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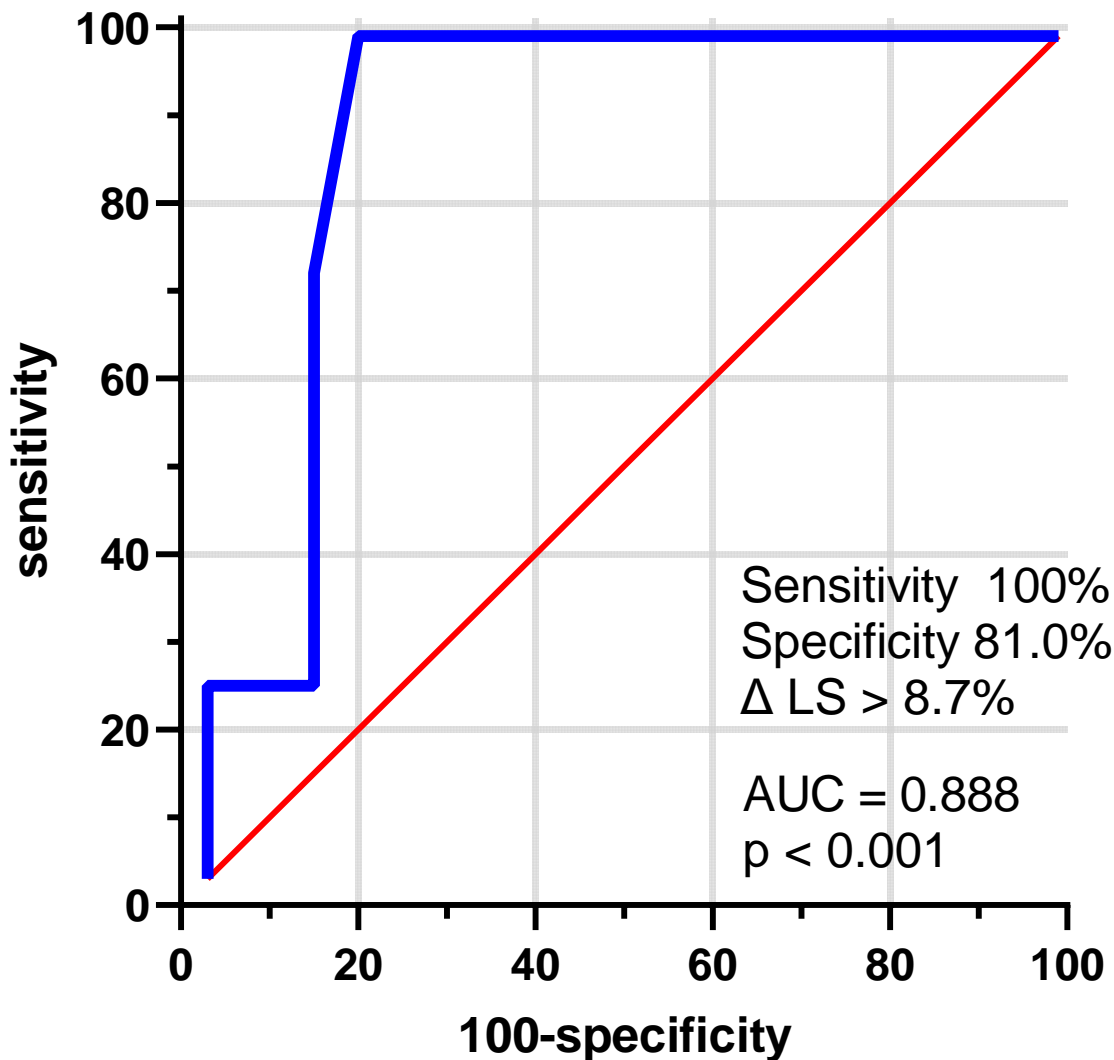
In-hospital interstage improves interstage survival after Norwood stage-one operation

--Manuscript Draft--

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Author Comments:	<p>Dear Editor, Dear prof Beyersdorf:</p> <p>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.</p> <p>I hope this revision fulfills and answers the last point raised by the reviewers. Best regards,</p> <p>Mr Guido Michielon, MD Consultant Neonatal and Paediatric Congenital Cardiothoracic Surgery Royal Brompton Hospital SW3 6NP London, UK</p>
Abstract:	Objective: interstage mortality after Norwood stage-one operation remains 12-20% in current series. In-hospital interstage facilitates escalation of care, possibly improving

	<p>outcome.</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>Response to Reviewers:</p>	<p>Reviewer 4:</p> <p>Comment: Unfortunately, analyzes presented in Figure 2a and Figure 2b were nicht 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</p> <p>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.</p>
<p>Order of Authors (with Contributor Roles):</p>	<p>Guido Michielon (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Writing – original draft)</p> <p>Giovanni DiSalvo (Conceptualization; Data curation; Software; Writing – review & editing)</p> <p>Alain Fraisse (Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing – review & editing)</p> <p>Julene Carvalho (Data curation; Methodology; Supervision; Validation; Writing – review & editing)</p> <p>Sylvia Krupickova (Resources; Writing – review & editing)</p> <p>Slavik Zdenek (Investigation; Resources; Writing – review & editing)</p> <p>Margarita Bartsota (Resources; Writing – review & editing)</p> <p>Pierce Daubeney (Data curation; Resources; Writing – review & editing)</p> <p>Carles Bautista (Resources; Writing – review & editing)</p> <p>Ajay Desai (Data curation; Investigation; Project administration; Resources; Writing – review & editing)</p> <p>Margarita Burmester (Data curation; Investigation; Methodology; Project administration; Resources; Writing – review & editing)</p> <p>Duncan Macrae (Methodology; Supervision; Validation; Writing – review & editing)</p>

