American Journal of Multidisciplinary Research & Development (AJMRD)
*Volume 08, Issue 09 (**September - 2026**), PP 01-15*
ISSN: 2360-821X
www.ajmrd.com

Research Paper **Open Access**

Analysis of Treatment Outcomes in Children with Hypo Plastic Left Heart Syndrome in Republic Of Croatia - Clinical Epidemiological Study (1999-2011)

Andrea Dasović Buljević[1], Bruno Buljević[2], Ana Viktorija Fanuko[1], Domagoj Kifer[3], Peter Ewert[4], Gerald Tulzer[5] Rudolf Maier[5], Jürgen Hörer[4] Christian Schreiber[4††], Ivan Malčić[6]

Department of Pediatrics, Clinical Hospital Centre Zagreb, Department of Neonatology and Intensive Care[1]
Internist cardiologist, Department of cardiology Clinical Hospital Centre Zagreb (previously), Clinic Eichholz, Department of cardiology and Angiology, Lippstadt, *Germany [2]*,
Department of Biophysics, Faculty of Pharmacy and Biochemistry, University of Zagreb[3],
Deutsches Herzzentrum München – Germany[4],
Landes-Frauen und -KInderklinik Linz-Austria[5],
Reference Center for Pediatric Cardiology, Clinical Hospital Centre Zagreb, Croatia[6].
Corresponding author: Ivan Malčić,
Medical School, Medical Faculty Zagreb, Department of Pediatric Cardiology, Zagreb, Croatia. Email: ivan.malcic1@gmail.com

SUMMARY: Hypoplastic Left Heart Syndrome (HLHS) refers to a spectrum of developmental disorders of all left heart components. The diagnosis is made echocardiographically, preferably in utero already. It belongs to a group of defects that can be treated highly successfully, especially if active treatment begins immediately after birth. After initial care (prolonged maintenance of fetal circulation), three palliative surgeries are performed that allow gradual bypassing of the right ventricle and its transformation into a functional systemic ventricle; stage I palliation (Norwood I procedure), stage II palliation (bidirectional or partial cavo-pulmonary anastomosis PCPC) and stage III palliation (complete cavo-pulmonary connection - TCPC procedure). The main aim of this study was to evaluate the outcome of treatment in 57 patients with HLHS, following each palliative procedure over a prolonged period of 12 years (1999-2011). Thus, the study took on the characteristics of clinical epidemiological study. The first children born with HLHS in the Republic of Croatia started treatment in 1999. All of them were initially cared for in the Reference Center for Pediatric Cardiology of, Clinical Hospital Centre Zagreb, Croatia and were operated on in two foreign centers: "Deutsches Herzzentum München", and "Landes-Frauen-und-Kilderkin Linz". The course and outcome of the disease in these children is shown using precise statistical methods created according to clinical and demographic characteristics. The outcome of treatment was assessed according to survival after and between operations (1. Norwood operation in newborns, 2. bidirectional Glenn operation in infants – (mono-cavo-bi-pulmonary anastomosis) and 3. complete right ventricular bypass with modified Fontan operation (complete cavo-pulmonary connection – TCPC). Most subjects died between the first and second palliation (period of 3-6 months), and the same number of patients died between the second and third operations (period of 3 years), and then a quiet period sets in. Overall long-term survival determined by the Kaplan-Meier method is 54% (43-69%). Almost 80% of patients have an excellent life quality, while a minor number have poor or poor life quality (4%). Ever more patients are reaching adulthood.

Key words: *Hypoplastic left heart syndrome (HLHS), treatment outcome in the Republic of Croatia, clinical epidemiological study.*

I. INTRODUCTION:

Hypoplastic Left Heart Syndrome (HLHS) is a heterogeneous group of cardiac malformations with varying degrees of underdevelopment of the structures of the left heart and aorta. This results in significant obstruction of blood flow to the systemic circulation, or the inability of the left heart to maintain it (1,2). The incidence of HLHS in Croatia according to a national population study is 2.3% (3). We decided to conduct this study due to the observation that a significantly higher number of patients with a defect that was considered incurable survive before the knowledge of the importance of maintaining parallel fetal circulation, as well as the

acquisition of complex experiences in cardiac surgical teams. Today, the results of surgical procedures and other forms of treatment are unexpectedly good, in fact, a certain number of previously incurable children are already approaching adulthood with a high quality of life. Another motive is the fact that in our conditions there are very few clinical epidemiological studies, i.e. studies that follow the course and outcome of treatment in an argumentative manner. In this way, we want to move from purely population-based epidemiological research to clinical epidemiological research. With this work, we also wanted to show how organized teamwork can improve pediatric cardiology. Another reason is that the literature suggests that the outcome of complex heart defects is significantly affected by the time of diagnosis (prenatal-postnatal, time and method of transport to a tertiary care center). Significantly higher chances of survival and better quality of life were shown in a clinical epidemiological study of simple transposition of the great vessels (d-TGA) in 1999 by Bonnet et al. (4). It was in 1999 that the treatment of children with HLHS began in the Republic of Croatia (RH). Previously, during the Homeland War and the independence of our homeland, we had to overcome numerous obstacles not only in knowledge and skills, but also in the development of fetal cardiology, the transport of children from distant maternity hospitals to the Reference Center for Pediatric Cardiology of the Republic of Croatia (founded and recognized by the Ministry of Health of the Republic of Croatia only in 2005), and after initial care, the organization of the child's transport to foreign centers. The efforts have been partially presented in recent literature (3,5). It is particularly important to emphasize that in complex heart defects, including HLHS, it is important to first establish a balance according to the Frank-Starling law (the relationship between preload and afterload) by intensively maintaining the fetal circulation pattern (parallel circulation - keeping the ductus arteriosus and the foramen oval open, the negative effect of oxygen, and the beneficial effect of CO_2 on the blood flow balance) as well as to take into account the fact that a seriously ill patient can only be transported when he is fully cared for (with the aforementioned criteria), and only then refer the child to a tertiary center. This is of crucial importance, especially in our country, because children are transported over distances of several hundred kilometers, by road or by plane, most often by airlift. If doctors in neonatal units adhere to these basic guidelines, they will respect them and thus participate in saving a valuable life, and they must not act in haste and frustration in order "just get rid of the patient". With this work, we also wanted to show how organized teamwork, regardless of difficult conditions, can improve pediatric cardiology. The Croatian Society for Pediatric Cardiology and Rheumatology was founded in 1996.

Hypothesis

Since the beginning of systematic treatment of patients with HLHS for about 30 years, there has been a steady trend of improved survival in individual phases of the disease/treatment and overall. At the beginning of the 21st century, these outcomes in the Republic of Croatia showed a tendency to approach those of highly developed countries, in terms of the survival rate and quality of life of young patients. Accordingly, in the coming years, in every environment that has achieved such a level of care, a high percentage of patients will experience adulthood and thus represent a new public health problem. Our first patients are already over 25 years old.

Prerequisites for a clinical epidemiological study in pediatric cardiology and pediatric cardiac surgery.

In order to be able to carry out purposeful research and global communication in the field of pediatric cardiology and pediatric cardiac surgery, criteria have been established within professional societies at the European (AEPC - Association for European Pediatric and Congenital Cardiology) (6) or global (IPCCC - International Conference on Pragmatics and Cross-Cultural Communication) level (7). In order to be able to discuss at that level at all, the Reference Center for Pediatric Cardiology of the Republic of Croatia created a database with the registry of CHD for the entire Republic of Croatia, based on the globally recognized large epidemiological studies EUROCAT (European registry of congenital anomalies and twins) (8) and BWIS (Baltimore-Washington infant study) (9). This registry allows us to use in this study two models published between 1993-1995. They assess the various competencies of cardiac surgical centers at an international level. They are necessary because the skills and capabilities in pediatric cardiac surgery develop much more slowly than diagnostic capabilities. Any cardiac surgical center can access CHD surgery if it meets the criteria of the ABC model and/or the RACHS-1 model.

