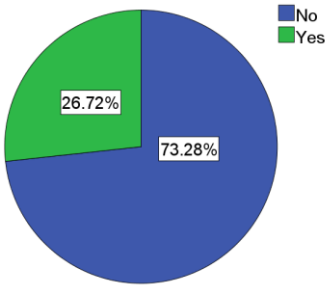
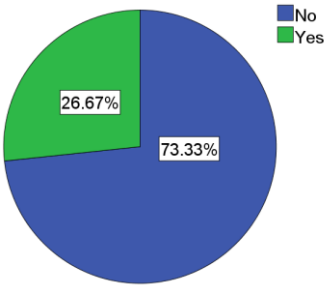


FIGURE 49. Secondary analysis: Endocardial fibroelastosis. (A) Stage II cohort (N = 131). (B) Survivors to stage III (N = 90). (C) Non-survivors to stage III (N = 16). (D) Awaiting stage III (N = 25).

B



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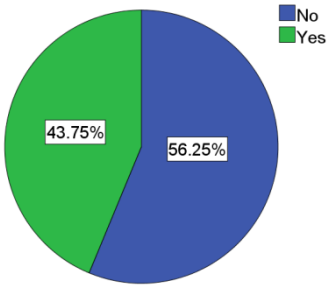

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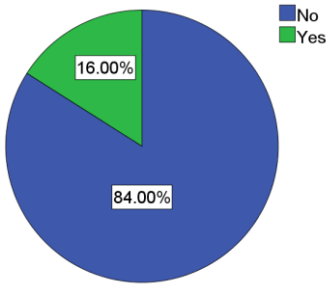


Persistent left superior vena cava

A persistent left superior vena cava was present in 17 patients of the stage II cohort. Ten patients survived to the stage III procedure, but two patients died between the stage II and stage III procedures. Five patients were awaiting the stage III procedure. Percentages of patients with a persistent left superior vena cava among these groups are shown in Figure 50.

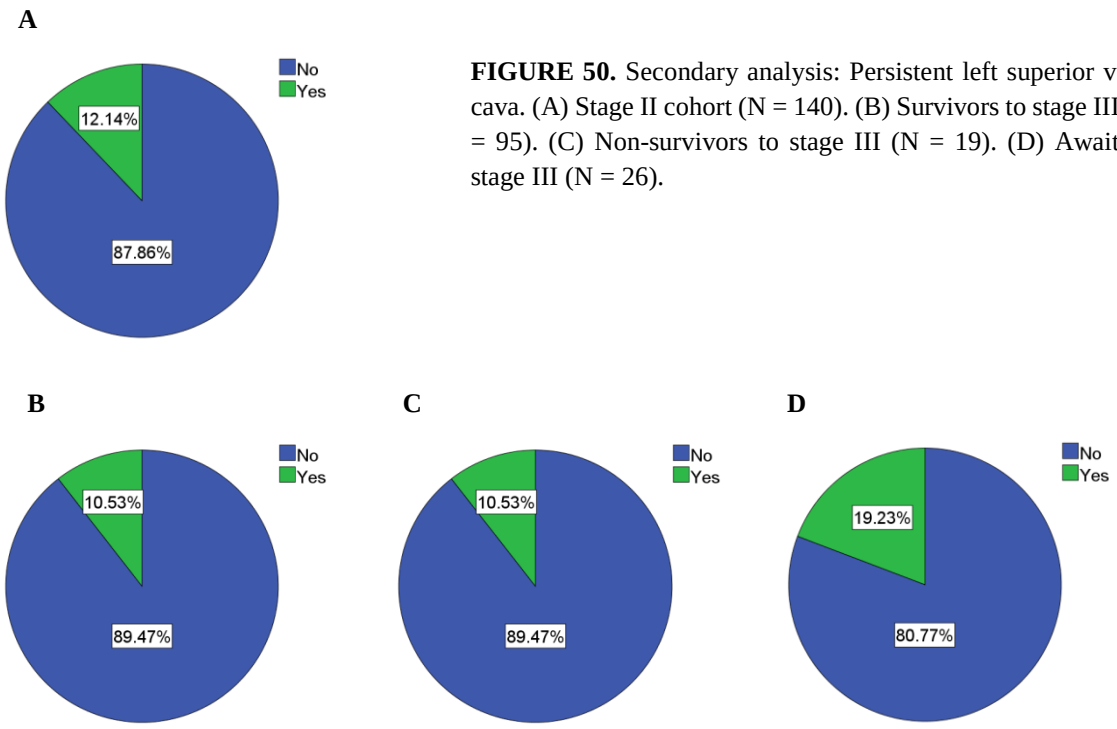


FIGURE 50. Secondary analysis: Persistent left superior vena cava. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

Preoperative neo-aortic valve insufficiency grades I - IV

A neo-aortic valve insufficiency grades I – IV was present in 41 patients of the stage II cohort before the stage II procedure. Twenty-five patients survived to the stage III procedure, but seven patients died between the stage II and stage III procedures. Nine patients were awaiting the stage III procedure. Percentages of patients with neo-aortic valve insufficiency grades I – IV before the stage II procedure among these groups are shown in Figure 51.

A

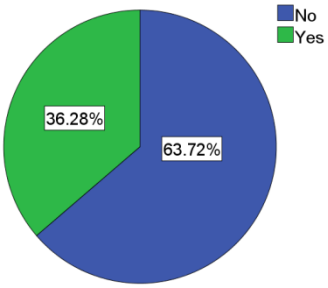
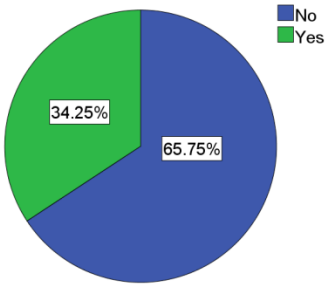


FIGURE 51. Secondary analysis: Preoperative neo-aortic valve insufficiency grades I - IV. (A) Stage II cohort (N = 113). (B) Survivors to stage III (N = 73). (C) Non-survivors to stage III (N = 17). (D) Awaiting stage III (N = 23).

B



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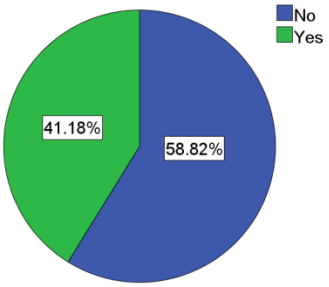

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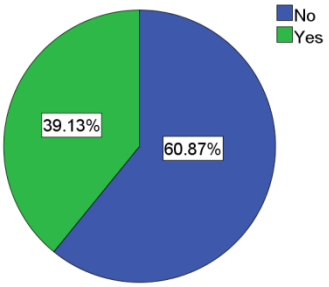


Preoperative tricuspid valve insufficiency grades II+ - IV

A tricuspid valve insufficiency grades II+ - IV was present in 41 patients of the stage II cohort before the stage II procedure. Twenty-four patients survived to the stage III procedure, but two patients died between the stage II and stage III procedures. Fifteen patients were awaiting the stage III procedure. Percentages of patients with tricuspid valve insufficiency grades II+ - IV before the stage II procedure among these groups are shown in Figure 52.

A

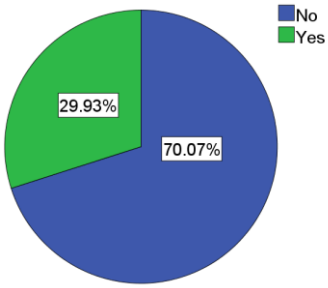
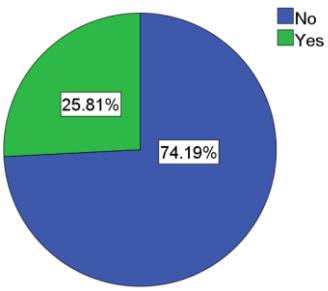


FIGURE 52. Secondary analysis: Preoperative tricuspid valve insufficiency grades II+ - IV. (A) Stage II cohort (N = 137). (B) Survivors to stage III (N = 93). (C) Non-survivors to stage III (N = 18). (D) Awaiting stage III (N = 26).

B



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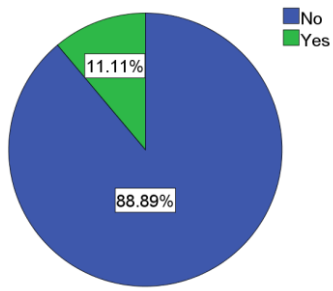

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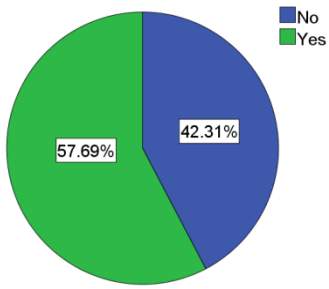

Postoperative tricuspid valve insufficiency grades II+ - IV

A tricuspid valve insufficiency grades II+ - IV was present in 31 patients of the stage II cohort after the stage II procedure. Twenty patients survived to the stage III procedure, but three patients died between the stage II and stage III procedures. Eight patients were awaiting the stage III procedure. Percentages of patients with tricuspid valve insufficiency grades II+ - IV after the stage II procedure among these groups are shown in Figure 53.

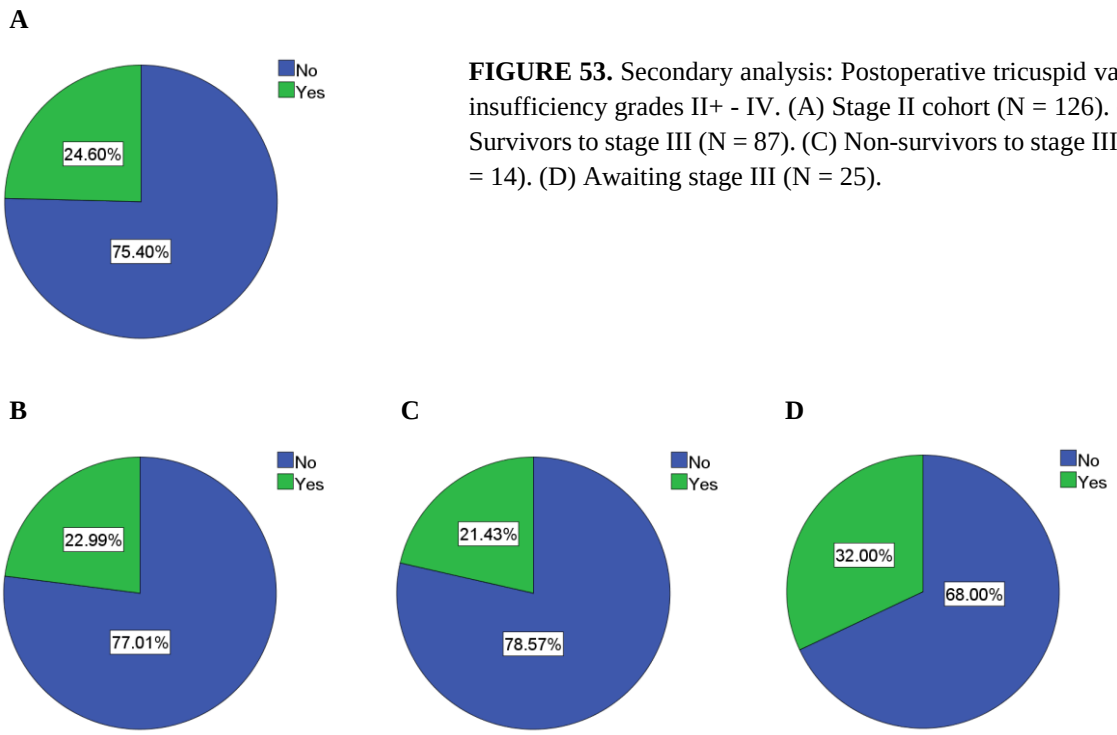

FIGURE 53. Secondary analysis: Postoperative tricuspid valve insufficiency grades II+ - IV. (A) Stage II cohort (N = 126). (B) Survivors to stage III (N = 87). (C) Non-survivors to stage III (N = 14). (D) Awaiting stage III (N = 25).

Preoperative impaired right ventricular function

The right ventricular function was impaired in 18 patients of the stage II cohort before the stage II procedure. Ten patients survived to the stage III procedure, but four patients died between the stage II and stage III procedures. Four patients were awaiting the stage III procedure. Percentages of patients with an impaired right ventricular function before the stage II procedure among these groups are shown in Figure 54.

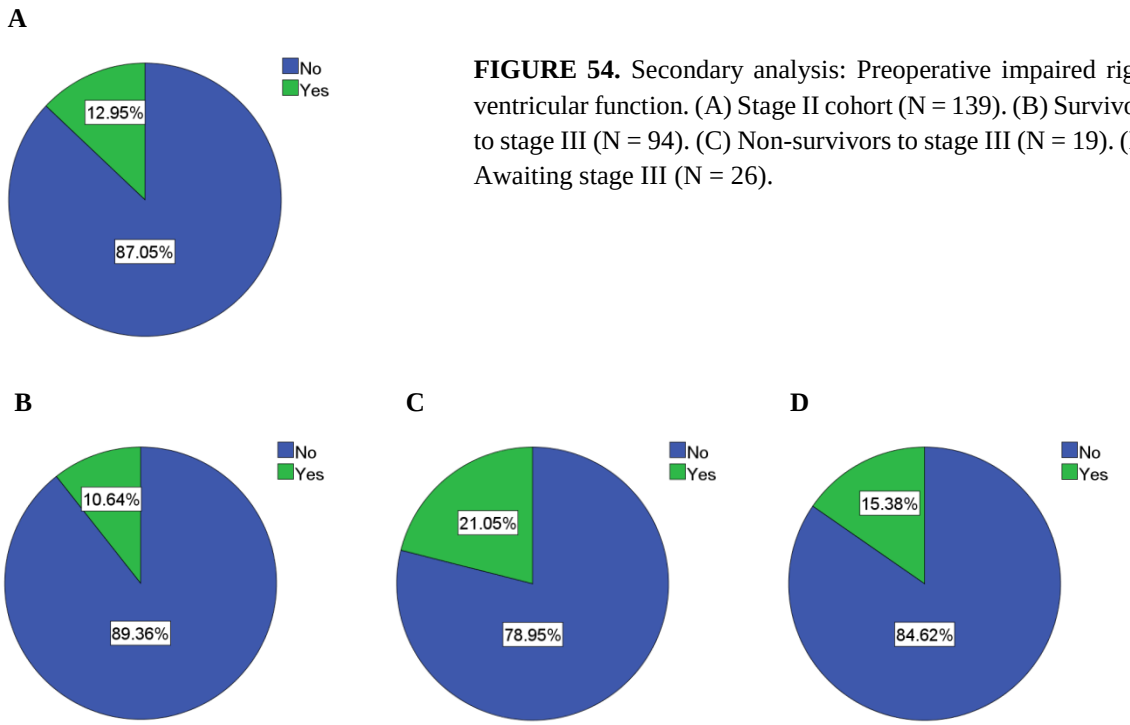

FIGURE 54. Secondary analysis: Preoperative impaired right ventricular function. (A) Stage II cohort (N = 139). (B) Survivors to stage III (N = 94). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

Postoperative impaired right ventricular function

The right ventricular function was impaired in 21 patients of the stage II cohort after the stage II procedure. Fourteen patients survived to the stage III procedure, but five patients died between the stage II and stage III procedures. Two patients were awaiting the stage III procedure. Percentages of patients with an impaired right ventricular function after the stage II procedure among these groups are shown in Figure 55.

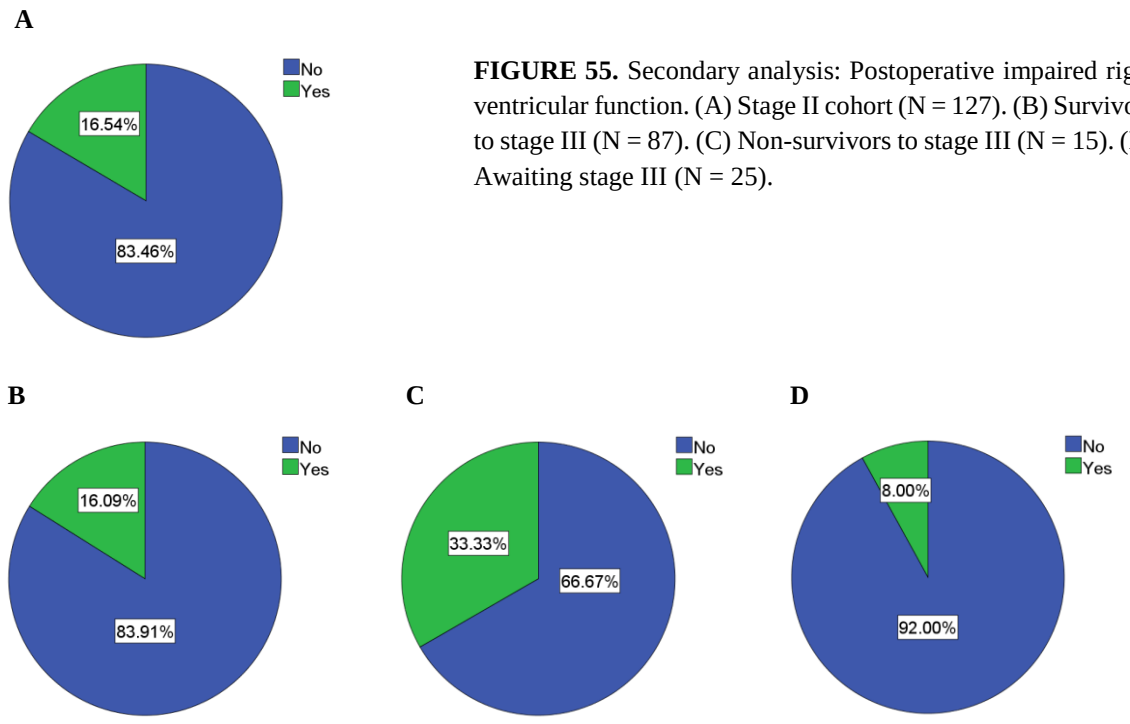

FIGURE 55. Secondary analysis: Postoperative impaired right ventricular function. (A) Stage II cohort (N = 127). (B) Survivors to stage III (N = 87). (C) Non-survivors to stage III (N = 15). (D) Awaiting stage III (N = 25).

