Doctoral School in Medical Sciences

Manuscript title:
U.D.C.: 616.132-007-053.1-053.2(043.2)

GAVRILIUC Natalia

RISK FACTORS AND EARLY DIAGNOSIS IN COMPLICATIONS OF PEDIATRIC CONGENITAL AORTOPATHIES

322.01 - PEDIATRICS AND NEONATOLOGY

Summary of Ph.D. Thesis in Medical Sciences

Chisinau, 2020

The thesis was elaborated within the Department of Pediatrics, at "Nicolae Testemitanu" State University of Medicine and Pharmacy of the founding Consortium of the Doctoral School in Medical Sciences.

Scientific advisor:
Palii Ina,
Habilitated Doctor of Medical Sciences, Associate professor
Scientific co-advisor
Ciubotaru Anatol,
Habilitated Doctor of Medical Sciences, University professor

Members of the guidance committee:
Revenco Ninel,
Habilitated Doctor of Medical Sciences, University professor
Sglimbea Anca,
PhD in medical sciences
Caraman Anatolie,
PhD in medical sciences

Ph.D. thesis defense will take place on 24.06.2020, at 14 pm, at the meeting of the Scientific Council of "Nicolae Testemitanu" State University of Medicine and Pharmacy, the Republic of Moldova (Ștefan cel Mare și Sfânt, 165 Bd, Chisinau MD -2004)

The specialized scientific council consists of:

Chairman:
Țurea Valentin,
Habilitated Doctor of Medical Sciences, University professor
Members:
Stamati Adela,
Doctor of Medical Sciences, Associate professor
Repin Oleg,
Habilitated Doctor of Medical Sciences, Associate professor
Palii Ina,
Habilitated Doctor of Medical Sciences, Associate professor
Grosu Victoria,
Habilitated Doctor of Medical Sciences, University professor
Ciobanu Nicolae,
Habilitated Doctor of Medical Sciences, University professor
Caraman Anatolie
Doctor of Medical Sciences

Author
Gavriliuc Natalia

SUMMARY

LIST OF ABBREVIATIONS

AA	aortic aneurysm
AA	aldosterone antagonists
AAA	abdominal aortic aneurysm
ACC/AHA	American College of Cardiology / American Heart Association
ACEI	angiotensin converting enzyme inhibitors
AHT	arterial hypertension
Ao	aorta
AoC	aortic coarctation
AoS	aortic stenosis
BAV	bicuspid aortic valve
BB	beta blocker
BMI	body mass index
BSA	body surface area
C/GAo	congenital / genetic aortopathy
CAo	congenital aortopathy
CHF	congestive heart failure
CHM	congenital heart malformation
CI	confidence interval
CT	computer tomography
CTI	cardiothoracic index
dBP	diastolic blood pressure
LAD	left atrial diameter
RAD	right atrial diameter
RVD	right ventricular diameter
ECG	electrocardiogram
Eco-CG	echocardiography
EF	Ejection fraction
ESC	European Society of Cardiology
ESR	erythrocytes sedimentation rate
FHC	frequency of heart contractions
H	height
Hg	hemoglobin
LVH	left ventricular hypertrophy
HRD	heart rhythm disorders
IAA	interrupted aortic arch
IAV	insufficiency of the aortic valve
LA	left atrium
LDH	lactate dehydrogenase
LV	left ventricle
MCI	Mother and Child Institute
MCT	multislice computed tomography
MRI	magnetic resonance imaging

MS	Marfan syndrome
NCP	national clinical protocol
NYHA	New York Heart Association (Asociația din New York a Inimii)
PG	pressure gradient
PMSI	public medical-sanitary institution
TEVAR	thoracic endovascular aortic repair ()
RM	Republic of Moldova
RR	respiratory rate
sBP	systolic blood pressure
SD	standard deviation
SEF	short ejection fraction
SPO_2	peripheral saturation with oxygen
SPPA	systolic pressure in the pulmonary artery
TAA	thoracic aortic aneurysm
LVED	left ventricular end-diastolic diameter
LVES	left ventricular end-systolic diameter
TEE	transesophageal ecocardiography
TGF- β	tissue growth factor- β
TTE	transthoracic ecocardiography
VAoS	valvular aortic stenosis

THE RESEARCH CONCEPTUAL FRAMEWORK

Introduction. The study of congenital heart defect (CHM) has been of paramount importance for today's medicine, due to its increased incidence rate, which has become a major research issue for many fields of medicine: neonatology, pediatrics, cardiology, genetics, and medical imaging [1].

It should be mentioned that management of CHM patients has improved over the last decades, thus reducing the mortality rate by 39% across Western Europe and North America. One of the main objective that led to a significant decrease in the CHM-induced mortality rate is the early age of children or newborns, undergoing the corrective surgery, followed by a holistic approach to CHM , which is used in both highly developed countries and our country. Despite the current medical advances, congenital heart malformations still result in about 30% of deaths due to malformations and 5.7% of infant mortality [2].

The recent research studies have reported great interest in factors favoring the development of major CHM-associated complications [7]. Therefore, a category of obstructive valvulo-vascular MCCs seems to exhibit higher risk for developing lethal complications, since they are characterized by an expansive pre- or post-obstructive mechanism [2, 7]. This group of cardiac malformations includes congenital aortopathies (CAo) that is a relatively new concept in pediatric cardiology within the Republic of Moldova (RM). We initiated this research study while considering the high incidence of CAo (about 10-15%) out of the total CHM cases in children from the Republic of Moldova [9].

Congenital aortopathies lead to an increased global cardiovascular mortality rate, both in childhood and in adulthood. These entities include the aortic stenosis (AoS), aortic coarctation (AoC), bicuspid aortic valve (BAV), but also some other genetic diseases involving the aorta: Marfan syndrome (MS), Ehlers-Danlos syndrome, Turner syndrome, and other disorders [4, 8, 10].

According to specialized literature, the estimated incidence of the aortic stenosis makes up 2-11% of the total number of CHMs in children, showing a prevalence of 3-5 cases per 1000 live births. Aortic coarctation accounts for 5-8% of cases with a prevalence of 3 to 10,000 live births [2]. Aortic dilatation occurs in 0.4% of patients with CAo, whereas aortic valvulopathies (e.g. BVA) are the most common malformations (a 1-2% prevalence), exhibiting up to 40% of dissection risks [4].

Aortopathies are sometimes completely asymptomatic in children, compared to adults, thus no suspicion might arise for any complication development. Congenital aortopathies require early diagnosis and prompt therapy to improve the extremely unfavorable prognosis for some cases. Based on these assumptions and beliefs, we would like to emphasize the value of this research project in order to identify the prognostic factors, which might positively influence the future life of CHM children. This present research work, entitled *Risk factors and early diagnosis of complications in congenital aortopathies of children* is aimed to develop a unique, well-systematic approach, as well as to estimate the prognostic key points of CAo complications in children. Based on the aforementioned, the ***purpose*** of this scientific study is as following: to assess the risk and prognostic factors involved in the occurrence of complications among children with congenital aortopathies, in order to highlight their potential probability and develop an integrated algorithm for their early diagnosis.

In order to achieve this purpose, the following **objectives** have been outlined**:**

1. To elucidate the clinical and paraclinical peculiarities in children with congenital aortopathies with or without complications.
2. To study the morphometric parameters of the aorta in children with congenital aortopathies in order to detect early signs of complications (dilatation, aneurysm, dissection, and aortic rupture).
3. To identify the risk and the predictor factors, leading to specific complications of pediatric congenital aortopathies.
4. To develop an integrated algorithm to prevent the potential complications of pediatric congenital aortopathies.

The scientific novelty and originality. A prognostic cohort study was conducted on a group of children from the Republic of Moldova, over a period of 4 years, by analyzing the clinical and paraclinical peculiarities of CAo in children. The study was aimed at monitoring the complication development in pediatric congenital cardiovascular disorders, as well as detecting the risk and predictor factors via the morphometric assessment of the aortic diameters, with a primary follow up, at 6 and 12 months, using the Detroit Z score data. It's the first time, the genetic predisposition for dilatation has been proved, though no evidence for aortic dissection / rupture was found.

The scientific issue solved within this thesis underlies upon outlining clear directions on the management of pediatric CAo, by establishing an early diagnosis, performing an accurate monitoring of the disease evolution (via the aortic morphometry) and raising awareness among the pediatric cardiologists upon the potential risk factors for developing the following complications in children: dilatation, aneurysm, dissection, and aortic rupture.

Theoretical significance of the study. The study results demonstrate the importance of morphometric parameter assessment by the two-dimensional echocardiography and other state-of-the-art techniques, such as the CT angiography of the aorta, used for a good imaging of the aortic geometry and for decreasing the risks of developing sudden lethal complications in patients with CAo.

The applicative value of the PhD thesis. The importance of an early diagnosis in pediatric CAo has been widely discussed, as well as the need for a proper monitoring of the disease evolutionary dynamics via sensitive and aortic imaging methods to assess the types of pathological expansion in the aortic wall and their localization levels. In addition, an integrated algorithm for CAo complications was created based on the *2014 European Society of Cardiology Guide* regarding the diagnosis and treatment of aortic diseases. These findings will allow outlining the children at high risk for developing CAo, according to certain parameters, as well as providing early intervention and prevention of aortic expansive mechanism or even its regression, by administering proper treatment and, thus, significantly reducing the incidence of CAo complications in children.

Implementation of research findings. The study results were obtained during the practical activity at the Pediatric Cardiology Clinic of IMPH Mother and Child Health Care Institute, as well as during the educational and teaching process at the Department of *Pediatrics* of PI *Nicolae Testemitanu* SUMPh, in Chisinau, the Republic of Moldova.