1. ABC model (Aristotle basic complexity score) includes 50 centers in 23 countries and contains 145 diagnoses, and the total complexity of heart defects in relation to the severity of the surgical approach is rated from 1.5 to 15 points; it is divided into four subgroups according to the severity of the congenital heart defect: 1.5-5.9; 6.0-7.9; 8.0-9.9 and 10.0-15.0. (10)
2. The RACHS-1 model (Risk adjustment for congenital heart surgery-1) classifies CHD according to complexity into 6 categories, i.e. six subgroups, from the simplest to the most complex CHD. We used both models, with the additional aim of comparing their complementarity, which was published in domestic literature, and here follows a brief overview, necessary for understanding the choice of a foreign center and assessing one's own capabilities (11).

We classified patients into surgical groups according to the ABC and RACHS-1 models and measured early mortality and prolonged postoperative care in the intensive care unit (*Prolonged length of stay* PLOS). PLOS in the intensive care unit is a period of more than 21 days. First, the entire group is analyzed, then the group operated on in the Republic of Croatia, and finally the group operated on abroad. The results are compared, based on which a discussion is developed on the current development of pediatric cardiology and cardiac surgery in the Republic of Croatia and the perspective in cooperation between domestic and foreign centers for pediatric cardiology and cardiac surgery. Even after the completion of the second clinical epidemiological study, the monitoring of the dynamics of the development of cardiac surgery and pediatric cardiology for the period from 2008 to 2011 continues, which may open a projection for the future (the appearance of many adult patients with CHD). Such a cross-section allows us to understand heart defects as a public health problem in our country (10,11,12.).

For the assessment of the completeness and accuracy of the data (Verifying data completeness and accuracy) an independent body organized within the framework of the European Society for Cardiothoracic Surgery (EACTS congenital database) must be asked. In addition to the numerous rules of this assessment body, the following should be emphasized: 1. To equalize the criteria for assessing complexity throughout the world, and with the aim of being able to assess the quality of CHD care, first of all to assess the extent to which a center is capable of providing PSG care with a low level of morbidity and mortality and to minimize risk factors. This considers registries that are harmonized for all those participating in it. 2. The goal of the EACTS database (Database set) is to globally improve early and late survival and quality of life of surgically treated patients with CHD. 3. This committee does not serve for marketing good centers, the results are anonymous and no other center, cardiac surgeon or individual patient can be identified from the reports sent to the participants. 4. The basis of the assessment center's activities is not of a commercial nature (11, 12.)

Objectives of the study.

1. The main goal and purpose of this study is to assess the outcomes of treatment of patients with HLHS in the Republic of Croatia. The results were obtained based on the analysis of a group of 57 children born with HLHS.
2. We want to assess the outcomes of treatment according to the outcome of each of the three basic palliative surgeries and in total. The summary results of the study last from the first treated patients with HLHS on 03.11.1999. to 01.09. 2011 (12 years).
3. A further goal of the study is to make projections about the number of children with HLHS who will reach adolescence and adulthood in the next 10-year period in the Republic of Croatia, based on data on survival and incidence. Given that this is the most difficult CHD, in the discussion we would like to review the assessment of the level of development of pediatric cardiac surgery in the Republic of Croatia, taking into account controlled models and the high rating of selected cardiac surgical centers according to the (EACTS congenital database) (12).

II. MATERIALS AND METHODS (RESPONDENTS-SAMPLE)

Respondents

Respondents are children born in the Republic of Croatia with HLHS from 03.11.1999 to 01.09.2011. These are 57 newborns who were primarily cared for at the Pediatric Clinic of the University Hospital Center in Zagreb and then operated on in two foreign centers and then further cared for and monitored at the Pediatric Clinic of the University Hospital Center in Zagreb. The operations were performed in foreign centers as follows; 1st degree of palliation (Norwood operation) in the newborn age (Norwood I; the pulmonary artery is separated from the bifurcation and its trunk is connected to the hypoplastic ascending aorta with the additional use of patch plastic to ensure the flow through the ascending aorta that also supplies the coronary blood vessels. The right branch of the pulmonary artery is connected to the brachiocephalic trunk via mBT anastomosis (modified Blalock-Taussig anastomosis), and today some do the so-called Sano shunt (communication between the right ventricle and the pulmonary artery with a non-valved conduit); 3-6 months after the Norwood I operation, a bi-directional cavo-pulmonary connection is performed - PCPC according to Glenn, or hemi Fontan operation op.), 3rd degree of palliation; operation of complete bridging of the right ventricle by modification of the Fontan operation, using the TCPC model, i.e. total cavo-pulmonary connection (eng. Total cavopulmonary connection) at the age of 2.5-4 years (13,14,15). In the period between operations, as well as after the completion of cardiac surgical treatment, all diagnostic and therapeutic measures (invasive and non-invasive) were conducted in the Reference Center for Pediatric Cardiology of the Ministry of Health of the Republic of Croatia (recognized only in 2005). The data were collected from foreign institutions where children were operated on and from the Clinical Hospital Centre - Pediatric Clinic, where complete medical documentation was archived (disease histories, discharge letters, outpatient records). Operation were performend in the following institutions: "Deutsches Herzentum München" and "Landes-Frauen-und-Kinderklinik Linz". Referral to one of these institutions was not a matter of privilege, but the possibility of admission as soon as possible after initial care in our Clinic and due to the fact that these institutions which have strict control of the success and ability to survive

with congenital heart disease according to the two mentioned models ABC and RACHS-1 on a global level, presented previously (10)

To conduct purposeful research and global understanding in the field of pediatric cardiology and cardiac surgery, criteria have been established within professional societies at the European (AEPC - Association for European Pediatric and Congenital Cardiology) or global (IPCCC - International Conference on Pragmatics and Cross-Cultural Communication) level. In order to be able to discuss at that level, a database with a CHD registry for the entire Republic of Croatia was created at the Referral Center for Pediatric Cardiology of the Republic of Croatia, based on the globally recognized large epidemiological studies EUROCAT (European Network of Population Registries for Epidemiological Surveillance of Congenital Anomalies in Twins) and BWIS (Baltimore-Washington Infant Study). This registry allows us to use the models between 1993-1995 in this work, and they assess the capacity of cardiac surgery centers at the international level. Each cardiac surgical team must not have more than 5% of deaths in one of the four groups in the ABC model, or in one of the 6 groups in the RASCH-1 model. Since HHLS belongs to the most severe group in both models (i.e., the fourth, or sixth, respectively), in the Republic of Croatia, patients with HHLs can be operated on only if their mortality is less than 5%. Both centers available to us in neighboring and closest countries have a positive rating. This is also proof that we strive for controlled and established criteria, so any further question of the method of center selection is incoherent center selection

III. METHODS

Systematic review of publications: The literature review is limited to publications from advanced countries where patients with HHLS are treated independently (most EU members and the USA, Canada, Australia and New Zealand). Search according to the terms "hypoplastic left heart syndrome + survival", through electronic databases: PubMed Central, Ovid Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Clinical Trials, EMBASE and Scopus.

IV. STATISTICAL ANALYSIS:

The survival probabilities of children with hypoplastic left heart syndrome (HLHS) who underwent left ventricular bypass surgery, depending on age, were estimated to use the Kaplan-Meier method (ref. 14,15). The confidence interval of the survival probability, with a type 1 error (α) of 5%, was estimated using the Greenwood formula. The log-rank test was used to test the statistical significance of the difference between survival groups (groups) obtained by dividing the total patient population based on potential risk factors (sex, year of diagnosis, time of diagnosis of HLHS, anatomical subgroups, birth weight, place of birth, site of surgery, and extracardiac malformations). Any p value less than 0.05 was considered statistically significant. The number of live births with HLHS for each year was estimated using Poisson distribution modeling, where the average number of live births with HLHS (parameter λ) was estimated as the product of the total number of live births in the Republic of Croatia for a given year (6), the incidence of cardiac anomalies in the Croatian population of 0.78% (3), and the proportion of HLHS in cardiac anomalies (2.3%) (7). The proportion of children who will survive to adulthood was obtained by multiplying the number of children with HLHS, the probability that the child will undergo surgery (until 1999 0%, after 1999 76%) and the probability of survival from completely left ventricular bypass to adulthood, which was estimated in this study. The obtained values are presented as the theoretically most likely number of adults with HLHS and the 95% confidence interval. The R programming language (13) with the “survival” extension (14) was used for statistical processing and evaluation (15).

