# Prognostic value of troponin in infants with hypoplastic left heart syndrome between Stage I and II of palliation

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## ABSTRACT

**Background** : **The period between stage I and II procedure for treatment of hypoplastic left heart syndrome (HLHS) bears high mortality and morbidity.**

**Methods** : **We sought to analyze the prognostic value of Troponin T/I (Trop), a well-recognized marker for myocardial damage and heart failure, for predicting outcome in a retrospective analysis of 70 infants with HLHS at our institution between March 2001 and October 2014.**

**Results** : **Stage I procedure consisted of Norwood I operation in 35 (50%) and Hybrid-approach in 22 (31%) patients. Palliative care was chosen for 13 (19%) patients. Trop values were collected from clinical charts and were analyzed in relation to the overall outcome. Trop was significantly higher after Norwood I operation in comparison to Hybrid-approach (median 7.1 μg/l (0.7-20.9), vs 1.2 μg/l (0.3-17.9), $P < 0.001$). Overall mortality of treated patients was 39% (22 patients). Survival was 54% (19 patients) after Norwood and 73% (16 patients) after Hybrid-approach. Independently from the procedure used, maximal Trop and initial lactate values were significantly higher in non-survivors than in survivors, with median Trop of 9 μg/l (0.6-18.8) vs. 3.4 μg/l (0.4-20.9), $P$ 0.007, and median lactate of 3.7 mmol/L (1.6-25) vs. 2.9 mmol/L (0.3-14.6), p 0.03. Reinterventions were required in 17 (30%) patients, 4 (11%) after Norwood and 13 (59%) after Hybrid procedure. No correlation was found between the need for reintervention and Trop levels in the interstage period.**

**Conclusions** : **Patients with HLHS have significantly higher Trop levels after Norwood procedure than after Hybrid-approach. Maximal Trop values were related to mortality, but did not correlate with the need for reinterventions.**

**Keywords** : Hypoplastic left heart syndrome, palliation, troponin

## INTRODUCTION

Hypoplastic left heart syndrome (HLHS) belongs to the congenital heart defects with the highest morbidity and mortality.[1] Norwood *et al.*[2] introduced the surgical three-stage palliation in the early 1980s; before that, it was not possible to offer any treatment and comfort care was the only option for infants diagnosed with this heart defect.[3] With the improvement of diagnostic modalities and surgical techniques, nowadays, survival rates of above 75% are reported.[3,4] The highest mortality is reported from Stage I palliation as well as during the frail interstage period between Stage I and Stage II (bidirectional cavopulmonary connection). Several

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studies analyzed potential risk factors for mortality during the course of the disease. The diameter of the ascending aorta, atrioventricular valve regurgitation, and a restrictive foramen ovale have been associated with increased morbidity and mortality.[5] In addition, prematurity, low birth weight, and chromosomal abnormalities adversely affect outcome, whereas the impact of a prenatal diagnosis remains controversial.[3,6] Troponins (Trop) are highly specific biomarkers for injury of the cardiac muscle, used not only for detecting myocardial ischemia but also in heart failure.[7] Trop show a rise 2–4 h after myocardial damage with peak values after 18–36 h.[7]

Children with HLHS are at high risk for myocardial damage and infarction not only perioperative but also postnatal before the diagnosis is established as well as during the interstage period.[3] Little is known about Trop in this patient population.[8,9] The aim of our study was to analyze Trop values in infants with HLHS before and after Stage I palliation and during interstage until Stage II palliation and to analyze if Trop can be used as an additional marker for morbidity and mortality.

## METHODS

All patients with HLHS treated in our institution between March 2001 and July 2015 were identified from the electronic database. Medical records including echocardiograms and laboratory analysis were retrospectively reviewed. Before February 2009, an assay for Troponin I was performed; thereafter and until now, Troponin T (Roche®) is measured. Both markers have a similar sensitivity for myocardial damage.[7] Trop values were measured:

- Preoperative: In seriously ill children
- Postoperative after Stage I palliation: Directly following surgery/intervention and after 24 and 48 h.

Afterwards, Trop values were measured occasionally or because of clinical deterioration. Renal function was monitored by measuring creatinine values directly as well as 24 and 48 h and 1 week after surgery/intervention. Since 2006, hybrid procedures are performed in our institution.

