

Improvements in Survival and Neurodevelopmental Outcomes in Surgical Treatment of Hypoplastic Left Heart Syndrome: A Meta-Analytic Review

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Abstract: The purpose of this study was to analyze the changes over the past two decades in hospital survival and neurodevelopmental outcomes after surgical treatment for hypoplastic left heart syndrome. The hypothesis for this study is that increasing hospital survival following the Stage I Norwood (S1N) procedure is associated with improvements in neurodevelopmental outcomes. Studies included in the meta-analysis were identified by searching Ovid MEDLINE® from January 1980 to October 2010. A total of 72 articles were identified. Fifteen single-center study articles were appropriate for obtaining survival data and 14 were used for neurodevelopmental outcomes. Wechsler Intelligence Test IQ scores and the Bayley II Mental Development (MDI) and Psychomotor Development Indices (PDI) were the primary neurodevelopmental outcomes included in this meta-analysis. Metaregression analysis using a

mixed-effects model compared the percent survival and neurodevelopmental scores with the year of surgery. Hospital survival for the S1N operation increased significantly from 1996 to 2007 ($p < .05$). The overall mean survival during this time period was 80.05% (95% confidence interval [CI], 76.4–84.0%). Standardized Wechsler IQ scores increased significantly from 1989 to 1999 ($p < .05$) and the mean IQ was 85.09 (95% CI, 82.3–89.5). The Bayley II MDI increased significantly from 1998 to 2005 ($p < .05$) with a mean MDI of 86.9 (95% CI, 84.9–88.9). The Bayley II PDI increased significantly from 1998 to 2005 ($p < .05$) with a mean PDI of 73.4 (95% CI, 71.2–75.5). Increased survival has been associated with improved but below normal neurodevelopmental outcomes. **Keywords:** hypoplastic left heart syndrome, mortality rate, neurodevelopmental outcomes, Norwood operation. *JECT. 2012;44:216–223*

Hypoplastic left heart syndrome (HLHS) is a serious congenital heart defect that occurs in one out of every 5000 births (1) and is manifested by underdevelopment of the left ventricle, aortic or mitral stenosis or atresia, and hypoplasia of the ascending aorta. Without surgical treatment, HLHS has a high mortality in the first month of life (1). The development of a staged palliation surgical approach (three separate surgical procedures), although highly successful, is still associated with significant mortality and morbidity (2). The Stage I Norwood Procedure (S1N) has the highest mortality and incurs the greatest risk for neurological injury of the three surgical stages (3,4).

The Pediatric Heart Network and National Heart Lung and Blood Institute Working Group on Perioperative Management of Congenital Heart Disease identified

that “the effects of cardiopulmonary bypass on early recovery and long-term sequelae such as neurodevelopmental deficits remain significant issues for neonates undergoing surgery for CHD” (5). Their recommendation was that “clinical trials aimed at novel therapies to address these problems should be a top priority.” This call demonstrates a broad understanding that neurodevelopmental deficits are a continued problem after neonatal heart surgery.

The purpose of this study is to define the changes in survival and neurodevelopmental outcomes over the past two decades. Reduction in the mortality rate for the S1N operation has been reported over the past two decades as a result of increased surgical experience in major academic medical centers along with refinements in diagnosis, surgical treatment, perfusion and anesthetic techniques, and postoperative care and monitoring. Survival may be associated with neurodevelopmental deficits, which impact long-term quality of life. The patients are at risk for neurological injury not only related to the surgical procedures, but also to preoperative factors related to fetal neurological development and postoperative factors such as low arterial oxygen saturation. The multiplicity of these factors makes

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it difficult to associate one specific factor with long-term neurodevelopmental outcomes.

The aim for this study is to determine whether increased survival is associated with improved neurodevelopmental outcomes. To determine the survival rate and the neurodevelopment outcome scores, a meta-analysis of previously published data will be examined. Meta-analysis provides the highest level of evidence and will be used to demonstrate the impact of survival on neurodevelopmental outcomes.