V. RESULTS:

The outcome of treatment in all subjects was assessed according to survival after and between operations: 1. from Norwood in the newborn to Glenn (PCPC) anastomosis (3-6 months), 2. from Glenn during infancy to Fontan operation (at the age of two to four years) and 3. after modified Fontan (TCPC) operation (Table 1). Table 1 shows an overview of mortality and survival (95% CI) for the entire group of patients. The largest number died between Norwood II operation and complete right ventricular bypass; immediately after Norwood I operation one in the first week and five during the first month of life, another 13 patients by the end of the first year of life, and another 6 patients before the age of three (before TCPC anastomosis). Only one child died after TCPC anastomosis in the group of patients followed. The number of survivors for more than 6 years is 54%. Most subjects died during the first 6 months of life (16 patients), and a smaller number of children aged six months to three years (9 patients). The Kaplan-Meier survival curve shows a steady increase in mortality until the age of 2.5 to 3 years when the first two phases of treatment were completed: 1. Norwood operation (period between the first two operations), 2. Glenn operation – (PCPC) period between the 2nd and 3rd operations). 3. modified Fontan operation (TCPC). There is no difference in the number of deaths in the period between the first and second and in the period between the second and third operations (21:23%). It is clearly visible that the number of deaths abruptly stops with the achievement of complete cavo-pulmonary

anastomosis (TCPC) (Fig. 1.). In Table 2, patients are classified according to the periods between operations. In the period between Norwood, I and PCPC anastomosis, 12 patients died, and in the period between PCPC and TCPC anastomosis, thirteen patients died, so no difference is found on this basis. However, it should be considered that the first period includes only 3-6 months, and the second period more than three years. After the third palliative operation - TCPC, only one child died. However, since the number of deaths in the period of 3 months is the same as in the period of more than 30 months, we can freely conclude that the survival rate in the second period is ten times higher than in the first period. We ask the question, are there not some other factors that are the reason for the continued death of children, although the survival criteria are optimal. Is not the age of the children, or factors that are rarely mentioned or are not consedered, a sufficient reason for this mortality? Table 3 shows that no influence of defined demographic or clinical characteristics was observed on survival; there is no difference according to gender ($p = 0.719$), birth weight ($p = 507$), time of diagnosis - prenatal or postnatal ($p = 0.716$), anatomical subgroups ($p = 0.479$), birth weight ($p = 0.507$), place of birth, i.e. speed and method of transport ($p = 0.438$), place of operation ($p = 0.700$) or with regard to extracardiac anomalies ($p=0.469$). Table 4 shows the overall survival of patients operated on according to Norwood in the period up to and after one year, depending on the type of systemic-pulmonary connection (mBT and RV-PA). There are no statistically significant differences between Norwood's associated operations (mBT and RVPA), $p =0.446$. Nevertheless, percentage survival with mBT anastomosis is better both up to one year (75%) and after one year (67%), compared to RV-PA in both periods. This is an example of how innovations in pediatric cardiac surgery are initially presented as great progress, but the results cannot confirm this. The question is, didn't the pulsatile flow in the mBT anastomosis preserve the enzymatic function of the endothelial cells of the small pulmonary arteries - arterioles (PAS-pulmonary artery small), while the RV-PA anastomosis with a conductor could not do that? The question remains open for further discussion. The estimate of the number of patients who will reach adulthood in a certain year is based on the probability of surviving surgery determined by this study, which is 54% and the probability of surviving until surgery, which is for the period from 1999. Seventy-six percent, and before 1999 0%. Although the results of our work show the advantage of mBT anastomosis compared to RV-PA anastomosis, some authors have proven the advantage of Sano anastomosis in a larger number of patients (16). By 2017, when the first patients included in this study reached adulthood, a total of three were expected, while in the next ten-year period, based on their cumulative number, there will be an average of between 34 and 37 (Table 5). This means that we saved 34 lives in the described period. The calculation easily yields the data that in a 40-year working life, a pediatric cardiologist successfully participates in saving at least 140 lives, and this in conditions that are incomparable with advanced countries. The quality-of-life analysis was performed according to the guidelines of Sommerville J. (17), which was adapted to low age groups. According to the attached graph, most patients (79%) do not differ from healthy ones. About 14% of patients have limited possibilities that, however, allow a normal life with freedom from competitive sports and heavy physical exertion. Only 3.5% of the respondents have significantly limited physical activities, and the same number are bedridden, i.e. stay at home exclusively. (Fig2).

VI. DISCUSSION

The results of our study show the probability of patient survival by age interval (Table 1), which shows that most subjects died during the first six months of life, 16 out of 57 (28%), and another nine by the end of the third year of life, 9 out of 57 (15.8%). This is unmistakable evidence of a significantly reduced mortality after the second palliation (PCPC) compared to mortality after the first palliation, although the time from the second to the third palliation is many times greater than the time from the first to the second palliation. From the third year onwards, only one more child died, and the total survival after more than 6 years is 54%. These indicators lead us to the assumption that the criteria for the time of access to individual palliations should change over time. The Kaplan Meier survival curve (Figure 1) shows a constant increase in mortality until the time when subjects complete the first and second phases of surgical treatment, when they live from 2.5 to 3 years. The number of deaths abruptly stops with the achievement of complete right ventricular bypass (TCPC). This suggests the need to approach the final palliative treatment, TCPC anastomosis, earlier, as soon as the patient reaches a body weight of ten kilograms. It is possible that the waiting period for the third operation, which for our subjects is associated with significant financial support, is also prolonged in our conditions by technical difficulties. On the other hand, if we look at the physiological maturation of the pulmonary vasculature (compliance - the elasticity of the pulmonary arterioles) and the distensibility of the chest, which apparently reach their best phase at the age of 2.5 years, then this thinking leaves the need for further discussion. Furthermore, the first criteria according to Choussat-Fontan (18) were set so that children are not operated on before the age of four. Experienced cardiologists who monitor patients with HLHS, as well as those with cardiac anomalies treated with right ventricular bypass, suggest that children should not wait even 30 months for this operation, but that the limit of 10 kg of body weight should be taken as a criterion. It is possible that these criteria, including the results of our study, will need to be changed over time. The gradual change in the Choussat-Fontan criteria from 1977 to the present day can be seen in Table 13.1 in the book on pulmonary

hypertension (19). It is clearly shown that the TCPC anastomosis should be performed 1.5-2 years after the Glenn anastomosis, and not > 4 years as initially stated. The only thing missing from the table is the statement that a body weight of 10 kg is sufficient. It is worth noting the statement from the table that refers to the importance of pulsatile flow through the PAS for maintaining the physiological function of the capillary endothelium. In monitoring survival, we also classified patients according to the periods between and after the operations (Table 2). In the period between the Norwood I operation and the PCPC anastomosis, 12 patients died, and between the PCPC and TCPC 13, so there is no difference if we read only the fractographic values. However, it should be considered that the first period includes only a few months, and the second more than three years. These results are also in line with the effort that, according to recent research, the period between the first and second operations should be shortened even further. In the presentation of the probability of survival of children with HLHS, considering certain demographic and clinical characteristics most often used in other epidemiological studies (20), we find that none of the characteristics among our subjects is statistically significant. However, it is suspected that there is a difference in the mean values and it is likely that a difference does exist, but we were unable to detect it due to the small sample size. Therefore, it is possible that the results presented may potentially represent prognostic factors. However, further research is necessary for a real assessment. Thus, we have more than twice as many males as females, which is significantly different from the 1.5:1 ratio in favor of males found in the data of the Croatian population study (21). Among our patients, this ratio is 2.2:1. It should be considered that the incidence in males compared to females of 1.5:1 refers to the incidence of HLHS, and our patients represent a group of patients who have undergone their first surgery. The survival of male children among our subjects is 62% (14 out of thirty-nine died), and only 39% of females (7 out of 18 subjects survived). Higher mortality in female children is found in most reports, and interesting are the results of Lara et al., who in their population study documented significantly higher mortality in patients with HLHS who also have Turner syndrome. In doing so, they consider the possibility of underdiagnosis of Turner syndrome, given the higher mortality among patients with HLHS (22). We did not identify patients with monosomy XO among our subjects and given the absence of female newborns of low birth weight in relation to gestational age, and especially those with reduced birth length (not shown in the table), we believe that we did not fail to diagnose monosomy XO. Since our group of subjects was defined by survival to the first surgery, it is possible that "hidden" patients with monosomy X are among those who did not undergo surgical treatment, because the early neonatal period represents the most vulnerable period in these patients. The absence of a difference in survival depending on the years of the first half of the study (1999-2005) compared to the second (2006-11), could be due to a greater number of those diagnosed in the second six-year period (61%); it is also possible that the most severe patients were better cared for and underwent surgery, while patients from that category in the first period may have died before the diagnosis was established. Among the anatomical characteristics, we find data on the best survival of patients with the otherwise most unfavorable anatomy of aortic stenosis and mitral atresia, but there were only two of them (3.5% of all subjects) and both survived. According to the literature, another prognostically unfavorable anatomy of aortic atresia and mitral stenosis had a survival rate of only 36% (23).