10.1.4 Catheterization parameters

Right ventricular end-diastolic pressure

The median right ventricular end-diastolic pressure for the stage II cohort was 8.0 ± 5.0 mmHg. The median right ventricular end-diastolic pressure in survivors to the stage III procedure was 8.0 ± 4.0 mmHg. The mean right ventricular end-diastolic ventricular pressure in patients who died between the stage II and stage III procedures was 10.1 ± 4.5 mmHg. The mean right ventricular end-diastolic pressure in patients who were awaiting the stage III procedure was 9.7 ± 3.6 mmHg. Distributions of right ventricular end-diastolic pressures among these groups are shown in Figure 56.

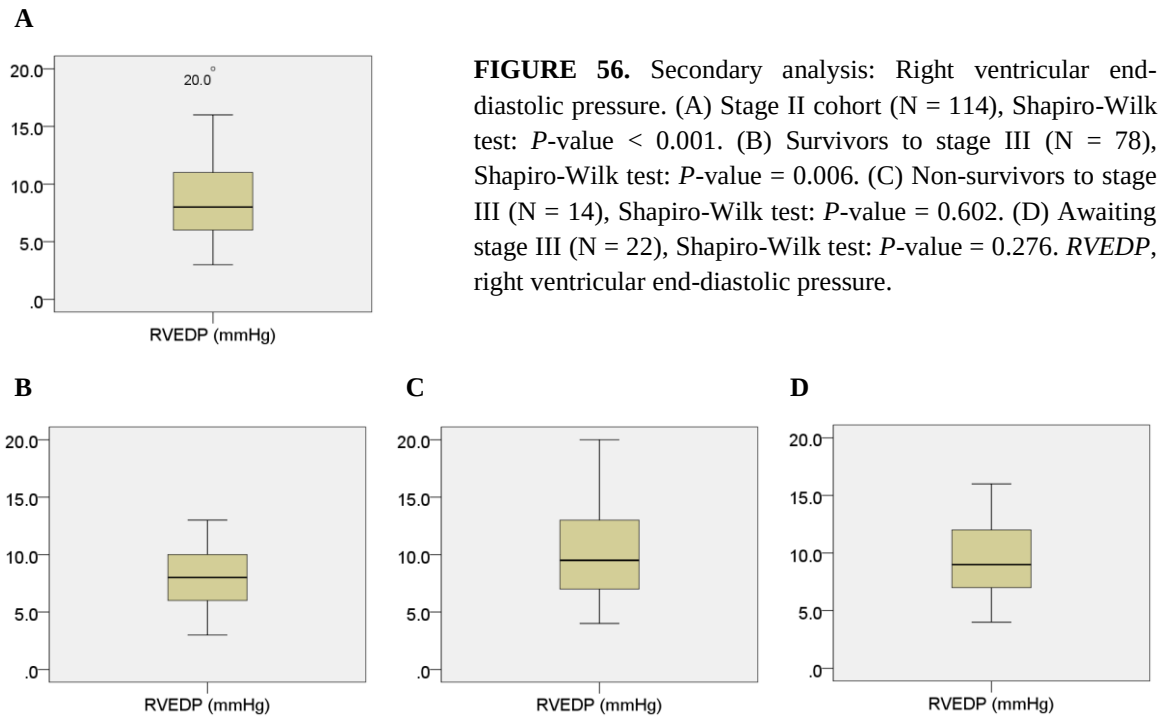

FIGURE 56. Secondary analysis: Right ventricular end-diastolic pressure. (A) Stage II cohort (N = 114), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage III (N = 78), Shapiro-Wilk test: *P*-value = 0.006. (C) Non-survivors to stage III (N = 14), Shapiro-Wilk test: *P*-value = 0.602. (D) Awaiting stage III (N = 22), Shapiro-Wilk test: *P*-value = 0.276. *RVEDP*, right ventricular end-diastolic pressure.

Pulmonary artery mean pressure

The median pulmonary artery mean pressure for the stage II cohort was 14.0 ± 6.3 mmHg. The mean pulmonary artery mean pressure in survivors to the stage III procedure was 15.2 ± 5.2 mmHg. The mean pulmonary artery mean pressure in patients who died between the stage II and stage III procedures was 15.2 ± 6.5 mmHg. The median pulmonary artery mean pressure in patients who were awaiting the stage III procedure was 14.0 ± 2.5 mmHg. Distributions of pulmonary artery mean pressures among these groups are shown in Figure 57.

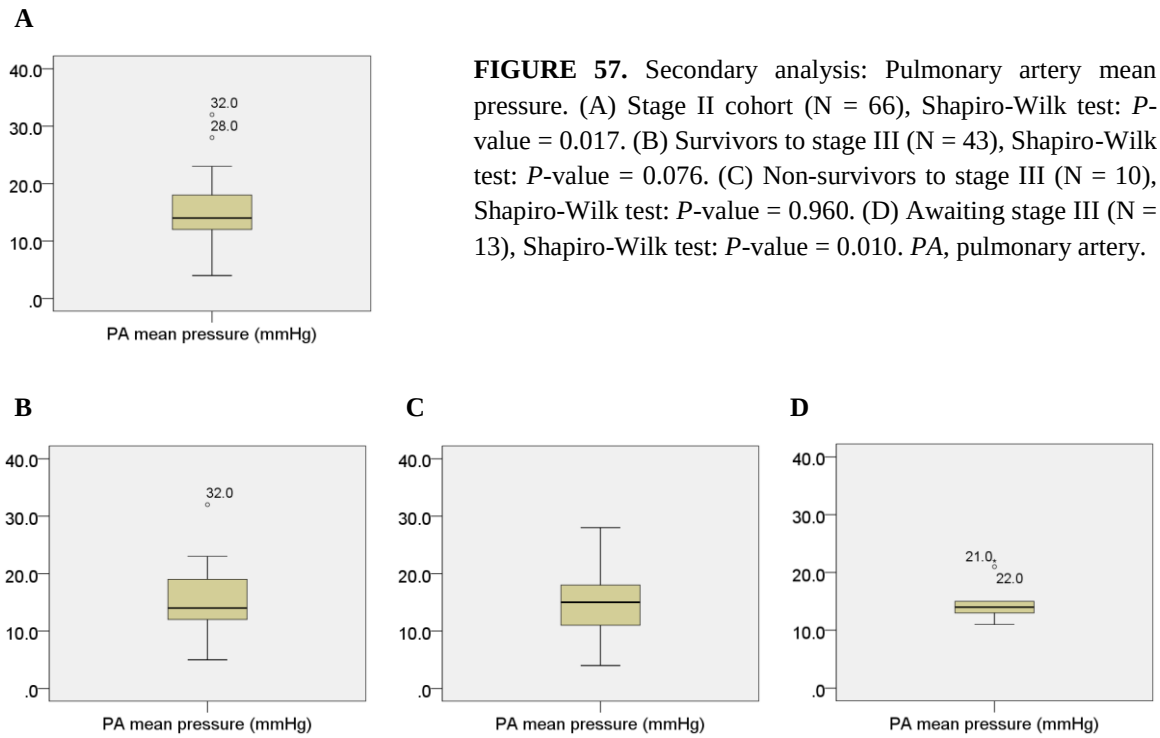

FIGURE 57. Secondary analysis: Pulmonary artery mean pressure. (A) Stage II cohort (N = 66), Shapiro-Wilk test: *P*-value = 0.017. (B) Survivors to stage III (N = 43), Shapiro-Wilk test: *P*-value = 0.076. (C) Non-survivors to stage III (N = 10), Shapiro-Wilk test: *P*-value = 0.960. (D) Awaiting stage III (N = 13), Shapiro-Wilk test: *P*-value = 0.010. *PA*, pulmonary artery.

Pulmonary vascular resistance

The median pulmonary vascular resistance for the stage II cohort was 200.0 ± 133.3 dyn.s.cm^{-5}. The median pulmonary artery vascular resistance in survivors to the stage III procedure was 203.5 ± 139.5 dyn.s.cm^{-5}. One patient who died between the stage II and stage III procedures did have pulmonary vascular resistance 80.0 dyn.s.cm^{-5}; the values were missing in 18 patients who did not survive to the stage III procedure. The mean pulmonary vascular resistance in patients who were awaiting the stage III procedure was 173.0 ± 62.5 dyn.s.cm^{-5}. Distributions of pulmonary vascular resistances among these groups are shown in Figure 58.

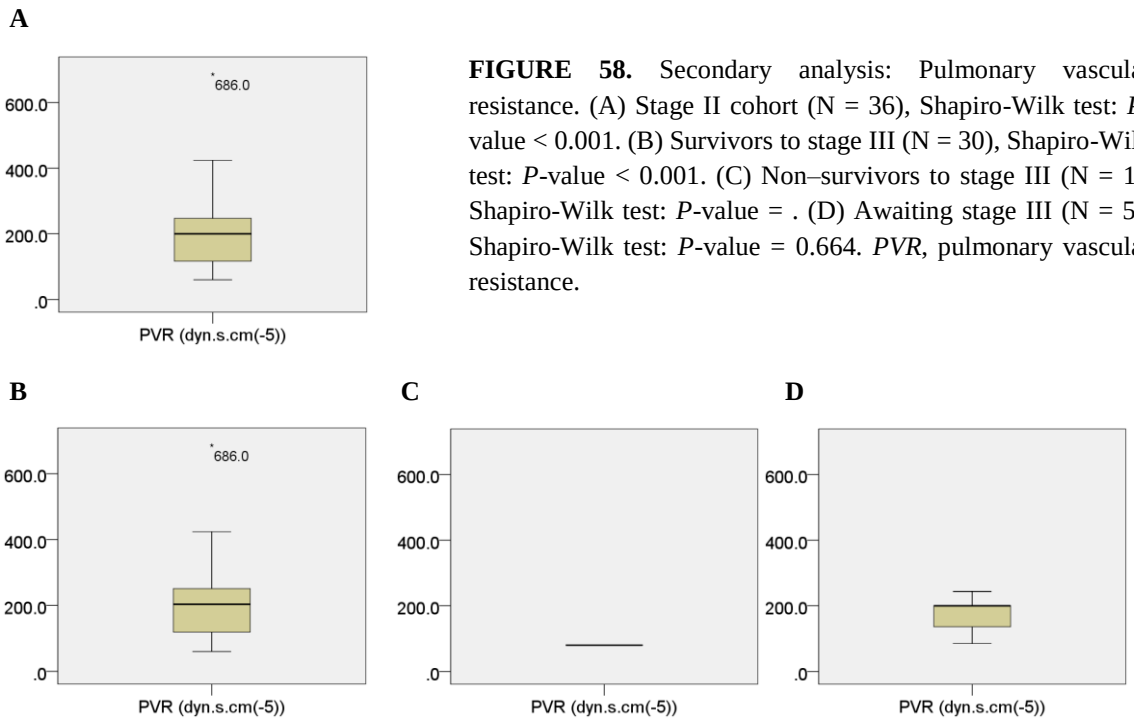

FIGURE 58. Secondary analysis: Pulmonary vascular resistance. (A) Stage II cohort (N = 36), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage III (N = 30), Shapiro-Wilk test: *P*-value < 0.001. (C) Non–survivors to stage III (N = 1), Shapiro-Wilk test: *P*-value = . (D) Awaiting stage III (N = 5), Shapiro-Wilk test: *P*-value = 0.664. *PVR*, pulmonary vascular resistance.

Pulmonary to systemic blood flow ratio

The mean pulmonary to systemic blood flow ratio for the stage II cohort was 1.0 ± 0.4. The mean pulmonary to systemic blood flow ratio in survivors to the stage III procedure was 0.9 ± 0.4. The mean pulmonary to systemic blood flow ratio in patients who died between the stage II and stage III procedures was 1.2 ± 0.1. The mean pulmonary to systemic blood flow ratio in patients who were awaiting the stage III procedure was 1.1 ± 0.4. Distributions of pulmonary to systemic blood flow ratios among these groups are shown in Figure 59.

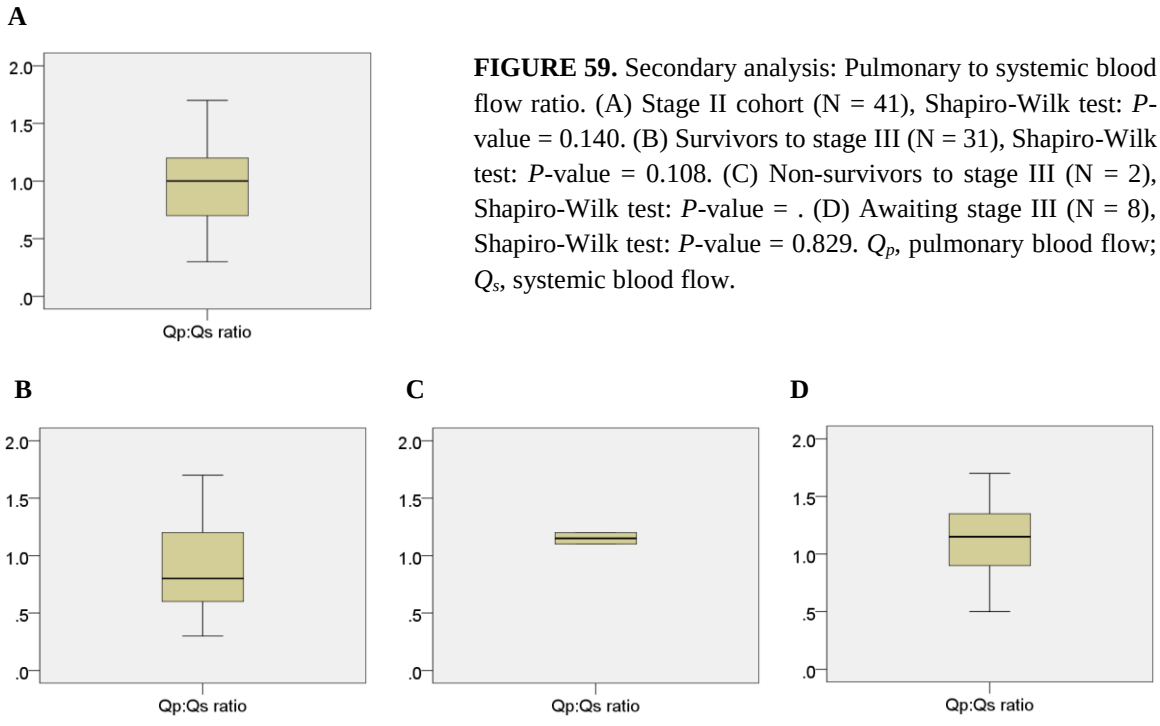

FIGURE 59. Secondary analysis: Pulmonary to systemic blood flow ratio. (A) Stage II cohort (N = 41), Shapiro-Wilk test: *P*-value = 0.140. (B) Survivors to stage III (N = 31), Shapiro-Wilk test: *P*-value = 0.108. (C) Non-survivors to stage III (N = 2), Shapiro-Wilk test: *P*-value = . (D) Awaiting stage III (N = 8), Shapiro-Wilk test: *P*-value = 0.829. Q_p, pulmonary blood flow; Q_s, systemic blood flow.

Arterial oxygen saturation

The mean arterial oxygen saturation for the stage II cohort was 71.4 ± 6.5 %. The median arterial oxygen saturation in survivors to the stage III procedure was 70.0 ± 9.3 %. The mean arterial oxygen saturation in patients who died between the stage II and stage III procedures was 72.5 ± 3.8 %. The mean arterial oxygen saturation in patients who were awaiting the stage III procedure was 74.6 ± 5.6 %. Distributions of arterial oxygen saturations among these groups are shown in Figure 60.