Δ LS at 1 month after Norwood stage-one



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

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25 Keywords: congenital, HLHS, interstage,

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1 **Visual abstract**

2

3 **Key question:**

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

6

7 **Key findings**

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

9 Longitudinal strain can predict Norwood failure

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11 **Take-home message**

12 In-hospital interstage converts interstage mortality into escalation of care

13 Speckle-tracking should be integrated in Norwood follow-up

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1 **ABSTRACT**

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3 **Objective:** interstage mortality after Norwood stage-one operation remains 12-20% in current series.

4 In-hospital interstage facilitates escalation of care, possibly improving outcome.

5 **Methods:** retrospective study designed for HLHS and HLHS-variants, offering in-hospital stay after

6 Norwood operation until stage-two completion. Daily and weekly investigations were systematically

7 conducted, including 2-D and speckle-tracking echocardiography. Primary end-points included

8 aggregate survival until stage-two completion and interstage freedom from escalation of care.

9 Secondary end-point calculated sensitivity and specificity of speckle-tracking echocardiographic RV

10 deformation in predicting death/transplant after Norwood.

11 **Results:** between 2015 and 2019, 33 neonates with HLHS (24) or HLHS-variants (9), underwent

12 Norwood stage-one (31) or hybrid-palliation followed by comprehensive stage-two operation (2).

13 Stage-one Norwood-Sano was preferred in 18 (54.5%), while Norwood-BT shunt in 13 (39.4%).

14 Norwood stage-one 30-day mortality was 6.2%. In-hospital interstage was endorsed in 29/31 survivors

15 (93.6%) with 3.4% interstage mortality. Aggregate Norwood stage-one and interstage KM-survival was

16 $90.6 \pm 5.2\%$. Escalation of care was necessary in 5 (17.2%) at 2.5 ± 1.2 months during interstage for

17 compromising atrial arrhythmias (2), Sano-shunt stenosis (1) and pneumonia requiring high-frequency

18 oscillator (2), with no mortality. Bidirectional-Glenn (25) or comprehensive-Norwood stage-two (2)

19 were completed in 27 patients at 4.7 ± 1.2 months with 92.6% survival. Overall KM-survival is

20 $80.9 \pm 7.0\%$ at 4.3 years (mean 25.3 ± 15.7 months). An 8.7% Δ longitudinal strain 30 days after Norwood

21 stage-one had 100% sensitivity and 81% specificity for death/transplant.

22 **Conclusions:** in-hospital interstage facilitates escalation of care, which seems efficacious in reducing

23 interstage Norwood mortality. Significant reduction of longitudinal strain after Norwood stage-one is

24 a strong predictor of poor outcome.

25

1 **Background**

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

18 **Methods**

19 *Ethical statement*

20 *The NHS National Ethical review approved this study as UK Health Research Authority project ID*
21 *235600, reference 17/EE/0417.*

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

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

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1 **Statistical analysis**

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

16 **Results**

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

24

1 **Norwood stage-one**

2 A Norwood stage-one operation was performed at 3.4 ± 2.1 day of life, and 3.1 ± 0.4 kg mean body
3 weight. Two premature babies (<37 weeks gestation) and 2.4 Kg body weight were initially palliated
4 by bilateral PA-banding while continuing PGE1 infusion until Norwood operation **at 2 weeks of life.**
5 There was a slight preference for the Norwood-Sano modification (54.5%) versus the classic Norwood
6 operation with RmBT-shunt (39.4%), with a strong correlation between Norwood-Sano and aortic
7 diameter ≤ 2.0 mm (Fisher exact-testing p-value < 0.01 , $\chi^2 16.1$). **Shunt size was uniformly 5.0 mm for**
8 **the Sano modification and 3.5 mm for the classic Norwood operation with RmBT-shunt.** Associated
9 procedures concomitant with Norwood stage-one included repair of TAPVC, exclusion of a hypoplastic
10 but severely regurgitant mitral valve and patch exclusion of an absent aortic valve. The nomogram of
11 surgical strategy is depicted in Figure 1. Thirty-day mortality was 6.4% (2 patients). One patient died
12 19 days after Norwood-Sano operation because of intractable heart failure due to early development
13 of multiple aorto-pulmonary collaterals (APC). ECMO was instituted on 16th postoperative-day and
14 subsequent cardiac catheterization demonstrated 5 large APC mainly for the right lung. Effective
15 coiling of all APC was achieved but ventricular function did not recover, and mechanical support
16 discontinued. The second postoperative death was secondary to ANCA-associated vasculitis with
17 systemic vasospasm and pulmonary alveolar hemorrhage at 5 days after Norwood-Sano operation.
18 ECMO support was ineffective. Microscopic polyangiitis was detected at postmortem examination.
19 Complications after Norwood stage-one are described in Table 2. The 30-day survival was $93.3 \pm 4.6\%$.
20 Mean combined ICU/HDU stay after Norwood stage-one was 42.3 ± 6.4 days.