Aortic and mitral stenosis have a survival rate of 61%, and aortic and mitral atresia 54%. Considering only three patients (5.3%) born with a birth weight of less than 2,500 grams, there is no indication of their expected poorer survival. It is encouraging that possible early mortality is not related to the place of birth (Zagreb, outside Zagreb), which means that our country is well networked with informed and educated neonatologists and pediatric cardiologists. This is a sign that children are brought to a stable state with prostaglandin infusion before transport and that they are adequately cared for during transport in controlled conditions of a transport incubator with continuous monitoring of vital functions. Although intensive neonatal transport (so-called two-way transport) is not organized in the Republic of Croatia, in which a team from a tertiary center comes to pick up a newborn at risk (except for the area of South Dalmatia and Split), teams from the vast majority of Croatian maternity hospitals, the so-called with one-way transport, they are capable of providing care to a newborn with a critical heart defect dependent on ductal flow, without allowing his condition to deteriorate during transport. Two venous lines are provided: one for continuous administration of prostaglandins, and the other for the administration of glucose solution and, if necessary, the administration of other drugs, such as vasoactive ones and those to suppress possible adverse effects of prostaglandins. There is also the possibility of mechanical ventilation. At least two medical professionals, a doctor and a nurse, participate in the transport, and if necessary, an anesthesiologist or another doctor supplements the team. This ensures an uninterrupted treatment process from the suspected diagnosis to arrival at the neonatal intensive care unit (23,24). This also means that teamwork in preoperative preparation and complex air transport is also at an enviable level. We referred patients for treatment according to our own choice and knowledge, but according to the possible available appointments in the institutions where they were operated on, considering the ABC score and RACHS criteria. This means that both centers participate in the continuous control of successful treatment, respecting the principles of that control according to the mentioned literature (17). When taking into account the fact that with the Sano anastomosis the tissue of the only remaining (right) ventricle is cut, in the future it would

probably be appropriate to return the focus to the mBT anastomosis in most patients or work further on improving the RV-PA connection (16,25).

Based on the quality of life of many patients shown in the graph in Figure 6, it is evident that it is possible to achieve very good results by treating children with HLHSy heart. Although we should always been in mind possible late complications (protein loss syndrome, heart rhythm disorders, veno-venous fistulas, thrombotic complications, liver disease, plastic bronchitis, tricuspid valve insufficiency, heart failure) and regular check-ups, we could look to the future with greater optimism (26, 27,28). One of the aims of this study was to estimate the number of patients who will reach adulthood in the coming years. This estimate is based on the probability of survival from surgery determined in this study and the probability of survival to surgery (Table 5). The estimate of the number of live births with HLHS in the Republic of Croatia is based on a Poisson distribution with an expectation calculated based on the number of births (Annual reports of the Central Bureau of Statistics) (6) and an annual incidence of cardiac anomalies of 0.80‰, of which 2.3% are patients with HLHS (3,6,7). The probability of overall survival is 54% (with a 95% CI of survival between 45 and 69%). The probability of survival to surgery for the period from 1999 is 76%, and before 1999 it was 0%, given that children with HLHSy. we're not treated until then, regardless of severe complications (29,30). Estimates assume that the incidence and survival rate have not changed over this period. By 2017, when the first patients included in this study reached adulthood, it is expected that there will be between 34 and 37 in the next ten-year period based on their cumulative total.

In the 1990s, most reports on patients with HLHS were based on retrospective studies, usually from a single institution, with surgical techniques being the most discussed predictor of outcome. Thus, Bove and Lloyd, in their review of the effects of three palliative operations in the treatment of HLHS in their 158 patients, followed for five years during which the survival rate was high at 58 (+/-9) %, emphasized that the improvement of surgical techniques was largely responsible for the outcome of treatment. The importance of a meticulous cardiac surgical approach is particularly emphasized in a retrospective review from Harvard University, in which Van Praagh also participated. The study included 122 patients who did not survive the modified Norwood operation between 1980 and 1995. They included coronary hypoperfusion, pulmonary artery or neo aortic obstruction, tricuspid valve dysfunction, and single ventricular failure as common causes of death, calling them "mostly correctable surgical technical problems" that caused disruption of lung, heart, and systemic organ perfusion (31). Among the early reports on the outcome of patients with HLHS is one from Indianapolis, where proper patient selection was singled out as the basic criterion for survival after palliative surgery, and during a six-year study, they recorded significantly higher survival to the end of the first year of life: from 38% in 1989 to 75% in 1995 (32,33). A Danish group reports on early experiences with the Norwood operation among 19 subjects. In four years, early mortality was 31.5%, eight patients continued treatment until Glenn surgery, and one patient underwent a Fontan operation. Overall survival was 47%, and they singled out nitric oxide inhalation as a positive predictor for early postoperative recovery. There have been various attempts to isolate individual clinical or laboratory findings as predictors of treatment success, which are still not insignificant in the mosaic of characteristics, but have not proven to be significant individually. As experience has become richer, the definition of predictors has changed significantly (34). For example, Forbes et al. in 1995 first reported on the ten-year outcome of 212 patients after the first palliative surgery, emphasizing that the greatest influence on the outcome is exerted by anatomical variations (poor predictors are small ascending aorta, aortic atresia and mitral atresia, and good predictors are aortic stenosis and mitral stenosis), body weight (less than 3 kg is a poor predictor) and the first preoperative pH value. Two years later, the same authors reviewed the survival of the same 212 patients over a ten-year period who had survived the first operation and were undergoing their second or third operation, highlighting the choice of bidirectional cavo-pulmonary anastomosis as the most important factor in reducing mortality during the operation itself, as well as in the subsequent interoperative period. They also stated that predictors of success/failure for the first operation lost their importance with further analysis (35,36)). At the beginning of the new millennium, some twenty years after the first Norwood operation, the results of multicenter studies began to appear in the literature, and some authors regularly published new findings on the treatment and outcomes of patients with HLHS, including our study (37,38).

In 2001, the National Institutes of Health in 24 North American countries founded the "Pediatric Heart Network". Four other affiliated centers from other countries participate in their research, one in Toronto (Canada), two in Seoul (South Korea) and one in Ghent (Belgium). Among other projects, the "Single Ventricle Reconstruction Trial" is underway, which has resulted in several notable papers with different aspects of interest and a broader basis for analyzing the outcome of treatment of patients with HLHS, from socioeconomic and psychoemotional aspects, to a detailed breakdown of surgical techniques and non-surgical treatment (39). Ohye et al. published a study that included 555 patients, and the results show how many deaths in patients with HLHS occurred within 12 months of the operation (within 0.6 to 3.7 months). The most common cause of death was unknown, followed by multiple organ failure (40). Cross et al. Cardiology-Quality Improvement Collaborative (National cooperation for improving the quality of pediatric cardiology); the mortality was 9%, and among the