METHODS

Peer-reviewed studies included in the meta-analysis were identified by searching Ovid MEDLINE® from January 1980 to December 2010. Primary key words included: hypoplastic left heart syndrome, Norwood procedure, Sano, and right ventricle to pulmonary artery conduit. These key words were combined with the following key words: mor-

tality, neurodevelopmental outcomes, Bayley scales, and IQ. A total of 72 articles were identified. Articles were included in this review if they reported any of the following outcomes for S1N procedure: hospital mortality or survival, Wechsler standardized IQ scores, the Bayley II Mental Development Index (MDI) or the Bayley Psychomotor Development Index (PDI). Fifteen articles were appropriate for obtaining survival data and 14 articles were used for neurodevelopmental outcomes. All articles reported single-center studies and included a combination of case series and clinical trials. In all studies, the time period for mortality reporting after the S1N procedure was either 30-day mortality or hospital discharge.

Meta-analysis was accomplished using Comprehensive MetaAnalysis Version 2.2 (Biostat Software, Englewood, NJ) to calculate a weighted mean and 95% confidence interval for each of the parameters. Homogeneity assessments preceded all meta-analytic tests using the Cochrane Q test and if found significant, then a random-effects model

Meta Analysis Random Effects Model for Survival

Stage I Norwood Procedures 1996-2007

*Subgroup Analysis: Modified Blalock-Taussig Shunt (MBTS)
vs. Right Ventricular to Pulmonary Artery (RVPA) Conduit*

