UDC 612.17: 616.1
DOI: 10.21668/health.risk/2022.2.14.eng

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Research article

ANALYSIS OF RISK FACTORS CAUSING HEALTH DEFICIENCY AND ITS INDICATORS IN CHILDREN WITH CONGENITAL HEART DISEASES TWO YEARS AFTER RADICAL SURGERY

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Our research goal was to analyze risk factors that could cause health disorders in children two years after a radical heart surgery. It is vital for optimizing diagnostics and predicting negative outcomes of surgical treatment for congenital heart diseases (CHD) using data taken from anamnesis vitae and genetic indicators.

We performed prospective cohort monitoring of 89 children with CHD during two years starting from the moment they had a radical heart surgery. The study design included the following stages: quality of life assessment using "Cardiac Module" in the Pediatric Quality of Life Questionnaire (USA, 2001); collecting data to create anamnesis vitae by questioning; identifying types of polymorphisms of xenobiotic biotransformation genes, inborn and adaptive immunity genes participating in embryogenesis of the cardiovascular system; logistic regression incremental multifactorial analysis of independent variables in anamnesis vitae, peculiarities of a radical surgery, health indicators prior to an operation, as well as polymorph variants of the examined genes with dependent variants: types of functioning and the complex integral health indicator two years after surgical treatment.

*The complex integral health indicator and indicators of physical functioning were significant ones in 2-year dynamics of patients' health after surgical treatment for CHD. These indicators reflected children's quality of life long time after a radical heart surgery. Health deficiency and impaired quality of life two years after a radical heart surgery was associated with HLADRB1*04, HLADRB1*11, HLADRB1*12, HLADRB1*13 alleles and the major allele T in the polymorph variant of CYP1A1 T/C (rs1048943) gene. Influence exerted by these alleles on quality of life long time after a radical heart surgery is determined by long-term toxic inflammation in an operated heart. CHD severity, an age when a radical surgery was performed, as well as unsatisfactory material benefits and living conditions are common medical and social risk factors that cause health deficiency and impaired quality of life long time after a radical heart surgery.*

Keywords: *CYP1A1, HLADRB1, congenital heart diseases, quality of life, risk factors, radical heart surgery, complex integral health indicator, indicators of physical functioning.*

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Over the last decade, considerable changes have occurred in both domestic and world cardiac surgery. They make it possible to perform surgical treatment of congenital heart diseases (CHD) during the first year of a child's life; critical and severe CHD can be treated even in the neonatal period[1]. Advanced surgery technologies applied in the early postnatal period gave an opportunity to achieve a substantial decrease in neonatal mortality including deaths due to severe and critical CHD. An open-heart surgery involving artificial circulation remains the gold standard of surgical treatment for CHD. A radical heart surgery is what complex CHD treatment is based on since it corrects anatomic defects in the cardiovascular system most effectively. At the same time, a following drug therapy and rehabilitation provided to children with CHD compensate for residual hemodynamic and functional disorders in the cardiovascular system. Many studies have established that it is impossible to reach full compensation regarding the cardiovascular system functioning in children who have undergone a radical heart surgery [1]. This influences other health indicators, for example, retarded physical development [2]. Mussato with colleagues showed that speech disorders developed in 56 % of children with CHD after surgical intervention and 21 % of them had certain cognitive disorders [3].

We should remember that *Health* is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity[2]. Therefore, we can state that children have certain health deficiency after a radical heart surgery in a remote post-operation period. If we return to how the World Health Organization defines health, we can speak about physical, emotional, social and mental functioning as integral components of an individual's health. Accordingly, each of these functioning types can be impaired and this requires specific rehabilitation impacts. A vital task that should be solved within individual rehabilitation after a radical heart surgery to treat CHD is to detect disorders in a certain type of functioning.

Another important issue is to create an individual rehabilitation program after a radical heart surgery performed to treat CHD. To do that, it is necessary to predict risks of health deficiency, both in general and as per specific types of functioning in particular, in a remote post-operation period. Health deficiency can have several predictors; they can be both constitutional (genetic) markers and anamnesis vitae indicators (social factors related to a patient's family and individual medical factors) since their associations with CHD have been described in many studies [4–6].

We would like to pay special attention to immune response genes (*HLA-DRB1*) and signaling membrane receptors of inborn immunity (*TREM1*) that can participate in CHD induction, both as inflammatory embryopathies and maintaining inflammation in the cardiovascular system prior to and after the pathology has been treated surgically [7].

Health deficiency in a remote period after a radical heart surgery can occur due to a long-term immune-inflammatory process in the cardiovascular system or, on the contrary, due to frequent respiratory infections as signs of immune deficiency.

Given all the aforementioned, we set our research goal as optimizing diagnostics and predicting negative health outcomes in children two years after a radical heart surgery that was performed to treat CHD. This goal should be achieved by analyzing risk factors with the use of anamnesis vitae indicators and genetic markers.

Materials and methods. To solve the set tasks, we performed a prospect cohort study at the Research Institute for Complex Issues of Cardiovascular Diseases and the Kemerovo Regional Clinical Cardiology Dispensary named after academician L.S. Barbarash. A test group was created in the children division of the latter healthcare institution in 2019–2020 by overall inclusion

[1] Bokeriya L.A., Gudkova R.G. Serdechno-sosudistaya khirurgiya – 2014. Bolezni i vrozhdennye anomalii sistemy krovoobrashcheniya: ezhegodnyi stat. sbornik [Cardiovascular surgery – 2014. Diseases and congenital anomalies of the circulatory system: annual statistical collection]. Moscow, 2015, 226 p. (in Russian).

[2] Constitution of the World Health Organization. *WHO*, 2006, 45th ed., 20 p. Available at: https://www.afro.who.int/sites/default/files/pdf/generic/who_constitution_en.pdf (October 15, 2021).

of all patients who had a radical heart surgery with artificial circulation in their case history.