predictors of a poor interoperative outcome, the anatomy of aortic stenosis/mitral atresia (AoS/MA), the need for anticonvulsant drugs, and a gestational age lower than 34 weeks stand out (41). An extremely large amount of information about the long-term outcome of patients with HLHS can be found in the study by Pundi and colleagues entitled "40-year follow-up after the Fontan operation", in which 1052 patients treated at the Mayo Clinic, in Rochester, Minnesota, were analyzed. For the whole group, they defined overall survival after 10, 20 and 30 years of 74%, 61% and 43%. They state that long-term survival does not differ significantly according to the morphology of the single ventricle, which is rare data, because in most studies on the single-ventricular heart, the right-ventricular morphology stands out as having a worse prognosis (42). Among the most important positive long-term predictors of survival, they list sinus rhythm during and after surgery, while the main negative predictors for overall and late survival are the following: preoperative diuretic use, prolonged cardiopulmonary bypass, surgery performed before 1991, need for atrioventricular valve replacement during Fontan surgery, postoperative thoracic drainage for effusion for more than 21 days, postoperative ventricular arrhythmia, renal insufficiency, and the development of protein-losing enteropathy (PLE) (28,29,30). They conclude that survival has improved significantly over time due to improvements in the surgery itself, but that challenges for further improvement lie in arrhythmia and PLE, which, as late complications, are still too frequent companions of patients undergoing Fontan surgery and are causes of late mortality. Among all the available studies, the one that we could compare well with ours is the study by Siffel, who and her colleagues conducted a population-based study of 212 patients with non-syndromic HLHS born between 1979 and 2005, identified through the Metropolitan Atlanta Congenital Program. They estimated the probability of survival according to selected demographic and clinical characteristics. Demographic characteristics are: birth in a specific study period (1979-84, 1985-91, 1992-98 and 1999-2005), race or ethnicity (non-Hispanic white, non-Hispanic black and other), gender (male, female), maternal age (<20, 20-34, > or equal to 35 years of age) and socioeconomic status (poor, good). Clinical characteristics were: birth weight (<1500, 1500-2499 and > or equal to 2500 gr), gestational age at birth (premature infants or <37 weeks and term infants > or equal to 37 weeks), multiple birth (birth of one child or more), presence of major extracardiac anomalies and cardiac surgery shortly after birth (yes or no); only data on patients from 1992 to 2005 were included (111 of them, 23 of whom did not undergo surgery) because in the first 12 years of the study, information on surgical interventions was very scarce. Among the above characteristics, two factors showed the strongest statistical significance in the probability of survival: birth in a certain period of the study (from 0% in the period from 1979-84, to 42.5% in the period from 1999-2005), and cardiac surgery – in 88 children (0% among those not operated on, 52.1% among those operated on); among those operated on, premature infants had significantly lower overall survival. Low birth weight and poor socioeconomic status also showed statistical significance, indicating significantly poorer survival. The overall probability of survival by the end of 2009 was 24% with the highest number of deaths in the first year of life, and it increased significantly during the study. Within the first week of life, the probability of survival was 66%, during the first year 27% and during the first ten years of life 24%. Among those who underwent surgery, the situation is completely different: in the first week 95%, in the first year 58%, and overall, by the age of 18, the probability of survival was 52%, i.e., among those who survived infancy, long-term survival is around 90% (37). Our group of subjects is too small for statistical comparability, as already stated in the analysis of the data obtained. However, we must highlight some characteristics of our subjects compared to those from the American study. This is primarily because all our patients enjoy the same rights from the Croatian Health Insurance Institute, regardless of the socioeconomic status of the family. A lower socioeconomic status does not significantly affect the possible poorer supervision and care of patients with HLHS at home, given the extremely good organization of outpatient check-ups, as well as the support to families from the association of parents' doctors and other medical staff called "Big Heart for a Small Heart", which has been operating continuously since 1994.

Until the end of the 1990s, children with HLHS in Croatia were not treated. Since then, we have been referring all newborns with this diagnosis for cardiac surgical treatment to geographically close foreign centers, in Germany (Deutsches Herzzentum München) and Austria (Landes-Frauen-und-Kinderklinik Linz). These are institutions with which we have been continuously developing cooperation for almost four decades. Based on the previous outcomes of patients with HLHS, we can confidently continue to refer them to the centers (19, 37,38).

In the daily work of a pediatric cardiologist, it is very important to follow ethical principles that are in line with biophilic orientation. The most severe cardiac defect described in this paper is proof that this philosophy gives us the strength to fight the challenges we must overcome to deserve the privilege that is given to us by choosing this demanding profession (43).

VII. CONCLUSION:

Thanks to excellent diagnostic capabilities and well-organized transport to the Referral Center of the Pediatric Clinic and primary care in the Department of Neonatology and Neonatal Intensive Care, cardiac surgical skills are gradually developing among our pediatric cardiac surgeons. Provided that the registry of

congenital heart defects in the Republic of Croatia continues, the pediatric cardiac surgical team must undergo objective testing by independent controls. When such results are achieved that according to the ABC model (4 groups of complexity) and the RASCH-1 model (6 groups of complexity) no more than 5% of children die in the last group, complete cardiac surgical treatment of HHLS will be able to be performed in the Republic of Croatia. It is not good to undertake treatment without controlling the criteria because we do not align ourselves with objective criteria but rather prejudge our own capabilities.

TABLE:

Table 1. Survival in each age interval in children with HLHS. Survival was determined using the Kaplan-Meier method, and the 95% confidence interval (CI) was determined using the Greenwood method.
/w-week, mo-month, y-year, N-number)

interval of age	***N of children with risk***	***Mortality number***	***Number of unfollows***	**% (95%CI) *survival***
≤ 1 *w*	57	1	0	98 (95 -100)
1 w –1 *mo*	56	5	0	89 (82 - 98)
1 *mo* – 3 *mo*	51	6	0	79 (69 - 90)
3 *mo* – 6 *mo*	45	4	0	72 (61 - 85)
6 *mo* – 1 *y*	41	3	0	67 (55 - 80)
1 *y* – 3 *y*	38	6	0	56 (45 - 71)
3 *y* – 6 *y*	32	1	12	54 (43 - 69)
> 6 *y*	19	0	19	54 (43 - 69)

Table 2. Probability of survival between or after surgery in children with HLHS. Survival was determined by the Kaplan-Meier method, and the 95% confidence interval (CI) was determined by the Greenwood method.

Period between operations	***N of children with risk***	***Mortality number***	***Number of unfollows***	**% (95%CI) *Survival***
Norwood – PCPC	57	12	0	79 (69 - 90)
PCPC – TCPC	45	13	3	56 (45 - 71)
Nakon*(after)*TCPC	29	1	28	54 (43 - 69)

Table 3. Overall survival of children with HLHS presented with respect to selected divisions based on demographic and clinical characteristics. Survival was determined by the Kaplan-Meier method, and 95% confidence intervals (CI) were determined by the Greenwood method. The difference between groups was tested using the log-rank test. Abbreviations: AoS – aortic stenosis, AoA – aortic atresia, MS – mitral stenosis, MA – mitral atresia.

Basic divisions into group	***N of children with risk***	***Mortality number***	**% (95% CI) *Survival***	**P**
Sex				
m	39	14	62 (48 - 79)	0,153
f	18	11	39 (22 - 69)	
Year of birth				
1999. – 2005.	22	9	59 (42 - 84)	0,719
2006. – 2011.	35	17	51 (37 - 71)	
Time of diagnosis				
Prenatal/no	6	2	67 (38 - 100)	0,716
Postnatal/no	51	24	53 (41 - 69)	

Morphological subgroup[A]					
	AoS/MS	18	7	61 (42 - 88)	0,479
	AoA/MS	11	7	36 (17 - 79)	
	AoS/MA	2	0	100 (100 - 100)	
	AoA/MA	24	11	54 (37 - 78)	
Birth weight					
	< 2500 g	3	2	33 (7 - 100)	0,507
	≥ 2500 g	54	24	56 (44 - 71)	
Birthplace					
	Zagreb [B], Z.	34	14	59 (44 - 78)	0,438
	aut of Z.	23	12	48 (31 - 73)	
Place of op. [C]					
	Linz	25	12	52 (36 - 76)	0,700
	München	31	14	55 (40 - 75)	
Ekstracardiac malfomatios malformacije					
	yes	7	4	43 (18 - 100)	0,469
	no	50	22	56 (44 - 72)	

[A] two patients were omitted because they have unbalanced CAVC (*common atrioventricular canal*)
[B] one patient was born in Linz and was sent there after prenatal diagnosis in Zagreb
[C] one patient operated on in Zagreb was omitted

Table 4. Overall survival of patients operated on according to Norwood in the period up to and after one year, depending on the type of systemic-pulmonary connection (mBT and RV-PA). Survival was determined by the Kaplan-Meier method, and 95% confidence intervals (CI) were determined by the Greenwood method. The difference between groups was tested using the log-rank test.