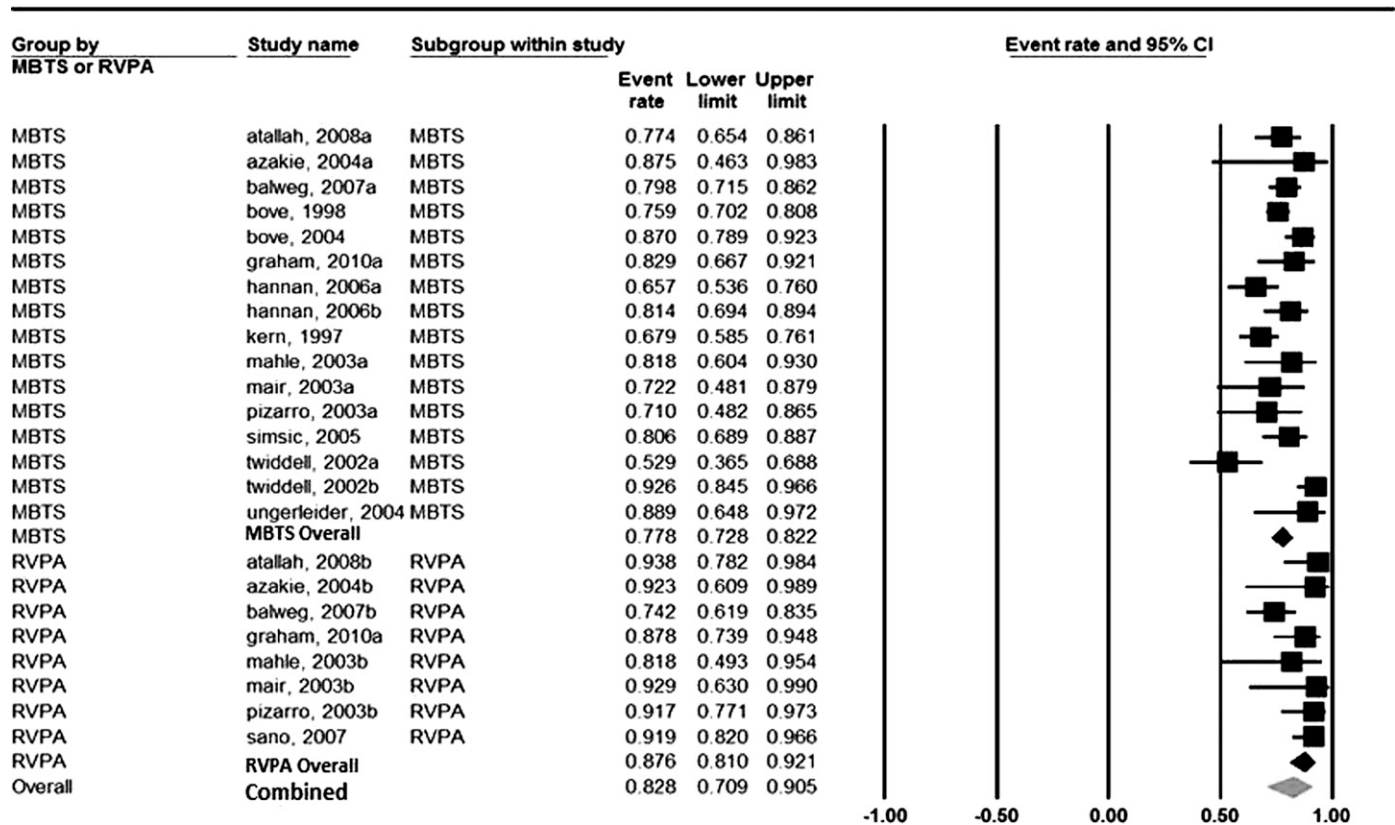


Figure 1. Hospital survival after Stage I Norwood from 1996–2007 and 95% confidence intervals. Subgroup analysis includes: modified Blalock-Taussig shunt (MBTS) vs. right ventricular to pulmonary artery (RVPA) conduit.

**Meta Regression Mixed Effects Model for Year of Surgery on Survival
Stage I Norwood Procedures 1996-2007**

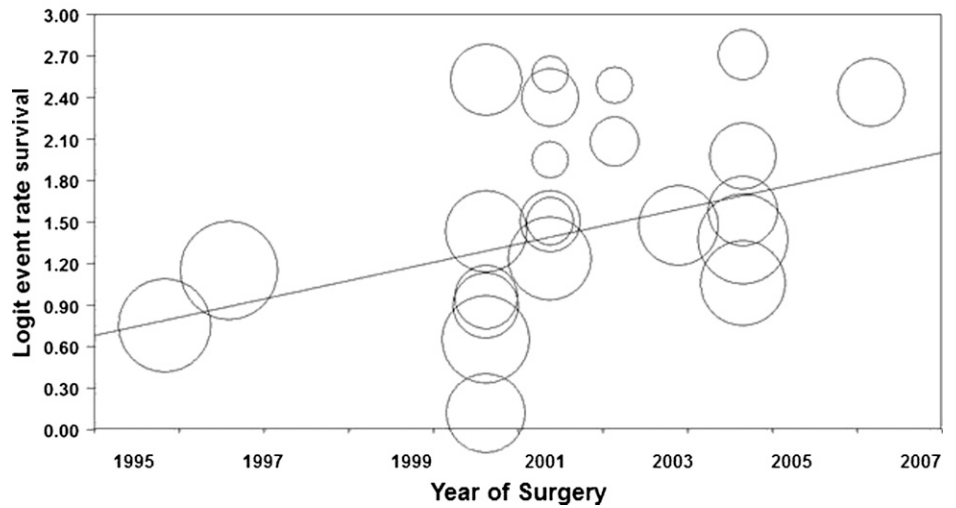


Figure 2. Hospital survival following Stage I Norwood significantly increased from 1996–2007 ($p < .05$) (15 studies). Circle sizes are proportional to the study sample sizes.

was used for meta-analysis and a mixed-effect model for metaregression.

Metaregression analysis was used to analyze the relationship between the year of surgery and 1) survival, 2) Wechsler standardized IQ, and 3) the Bayley II PDI and MDI. Studies included in the analysis were limited

to surgical procedures done within a 7-year period. The final year of surgery in the study was reported in the metaregression analysis. The slope of the regression line indicated the direction of change over time and was considered significant if different from 0 at a significance level of $p < .05$. Meta-analysis on survival after S1N for