We applied the following criteria to include patients into the test group within our prospect study:

- a patient was aged from 0 to 15 years inclusively at the moment of a surgery;
- a patient suffered from a congenital heart disease that required radical surgical intervention with artificial circulation;
- an entry was made into the CHD register as per anamnesis vitae and instrumental research methods.

We used the following criteria for excluding a patient:

- a congenital heart disease that required an x-ray endovascular surgery;
- a congenital heart disease that required palliative surgical intervention with artificial circulation;
- genetic chromosome diseases;
- no entry into the CHD register.

Our prospective study group consisted of 89 children (44 girls and 45 boys). CHD were distributed as per nosologic groupings in the way shown in Table 1.

Our analysis of the children's anamnesis vitae established that one third of them were born by cesarean section; more than a half of the children received formula feeding instead of breast milk; each fifth child had neonatal pneumonia and conjugated jaundice (Table 2). Approximately 80 % of the children did not receive all the necessary vaccinations. More than a half of the children were assigned into the category "get sick too often with illnesses lasting for a long time" according to the criteria developed by V.Yu. Albitskii and A.A. Baranov (1985). Each fifth child had concomitant diseases of the central nervous system and on average approximately 8 % of the patients with CHD had concomitant diseases of the genitourinary system and gastrointestinal tract as well as atopic dermatitis.

Infectious exacerbations occurred in 35 children (39.33 %) in the early period after a radical heart surgery and eight children (8.99 %) had non-infections exacerbations. Infectious exacerbations included long-term (more than 5 days) fever, pneumonia, hydrothorax, hydropericardium, pericarditis, and some septic symptoms. Non-infectious exacerbations that developed after CHD surgical treatment included heart rhythm and conduction disorders accompanied with lower ejection function, convulsions, and diaphragmatic cupula paresis.

Complex health assessment. We assessed health of all the examined patients concerning their physical, psychoemotional, social and mental functioning. We also estimated their intelligence quotient (IQ) and language development prior to surgical treatment for CHD and 2 years after it.

Table 1

CHD distributed as per nosologies

CHD nosology	An absolute number of children	Specific weight, %
Congenital malformations of cardiac septa	31	34.83
Ventricular septal defect	14	15.73
Septal defects	4	4.5
Atrioventricular septal defect	3	3.37
Tetralogy of Fallot, congenital malformations of great arteries	15	16.9
Single ventricle heart	6	6.74
Coarctation of the aorta	5	5.62
Congenital stenosis of aortic valve	3	3.37
Coarctation of the aorta and ventricular septal defects combined, hyperplasia of aorta	3	3.37
Total anomalous pulmonary venous connection	2	2.25
Partial anomalous pulmonary venous connection	1	1.12
Atresia of pulmonary artery type I	1	1.12
Ebstein anomaly	1	1.12
Total	89	100

Table 2

The group profile of the examined children

Data from anamnesis vitae	Absolute number	Specific weight, %
Born by cesarean section	29	32.58
Breast-fed only up to 6 months of age	60	67.42
Early neonatal diseases:		
Pneumonia	17	19.1
Conjugated jaundice	19	21.3
Vaccination:		
Complete	18	20.2
Incomplete	71	79.8
Frequency of respiratory infections during the first year of life (more than 2 times)	29	32.58
Frequency of respiratory infections during the second and third year of life (ARI, otitis, bronchitis, pneumonia)	74	83.15
Allergic dermatitis	5	5.6
GIT diseases* after the first year of life (GERD**, gastritis, duodenitis)	5	5.6
GUS diseases*** (UTI****)	8	8.9
Diseases of the nervous system	22	24.7
Conduction defeats in anamnesis (transitoryAB-blockade, 1–2 degree)	12	13.48

N o t e : *GIT is the gastrointestinal tract, **GERD is gastroesophageal reflux disease, ***GUS is the genitourinary system, ****UTI is urinary tract infection.

Quality of life is a significant indicator in assessing a patient's health. We estimated it as per questioning results produced by using psychometric tests and certain questionnaires such as Pediatric Quality of Life Questionnaire, PEDsQL 4.0 (J.W. Varni et al., USA, 2001). They are aimed at estimating physical functioning (PH), emotional functioning (EF), social functioning (SF), school functioning (ScF), mental health and the complex integral health indicator [8, 9].

We used "Cardiac Module" of the PEDsQL 4.0 in our study. Two parallel forms of the questionnaire, one filled in by a child (self-report) and the other filled in by a parent (proxy-report), made it possible to objectively estimate the children's quality of life.

The testing completed, all the data were coded into Quality of Life scores as per the copyrighted procedures (Multinational Center for Quality of Life Research) provided by the authors of the applied questionnaire. We applied the invert correlation meaning the lower a score was, the higher a percent of functioning was. We accepted the following scale. One score corresponded to 100–76 % or perfect functioning; 2 scores were equal to 75–51 % or good functioning; 3 scores were equal to 50–26 % or satisfactory functioning; and 4 scores were equal to 25–0 % or poor functioning. The estimates were made for each type of functioning, physical, psychoemotional, social and mental; all these types were estimated by a parent, a patient (child) and a doctor.

The children's physical, psychoemotional, social and mental functioning as well as their intelligence quotient (IQ) and language development were estimated starting from a certain age. Table 3 provides data on an age when estimates of a specific functioning type started as well as on a number of children who participated in these estimates.

Samples of peripheral blood were taken from all the examined children to determine their immune genetic types.

We identified types of polymorphisms of xenobiotic biotransformation genes, inborn and adaptive immunity genes two years after surgical treatment for CHD. It was done to analyze a role played by constitutional factors in determining health deficiency in the examined children.

