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In-hospital interstage improves interstage survival after Norwood stage-one operation

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Article Type:	Original Article
Order of Authors:	Guido Michielon
	Giovanni DiSalvo
	Alain Fraisse
	Julene Carvalho
	Sylvia Krupickova
	Slavik Zdenek
	Margarita Bartsota
	Pierce Daubeney
	Carles Bautista
	Ajay Desai
	Margarita Burmester
	Duncan Macrae
Corresponding Author:	Guido Michielon Royal Brompton Hospital London, UNITED KINGDOM
Corresponding Author E-Mail:	michielon.guido@gmail.com;g.michielon@rbht.nhs.uk
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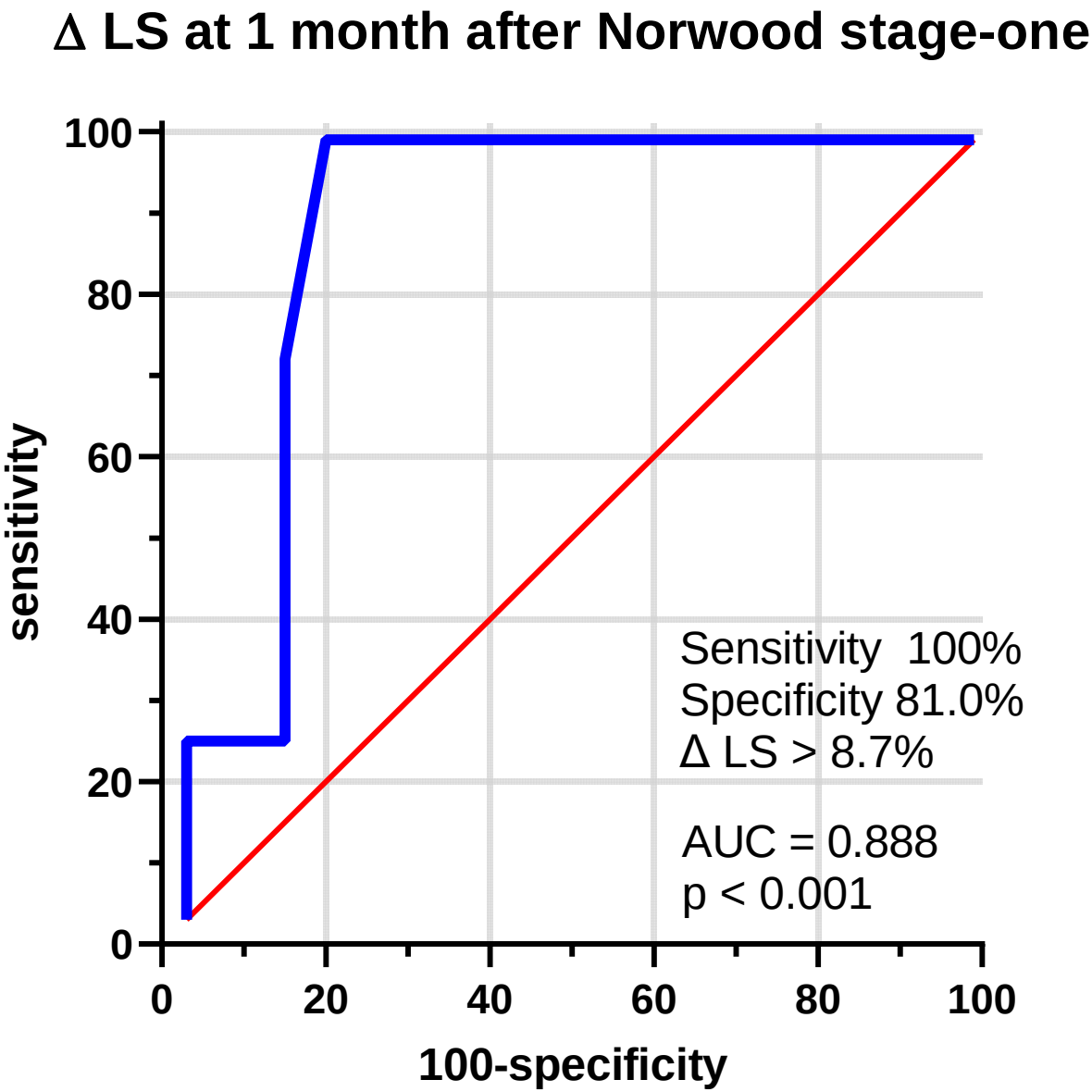
Author Comments:	Dear Editor, Dear prof Beyersdorf: I would like to submit the revised version of manuscript entitled: "In-Hospital Interstage Improves Interstage Survival after Norwood Stage-One Operation", as an original paper to the Editorial Office of the European Journal of Cardiothoracic Surgery. I revised the key question as requested. I moreover changed the central image with one of the relevant findings of the study, the delta longitudinal strain of the right ventricle as early predictor of Norwood failure. I revised figure 2 changing the end-points to reintervention-free interstage survival and escalation of care-free interstage survival and repeating the analysis as requested. The only patient that died during interstage underwent a reintervention prior to his demise, therefore this reintervention was marked as an event (uncensored) and the contribution to interstage follow-up was deleted at this time. I hope this revision fulfills and answers the last point raised by the reviewers. Best regards, Mr Guido Michielon, MD Consultant Neonatal and Paediatric Congenital Cardiothoracic Surgery Royal Brompton Hospital SW3 6NP London, UK
Abstract:	Objective: interstage mortality after Norwood stage-one operation remains 12-20% in current series. In-hospital interstage facilitates escalation of care, possibly improving

	outcome. Methods: retrospective study designed for HLHS and HLHS-variants, offering in-hospital stay after Norwood operation until stage-two completion. Daily and weekly investigations were systematically conducted, including 2-D and speckle-tracking echocardiography. Primary end-points included aggregate survival until stage-two completion and interstage freedom from escalation of care. Secondary end-point calculated sensitivity and specificity of speckle-tracking echocardiographic RV deformation in predicting death/transplant after Norwood. Results: between 2015 and 2019, 33 neonates with HLHS (24) or HLHS-variants (9), underwent Norwood stage-one (31) or hybrid-palliation followed by comprehensive stage-two operation (2). Stage-one Norwood-Sano was preferred in 18 (54.5%), while Norwood-BT shunt in 13 (39.4%). Norwood stage-one 30-day mortality was 6.2%. In-hospital interstage was endorsed in 29/31 survivors (93.6%) with 3.4% interstage mortality. Aggregate Norwood stage-one and interstage KM-survival was 90.6±5.2%. Escalation of care was necessary in 5 (17.2%) at 2.5±1.2 months during interstage for compromising atrial arrhythmias (2), Sano-shunt stenosis (1) and pneumonia requiring high-frequency oscillator (2), with no mortality. Bidirectional-Glenn (25) or comprehensive-Norwood stage-two (2) were completed in 27 patients at 4.7±1.2 months with 92.6% survival. Overall KM-survival is 80.9±7.0% at 4.3 years (mean 25.3±15.7 months). An 8.7% Δ longitudinal strain 30 days after Norwood stage-one had 100% sensitivity and 81% specificity for death/transplant. Conclusions: in-hospital interstage facilitates escalation of care, which seems efficacious in reducing interstage Norwood mortality. Significant reduction of longitudinal strain after Norwood stage-one is a strong predictor of poor outcome.
Response to Reviewers:	Reviewer 4: Comment: Unfortunately, analyzes presented in Figure 2a and Figure 2b were nocht corrected according to my suggestions. Please change the endpoints towards "reintervention-free survival" and "escalation-free survival" and reanalyze the data or analyze the hitherto endpoints using competing risk regression (Fine and Gray method) with death as a competing events ANSWER and CHANGES:I revised figure 2 changing the end-points to reintervention-free interstage survival and escalation of care-free interstage survival and repeating the analysis as requested. The only patient that died during interstage underwent a reintervention prior to his demise, therefore this reintervention was marked as an event (uncensored) and the contribution to interstage follow-up was deleted at this time. Hope this answer your query.
Order of Authors (with Contributor Roles):	Guido Michielon (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Writing – original draft)
	Giovanni DiSalvo (Conceptualization; Data curation; Software; Writing – review & editing)
	Alain Fraisse (Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing – review & editing)
	Julene Carvalho (Data curation; Methodology; Supervision; Validation; Writing – review & editing)
	Sylvia Krupickova (Resources; Writing – review & editing)
	Slavik Zdenek (Investigation; Resources; Writing – review & editing)
	Margarita Bartsota (Resources; Writing – review & editing)
	Pierce Daubeney (Data curation; Resources; Writing – review & editing)
	Carles Bautista (Resources; Writing – review & editing)
	Ajay Desai (Data curation; Investigation; Project administration; Resources; Writing – review & editing)
	Margarita Burmester (Data curation; Investigation; Methodology; Project administration; Resources; Writing – review & editing)
	Duncan Macrae (Methodology; Supervision; Validation; Writing – review & editing)