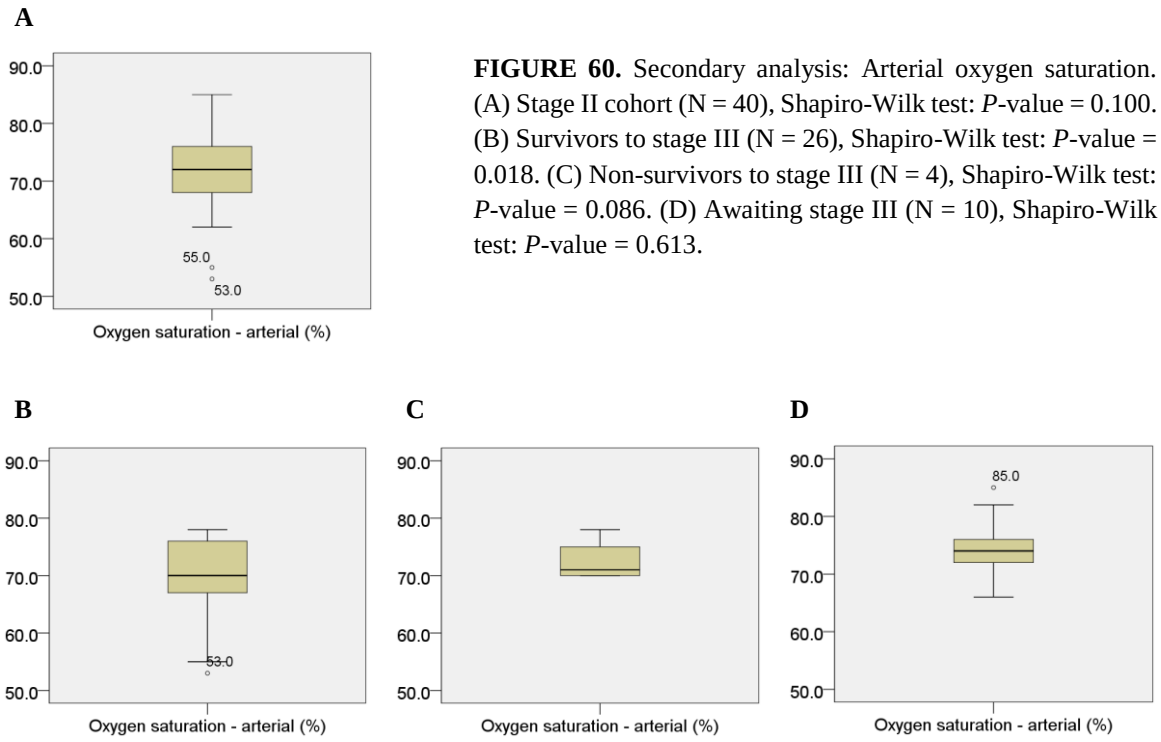

FIGURE 60. Secondary analysis: Arterial oxygen saturation. (A) Stage II cohort (N = 40), Shapiro-Wilk test: *P*-value = 0.100. (B) Survivors to stage III (N = 26), Shapiro-Wilk test: *P*-value = 0.018. (C) Non-survivors to stage III (N = 4), Shapiro-Wilk test: *P*-value = 0.086. (D) Awaiting stage III (N = 10), Shapiro-Wilk test: *P*-value = 0.613.

Oxygen saturation in the superior vena cava

The mean oxygen saturation in the superior vena cava for the stage II cohort was 43.0 ± 6.2 %. The mean oxygen saturation in the superior vena cava in survivors to the stage III procedure was 43.6 ± 6.7 %. The mean oxygen saturation in the superior vena cava in patients who died between the stage II and stage III procedures was 45.2 ± 5.1 %. The mean oxygen saturation in the superior vena cava in patients who were awaiting the stage III procedure was 40.2 ± 4.9 %. Distributions of oxygen saturations in the superior vena cava among these groups are shown in Figure 61.

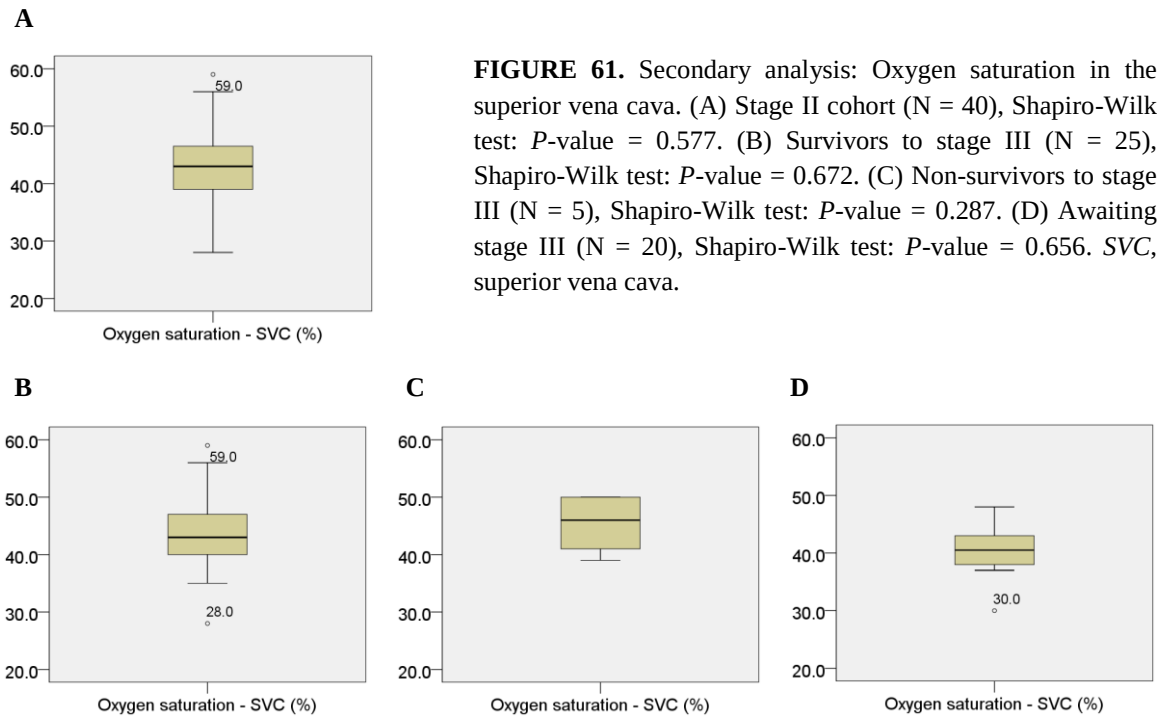

FIGURE 61. Secondary analysis: Oxygen saturation in the superior vena cava. (A) Stage II cohort (N = 40), Shapiro-Wilk test: *P*-value = 0.577. (B) Survivors to stage III (N = 25), Shapiro-Wilk test: *P*-value = 0.672. (C) Non-survivors to stage III (N = 5), Shapiro-Wilk test: *P*-value = 0.287. (D) Awaiting stage III (N = 20), Shapiro-Wilk test: *P*-value = 0.656. *SVC*, superior vena cava.

10.1.5 Operative parameters

Age at the stage II procedure

The median age at the stage II procedure for the stage II cohort was 4.1 ± 1.7 months. The median age at the stage II procedure in survivors to the stage III procedure was 4.1 ± 1.8 months. The mean age at the stage II procedure in patients who died between the stage II and stage III procedures was 4.3 ± 1.1 months. The mean age at the stage II procedure in patients who were awaiting the stage III procedure was 3.8 ± 1.3 months. Distributions of ages at the stage II procedure among these groups are shown in Figure 62.

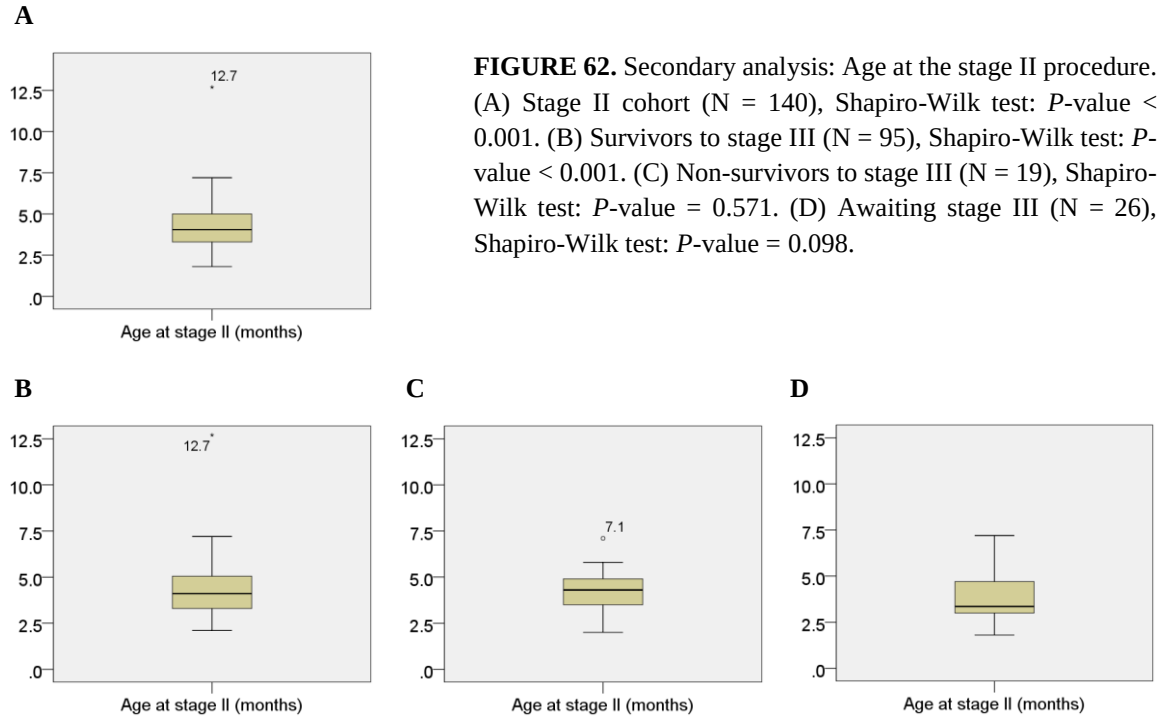

FIGURE 62. Secondary analysis: Age at the stage II procedure. (A) Stage II cohort (N = 140), Shapiro-Wilk test: *P*-value < 0.001. (B) Survivors to stage III (N = 95), Shapiro-Wilk test: *P*-value < 0.001. (C) Non-survivors to stage III (N = 19), Shapiro-Wilk test: *P*-value = 0.571. (D) Awaiting stage III (N = 26), Shapiro-Wilk test: *P*-value = 0.098.

Early stage II procedure

Twenty-one patients of the stage II cohort underwent an early stage II procedure. Fourteen patients survived to the stage III procedure, but one patient died between the stage II and stage III procedures. Six patients were awaiting the stage III procedure. Percentages of patients who underwent an early stage II procedure among these groups are shown in Figure 63.

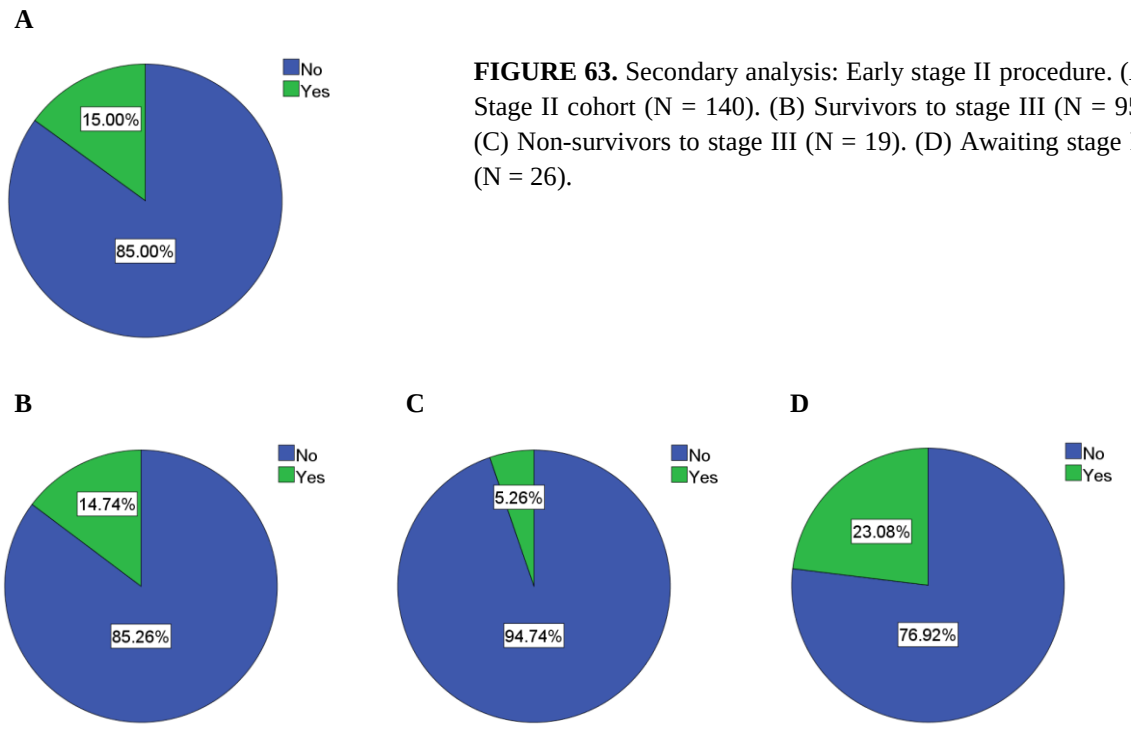

FIGURE 63. Secondary analysis: Early stage II procedure. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

Pulmonary artery augmentation during the stage II procedure

Seventy-one patients of the stage II cohort underwent pulmonary artery augmentation during the stage II procedure. Fifty-one patients survived to the stage III procedure, but nine patients died between the stage II and stage III procedures. Eleven patients were awaiting the stage III procedure. Percentages of patients who underwent pulmonary artery augmentation during the stage II procedure among these groups are shown in Figure 64.

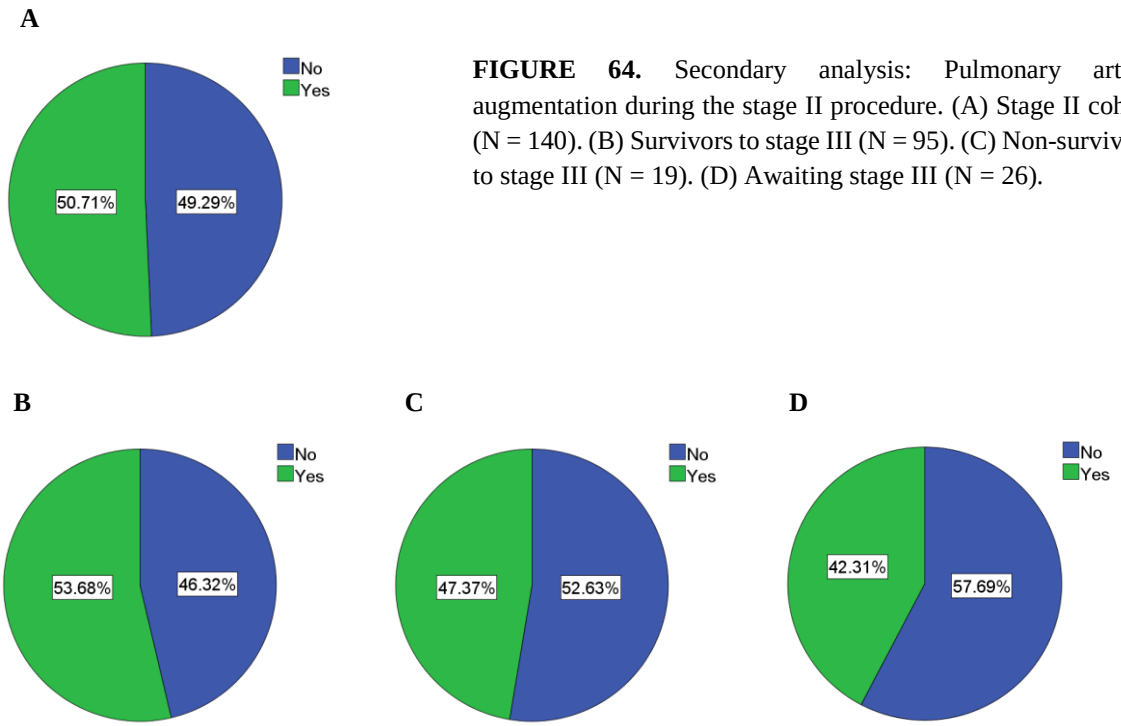

FIGURE 64. Secondary analysis: Pulmonary artery augmentation during the stage II procedure. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

Tricuspid valve intervention during the stage II procedure

Nineteen patients of the stage II cohort underwent tricuspid valve intervention during the stage II procedure. Ten patients survived to the stage III procedure, and one patient died between the stage II and stage III procedures. Eight patients were awaiting the stage III procedure. Percentages of patients who underwent tricuspid valve intervention during the stage II procedure among these groups are shown in Figure 65.

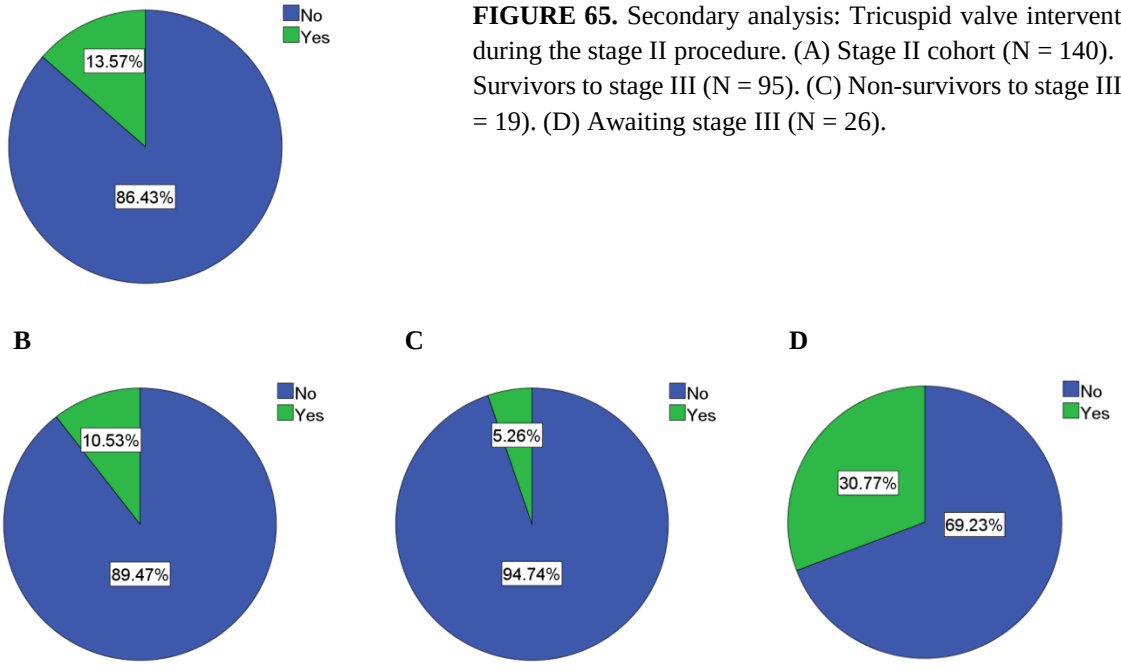

FIGURE 65. Secondary analysis: Tricuspid valve intervention during the stage II procedure. (A) Stage II cohort (N = 140). (B) Survivors to stage III (N = 95). (C) Non-survivors to stage III (N = 19). (D) Awaiting stage III (N = 26).