Molecular and genetic research. We examined genome DNA extracted from peripheral blood leukocytes. Genome DNA was obtained by using phenol-chloroform extraction according

Table 3

Age limits and children samplings to estimate their physical, psychoemotional, social and mental functioning as well as intelligence quotient (IQ) and language development

Estimate	Age	A number of children participating in estimations
Physical functioning	Older than 2 years	76
Psychoemotional functioning	Older than 5 years	51
Social functioning		
Mental functioning		
Intelligence quotient (IQ)		
Language development		

to the conventional procedure. Blood samples were taken from all the participants prior to a heart surgery. Blood was taken from the ulnar vein into a tube with Ethylenediaminetetraacetic acid (EDTA, Becton Dickinson Vacutainer, USA). Next, blood aliquots of 700 μl were put into 1.5-ml eppendorf tubes (Axygen, USA) with tightly locking caps. All the samples of biological materials were marked properly and then stored under -80ºC until the research started. Concentrations of extracted DNA were estimated using NanoDrop ND-2000C spectrophotometer (Thermo, USA). Our choice on single-nucleotide polymorphic sites for molecular genotyping was determined by localization in the following genes: those coding enzymes of xenobiotics biotransformation (*GSTP, CYP1A2, CYP1A1*), participating in determination of heart development (*CRELD1, GATA6*), signaling membrane (*TREM1*) and intracellular (*NOTCH1*) receptors of inborn immunity and a classic immune response gene (*HLADRB1*). Minor allele frequency for SNP did not exceed 5 % in the population according to data provided by HapMap.

We resorted to open research data[3] to estimate expected or proven molecular outcomes in determining CHD occurrence for selected SNP. Overall, we selected 20 gene polymorphisms that are given in Table 4.

Genotyping was performed by using PCR with TaqMan probes (Thermo Fisher Scientific, USA) on ViiA™ 7 Real-Time PCR System (Life Technologies, USA).

We analyzed *HLA-DRB1* by the polymerase chain reaction method considering the results in real time. The analysis was accomplished with kits manufactured by "DNA-technologies" company (Russia) and with DT-96 detector amplifier manufactured by the same company according to the procedures established by the manufacturer. Genotyping quality control was performed by repeated genotyping of 10 % of randomly selected samples. We focused on analyzing frequencies of 14 *HLA-DRB1* gene alleles.

Statistical analysis. We analyzed our research results with Statistica for Windows software package produced by StatSoft Inc., Version 10.0, and MedCalc 17.5.3.

Within the present study, distribution of each quantitative indicator was examined by using Kolmogorov – Smirnov test and Shapiro – Wilkes test. Quantitative data were given as median values (Me) as well as the 25th and 75th quartiles (Q25 – UQ and Q75 – LQ). We compared non-parametric indicators by using Wilcoxon test; pair comparisons were accomplished by using Mann – Whitney test. Statistical significance of differences between qualitative indicators was determined by using chi-square (χ^2) with Yates' correction. We used Spearman's correlation coefficient to determine how strong correlations were between the examined indicators. Those indicators with *p*-level not exceeding 0.05 were considered statistically significant; that is, a zero hypothesis was abandoned when an

[3] SNPedia. Available at: https://www.snpedia.com/index.php/Rs (October 20, 2021); dbSNP. *National Library of Medicine*. Available at: https://www.ncbi.nlm.nih.gov/snp/rs (October 20, 2021).

Table 4

Characteristics of the examined gene polymorphisms

Gene	SNP type	SNP ID	Amino acid replacement	Localization on a chromosome as per GRCh.p12*	Nucleotide replacement
GSTP1	Upstream variant	rs6591256	-	Chr11.67582428	A/G
GSTP1	Upstream variant	rs17593068	-	Chr11.67583461	G/T
GSTP1	Intron variant	rs1871042	-	Chr11.67586373	C/T
GSTP1	Missense variant	Rs1695	Missense mutation Ile105Val	Chr11.67585218	A/G
CYP1A1	Missense variant	rs1048943	Missense mutation Ile462Val	Chr15.74720644	T/C
CYP1A2	Intron variant	rs762551	-	Chr15.74749576	C/A
CRELD-1	Missense variant	rs73118372	Missense mutation Met383Arg	Chr3.9943989	T/C
CRELD-1	Intron variant	rs9878047	-	Chr3.9943773	T/C
CRELD-1	Synonymous variant	rs3774207	Amino acid codon H [CAC] > H [CAT]	Chr3.9943972	C/T
GATA6	Intron variant	rs10454095	-	Chr18.22197478	T/C
NOTCH1	Intron variant	rs13290979	-	Chr9.136531182	A/G
TREM1	Intron variant	rs1817537	-	Chr6:41276829	C/G
TREM1	Intron variant	rs3804277	-	Chr6.41277434	C/T
TREM1	Intron variant	rs6910730	-	Chr6.6:41278895	A/G
TREM1	Upstream variant	rs7768162	-	Chr6.41276829	A/G
TREM1	Downstream Variant	rs2234246	-	Chr6.41276002	C/T
TREM1	Downstream transcript variant	rs4711668	-	Chr6.41278735	C/T
TREM1	Upstream variant	rs9471535	-	Chr6.41287752	C/T
TREM1	Missense variant	rs2234237	Missense mutation Thr25Ser	Chr6.41282728	A/T

Note: *GRCh38.p12 is the Genome Reference Consortium for checking SNP localizations.

error was less than 5 %. This fully conforms to the conventional standards applied in biomedical research[4].