Research findings approval. Some research findings were presented and discussed at various national and international scientific events such as : The annual scientific conference of *Nicolae Testemitanu* SUMPh PI (Chisinau, 2015, 2016, 2017, 2018); National conference with

international participation *Updates in Pediatrics*, dedicated to the 70 year anniversary of *N. Testemitanu* SUMPh (Chisinau, 2015); National Conference with International Participation C*hildren's health problems and ways of solving them* (Chisinau, 2016); International Pediatrics Conference, dedicated to the *Year of Nicolae Testemitanu* (Chisinau, 2017); The National Pediatrics Congress, the 7th edition, *Pediatric emergency medicine and its management*, organized by the Pediatrics Society of the Republic of Moldova and of Romania (Chisinau, 2018); National Pediatrics Conference; the 7th International Medical Congress for Students and Young Doctor *MedEspera* (Chisinau, 2018); the 57th National Congress of Cardiology (Sinaia, Romania, 2018); Congress of Pediatric Cardiology (Iași, Romania, 2018); the 1st International Congress of Hypertension in Children and Adolescents - ICHCA (Valencia, Spain, 2018).

Publications related to PhD thesis. The obtained scientific results were rendered in 24 scientific papers (10 national, 14 international, and 1 with no co-authorship), including 7 articles (3 articles in scientific journals abroad and 4 articles in accredited national scientific journals, category B) and 16 theses.

Keywords: congenital aortopathies, genetic syndromes (Marfan, Turner syndrome, etc.), children, dilation, aneurysm, dissection, aortic rupture.

This research project received the positive opinion of the Research Ethics Committee of the "Nicolae Testemitanu" SUMPh from the Republic of Moldova (report no. 76 of 12.05.2017, by Viorel Nacu, chairman of REC, PhD in medical sciences and professor), within the Department of Pediatrics of "Nicolae Testemitanu" State University of Medicine and Pharmacy.

Summary of the thesis. This research paper includes 103 pages of electronic text and consists of introduction, 4 chapters, conclusions and practical recommendations. The reference list cites 207 bibliographic sources. The thesis comprises 36 tables, 28 figures and 5 annexes.

1. THE RESEARCH MATERIAL AND METHODS

General characteristics of the research and sample size design

An analytical follow-up study was planned to achieve the purpose and objectives of the research. The representative sampling volume was obtained after introducing the data into the formula:

$n = 0.034 \times 0.966 \ (1.96 / 0.05)^2 = 50.47$, and 10.0% for non-response rate, the representative sampling size = 84 children.

The number of patients required within a study group (patients with a Z score value >2 SD) should be no less than 84 respondents viz. representative sample.

Thus, the study group (LI) includes children with aortic diameter changes (Z score> 2 SD), and the control group (L II) - children with no aortic diameter changes (Z score <2 SD, Z score = 2 SD).

During 2016–2020, 180 children with CAo were examined complex, according to the elaborated study protocol, with the objectives of determining risk and prognostic factors in developing CAo complications, with a 6-month follow-up (30%)) and 12 months (60%) from the primary evaluation.

The study sampling was carried out according to the inclusion and exclusion criteria of 180 children with CAo.

Inclusion criteria were as follows:

- children aged between 1 month to 17 years, 11 months and 29 days with CAo (implicit criterion); a confirmed diagnosis of AoS with PG> 30 mmHg, operated / unoperated CAo; patients with BAV and other genetic aorta –related syndromes: Marfan, Turner, etc.;
- the written tutor's consent for participation within the study and the children's assent, aged ≥14 years.

Exclusion criteria:

- children (parents or tutors) who refuse to participate in the study;
- patients with severe concomitant diseases (renal and hepatic impairment, end-stages, severe neurological disorders);
- children with acquired (rheumatic) valvulopathies.

The consent of the parents or the legitimate custodian and the consent of the children aged ≥14 years were obtained; they were not remunerated, they did not bear financial expenses related to participating in the study. The study was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy Nicolae Testemitanu (report Nr. 76 of 12.05.2017).

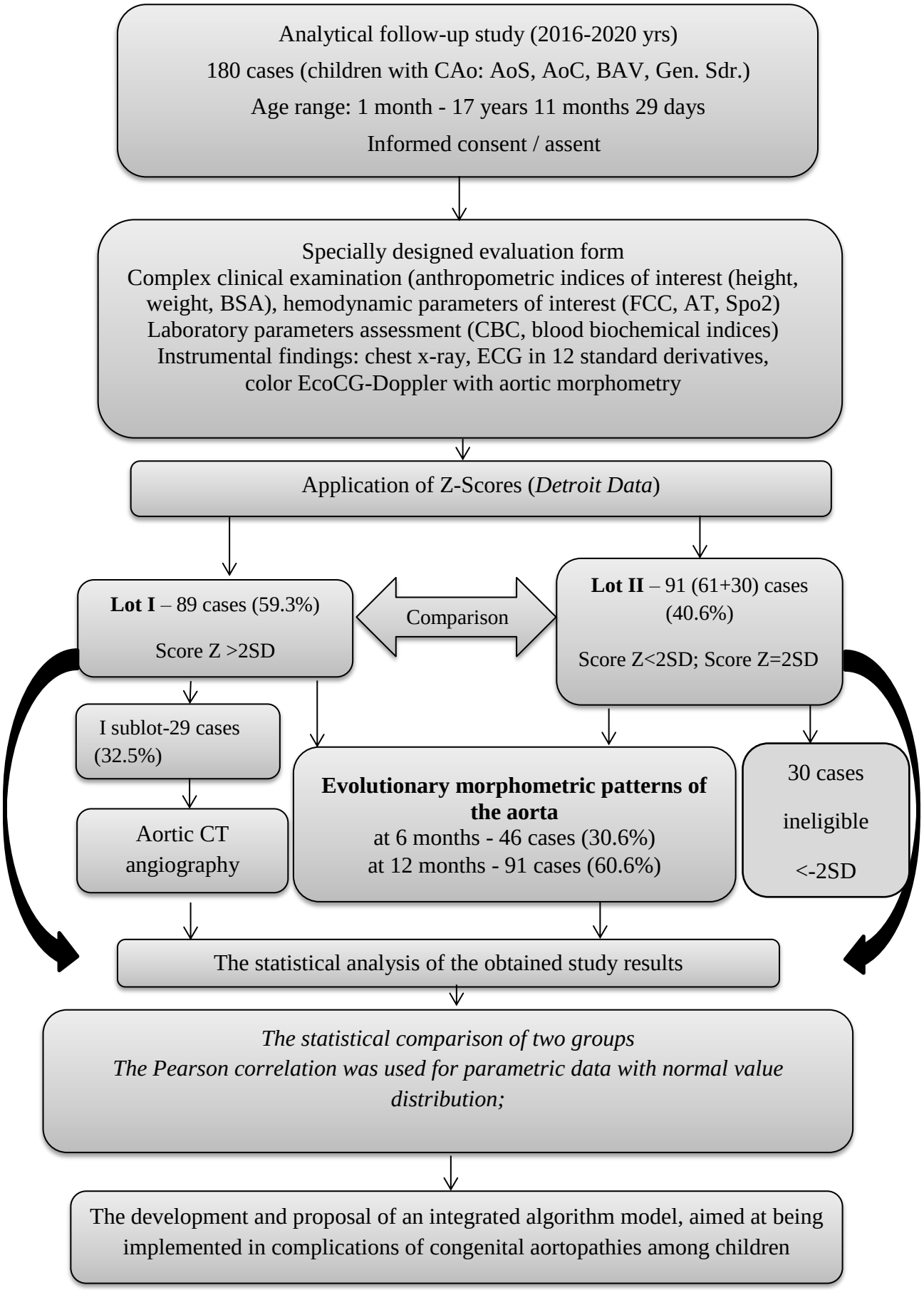

Figure 1. **Study design**

The patients underwent the following assessment stages (*figure 1****).***

Stage 1. 180 children with CAo were admitted within the research, based on the inclusion and exclusion criteria. They formed the general study sample, being subjected to a thorough survey questionnaire regarding the prenatal and postnatal medical history, disease history, current disease status; objective physical examination (anthropometric indices: weight, height, body surface area), laboratory findings of an obstructive CHM type, basic instrumental investigations (two-dimensional EcoCG and color Doppler, aortic CT angiography with contrast media).

Stage 2. The general group was divided into two subgroups, based on a two-dimensional echocardiographic examination and calculation of the Z score. At first, the echocardiographic examination based on the aortic morphometry was performed at 6 aortic levels: the root of the aorta (the valvular ring, sinus Valsalva, and sinotubular junction diameters); the ascending aorta; the aortic arch (between the brachiocephalic trunk and the left subclavian artery); the descending aorta (immediately below the aortic isthmus). The aortic morphometry was performed by using the *Petterson's* criteria with the *Toshiba Aplio 300* echocardiographic model, type MODEL TUS-A300, and by estimating the Z-score, based on *Detroit Data* [3, 5].

Subsequently, the Z score values were calculated online, by introducing the values of the aortic diameter (cm) related to the child's body surface area (height - cm, weight - kg), resulting in self-division of the study sample into two research subgroups : the main lot (L I) included children with aortic diameter changes (Z score>2SD) and the control lot (L II) - children with no aortic diameter changes (Z score ≤2 SD). The first group included 89 children, that is 62 boys and 27 girls, with the mean age of 102,8 ± 7,13 months, and the second group - 91 children (of which 30 children were reported ineligible with a Z score <2 SD), consisted of 61 children , 48 boys and 13 girls, respectively, with a mean age of 121,4 ± 7,2 months.