10.2 *Mortality between stage II and stage III*

A competing risk analysis was used to evaluate the mortality between the stage II and stage III procedures. The relative proportion (percentage) of each patient subgroup is shown in Figure 66.

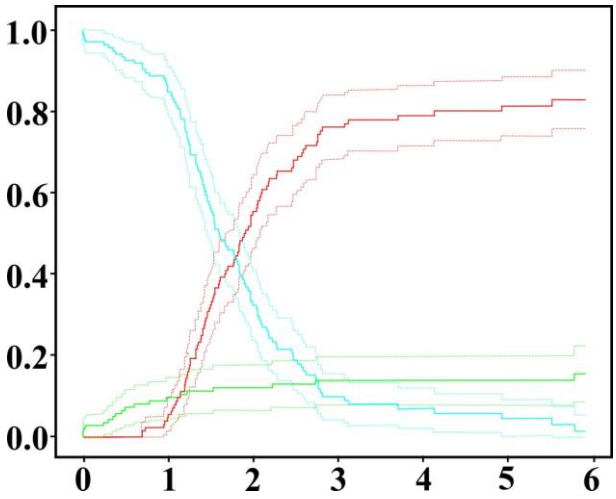

FIGURE 66. Competing risk analysis after the stage II procedure. The *X*-axis represents time (years after the stage II procedure); the *Y*-axis represents the entire population (%). Patients who are awaiting the stage III procedure (*blue curve*), non-survivors who died before the stage III procedure (*green*) and patients transitioned to the stage III procedure *(red curve*). Solid curves represent parametric point estimates. Dashed curves show the 95% confidence interval of each curve.

Immediately after the stage II procedure, all patients were alive (blue curve) and remained in this state until they proceeded to one of the mutually excluding end-states: they either died (green curve) or survived to the stage III procedure (red curve). The parametrical model showed that six years after the stage II procedure 82.9% of patients had proceeded to the stage III procedure, 1.4% remained in the transition state awaiting the stage III procedure, and 15.7% patients had died. Mortality increased most rapidly in the first year after the stage II procedure and remained relatively steady afterwards. No patient had received heart transplantation before the end of data gathering in January 2016.

Four patients (2.9%) died in the first 30 days after the stage II procedure, and five patients (3.6%) died during the hospitalization following the stage II procedure. Late and overall mortality between the stage II and stage III procedures could not be calculated because 26 patients were still awaiting the stage III procedure. As of January 2016, of 140 patients who had undergone the stage II procedure, 19 patients died and 95 patients underwent the stage III procedure. The causes of death between the stage II and stage III procedures are summarized in Table 19.

TABLE 19. Causes of death: stage II - stage III.

Cause of death	Early period (≤ 30 days)	Late period (> 30 days)	stage II – stage III (total)
Acute heart failure	3	3	6
Obstruction of the pulmonary blood flow	0	0	0
Coronary malperfusion	1	2	3
Unknown	2	1	3
Chronic heart failure	0	4	4
Cerebrovascular event	0	0	0
ARDS	1	0	1
Sepsis	0	2	2
Unknown	0	6	6

ARDS, adult respiratory distress syndrome.

10.3 *Risk factors for mortality between stage II and stage III*

10.3.1 Univariate analysis: Secondary endpoint

Parametric regression models using a competing risk methodology were constructed and used to perform a univariate analysis. Fourteen potential risk factors for mortality between the stage II and stage III procedures met the inclusion criteria for a univariate analysis, including 13 categorical variables and one continuous variable. Five met the screening criteria for statistical association: prematurity (*P*-value = 0.060), shunt type at the Norwood procedure (*P*-value = 0.063), HLHS subtype aortic atresia and mitral atresia (*P*-value = 0.130), endocardial fibroelastosis (*P*-value = 0.160), and postoperative impaired right ventricular function (*P*-value = 0.089). The results of the univariate analysis are summarized in Table 20.

TABLE 20. Results: secondary univariate analysis.

Variable	*P*-value
Demographic parameters	
Gender	0.990
Weight at stage II	0.550
Prematurity	0.060
Clinical parameters	
Shunt type at Norwood	0.063
PA intervention after Norwood	0.550
Neo-aorta intervention after Norwood	0.550
Anatomic/echocardiographic parameters	
HLHS subtypes:	
AA/MA	0.130
AA/MS	0.490
AS/MA	0.780
AS/MS	0.220
Endocardial fibroelastosis	0.160
PLSVC	0.930
Preoperative TI grade (II+ - IV)	0.990

TABLE 20. Results: secondary univariate analysis (continued).

Postoperative TI grade (II+ - IV)	0.740
Preoperative impaired RV function	0.440
Postoperative impaired RV function	0.089
Operative parameters	
Age at stage II (months)	0.930
Early stage II	0.230
PA augmentation during stage II	0.640
TV intervention during stage II	0.320

AA, aortic atresia; *AS*, aortic stenosis; *HLHS*, hypoplastic left heart syndrome; *MA*, mitral atresia; *MS*, mitral stenosis; *PA*, pulmonary artery; *PLSVC*, persistent left superior vena cava; *RV*, right ventricle; *TI*, tricuspid valve insufficiency; *TV*, tricuspid valve.

10.3.2 Multivariate analysis: Secondary endpoint

A parametric regression model using a competing risk methodology was constructed and used to perform a multivariate analysis, where no statistically significant risk factor was identified. The multivariate risk model is shown in Table 21.

TABLE 21. Results: multivariate secondary analysis.

Variable	Hazard ratio	95% CI	*P*-value
Prematurity	0.59	(0.24 – 1.43)	0.240
Shunt type at Norwood	0.86	(0.59 –1.26)	0.440
AA/MA subtype	1.05	(0.69 – 1.60)	0.830
Endocardial fibroelastosis	0.72	(0.46 – 1.13)	0.160
Postoperative impaired RV function	0.74	(0.40 – 1.38)	0.340

AA, aortic atresia; *MA*, mitral atresia; *RV*, right ventricle.

11 Survival analysis

This cohort was followed for 757.7 person-years until January 2016. The estimated 1- and 5-year survival after the Norwood stage I procedure was 73.0% and 67.6%, respectively. The Kaplan-Meier estimates of survival time for the entire cohort after the Norwood stage I procedure are shown in Figure 67.

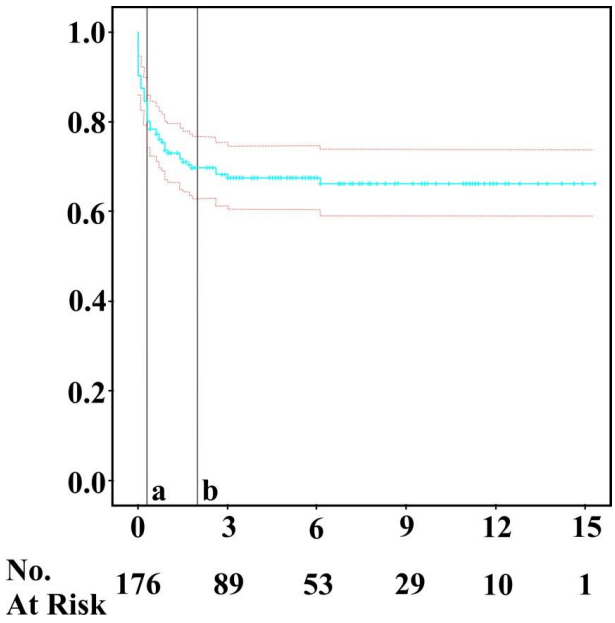

FIGURE 67. Kaplan-Meier analysis after the Norwood stage I procedure. The *X*-axis represents time (years after the Norwood procedure), the *Y*-axis represents the entire cohort who underwent the Norwood procedure. The blue curve represents the Kaplan-Meier estimates of survival. Solid curves show the 95% confidence interval of the survival curve. *a*, time of stage II procedure (median years after the Norwood procedure); *b*, time of stage III procedure (median years after the Norwood procedure).

CHAPTER IV: DISCUSSION

12 Mortality

Mortality after the Norwood procedure

The 30-day and hospital mortality after the Norwood procedure were reported to be 10 - 12% and 15 - 21%, respectively (Stasik *et al.*, 2006; Hehir *et al.*, 2008; Tabbutt *et al.*, 2012). Studies that were comprised only of patients with HLHS reported 30-day and hospital mortality after the Norwood procedure 10% and 17.4%, respectively (Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015). The mortality rates in this study were within a similar range: the 30-day mortality was 11.9%, and 14.8% of patients died during hospitalization following the Norwood procedure.

Interstage I mortality after the Norwood procedure in patients with HLHS was reported to be 10 – 15% (Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015). In the current study, the interstage I mortality was not evaluated. Medical records, mainly from the beginning of the study period, were often incomplete. Although there were 10 recorded deaths after the hospital discharge, the sum of all patients who proceeded to the interstage I period was unknown. Thus, the interstage I mortality could not be calculated.

The overall mortality between the Norwood stage I and stage II procedures in this study was 20.5%. Although these results are comparable to the recently published studies, which reported 75% survival to the stage II procedure in HLHS patients (Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015), the mortality rate remains high compared to other pediatric cardiac surgeries.

The Single Ventricle Reconstruction (SVR) trial reported that the most common cause of death in the first year after the Norwood procedure was cardiovascular in origin, followed by unknown causes, and multisystem organ failure. The majority of deaths occurred during hospitalization related to the Norwood procedure (Ohye *et al.*, 2012). Although the current study focused on mortality between the Norwood stage I and stage II procedures, a similar sequence of causes of death was found. The major cause of death between the Norwood stage I and stage II procedures in this study were acute heart failure, followed by unknown causes, and multisystem organ failure due to sepsis. The majority of deaths occurred within the first 30 days after the Norwood procedure (Table 9).

Mortality after the stage II procedure

The 30-day mortality in patients with single right and left ventricle pathologies, who underwent the Glenn or hemi-Fontan procedure, was reported to be 1.8%. However, the mortality in the HLHS subgroup reached 2.5% (Scheurer *et al.*, 2007). Mortality within the first 30 postoperative days, or during the hospitalization related to the stage II procedure, was reported in some other studies. They included either patients with single right and left ventricle pathologies (Lee *et al.*, 2012), or patients with HLHS (Hansen *et al.*, 2011; Menon *et al.*, 2013). The Glenn procedure was performed on all patients (Menon *et al.*, 2013), or

patients underwent either the Glenn or hemi-Fontan procedure (Hansen *et al.*, 2011; Lee *et al.*, 2012). The reported mortality rates in all of these studies ranged between 3 – 4.7%. Although the present study included only patients with HLHS, who all underwent the Glenn procedure, similar mortality rates were observed: the 30-day mortality was 2.9%, and 3.6% of patients died during the hospitalization related to the Glenn procedure. Since 26 patients were awaiting the stage III procedure, interstage II mortality could not be calculated.

In the current study, the leading cause of death between the stage II and stage III procedures were acute heart failure, followed by unknown causes, and chronic heart failure (Table 19). Although the acute heart failure was identified as the most common cause of death between the Norwood stage I and stage II procedures, this trend persists beyond the stage II procedure in the current study. Chronic heart failure, which was the third most common cause of death, occurred only in the late period after the stage II surgery. This suggests that the compensatory capacity of the volume overloaded right ventricle, which may be sufficient in the early postoperative period, decreases as patients approach the stage III procedure.

In contrast to the period between the Norwood stage I and stage II procedures, the majority of deaths between the stage II and stage III procedures occurred in the late period. This corresponds with reported low early mortality after the stage II procedure and suggests that after the initial decrease in mortality following the stage II procedure, the risk of death increases as patients move toward the stage III procedure.

Mortality after the stage III procedure

As of January 2016, only one death was recorded after the stage III procedure in the current study, which corresponds with reported excellent survival rates following the stage III procedure. Despite low mortality rates after the stage III procedure, concerns regarding the morbidity and mortality of the HLHS population in the long-term persist (Feinstein et al., 2012).

Overall mortality

The estimated 1- and 5-year survival after the Norwood procedure in the current study were 73.0% and 67.6%, respectively (Figure 67). The mortality was highest between the Norwood stage I and stage II procedures, and the majority of deaths occurred within the first 30 days after the stage I surgery. Although mortality declined significantly in the early period after the second stage operation, the competing risk model revealed that the increased risk of death persists up to one year after the stage II surgery (Figure 66). After that, the risk of death remained very low and corresponds with excellent survival rates after the stage II and stage III procedures, respectively.

Kaplan-Meier estimates showed that the survival of the entire cohort in the mid-term period was mainly determined by the mortality in the first year after the Norwood procedure (Figure 67). Consequently, improving outcomes in the early phase of the multi-stage reconstructive surgery could dramatically improve mid- to long-term survival in the HLHS population.

13 Risk factors for mortality

13.1 *Risk factors for mortality between Norwood stage I and stage II*

Although many studies have evaluated risk factors associated with higher mortality after the Norwood procedure, discrepancies among published results persist. Since patients with different underlying single ventricle pathologies may also differ in the risk factors for the Norwood procedure, these discrepancies may be partially attributed to the diversity of the patient population. The current study focused on patients with HLHS who primarily underwent the Norwood procedure as a stage I surgery. Potential factors associated with an increased risk of death between the Norwood stage I and stage II procedures were evaluated; these included demographic, clinical, anatomic/echocardiographic and operative parameters.

13.1.1 Demographic parameters

Gender

Several studies found that female patients undergoing pediatric cardiac surgery are at higher risk of hospital mortality, although the exact mechanism by which gender acts as a risk factor remains unknown (Chang *et al.*, 2002; Seifert *et al.*, 2007). Gender as a risk factor for mortality after the Norwood procedure has been evaluated several times; however, no association between gender and risk of hospital, interstage I, or overall mortality between the Norwood stage I and stage II procedures has been found (Stasik *et al.*, 2006; Hehir *et al.*, 2008; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015).

The current study was comprised of 125 males and 51 females (Figure 9). Consistent with the published results, this study found no significant association between gender and an increased risk of death between the Norwood stage I and stage II procedures in HLHS patients (Table 10).

Ethnic group

The relationship between various ethnic groups and higher risk of dying after the cardiac surgery in children with congenital heart defects was evaluated in several studies, predominantly from the USA. In risk-adjusted analyses, non-white groups, including blacks and Hispanics, had a higher risk of dying after congenital heart surgery than whites (Gonzalez *et al.*, 2003; Benavidez *et al.*, 2006; Oster *et al.*, 2011; Chan *et al.*, 2012; DiBardino *et al.*, 2012). Although these ethnic disparities in postoperative mortality were partially explained by unequal access to medical care and by the regional quality of health care providers, the evidence remains inconclusive (Gonzalez *et al.*, 2003; Benavidez *et al.*, 2006; Chan *et al.*, 2012). In studies that focused on the hospital and interstage I mortality after the Norwood procedure, Hispanic, black, Asian, and native American ethnicities were all identified as risk factors for increased mortality rates in the postoperative period (Ghanayem *et al.*, 2012; Dean *et al.*, 2013).

In the current study, almost all patients were of Caucasian origin. Thus, ethnicity as a potential risk factor for mortality between the Norwood stage I and stage II procedures was not evaluated.

Economic and social background

In the SVR trial, interstage I mortality was reportedly higher in patients from communities with higher poverty levels than in patients from more affluent communities. Surprisingly, patients from the poorest communities did not have the highest mortality rates (Ghanayem *et al.*, 2012).

The current study did not evaluate the economic and social background as potential risk factors for mortality because the required data were not available. The SVR trial suggested that limited access to health care in the population with limited resources was one possible mechanism for how the poverty level could influence the mortality after the Norwood procedure (Ghanayem *et al.*, 2012). This would not be the case in Germany where the public insurance system allows access to health care for all citizens, irrespective of their wealth or social status. However, poverty is often associated with a lower educational level, which may decrease compliance with treatment, including adherence to the therapy and outpatient visits in the interstage I period. Although the compliance of the families was not examined in the current study, decreased compliance in families with lower educational level may partially explain higher mortality rates in patients from the poorest communities.

Birth weight

Several studies identified low birth weight as a risk factor associated with adverse outcomes after the Norwood procedure (Stasik *et al.*, 2006; Tabbutt *et al.*, 2012; Alsoufi *et al.*, 2015). Smaller cardiac structures and increased tissue vulnerability in patients with lower birth weight can make the surgery more challenging. Determining the balance between the pulmonary and systemic circulation, including the selection of an adequate shunt size, which is vital in patients with univentricular hearts, can be more complicated in small patients. Low birth weight was associated with higher 30-day and hospital mortality after the Norwood procedure in some studies (Stasik *et al.*, 2006; Tabbutt *et al.*, 2012; Alsoufi *et al.*, 2015). Since no association between low birth weight and interstage I mortality has been observed (Simsic e*t al.*, 2005; Hehir *et al.*, 2008), low birth weight probably affects survival more in the early than in the late postoperative period.