We created mathematical models to predict how probable risks of health deficiency were two years after surgical treatment for CHD and to classify these risks. To do that, we applied multiple logistic regressions, including a stepwise variant for four-score categories of a dependent variable; classification trees; ROC-analysis. Classification trees made it possible to identify significant predictors and rank them. ROC-analysis enabled estimating significance of an obtained equation that was used to calculate probability of health deficiency two years after surgical treatment for CHD. This analysis included the following parameters: AUC (area under curve) described diagnostic value of an indicator (0.9–1.0, perfect; 0.8–0.9, very good; 0.7–0.8, good; 0.6–0.7, average; 0.6 and lower, unsatisfactory)), factor sensitivity (Se) and specificity (Sp).

Results and discussion. Table 5 provides data on distribution of scores that estimated functioning (PD) as per different types of health estimates made by a doctor, a patient, and a parent.

We did not detect any significant differences between estimates made by a doctor, a patient, and a parent. We additionally performed a correlation analysis between estimates of various functioning types made by parents, patients, and doctors two years after a radical heart surgery. The analysis revealed highly authentic correlations (Table 6).

[4] Lakin G.F. Biometriya: uch. posobie dlya biol. spets. vuzov, 4-e izd., pererab. i dop. [Biometry: the manual for biological specialties in higher education, the 4th edition, revised and supplemented]. Moscow, Vysshaya shkola Publ., 1990, 352 p. (in Russian).

Table 5

Distribution of functioning scores (PD) as per different types of health estimates given by a doctor, a patient, and a parent

Indicators	1– Doctor			2 – Patient			3 – Parent			*p* 1,2	*p* 1,3	*p* 2,3
	Me	25 % PQ	75 % PQ	*Me*	25 % PQ	75 % PQ	*Me*	25 % PQ	75 % PQ			
PD phys.	2.66	1.75	3.56	2.67	1.66	3.69	2.64	1.65	3.63	-0.04	0.04	0.08
PD emot.	2.51	1.70	3.31	2.46	1.61	3.31	2.49	1.69	3.30	0.13	0.04	-0.09
PD soc.	2.44	1.55	3.33	2.57	1.73	3.42	2.48	1.63	3.32	-0.34	-0.09	0.26
PD mental	2.39	1.32	3.46	2.41	1.53	3.29	2.46	1.57	3.35	-0.04	-0.16	-0.13

N o t e : PD is a functioning score: phys means physical; soc, social, emot, emotional; p is the significance level.

Table 6

Correlations between score estimates made by doctors, children, and parents two years after a radical heart surgery

Indicators	Spearman *R*	$t \cdot (n\text{-}2)$	*p*-value
PD phys. doctor & PD phys. patient	0.967	29.948	0.000
PD emot. patient & PD emot. parent	0.848	12.574	0.000
PD soc. doctor & PD soc. patient	0.927	19.449	0.000
PD mental doctor & PD mental patient	0.916	17.928	0.000
PD phys. patient & PD phys. parent	0.964	28.646	0.000
PD emot. patient & PD emot. parent	0.840	12.200	0.000
PD soc. patient & PD soc. parent	0.837	12.045	0.000
PD mental patient & PD mental parent	0.849	12.656	0.000
PD phys. doctor & PD phys. parent	0.933	20.475	0.000
PD emot. doctor & PD emot. parent	0.836	11.985	0.000
PD soc. doctor & PD soc. parent	0.832	11.828	0.000
PD mental doctor & PD mental parent	0.769	9.469	0.000

N o t e : PD is a functioning score: phys. means physical; soc., social, emot., emotional; *p* is the significance level, *R* is Spearman's correlation coefficient.

Given that, we applied integral indicators in our logistic regressions (a simple mean of estimates made by parents, children, and doctors) for each type of functioning (physical, emotional, social and mental) as well as for the complex integral health indicator.

We searched for associations between independent factors including anamnesis vitae, circulatory disorders prior to surgical treatment, peculiarities of a radical heart surgery, health indicators prior to a radical heart surgery as well as polymorphisms of the examined genes, on one hand, and dependent variables including integral indicators of various functioning types and the complex integral health indicators, on the other hand. This done, we established several significant associations shown in Tables 7 and 8.

Table 7 provides data on statistically significant associations between independent variables related to anamnesis vitae, circulatory disorders prior to surgical treatment, peculiarities of a radical heart surgery, health indicators prior to a radical heart surgery as well as polymorphisms of the examined genes and the integral indicator of physical functioning two years after surgical treatment for CHD.

Obviously, statistically significant associations occurred only for the genetic markers (*HLA-DRB1*11* and *HLA-DRB1*12)*. Both these alleles code the same serological specificity, HLA-DR5, and this indicates that HLA II class molecules as antigen-representing receptors have a special role in determining physical functioning two years after surgical treatment for CHD.

We can assume that an immune phenotype determines phenotypic manifestations of one's health. We established a positive association with immune-inflammatory diseases,

such as unspecified spondyloarthritis, juvenile arthritis and antiphospholipid syndrome both for HLA-DR5 antigen and *HLA-DRB1*12* allele [10, 11]; and simultaneously a positive association was established between *HLA-DRB1*11* allele and autoimmune thyroid disease [12]. Possibly, subclinical immune inflammation in children with *HLA-DRB1*11* and *HLA-DRB1*12* could become apparent through inhibited physical functioning. Accordingly, high frequency of *HLA-DRB1*12* among children with CHD can result in its higher relative frequency among children with poor physical functioning. In any case, HLA-DR5 phenotype has positive associations with poor physical functioning two years after a radical heart surgery.

We did not establish any significant associations with any other independent variables for other types of functioning estimated two years after a radical heart surgery.

We estimated the complex integral health indicator as a simple mean of all the integral indicators of various types of functioning (physical, emotional, social and mental) two years after a radical heart surgery. We similarly examined associations between the complex integral heath indicator and independent variables related to anamnesis vitae, circulatory disorders prior to surgical treatment, peculiarities of a radical heart surgery, health prior to a radical heart surgery as well as polymorphisms of the examined genes. Table 8 provides the results.