**Meta Analysis Random Effects Model for Mean IQ
(Stage Norwood Procedures 1989 to 1999)**

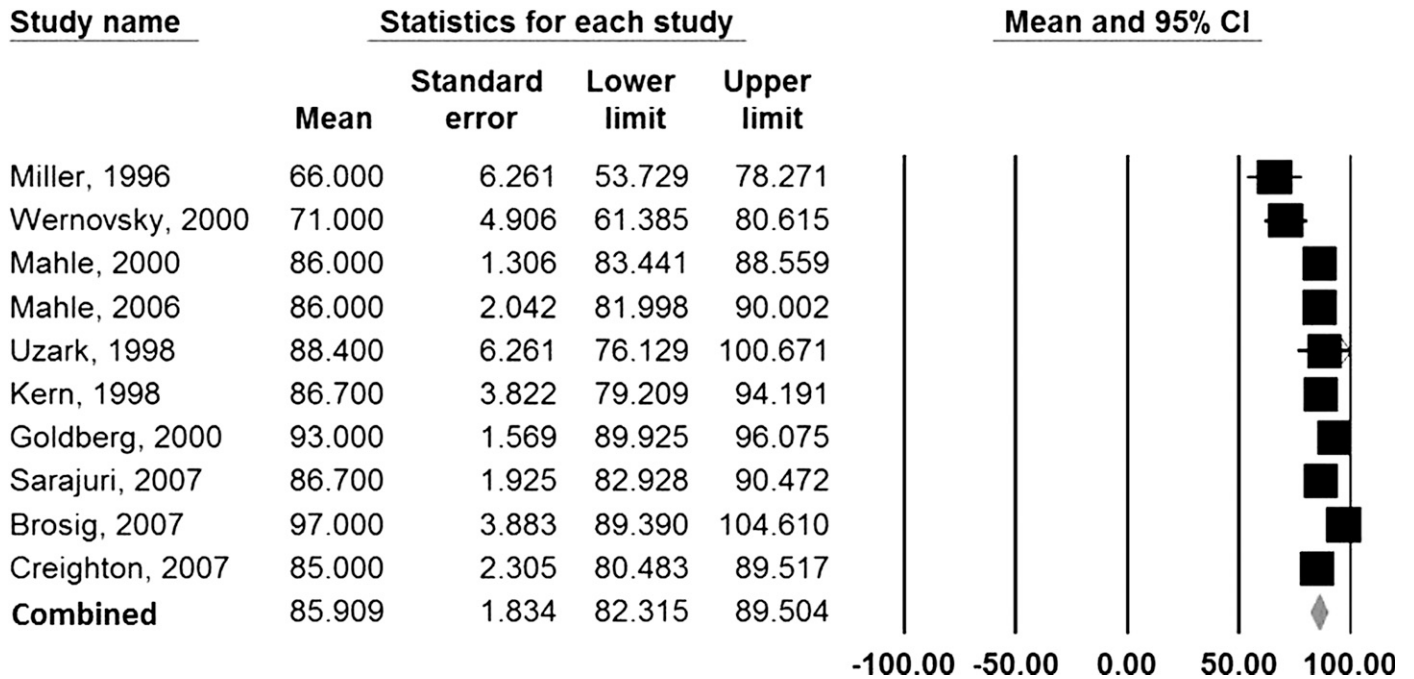


Figure 3. Mean IQ after Stage I Norwood from 1989–1999 and 95% confidence intervals.

modified Blalock-Taussig shunt (MBTS) vs. right ventricular to pulmonary artery (RVPA) conduit was also performed using the same criteria.

RESULTS

Findings from the meta-analysis using a random-effects model and metaregression analysis using the mixed-effects model were the following.

The mean survival for S1N from 1996–2007 (Figure 1) was 82.8% (95% confidence interval [CI], 70.9–90.5%). Hospital survival (Figure 2) after the S1N operation increased significantly during this time period ($p < .05$) (6–22).

Subgroup analysis demonstrates the impact of RVPA conduit on hospital survival for S1N. The random-effects model for MBTS vs. RVPA conduit for S1N operation revealed a mean survival of 77.8% (95% CI, 72.8–82.2%) for MBTS vs. a 87.6% (95% CI, 81.0–92.1%) survival for RVPA. Because the 95% CIs minimally overlap by 1.2%, it approaches statistical significance at $p = .05$.

The overall mean Wechsler IQ from 1989–1999 was 85.9 (95% CI, 82.3–89.5) (Figure 3). The mean IQ increased significantly during this time period ($p < .05$) (Figure 4) (22–32).