The current study showed that patients with low birth weight (Figure 10) are at higher risk of dying between the Norwood stage I and stage II procedures (Tables 10, 17, 18). Within the interval between 1.8 and 4.6 kilograms, the risk decreases approximately 3-fold for every additional kilogram at birth (Table 17). Although the birth weight was dichotomized in the current study (Figure 11), a continuous variable was selected for the risk analysis because it provides more robust data.

Prematurity

The final weeks of gestation are essential for proper lung maturation. In patients with parallel pulmonary and systemic circulation, increased pressure in the pulmonary

vasculature of immature lungs can critically decrease pulmonary to systemic blood flow ratio. This decrease may reduce the oxygen delivery to vital organs (Barnea *et al.*, 1994; Barnea *et al.*, 1998). In addition, preterm newborns tend to weigh less than children delivered at term, and the low birth weight may pose an additional risk for these children. Reduced lung function and an increased rate of gastrointestinal and neurological complications may further contribute to the higher vulnerability of preterm born infants (Friedrich *et al.*, 2006; Thompson *et al.*, 2008; Natarajan *et al.*, 2011). Some studies suggested that patients with a single ventricle who were born prematurely tend to have a higher risk of interstage I death (Ghanayem *et al.*, 2012; Cross *et al.*, 2014). Other studies found no significant association between prematurity and an increased risk of hospital or interstage I mortality (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Hehir *et al.*, 2008).

Initially, this study sought to perform risk analysis using gestational age (Figure 12); however, since the data on gestational age were incomplete in almost 20% of patients (Table 3), prematurity (Figure 13) was evaluated instead. Prematurity was significant in the univariate risk analysis (Table 10), but it was excluded from further analysis due to its correlation with low birth weight (Figure 37). Although the association of prematurity with an increased risk of death between the Norwood stage I and stage II procedures was not evaluated in this study, increased pulmonary vascular resistance of immature lungs as well as increased vulnerability of other organ systems predispose preterm born children to increased postoperative morbidity and mortality. This may be especially true in a critically ill population, such as HLHS patients.

13.1.2 Clinical parameters

Genetic disorders and major extracardiac anomalies

The presence of genetic disorders and/or major extracardiac anomalies probably worsen the prognosis of patients with HLHS. The impact of these disorders or anomalies on survival of HLHS patients may become more obvious in the postoperative period, when increased stress after the surgery places greater demands on the compensatory capacity of all organ systems. The presence of genetic disorders and/or major extracardiac anomalies was identified as a risk factor for 30-day and hospital mortality after the Norwood procedure in some studies (Stasik *et al.*, 2006; Tabbutt *et al.*, 2012; Alsoufi *et al.*, 2015); however, other authors did not find any significant association with an increased risk of dying after the stage I surgery (Simsic *et al.*, 2005; Hehir *et al.*, 2008; Shamszad *et al.*, 2014).

In the current study, the analysis of genetic disorders and/or major extracardiac anomalies as potential risk factors for mortality between the Norwood stage I and stage II procedures was not performed. Genetic tests were not routinely carried out and the relevant early patients' medical records, primarily from the beginning of the study period, were often incomplete. Thus, potential implications of genetic disorders and/or major extracardiac anomalies for the survival of HLHS patients could not be established in the current study.

Preoperative cardiopulmonary resuscitation

The need for cardiopulmonary resuscitation after the Norwood procedure was one of the primary endpoints in the SVR trial; however, the impact of cardiopulmonary resuscitation before the Norwood procedure on postoperative outcomes was not examined (Tabbutt *et al*., 2012). The need for cardiopulmonary resuscitation in the preoperative period may signal underlying circulatory problems, which may worsen during or soon after the Norwood procedure, when the ventricle is forced to work under the maximal hemodynamic stress. In addition, the myocardial function following the cardiopulmonary resuscitation may be impaired (Checchia *et al.*, 2003), and open heart surgery with cardiopulmonary bypass may further decrease the myocardial function.

Since only 4% of patients underwent cardiopulmonary resuscitation in the preoperative period (Figure 14), the frequency of resuscitations was too low to support a reliable statistical analysis. Thus, the preoperative cardiopulmonary resuscitation as a potential risk factor for mortality was not evaluated in the current study. Since this study was comprised only of patients who underwent the Norwood procedure, patients who underwent cardiopulmonary resuscitation prior to the stage I surgery and died afterwards were not included. This may partially explain the low frequency of resuscitations observed in this study.

Preoperative catheter-based septal intervention

Preoperative catheter-based septal intervention is performed predominantly on patients with an intact or restrictive atrial septal defect to relieve the symptoms of obstructed pulmonary venous return. Although the intervention can be performed relatively safely in the majority of patients (Gossett *et al.*, 2006; Holzer *et al.*, 2008), underlying pathology of the pulmonary vasculature as a consequence of prolonged restriction before the intervention may persist beyond the Norwood procedure (Rychik *et al.*, 1999).

The catheter-based septal intervention was performed on four patients prior to the Norwood procedure (Figure 15). The Rashkind balloon atrial septostomy was performed on three patients, and one patient underwent a stent implantation. Similar to preoperative cardiopulmonary resuscitation, the frequency of performed catheter-based septal interventions was too low to support a reliable statistical analysis. Thus, the association between the performance of catheter-based septal intervention in the preoperative period and an increased risk of death between the Norwood stage I and stage II procedures was not evaluated.

Preoperative mechanical ventilation

Although the majority of patients with HLHS do not require mechanical ventilation before the Norwood procedure, some patients with markedly decreased arterial saturation may require mechanical ventilatory support. The need for mechanical ventilation prior to the Norwood procedure in patients with single ventricle was previously evaluated, but no significant association with an increased risk of death in the postoperative period was observed (Simsic *et al.*, 2005; Shamszad *et al.*, 2014).

The present study included 64 patients who had been mechanically ventilated at some point before the Norwood procedure (Figure 16). In the univariate risk analysis, no significant association between the need for mechanical ventilation in the preoperative period and an increased risk of death between the Norwood stage I and stage II procedures was observed (Table 10). Since some patients had been transported to our facility for the stage I surgery from abroad, and the long-distance transport may have affected the decision making process with respect to the need for mechanical ventilatory support during the transportation, the results presented in this study should be interpreted with caution.

13.1.3 Anatomic/echocardiographic parameters

Hypoplastic left heart syndrome–forme fruste

Because HLHS is morphologically a heterogeneous disease, various incomplete forms on the milder end of the spectrum may occur. Although several studies have evaluated the impact of various anatomic subtypes of HLHS on mortality following the Norwood procedure (Ghanayem *et al.*, 2012; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015), the impact of the incomplete form of HLHS on the mortality has not been evaluated.

This study sought to evaluate the association between the presence of an incomplete form of HLHS and an increased risk of death between the Norwood stage I and stage II procedures. Since the incomplete form of HLHS was present in only 2% of patients (Figure 17), the prevalence in the study population was too low to support a reliable statistical analysis. The low prevalence may be partially explained by the therapeutic options in this subset of HLHS patients. If left cardiac valves are patent and the left ventricle is capable of supporting the systemic circulation, a biventricular repair may be considered as an alternative to the Norwood procedure. Since this study focused on patients who primarily underwent the Norwood procedure as a stage I surgery, patients with milder forms of the disease who were candidates for and who subsequently underwent biventricular repair were not included.

Hypoplastic left heart syndrome subtypes

The impact of anatomic subtypes of HLHS on outcomes after the Norwood procedure have been analyzed in many studies, and several mechanisms have been proposed to explain how the specific anatomic subtype may affect the survival. Variants with aortic atresia were shown to be associated with a smaller diameter of the hypoplastic ascending aorta (Sathanandam *et al.*, 2010). Since the coronary perfusion depends on the retrograde blood flow through the ascending aorta, recurrent ischemic episodes, which may occur in the preoperative period, as well as during the Norwood procedure, may negatively impact right ventricular function and affect the survival in the postoperative period. Patients with aortic atresia and mitral stenosis were shown to have higher hospital mortality rates or greater need for transplantation after the Norwood stage I procedure than those with other anatomic subtypes (Vida *et al.*, 2008). Moreover, aortic atresia and mitral stenosis, and aortic stenosis and mitral atresia, were identified as risk factors for interstage I mortality (Cross *et al.*, 2014). The SVR trial identified only the anatomic subtype aortic atresia and mitral atresia as a risk factor for interstage I mortality (Ghanayem *et al.*, 2012). Several other studies

focused on the anatomic subtype aortic atresia and mitral stenosis, and this anatomic subtype was not significantly associated with an increased risk of 30-day, surgical, or interstage I mortality in these studies (Sathanandam *et al.*, 2010; Polimenakos *et al.*, 2011). Studies that evaluated all anatomic subtypes with respect to the outcomes between the Norwood stage I and stage II procedures found no significant association with an increased risk of death in the postoperative period (Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015).

The risk analysis performed in this study found no association between any of the anatomic subtypes and an increased risk of death between the Norwood stage I and stage II procedures (Figure 18; Table 10). These findings in conjunction with results from other studies that focused on HLHS patients (Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015) suggest that anatomic subtypes of HLHS do not affect survival between the Norwood stage I and stage II procedures in this population. However, the evidence remains inconclusive (Ghanayem *et al.*, 2012).

Anomalous pulmonary vein connection

An anomalous pulmonary vein connection was reported in about 5 - 6% of HLHS patients, who underwent the Norwood procedure (Seliem *et al.*, 1992; Furck *et al.*, 2010). Some forms of anomalous pulmonary vein connection may be associated with the restriction at the atrial level (Ward *et al.*, 1986), and HLHS patients with a such restriction have higher rates of pulmonary vascular abnormalities (Rychik *et al.*, 1999). Obstruction of the blood flow at the level of abnormally connected pulmonary veins, as well as restriction at the atrial level, may retrograde increase the pulmonary venous pressure. Increased pulmonary venous pressure may irreversibly damage the pulmonary vasculature, and if increased long enough, it may lead to the development of fixed pulmonary hypertension. Since maintaining the balance between the pulmonary and systemic perfusion is crucial in patients with HLHS (Barnea *et al.*, 1994; Barnea *et al.*, 1998), and this balance depends on the vascular resistance in the pulmonary circulation relative to the systemic circulation, the fixed pulmonary hypertension may increase the mortality in the preoperative as well as in the postoperative periods, and preclude the safe completion of the Fontan circulation.

In the current study, an anomalous pulmonary vein connection was present in 10 patients (Figure 19). A final multivariate model showed that patients with an anomalous pulmonary vein connection were at almost a 4-fold higher risk of death than patients with normally connected pulmonary veins (Table 17). However, the statistical significance shifted to a borderline area after final model validation (Table 18), which may be most likely attributed to the unobstructed variants of anomalous pulmonary vein connection. Since the data indicating whether the obstruction of the blood flow in these patients was or was not present were not available, this hypothesis could not be confirmed.

Ventricular septal defect

The ventricular septal defect allows transseptal blood flow during the cardiac development that may affect the size of the hypoplastic left ventricle as well as the morphology of left cardiac valves (Freedom *et al.*, 1977; Smith *et al.*, 2005). Tricuspid valve leaflets may be dysplastic, if the defect is localized in the perimembranous location (Smith *et al.*, 2005).

Since the ventricular septal defect is not an integral part of the anatomic abnormalities associated with HLHS, its impact on the mortality after the Norwood procedure is not well established.

In this study, a ventricular septal defect was present in 34 patients (Figure 20), constituting almost 20% of the entire cohort. In the univariate risk analysis, no association between the presence of a ventricular septal defect and a higher risk of death between the Norwood stage I and stage II procedures was observed (Table 10). Since the data with respect to the location of the ventricular septal defect and character of the blood flow across the interventricular septum were not available, the impact of specific subtypes of ventricular septal defects on mortality between the Norwood stage I and stage II procedures could not be evaluated.

Endocardial fibroelastosis

Endocardial fibroelastosis of the left ventricle was reported in approximately one third of HLHS fetuses, and its increased incidence was observed in patients with left ventricular patent inflow and obstructed outflow tract (O'Connor *et al.*, 1982; Axt-Fliedner *et al.*, 2014). Some authors reported that the right ventricle may be affected by endocardial fibroelastosis as well (Ucak *et al.*, 2010; Seki *et al.*, 2013).

In the current study, the endocardial fibroelastosis of the left ventricle was present in almost 30% of patients (Figure 21). In the univariate risk analysis, no significant association between the endocardial fibroelastosis of the left ventricle and an increased risk of death between the Norwood stage I and stage II procedures was observed (Table 10). The presence of endocardial fibroelastosis in this study was based on the macroscopic observations during the preoperative echocardiographic examinations. Since microscopic changes of the endo- and myocardial structure are the main characteristics of the disease (Bohlmeyer *et al.*, 2003), and the histological specimens were not obtained from the patients, milder or not fully developed forms may have been overlooked. Thus, the study results should be interpreted with caution.

Restrictive atrial septal defect

Some authors reported that patients with highly restrictive or intact atrial septal defect tend to have higher interstage I mortality rates (Hehir *et al.*, 2008). Sata and colleagues found that a restrictive atrial septal defect becomes a risk factor for the Norwood procedure only when it is combined with mitral or aortic atresia (Sata *et al.*, 2015). Studies which included only HLHS patients found no association between the presence of a restrictive atrial septal defect and an increased risk of death between the Norwood stage I and stage II procedures (Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015).

The data used in the current study showed that almost 55% of patients had some form of restriction at the atrial level (Figure 22). However, the data were incomplete in almost 23% of patients (Table 3), so no reliable risk analysis could be performed. Although the analysis was not performed, there are some risks connected to circulation in HLHS patients which should be taken into account. Obstruction of the blood flow at the atrial level due to the presence of a highly restrictive atrial septal defect may lead to congestion in pulmonary

veins and an increase in pulmonary artery pressure, especially if the mitral valve is not patent and decompression of the left atrium only takes place via the interatrial septum. Despite the atrial septectomy during the Norwood procedure, the underlying pathology of the pulmonary vasculature may be irreversible (Rychik *et al.*, 1999) and may preclude the safe performance of the stage II procedure. Since the decompression of the left atrium and thus increased pressures in the pulmonary circulation depend on the severity of the restriction, the restrictive atrial septal defect most likely affects the mortality in a severity-dependent manner.

Ascending aorta diameter

In a ductus-dependent circulation, coronary perfusion depends on the retrograde blood flow through the ascending aorta. In patients with a narrow ascending aorta, episodes of insufficient retrograde blood flow may lead to ischemic myocardial injury due to coronary hypoperfusion. Several studies have evaluated the impact of the diameter of the ascending aorta on survival after the Norwood procedure, but no association has been found (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Alsoufi *et al.*, 2015). Some authors performed risk analyses dividing patients into two groups based on the diameter of the ascending aorta, using as cut-off values 2 or 3 mm (Alsoufi *et al.*, 2015).

Although patients were also divided into two groups based on the diameter of the ascending aorta in the current study (Figure 24), a continuous variable (Figure 23) was used for the risk analysis instead. In the univariate risk analysis, no significant association between the diameter of the ascending aorta and an increased risk of death between the Norwood stage I and stage II procedures was observed (Table 10). This supports previously reported results and suggests that the diameter of the ascending aorta probably does not play a significant role in the mortality of HLHS patients between the Norwood stage I and stage II procedures.

Pulmonary valve insufficiency

The underlying pathology of the pulmonary valve is very rare in patients with HLHS and usually includes the various degrees of stenosis (Farra *et al.*, 2005; Cantinotti *et al.*, 2010); therefore, the consequences of pulmonary valve insufficiency in this population are not well established.

A pulmonary valve insufficiency grades I - IV was present in 19 patients before the Norwood procedure; two of them died between the Norwood stage I and stage II procedures (Figure 25). Grades III and grade IV insufficiency were not present. Because the data with respect to the pulmonary valve insufficiency were incomplete in almost 45% of patients (Table 3), no risk analysis was performed. However, based on previously reported results, the native pulmonary valve performance in the systemic circulation does not seem to pose a problem in the mid- to long-term after the surgery (Jenkins *et al.*, 1991; Schmid *et al.*, 1998).

Tricuspid valve insufficiency

A tricuspid valve insufficiency in patients with HLHS may be a result of an intrinsic abnormality of valve anatomy (Stamm *et al.*, 1997), or it may develop due to extrinsic

factors, such as dilatation of the right ventricle or myocardial ischemic injury during the surgery. In addition, the morphologic tricuspid valve is subjected to systemic pressure in HLHS patients and may not be capable of sustaining the competency in the high-resistance systemic circulation, even if the morphology of the valve is intact. All these factors may contribute to the development of the tricuspid valve insufficiency in HLHS patients.

A moderate to severe tricuspid valve insufficiency was reported in up to 10% of patients immediately after the Norwood procedure (Elmi *et al.*, 2011). Since the survival of HLHS patients depends on the performance of the right ventricle, an acute or chronic volume overload produced by significant tricuspid valve insufficiency may increase mortality and morbidity in the postoperative period. Shamszad and colleagues showed that a moderate to severe tricuspid valve insufficiency was associated with a higher risk of overall mortality between the Norwood stage I and stage II procedures in HLHS patients (Shamszad *et al.*, 2014). Other authors did not observe this association, neither for the interstage I mortality, nor for the overall mortality between the two stages (Hehir *et al.*, 2008; Alsoufi *et al.*, 2015).