Type of Norwood operation and age	**N. of children wih risk**	***N. of mortality***	***% (95% CI) survival***	**p**
mBT				0,446
up to a year	12	3	75 (54 - 100)	
after a year	9	1	67 (45 - 99)	
RV-PA				
up to a year	45	16	64 (52 - 80)	
after a year	29	6	51 (38 - 68)	

Table 5. Estimated number of patients who will reach adulthood each year. The estimate of the number of live births with HLHS is based on a Poisson distribution with an expectation calculated based on the number of births (report of the Central Bureau of Statistics 2016) and the annual incidence of cardiac anomalies (0.78%), of which 2.3% are HLHS patients [lit Lijec Vjesn 2003;125(9-10):232-41]. The estimate of the number of adults is based on the probability of survival from surgery (54%, 95% CI = 43% - 69%) determined by this study and the probability of survival to surgery (76% for the period from 1999 [lit Lijec Vjesn 2011;133(3-4):81-8], and 0% before 1999 – since surgeries were not performed at that time). Estimates were made based on the assumption that incidence and survival probability do not change during the specified period.

Year of adultho -odd	***Year of birth***	***N. of live births in Croatia***	(95% CI) ***Estimated N live births with HLHS***	***Sampled by study***	(95% CI) ***Estimated number of adults with HLHS***	(95% CI) ***Estimates of the cumulative N of adults with HLHS***

2009	1991	51829	9 (4 - 16)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2010	1992	46970	8 (3 - 15)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2011	1993	48535	9 (3 - 15)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2012	1994	48584	9 (3 - 15)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2013	1995	50182	9 (4 - 15)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2014	1996	53811	9 (4 - 16)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2015	1997	55501	10 (4 - 17)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2016	1998	47068	8 (3 - 15)		0,0 (0,0 - 0,0)	0,0 (0,0 - 0,0)
2017	1999	45179	8 (3 - 14)	3	3,3 (0,9 - 7,6)	3,3 (0,9 - 7,6)
2018	2000	43746	8 (3 - 14)	0	3,2 (0,9 - 7,6)	6,6 (1,7 - 15,2)
2019	2001	40993	7 (3 - 13)	3	3,0 (0,9 - 7,6)	9,6 (2,6 - 22,7)
2020	2002	40094	7 (2 - 13)	1	3,0 (0,4 - 6,9)	12,6 (3,0 - 29,6)
2021	2003	39668	7 (2 - 13)	3	2,9 (0,4 - 6,9)	15,5 (3,4 - 36,5)
2022	2004	40307	7 (3 - 13)	5	3,0 (0,4 - 7,6)	18,5 (3,8 - 44,1)
2023	2005	42492	7 (3 - 13)	7	3,1 (0,9 - 7,6)	21,6 (4,7 - 51,7)
2024	2006	41446	7 (3 - 13)	4	3,1 (0,9 - 7,6)	24,7 (5,5 - 59,2)
2025	2007	41910	7 (3 - 13)	9	3,1 (0,9 - 7,6)	27,8 (6,4 - 66,8)
2026	2008	43753	8 (3 - 14)	9	3,2 (0,9 - 7,6)	31,0 (7,3 - 74,4)
2027	2009	44577	8 (3 - 14)	9	3,3 (0,9 - 7,6)	34,3 (8,1 - 82,0)
2028	2010	43361	8 (3 - 14)	2	3,2 (0,9 - 7,6)	37,5 (9,0 - 89,5)
2029	2011	41197	7 (3 - 13)	2	3,0 (0,9 - 7,6)	40,6 (9,8 - 97,1)
2030	2012	41771	7 (3 - 13)		3,1 (0,9 - 7,6)	43,6 (10,7 - 104,7)
2031	2013	39939	7 (2 - 13)		3,0 (0,4 - 6,9)	46,6 (11,1 - 111,6)
2032	2014	39566	7 (2 - 13)		2,9 (0,4 - 6,9)	49,5 (11,5 - 118,5)
2033	2015	37503	7 (2 - 12)		2,8 (0,4 - 6,9)	52,3 (11,9 - 125,4)
2034	2016	37537	7 (2 - 12)		2,8 (0,4 - 6,9)	55,1 (12,4 - 132,2)
2035	2017	36556	6 (2 - 12)		2.7 (0.4 - 6.9)	57.8 (12.8 - 139.1)
2036	2018	36945	6 (2 - 12)		2.7 (0.4 - 6.9)	60.5 (13.2 - 146)
2037	2019	36135	6 (2 - 12)		2.7 (0.4 - 6.9)	63.2 (13.7 - 152.9)
2038	2020	35845	6 (2 - 12)		2.6 (0.4 - 6.9)	65.8 (14.1 - 159.8)
2039	2021	36508	6 (2 - 12)		2.7 (0.4 - 6.9)	68.5 (14.5 - 166.7)
2040	2022	33883	6 (2 - 11)		2.5 (0.4 - 6.2)	71 (14.9 - 172.9)
2041	2023	32170	6 (2 - 11)		2.4 (0.4 - 6.2)	73.4 (15.4 - 179.1)
2042	2024	32069	6 (2 - 11)		2.4 (0.4 - 6.2)	75.8 (15.8 - 185.3)

Table 6. Level of quality of life in patients with HLHS according to Sommerwill[12]

Level of quality of life	***Number (proportion) of patients***
1) Normal life, normal school attendance, possible pregnancy	45 (79%)
2) Normal life only part of the time, the rest is subject to symptoms	8 (14%)
3) Inability to work, significantly limited activities	2 (3,5%)
4) Pronounced limitation, dependence on the environment, attachment to the house or bed	2 (3,5%)

FIGURES:

Figure 1. Kaplan-Meier survival curve for patients with HLHS. The solid curve shows survival, and the dashed lines show the upper and lower limits of the 95% confidence interval (determined by the Greenwood method). The shaded backgrounds indicate the age ranges in which each operation was performed. The solid dots indicate each death, with the color of the dot indicating the last operation performed. The letter "X" marks indicate the cessation of patient follow-up, and the color also indicates the last operation performed (pink: Norwood, green: PCPC, and blue: TCPC).