The Bayley II MDI overall mean MDI from 1998–2005 was 86.9 (95% CI, 83.5–90.2) (Figure 5). The mean MDI increased significantly during this time period ($p < .05$) (Figure 6) (6,29,30,32–34).

The Bayley II PDI overall mean PDI from 1998–2005 was 73.8 (95% CI, 70.7–76.8) (Figure 7). The mean PDI increased significantly ($p < .05$) (Figure 8) (6,29,30,32–34).

DISCUSSION

Increased survival after the Norwood procedure has been associated with significant improvements in neurodevelopmental outcomes. Bayley scales for both mental and psychomotor development (1–5 years of age) and IQ (6–12 years of age) are improving; however, tests in older children still generally reflect surgical and perfusion practices of the previous decade.

There have been many surgical, perfusion, anesthetic, and postoperative management changes during the current decade that may be contributing to these improvements. A major surgical change during this period was the adoption of the RVPA conduit as an alternative to the MBTS. In the multicenter randomized study, the RVPA conduit was associated with a higher transplantation free survival at 12 months after surgery (33). In our meta-analysis study, S1N survival was nearly significantly better for the RVPA conduit vs. the MBTS.

Another surgical modification has been the adoption of regional cerebral perfusion (RCP). This reduces cerebral circulatory arrest time and may impact long-term neurodevelopmental outcomes. RCP is being now being used in a majority of pediatric heart centers. In a 2007 study, the adoption rate for RCP was 56% (34) and this has increased to 83% in a later study with only 20% of centers routinely or exclusively using deep hypothermia circulatory arrest (DHCA) (35). There is only one randomized clinical trial that has compared the neurodevelopmental outcomes of RCP vs. DHCA in single-ventricle patients and this study did not find a significant difference in Bayley II PDI and MDI at 1 year of age (36). There is no published data on IQ scores in patients with HLHS since the institution of RCP.

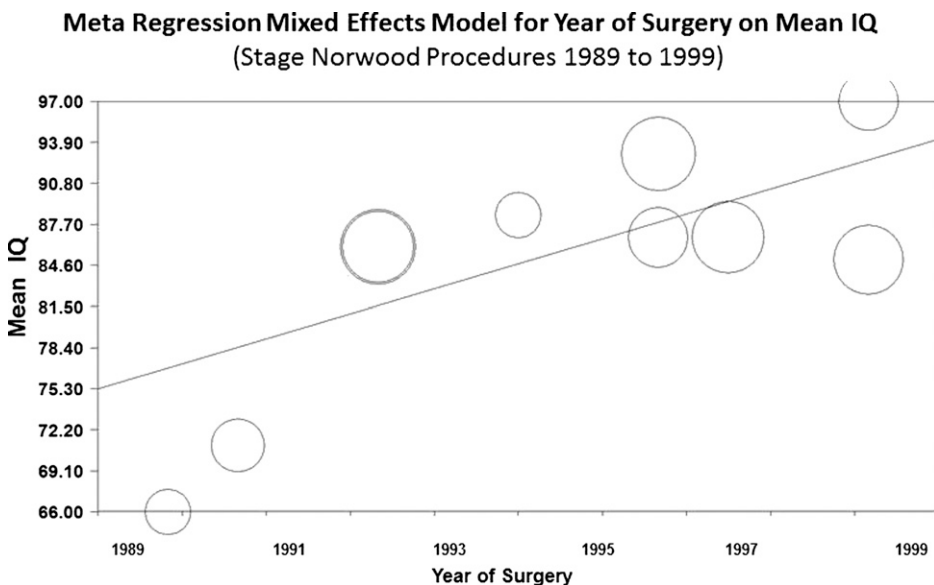


Figure 4. Mean IQ after Stage I Norwood significantly increased from 1989 to 1999 ($p < .05$). Circle sizes are proportional to the study sample sizes.