Stage 3. The evolutionary clinical and paraclinical characteristics of CAo were assessed and compared in both study groups, followed by an assessment of the potential CAo complication development, the risk factors and their predictive factors.

Stage 4. A subgroup was created to include children who underwent the aortic CT angiography, whereas the obtained data were statistically assessed and analyzed while undergoing the aortic morphometric measurement.

Stage 5. The evolutionary particularities in some children from both groups were assessed via a dynamic examination at 6 months (30%) and at 12 months (60%), by comparing some parameters obtained in primary assessment with those from 6 and 12-month intervals, respectively. In addition, some factors were selected as prognostic elements in children who were assessed at 12 months since being admitted to research (depending on the type of evolution - favorable or unfavorable).

Stage 6. An integrated algorithm model regarding CAo complications in children has been developed and proposed for further implementation. Conclusions and practical recommendations have been formulated in order to prevent the occurrence of potential complications in children with CAo.

2. CHAPTER SUMMARY

2.1 Clinical and paraclinical features in children with congenital aortopathies

Study of the demographic, anamnestic and clinical profile of children with congenital aortopathies

To assess the clinical-paraclinical features in children with CAo, a study was performed which included 150 patients eligible with CAo (default criterion), with or without changes in diameter in the aorta.

Analysis of the distribution of study participants according to age groups. In the research were included children aged between 1 month to 17 years 11 months and 29 days. Group I consisted of 89 children (59.3%), of whom 18 (20.2%) aged ≤ 1 year (≤ 12 months), 11 (12.4%) aged 1– 5 years (12–60 months), 29 (32.6%) aged between 5 and 12 years (60–144 months) and 31 (34.8%) aged> 12 years. Group II consisted of 61 (40.6%) children, of whom one (1.6%) was under the age of ≤ 1 year (≤ 12 months), 10 (16.4%) were aged between 1 and 5 years (12–60 months), 26 (42.6%) 5–12 years (60–144 months) and 24 (39.6%) older than 12 years ($\chi 2 = 11.48$; $p< 0.01$).

CAo with changes in diameter in the aorta (score Z>2 SD) in subjects aged ≤ 1 year (≤ 12 months) in 20.2% of cases, confirming the possibility of expansive complications (dilation, dissection, aortic rupture) from an early age.

Analysis of the type of congenital aortopathy depending on the presence / absence of diameter changes in the aorta.

AoS was encountered with a frequency of 38.2% of cases in group I versus 37.7% of cases in group II (p>0.05). AoC was recorded with a frequency of 33.7% cases in the baseline group versus 29.5% cases in the control group (p> 0.05). BAV was found with a frequency of 23.6% of cases in group I versus 29.5% in group II (p>0.05). *Genetic syndromes* with aortic involvement were recorded with a frequency of 4.5% cases in the baseline group versus 3.3% cases in the control group (p> 0.05). The results are shown in Figure 2.

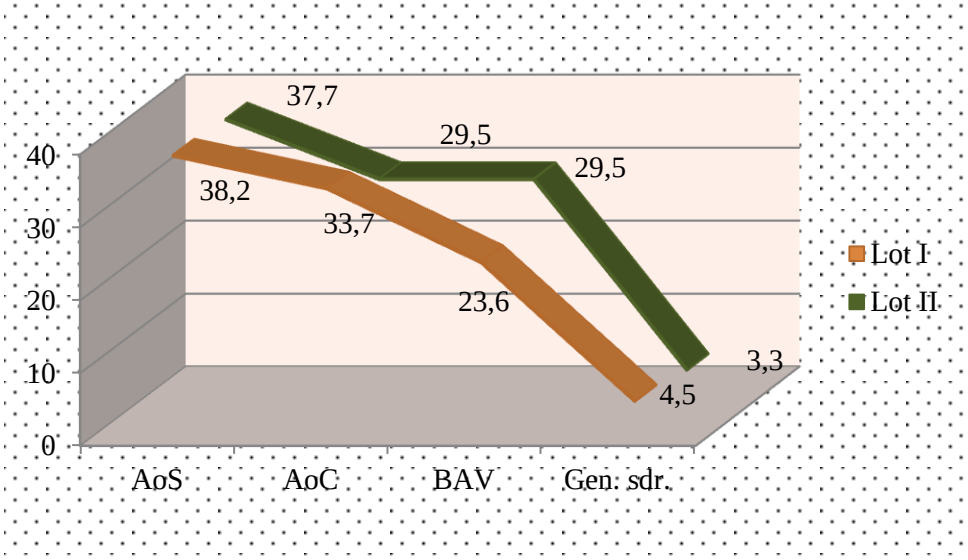

Figure 2. **Type of congenital aortopathy in the children in the study depending on the presence / absence of diameter changes in the aorta**

Note: *AoS-aortic stenosis; AoC-aortic coarctation; BAV-bicuspid aortic valve; Sdr. gen.-genetic syndromes; p> 0.05;*

Analysis of some elements of the anamnesis of the children taken in research. The study of the anamnesis was directed towards the identification of some risk factors that could lead to the development of complications in children with Cao.

The presence of CAo in relatives of grades I-II in the baseline group was attested in 30 (33.7%) children versus 59 (66.3%), and in the control group - in 22 (36.1%) vs 39 (63.9%) subjects ($p<0.05$).

Age of diagnosis of CAo. This diagnosis was established at 43.29 ± 6.28 months (3.5 years) in group I and at 29.5 ± 6.59 months (2.5 years) in group II ($p<0.05$).

The spectrum of clinical manifestations. In both groups, the participants had signs distinctive for the clinic of an CAo. Tachypnea was recorded in 54 (60.7%) children in group I and in 41 (67.2%) in group II. Presyncopal conditions (with high specificity in the case of CAo) accounted for 6 (6.7%) children in the baseline group and 9 (14.8%) in the control group. Syncopes were noted in 2 (2.2%) children with CAo with changes in aortic diameter and in 4 (6.6%) without changes in aortic diameter. Chest pain was present in 44 (49.4%) subjects of group I versus 33 (54.1%) of group II. Fatigue was found in 42 (47.2%) children in the baseline group vs. 35 (57.4%) in the control group ($p>0.05$). Analyzing the complains according to the group, we noticed that, regardless of the presence / absence of diameter changes in the aorta, the children presented the same symptomatic palette, without statistical differences.

Study of some hemodynamic parameters. *Blood pressure*, a hemodynamic parameter with an impact on the pathophysiology of the expansive mechanism researched in children with CAo and found in the literature as a risk factor in some complications of CAo in children such as aortic aneurysms was evaluated on the research groups and presented the following values : Mean SBP expressed as the mean of the Z Score (SD) / percentiles in group I was - 1.37 ± 0.18 / 91% versus group II 0.82 ± 0.16 / 79%, ($p<0.05$). DBP did not show statistical value, only trend, namely in group I: 1.12 ± 0.15 / 87% versus group II 0.95 ± 0.13 / 83%, $p>0.05$).

Paraclinical features (laboratory, radiological, electrocardiographic parameters) in children with congenital aortopathies.

Analysis of biochemical parameters. The children enrolled in the research were also evaluated in the light of laboratory indices recommended by the NCP in obstructive CHM in children. Considering the fact that the subjects included in the study are with valvulo-vascular obstructive CHM, we analyzed the values and correlations of some parameters more specific to a CHM within the biochemical ones (ALAT, ASAT, CK-MB, LDH). No statistical differences were recorded in the values of the indicators mentioned in the research groups ($p>0.05$).

Evaluation of manifestations at the radiological examination. According to the obtained results, at the radiological examination, data on the increase of LV size were recorded in 29 (32.6%) children in the baseline and in 14 (23.0%) in the control group; prominence of the aortic bud was recorded in 49 (55.1%) subjects in the group with increasing changes in diameter in the aorta and in 34 (55.7) in the group without changes in aortic diameter; the increase of the pulmonary hilums was detected in 10 (11.4%) children from the basic group and in 4 (6.6%) from the control group ($p>0.05$).

Analysis of the variability of electrocardiographic parameters. The presence of rhythm and driving disorders was determined, and left ventricular hypertrophy (LVH) was identified in children from the groups included in the research. Rhythm and driving disorders were recorded in 30 (33.7%) children in the baseline group and in 27 (44.3%) in the control group ($p>0.05$).

HVS was present in 17 (19.1%) children of those with CAo with expansive changes of aortic diameter and in 9 (14.8%) of those without expansive changes of aortic diameter ($p>0.05$). According to the results obtained in the study, ECG in 12 standard leads, being a method with low sensitivity, can not be used to establish the diagnosis of heart failure and / or complications in these patients.

Morphometric echocardiographic features of the aorta in children with congenital aortopathies

Echocardiographic evaluation of aortic arch morphometry. Advances in the field of color Doppler EcoCG and the application of this method in the investigation of aortic arch morphometry allow the determination of the risk of development and / or changes in diameter already occurring in the aorta. The possibility of early identification by echocardiography of the risk and / or the presence of a complication is very important both in the practice of pediatric cardiology and in that of the adult.

The types of congenital aortopathies present in the children in the study, determined echocardiographically. The study included four types of CAo: AoS - 57 cases (38.0%), AoC - 48 cases (32.0%), BVA - 39 cases (26.0%) and genetic syndromes involving aorta - 6 cases (4.0%), (Figure 3).