Obviously, the complex integral health indicator had a positive association with CHD score as per its severity and criticality, family structure and *HLA-DRB1*13* allele two years after a radical heart surgery. A negative statistically significant association was established for material benefits. These associations indicate that the more critical a CHD is, the poorer results are produced by two-year rehabilitation with a higher complex integral indicator that describes poor quality of one's health.

When it comes down to family structure, we should note that one score was assigned to a two-parent family; two scores, a large two-parent family; three scores, a single-parent family; four scores were assigned to children who did not have parents or family (and lived in an orphanage). Given this scoring system, the association with this variable indicates that the higher the score describing family issues is, the higher the score is that describes poor quality of one's health. Accordingly, children from orphanages had the poorest quality of life two years after surgical treatment for CHD.

Table 7

Results produced by the logistic regression stepwise multifactorial analysis

Indicators	β-coefficient	Standard error of β-coefficient	B-coefficient	Standard error of B-coefficient	*p*-value
Intercept			1.969	0.143	0.000
*HLA-DRB1*12*	0.343	0.146	0.874	0.372	0.025
*HLA-DRB1*11*	0.329	0.147	0.399	0.178	0.032

N o t e : Intercept is a free coefficient in logistic regression.

Table 8

Logistic regression stepwise multifactorial analysis of independent variables

Indicators	β-coefficient	Standard error of β-coefficient	B-coefficient	Standard error of B-coefficient	*p*-value
Intercept			1.711	0.206	0.000
CHD score as per severity and criticality	0.633	0.123	0.065	0.013	0.000
Material benefits	-0.531	0.120	-0.559	0.127	0.000
*HLA-DRB1*13*	0.605	0.133	0.722	0.159	0.000
Family structure	0.428	0.132	0.450	0.138	0.003

N o t e : Intercept is a free coefficient in logistic regression.

Table 9

Descriptive statistical characteristics and boundaries of "poor" and "good" score estimates for the complex integral health indicator two years after CHD surgical treatment

Indicator	Average	Median	25-th percentile	75-th percentile
The complex integral health indicator two years after surgical treatment for CHD	2.276	2.125	2.000	2.500
Indicator	Below or equal to	Result (a score for regression)	Above or equal to	Result (a score for regression)
The complex integral health indicator two years after surgical treatment for CHD	2.000	"good" (0 scores)	2.250	"poor" (1 score)

The score estimate given to material benefits was linked to the official Russia's Minimum Wage (RMW) per each family member. If wages per one family member were lower than RMW, then such a family was considered poor (0 scores); if the indicator was equal to RRMW or higher, a family was considered wealthy (1 score). Accordingly, the established negative association with material benefits indicates that the lower family incomes are, the higher the score is that describes poor quality of one's health two years after surgical treatment for CHD.

Other mechanism can be associated with HLA-DR6 molecular itself that is coded by *HLA-DRB1*13* allele. The molecule was found to have weal antigen properties as far back as in 80ties last century. They can become apparent through an ineffective immune response to environmental antigens. That is, this allele and a membrane receptor with HLA-DR6 isotype are associated with functional Ir-associated immune deficiency [13]. General poor quality of health can become obvious exactly due to weak immunity phenomenon.

Our next step was to develop methodical approaches to complex diagnostics and prediction of health disorders in children who had a radical heart surgery due to CHD. To do that, we used a multiple logistic regression with its major dependent variable being occurrence or absence of health deficiency in children two years after surgical treatment for CHD.

All the aforementioned data indicate that the complex integral health indicator describes children's health in a remote post-operation period. We calculated a simple mean and median value of the complex integral health indicator as well as its percentile and standard deviations. These descriptive statistical indicators gave grounds for determining a boundary between "poor" and "good" estimates for the complex integral health indicator in a remote post-operation period. The data are provided in Table 9.

Therefore, we introduced boundaries of "poor" and "good" results of the complex health assessment two years after a radical heart surgery to treat CHD. This made it possible to create a multiple logistic regression with a binary dependent variable ("either a "good" or a "poor" complex integral health indicator) that was subsequently used to build a logarithmic equation for predicting a risk of a certain event. Accordingly, "a poor" complex integral health indicator was taken as health deficiency two years after surgical treatment for CHD.

Table 10 provides results produced by the logistic regression for the complex integral health indicator two years after surgical treatment for CHD.

Obviously, we established many significant associations for the complex integral health indicator that described good health or its deficiency two years after surgical treatment for CHD with simultaneous significant dimensionality of a free coefficient in logistic regression (intercept). This indicates an expected event can be predicted quite effectively.

We should note that β-coefficients show relative influence exerted by a predictor on the dependent variable whereas B-coefficients show prognostic value of a predictor.

Table 10

Results produced by the logistic regression for the complex integral health indicator

Regression of the dependent variable: "poor" complex integral health indicator – 1 / "good" – 0	β-coefficient	Standard error of β-coefficient	B-coefficient	Standard error of B-coefficient	*p*-value
Intercept			-0.759	0.350	0.041
Family structure	0.524	0.108	0.541	0.112	0.000
Material benefits	-0.615	0.103	-0.634	0.106	0.000
CHD score as per severity and criticality	0.705	0.127	0.071	0.013	0.000
An age when a radical heart surgery was performed	0.424	0.099	0.072	0.017	0.000
*CYP1A1 T/C rs1048943*T*	0.215	0.094	0.396	0.174	0.033
*HLA-DRB1*04*	0.303	0.095	0.334	0.105	0.004
Living conditions	0.443	0.112	0.465	0.117	0.001
*HLA-DRB1*13*	0.457	0.113	0.534	0.132	0.001
*HLA-DRB1*01*	-0.223	0.098	-0.258	0.113	0.033

N o t e : Intercept is a free coefficient in logistic regression.