In the current study, patients with a moderate to severe tricuspid valve insufficiency, either in the preoperative (Figure 26) or early postoperative period (Figure 27), were not at a higher risk of death prior to the stage II procedure than were patients with no or mild insufficiency (Table 10). Since the stage II procedure was performed relatively early in this study (median 3.7 months after the Norwood procedure), the volume overload produced by significant tricuspid valve insufficiency may have been compensated for by the increased work of the right ventricle in this short period. Although the mortality did not increase in these patients prior to the stage II surgery, increased demands on the performance of the right ventricle due to the volume overload may have impaired the right ventricular function. An impaired function of the right ventricle may affect survival in the later period, even if the tricuspid valve insufficiency is resolved during the stage II surgery. The association between the significant tricuspid valve insufficiency and an impaired right ventricular function was not examined in the current study.

Impaired right ventricular function

Since the circulation in patients with HLHS is supported only by the right ventricle, its performance is crucial for maintaining organ perfusion. Patients with an impaired right ventricular function are more prone to suffer from episodes of hemodynamic instability with detrimental effects on all organ systems.

A moderately to severely impaired right ventricular function at time of hospital discharge was identified as a risk factor for interstage I mortality in patients with single ventricle pathologies (Simsic *et al.*, 2005). However, some studies reported contradictory results. The interstage I and overall mortality between the Norwood stage I and stage II procedures was not higher in patients with a moderately to severely impaired right ventricular function (Hehir *et al.*, 2008; Alsoufi *et al.*, 2015). The SVR trial found no association between an increased risk of interstage I mortality and the right ventricular ejection fraction, right ventricular end-systolic and end-diastolic volumes, or right ventricular fractional area change (Ghanayem *et al.*, 2012).

In the current study, the right ventricular function before the Norwood procedure was impaired in 9 patients, and all 9 patients survived to the stage II procedure (Figure 28). Since the data were incomplete in almost 20% of patients and no death was recorded between the Norwood stage I and stage II procedures, the risk analysis with respect to the impaired right ventricular function in the preoperative period was not performed. The right ventricular function in the early period after the Norwood procedure was impaired in 22 patients (Figure 29) and the risk analysis showed that these patients had a 3-fold higher risk of dying between the Norwood stage I and stage II procedures, compared to patients with a postoperative preserved right ventricular function (Tables 17, 18). These findings underscore the importance of the right ventricular function in the post-Norwood period, when the right ventricle has to work under maximal hemodynamic stress.

13.1.4 Operative parameters

Age at the Norwood procedure

The Norwood procedure is usually performed early in the neonatal period. However, in certain patients, the procedure is performed at an older age for several reasons, including the late referral from primary and secondary care centers, delayed diagnosis, and a previously failed biventricular repair in borderline anatomic cases. Several studies suggested that an older age at the time of the Norwood procedure is associated with a higher risk of dying prior to the stage II procedure, possibly due to the development of a postoperative pulmonary hypertensive crisis and a prolonged excessive pulmonary blood flow in the preoperative period (Alsoufi *et al.*, 2011; Sames-Dolzer *et al.*, 2015).

Hehir and colleagues found that patients older than seven days at the time of the Norwood procedure were at a higher risk of interstage I death (Hehir *et al.*, 2008). Two major studies that focused on age at the time of the Norwood procedure and the subsequent mortality in patients with HLHS and other single ventricle pathologies found a higher mortality between the Norwood stage I and stage II procedures in patients older than two to three weeks at the time of the Norwood procedure (Alsoufi *et al.*, 2011; Sames-Dolzer *et al.*, 2015). Alsoufi and colleagues showed that this higher risk persists through all steps of the multi-stage reconstructive surgery (Alsoufi *et al.*, 2011). However, some authors found no association between the age at the time of the Norwood procedure and an increased risk of death in the postoperative period (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Alsoufi *et al.*, 2015).

The median age of patients at the Norwood procedure in this study was eight days, and 17 patients were older than two weeks at the time of the surgery (Figure 30). The risk analysis showed no significant association between the age at the Norwood procedure and a higher risk of dying prior to the stage II procedure (Table 10). Although these findings support some of the reported results and suggest that, with respect to the mortality, the Norwood procedure can be performed safely at older age, the evidence remains inconclusive (Alsoufi *et al.*, 2011; Alsoufi *et al.*, 2015; Sames-Dolzer *et al.*, 2015).

Shunt type at the Norwood procedure

Several retrospective studies analyzed the impact of the shunt type implanted during the Norwood procedure on postoperative outcomes; however, the results are inconsistent

(Hehir *et al.*, 2008; Alsoufi e*t al.*, 2015). The SVR trial, a prospective multicenter randomized study, compared the right ventricle-to-pulmonary artery conduit and modified Blalock-Taussig shunt; however, no significant association between the shunt type and 30-day or hospital mortality was observed (Tabbutt *et al.*, 2012). A modified Blalock-Taussig shunt was associated with a higher risk of interstage I mortality in patients with absent or mild tricuspid valve insufficiency. Although this association could not be explained, the authors speculated that the diastolic run-off associated with the modiefied Blalock-Taussig shunt may contribute to episodes of hemodynamic instability, which may become more evident during periods of an increased stress (Ghanayem *et al.*, 2012).

Although significant in a univariate analysis (Table 10), multivariate models which included the shunt type implanted during the Norwood procedure as a variable showed no significant association between the shunt type and an increased risk of death between the Norwood stage I and stage II procedures. In addition, subsequent evaluation (Tables 14, 15) and calibration (Figures 38, 39; Table 16) of the candidate multivariate models eliminated all models which included the shunt type as a variable. Thus, despite having adequate data for a reliable statistical analysis (Figure 31), the superiority of one type of shunt over another with respect to the mortality prior to the stage II procedure could not be confirmed. Unlike in the SVR trial, the shunt type was not randomized and the propensity score matching was not performed in the current study. Thus, the results presented in this study should be interpreted with caution.

Shunt revision during the Norwood procedure

Shunt revision during the Norwood procedure was performed on 14 patients in the current study (Figure 32) and included shunt exchange, either for a shunt of another size or for another shunt type, as well as revision of the proximal or distal anastomosis. Shunt exchange due to inappropriate shunt size, or reduction of the blood flow through the shunt with clipping, were carried out perioperatively in four patients. Revision of shunt anastomosis was performed perioperatively in most cases because of bleeding or to correct the length of the shunt. In the univariate analysis, the perioperative shunt revision was associated with an increased risk of death between the Norwood stage I and stage II procedures (Table 10). However, the final multivariate model showed no association between the perioperative shunt revision and an increased risk of death between the Norwood stage I and stage II procedures (Table 18). Thus, if problems with proximal or distal anastomosis, or inadequate shunt size, are recognized and corrected during the surgery, the survival prior to the stage II procedure may not be affected.

Neo-aorta revision during the Norwood procedure

Revision of the newly reconstructed aorta during the Norwood procedure was performed on five patients in the current study (Figure 33), while 14 patients underwent the shunt revision. This suggests that the selection of an adequate shunt size, as well as its implantation, may lead to more complications during the surgery than the reconstruction of the ascending aorta and aortic arch. However, postoperative complications associated with the neo-aorta, including the risk of recoarctation, may be higher in patients who required

perioperative revision of the anastomoses used to reconstruct the ascending aorta and the aortic arch. In a report from the SVR trial, patients who underwent the intervention due to a recoarctation had higher pulmonary artery pressure, higher pulmonary vascular resistance, and an increased right ventricular end-diastolic volume at the pre-stage II evaluation. Mortality at one year after the Norwood procedure in the intervention group did not increase (Hill *et al.*, 2013).

Since the revision of the neo-aorta was performed on only 3% of patients in the current study, the frequency for the statistical analysis was too low to support a reliable risk analysis. The association between the revision of the neo-aorta during the stage I surgery and an increased risk of recoarctation in the postoperative period was due to the low frequency also not established.

Deep hypothermic circulatory arrest duration

A prolonged duration of the deep hypothermic circulatory arrest may signal more extensive surgery or higher rate of perioperative complications, and thus may be associated with decreased survival rates in the early and late postoperative periods. In addition, a higher rate of neurological injuries was reported with an increasing duration of the deep hypothermic circulatory arrest in non-linear manner (Wypij *et al.*, 2003), and these injuries may contribute to higher mortality rates in the postoperative period. The duration of the deep hypothermic circulatory arrest was identified as a risk factor for 30-day mortality (Tabbutt *et al.*, 2012); hospital and interstage I mortality do not seem to be affected (Simsic *et al.*, 2005; Stasik *et al.*, 2006; Hehir *et al.*, 2008).

The risk analysis performed in this study showed that the overall mortality between the Norwood stage I and stage II procedures in patients with HLHS was not affected by the duration of the deep hypothermic circulatory arrest (Table 10). Since the current study focused on the whole period between the first and second stage surgeries, the impact on the mortality in the first 30 days after the Norwood procedure was not evaluated. In addition, the maximal duration of the deep hypothermic circulatory arrest in the current study was about 80 minutes (Figure 34). Thus, the risk analysis presented in this study refers to the interval with an upper limit of 80 minutes, and the possible implications of longer durations on mortality cannot be drawn. Furthermore, the impact of the duration of the deep hypothermic circulatory arrest on the morbidity, including the possible neurologic injury and neurodevelopmental outcomes after the Norwood procedure, was not examined in the current study.

Lowest temperature during the Norwood procedure

The protective effect of hypothermia during the cardiac surgery is well established. In addition to neuroprotection as a consequence of decreased cerebral metabolism and oxygen demand (Nussmeier, 2005), hypothermia provides myocardial protection as well. Some authors reported that after the myocardial ischemia, the proportion of the ischemic risk zone that becomes necrotic directly correlated with the temperature (Hale et al., 1999; Hale *et al.*, 2011).

The vast majority of patients in the current study underwent the Norwood procedure with the use of the deep hypothermic circulatory arrest and targeted temperature 16 – 20°C during the arrest; in a few patients antegrade cerebral perfusion in mild hypothermia was employed (Figure 35). In the univariate risk analysis, no significant association between the lowest temperature during the Norwood procedure and an increased risk of death prior to the stage II surgery was observed (Table 10). Since the impact of preoperative factors on increased morbidity in the postoperative period was not in the scope of the current study, the association between the lowest temperature during the stage I surgery and increased rates of myocardial dysfunction or neurological injury in the postoperative period was not examined.

Concomitant cardiac surgery

The Norwood procedure is technically very complicated and has one of the highest mortality rates in the pediatric cardiac surgery (Jacobs *et al.*, 2005; Feinstein et al., 2012). Patients with additional cardiac anomalies may require more extensive surgery, which may be reflected in higher mortality rates in the postoperative period. However, Alsoufi and colleagues reported that the additional cardiac lesions requiring concomitant cardiac surgery do not affect overall mortality between the Norwood stage I and stage II procedures in HLHS patients (Alsoufi *et al.*, 2015). Since the concomitant cardiac surgery was performed on only 4% of patients in the current study (Figure 36), a reliable risk analysis could not be performed.

13.2 *Risk factors for mortality between stage II and stage III*

Several studies have analyzed potential risk factors for mortality after the stage II procedure, but similar to the risk factors for mortality after the Norwood procedure, discrepancies in published results persist. These discrepancies may be attributed to the diversity of the patient population with single ventricle pathology, as well as to various technical modifications for the stage II surgery. Thus, the extrapolation of the published results to similar but actually quite different populations may not be justifiable. Because this study focused on patients with HLHS who all underwent the Glenn procedure as a stage II surgery, results presented in the current study should be generalized to this specific population. Potential factors associated with an increased risk of death between the stage II and stage III procedures were evaluated; these included demographic, clinical, anatomic/echocardiographic, catheterization, and operative parameters.

13.2.1 Demographic parameters

Gender

Since female pediatric patients undergoing cardiac surgery were ssociated with an increased risk of death (Chang *et al.*, 2002; Seifert *et al.*, 2007), several studies analyzed gender as a risk factor for mortality after the stage II procedure. A multicenter retrospective study published by Dean and colleagues, which was comprised of 844 males and 435 females with HLHS who underwent the Glenn procedure, found no association between gender and an increased risk of death during the hospitalization following the stage II

procedure (Dean *et al.*, 2013). Gender was also not identified as a risk factor for interstage II mortality (Carlo *et al.*, 2011).

The current study was comprised of 102 males and 38 females (Figure 42). Similar to the period between the Norwood stage I and stage II procedures, gender was not identified as a risk factor associated with an increased risk of death between the stage II and stage III procedures (Table 20). Thus, based on the risk analysis performed in this study, gender does not seem to increase the risk of death prior to the completion of the Fontan circulation in HLHS patients, who underwent the Norwood and the Glenn procedures.

Weight at the stage II procedure

A failure to thrive and poor weight gain between the Norwood stage I and stage II procedures is a common finding in children with HLHS (Kelleher *et al.*, 2006; Anderson *et al.*, 2010). Poorer nutritional status and lower weight-for-age z-score at the Glenn procedure are seen in patients with worse right ventricular function, more frequent readmissions during the interstage I period, and higher arterial oxygen saturation, reflecting the imbalance between the pulmonary and systemic circulation (Kelleher *et al.*, 2006). A risk analysis performed by Kogon and colleagues showed no association between the weight at the time of the stage II surgery and death occurring within the 30 days after the stage II surgery. Although all patients underwent the Glenn procedure as a stage II surgery, patients with both single right and left ventricle pathologies were included (Kogon *et al.*, 2008). However, lower weight-for-age z-score at the time of the Glenn procedure was identified as risk factor for interstage II mortality (Carlo *et al.*, 2011).

The median weight at the stage II procedure in the current study was 5.1 ± 1.2 kg (Figure 43). The risk analysis showed no association between the weight at the stage II procedure and an increased risk of death between the stage II and stage III procedures. Although the weight at the stage II procedure (5.2 ± 1.0 kg in survivors and 5.2 ± 0.9 kg in non-survivors) was considerably lower than reported in the study from Carlo and colleagues (6.16 ± 1.02 kg in survivors and 5.32 ± 0.79 kg in non-survivors), which could be most likely attributed to the early performance of the stage II surgery in the current study (median of age 4.1 ± 1.7 months for the entire cohort), the current study showed that the stage II surgery can be performed safely at these lower weights. Since this study focused on the mortality during the whole period between the stage II and stage III procedures, the impact of the weight at the stage II procedure on the interstage II mortality was not evaluated.

Prematurity

Although several studies have analyzed preterm birth as a risk factor for the Norwood procedure (Stasik *et al.*, 2006; Ghanayem *et al.*, 2012; Alsoufi *et al.*, 2015), the impact of prematurity on survival after the stage II procedure is not well established. An increased pressure in pulmonary circulation of immature lungs trigger vascular remodeling with intimal and medial proliferation in the pulmonary arteries. Structural alterations of the pulmonary vasculature associated with pulmonary hypertension (Shimoda *et al.*, 2013) may persist beyond the neonatal period, and thus may preclude the safe completion of the Fontan circulation.

In the current study, 13 patients who underwent the stage II procedure were born prematurely (Figure 44). Although prematurity was identified as a risk factor for mortality in the univariate analysis (Table 20), the multivariate model showed no significant association between prematurity and an increased risk of death between the stage II and stage III procedures (Table 21). Although prematurity may pose a risk for the Norwood procedure (Ghanayem *et al.*, 2012; Alsoufi *et al.*, 2015), the risk analysis performed in the current study showed that if preterm born children survive to the stage II procedure, their survival to the stage III procedure may be similar to those who were born at term.

13.2.2 Clinical parameters

Shunt type at the Norwood procedure

Lai and colleagues studied 56 patients, predominantly with HLHS, all of whom underwent the Glenn procedure as a stage II surgery. They found no difference in 12-month survival after the Glenn procedure between the patients who received a modified Blalock-Taussig shunt or a right ventricle-to-pulmonary artery conduit during the Norwood procedure (Lai *et al.*, 2007). The initial SVR trial report showed superior transplant-free survival to 12 months after the Norwood procedure in patients who initially received a right ventricle-to-pulmonary artery conduit (Ohye *et al.*, 2010). However, the superiority of the right ventricle-to-pulmonary artery conduit over a modified Blalock-Taussig shunt with respect to the survival was not confirmed at three years after initial randomization (Newburger *et al.*, 2014).

The current study showed that in patients who underwent the Glenn procedure, the shunt type implanted during the Norwood procedure (Figure 45) was not significantly associated with an increased risk of death between the stage II and stage III procedures (Table 21). Although this supports the results from the SVR extension trial (Newburger *et al.*, 2014), the period prior to which mortality was evaluated differs. This study focused on the period between the stage II and stage III procedures, whereas the SVR extension trial evaluated survival to three years after the Norwood procedure. Moreover, all patients included in the current study underwent the Glenn procedure as a stage II surgery, which was not the case in the SVR trial. Since the Glenn procedure was performed at a median of three months and the stage III procedure at a median of two years after the Norwood procedure in the current study, the superiority of the right ventricle-to-pulmonary artery conduit over a modified Blalock-Taussig shunt in survival to 12 months after the Norwood procedure, as reported in the initial report from the SVR trial (Ohye *et al.*, 2010), was not evaluated.

Pulmonary artery intervention after the Norwood procedure

Stenosis of pulmonary arteries is a potential complication after the Norwood procedure in patients with HLHS. The risk of undergoing the pulmonary artery intervention after the Norwood procedure was reported higher in patients who received a right ventricle-to-pulmonary artery conduit compared to patients who received a modified Blalock-Taussig shunt (Ohye *et al.*, 2010; Gist *et al.*, 2013), and the implantation of the conduit on the right side was associated with a higher rate of pulmonary artery interventions than the left-sided placement (Gist *et al.*, 2013).