21 **Interstage**

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

1 (57.1%) while b-blockers were used seldom during interstage (7.4%). One patient died at 4.07 months
2 during in-HIP, accounting for a 3.4% in-HIP mortality. Cause of death was progressive diastolic
3 dysfunction leading to ventricular failure. Persistently high O₂ saturation exceeding 90% after a
4 classic-Norwood operation prompted a cardiac catheterization at 3 months of age, which detected
5 multiple APC and elevated EDP (18 mmHg). Despite APC coiling and maximal medical therapy, EDP did
6 not improve and the patient was not considered a candidate for Norwood stage-two. Nine patients
7 (31%) required further surgical (2) or catheter (7) reintervention during in-HIP. Two unplanned
8 reoperations were performed during in-HIP (6.8%). The first unplanned surgery was indicated to repair
9 a progressively incompetent neo-aortic valve, detected at serial postoperative echocardiograms after
10 Norwood-Sano operation. Although clinically tolerated, the increment in vena-contracta prompted
11 reoperation at 1.5 months after initial Norwood stage-one. The anterior left cusp of the neo-aortic
12 valve was found to be retracted, generating an eccentric jet. The neo-aortic-valve was repaired by
13 augmenting the retracted cusp with a pulmonary homograft leaflet patch. Valve continence was
14 restored with uneventful recovery and long-term efficacy. This patient recently underwent successful
15 fenestrated extracardiac-Fontan completion and his perfect neo-aortic valve competence was
16 documented at intraoperative TOE. Persistent non-invasive ventilation dependency prompted CT-
17 angiography in another patient, 3.2 months after classic-Norwood operation complicated by Gram-
18 negative mediastinitis. Despite control of the infection and good healing of the sternotomy wound,
19 respiratory symptoms were investigated. A rapidly expanding pseudo-aneurysm compressing the left
20 pulmonary artery and the left bronchus was confirmed at two consecutive CT-angiograms, prompting
21 urgent reoperation. A pulmonary homograft patch was utilized to reconstruct and repair the ventral
22 portion of the aortic arch, excluding the aneurysm, under deep hypothermic circulatory arrest. The
23 procedure was well tolerated, and 30-day control CT-angiogram confirmed proper arch anatomy and
24 resolution of the arch aneurysm. Additional unplanned catheter interventions were indicated at 2.7±
25 0.4 months during in-HIP in 7 patients (24.1%), to occlude multiple APC (4=13.8%), stent a stenotic
26 Sano-shunt (1), balloon dilate a recurrent coarctation (1) and stent a compressed left pulmonary artery

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

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

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

21 ***Norwood stage-two***

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

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

17 **Fontan completion**

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

21 **Discussion**

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

1 a 12% interstage mortality [1]. Noticeably this study highlighted an 18% interstage mortality for the
2 classic-Norwood operation with RmBT-shunt [1]. These and similar findings support the inference that
3 interstage mortality can be close or even higher than contemporary surgical mortality for Norwood
4 stage-one operation [5]. Several risk factors have been identified as independent predictors of
5 interstage mortality, including gestational age, ethnicity, census, anatomic subgroup, surgical
6 technique, residual lesions, arrhythmias or acquired intercurrent illnesses [2]. HMP has been
7 implemented as a key effort to improve interstage outcomes and consists of home oxygen-saturation
8 monitoring and weight-checks. HMP ambition is to flag deteriorations in clinical conditions, with
9 earlier detection possibly translating into improved outcomes [3,6,7]. Rudd [3] reported a significant
10 reduction of interstage mortality from 16% to 2% over a 10-year HMP experience, compared with
11 historical controls at Children’s Hospital of Wisconsin. With NPC-QIC implementation, HMP for HLHS
12 has been widely adopted in the US and expanded to include all shunt-dependent single ventricles (SV-
13 HMP) [6,8]. A similar strategy has been endorsed by other non-US centers [9]. HMP is a complex
14 endeavor that relies heavily on parental involvement and education, requires dedicated cardiac teams
15 with specialist-nurses and cardiologists (among others) available 24 hours/day to triage all the events
16 that result in breach of predetermined parameters, it involves frequent home visits, dedicated
17 hospital clinics with outpatient or emergency-room evaluation by professionals familiar with HLHS
18 management. Finally, when indicated, hospital admission must be organized whereby a pediatric ICU
19 and HLHS expertise is available. Interestingly most centers report 60% hospital readmission rate at
20 least once during HMP interstage, with 85% flagged home-events requiring in-hospital evaluation
21 [3,10]. These findings essentially underline the interstage vulnerability status. Despite this intensive
22 effort, some concerns have emerged regarding HMP efficacy. On a large multicenter study, Oster et
23 al. [4], on behalf of the NPC-QIC, failed to demonstrate any benefit of interstage daily home-oxygen
24 or weight-monitoring regarding reduced interstage mortality, transplantation, unscheduled clinic
25 visits, or unplanned readmissions. Oster reported 8.1% interstage HLHS mortality, lower than in
26 previous cohorts, suggesting an improved overall care coordination independent of HMP. Oster