Central image



In-Hospital Interstage Improves Interstage Survival after Norwood Stage-One Operation

Guido Michielon[1],MD; prof Giovanni DiSalvo[2]; prof Alain Fraisse[2]; prof Julene Carvalho[2]; Sylvia Krupickova[2],MD,PhD; Slavik Zdenek[2],MD; Margarita Bartsota[2],MD; prof Pierce Daubeney[2], Carles Bautista[2],MD,PhD; Ajay Desai[3],MBBS; Margarita Burmester[3],MD and prof Duncan Macrae

Department of Congenital Heart Surgery[1], Paediatric Cardiology[2] and Paediatric Intensive Care[3]

Royal Brompton Hospital, Imperial College, London, UK

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Corresponding Author:
Guido Michielon, MD
Royal Brompton Hospital
Sydney Street
SW3 6NP, London, UK
g.michielon@rbht.nhs.uk

Keywords: congenital, HLHS, interstage,

Visual abstract

Key question:

In view of 12% interstage mortality after Norwood stage-one, can another strategy with new parameters improve outcome?

Key findings

In-hospital interstage allowed 3.4% mortality with 17.2% escalation of care

Longitudinal strain can predict Norwood failure

Take-home message

In-hospital interstage converts interstage mortality into escalation of care

Speckle-tracking should be integrated in Norwood follow-up

ABSTRACT

Objective: interstage mortality after Norwood stage-one operation remains 12-20% in current series. In-hospital interstage facilitates escalation of care, possibly improving outcome.

Methods: retrospective study designed for HLHS and HLHS-variants, offering in-hospital stay after Norwood operation until stage-two completion. Daily and weekly investigations were systematically conducted, including 2-D and speckle-tracking echocardiography. Primary end-points included aggregate survival until stage-two completion and interstage freedom from escalation of care. Secondary end-point calculated sensitivity and specificity of speckle-tracking echocardiographic RV deformation in predicting death/transplant after Norwood.

Results: between 2015 and 2019, 33 neonates with HLHS (24) or HLHS-variants (9), underwent Norwood stage-one (31) or hybrid-palliation followed by comprehensive stage-two operation (2). Stage-one Norwood-Sano was preferred in 18 (54.5%), while Norwood-BT shunt in 13 (39.4%). Norwood stage-one 30-day mortality was 6.2%. In-hospital interstage was endorsed in 29/31 survivors (93.6%) with 3.4% interstage mortality. Aggregate Norwood stage-one and interstage KM-survival was 90.6±5.2%. Escalation of care was necessary in 5 (17.2%) at 2.5±1.2 months during interstage for compromising atrial arrhythmias (2), Sano-shunt stenosis (1) and pneumonia requiring high-frequency oscillator (2), with no mortality. Bidirectional-Glenn (25) or comprehensive-Norwood stage-two (2) were completed in 27 patients at 4.7±1.2 months with 92.6% survival. Overall KM-survival is 80.9±7.0% at 4.3 years (mean 25.3±15.7 months). An 8.7% Δ longitudinal strain 30 days after Norwood stage-one had 100% sensitivity and 81% specificity for death/transplant.

Conclusions: in-hospital interstage facilitates escalation of care, which seems efficacious in reducing interstage Norwood mortality. Significant reduction of longitudinal strain after Norwood stage-one is a strong predictor of poor outcome.

Background

Interstage mortality after Norwood stage-one operation for hypoplastic left heart syndrome (HLHS) and HLHS-variants remains between 12% and 20% in most reported series despite close surveillance [1]. This attrition essentially presents as sudden death at home and is predominantly related to the intrinsic fragility of the parallel model of Norwood stage-one circulation [2]. Shunt take-down and creation of a cavopulmonary anastomosis converts the frail parallel circulation to the more stable in-series circulation model of Norwood stage-two. Home-monitoring (HMP) with daily detection of peripheral oxygen-saturation level and weight change has been advocated by Rudd et al. [3] to neutralize the adverse events, with an excellent 2% interstage mortality. However, this unique experience has not been confirmed by others. The multicenter Single Ventricle Reconstruction (SVR) trial reported an 18 % interstage mortality after Norwood stage-one with modified BT-shunt despite HMP [1], while the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) study failed to identify any associations of home oxygen-saturation or weight monitoring with mortality or readmission during interstage [4]. The interstage between Norwood stage-one and Norwood stage-two remains a vulnerable transition which might justify an alternative strategy to current HMP. This study evaluates the efficacy of a preliminary experience with a systematic HLHS-dedicated in-hospital interstage program (in-HIP).

Methods

Ethical statement

The NHS National Ethical review approved this study as UK Health Research Authority project ID 235600, reference 17/EE/0417.

A retrospective single-centre study was conducted at the Royal Brompton Hospital including all patients with diagnosis of HLHS or HLHS-variants undergoing Norwood stage-one palliation. The distinctive feature of this investigation was to implement in-HIP after Norwood stage-one operation

until completion of Norwood stage-two. This strategy was introduced in June 2015 and we reviewed outcome until current date. The rationale for in-HIP was to maximize escalation of care as prompt response to cardiac or extra-cardiac adverse events, while boosting interstage screening. Interstage was defined as the time interval between the patient's discharge from the paediatric intensive care unit (PICU) to the regular ward, until Norwood stage-two completion. Escalation of care was defined as the need for PICU re-admission from the regular ward due to cardiac or extracardiac life-threatening events occurring during in-HIP and requiring intensive medical/respiratory care or reintervention. During in-HIP daily and weekly investigational plans were systematically implemented. Telemetry and peripheral oxygen-saturation were monitored, while precise intake and vital signs were detected every 8 hours. Weight change was traced on daily basis. ECG, troponin, BNP and 2D echocardiography were performed on a weekly basis or earlier if clinically indicated. Beyond the usual echocardiographic parameters, the tricuspid annulus peak systolic excursion (TAPSE), fractional area change (FAC), longitudinal strain (LS) and strain rate (LSR) were measured from the apical view at specific time intervals: baseline pre-Norwood, one-month after Norwood stage-one, one-week prior to Norwood stage-two and two-months after hospital discharge following Norwood stage-two completion. A Δ LS was defined by [{baseline LS – post Norwood LS}/ baseline LS] *100). Based on clinical outcomes, these parameters were compared between Norwood transplant-free survivors and Norwood failures (including non-survivors or heart transplant). The two primary end-points of this research evaluated the aggregate transplant-free survival (including Norwood stage-one, in-hospital interstage and Norwood stage-two) and the freedom from escalation of care during in-HIP. As secondary endpoint, this study calculated the sensitivity and specificity of speckle-tracking echocardiographic assessment of RV deformation in predicting death or transplant after Norwood stage-one operation.