Meta Analysis Random Effects Model for Bayley II Mental Development Index (MDI) (Stage 1 Norwood Procedures 1998 to 2005)

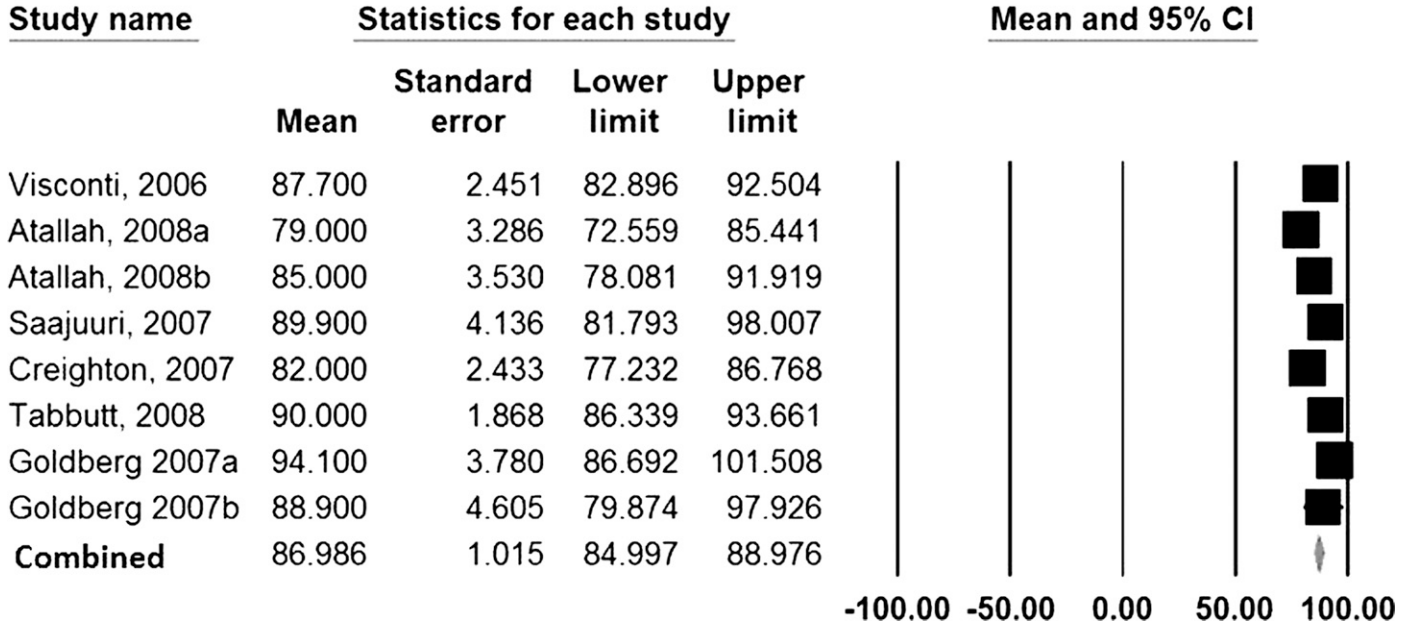


Figure 5. Bayley II Mental Development Index (MDI) after Stage 1 Norwood from 1998–2005 and confidence intervals.

During this same time period, many modifications in perfusion techniques have occurred (37). These include the use of low prime cardiopulmonary bypass (CPB) circuits and modified ultrafiltration. The use of higher hematocrits on CPB and pH stat blood gas management strategy during cooling along with monitoring the cerebral oxygen delivery

with near infrared cerebral oximetry has been demonstrated in both animal and clinical studies to improve outcomes and have been widely adopted (38,39). Improvement in neuro-developmental outcomes is likely a combination of these many changes. The need to be better define the impact of these treatments has resulted in a call for more outcomes

Meta Regression Mixed Effects Model for Year of Surgery on Bayley II Mental Development Index (MDI) (Stage 1 Norwood Procedures 1998 to 2005)