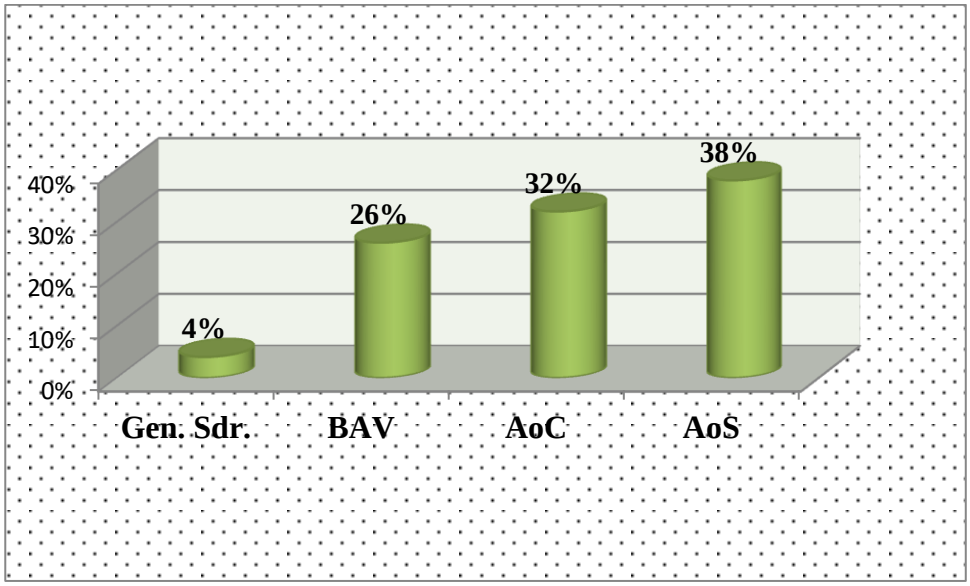

Figure 3. **The structure of the types of congenital aortopathies in children included in the research**

Note: *AoS-aortic stenosis; AoC-aortic coarctation; BAV-bicuspid aortic valve; Gen.sdr.-genetic syndromes;*

Aortic diameters and Z score. The diameters were estimated at six segments of Ao, being related to the area of the body surface. Z-score assessment - a method of highlighting the deviation of the value of a certain parameter evaluated from the average population specific to size or age, used in both cardiology and pediatric echocardiography [26] - was performed in subjects with or without changes in diameter in the aorta. An increased Z-score was considered informative for the suspicion and detection of progressive dilation of aortic diameters in a child with CAo, warning the clinician of the risk of developing a complication even during harmonious physical development.

Aortic diameters of CAo children in group I through the Z score. In the research, the evaluation of the aortic diameters (Ø) was performed based on the Z score, obtaining the following results:

Z score of Ao valve ring Ø. The value of the score Z <2 SD was recorded at 61 (68.5%), and ≥2 SD – at 28 (31.5%) participants ($\chi 2 = 23.5$; $p = 0$).

Z score of the Valsalva sinus Ø. The value of the Z <2 SD score was attested in 66 (74.2%), and ≥2 SD – in 23 (25.8%) children ($\chi 2 = 18.6$; $p = 0$).

Z score of sinotubular junction Ø. The value of the Z <2 SD score was present in 82 (92.1%), and ≥2 SD - in 7 (7.9%) subjects ($\chi 2 = 5.03$; $p < 0.05$).

Z score of ascending Ao Ø. The value of the score Z <2 SD was recorded at 44 (49.4%), and ≥2 DS - at 45 (50.6%) participants ($\chi 2 = 44.06$; $p = 0$).

Z score of aortic arch Ø. The value of the Z <2 SD score was present in 76 (85.4%), and ≥2 SD – in 13 (14.6%) subjects ($\chi 2 = 9.7$; $p < 0.01$).

Z score of descending Ao Ø. The value of the Z <2 SD score was noted in 51 (57.3%), and ≥2 SD – in 38 (42.7%) children ($\chi 2 = 34.8$; $p = 0$). The respective data are presented in Figure 4.

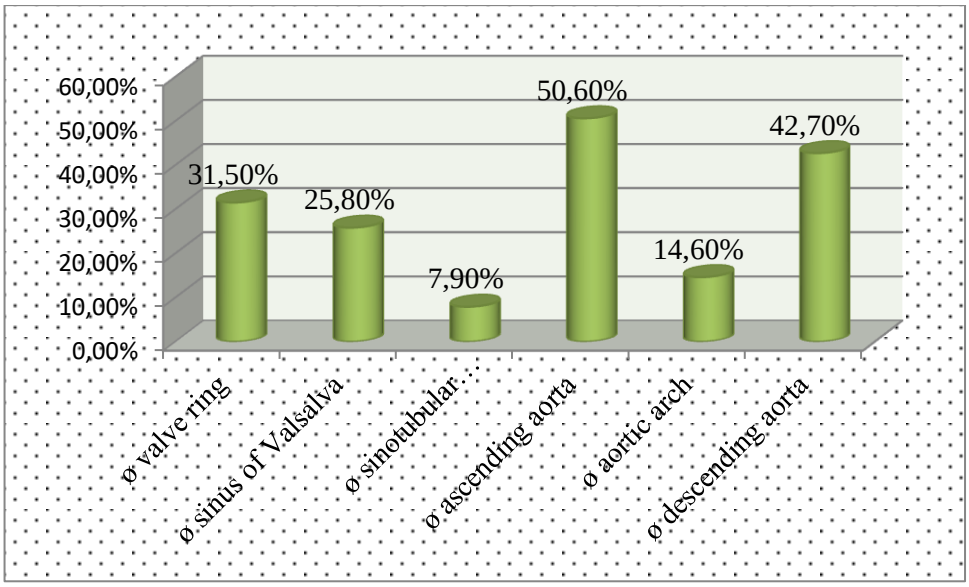

Figure 4. **Aortic diameter values > 2** SD **of the Z score in CAo children in the research group**

Analysis of the correlation coefficient of aortic diameters at the level of the six segments of the aorta

A strong correlation between the diameters of the evaluated Ao segments demonstrates a dilation at at least a portion of the researched ones, becoming a risk factor for the growth of the other aortic segments as well.

Diameter of the aortic valve ring. In the performed research, the diameter of the aortic ring showed a strong positive correlation with II (r=0,8**, p <0,001), III (r=0,8**, p<0,001), IV (r=0,7**, p<0,001) and an average positive correlation with V (r=0,5**, p<0,01) and VI (r = 0.5 **, p<0.01).

Valsalva sinus diameter. The diameter of the Valsalva sinus showed a strong positive correlation with I (r=0,8**, p<0,001), III (r=0,9**, p<0,001), IV (r=0,7**, p<0,001 and a positive correlation of medium intensity with V (r=0,5**, p<0,01) and VI (r=0,5**, p<0,01).

The diameter of the sinotubular junction. The given diameter, being a component part of the aortic root, showed a strong positive correlation with I (r=0,8**, p<0,001), II (r=0,9**, p<0,001), IV (r=0,7**, p<0,001), V (r=0,6**, p<0,001) and VI (r=0,6**, p<0,001).

Diameter of the ascending aorta. The ascending Ao diameter showed a statistically significant correlation with almost all aortic diameters, probably due to the large surface area it occupies and the direct action it exerts on the other diameters, namely: I (r=0,7**, p<0,001), II (r=0,7**, p<0,001), III (r=0,7**, p<0,001), V (r=0,6**, p<0,001), VI (r=0,5**, p<0,01). The correlations are shown in Figure 5.

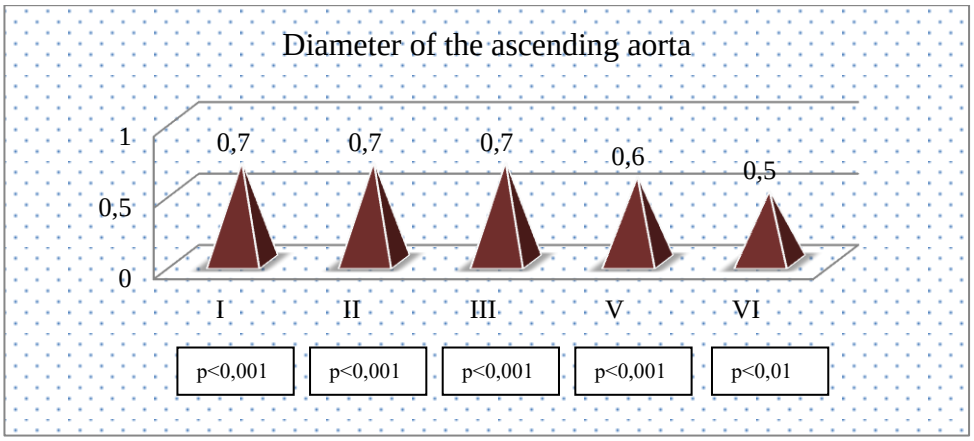

Figure 5. **Correlation between the diameter of the ascending aorta and the other five aortic diameters**

Note: coding: Ø of the valve ring - I, Ø of the Valsalva sinus - II, Ø of the sinotubular junction - III, Ø of the ascending aorta - IV, Ø of the aortic arch - V, Ø of the descending aorta - VI;

Diameter of the transverse aortic arch. It registered a direct type correlation, of moderate intensity with I (r=0,6**, p<0,01), II (r=0,5**, p<0,01), III (r=0,6**, p<0,01) and VI (r=0,5**, p<0,01).

Diameter of the descending aorta. The diameter of the descending aorta showed a direct correlation of moderate intensity with the other five: I (r=0,5**, p<0,01), II (r=0,5**, p<0,01), III (r=0,6**, p<0,01), IV (r=0,5**, p<0,01), V (r=0,5**, p<0,01).