In this study, 11 pulmonary artery interventions were performed between the Norwood stage I and stage II procedures on ten patients who proceeded to the post-stage II period (Figure 46); there were two surgical and nine catheter-based interventions. In all patients, the indication for the pulmonary artery intervention was pulmonary artery stenosis, in most cases localized on the left side. Consistent with previously published studies, the majority of patients who underwent the pulmonary artery intervention received a right ventricle-to-pulmonary artery conduit during the Norwood procedure. The risk analysis performed in the current study did not reveal a significant association between the pulmonary artery intervention prior to the stage II procedure and a higher risk of death between the stage II and stage III procedures (Table 20). This suggests that if patients with pulmonary artery stenosis who undergo the pulmonary artery intervention after the Norwood procedure survive to the stage II procedure, their further survival to the stage III surgery may not be affected.

Neo-aorta intervention after the Norwood procedure

The recoarctation of the neo-aorta contributes significantly to the morbidity after the Norwood procedure. In the SVR trial, almost 20% of patients underwent the neo-aorta intervention due to the recoarctation within the first year after the Norwood procedure, and the recoarctation rate was higher in patients with the right ventricle-to-pulmonary artery conduit than in patients with a modified Blalock-Taussig shunt. However, the intervention was not associated with decreased transplant-free survival at one year after the initial randomization (Hill *et al.*, 2013).

In the current study, neo-aorta intervention was performed on 15 patients who proceeded to the post-stage II period (Figure 47); there were three surgical and 12 catheter-based interventions. Neo-aorta intervention was not significantly associated with the right ventricle-to-pulmonary artery conduit in this study, and the risk analysis showed no significant association between the neo-aorta intervention prior to the stage II procedure and a higher risk of death between the stage II and stage III procedures (Table 20). These results are consistent with those reported by Hill and colleagues and suggest that the neo-aorta intervention after the Norwood procedure does not affect the survival of these patients in the short-term.

13.2.3 Anatomic/echocardiographic parameters

Hypoplastic left heart syndrome subtypes

Although the anatomic subtypes of HLHS have more often been evaluated as risk factors for the Norwood procedure than for the stage II procedure (Ghanayem *et al.*, 2012; Shamszad *et al.*, 2014; Alsoufi *et al.*, 2015), some studies have analyzed the association between the various anatomic subtypes and outcomes after the stage II procedure. Friedman and colleagues analyzed 194 patients who underwent the Glenn procedure, 141 of whom were diagnosed with HLHS. The anatomic subtype aortic atresia and mitral stenosis was not associated with an increased risk of death at 18 months after the Glenn procedure (Friedman *et al.*, 2011). Carlo and colleagues showed no association between any of the

four anatomic subtypes and an increased risk of death in the interstage II period (Carlo *et al.*, 2011).

The risk analysis performed in this study showed that none of the anatomic subtypes (Figure 48) were significantly associated with an increased risk of death between the stage II and stage III procedures (Tables 20, 21). Although the anatomic subtype aortic atresia and mitral atresia showed statistical significance in the univariate analysis (Table 20), the multivariate model revealed no association of this HLHS subtype with an increased risk of death prior to the completion of the Fontan circulation (Table 21).

Endocardial fibroelastosis

Although the endocardial fibroelastosis was reported in up to one third of fetuses with HLHS (Axt-Fliedner *et al.*, 2014), its impact on survival after the stage II procedure in patients with HLHS was not previously examined. The endocardial fibroelastosis was present in almost 27% patients of the stage II cohort (Figure 49). Similar to the period between the Norwood stage I and stage II procedures, no significant association between the endocardial fibroelastosis of the left ventricle and an increased risk of death between the stage II and stage III procedures was found (Table 21). Since the diagnosis of endocardial fibroelastosis of the left ventricle was based on macroscopic observations during the echocardiographic examination before the Norwood procedure, similar limitations with respect to the possible underdiagnosis of this condition as for the period between the Norwood stage I and stage II procedures apply.

Persistent left superior vena cava

The presence of the persistent left superior vena cava may pose a technical challenge to performing a superior cavopulmonary anastomosis. In addition, the blood flow patterns in the central pulmonary arteries may be altered after the bilateral bidirectional Glenn procedure compared to the unilateral approach. Higher rates of postoperative complications, including an increased risk of thrombus formation and unfavorable growth of the central pulmonary arteries, as well as lower rates of conversions to Fontan circulation, were reported in patients with bilateral superior cavopulmonary anastomosis (Iyer *et al.*, 2000).

A persistent left superior vena cava was present in 17 patients of the stage II cohort (Figure 50), all of whom underwent the bilateral bidirectional Glenn procedure. Despite reported higher rates of postoperative complications after the bilateral approach, this study did not identify the persistent left superior vena cava as a risk factor for mortality between the stage II and stage III procedures (Table 20). However, the long-term impact of bilateral cavopulmonary anastomosis on morbidity and mortality in this specific subset of HLHS patients still needs to be determined.

Neo-aortic valve insufficiency

A mild insufficiency of the autologous pulmonary valve in systemic circulation is a frequent finding after the surgery, but it is usually not hemodynamically significant (Schmid *et al.*, 1998). Although the autologous pulmonary valve seems to perform

adequately in mid- to long-term (Schmid *et al.*, 1998; Jenkins *et al.*, 1991), a recurrent pathology of the ascending aorta and aortic arch may lead to a significant neo-aortic valve insufficiency even long after the initial surgery (Pusca *et al.*, 2006), and some authors raise concerns about the performance of the neo-aortic valve into adulthood (Cohen *et al.*, 2003).

The neo-aortic valve insufficiency grades I - IV was present in almost 37% of patients during the echocardiographic examination before the stage II surgery (Figure 51); however, more than mild regurgitation was seen in only one patient. This corresponds to the published studies (Schmid *et al.*, 1998) and suggests that the neo-aortic valve performs well in the systemic circulation after the Norwood procedure in HLHS patients. Since the data with respect to the neo-aortic valve performance were incomplete in almost 20% of patients (Table 6), the risk analysis for mortality between the stage II and stage III procedures was not performed.

Tricuspid valve insufficiency

The function of the tricuspid valve in patients with a single right ventricle has important implications for survival during and after the multi-stage surgical reconstruction. Some authors speculated that volume unloading after the stage II procedure may promote remodeling of the right ventricle and decrease the grade of the tricuspid valve insufficiency. Although it has been shown that the relative size of the tricuspid valve annulus and the coaptation length of the anterior and septal leaflets improves concomitantly with the width of the vena contracta, the grade of the tricuspid valve insufficiency remains unchanged (Kasnar-Samprec *et al.*, 2012; Ugaki *et al.*, 2013). In a report from Lee and colleagues, clinically significant atrioventricular valve regurgitation was associated with a higher risk of death prior to the completion of the Fontan circulation. Patients with both single right and left ventricle pathologies were included, and hemi-Fontan procedure was performed predominantly as a stage II surgery (Lee *et al.*, 2012). In studies focusing on patients with HLHS, the presence of a significant tricuspid valve insufficiency in the early postoperative period was associated with a higher risk of death prior to the stage III procedure (Carlo *et al.*, 2011; Hansen *et al.*, 2011).

In the current study, moderate to severe tricuspid valve insufficiency, either in the preoperative (Figure 52) or early postoperative period (Figure 53), was not associated with an increased risk of death between the stage II and stage III procedures (Table 20). Since similar results were observed for the period between the Norwood stage I and stage II procedures (Table 10), a volume overload due to a significant tricuspid valve insufficiency may be compensated for in the short- to mid-term by the increased work of the right ventricle. Since the stage III procedure was performed at a median of 2 years after the Norwood procedure, sufficient time may not have passed for the right ventricle to decompensate. However, the compensatory capacity of the volume-overloaded right ventricle would most likely decrease in the long-term, and if the significant tricuspid valve insufficiency is not resolved early enough, it would most likely lead to the failure of the Fontan circulation. It should be noted that an association between the presence of significant tricuspid valve insufficiency and impaired right ventricular function was not analyzed in the current study.

Impaired right ventricular function

As in all patients with single right ventricles, the entire circulation in patients with HLHS depends on the right ventricular performance. Lee and colleagues reported that ventricular dysfunction was a significant risk factor for survival to Fontan completion; however, patients with both single right and left ventricle pathologies were included, and the hemi-Fontan was performed predominantly as a stage II surgery (Lee *et al.*, 2012). Moderately impaired right ventricular function was identified as a risk factor for interstage II mortality in patients with single right and left ventricle pathologies (François *et al.*, 2016); this was not the case if only HLHS patients were included (Carlo *et al.*, 2011).

A univariate risk analysis performed in the current study revealed a significant association between an impaired function of the right ventricle in the early post-stage II period and an increased risk of death prior to the stage III surgery (Table 20); however, this association was not confirmed in the multivariate analysis (Table 21). Although the crucial role of the right ventricular performance in patients with a single right ventricle is obvious, this study failed to identify impaired right ventricular function, either in the preoperative (Figure 54) or early postoperative period (Figure 55), as a risk factor for mortality between the stage II and stage III procedures; there are three possible explanations for this.

First, the evaluation of the right ventricular function in the early postoperative period was based on the first echocardiographic examination after the stage II surgery. In some patients, myocardial dysfunction following cardiopulmonary bypass and open heart surgery may have been present. Since this dysfunction may only be temporary, the right ventricular function may have improved over time. Second, the stage II surgery leads to volume unloading and remodeling of the right ventricle (Kasnar-Samprec *et al.*, 2012; Ugaki *et al.*, 2013), which may have led to an improvement of the right ventricular function over time in some patients (Bell e*t al.*, 2011). Third, the stage III procedure was performed at the median of 1.6 years after the stage II procedure. Although the mortality rates due to a chronic heart failure were increasing towards the stage III procedure compared to the early post-stage II period (Table 19), a longer time between the stage II and stage III procedures may have been needed to show a statistical significance for the myocardial dysfunction.

13.2.4 Catheterization parameters

Right ventricular end-diastolic pressure

Higher right ventricular filling pressures are seen in patients with an impaired right ventricular relaxation and may signal the presence of pulmonary hypertension (Murch *et al.*, 2015). Both right ventricular diastolic dysfunction and pulmonary hypertension may unfavorably affect survival after the stage II procedure and preclude the completion of the Fontan circulation. In the report from the SVR trial, which focused on postoperative outcomes and factors associated with a prolonged length of stay in the hospital following the stage II procedure, higher right ventricular end-diastolic pressure was identified as a risk factor for hospital mortality in the univariate analysis. A multivariate analysis was not performed due to a low hospital mortality/transplant rate following the stage II procedure

(Schwartz *et al.*, 2014). In several other studies, which included patients with single right and left ventricle pathologies (Friedman *et al.*, 2011; Lee *et al.*, 2012), or patients with HLHS (Carlo *et al.*, 2011; Hansen *et al.*, 2011), and who underwent the Glenn (Carlo *et al.*, 2011; Friedman *et al.*, 2011) or, in most cases, the hemi-Fontan (Hansen *et al.*, 2011; Lee *et al.*, 2012) procedures, no significant association between the ventricular end-diastolic pressure and increased risk of death at different periods after the stage II procedure was observed.

In the current study, the data with respect to the right ventricular end-diastolic pressures (Figure 56) were incomplete in almost 20% of patients (Table 6). Thus, a reliable risk analysis could not be performed.

Pulmonary artery mean pressure

The feasibility of the stage II procedure depends on the pressures in the pulmonary circulation, and the pressures in the pulmonary arteries are routinely assessed during the pre-stage II catheterization (Feinstein *et al.*, 2012). Increased pressures in the pulmonary circulation put extra demands on the right ventricular performance, and may retrograde increase pressure in the vena cava superior after the stage II procedure. The pulmonary artery mean pressure measured during the catheterization before the stage II procedure was not identified as a risk factor for interstage II mortality (Carlo *et al.*, 2011), for death prior to Fontan completion (Lee *et al.*, 2012), or for mortality at five years after the Glenn procedure (Scheurer *et al.*, 2007). The transpulmonary pressure gradient defined by the difference between pulmonary artery mean pressure and left atrial pressure has also not been associated with an increased risk of death after the stage II procedure (Scheurer *et al.*, 2007; Friedman *et al.*, 2011; Schwartz *et al.*, 2014).

Consistent with most published results, absolute values of pulmonary artery mean pressures between the patients who survived to the stage III procedure and patients who died between the stage II and stage III procedures, were similar (Figure 57). However, this risk analysis was not performed because the data with respect to the pulmonary artery mean pressure were incomplete in almost half of the patients (Table 6).

Pulmonary vascular resistance

High pulmonary vascular resistance may preclude the performance of the stage II procedure and successful completion of the Fontan circulation (Nakanishi, 2005). Alsoufi and colleagues found that the pulmonary vascular resistance index higher than 3 Wood units/m^2 in patients with single ventricle pathologies who underwent the Glenn procedure as a stage II surgery was associated with a higher risk of death prior to the stage III procedure (Alsoufi *et al.*, 2012). Although there were differences in absolute values of pulmonary vascular resistances between patients who survived and who died after the stage II procedure, no statistically significant association between the pulmonary vascular resistance and an increased risk of death during the hospitalization period (Schwartz *et al.*, 2014), interstage II period (Carlo *et al.*, 2011), or at 18 months after the stage II procedure (Friedman *et al.*, 2011) was observed.

In the current study, the data with respect to the pulmonary vascular resistance were incomplete in the majority of patients (Table 6). Thus, no reliable risk analysis could be performed. Since the value of pulmonary vascular resistance was available in only one of the patients who died between the stage II and stage III procedures, a comparison of the absolute values (Figure 58) between the patients who died and who survived to the stage III procedure was not possible.

Pulmonary to systemic blood flow ratio

A balance between the pulmonary and systemic circulation in patients with univentricular parallel anatomy is crucial to deliver sufficient oxygen to the tissues. In addition, pulmonary overcirculation in the pre-stage II period may lead to the development of pulmonary hypertension, and may induce structural changes of the pulmonary vasculature (Shimoda *et al.*, 2013). Several studies analyzed the pulmonary to systemic blood flow ratio as a potential risk factor for the stage II procedure. Although no statistically significant association has been found, the ratio was reported to be higher in patients who died than in survivors (Carlo *et al.*, 2011; Friedman *et al.*, 2011; Lee *et al.*, 2012).

Similar to published results, the pulmonary to systemic blood flow ratio was higher in patients who died between the stage II and stage III procedures than in patients who survived to the stage III procedure (Figure 59), suggesting pulmonary overcirculation in the deceased patients. The risk analysis with respect to the mortality between the stage II and stage III procedures was not performed, because the data on the pulmonary to systemic blood flow ratio were incomplete in the majority of patients (Table 6).

Oxygen saturation

The level of arterial oxygen saturation at the pre-stage II catheterization was analyzed in a study conducted by Friedman and colleagues; they found no association between the level of arterial oxygen saturation and an increased risk of death at 18 months after the Glenn procedure. The arterial oxygen saturation was reported higher in deceased patients (Friedman *et al.*, 2011). Hansen and colleagues reported results for HLHS patients that were similar to those of Friedman and colleagues (Hansen e*t al*, 2011). Furthermore, the level of oxygen saturation in the superior vena cava at the pre-stage II catheterization was not identified as a risk factor for the survival prior to the completion of the Fontan circulation (Lee *et al.*, 2012).

The association between the level of oxygen saturation in the ascending aorta and superior vena cava at the pre-stage II catheterization (Figures 60, 61) and an increased risk of death between the stage II and stage III procedures was not analyzed in the current study. Although the oxygen saturation values were available in the vast majority of patients, many patients were mechanically ventilated or required different amounts of oxygen support during the examination. Since patients with oxygen support tend to have higher levels of oxygen saturation, these values may have been overestimated if compared to patients without the oxygen support. After adjusting for the same level of inhaled oxygen during the examination, the largest group was comprised of patients without the oxygen support

(natural air, F_iO_2 = 0.21). However, the data were then available in only 28.6% patients of the stage II cohort (Table 6).

13.2.5 Operative parameters

Age at stage II procedure

Both the optimal timing of the stage II surgery, as well as the performance of the surgery at an earlier age in high risk patients, remain controversial. In a study conducted by Hansen and colleagues, patients with HLHS who underwent the stage II procedure at four months of age or earlier, did not have a higher risk of early or late adverse outcomes than the older group (Hansen *et al.*, 2011). Petrucci and colleagues analyzed 169 patients who underwent the Glenn procedure, 20 of whom were younger than three months at the time of surgery. Although the initial cohort included all patients who underwent the Glenn procedure irrespective of their diagnosis, when corrected for the patients with HLHS, no survival benefit after five years was observed between the two age groups (Petrucci *et al.*, 2010). Two reports from the SVR trial showed that patients who underwent the stage II procedure at a younger age had a prolonged length of stay in the hospital after the surgery and more frequent interstage adverse events (Cnota *et al.*, 2012; Schwartz *et al.*, 2014). The most recent report from the SVR trial showed that progress to the stage II procedure at three to six months after the Norwood procedure was associated with the best survival rate at three years after the Norwood procedure, given survival to the stage II procedure. Early performance of the stage II surgery did not improve the survival rate in high-risk patients (Meza *et al.*, 2017).

In the current study, the stage II procedure was performed at a median age of 4.1 ± 1.8 months in survivors and at a mean age of 4.3 ± 1.1 in non-survivors (Figure 62). Twenty-one patients underwent the stage II procedure at three months of age or earlier; of these, 14 patients survived and one patient died prior to the stage III procedure (Figure 63). The risk analysis supported the published results and showed no association between the age at the stage II procedure and an increased risk of death between the stage II and stage III procedures. The performance of the stage II surgery at three months of age or earlier was also not associated with adverse outcomes in the current study (Table 20). The rates of postoperative complications, including the length of stay in the hospital after the surgery, and their possible association with an early performance of the stage II surgery, were not analyzed in the current study.