Statistical analysis

Standard summary statistics were reported as mean and standard deviation for normally distributed continuous variables, while medians with interquantile ranges were used for skewed continuous variables. The Kolmogorov–Smirnov method was used to test normality for each variable. Categorical analysis was conducted by Fisher's exact testing, while continuous variables were compared by unpaired t-testing or Mann-Whitney test when appropriate. Analysis of freedom from events (death, transplant or reintervention) at different standpoints during surgical staging was conducted by Kaplan-Meier technique. Cumulative hazard was calculated for each event-free survival. The echocardiographic parameters assessing RV function were evaluated as potential risk factors for Norwood failures by logistic analysis, and then entered in a multivariable stepwise regression model to identify the independent predictors of the combined outcome death/heart transplant during Norwood staging. Operating characteristic curves (ROC) were finally plotted calculating the areas under the curves (AUCs) in order to verify sensitivity and specificity of the independent predictors of Norwood failure. Statistical analysis was performed with MedCalc, version 18.11 (MedCalc Software, Mariakerke, Belgium) and SPSS version 23.0 (SPSS, Chicago, IL).

Results

Since June 2015, 33 consecutive patients (19 males and 14 females) underwent Norwood stage-one operation (31 patients) or hybrid approach (bilateral pulmonary artery banding and ductal stenting) followed by comprehensive stage-two (2 patients). In-HIP was implemented after Norwood stage-one procedure. Prenatal diagnosis was available in 29 (93.5%). HLHS was the predominant diagnosis (24 patients, 77.4%). Anatomic details and associated lesions are depicted in Table 1. No patient's selection was applied, accepting referrals with HLHS and associated lesions (8/31=25.8) including TAPVC (1), PAPVC (1), intact/near-intact atrial septum (5) or absent aortic valve (1).

Norwood stage-one

A Norwood stage-one operation was performed at 3.4±2.1 day of life, and 3.1±0.4 kg mean body weight. Two premature babies (<37 weeks gestation) and 2.4 Kg body weight were initially palliated by bilateral PA-banding while continuing PGE1 infusion until Norwood operation at 2 weeks of life. There was a slight preference for the Norwood-Sano modification (54.5%) versus the classic Norwood operation with RmBT-shunt (39.4%), with a strong correlation between Norwood-Sano and aortic diameter ≤ 2.0 mm (Fisher exact-testing p-value <0.01, $X^2$16.1). Shunt size was uniformly 5.0 mm for the Sano modification and 3.5 mm for the classic Norwood operation with RmBT-shunt. Associated procedures concomitant with Norwood stage-one included repair of TAPVC, exclusion of a hypoplastic but severely regurgitant mitral valve and patch exclusion of an absent aortic valve. The nomogram of surgical strategy is depicted in Figure 1. Thirty-day mortality was 6.4% (2 patients). One patient died 19 days after Norwood-Sano operation because of intractable heart failure due to early development of multiple aorto-pulmonary collaterals (APC). ECMO was instituted on 16th postoperative-day and subsequent cardiac catheterization demonstrated 5 large APC mainly for the right lung. Effective coiling of all APC was achieved but ventricular function did not recover, and mechanical support discontinued. The second postoperative death was secondary to ANCA-associated vasculitis with systemic vasospasm and pulmonary alveolar hemorrhage at 5 days after Norwood-Sano operation. ECMO support was ineffective. Microscopic polyangiitis was detected at postmortem examination. Complications after Norwood stage-one are described in Table 2. The 30-day survival was 93.3±4.6%. Mean combined ICU/HDU stay after Norwood stage-one was 42.3±6.4 days.

Interstage

All 29 Norwood-survivors were followed closely after transfer to the ward until Norwood stage-two completion, according to the daily and weekly protocol described. Mean in-HIP duration was 3.3±1.4 months. Medical therapy included a systematic combination of diuretics (furosemide and spironolactone) and vasodilators (captopril or enoximone). Digoxin was administered frequently

(57.1%) while b-blockers were used seldom during interstage (7.4%). One patient died at 4.07 months during in-HIP, accounting for a 3.4% in-HIP mortality. Cause of death was progressive diastolic dysfunction leading to ventricular failure. Persistently high O2 saturation exceeding 90% after a classic-Norwood operation prompted a cardiac catheterization at 3 months of age, which detected multiple APC and elevated EDP (18 mmHg). Despite APC coiling and maximal medical therapy, EDP did not improve and the patient was not considered a candidate for Norwood stage-two. Nine patients (31%) required further surgical (2) or catheter (7) reintervention during in-HIP. Two unplanned reoperations were performed during in-HIP (6.8%). The first unplanned surgery was indicated to repair a progressively incompetent neo-aortic valve, detected at serial postoperative echocardiograms after Norwood-Sano operation. Although clinically tolerated, the increment in vena-contracta prompted reoperation at 1.5 months after initial Norwood stage-one. The anterior left cusp of the neo-aortic valve was found to be retracted, generating an eccentric jet. The neoaortic-valve was repaired by augmenting the retracted cusp with a pulmonary homograft leaflet patch. Valve continence was restored with uneventful recovery and long-term efficacy. This patient recently underwent successful fenestrated extracardiac-Fontan completion and his perfect neo-aortic valve competence was documented at intraoperative TOE. Persistent non-invasive ventilation dependency prompted CT-angiography in another patient, 3.2 months after classic-Norwood operation complicated by Gram-negative mediastinitis. Despite control of the infection and good healing of the sternotomy wound, respiratory symptoms were investigated. A rapidly expanding pseudo-aneurysm compressing the left pulmonary artery and the left bronchus was confirmed at two consecutive CT-angiograms, prompting urgent reoperation. A pulmonary homograft patch was utilized to reconstruct and repair the ventral portion of the aortic arch, excluding the aneurysm, under deep hypothermic circulatory arrest. The procedure was well tolerated, and 30-day control CT-angiogram confirmed proper arch anatomy and resolution of the arch aneurysm. Additional unplanned catheter interventions were indicated at 2.7± 0.4 months during in-HIP in 7 patients (24.1%), to occlude multiple APC (4=13.8%), stent a stenotic Sano-shunt (1), balloon dilate a recurrent coarctation (1) and stent a compressed left pulmonary artery