Imaging features of the aorta determined by computed tomography in children with congenital aortopathies.

The study consisted of a sublot of CAo children selected according to CAo type and high risk of developing complications, which were examined by angio-CT of the aorta, with three-dimensional evaluation of its diameters and geometry.

The following parameters, considered essential in CAo, were evaluated: age, sex, BSA, extracardiac aortic diameters.

Researched diameters of the aorta. Ao diameters were reported to BSA, with an average of 0.43 ± 0.09, subsequently interpreted by the Z score, respectively in 50% of children a Z score was ≥2 SD and in another 50,0% - ≤ ± 2 SD compared to the echocardiographically investigated group.

Valsalva sinus diameter. A Z score ≥2 SD was noted in 50,0% of children.

The diameter of the sinotubular junction. The sinotubular junction is an aortic segment less exposed to risk factors with expansive action, therefore the respective portion of the aorta is affected less often, showing a Z score ≥2 SD in about 20,0% of cases.

Diameter of ascending Ao. The ascending aorta is the one that requires the most attention and a morphometric evaluation in dynamics, because the highest percentage of development of dilation complications in CAo is recorded at this level. In the sublot of children studied, it was established that only 10,0% of cases had an ascending aortic dilatation, explained by the type of CAo and the prevalence of poststenotic dilatation compared to prestenotic in AoC.

Diameter of aortic arch. The aortic arch branches into the most important vascular ducts, being exposed to the risk of dilation due to tubular discontinuity, which has a Z score ≥2 SD in about 10,0% of cases.

Diameter of descending Ao. A score Z ≥2 SD was determined in over 50,0% of children, the explanation being the presence at this level of the stenotic gradient, the narrow jet and the increased speed of blood circulation - factors involved in the mechanism of expansion of Ao, with high risk development of the aneurysm or dissection at this level.

The data obtained are presented in Figure 6.

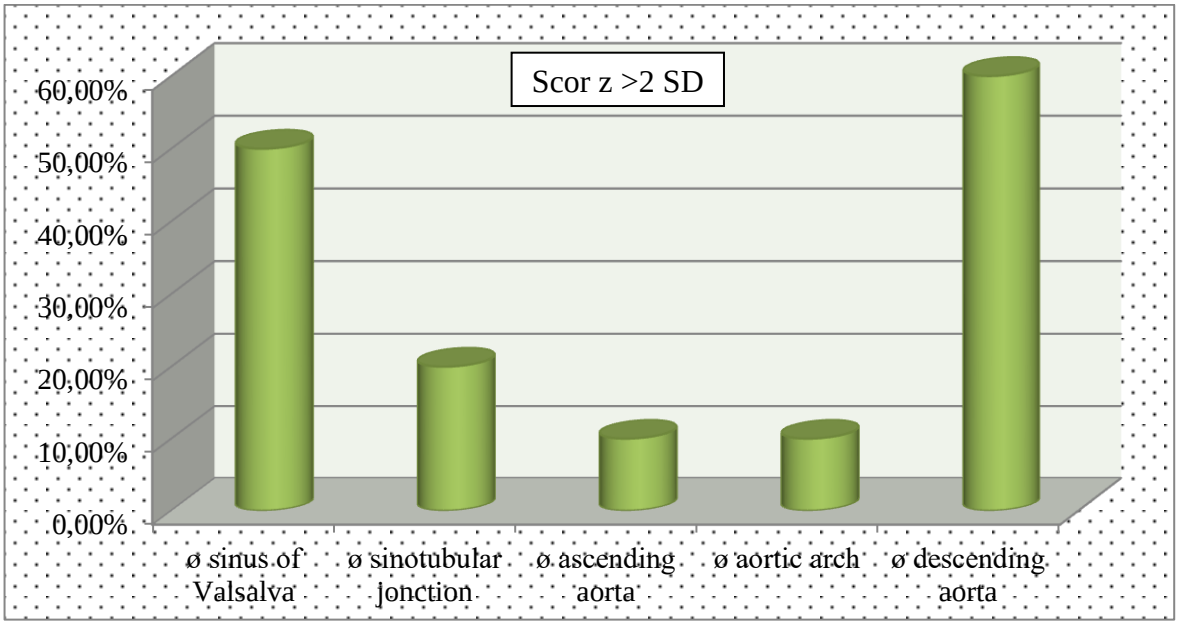

Figure 6. **Morphometric study of the aortic arch by Z score analysis (anthropometric + angiotomographic data)**

Three-dimensional analysis of the aorta by angio-CT in children with CAo offers a greater potential for analysis of aortic geometry, with the establishment of an early diagnosis of complications such as aneurysm, dilation or dissection of Ao. Following the study, values close to the angi - CT measurements were observed with those from transthoracic echocardiography, for the diameter of the Valsalva sinus, the aortic club and the descending aorta. The clear superiority of computed angiography over echocardiography was demonstrated by identifying children with Z>2 SD score diameters in 50.0%, Figure 7.

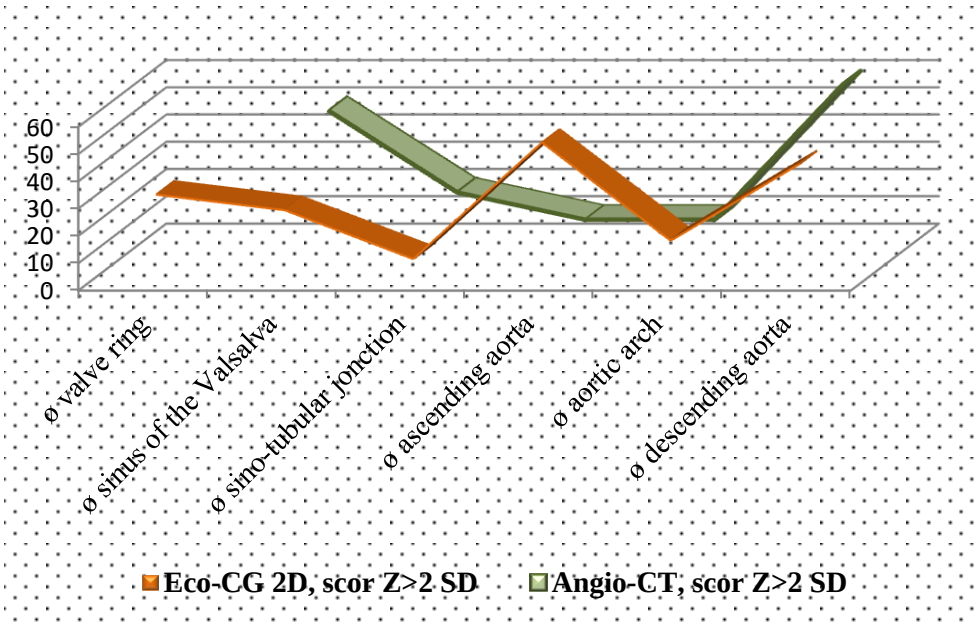

Figure 7. **Graph of the difference of aortic diameters expressed in Score Z (mean ± SD) between 2D echocardiographic and tomographic (CT) measurements.**

2.2. Evolutionary features and risk factors for complications of congenital aortopathies in children

Dynamics of Z scores of thoracic aortic segments in children with CAo in group I, 6 months after the initial assessment. From the moment of enrollment up to six months, in the group of children with CAo with increasing diameter changes it was observed that the parameters of the Z scores of the aortic diameters at the researched levels did not differ by a statistical veracity. The results are presented in table 1.

• *Z-score of the valve ring diameter* in children with CAo in the dynamics from six months after the initial assessment did not show a statistically significant increase in the research group: 1.58 ± 0.17 versus 1.52 ± 0.15 to 6 months with an increase of 0.13 ± 0.10 (p>0.05).

• *Z score of Valsalva sinus diameter* in these children at the initial assessment was 1.59 ± 0.11 and at 6 months 1.64 ± 0.19, recording an increase of 0.01 ± 0.072, (p>0.05).

• *Z-score of the diameter of the sinotubular junction* six months after the initial assessment showed no changes: 1.38 ± 0.10 versus 1.35 ± 0.192, and a dynamics of -0.006 ± 0.07, (p>0.05).

• *Z score of ascending aortic diameter* was at the initial stage on average 2.27 ± 0.09 at 6 months, 2.27 ± 0.14, the evolution of -0.04 ± 0.07 SD, p>0.05 .

• *Z-score of aortic arch diameter* in children with CAo six months after initial assessment was not statistically true: 1.05 ± 0.09 versus 1.26 ± 0.15 at 6 months, modified by 0.06 ± 0,04 (p>0.05).

• *Z score of the diameter of the descending aorta* at the initial stage was: 1.87 ± 0.11, at 6 months it was 2.29 ± 0.16, the dynamics of -0.01 ± 0.07 (p>0.05).

Table 1. **Dynamics of Z scores of thoracic aortic segments in children with CAo from group I, 6 months after the initial assessment**

Variables	Sample						p
	Lot I (initial)		Lot I (6 month)		Lot I (dynamics 6 month)		
	N	M ± m (scor Z)	N	M ± m (scor Z)	N	M ± m (scor Z)	
Ø valve ring	89	1.58±0,17	30	1.52±0.15	30	0.13±0.10	>0.05
Ø sinus of Valsalva	89	1.59±0,11	30	1.64±0.19	30	0.01±0.072	>0.05
Ø sinotubular jonction	89	1.38±0,10	30	1.35±0.19	30	-0.006±0.07	>0.05
Ø ascending Ao	89	2.27±0.09	30	2.27±0.14	30	-0.04±0.07	>0.05
Ø aortic arch	89	1.05±0.09	30	1.26±0.15	30	0.06±0.04	>0.05
Ø descending Ao	89	1.87±0.11	30	2.29±0.16	30	-0.01±0.07	>0.05

Dynamics of Z-scores of thoracic aortic segments in children with CAo from group II, 6 months after the initial assessment. Children with unchanged aortic diameters at the six-month assessment from baseline showed slightly elevated Z-score values at the level of the aortic club and descending aorta in Table 2.