Pulmonary artery augmentation during the stage II procedure

Insufficient growth of the pulmonary arteries and an uneven distribution of blood flow to the lungs are one of the main concerns after the Norwood procedure. The underdevelopment of the pulmonary arteries was reported to be associated with the specific shunt type, but the evidence remains inconsistent (Januszewska *et al.*, 2005; Rumball *et al.*, 2005; Caspi *et al.*, 2008; Pruetz *et al.*, 2009; Aiyagari *et al.*, 2014). Surgical augmentation of the underdeveloped pulmonary arteries during the stage II procedure is performed to facilitate the blood flow in the pulmonary circulation, and to prevent the development of complications related to the hypoplastic pulmonary arteries in the postoperative period.

Some authors reported that the risk of undergoing the surgical augmentation of the pulmonary arteries during the stage II procedure is not associated with the specific shunt type, but patients with right ventricle-to-pulmonary artery conduit to the right side required the augmentation more frequently than the patients with the left-sided conduit (Gist *et al.*, 2013)

In the current study, the augmentation of the pulmonary artery was performed on almost 50% of the stage II cohort; 53% of the survivors to the stage III and 47% of the non-survivors to the stage III underwent the augmentation (Figure 64). In the univariate risk analysis, pulmonary artery augmentation at the Glenn procedure was not associated with an increased risk of death prior to the completion of the Fontan circulation (Table 20). The shunt type implanted during the Norwood procedure was not significantly associated with the surgical augmentation during the stage II procedure; however, a subanalysis with respect to the implantation side of the right ventricle-to-pulmonary artery conduit was not performed in the current study.

Tricuspid valve intervention during the stage II procedure

A concomitant tricuspid valve surgery places an extra demand on the performance of the stage II surgery. In addition, it signals the presence of a significant tricuspid valve insufficiency with a chronic volume overload of the right ventricle in the pre-stage II period. In a study conducted by Schwartz and colleagues, a tricuspid valve intervention during the stage II procedure was identified as a significant risk factor for hospital mortality following the stage II surgery. However, only a univariate analysis was performed because the mortality rate in the postoperative period was too low (Schwartz *et al.*, 2014). Interstage II mortality in patients who underwent the tricuspid valve intervention during the stage II procedure was not reported to be higher than in patients without the intervention (Carlo *et al.*, 2011). A study conducted by Friedmann and colleagues showed that a tricuspid valvuloplasty during the stage II procedure was associated with worse outcomes in the 18 months period after the surgery. However, after adjusting for the grade of the tricuspid valve insufficiency, no difference between the intervention and non-intervention groups was seen (Friedman *et al.*, 2011).

In the current study, a tricuspid valve intervention during the stage II procedure was performed on almost 14% of patients (Figure 65). The risk analysis showed no difference in survival prior to the stage III procedure between patients who underwent and patients who did not undergo the intervention (Table 20). Because moderate to severe tricuspid valve insufficiency in the preoperative and early postoperative period was not significantly associated with increased mortality prior to the stage III procedure, adjusting for the grade of the tricuspid valve insufficiency was not performed in the current study.

14 Risk models

The mortality rates in patients with HLHS who undergo the multi-stage surgical repair differ considerably after the individual stages of the surgical reconstruction. The worst outcomes were reported after the Norwood procedure, with significant improvement in survival after the stage II and stage III procedures. The current study showed a similar

pattern of outcomes; the survival analysis revealed that mortality was highest between the Norwood stage I and stage II procedures, and the survival of the entire cohort in the mid-term period was largely determined by the survival to one year after the Norwood procedure.

Based on the presented risk models, patients with low birth weight, anomalous pulmonary vein connection, and impaired function of the right ventricle in the early period after the Norwood procedure contributed considerably to the overall mortality between the Norwood stage I and stage II procedures. Although lower birth weight and the presence of anomalous pulmonary vein connection are innate factors which cannot be influenced by perioperative management, identifying these risk factors might aid deciding whether the multi-stage surgical reconstruction with the Norwood procedure as a stage I surgery is an appropriate therapy in this high-risk population.

Some studies published over the past few years showed that patients who underwent the hybrid procedure as a stage I surgery have survival rates similar to those who underwent the Norwood procedure (Knirsch *et al.*, 2014; Lloyd *et al.*, 2014; Murphy *et al.*, 2015), despite higher prevalence of the potential risk factors in the hybrid group (Lloyd *et al.*, 2014). A study conducted by Lloyd and colleagues analyzed 138 patients with HLHS, 27 of whom underwent the hybrid stage I procedure; the remainder underwent the standard Norwood procedure. Although the Aristotle score was higher in the hybrid group, mortality did not differ significantly by treatment group at any stage (Lloyd *et al.*, 2014). Similar results were reported by Schranz and colleagues, whose study included 154 patients who underwent the modified "Giessen Hybrid" approach. They demonstrated that the comprehensive Aristotle score was not significantly predictive of the outcome; the mid- to long-term survival rates were comparable to those of the current Norwood procedure, with no significant impact of birth weight of less than 2.5 kg (Schranz *et al.*, 2015). A recently published multi-institutional study, which included 546 neonates with a critical left ventricular outflow tract obstruction, 527 of whom were diagnosed with HLHS, compared the survival rate after the Norwood procedure to the hybrid procedure. The best four-year survival rates after the stage I procedure were achieved by the Norwood procedure using the right ventricle-to-pulmonary artery conduit, compared to the Norwood procedure using the modified Blalock-Taussig shunt or the hybrid procedure. However, for neonates with low birth weight, the hybrid procedure resulted in a trend toward better survival rates than the Norwood procedure using either the right ventricle-to-pulmonary artery conduit or the modified Blalock-Taussig shunt (Wilder *et al.*, 2017).

Based on the significant impact of low birth weight on mortality after the Norwood procedure according to the risk model presented in this study, and taking into account other studies analyzing outcomes after the hybrid procedure in patients with low birth weight (Schranz *et al.*, 2015; Wilder *et al.*, 2017), the hybrid approach may be a preferred alternative to the Norwood procedure in this high-risk population. Although the optimal weight threshold for the performance of the hybrid procedure over the Norwood procedure is unknown, the weights of 2.0 – 2.5 kg were reported as cut-off values for analyses (Schranz *et al.*, 2015; Wilder *et al.*, 2017). However, caution is warranted because mid- to

long-term results with the hybrid procedure are based mainly on single-center retrospective studies. Whether the hybrid approach is superior to the Norwood procedure in patients with lower birth weights in long-term with respect to both morbidity and mortality is yet to be determined.

Patients with an obstruction at the left atrial or pulmonary venous levels are at increased risk of dying after the Norwood procedure (Tweddell *et al.*, 2012), most likely due to pulmonary vascular abnormalities seen in this population (Rychik *et al.*, 1999; Graziano *et al.*, 2002). An anomalous pulmonary vein connection was identified as a risk factor for mortality in the multivariate analysis, but the statistical significance shifted to a borderline area after the final model validation, which could most likely be attributed to the unobstructed variants. Although the prognosis of patients with a significant obstruction at any level remains poor, some reports suggest that catheter-based interventions in patients with a restrictive atrial septum successfully lead to a fast decompression, and could improve survival in this challenging group of patients (Vida *et al.*, 2007; Barker *et al.*, 2014). However, it remains unclear if the underlying lung injury can be reversed completely. Although there are reports of interventional relief of obstructive variants of an anomalous pulmonary vein connection (Coulson *et al.*, 1997; A McCrossan *et al.*, 2016), it is questionable whether single ventricle patients with an obstruction at the level of abnormally connected pulmonary veins would profit from the interventional procedure.

The risk model presented in this study identified an impaired right ventricular function in the early period after the Norwood procedure as a risk factor for mortality between the Norwood stage I and stage II procedures. Thus, evaluating the right ventricular function after the Norwood procedure could help identify high-risk patients who require more intensive monitoring prior to the stage II surgery. Increased monitoring could be ensured during the inpatient period, as well as by implementing interstage I home surveillance programs.

Interstage I home surveillance programs have been shown to identify patients with an increased risk of interstage I death and thus permit timely intervention, primarily with an early stage II procedure (Ghanayem *et al.*, 2003; Siehr *et al.*, 2014). This may be especially important in patients with an impaired function of the right ventricle, because the early performance of the stage II surgery shortens the period during which the ventricle has to work under maximum hemodynamic stress, and Bell and colleagues showed that the right ventricular function may even improve after the stage II surgery (Bell *et al.*, 2011). Although concerns had been raised about whether the decrease in interstage I mortality due to the early stage II surgery in the surveillance population may not be negatively compensated by an increased mortality in the early postoperative period, this was not confirmed. Earlier performance of the stage II surgery in the surveillance group did not increase mortality in the early post-stage II period (Hansen *et al.*, 2012). However, whether the implementation of surveillance programs, as well as the early performance of the stage II surgery, can improve outcomes of patients with post-Norwood impaired right ventricular function, remains unclear. Furthermore, the majority of deaths in patients with post-

Norwood impaired right ventricular function occurred during the hospitalization following the stage I surgery in the current study, and not during the interstage I period.

Interestingly, other factors such as moderate to severe tricuspid valve insufficiency or type of shunt implanted during the Norwood procedure showed no relevance for mortality in the current study, neither for the period between the Norwood stage I and stage II procedures, nor for the period between the stage II and stage III procedures.

Three separate analyses with respect to the significant tricuspid valve insufficiency were performed. First, the effect of the presence of significant tricuspid valve insufficiency before the Norwood procedure on survival prior to the stage II procedure was examined, and no statistically significant association was observed. Although significant tricuspid valve insufficiency is still considered a relative contraindication for the performance of the Norwood procedure, the results presented in this study indicate that the survival of such patients prior to the stage II procedure is similar to those whose tricuspid valve function is normal or near normal. It should be noted that no tricuspid valve intervention was performed during the Norwood procedure. Thus, irrespective of the tricuspid valve insufficiency in the preoperative assessment, the current study showed that the Norwood procedure can be performed safely in these patients. However, there are two limitations. First, the results are based on a small number of patients with significant tricuspid valve insufficiency; only 5.4% of patients had significant tricuspid valve insufficiency in the preoperative echocardiographic examination. Second, although the mortality in these patients prior to the stage II procedure did not significantly increase, no analysis beyond the stage II procedure was performed. Moreover, morbidity, which may increase in patients with significant tricuspid valve insufficiency, was not in the scope of the current study.

The second analysis focused on the impact of the significant tricuspid valve insufficiency in the early phase after the Norwood procedure on survival between the Norwood stage I and stage II procedures. The results presented in this study indicate that significant tricuspid valve insufficiency does not decrease the survival rate of these patients in the period between the Norwood stage I and stage II procedures. These findings do not support reoperation between the Norwood stage I and stage II procedures to address significant tricuspid valve insufficiency and indicate that the tricuspid valve intervention may be postponed until the stage II procedure.

The third analysis found that patients with significant tricuspid valve insufficiency in the early phase after the stage II procedure do not have a significantly higher mortality rate prior to the completion of the Fontan circulation than patients with normal or near normal tricuspid valve function. Thus, if the significant tricuspid valve insufficiency develops in the early phase after the stage II surgery, it may be possible to avoid the reoperation and to postpone the tricuspid valve intervention until the stage III procedure in selected patients.

However, there are some limitations to the delayed tricuspid valve intervention. The second and the third analyses examined the impact on mortality prior to the next-stage surgery, i.e. prior to the stage II or stage III surgery, respectively. Similar to the first analysis, the effects of the significant tricuspid valve insufficiency beyond the stage II or stage III procedures were not examined in the selected subpopulations. Although not relevant in the short-term,

postponing the tricuspid valve intervention to the next-stage surgery may negatively affect survival in the mid- to long-term. Moreover, the impact of significant tricuspid valve intervention on increased morbidity was not examined in the current study, neither was its association with right ventricular function. Patients with preserved right ventricular function may better tolerate significant tricuspid valve insufficiency and their survival prior to the next-stage surgery may not be influenced, as long as they are able to compensate for the significant volume overload.

Since the significant tricuspid valve insufficiency was identified as a risk factor for mortality after the stage II surgery in some studies (Carlo *et al.*, 2011; Hansen *et al.*, 2011), and some authors showed that volume unloading of the right ventricle after the stage II surgery does promote remodeling of the right ventricle but has no impact on the grade of the tricuspid valve insufficiency (Kasnar-Samprec *et al.*, 2012; Ugaki *et al.*, 2013), correction of the significant tricuspid valve insufficiency should probably be attempted during the stage II surgery. Although this study did not identify significant tricuspid valve insufficiency in the preoperative, as well as in the postoperative periods, as a risk factor for mortality prior to the next-stage surgery, the limitations mentioned above warrant a cautious interpretation of the presented results.

In addition to the significant tricuspid valve insufficiency, the risk models presented in this study did not identify the type of shunt implanted during the Norwood procedure as a risk factor for mortality. The survival between the Norwood stage I and stage II procedures in patients who received a systemic shunt was not significantly different from the patients who received a right ventricle-to-pulmonary artery conduit. Similarly, the survival between the stage II and stage III procedures was not significantly affected by the shunt type used during the Norwood procedure.

Based on the risk models presented in this study, both types of shunt are comparable alternatives when accounting for mortality after the Norwood procedure. This is supported by the most recent report from the SVR trial, which showed no difference in survival six years after the Norwood procedure between the group with modified Blalock-Taussig and the group with a right ventricle-to-pulmonary artery conduit (Newburger *et al.*, 2018). Unlike in the SVR trial, in the current study the shunt type was not randomized and the propensity score matching was not performed.

Although morbidity was not in the scope of the current study, several reports have shown that increased risk of some complications, such as pulmonary artery distortion or right ventricular dysfunction, were more often associated with the specific shunt type (Frommelt *et al.*, 2014; Aiyagari *et al.*, 2014; Hill *et al.*, 2015). Thus, if there is no difference in survival with respect to the shunt type, the preference of one type of shunt over another may depend more on the necessity to avoid specific complications, and this necessity may be suited for individual patients with predisposing factors to develop certain complications. Similar to studies focusing on mortality, a longer follow-up is needed to establish the association between the specific shunt type and different rates and types of complications.

Other factors associated with an increased risk of dying at some point after the Norwood procedure in some studies, such as anatomic subtype (Furck *et al.*, 2010; Ghanayem *et al.*,

2012; Tweddell *et al.*, 2012), diameter of the ascending aorta (Tweddell *et al.*, 2012), duration of the deep hypothermic circulatory arrest (Furck *et al.*, 2010; Tabbutt *et al.*, 2012), and age at the Norwood procedure (Hehir *et al.*, 2008; Sames-Dolzer *et al.*, 2015), were not significantly associated with increased mortality between the Norwood stage I and stage II procedures in the current study. Similarly, weight at the stage II procedure (Carlo *et al.*, 2011), shunt type used during the Norwood procedure (Ohye *et al.*, 2010), and an impaired right ventricular function (Lee e*t al.*, 2012), were not identified as risk factors for mortality between the stage II and stage III procedures in this study.

15 Limitations

The study is limited by its single-center, retrospective design. A larger cohort of patients would be required to increase the statistical power of the risk analyses and to decrease the probability of making type II errors.

Preoperative and postoperative echocardiographic examinations, as well as catheterizations before the stage II surgery, were performed by several physicians. Therefore, the values in the datasets of the corresponding variables may have been influenced by interpersonal variability. The surgeries were performed by several surgeons, and perioperative management, as well as the technical performance of the surgeries, may have evolved over the period of 15 years. This too may have influenced the results.

Some data could not be obtained due to the retrospective nature of the study, and imputation of the data was used to complete the datasets for the multivariate analysis. Although imputation is considered a reliable process to replace missing data with substituted values, it cannot fully replace the authenticity of the original data.

The accuracy of the probabilistic prediction of the final model for primary endpoint was good, but moderate discriminatory ability limits its overall performance. Therefore, the results presented in this study should be interpreted with caution.

CHAPTER V: SUMMARY

Hypoplastic left heart syndrome is morphologically a very heterogeneous disease, with mitral and aortic atresia associated with no discernable left ventricular cavity on the severe side of the spectrum, and hypoplastic valves associated with mild ventricular hypoplasia on the other side. Although considerable improvement in the management of this once fatal condition has been achieved over the last few decades, surgical correction of this syndrome remains one of the most challenging in pediatric cardiac surgery.

The objective of this dissertation was to develop risk models for mortality between the Norwood stage I and stage II procedures and between the stage II and stage III procedures. In addition, the survival analysis was intended to evaluate mid- to long-term results in the selected cohort.

The risk model for mortality between the Norwood stage I and stage II procedures identified low birth weight, the presence of an anomalous pulmonary vein connection, and an impaired right ventricular function in the early phase after the Norwood procedure as risk factors associated with an increased risk of dying. No risk factor for mortality between the stage II and stage III procedures could be identified. The shunt type used during the Norwood procedure and significant tricuspid valve insufficiency in the preoperative or postoperative periods were not associated with higher risk of dying prior to the next-stage surgery. The survival analysis revealed that the survival of the entire cohort in the mid-term period was largely determined by the mortality in the first year after the Norwood procedure; most deaths occurred between the Norwood stage I and stage II procedures.

Based on the risk models presented, and taking into account published studies, alternative strategies based on the hybrid approach may be considered in patients with lower birth weights. However, caution is warranted because mid- to long-term outcomes after the hybrid procedures are yet to be determined. Patients with obstructive forms of anomalous pulmonary vein connection may benefit from the catheter-based interventions prior to the Norwood procedure; however, this remains speculative. In patients with an impaired right ventricular function in the early phase after the Norwood procedure, increased monitoring during the inpatient and outpatient periods, as well as an early performance of the stage II surgery, may improve survival, but further studies of this population are needed to provide sufficient evidence.

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