(1). Freedom from any type of reintervention during in-HIP is depicted in Figure 2a. Five patients (17.2) required escalation of care from ward to ICU at a mean 2.5±1.2 months during in-HIP. De-novo multifocal narrow-complex atrial tachycardia developed at telemetry and was documented on ECG in two patients with no previous evidence of rhythm issues during in-HIP . These incidents proved to be hemodynamically compromising with hypotension and desaturation not responding to volume, electrolyte replacement or vagal maneuvers. Prompt echocardiographic assessment showed new onset of moderate-to-severe tricuspid valve incompetence and impaired ventricular function, compared with trivial tricuspid regurgitation and preserved ventricular function at multiple echocardiographic evaluations prior to the event. Both patients were immediately transferred to PICU where central IV access was gained after endotracheal intubation, and amiodarone infusion commenced after unsuccessful adenosine bolus and synchronized cardioversion. Resolution of the arrhythmia together with recovery of tricuspid valve and ventricular function was documented within 72 hours of acute treatment. Both babies had an otherwise uneventful recovery on oral amiodarone, and successful Norwood stage-two operation was completed at 4.7 and 4.2 months of life respectively. Aspiration (1) or RSV pneumonia (1) were the reasons for escalation of care in two additional patients who required urgent PICU readmission and institution of high-frequency oscillatory ventilation. This and subsequent management proved to be successful in both cases with no sequelae. Both patients were converted to conventional ventilation and then extubated after resolution of the radiographic opacifications. Both were discharged from PICU to the ward 10 and 13 days after the incident. Sudden hypoxic spell on the ward was the presenting symptom of acute RV-to-PA conduit critical stenosis in another patient at 2.2 months of an otherwise unremarkable in-HIP. Cardiac catheterization was promptly organized after stabilization in PICU with endotracheal intubation, sedation and paralysis. A proximal dynamic stenosis on the RV take-off of the Sano conduit was identified and successfully stented with resolution of the hypoxemia. In summary, endotracheal intubation was indicated in all cases requiring escalation of care. Mean time-interval between onset of the incident and endotracheal intubation was 25±8 minutes. Kaplan-Meier analysis showed a 90.6±5.2% aggregate Norwood stage-

one and in-HIP survival (Figure 3), an 81.9±7.3% freedom from escalation of care during in-HIP and a 63.3±6.9% freedom from any type of surgical or catheter-based reintervention during in-HIP (Figure 2a and 2b), therefore confirming the intensive management required during in-HIP. During in-HIP all patients underwent speckle-tracking echocardiography at the previously specified time-intervals. Figure 4 depicts the significant decline of TAPSE, LS, Δ LS and Δ LSR at one-month evaluation in Norwood-failures (death or transplant at any time during follow-up), as opposed to a constant longitudinal trend in transplant-free Norwood survivors. A similar pattern was identified after Norwood stage-two. LS and TAPSE at one month after Norwood were identified as independent predictors of death/transplant at stepwise multivariable analysis (Table 3). TAPSE ≤ 5 mm at one-month after Norwood stage-one showed 85.7% sensitivity and 66.7% specificity as predictive value for combined outcome death/transplant, with an AUC of 0.79. Δ LS (cut off > 8.7%) showed a 100% sensitivity and 81% specificity for death/transplant with an AUC of 0.89 (Figure 5).

Parental social and psychological impact of in-HIP was evaluated with a survey in September 2019. Ninety-six % of parents defined in-HIP as extremely useful in relieving parental responsibility and pressure related to the care and monitoring of their HLHS-baby, who had siblings in 93%. Easy-access to parental hospital accommodation, psychology support and in-hospital social activities were unanimously well received. According to the comments in the survey, in-HIP allowed the parents to spend more quality-time out-of-hospital for adequate attention to their other children, knowing that, in their absence, their HLHS-baby was in the most secure place at the most vulnerable time of his/her life.

Norwood stage-two

Norwood stage-two was completed in 27 patients by means of a right (23), left (1), bi-lateral (1) bi-directional Glenn (BDG) or comprehensive stage-two (2) at a mean age of 4.7±1.2 months. Three patients are currently alive and awaiting Norwood stage-two completion. No additional sources of pulmonary blood flow were maintained with stage-two and all RV-PA conduits or BT-shunts were

obliterated. Associated procedures with Norwood stage-two were common, mainly to augment the central pulmonary arteries (12), to repair the tricuspid valve (2), concurrently repair the tricuspid valve and augment the central pulmonary arteries (2) or to repair a PAPVC of the right superior and middle pulmonary veins to the right SVC (1). Mortality after Norwood stage-two was 7.4% (2 patients). The cause of death in the first was right ventricular failure, which became unmasked after volume un-loading by tricuspid valve repair. Medical management could not control the progressive deterioration of ventricular function prompting referral for heart transplantation. The patient died on the waiting list 3.8 months after Norwood stage-two. High PVR determined early failure of Norwood stage-two in the second patient, who had been ventilator-dependent since the initial Norwood stage-one operation. Treatment with pulmonary vasodilators including prostacyclin did not prove to be effective. BDG take-down with construction of a new BT-shunt was not considered feasible due to clotting of the pulmonary arterial system. One additional patient developed ventricular dysfunction secondary to progressive tricuspid regurgitation and hypoxemia (O2-saturation 60%), requiring multiple hospital readmissions after Norwood stage-two with tricuspid valve repair. She was referred for heart transplantation which was successfully performed 5.1 months after stage-two. There was no additional mortality between stage-two and Fontan completion

Fontan completion

Currently, an extracardiac fenestrated (4 mm) Fontan has been completed in 5 patients at a median age of 43 months with no mortality. The overall Kaplan-Meier transplant-free survival for the entire cohort is 80.9 ± 7.0% at 51 months (mean 25.3±15.7 months) (Figure 3).

Discussion

Despite major improvements occurred over the last two decades in prenatal diagnosis, surgical management and postoperative care of HLHS and HLHS-variants, the interstage between Norwood stage-one and stage-two palliation remains a time of notable morbidity and mortality. The Single-Ventricle-Reconstruction trial, the largest multicenter prospective study published to date, reported

a 12% interstage mortality [1]. Noticeably this study highlighted an 18% interstage mortality for the classic-Norwood operation with RmBT-shunt [1]. These and similar findings support the inference that interstage mortality can be close or even higher than contemporary surgical mortality for Norwood stage-one operation [5]. Several risk factors have been identified as independent predictors of interstage mortality, including gestational age, ethnicity, census, anatomic subgroup, surgical technique, residual lesions, arrhythmias or acquired intercurrent illnesses [2]. HMP has been implemented as a key effort to improve interstage outcomes and consists of home oxygen-saturation monitoring and weight-checks. HMP ambition is to flag deteriorations in clinical conditions, with earlier detection possibly translating into improved outcomes [3,6,7]. Rudd [3] reported a significant reduction of interstage mortality from 16% to 2% over a 10-year HMP experience, compared with historical controls at Children's Hospital of Wisconsin. With NPC-QIC implementation, HMP for HLHS has been widely adopted in the US and expanded to include all shunt-dependent single ventricles (SV-HMP) [6,8]. A similar strategy has been endorsed by other non-US centers [9]. HMP is a complex endeavor that relies heavily on parental involvement and education, requires dedicated cardiac teams with specialist-nurses and cardiologists (among others) available 24 hours/day to triage all the events that result in breach of predetermined parameters, it involves frequent home visits, dedicated hospital clinics with outpatient or emergency-room evaluation by professionals familiar with HLHS management. Finally, when indicated, hospital admission must be organized whereby a pediatric ICU and HLHS expertise is available. Interestingly most centers report 60% hospital readmission rate at least once during HMP interstage, with 85% flagged home-events requiring in-hospital evaluation [3,10]. These findings essentially underline the interstage vulnerability status. Despite this intensive effort, some concerns have emerged regarding HMP efficacy. On a large multicenter study, Oster et al. [4], on behalf of the NPC-QIC, failed to demonstrate any benefit of interstage daily home-oxygen or weight-monitoring regarding reduced interstage mortality, transplantation, unscheduled clinic visits, or unplanned readmissions. Oster reported 8.1% interstage HLHS mortality, lower than in previous cohorts, suggesting an improved overall care coordination independent of HMP. Oster