1 recommended further efforts beyond HMP to neutralize interstage mortality. Similarly, Petit et al [8]
2 reported 8.3% interstage mortality after the implementation of SV-HMP at Texas Children’s Hospital,
3 not significantly different from historic controls. In this single-centre retrospective review
4 encompassing 230 patients, including 34% non-Norwood palliations, two-thirds of the lethal
5 interstage events presented as sudden death, with no apparent identifiable cause even at autopsy.
6 Membership in the SV-HMP did not protect against interstage mortality [8]. This confirms the report
7 by Hehir et al [2], who noted that the majority of interstage deaths after Norwood stage-one were
8 sudden and unexpected events in infants with a history of arrhythmia. Pulse-oximetry may be a useful
9 tool to screen for shunt dysfunction, nevertheless shunt occlusion or thrombosis is not the leading
10 cause of interstage mortality. Li et al. [11] reported that the mortality rate after Norwood palliation
11 exceeds the rate of thrombosis with systemic-to-pulmonary shunts and suggested that a precipitating
12 cause may be linked to coronary events. The inference is that no tool currently available can reliably
13 screen and prevent sudden interstage death or adverse near-miss events. Therefore, a change in
14 strategy for interstage management **could be considered**. Our study evaluates the preliminary
15 experience with a different strategy after Norwood stage-one operation, the systematic in-hospital
16 interstage program (in-HIP). In primis, our 93.3%±4.6% Norwood stage-one 30-day survival and
17 80.9±7.0% aggregate transplant-free 4-year survival, favorably compares with the outcome reported
18 at leading and high-volume Norwood centers, confirming Checchia’s findings [12]. The adoption of
19 this strategy is based on the rationale that in-HIP facilitates escalation of care at its maximal speed
20 and capacity. Since the experience of others essentially demonstrated the unpredictable and sudden
21 nature of interstage mortality, the only tool left to impact on sudden death is speed of detection and
22 reaction against adverse events, essentially like a hospital “red-code”. This is in line with the
23 documented better outcome of in-hospital versus out-of-hospital management of cardiac arrest [13].
24 In-HIP is not a completely new concept. Even in centers where HMP is a well-established practice,
25 approximately 15-20% patients remain in-hospital until Norwood stage-two [3]. This strategy is
26 generally selected for patients with “high-risk” profile, although the definition of “high-risk” after

1 Norwood stage-one is not easily discernible. Nevertheless, Rudd [3] reported an acceptable outcome
2 for this “high risk” group who remained admitted until stage-two completion (83% survival), indirectly
3 suggesting the efficacy of this strategy. The novel concept of our systematic in-HIP assumes that every
4 patient after Norwood stage-one is, by definition, at high-risk for sudden death, because of the parallel
5 model of Norwood circulation. This unavoidable substrate predisposes to serious sudden cardiac and
6 extracardiac intercurrent events. Our study highlights two relevant findings. First, we could achieve a
7 3.4% in-HIP mortality, lower than in most reported series. The second relevant finding is the 17.2%
8 escalation of care that we observed during in-HIP. These incidents were abrupt, unexpected and
9 required aggressive invasive management within minutes from PICU admission. Only one event was
10 shunt-related, while the others were either respiratory accidents (requiring high-frequency oscillatory
11 ventilation) or de-novo onset of atrial arrhythmias affecting tricuspid valve and ventricular function.
12 These incidents occurred 2.5 ± 1.2 months during interstage, while the patients were on apparent
13 stable conditions in the ward. Typically, by this time the patients would have been at home under
14 HMP. Very likely, had these events occurred at home, they would have been invariably fatal, in
15 agreement with the experience of others on sudden death during interstage [8]. On the contrary,
16 expeditious escalation of care with appropriate PICU management was life-saving. Our 17.2%
17 escalation of care during in-HIP is not very different from the 18% interstage mortality reported by the
18 SVR trial for the classic-Norwood operation [1]. Our provocative inference is that in-HIP converted
19 interstage mortality in escalation of care, maximizing the chances of successful treatment of cardiac
20 and extracardiac interstage incidents, ultimately controlling mortality. In agreement with other
21 reports, unplanned operations or catheter reinterventions were frequent during interstage. A novel
22 finding of this study is the identification of early development of aorto-pulmonary collaterals in 13.4%
23 patients during interstage. We pursued an aggressive strategy to coil occlude these collaterals before
24 Norwood stage-two, to avoid competitive flow and reduce ventricular volume overload, possibly
25 affecting ventricular function and end-diastolic pressure. As a paired advantage, in-HIP facilitated the
26 internal coordination for unplanned interventions, with minimal impact on daily scheduling. The

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

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

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

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

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- 1 Figure legend.
- 2 Figure 1. Surgical strategy
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- 4 Figure 2a Interstage reintervention-free survival . Figure 2b. Interstage escalation of care -free survival
- 5
- 6 Figure 3. Overall transplant-free survival and staging
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- 8 Figure 4. TAPSE, longitudinal strain and longitudinal strain-rate at specified time intervals
- 9
- 10 Figure 5. Sensitivity and specificity of TAPSE and Δ LS at one month after Norwood stage-one as
- 11 predictive value for combined outcome death/transplant
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1 **Table 1. Anatomic details and associated lesions**