Given that, we can see that logistic regression analysis made it possible to estimate how probable a risk of a certain event was. In our case, this event was health deficiency that occurred two years after surgical treatment for CHD. B-coefficients of each significant predictor were included into a formula used for calculating this risk.

In this case, the analyzed risk of health deficiency two years after surgical treatment for CHD is calculated as per the following equation:

$$Y = (\text{EXP}(Z) / (1 + \text{EXP}(Z))) \cdot 100\ \%,$$

where

$$Z = (-0.759 + (X_1 \cdot 0.541) - (X_2 \cdot 0.634) + \\ + (X_3 \cdot 0.071) + (X_4 \cdot 0.072) + (X_5 \cdot 0.396) + \\ + (X_6 \cdot 0.334) + (X_7 \cdot 0.465) + (X_8 \cdot 0.534) - \\ - (X_9 \cdot 0.258)),$$

where

Y is a probable risk of health deficiency two years after CHD surgical treatment (the coefficient showing a probable risk of health deficiency, %);

-0.759 is a free coefficient in logistic regression;

X_1 is family structure (two-parent family, 1; large two-parent family, 2; one-parent family, 3; children from orphanages, 4);

X_2 is material benefits (poor families with incomes lower than RMW per one family member, 0; wealthy families with incomes per one family member being equal to RMW or higher, 1);

X_3 is a CHD score as per its severity, criticality and frequency (scores are given in Table 11);

X_4 is an age when a radical heart surgery was performed (years);

X_5 is allele T presence in CYP1A1 T/C, rs1048943 gene polymorphism (absence, 0; presence in heterozygote, 1; presence in homozygote, 2);

X_6 is allele 04 presence in HLADRB1 gene polymorphism (absence, 0; presence in heterozygote, 1; presence in homozygote, 2);

X_7 is living conditions (excellent, 1; good, 2; bad, 3; exceptionally bad, 4);

X_8 is allele 13 presence in HLADRB1 gene polymorphism (absence, 0; presence in heterozygote, 1; presence in homozygote, 2);

X_9 is allele 01 presence in HLADRB1 gene polymorphism (absence, 0; presence in heterozygote, 1; presence in homozygote, 2).

Scores for various nosologies within the CHD grouping were assigned considering three criteria, namely, their severity, criticality and frequency that made a radical heart surgery necessary (Table 11).

The equation based on the logistic regression for calculating Y (a probability of health deficiency two years after surgical treatment for CHD) has a logarithmic nature. This means risk rates fall within the range from 0 to 100 %. Thus, if Y tends to 50 %, then a risk of

Table 11

CHD scores for logistic regression considering their severity, criticality and frequency

Nosology	Score for logistic regression
Septal defects and their combination	1
Coarctation of the aorta	2
Heart valve disease (MV, TV)	2
Anomalies of great arteries	3
Coarctation of the aorta and ventricular septal defects combined, hyperplasia of aorta	4
Congenital stenosis of aortic valve	4
Tetralogy of Fallot, congenital malformations of great arteries	5
Atrioventricular septal defect	5
Partial anomalous pulmonary venous connection	5
Ebstein anomaly	6
Total anomalous pulmonary venous connection	7
Atresia of pulmonary artery type I	8
Single ventricle heart	9

N o t e : TV is tricuspid valve; MV is mitral valve.

this expected event is equally probable; if *Y* tends to zero, then a risk is unlikely; and on the contrary, if *Y* tends to 100 %, then health deficiency two years after surgical treatment for CHD is highly likely. Contributions made by all the predictors to health deficiency two years after a radical heart surgery were statistically significant ($p < 0.001$).

All the predictors for likelihood of health deficiency two years after surgical treatment for CHD can be estimated in a period prior to and after a surgery thereby establishing how probable this health deficiency is as well as creating an individual rehabilitation program for a specific patient to be applied during a post-operation period.

CHD severity and criticality (Table 11) and an age when a radical heart surgery required to treat it was performed were two basic predictors of health deficiency in a remote post-operation period. The established positive association indicated that the more severe and more critical a CHD was, the poorer quality of life would be expected in a remote post-operation period.

On the other hand, the positive association with an age when a radical heart surgery was performed indicated that the older a patient was, the poorer quality of life would be expected in a remote post-operation period. An age when a radical heart surgery should be performed on children with septal CHD remains disputable and requires separate research. Within this study, most patients had septal CHD and an age when a surgery was performed became a predictor of health deficiency two years after surgical treatment for CHD. Therefore, we can assume that septal sporadic non-syndromic CHD should be treated with a radical surgery at a younger age. This will help not only treat CHD more effectively but also rehabilitate a patient better after a radical heart surgery. At the same time, it is necessary to determine the youngest possible age for such surgeries bearing implantation materials in mind.

A role that belongs to each identified genetic predictor of health deficiency in a remote post-operation period is associated with its influence on CHD occurrence and effects that prolong immune inflammation in the heart after a surgery. In particular, *HLA-DRB1*04* allele that has strong correlations with systemic and organ-specific autoimmune and autoinflammatory diseases can determine elevated inflammation potential in such children [14]. On the contrary, *HLA-DRB1*13* allele that is associated with immune deficiency determines immune paresis to macro- and microenvironment antigens [15]. As we have already mentioned, immune deficiency associated with *HLA-DRB1*13* (HLA-DR6) can become obvious through frequent respiratory diseases and this will lead to deteriorating children's quality of life in a remote period after surgical treatment for CHD.

The established negative association with *HLA-DRB1*01* allele indicates that the more frequent this allele is, the less frequent health

deficiency is two years after surgical treatment for CHD. That is, this allele is a predictor of health deficiency and poor quality of life in a remote period after surgical treatment for CHD. *HLA-DRB1*01* allele is a dominant one in populations across the world [13] with its share reaching 25 %. This outlines its property to determine people's immune resistance to macro- and micro-environmental factors. In this case, this allele is a marker showing children's good adaptation capabilities after a radical heart surgery.