recommended further efforts beyond HMP to neutralize interstage mortality. Similarly, Petit et al [8] reported 8.3% interstage mortality after the implementation of SV-HMP at Texas Children's Hospital, not significantly different from historic controls. In this single-centre retrospective review encompassing 230 patients, including 34% non-Norwood palliations, two-thirds of the lethal interstage events presented as sudden death, with no apparent identifiable cause even at autopsy. Membership in the SV-HMP did not protect against interstage mortality [8]. This confirms the report by Hehir et al [2], who noted that the majority of interstage deaths after Norwood stage-one were sudden and unexpected events in infants with a history of arrhythmia. Pulse-oximetry may be a useful tool to screen for shunt dysfunction, nevertheless shunt occlusion or thrombosis is not the leading cause of interstage mortality. Li et al. [11] reported that the mortality rate after Norwood palliation exceeds the rate of thrombosis with systemic-to-pulmonary shunts and suggested that a precipitating cause may be linked to coronary events. The inference is that no tool currently available can reliably screen and prevent sudden interstage death or adverse near-miss events. Therefore, a change in strategy for interstage management could be considered. Our study evaluates the preliminary experience with a different strategy after Norwood stage-one operation, the systematic in-hospital interstage program (in-HIP). In primis, our 93.3%±4.6% Norwood stage-one 30-day survival and 80.9±7.0% aggregate transplant-free 4-year survival, favorably compares with the outcome reported at leading and high-volume Norwood centers, confirming Checchia's findings [12]. The adoption of this strategy is based on the rationale that in-HIP facilitates escalation of care at its maximal speed and capacity. Since the experience of others essentially demonstrated the unpredictable and sudden nature of interstage mortality, the only tool left to impact on sudden death is speed of detection and reaction against adverse events, essentially like a hospital "red-code". This is in line with the documented better outcome of in-hospital versus out-of-hospital management of cardiac arrest [13]. In-HIP is not a completely new concept. Even in centers where HMP is a well-established practice, approximately 15-20% patients remain in-hospital until Norwood stage-two [3]. This strategy is generally selected for patients with "high-risk" profile, although the definition of "high-risk" after

Norwood stage-one is not easily discernible. Nevertheless, Rudd [3] reported an acceptable outcome for this "high risk" group who remained admitted until stage-two completion (83% survival), indirectly suggesting the efficacy of this strategy. The novel concept of our systematic in-HIP assumes that every patient after Norwood stage-one is, by definition, at high-risk for sudden death, because of the parallel model of Norwood circulation. This unavoidable substrate predisposes to serious sudden cardiac and extracardiac intercurrent events. Our study highlights two relevant findings. First, we could achieve a 3.4% in-HIP mortality, lower than in most reported series. The second relevant finding is the 17.2% escalation of care that we observed during in-HIP. These incidents were abrupt, unexpected and required aggressive invasive management within minutes from PICU admission. Only one event was shunt-related, while the others were either respiratory accidents (requiring high-frequency oscillatory ventilation) or de-novo onset of atrial arrhythmias affecting tricuspid valve and ventricular function. These incidents occurred 2.5±1.2 months during interstage, while the patients were on apparent stable conditions in the ward. Typically, by this time the patients would have been at home under HMP. Very likely, had these events occurred at home, they would have been invariably fatal, in agreement with the experience of others on sudden death during interstage [8]. On the contrary, expeditious escalation of care with appropriate PICU management was life-saving. Our 17.2% escalation of care during in-HIP is not very different from the 18% interstage mortality reported by the SVR trial for the classic-Norwood operation [1]. Our provocative inference is that in-HIP converted interstage mortality in escalation of care, maximizing the chances of successful treatment of cardiac and extracardiac interstage incidents, ultimately controlling mortality. In agreement with other reports, unplanned operations or catheter reinterventions were frequent during interstage. A novel finding of this study is the identification of early development of aorto-pulmonary collaterals in 13.4% patients during interstage. We pursued an aggressive strategy to coil occlude these collaterals before Norwood stage-two, to avoid competitive flow and reduce ventricular volume overload, possibly affecting ventricular function and end-diastolic pressure. As a paired advantage, in-HIP facilitated the internal coordination for unplanned interventions, with minimal impact on daily scheduling. The

awareness of resource utilization for in-HIP prompted anticipation of Norwood stage-two whenever feasible. Cardiac catheterization was routinely planned around 3 months of age and followed by Norwood stage-two around the age of 4 months (mean 138±9 days). In agreement with the experience of others, associated procedures with Norwood stage-two were frequently indicated, especially to augment the capacitance of the central pulmonary arteries. Our study suggests that the need for combined procedures at Norwood stage-two was significantly associated with the Norwood-Sano modification. The secondary end-point of our study was the evaluation of the sensitivity and specificity of speckle-tracking echocardiographic assessment of RV deformation in predicting death or transplant after Norwood stage-one operation. Norwood stage-one palliation generates a high output state and ventricular strain, which affects both systolic and diastolic function. Recently speckle-tracking echocardiography has been shown to be a reliable technique in the evaluation of RV deformation without any geometric assumption [14]. Moreover, using myocardial deformation parameters, RV function can be assessed without the influence of acute preload changes [15]. Some studies [14-16] have used speckle-tracking analysis to estimate RV performance in HLHS, nevertheless its correlation with clinical outcome has not been clearly elucidated. This study indicates that a LS of > 8.7% at one-month after Norwood stage-one operation compared with basal pre-Norwood value is a powerful predictor of Norwood failure, defined as the combined outcome of death or transplantation during surgical staging. This finding could be a useful early indicator of outcome, independent of ventricular loading conditions, and we suggest it should be integrated in the routine echocardiographic longitudinal follow-up after Norwood operation.

This study has several limitations. According to Checchia's definition, the Brompton can be considered a high-volume Norwood center. However, despite the encouraging results, we recognize that this is preliminary experience and should be confirmed with time on a larger population scale. Only enduring with in-HIP will possibly corroborate these findings. Cost-effectiveness of this strategy is a legitimate concern for in-HIP. HLHS is resource-intensive disease. Hansen [17] calculated a median cost exceeding 360,000 $ for each 1-year HLHS survivor, reaching 390,000 $ for 5 year-survivors. ICU

accounted for over 40% of total costs. We cannot provide the exact budget details, however, we can state that in-HIP does not increase overall length of ICU-stay. Another criticism relates to possible alternative detection of the interstage events with appropriate HMP, therefore avoiding in-HIP. We could not detect any warning sign for the incidents that occurred during in-HIP. Only speed of reaction with escalation of care proved to be life-saving. The vulnerable nature of parallel circulation exposes all Norwood patients to the risk sudden death, with no reliable tool capable of secure screening in the experience of others. Considering the initial resource investment for HLHS management, a red-code type surveillance during in-HIP is justified for each Norwood survivor, in our opinion.

In conclusion, our coordinated strategy including in-HIP allowed a 90.6±5.2% aggregate Norwood stage-one plus interstage survival, with an 80.9 ± 7.0% survival at 4 years. Mortality during in-HIP was almost neutralized (3.4%). In-HIP converted interstage mortality into escalation of care, which proved to be lifesaving in all cases. A significant reduction of longitudinal strain (Δ LS of > 8.7%) at one-month after Norwood stage-one by speckle-tracking echocardiography was identified as a powerful early and load-independent parameter that could be helpful in predicting Norwood failure and should be integrated in the routine echocardiographic longitudinal evaluation of right ventricular function after Norwood operation.

Figure legend.