2 ***HLHS (24 patients)***

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

4

5 *Associated lesions*

6	TAPVC-CS	1
7	PAPVC	1
8	intact or near-intact muscular IAS	5
9	bilateral SVC	2
10	moderate-severe TR	2

11

12 ***HLHS-variants (9 patients)***

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14	<i>MS, AS (unicuspid), VSDs</i>	3
15	<i>unbalanced AVSD</i>	2
16	<i>DILV, malposed GA, sub-AS, arch hypoplasia</i>	1
17	<i>DORV, straddling AVV, sub-AS, arch hypoplasia</i>	1
18	<i>DORV, absent aortic valve</i>	1
19	<i>TGA, MS, PS, sub-PS</i>	1

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

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1 Table 2. Complications after Norwood stage-one

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3 patients management

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

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

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Independent variable	coefficient	Standard error (SE)	t	p-value
<i>longitudinal strain</i>	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

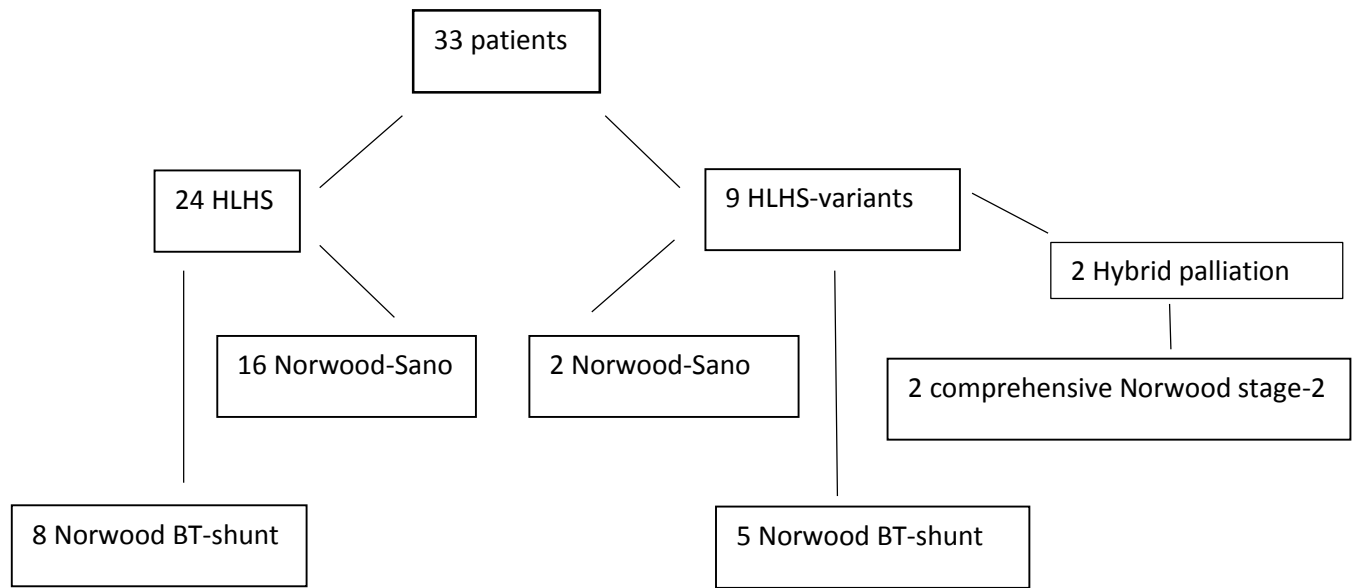


Figure 3

[Click here to access/download;Figure;figure 3 final.pdf](#)

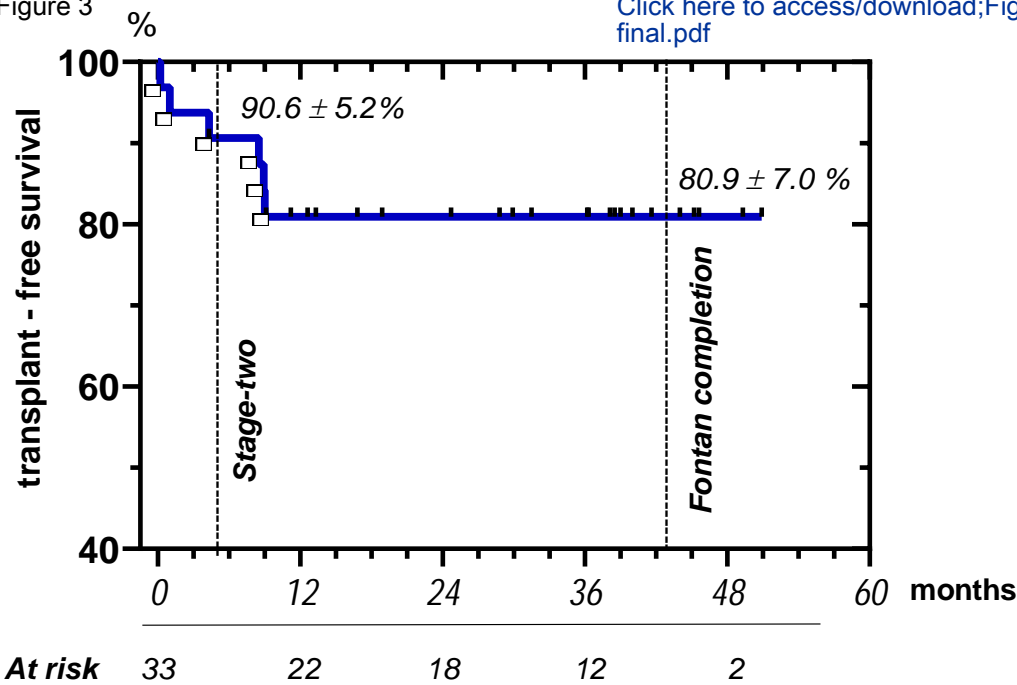


Figure 4.