Homozygosis as per major (wild type) allele T in *CYP1A1 T/C* (rs1048943) gene polymorphism determines elevated oxidation of xenobiotics and endobiotics with occurring adducts [16]. They stimulate an immune response and autoinflammatory reactions due to, among other things, arachidonic acid participating in metabolism [17]. Thereby a toxic-inflammatory process is activated also through this gene polymorphism. Overall, these gene polymorphisms will make for manifestation of a prolonged inflammatory response against the background of effector immune reactions being in deficiency. Frequent respiratory diseases in such children, which we mentioned earlier [18], result from immune genetic determination. Health deficiency develops in such children due to, among other things, prolonged subclinical inflammation [19, 20].

Contribution made by social factors to health deficiency in a remote post-operation period is associated with direct and indirect effects produced by them on effectiveness of rehabilitation and compliance-therapy. Poor living conditions and material benefits are major adverse factors that impose certain limitations on successful outpatient rehabilitation. Bearing this in mind, children from poor families should be provided with additional inpatient rehabilitation.

We performed ROC-analysis to establish the threshold value of the complex integral health indicator that described risks of health deficiency two years after surgical treatment for CHD and to test the quality of the derived regression equation. The analysis covered a qualitative indicator showing whether health deficiency was present (1) or absent (0) two years after a radical heart surgery, on one hand, and data on *Y* (the coefficient showing likelihood of health deficiency) calculated for each patient. The performed ROC-analysis established a cutoff score for likelihood of health deficiency two years after surgical treatment for CHD. This score equaled 57.66 ($p < 0.001$). The results are shown in Figure 1.

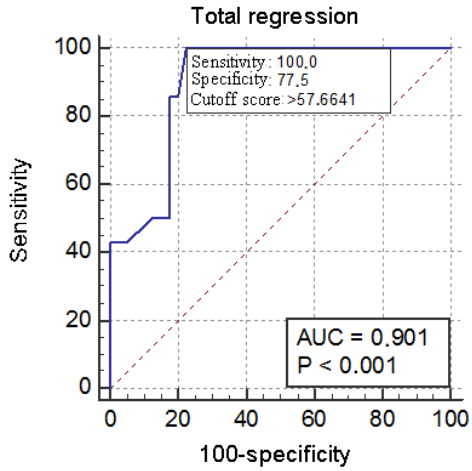

Figure 1. ROC-analysis to establish the threshold value of the complex integral health indicator that described risks of health deficiency two years after surgical treatment for CHD and to determine its diagnostic significance, sensitivity and specificity regarding calculated risks of this expected event

Obviously, the ROC-analysis established that the value of the complex integral health indicator two years after surgical treatment for CHD equal to 57.66 was the boundary between absence and presence of health deficiency. According to this criterion, the derived equation has excellent diagnostic value (AUC = 0.901), specificity (100.0 %) and sensitivity (77.5 %). That is, if we use it to calculate likelihood of health deficiency two years after surgical treatment for CHD, we can determine whether it will or will not occur with precision close to 90 %. Health deficiency will develop in children with the complex integral health indicator calculated for them being equal to or higher than 58 %. Children with this calculated indicator not exceeding 58 % do not have risks of health deficiency in future.

Significance of predictors for health deficiency occurrence two years after surgical treatment for CHD is also proven by estimating them with such a mathematical analysis method as "classification tree". We performed "classification tree" analysis and established two significant classification factors shown in Figure 2.

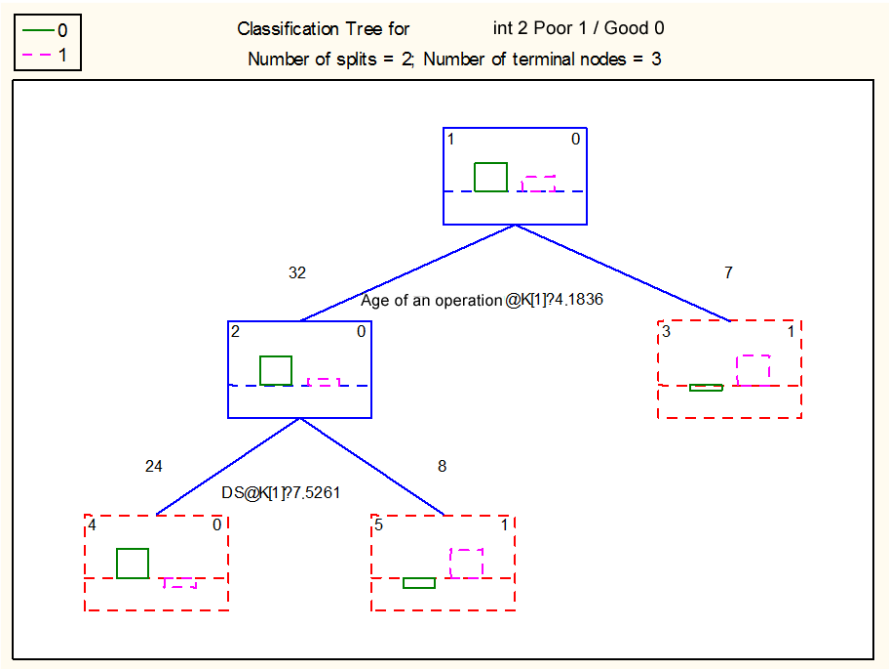

Figure 2. Classification trees of the complex integral health indicator in the second enacted period (qualitative estimate is as follows: 0 scores means "good" and 1 score means "poor") depending on factors related to anamnesis vitae, circulatory disorders prior to surgical treatment, peculiarities of a radical surgery, health prior to a radical surgery, as all as polymorphisms of the analyzed genes: DS is CHD score as per its severity, criticality and frequency (Table 11), @K[1]? is a cutoff score: it equals 4.1836 for an age when an operation was performed and 7.5261 for a CHD score