Figure 1. Surgical strategy

Figure 2a Interstage reintervention-free survival . Figure 2b. Interstage escalation of care -free survival

Figure 3. Overall transplant-free survival and staging

Figure 4. TAPSE, longitudinal strain and longitudinal strain-rate at specified time intervals

Figure 5. Sensitivity and specificity of TAPSE and Δ LS at one month after Norwood stage-one as predictive value for combined outcome death/transplant

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Table 1. Anatomic details and associated lesions

HLHS (24 patients)

	Aortic atresia	**Aortic stenosis**
Mitral atresia	17 (71%)	2 (8%)
Mitral stenosis	2 (8%)	3 (13%)

Associated lesions

TAPVC-CS	1
PAPVC	1
intact or near-intact muscular IAS	5
bilateral SVC	2
moderate-severe TR	2

HLHS-variants (9 patients)

MS, AS (unicuspid),VSDs	*3*
unbalanced AVSD	*2*
DILV, malposed GA, sub-AS, arch hypoplasia	*1*
DORV, straddling AVV, sub-AS, arch hypoplasia	*1*
DORV, absent aortic valve	*1*
TGA, MS, PS, sub-PS	*1*

Legenda: CS: coronary sinus; IAS: interatrial septum; GA: great arteries; AVV: atrioventricular valve; PS: pulmonary stenosis

Table 2. Complications after Norwood stage-one

	patients	management
Left thalamic infarct	1	no clinical implications
Neo-aortic valve incompetence	1	valve repair (reintervention)
Aortic arch pseudoaneurysm	1	redo arch reconstruction
Left diaphragmatic palsy	1	diaphragm plication
Mediastinitis (Gram negative)	1	wash-out and betadine lavage
Left vocal cord palsy	1	conservative
Low output requiring ECMO	4	2 successful weaning

Table 3. Least-squares stepwise multivariable regression analysis for death-or-transplant at any time during follow-up

Independent variable	coefficient	Standard error (SE)	t	p-value
$longitudinal\ strain$	0.089	0.002	3.321	0.0028
TAPSE	- 1.043	0.49	-2.09	0.046
Variables excluded by model (p>0.05)				
Fractional area shortening				
Longitudinal shortening				

Figure 1. Surgical strategy

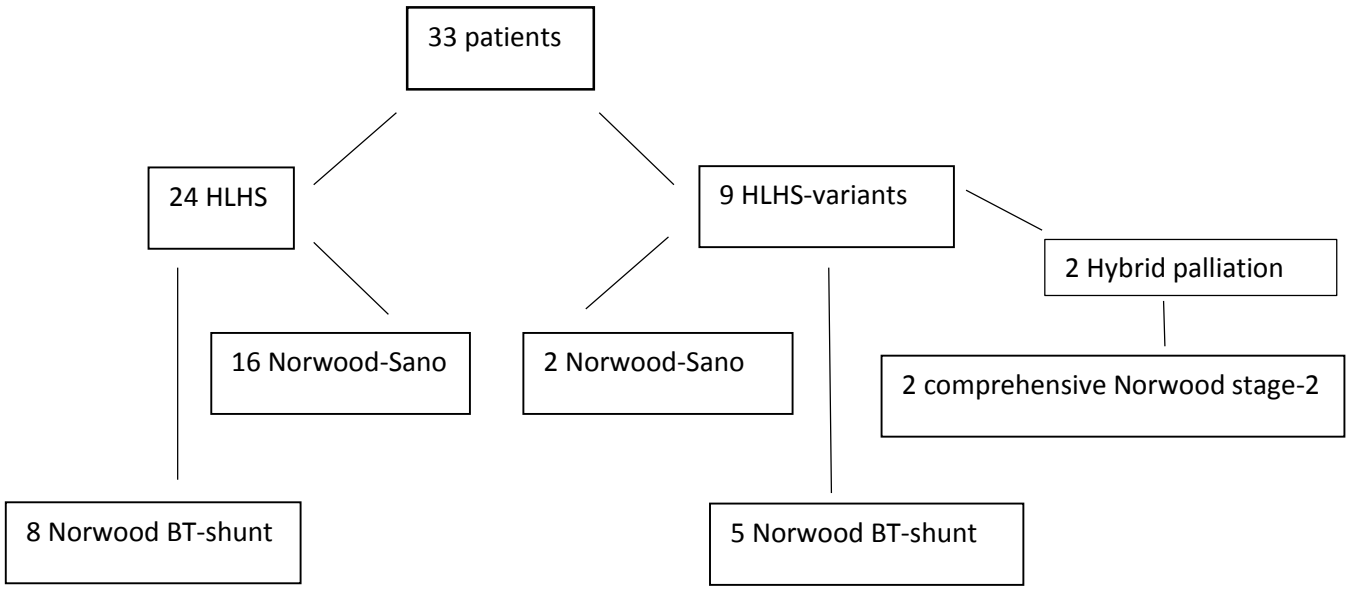

Figure 3

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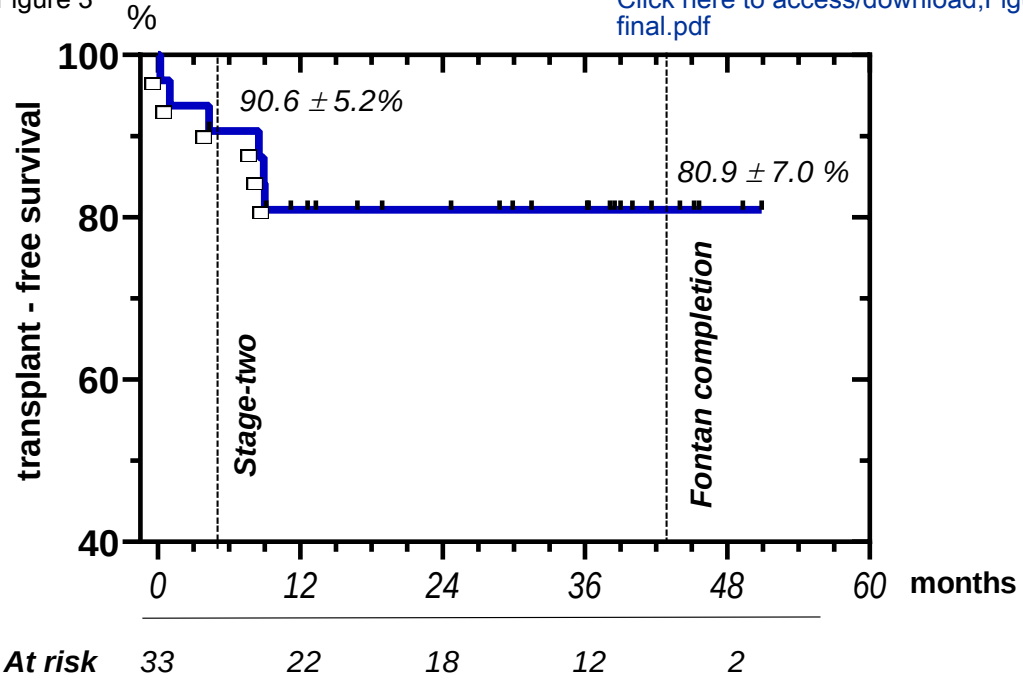
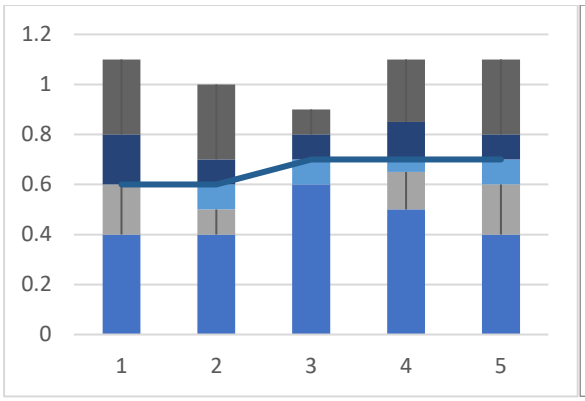
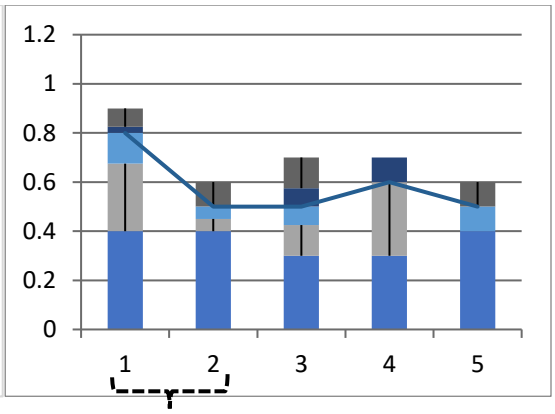


Figure 4.