### Statistics

Data are presented as median and interquartile range or mean ± standard deviation, as appropriate. Categorical data are expressed as counts and percentages. Differences between subgroups were tested using Fishers' exact test for categorical data and differences in subgroups for continuous variables were assessed using the Wilcoxon rank sum test or Student' *t*-test. Correlation coefficient was calculated and classified according to Cohen:[10] $r = 0.10$ corresponds to a weak, $r = 0.30$ to a medium, and $r = 0.50$ to a strong correlation. Significance testing was two-sided with the significance level set at $P < 0.05$. Statistical analyses were performed using SPSS version 22.0 (IBM, USA).

## RESULTS

In total, 70 infants with HLHS were included in the study with a median birth weight of 3055 g (range 1700–4150 g). Ten infants were born prematurely between 33 and 37 weeks of gestation. Genetic anomalies were found in five children. Following types of HLHS were present: 24 aortic atresia/mitral atresia (34%), 20 aortic stenosis/mitral stenosis (29%), 19 aortic atresia/mitral stenosis (27%), and 7 aortic stenosis/mitral atresia (10%). A restrictive foramen ovale was diagnosed in 16 patients (23%) and an obstructive total anomalous pulmonary venous return in 3 patients (4%). Before Stage I procedure, 13 (19%) patients died due to multi-organ failure or to parental decision for comfort care. Thirty-five (61%) of the remaining 57 patients underwent Norwood Type I procedure with a modified Blalock-Taussig shunt (Norwood group) and 22 (39%) were treated with a hybrid approach, which consisted of stenting the arterial duct and banding both pulmonary arteries (hybrid group). In each group, one patient was lost to follow-up. In total, 35 patients (61%) survived to Stage II procedure, 19 (54%) in the Norwood, and 16 (73%) in the hybrid group. No significant difference in mortality rate between Norwood and hybrid group was found ($P = 0.15$). Birth weight (3105 vs. 3095 g, $P = 0.47$), diameter of the ascending aorta (2.7 vs. 3.5 mm, $P = 0.2$), and preprocedural Trop level (0.13 vs. 0.07 μg/L, $P = 0.15$) showed no significant difference between both groups. In contrast, immediate postoperative Trop after Stage I (7.07 vs. 1.24 μg/L, $P < 0.001$) and maximal Trop in the interstage period (7.77 vs. 1.27 μg/L, $P < 0.001$) were significantly higher in the Norwood group than in the hybrid group. Analysis within each treatment group showed a trend toward higher Trop levels between nonsurvivors and survivors (Norwood group $P = 0.1$, hybrid group $P = 0.09$).

Reinterventions were performed in 17 patients (30%) between Stage I and II and were more frequently needed in the hybrid group (4 vs. 13 patients, $P < 0.001$). Reinterventions, included catheter interventions in 12 patients, with one patient needing two catheter interventions and reoperations in five patients. No correlation was found between the need for reintervention and Trop levels in the interstage period.

When comparing nonsurvivors to survivors, initial Trop after Stage I, maximal Trop levels in the interstage period, and lactate levels at admission were significantly higher in nonsurvivors, independently from the procedure

**Table 1: Comparison of nonsurvivors and survivors (median and range)**

| | Nonsurvivors | Survivors | *P* |
|---|---|---|---|
| Total | 22 (39) | 35 (61) | |
| Birth weight (g) | 2969±584 | 3172±363 | 0.059 |
| Days between birth and diagnosis | 1 (0-30) | 0 (0-49) | 0.42 |
| Diameter ascending aorta (mm) | 3.5 (1.5-7.7) | 3.0 (1.8-6.5) | 0.41 |
| Preoperative lactate (mmol/L) | 3.7 (1.6-25) | 2.9 (0.3-14.6) | 0.03 |
| Initial Trop (µg/l) | 0.62 (0.04-10.16) | 0.04 (0.03-0.2) | 0.16 |
| First Trop after Stage I (µg/l) | 7.35 (0.63-17.89) | 3.55 (0.27-20.88) | 0.049 |
| Maximal Trop between Stage I–II (µg/l) | 9.02 (0.63-18.8) | 3.37 (0.42-20.88) | 0.007 |
| Creatinine directly after Stage I (µmol/l) | 70.5 (34-105) | 66 (45-90) | 0.33 |
| Maximal creatinine 1st week after Stage I (µmol/l) | 74 (56-107) | 70 (52-113) | 0.21 |