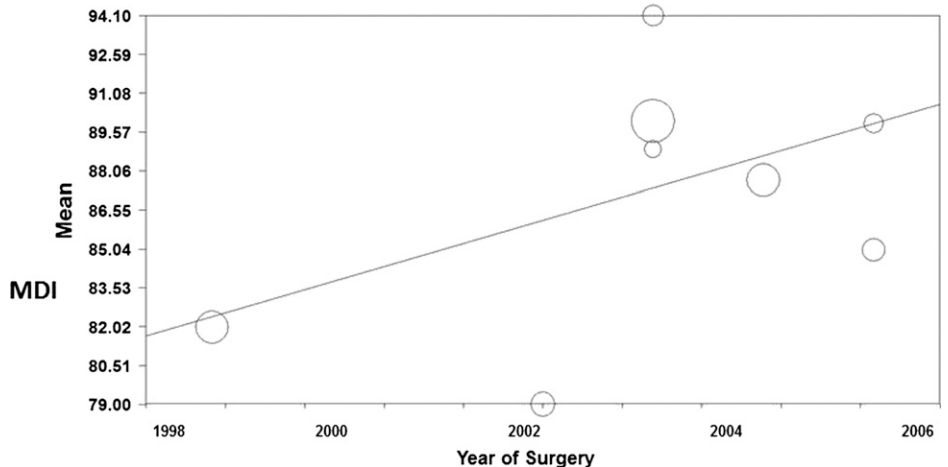


Figure 6. Bayley II Mental Development Index (MDI) after Stage 1 Norwood significantly increased from 1998–2005 ($p < .05$). Circle sizes are proportional to the study sample sizes.

Meta Analysis Random Effects Model
Bayley II Psychomotor Development Index (PSI)
 (Stage 1 Norwood Procedures 1998 to 2005)

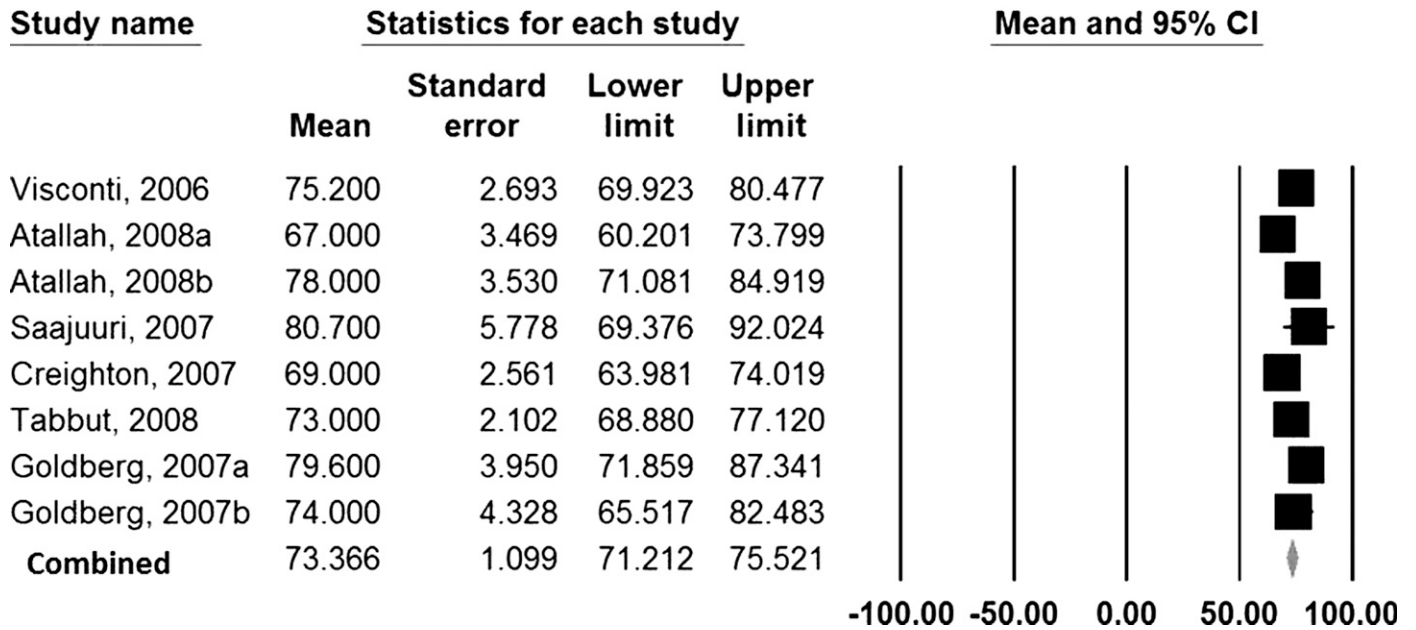


Figure 7. Bayley II Psychomotor Development Index (PSI) after Stage 1 Norwood from 1998–2005 and confidence intervals.

research by the Pediatric Heart Network and National Heart Lung and Blood Institute Working Group on Perioperative Management of Congenital Heart Disease.