TAPSE transplant-free survivors (0.7±0.1 cm)

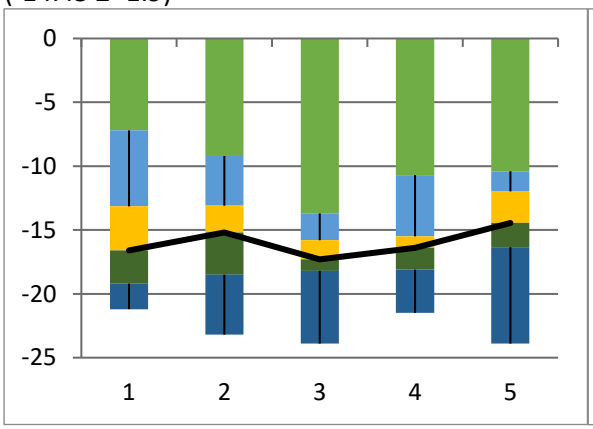


TAPSE death or transplant (0.5±0.05 cm)

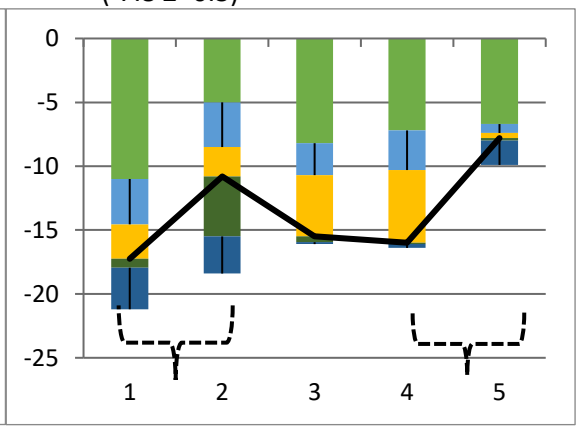


p <0.01

Longitudinal strain transplant-free survivors (-14.45 ± -1.9)

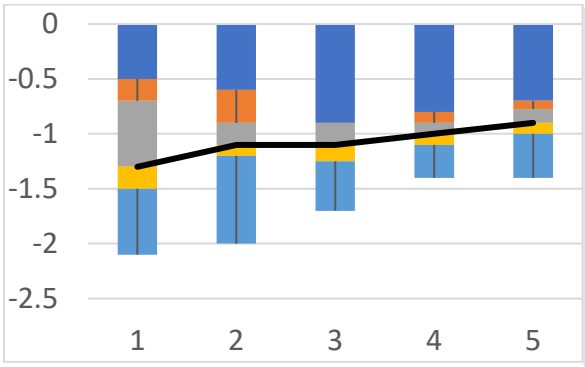


Longitudinal strain death or transplant (-7.8 ± -0.3)

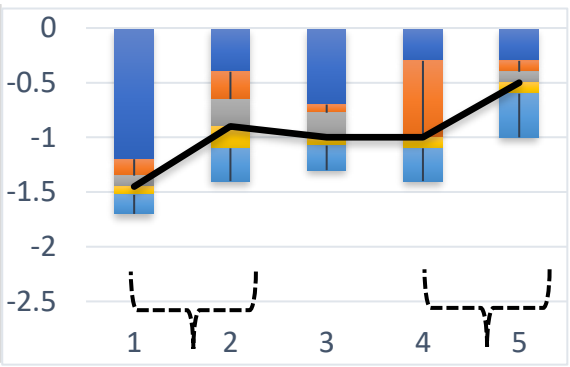


p<0.01 p<0.01

Longitudinal strain rate: transplant free survival (-0.9 ± -0.13)



Longitudinal strain rate: death or transplant (-0.5 ± -0.1)



p <0.01 p <0.01

Figure 5a

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TAPSE ≤ 5 mm at one month after Norwood stage-one