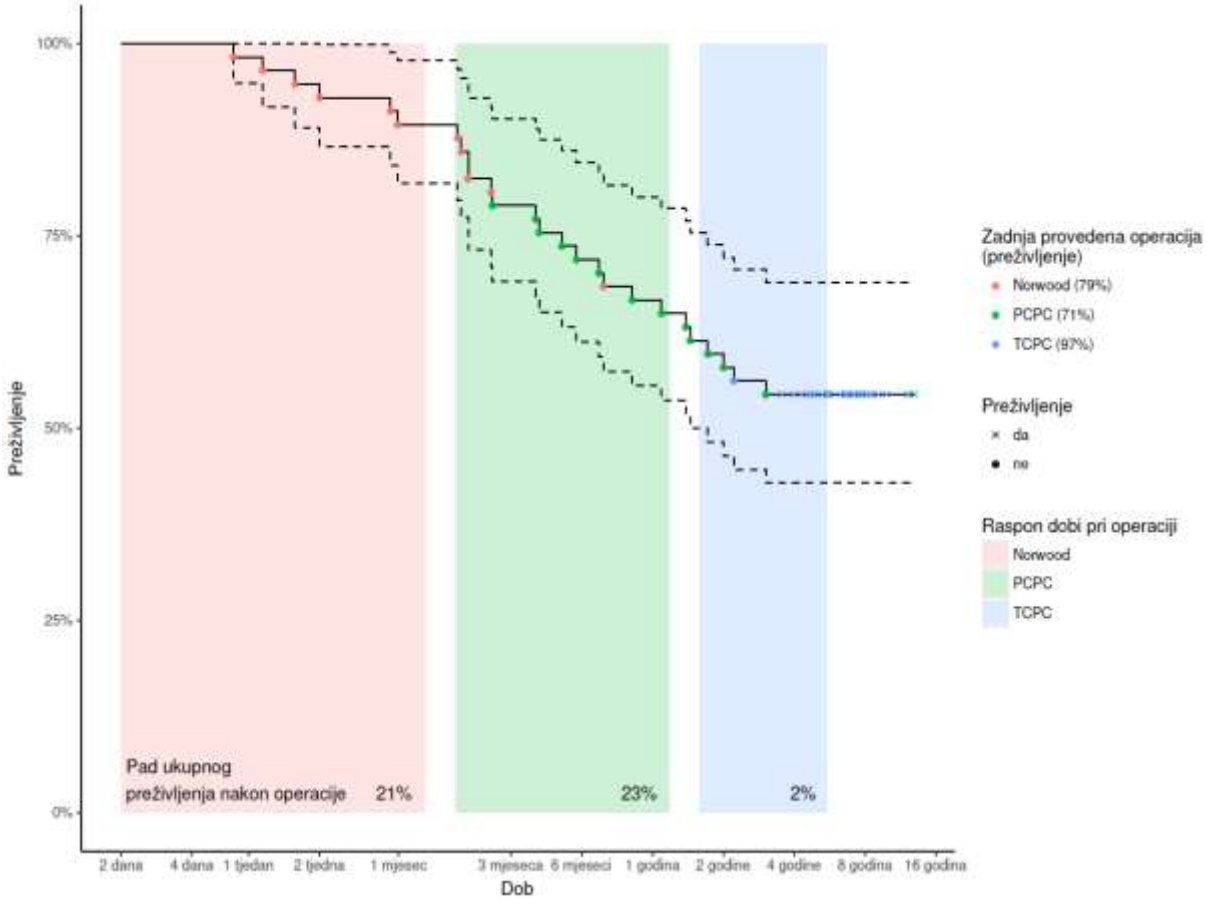
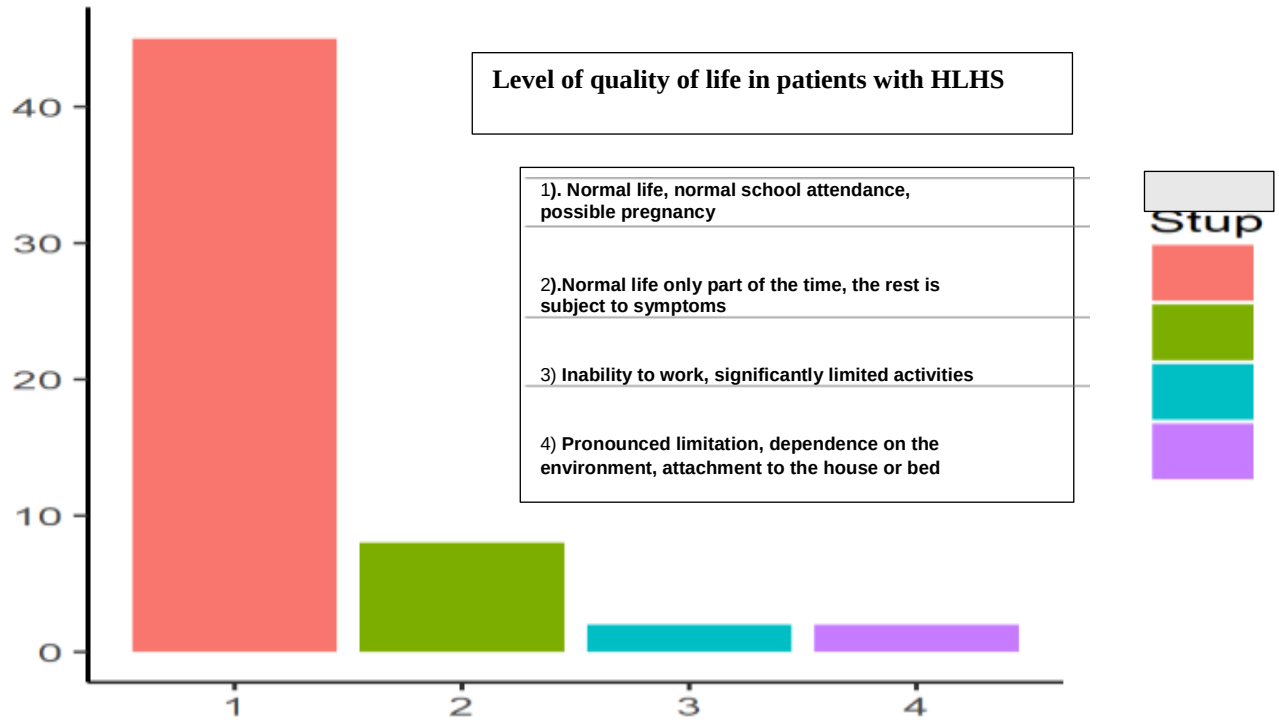


Fig 2. Figure 2. Level of quality of life in patients with HLHS



LITERATURE:

[1]. Tchervenkov CI , Jacobs JP, Weinberg PM, Aiello VD, Beland MJ, Colan SD, i sur. The nomenclature, definition and classification of hypoplastic left heart syndrome. Cardiol Young. 2006;16:339-68.

[2]. Franklin RCG, Jacobs JP, Tchervenkov CI, Béland M. Report from the Executive of The International Working Group for Mapping and Coding of Nomenclatures for Paediatric and Congenital Heart Disease: Bidirectional Crossmap of the Short Lists of the European Paediatric Cardiac Code and the International Congenital Heart Surgery Nomenclature and Database Project. Cardiol Young. 2002; 12 (Suppl 2): 18–22.

[3]. Rojnić-Putarek N, Putarek K, Dasović-Buljević A, Rudan I, Malčić I. Epidemiology of congenital heart disease in Croatia–1995-2000. Progress in Medical Research 2005;3:8-11

[4]. Bonnet D, Coltri A, Butera G, Fermont L, Le Bidois J, Kachaner J, et al. Detection of transposition of the great arteries in foetuses reduces neonatal morbidity and mortality. Circulation. 1999;99(7):916–8.

[5]. Malcic I, Anic D Pediatric ´ Cardiac Service Development in Croatia. Front.

[6]. Cardiovasc. Med. 2022;9:793166. doi: 10.3389/fcvm.2022.793166van

[7]. Mavroudis C, Jacobs JP. Congenital heart disease outcome analysis. Methodology and rationale. J Cardiovasc International Paediatric and Congenital Cardiac Code (IPCCC)Surg 2002;123:6-7

[8]. Schoetzau A, Sauer U, van Santen F. Klassifizeierung angeborener kardiovaskularer Fehlbindungen nach pathogenetischen Mechanismen: daten der bayerischen Fehlbildungsstudien 1984-1991. In: Schumacher G, Sauer U. Herzfehler und Genetik (Genetics of cardiomyopathies): Herzfehler und Genetik. Stuttgart: Wiss. Verl.-Ges; 1999:67-74.

[9]. Pexieder T, Bloch D, EUROCAT working party on congenital heart disease. EUROCAT subproject on epidemiology of congenital heart disease: first analysis of the completed study: In Clark EB, Markwald RR , Takao A, ed. Developmental mechanisms of heart disease. New York : Futura Publishing Company, Mount Kisco 1995,655-68.

[10]. Ferenz C, Rubin JD, Loffredo CA, Magee CA. Epidemiology of congenital heart disease. The Baltimor-Washington Infant Study 1981-1989. New York: Futura Publishing Company, Mount Kisco;1995

[11]. Jacobs ML, Jacobs JP, Jenkins KJ, Gauvreau K, Clarke DR, Lacour-Gayer F: Stratification of complexity: the risk adjustement for congenital heart surgery-1 method and the Aristotle complexity score – past, present and future, Cardiology in the young 2008;18:163-168.

[12]. Gittenberger-de Groot AC, Bartelings MM, Poelmann RE. Normal and abnormal morphogenesis in the outfl ow tract. In: Clark EB, Markwald RR, Takao A (eds). Developmental Mechanisms of Heart Disease. Proceedings of the Fourt International Symposium on Etiology and Morphogenesis of Congenital Heart Disease. Mount Kisco, New York: Futura Press;1995:249-54.

[13]. Gaynor JW1, Jacobs JP, Jacobs ML, Elliott MJ, Lacour-Gayet F, Tchervenkov CI, Maruszewski B, Mavroudis C; International Congenital Heart Surgery Nomenclature and Database Project. Congenital Heart Surgery Committees of the Society of Thoracic Surgeons. European Association for Cardio-Thoracic Surgery. Ann Thorac Surg. 2002;;73(3):1016-8

[14]. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

[15]. Therneau T (2015). A Package for Survival Analysis in S. version 2.38. 2017 Apr 04. available on: https://CRAN.R-project.org/package=survival

[16]. Therneau T and Grambsch P (2000). Modeling Survival Data: Extending the Cox Model. Springer, New York. ISBN 0-387-98784-3.