Trop: Troponin T/I

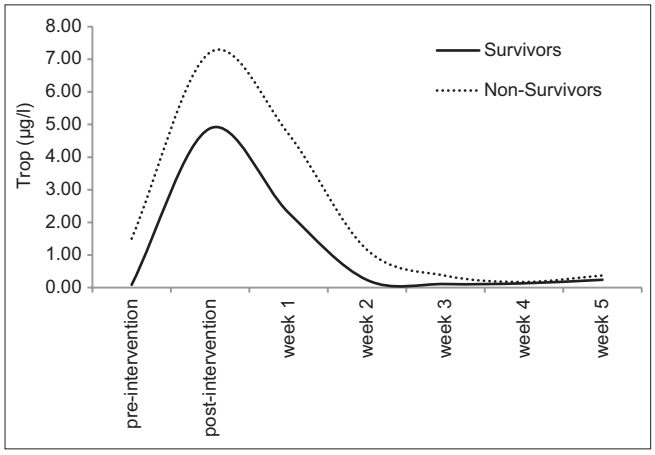


**Figure 1: Troponin course in survivors and nonsurvivors**

used [Table 1 and Figure 1]. Nonsurvivors showed a trend to lower birth weight [Table 1].

All patients showed only slightly impaired creatinine values in the 1st week after surgery or catheter intervention (highest value [median]: 72 µmol/L [76–83] [normal values for this age group: <60 µmol/L]). There was neither a significant difference in creatinine values in all time points between the Norwood and the hybrid group (e.g., directly postoperatively: median 69 vs. 67.5 µmol/L, $P = 0.32$) nor between survivors and nonsurvivors (e.g., highest value during the 1st week after intervention: median 70 versus 74 µmol/L, $P = 0.21$) [Table 1]. No correlation was found between Trop values and the highest creatinine values during the 1st week after intervention ($r = -0.003$, $P = 0.98$).

## DISCUSSION

Risk factors associated with morbidity and mortality in neonates with HLHS have been studied extensively in the last decades.[3,4,11] The role of Trop levels until Stage II of treatment has been poorly investigated.

We found a significant difference in Trop levels measured immediately after Stage I procedure and during the interstage period between survivors and nonsurvivors. These results suggest that Trop might be an additional marker of outcome in this high-risk cohort of patients. We further suggest that an increase in Trop levels in the postoperative phase and during the interstage period should be considered as an alert sign.

Our results demonstrate a relatively high mortality rate in contrast to recently published studies.[12] This might be explained partly by the long time period with different treatment strategies and possibly different patient selections in our observation in contrast to other observations.

It has been previously reported that in neonates with various congenital heart defects, Trop I was a predictor for early in-hospital mortality after cardiac surgery.[13] Particularly, neonates with HLHS represented a very high-risk group, with clear correlation between high Trop I levels and mortality. In our cohort, higher Trop levels found in the Norwood group can be explained by the extent of myocardial damage set by the surgical technique with aortic cross-clamp and cardiopulmonary bypass, which is known to raise Trop.[14] In our analysis, we found only a trend toward higher Trop levels between nonsurvivors and survivors in the respective treatment group; this may be explained by the small sample size of each group as HLHS is a rare lesion and hybrid procedures for HLHS have been performed since 2006 in our institution only.

It is known that different factors might influence the Trop values[7] besides myocardial damage during surgery or cardiac interventions. Especially an impaired renal function or sepsis should always be taken into account when interpreting Trop values. In addition, it has been shown that pressure overload might have an influence on Trop values before treatment, especially in neonates and infants,[8] and that circulating autoantibodies to cardiac Trop can be an interfering factor in the measurement of serum levels of Trop.[15] Our results showed only a slightly reduced renal function with no difference between the Norwood and the hybrid group and no difference between survivors and nonsurvivors. In addition, we found no correlation between renal function and height of Trop values. Autoantibodies to Trop have not been analyzed in our patient group.

Taken together, our results suggest that Trop might be used as an additional tool for the outcome prediction in combination with other well-known clinical parameters in HLHS. The real role of Trop in the postoperative management and risk stratification of neonates after Stage I procedure for HLHS needs to be defined by the

future prospective studies, with serial measurements of Trop and analysis of all potential confounding factors.

## CONCLUSION

Trop levels in neonates after Stage I procedure for HLHS might be an additional marker for outcome prediction, to be used in combination with other clinical and laboratory parameters.

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**Conflicts of interest**

There are no conflicts of interest.

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