• *Z-score of the valve ring diameter* in children with CAo from group II in the dynamics at six months after the initial assessment did not show a statistically significant increase: 0.64 ±0.15 versus at 6 months 0.83 ± 0.33 with an increase of 0.10 ± 0.07, (p>0.05).

• *Z score of Valsalva sinus diameter* in these children at the initial assessment was 0.42 ± 0.17 and at 6 months 1.77 ± 0.34, recording an increase of 0.11 ± 0.06, (p>0.05).

• *Z-score of the diameter of the sinotubular junction* six months after the initial assessment showed no changes: 0.36 ± 0.14 versus 0.43 ± 0.16, and a dynamics of 0.03 ± 0.05, (p>0.05).

• *Z score of the diameter of the ascending aorta* was at the initial stage on average 1.84 ± 0.11 at 6 months, 1.93 ± 0.18, the evolution of 0.04 ± 0.03 SD, p>0.05.

• *Z-score of the diameter of the aortic arch* in children with CAo six months after the initial assessment was statistically true: 0.75 ± 0.07 versus 0.90 ± 0.10 at 6 months, modified by 0.17 ± 0, 04, (p<0.001).

• *Z score of the diameter of the descending aorta* at the initial stage was: 1.44 ± 0.10, at 6 months it was 1.66 ± 0.20, dynamics of 0.09 ± 0.03, (p<0.05).

Table 2. Dynamics of Z scores of thoracic aortic segments in children with CAo in group II, 6 months after the initial assessment

Variables	Sample						p
	Lot II (initial)		Lot II (6 months)		Lotul II (dynamics 6 months)		
	N	M ± m (scor Z)	N	M ± m (scor Z)	N	M ± m (scor Z)	
Ø valve ring	61	0.64±0.15	16	0.83±0.33	16	0.10±0.07	>0.05
Ø sinus of Valsalva	61	0.42±0.17	16	1.77±0.34	16	0.11±0.06	>0.05
Ø sinotubular jonction	61	0.36±0.14	16	0.43±0.16	16	0.03±0.05	>0.05
Ø ascending Ao	61	1.84±0.11	16	1.93±0.18	16	0.04±0.03	>0.05
Ø aortic arch	61	0.75±0.07	16	0.90±0.10	16	0.17±0.04	**<0.001**
Ø descending Ao	61	1.44±0.10	16	1.66±0.20	16	0.09±0.03	**<0.05**

Dynamics of Z scores of thoracic aortic segments in children with AoC from group I, 12 months after the initial assessment. The children with CAo from group I at the 12-month evaluation showed increasing dynamic values of the Z score at the level of the aortic valve ring, ascending aorta, aortic arch and at the level of the descending aorta with important statistical truths, table 3.

• *Z-score of the valve ring diameter* in children with CAo from group I in the dynamics from 12 months after the initial assessment showed a statistically significant significant increase: 1.58 ± 0.17 versus 12 months 2.00 ± 0.15 with an increase of 0.37 ± 0.10 (p>0.01).

• *Z-score of Valsalva sinus diameter* in these children at the initial assessment was 1.59 ± 0.11 and at 12 months 1.77 ± 0.15, recording a dynamics of 0.17 ± 0.09, (p>0,05).

• *Z-score of the diameter of the sinotubular junction* at 12 months after the initial assessment did not show statistically significant values: 1.38 ± 0.10 versus 1.40 ± 0.15, and a dynamics of -0.02 ± 0.09, (p>0,05).

• *Z score of the diameter of the ascending aorta* was at the initial stage on average 2.27 ±0.09 at 12 months, 2.56 ± 0.10, the evolution of 0.17 ± 0.06 SD, p<0.01.

• *Z-score of the diameter of the aortic arch* in children with CAo at 12 months after the initial assessment showed important statistical truth: 1.05 ± 0.09 versus 1.69 ± 0.12 at 12 months, an increasing dynamics of 0.76 ± 0.11 (p<0.001).

• *Z score of the diameter of the descending aorta* at the initial stage was: 1.87 ± 0.11, at 12 months it was 0.24 ± 0.07, the dynamics of 0.24 ± 0.07 (p <0.001).

Table 3. **Dynamics of Z scores of thoracic aortic segments in children with CAo in group I, 12 months after the initial assessment**

Variables	Sample						p
	Lot I (initial)		Lot I (12 months)		LotI (dynamics 12 months)		
	N	M ± m (scor Z)	N	M ± m (scor Z)	N	M ± m (scor Z)	
Ø valve ring	89	1.58±0,17	56	2.00±0,15	56	0.37±0,10	**<0.001**
Ø sinus of Valsalva	89	1.59±0,11	56	1.77±0,15	56	0.17±0,09	>0.05
Ø sinotubular jonction	89	1.38±0,10	56	1.40±0,15	56	-0.02±0,09	>0.05
Ø ascending Ao	89	2.27±0,09	56	2.56±0,10	56	0.17±0,06	**<0.01**
Ø aortic arch	89	1.05±0,09	56	1.69±0,12	56	0.76±0,11	**<0.001**
Ø descending Ao	89	1.87±0,11	56	2.23±0,13	56	0.24±0,07	**<0.001**

Dynamics of Z scores of thoracic aortic segments in children with CAo from group II, 12 months after the initial assessment. Children with CAo from group II at the 12-month evaluation showed increasing dynamic values of the Z score at the level of the aortic valve ring, the aortic arch and at the level of the descending aorta with important statistical truths, table 4.

• *Z score of the valve ring diameter* in children with CAo from group II in the dynamics from 12 months after the initial assessment showed a statistically significant increase, (p>0.01), initial stage: 0.64 ± 0.15, at 12 months: 0.77 ± 0.19, with an increase of 0.32 ± 0.10.

• *Z score of Valsalva sinus diameter* in these children at the initial assessment was 0.42 ± 0.17 and at 12 months 0.38 ± 0.22, recording a dynamics of -0.04 ± 0.11, (p>0.05).

• *Z-score of the diameter of the sinotubular junction* at 12 months after the initial assessment did not show statistically significant values: 0.36 ± 0.14 versus, 0.36 ± 0.23 and a dynamics of 0.07 ± 0.17, (p>0,05).

• *Z score of the diameter of the ascending aorta* was at the initial stage on average 1.84 ± 0.11 at 12 months, 2.14 ± 0.12, the evolution of 0.22 ± 0.11 SD, p>0.05.

• *Z score of the diameter of the aortic arch* in children in group II with CAo at 12 months after the initial evaluation showed important statistical truth: 0.75 ± 0.07 versus 2.00 ± 0.19 at 12 months, an increasing dynamic of 1.25 ± 0.19 (p<0.001).

• *Z score of the diameter of the descending aorta* at the initial stage was: 1.44 ± 0.10, at 12 months it was 1.84 ± 0.13, the dynamics of 0.48 ± 0.13 (p<0.01).

Tabel 4. **Dynamics of Z scores of thoracic aortic segments in children with CAo from group II, 12 months after the initial assessment**

Variables	Sample						p
	Lot II (initial)		Lot II (12 months)		Lot II (dynamics 12 months)		
	N	M ± m (scor Z)	N	M ± m (scor Z)	N	M ± m (scor Z)	
Ø valve ring	61	0.64±0.15	35	0.77±0.19	35	0.32±0.10	**<0.01**
Ø sinus of Valsalva	61	0.42±0.17	35	0.38±0.22	35	-0.04±0.11	>0.05
Ø sonotubular jonction	61	0.36±0.14	35	0.36±0.23	35	0.07±0,17	>0.05
Ø ascending Ao	61	1.84±0.11	35	2.14±0,12	35	0.22±0.11	>0.05
Ø aortic arch	61	0.75±0.07	35	2.00±0.19	35	1.25±0.19	**<0.001**
Ø descending Ao	61	1.44±0,10	35	1.84±0,13	35	0.48±0,13	**<0.01**

Risk factors for complications of congenital aortopathies in children.

The research highlighted the risk factors with potential for the development of a complication (anamnestic, demographic, clinical-paraclinical parameters), which would condition the unfavorable evolution of an CAo with the development of dilation, aneurysm, dissection or aortic rupture.

Study of demographic, anamnestic, genetic and familial factors in children studied according to the presence / absence of diameter changes in the aorta

Age. Children aged <12 months had a higher prevalence in group I compared to group II (20.2% vs 1,6%), and those aged 13–60 months, 61–144 months and >144 months had a higher prevalence in group II compared to group I (respectively 16.4% vs 12.4%; 42.6% vs 32.6% and 39.4% vs 34.8%; p<0.01). These data show that children with aortic dilatations prevail at an early age, and with increasing age the risk of dilation is equal to both groups of children with CAo.

Genetic aspects and family factors. Both genetic and familial factors prevailed in group I compared to group II (33.7% vs 16.3%; p<0.05, and 51.6% versus 34.4, p<0.05). The results obtained are presented in Table 5.