The primary step in classifying a risk of health deficiency two years after surgical treatment for CHD relies on an age when a radical surgery was performed. The dividing factor is an age of 4 years and 2 months. In case an operation has been performed at an older age, a risk of health deficiency grows; and if it has been performed at a younger age, it decreases. A CHD score (Table 11) as per its severity, criticality and frequency is the next classification factor. A cutoff score equals 7.5. If a CHD score is higher than this value, health deficiency two years after surgical treatment for CHD is highly likely. Accordingly, children who had Tetralogy of Fallot and had an operation at an age younger than 4 years should recover completely two years after a radical heart surgery, as their complex integral health indicator shows.

We ranked the analyzed predictors by using "classification trees' procedure for mathematical analysis as per their significance for occurrence of health deficiency two years after surgical treatment for CHD. Figure 3 provides the results.

It is obvious that a CHD score as per its severity, criticality and frequency (Table 11) is the most significant predictor of health deficiency two years after CHD surgical treatment. Its influence on the dependent variable (presence or absence of health deficiency two years after surgical treatment for CHD) reached 99 %. The second rank place belongs to an age when a radical heart surgery was performed. Accordingly, a functional category (FC) prior to surgical treatment for CHD holds the third rank place. Therefore, the most significant influence on health deficiency in a remote post-operation period was exerted by factors related to a CHD itself (its severity and criticality, a child's age when a radical surgery took place and a functional category during that period). Genetic markers made the smallest contributions according to this rank scale, from 35 to 20 %.

The overall practical conclusion results from calculating the complex integral health indicator two years after surgical treatment for CHD. If this indicator calculated for a child is higher than 58 % in a post-operation period, this child needs mandatory additional inpatient rehabilitation during the first two years after a radical heart surgery.

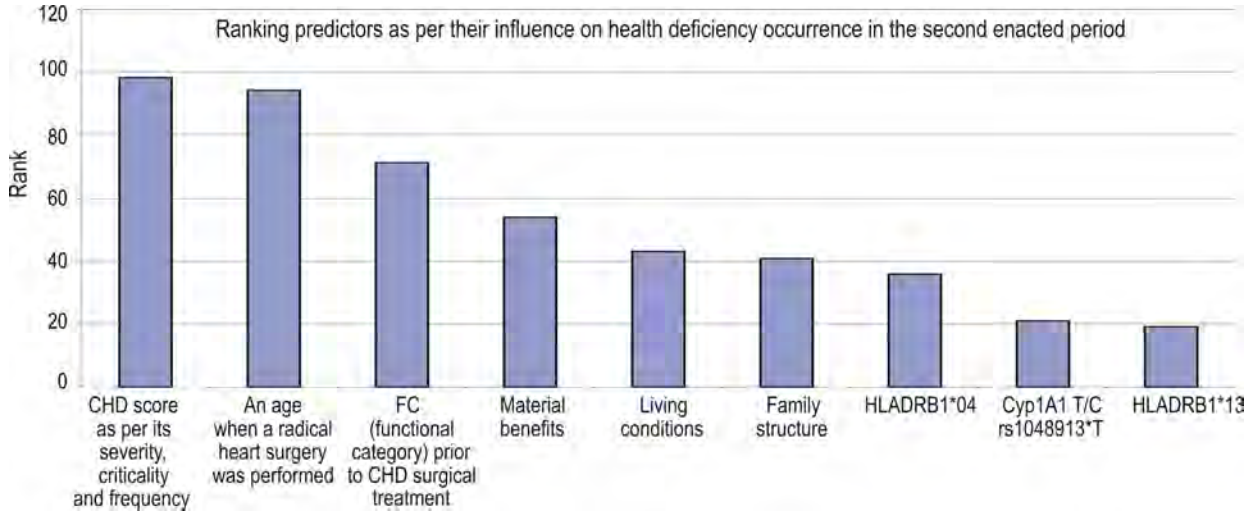

Figure 3. Ranks assigned to the significant predictors of the dependent variable showing health deficiency or its absence (1 / 0) two years after surgical treatment for CHD produced by using "classification trees" procedure for mathematical analysis

Conclusion. Therefore, this study has established that indicators of physical functioning and the complex integral health indicator are among most significant predictors of health deficiency two years after surgical treatment for CHD. These indicators describe children's quality of life in a remote period after a radical heart surgery.

Health deficiency and impaired quality of life two years after a radical heart surgery are associated with alleles *HLA-DRB1*04, HLA-DRB1*11, HLA-DRB1*12, HLA-DRB1*13* and major allele *T* in *CYP1A1 T/C* (rs1048943) gene polymorphism. Effects produced by these alleles on quality of life in a remote period after a radical heart surgery can occur due to their capability to induce prolonged toxic-inflammatory process in the great after a surgery.

Certain medical and social risk factors also can induce health deficiency and lead to impaired quality of life in a remote period after a radical heart surgery. Among them, we should primarily mention severity and criticality of a CHD itself, an age when a radical operation was performed, as well as poor material benefits and unsatisfactory living conditions. Additional inpatient rehabilitation might become a solution to the problem. It is necessary to provide better rehabilitation for children after surgical treatment for CHD considering the complex integral health indicator with its threshold value being 58 %.

Funding. The study was accomplished due to support provided within the complex fundamental research program of the RAS Siberian Branch within the fundamental subject of the Research Institute for Complex Issues of Cardiovascular Diseases No. 0419-2022-0001.

Competing interests. The authors declare no competing interests.

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Received: 29.10.2021
Approved: 10.06.2022
Accepted for publication: 21.06.2022