Although the meta-analysis shows improvements over the past two decades, the mean IQ and the Bayley II MDI

and PDI are still below normal. This may be the result of some noncontrollable factors such as genetic syndromes and in utero neurodevelopmental delays. However, further investigation is warranted to identify the reasons for the continued low scores and methods for improvement.

Meta Regression Mixed Effects Model for Year of Surgery
on Bayley II Psychomotor Development Index (PDI)
 (Stage 1 Norwood Procedures 1998 to 2005)

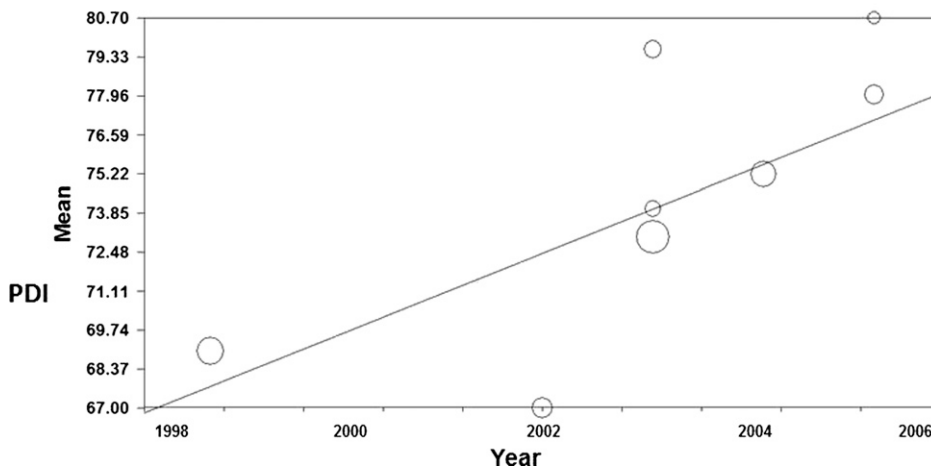


Figure 8. Bayley II Psychomotor Development Index (PSI) after Stage 1 Norwood significantly increased from 1998–2005 ($p < .05$). Circle sizes are proportional to the study sample sizes.

Limitations

There were five main limitations of this study: 1) possible selection bias; 2) limited data on IQ; 3) the need to estimate surgical year; 4) differences in reporting survival time; and 5) outcomes found may be the result of numerous factors.

1. There may be selection bias resulting from the inclusion of publications that report positive outcomes and this may not be an accurate reflection of the entire population of SN1 survivors.
2. There is very limited reporting of IQ results as a result of the 8-year time period required after surgery for testing; therefore, results for surgical procedures after 1999 are not available.
3. The use of the mean age to estimate the surgical year in a case series that spans up to 7 years may reduce the precision of the results; however, this was necessary because the survival in these large case series did not report yearly mortality rates.
4. The survival time period was not exact; some studies included mortality within 30 days after surgery and others until hospital discharge. Because many of these infants have hospital stays beyond 30 days, it was appropriate to include both categories. However, this may also reduce the precision of the results.
5. Like with all retrospective studies, it is likely that the outcomes found in this study are not attributable solely to changes in the surgical procedure. There are numerous other factors that may have contributed to the reported outcome.

CONCLUSIONS

Findings from the current study demonstrate that the many improvements in surgical treatment for HLHS have led to improved neurodevelopmental outcomes. Although outcomes are improving, they are still below normal and are an important area for future research. A related area of concern is the incidence of attention deficit hyperactivity disorder (ADHD) in children after S1N. The incidence of ADHD in 5–10 year olds after infant cardiac surgery is three to four times greater than the normal population and is highest in the patients undergoing S1N. Nearly half of these patients (49%) require remedial school services (40). Further research is warranted, on this topic and others, to monitor whether more resources are needed to allow the greater number of survivors the best possible quality of life.

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