Table 5. **Structure of risk factors (genetic, familial, hemodynamic and anamnestic) in group I compared to group II**

	Risk factors	Lot I	Lot II	P
Genetic	Syndromic, non-syndromic genetic defects	33.7%	16.3%	**<0.05**
Familial	The presence of relatives with gr. I-II with CAo / complications (aneurysm, dissection, sudden death)	51.6%	34.4%	**<0.05**
Hemodynamic	Mean systolic blood pressure (Z score / percentile)	1.37±0,18/ 91%	0.82±0,16/ 79%	**<0.05**
	Mean diastolic blood pressure (Z score / percentile)	1.12±0.15 / 83%	0.95±0.13 / 83%	**>0.05**
Anamnestic	Age at which the diagnosis of congenital / genetic aortopathy was established (months)	43.29±6.29	29.5±6.59	**<0.05**

Hemodynamic factors. High BP values also play a major role in the mechanism of aortic dilation in children, especially in those with obstructive-stenotic CAo (ex, AoC), respectively a statistical difference was present in the researched groups, marking o increased mean BP in the group with increasing diameter changes in the aorta compared to the group without such changes (1,37±0,15 / 91% versus 0,82±0,16 / 89%, p<0,05). The DBP values did not register statistically true values between the two groups (1,2±0,15 / 83% versus 0,95±0,13 / 83%), p>0,05.

2.3 Factors with a prognostic role in the complications of congenital aortopathies in children.

Early detection and prevention of the development of the area prone to complication in AoC in children, by studying predictive factors, was one of the objectives of the research. To be performed, a mathematical-statistical analysis of the group of children (n=91) with CAo and predisposition to complications was performed 12 months after the initial assessment.

The discriminant analysis in which all the clinical-paraclinical factors investigated were subjected to a selective and thorough evaluation highlighted six important factors, with statistically significant value, which distinguish the two subgroups. These impact factors were: decreased tolerance to physical exertion, dilated aortic diameter at the level of the aortic valve, dilated aortic diameter at the sinotubular junction, dilated diameter at the level of the ascending aorta, dilated aorta at the level of the arch, and changes in diameter in the left ventricle (Table 6).

Table 6. **Prognosis of complications in children with congenital aortopathies**

Parameters	**Lot I_R; N=52**	**Lot II_R; N=39**
1. Decreased tolerance to physical exertion	43 (82.7%)	37 (94.9%)
2. Aortic diameter at the level of the aortic valve (Score Z ±2 SD)	1.65±0.14	0.51±0.21
3. Aortic diameter at the sinotubular junction (Score Z ±2 SD)	1.46±0.14	0.42±0.18
4. Diameter at the level of the ascending aorta (Score Z ±2 SD)	2.38±0.12	1.90±0.12
5. Diameter of aorta at the level of the arch (Score Z ±2 SD)	0.79±0.11	0.92±0.12
6. Changes in diameter in the left ventricle (Score Z ±2 SD)	0.00±0.00	0.13±005
Prognosis	**78.85%**	**71.79%**

Discriminant analysis of these six variables allows us to predict the occurrence of complications: dissection, aneurysm, aortic rupture in children with CAo with changes in aortic diameter in 78.85% of cases and in those without changes in aortic diameter in 71,79% of cases.

General conclusions

1. The study found that in children with congenital aortopathies (CAo) with/without changes in increasing aortic diameters there are no differences in clinical and paraclinical aspects (symptomatology, objective data, laboratory data, instrumental - ECG 12 standard leads, thoracic Rg), confirming the subtlety and difficulty of differentiating an CAo prone to, dissection or aneurysm or aortic rupture.

2. As a result of the research of children with AoC, the presence of aortic dilation was confirmed (Z score>2 SD), in aortic coarctation: at the level of the diameter of the valve ring (22.9%), of the Valsalva sinus (25.0%), of the sino-tubular jonction (8.3%) and aortic arch (20.8%); in aortic stenosis and bicuspid aortic valve: at the diameter of the ascending (36.8%) and descending aorta (31.6%); in genetic syndromes: at the diameter of the valve ring (33.3%) and the ascending aorta (50.0%). The analysis of the correlation coefficient between the 6 diameters certifies the hypothesis according to which a dilation at at least one aortic segment becomes a risk factor for its development at the other levels of the aortic arch.

3. In the study, the 6-month follow-up of the values of the Z scores of the aortic diameters in the research group did not show statistical differences at any level of the aortic diameter, while at the 12-month evaluation from the beginning they were assessed changes in the increase of aortic diameters at the level of: the valvular ring ($p<0.01$), the ascending aorta ($p<0.01$), the aortic arch ($p<0.001$) and the descending aorta ($p<0.001$). In group II, the evolution of the Z scores of the diameters of the thoracic aorta at 6 months registered a significant increase in the aortic arch ($p<0.001$) and that of the descending aorta ($p<0.05$), while at 12 months from the beginning they showed values increased in valve ring diameter ($p<0.01$), aortic arch diameter ($p<0.001$) and descending aorta ($p<0.01$).

4. In the study, 7 risk factors with statistical significance were identified for the probability of occurrence of a specific CAo complication: demographic factors (age), genetic factors (syndromic, non-syndromic genetic defects), anamnestic factors (child's age when diagnosing AoC) , familial factors (presence of relatives of grades I-II with CAo / complications (aneurysm, dissection, sudden death), hemodynamic factor (BP), factors related to the type of aortic dilation $p<0.05$).

5. The discriminant analysis of the group of predictive factors (decreased tolerance to physical exertion, dilation of the aortic diameter at the level of the aortic valve, sinotubular junction, ascending aorta, aortic arch and changes in the diameter of the left ventricle) predicted the occurrence of complications: aneurysm, aortic rupture in children with **CAo with changes in aortic diameter** in 78.85% of cases and in those **without changes in aortic diameter** in 71,79% of cases.

6. Obtained results allow the development and implementation of an integrated model of algorithm on CAo complications in children based on Guide of the European Society of Cardiology on the diagnosis and treatment of aortic diseases (2014), Guide of the American Cardiology Association / American College of Cardiology on the diagnosis and management of patients with thoracic aortic diseases (2010).

Practical recommendations

1. Children with aortic pathology require a lifelong follow-up, regardless of the initial treatment strategy (medical, interventional or surgical), with a clinical evaluation, with re-evaluation of aortic therapy and imaging. This follow-up requires performing aortic morphometry, with the calculation of Z scores of aortic diameters every 12 months.
2. It is recommended to create a register for children with CAo, in which a record will be kept of the dynamics of aortic diameters, established echocardiographically and, if necessary, by angio-CT.
3. It is proposed to collaborate with other centers that highlight children with congenital aortic diseases (genetic centers, heart surgery), with the implementation of the same unanimous principles of supervision of children with CAo and making a common decision in detecting a complication.

SELECTIVE BIBLIOGRAPHY

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. ESC/EACTS guidelines for the management of valvular heart disease. *European heart journal*. 2017 Aug 26;38(36):2739-91. Available from: 10.1093/eurheartj/ehx391 [Accessed 04.03.2020]
2. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *European heart journal*. 2014 Aug 29;35(41):2873-926. Available from : 10.1093/eurheartj/ehu281 [Accessed la 04.03.2020]
3. Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G, et al. Echocardiography in aortic diseases: EAE recommendations for clinical practice. *European Journal of Echocardiography*. 2010 Sep Available from 1;11(8):645-58.: https://doi.org/10.1093/ejechocard/jeq056 [Accessed la 04.03.2020]
4. Fernandes S, Khairy P, Graham DA, Colan SD, Galvin TC, Sanders SP, et al. Bicuspid aortic valve and associated aortic dilation in the young. *Heart*. 2012 Jul 1;98(13):1014-9. Available from : 10.1136/heartjnl-2012-301773 [Accessed 04.03.2020]
5. Gautier M, Detaint D, Fermanian C, Aegerter P, Delorme G, Arnoult F, et al. Nomograms for aortic root diameters in children using two-dimensional echocardiography. *The American journal of cardiology*. 2010 Mar 15;105(6):888-94. Available from: 10.1007/s00246-018-2025-2 [Accessed 04.03.2020]
6. Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. *Circulation*. 2013 May 21;127(20):2031-7. Available from: 10.1161/CIRCULATIONAHA.112.000483 [Accessed 04.03.2020]
7. Kim JB, Spotnitz M, Lindsay ME, MacGillivray TE, Isselbacher EM, Sundt TM. Risk of aortic dissection in the moderately dilated ascending aorta. *Journal of the American College of Cardiology*. 2016 Sep 13;68(11):1209-19. Available from: 10.1016/j.jacc.2016.06.025 [Accessed 04.03.2020]
8. Lindsay ME. Medical management of aortic disease in children with Marfan syndrome. Current opinion in pediatrics. 2018 Oct 1;30(5):639-44.
9. Protocol clinic național ”Malformațiile congenitale de cord valvulare și vasculare obstructive, fără șunt asociat, la copil”, nr. 146, 2018, p. 8.
10. Sophocleous F, Milano E, Pontecorboli G, Chivasso P, Caputo M, Rajakaruna C, et al. Enlightening the association between bicuspid aortic valve and Aortopathy. *Journal of cardiovascular development and disease*. 2018 Jun;5(2):21. Available from : 10.3390/jcdd5020021 [Accessed 04.03.2020]
11. Zhao Q, Shi K, Yang ZG, Diao KY, Xu HY, Liu X, et al. Predictors of aortic dilation in patients with coarctation of the aorta: evaluation with dual-source computed tomography. *BMC cardiovascular disorders*. 2018 Dec;18(1):124.Available from: 10.1186/s12872-018-0863-8 [Accessed 04.03.2020]

LIST OF SCIENTIFIC PUBLICATIONS AND EVENTS
at which the PhD thesis-related research findings were presented on, entitled
***Risk factors and early diagnosis in complications of congenital aortopathies in children*,**
at the Department of *Pediatrics*, within the PI "Nicolae Testemitanu" SUMPh,
of the PhD candidate, Gavriliuc Natalia

SCIENTIFIC WORKS

- **Articles submitted to scientific journals abroad:**
  - ✓ articles in ISI, SCOPUS journals and other international databases

Гаврилюк Н., Палий И., Ешану В. Факторы, имеющие потенциал развития дилатации аорты у детей с врожденным заболеванием аорты. В: Международный научный медицинский журнал "MEDICUS". Волгоград, Россия, 2017, № 6(18), с. 33-36. ISSN 2409-563X (indexat în bazele: Global Impact Factor, Австралия ResearchBib, Япония).