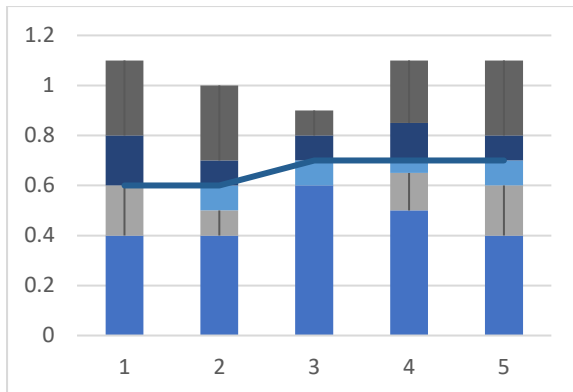
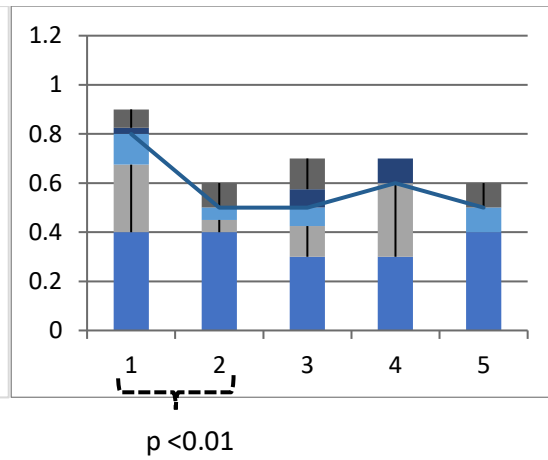
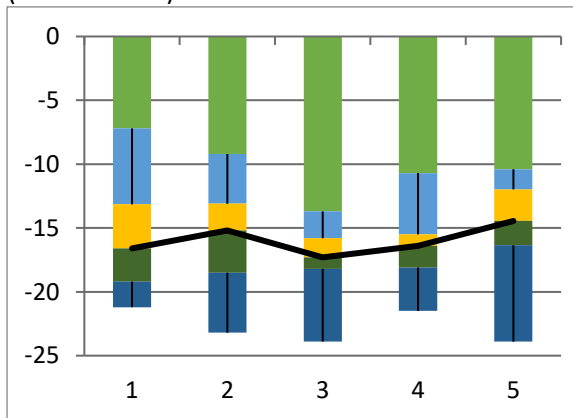
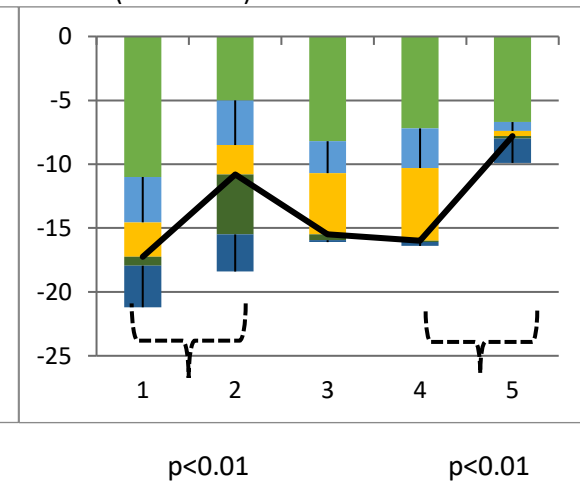
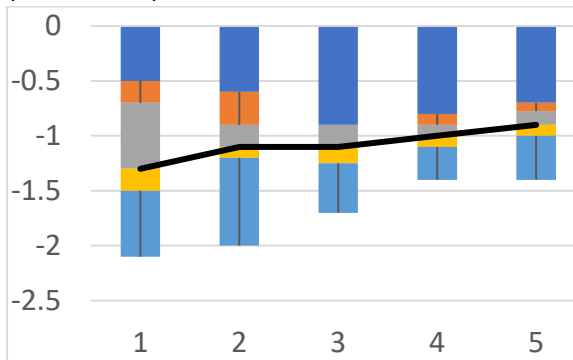
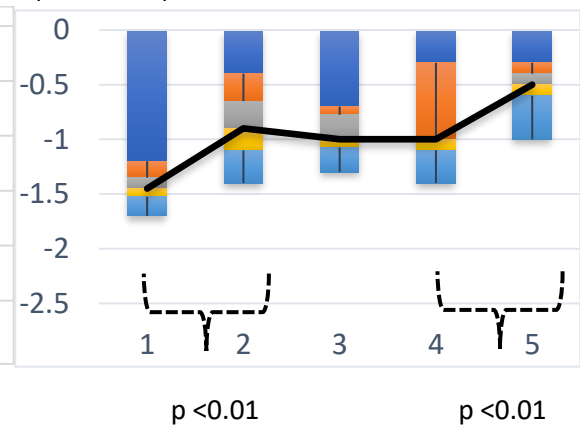
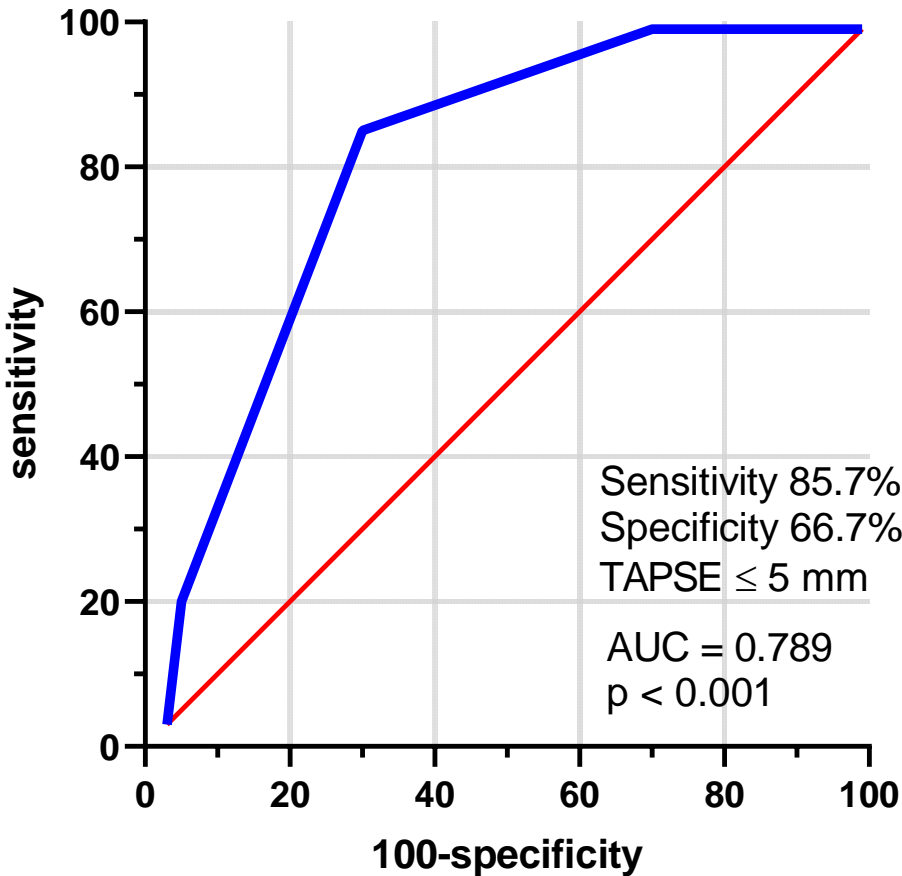
TAPSE transplant-free survivors (0.7 ± 0.1 cm)TAPSE death or transplant (0.5 ± 0.05 cm)Longitudinal strain transplant-free survivors (-14.45 ± -1.9)Longitudinal strain death or transplant (-7.8 ± -0.3)Longitudinal strain rate: transplant free survival (-0.9 ± -0.13)Longitudinal strain rate: death or transplant (-0.5 ± -0.1)