[17]. Samez-Dolzer E,Gierlinger G, Kreuzer M, Schrempl J, Gitter R, C, Predntstetter Ch, Tulzer G, Mair R. Unplanned cardiac reoperation and interventions during long-term follow-up after the Norwood procedure. European Journal of Cardiothoracic Surgery.2017;51:1044-1050

[18]. Somerwille J; Grown-up congenital heart (GUCH) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the K.Heart.2002;88:1-14

[19]. Choussat A, Fontan F, Besse P, Vallot F, Chauve A, Bricaud H. Selection criteria for Fontan procedure. U: Andrerson RHShineborn EA. Pediatric cardiology 1977. Edinburgh: Churchil Livingstone; 1978:559-66.

[20]. Malčić I. Texbook, „Pulmonary Hypertension“ , University of Medical Faculty Zagreb Pulmonary hypertension, Textbook of the Faculty of Medicine, University of Zagreb, Chapter 13, pgs 215-224, Tbl. 13-1, Medicinska naklada, Zagreb, 2022.

[21]. Siffle C, Riehle-Colarusso T, Oster ME, Correa A. Survival of children with hypoplastic left heart syndrome. Pediatrics 2015;136(4):864-70. doi: 10.1542/peds.2014-1427

[22]. Malčić I, Kniewald H, Anić D, Belina D, Šarić D. Hrvatske populacijske i kliničke epidemiološke studije prirođenih srčanih grješaka (1995.-2011): primjena pokazatelja ABC i kardiokirurškog modela RACHS-1 za procjenu kvalitete zbrinjavanja prirođenih srčanih grješaka. Croatian population and clinical epidemiological studies of congenital heart disease (1995-2011): the use of ABC score and RACHS cardiosurgical model for the assessement of quality of treatment of congenital heart disease. Liječn Vjesn. 2015;137:348-58.

[23]. Lara DA, Ethen MK, Canfield MA, Nembhard WN, Morris SA. A population based analysis of mortality in patients with Turner sindrome and hypoplastic left heart syndrome using the Texas Birth Defects Registry. Congenit Heart Dis 2017;12(1):105-12. doi:10.1111/chd.12413.

[24]. Feinstein JA, Wodroow Benson D, Dubin AM, Cohen MS, Maxey DM, Mahle WT i sur. Hypoplastic left heart sindrome. Current considerations and Expectations. JACC 2012;59(1)Suppl S:S1-42. doi: 10.1016/j.jacc2011.09.022.

[25]. Dasović Buljević A. Postupnik za intenzivni transport djeteta sa srčanom bolešću. U Malčić I. ur Pedijatrijska kardiologija, odabrana poglavlja, 3. dio. Zagreb: Medicinska naklada;2008. Str 89-101.

[26]. Procedure for intense transposrt of children with cardiac disease. In Malčić et co-workers, Pediatric cardiology, selected chapters, part 3, Zagreb, Medicinska naklada , 2008, pgs 89-101.

[27]. Newburger JW, Sleeper LA, Frommelt PC, Pearson GD, Mahle WT, Chen S i sur. Transplatation free survival and interventrions at 3 years int he single ventricle reconstruction trial. Circulation 2014;129(20)2013-20. doi: 101161/CIRCULATION AHA.113.006191.

[28]. Pundi KavithaN, Johnson JN, Dearani JA, Pundi KrishnaN, Li Z, Hinck CA i sur. 40-year Follow-up After the Fontan Operation. JACC 2015;66(15):1700-10. doi:

[29]. Bentham JR, Baird CW, Porras DP, Rathod RH, Marshall AC. A reinforced right-ventricle-to-pulmonary-artery conduit for the stage-1 Norwood procedure improves pulmonary artery growth. J Thorac Cardiovasc Surg. 2015; 149(6):1502-8. *doi: 10.1016/j.jtcvs.2015.02.046.*

[30]. Mertens L, Hagler JH, Sauer U, Sonverville J, Gewelling H. Protein- losing enteropathy after the Fontan operation: an international multicenter study (Multicentric study, Malčić, Croatia). J Thorac Cardiovasc Surg. 1998; 115(5):1063-73.

[31]. Malčić I, Sauer U, Greil G, Soppa C, Vogt M, Kirchner K, i sur. Protein losing enteropathy after Fontan operation. Paediatr Croat. 1998 ;42:61-8.

[32]. Srkoč Majčica L, Bartoniček D, Belina D, Seiwert S, Malčić I. Plastični bronhitis – je li riječ o sindromnoj bolesti. Plastic bronchitis – is it a syndromic disease? Acta Med Croatica, 2020;74:249-256

[33]. Bove EL, Lloyd TR. Staged reconstruction for HLHS. Contemporary results. Ann Surg 1996;22(3):387-94, discussion 394-5.

[34]. Bando K, Turentine MW, Sun K, Sharp TG, Caldevel RL, Daarragh RK et al. Surgical management of hypoplastic left heart syndrome. Ann Thorac Surg 1989;62:70-6. discussion 76-7.

[35]. Conte S, Hansen PB, Jensen T, Jacobsen JR, Helvind M, Lauridsen P i su. Early experience with the Norwood procedure. Cardiovasc surg 1997;5(3)315-19.

[36]. Malec E, Januszewska K, Kolz J, Pajak J. Factors influencing early outcome of Norwood procedure for hypoplastic left heart syndrome. Eur J Cardiovasc Surg 2000;18(2):202-6.

[37]. Forbes JM, Cook N, Roth SJ, Serraf A, Mayer JE Jr, Jonas R. 10-year institutional experience with palliative surgery for hypoplastic left heart syndrome. Risk factors related to stage I mortality. Circulation 1995;92(Suppl9):II262-6.

[38]. Forbes JM, Cook N, Serraf A, Burke RP, Mayer JE Jr, Jonas R. Institutional experience with second and third- stage opalliative procedures for hypoplastic left heart syndrome: the impact of the bidirectional cavopulmonary shunt. J Am Coll Cardiol. 1997 ;29(3):665-70.

[39]. Oberhuber R, Huemer S, Maire R, Samez-Dolzer E,Kreuzer M, Tulzer G. Cognitive development of School -Age Hypoplastic left Heart Syndrome Survivors: A Single Center Study. Pediatr Cardiol 2017;38;1089-1096.

[40]. Samez-Dolzer E, Hekami L, Innenhuber M, Tulzer G, Mair R. Older age at the time of the Norwood pro-cedure is a risk factor early postoperative mortality. Europen Journa of Cardiothoracic Surgery. 2014;1-5.

[41]. Granayem NS, Allen KR, Tabbutt S, Atz AM, Clabby ML, Cooper DS i sur. Interstage mortality after the Norwood procedure: Results of the multicenter Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2012;144(4)896-906. doi: 10.1016/j.jtcvs.2012.05.020

[42]. Ohye RG, Schonbeck JV, Eghtesady P, Laussen PC, Pizarro C, Shrader P, i sur. Pediatric Heart Network Investigators. Cause, timing, and location of death in the Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg. 2012;144(4):907-14. doi:10.1016/j.jtcvs.2012.04.028.

[43]. Cross RR, HarahshekAS, McCarter R, Martin GR. Identified mortality risk factors associated with presentation, initial hospitalisation and interstage period for the Norwood operation in a multicentre registry: a report from the National Pediatric Cardiology-Quality Improvement Collaborative. Cardiol Young 2014;24(2):253-62. doi:10.1017/S1047951113000127

[44]. Pundi KavithaN, Johnson JN, Dearani JA, Pundi KrishnaN, Li Z, Hinck CA i sur. 40-year Follow-up After the Fontan Operation. JACC 2015;66(15):1700-10. doi: 10.1016/j.jacc.2015.07.065.

[45]. Malčić I.: Etički izazovi u ranoj dijagnostici i terapiji prirođenih srčanih bolesti – otpori prekidu trudnoće zasnovani na medicini temeljnoj na dokazima. Ehical challenges in the early diagnosis and treatment on congenital heart diseases – resistence to abortion based on evidence-based medicine. Knjiga izlaganja na XIV. proljetnom simpoziju medicinske etike Hrvatskog liječničkog zbora, Book of presentations at the 14th Spring Symposium on Medical Ethics of the Croatian Medical Association Zagreb.2014.

Corresponding author: Ivan Malčić,
Medical School, Medical Faculty Zagreb, Department of Pediatric Cardiology, Zagreb, Croatia.