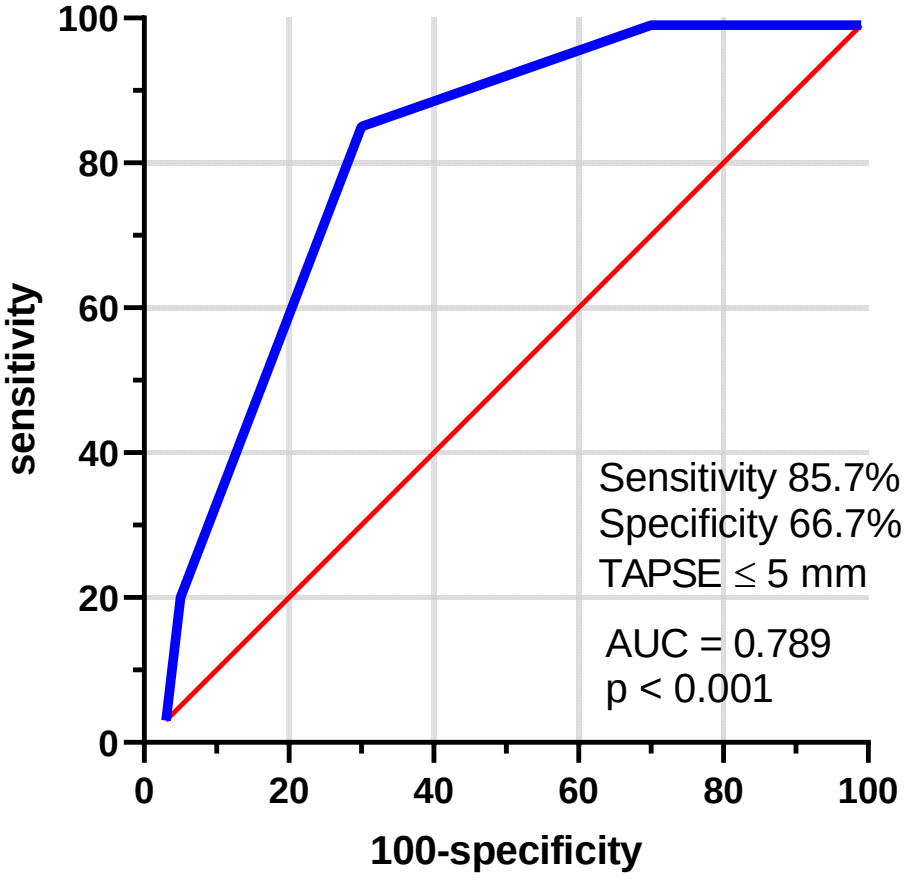

Figure 5b

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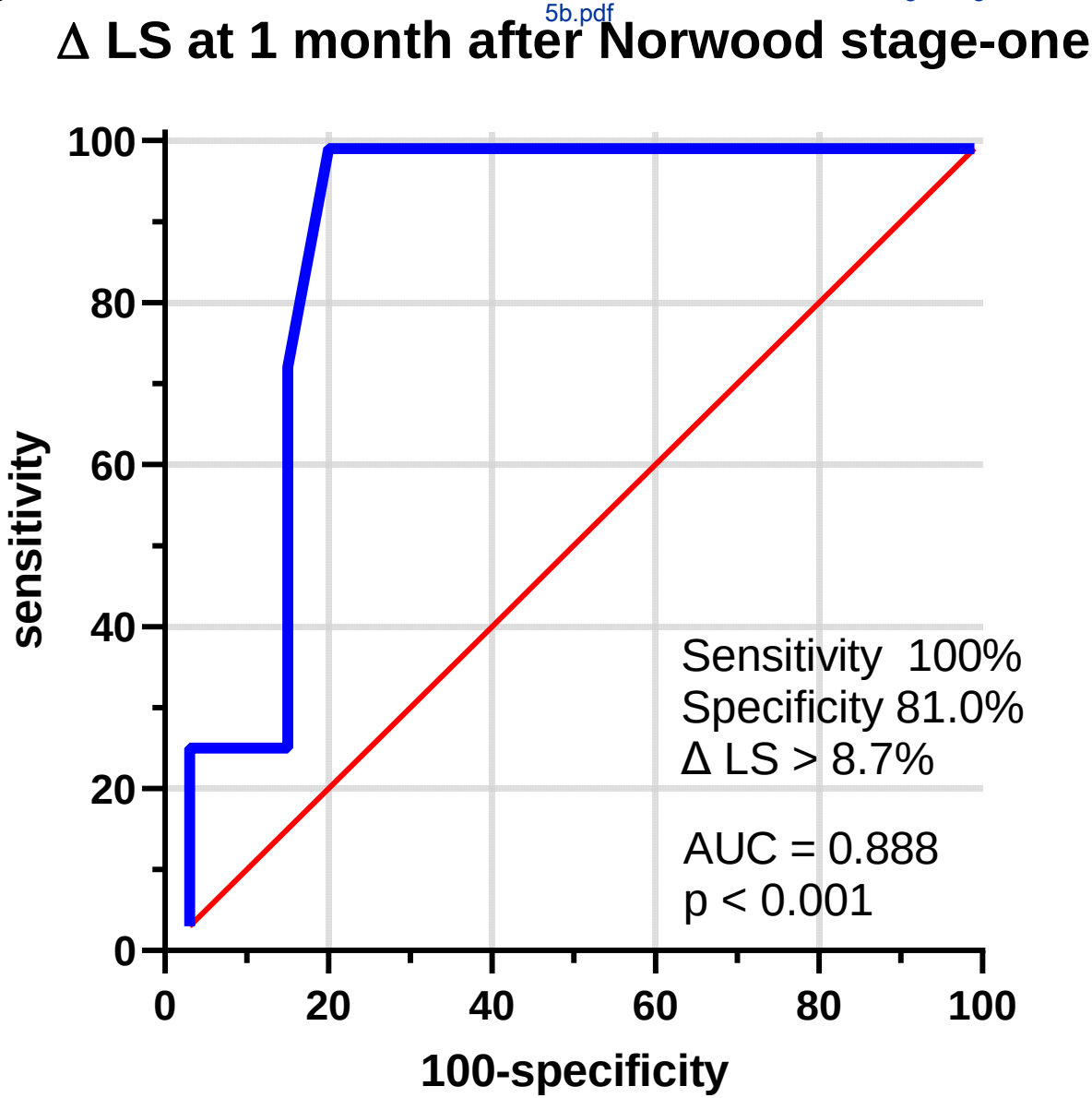

Figure 2a.

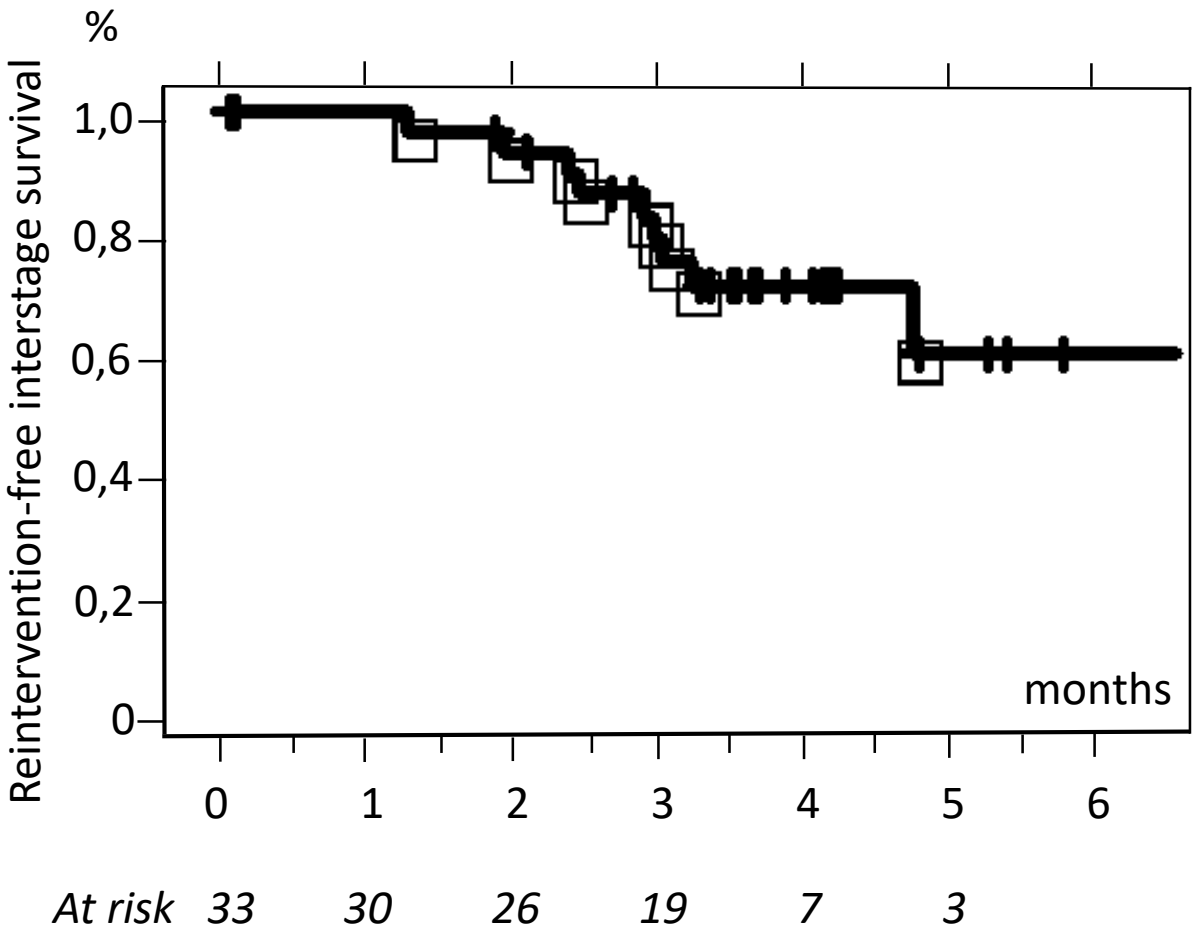

Figure 2b.