Figure 5a



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



Δ LS at 1 month after Norwood stage-one

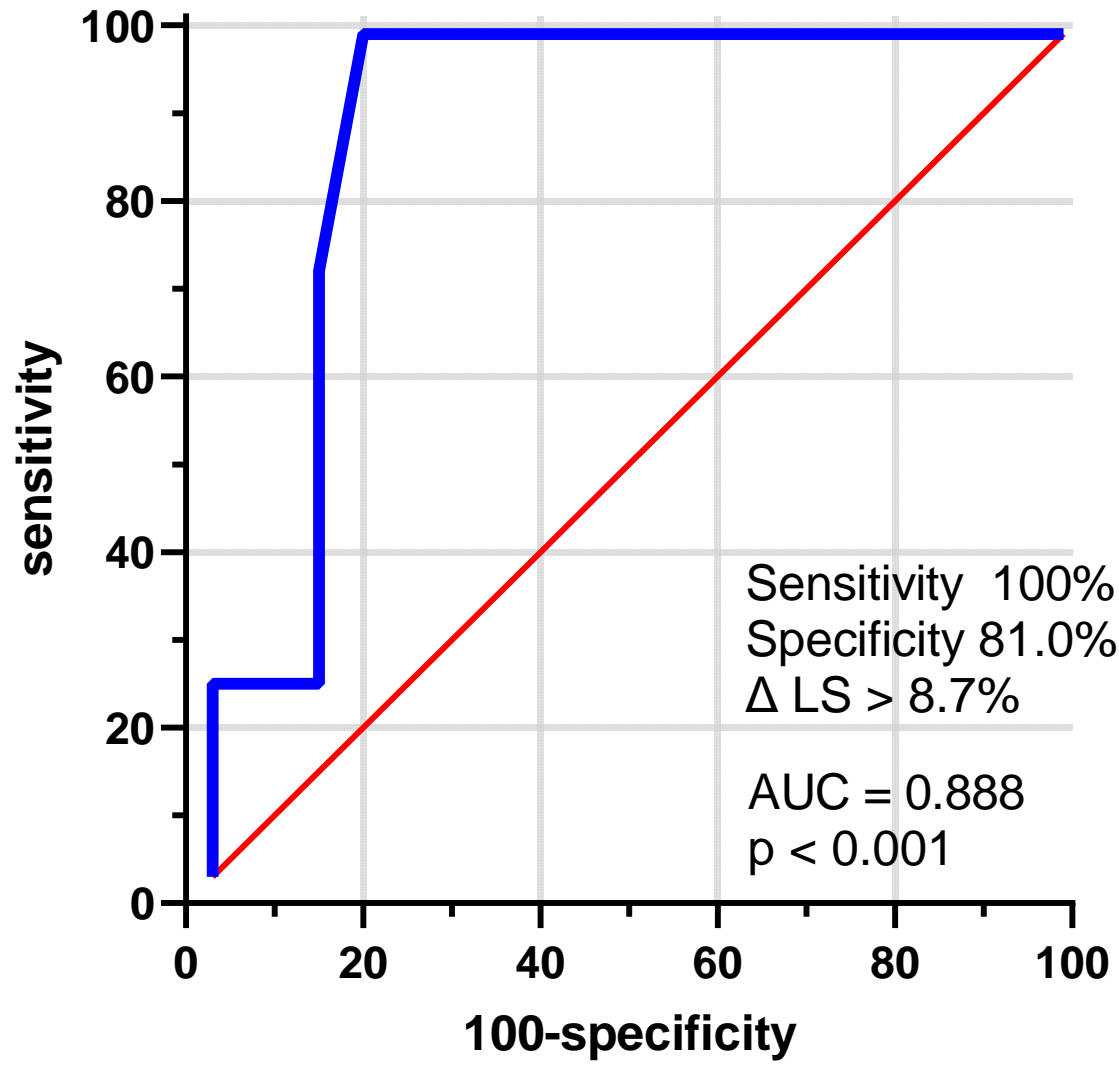


Figure 2a.

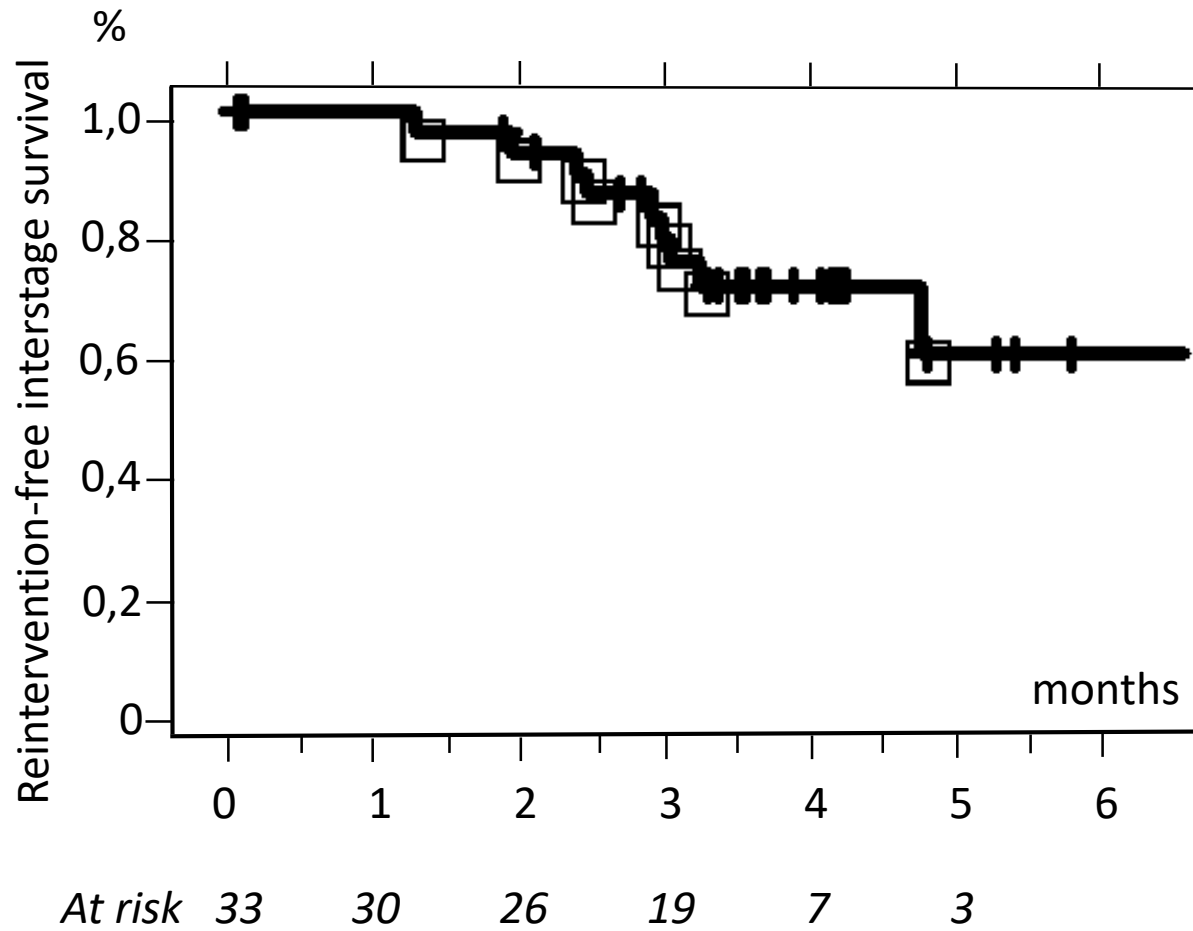


Figure 2b.