  - ✓ articles in scientific journals abroad

1. **Gavriliuc N.**, Palii I., Eșanu V., Pîrțu L., CrivceanschI M., Sglimbea A. Fate of coarctation of the aorta complicated with rupture of a postcoarctation giant aneurysm in a child – case raport. In: Romanian Journal of Pediatric Cardiology. Iași, România, 2018, nr. 1(1), p. 21-24. ISSN 2601-579X.
2. **Gavriliuc N.**, Eșanu V., Palii I. Association of metabolic syndrome with congenital aortopathy in the child. Case report. In: Romanian Journal of Pediatric Cardiology. Iași, România, 2018, nr. 1(1), p. 15-17. ISSN 2601-579X.

- **Articles submitted to accredited national scientific journals:**
  - ✓ articles in B-category journals

3. **Gavriliuc N**. Factorii de risc și diagnosticul precoce în complicațiile din aortopatiile congenitale la copii. În: Buletin de perinatologie. 2019, nr. 2(83), p. 42-47. ISSN 1810-5289.
4. Popovici I., Palii I., Liuba P., **Gavriliuc N**. Urmărirea clinică a tratamentului coarctației de aortă cu o nouă generație de dispozitive În: Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale. Chișinău, 2019, nr. 1(61), p. 217-223. ISSN 1857-0011.
5. **Gavriliuc N**., Eșanu V., Palii I. Sindromul metabolic și aortopatiile congenitale la copil: contribuţia la riscul cardiometabolic global – prezentare de caz. În: Buletin de perinatologie. 2018, nr. 4(80), p. 17-20. ISSN 1810-5289.
6. **Gavriliuc N**., Palii I., Ciubotaru A., Repen O., Zahariuc T., Crivceanschi E. Un caz rar de coarctație de aortă, complicată cu ruptură de anevrism gigantic la copil – raport de caz. În: *Buletin de perinatologie*, 2017, nr. 3(75), p. 66-69. ISSN 1810-5289.

- **Abstracts / theses submitted within national or international scientific conferences**

7. **Gavriliuc N.,** Palii I., Eșanu V., Pîrțu, L., Rodoman I. Scorul Z al diametreor aortice la copiii cu aortopatii congenitale. În: *Volum de rezumate. Revista română de Pediatrie. Conferința Națională de Pediatrie "Ghiduri și protocoale în Pediatrie"*. București, România, 3-6 aprilie, 2019, vol. LXVIII (suppl.), p. 24. ISSN 1454-0398.
8. **Гаврилюк Н.В.,** Палий И.И., Ешану В.Г., Пырцу Л.Г., Ешану В.Ф. Осложнения врожденных аортопатий у детей. В: *Сборник тезисов XXI Конгресса педиатров россии с международным участием"Актуальные проблемы педиатрии"*, Москва, 15–17 февраля 2019 г., с. 51.
9. **Gavriliuc N**., Palii I., Revenco N., Eșanu V., Pîrțu L., Jumiga D. Implicații genetice în aortopatiile congenitale la copii. În: *Volum de rezumate. Congresul de cardiologie pediatrică*. Iași, România, 17-19 mai 2018, p. 50. ISSN 2601-6796.
10. **Gavriliuc N**., Esanu V., Pirtu L., Palii I. The impact of arterial hypertension on aorta geometry after surgical repair of aorta coarctation in children. In: *Abstract Book. The 7th*

International Medical Congress for Students and Young Doctor. MedEspera. Chișinău, Republica Moldova, 3-5 mai 2018, p. 51.

11. **Gavriliuc N**., Palii I., Eșanu V., Caraman A. Associated complications of congenital aortopathies in children. In: *Abstracts. The Moldovan Medical Journal. The IVth Congress of Radiology and Medical Imaging of the Republic of Moldova with international participation.* Chișinău, Republica Moldova, 31 mai – 2 iunie 2018, vol. 61, p. 65. ISSN 2537-6373.
12. **Gavriliuc N**., Palii I., Sglimbea A., Ciubotaru A., Caraman A. Substratul genetic în aortopatiile congenitale la copii. În: *Volum de rezumate. Buletin de perinatologie*. Chișinău, Republica Moldova, 2018, nr. 4(80), p. 86. ISSN 1810-5289.
13. **Gavriliuc N**., Eșanu V., Palii I. Interferența dintre aortopatiile congenitale și sindromul metabolic la copil. În: *Volum de rezumate. Revista română de Pediatrie. Conferința Națională de Pediatrie „Progrese în Pediatrie”*. București, România, 21-24 martie 2018, vol. LXVII (suppl.), p. 120. ISSN 1454-0398. 30 P.
14. Ciuhrii O., Palii I., Stamati A., Ivas T., Eșanu V., **Gavriliuc N.** Principii de conduită în miocardita acută virală la copii. În: *Volum de rezumate. Congresul de cardiologie pediatrică.* Iași, România, 17-19 mai 2018, p. 30-31. ISSN 2601-6796.
15. **Gavriliuc N**., Esanu V., Palii I. Arterial hypertension – the impact on aorta geometry after surgical repair of aorta coarctation in children. In: *Abstracts. 1st International Congress of Hypertension in Children and Adolescents (ICHCA).* Valencia, Spain, 9-11 February 2018, p. 16.
16. **Gavriliuc N**., Eșanu V., Pirtu L., Ciubotaru A., Palii I. Patternul diametrelor aorticice la copii cu aortopatii congenitale. În: *Volum de rezumate. Supliment la Revista Română de Cardiologie. Al 57-lea Congres Național de Cardiologie.* Sinaia, România, 19-22 septembrie 2018, vol. 28, p. 106-107. ISSN 2392-6910.
17. **Gavriliuc N.,** Palii I., Eșanu V., Ciubotaru A., Pîrțu L. O combinație de aortopatii congenitale cu multiple implicații terapeutice. Prezentare de caz. În: *Volum de rezumate. Revista Română de Pediatrie. Conferința Națională de Pediatrie „Progrese în Pediatrie”.* București, România, 21-24 martie 2018, vol. LXVII (suppl.), p. 121. ISSN 1454-0398. 33P.
18. **Gavriliuc N**., Palii I., Eșanu V., Pîrțu L., Caraman A. Aortopatiile congenitale la copii. În: *Volum de rezumate. Revista Română de Pediatrie. Conferința Națională de Pediatrie ”Progrese în Pediatrie”.* București, România, 21-24 martie 2018, vol. LXVII (suppl.), p. 120-121. ISSN 1454-0398. 32P.
19. **Gavriliuc N.,** PaliI I., Eșanu V., Zahariuc T., Repen O., Crivceanschi E. Formarea aneurismului gigant în aorta descendentă asociată cu coarctaţie aortică la copil – raport de caz. În: *Volum de rezumate. Congresul de Cardiologie Pediatrică.* Iași, România, 17-19 mai 2018, p. 48. ISSN 2601-6796.
20. Pîrţu L., Palii, I., Revenco N., Eşanu V., **Gavriliuc N**., Moţpan O. Factori de risc în hipertensiunea arterială la copii. În: *Volum de rezumate. Congresul de Cardiologie Pediatrică.* Iași, România, 17-19 mai 2018, p. 93. ISSN 2601-6796.
21. **Gavriliuc N.,** Palii I., Eşanu V., Eşanu V. ș.a. Aortopatiile congenitale: similitudini clinico-evolutive, diagnostice și prognostice. În: *Volum de rezumate. Conferinţa Naţională cu Participare Internaţională „NETINCARE – standarde europene şi bune practici în ocrotirea sănătăţii mamei şi copilului”*. Chişinău, 2016, p. 28-30. ISBN 978-9975-4464-4-0.
22. **Gavriliuc N**., Palii I., Eșanu V., Eșanu V. ș.a. Malformații cardiace congenitale severe la copii. În: *Volum de prezentări și rezumate. Conferința Națională de Pediatrie cu participare internațională „Probleme şi căi de soluționare în asistența medicală copiilor”.* Chişinău, 2016, p. 26-27. ISBN 978-9975-4464-5-7.

23. **Gavriliuc N.,** Palii I., Eşanu V., Eşanu V. Aspecte clinico-evolutive ale aortopatiilor congenitale la copii. În: *Volum de prezentări, postere şi rezumate. Conferinţa Naţională cu participare internaţională "Actualităţi în pediatrie", consacrată celei de-a 70-a aniversări a Universităţii de Stat de Medicină şi Farmacie „Nicolae Testemiţanu"*, în cadrul Expoziției „MoldMedizin & MoldDent". Chișinău, 2015, p. 29.

- **Active participations with communications in scientific forums:**
  - ✓ International events

24. **Gavriliuc N**. Factorii de risc și diagnosticul precoce în complicațiile din aortopatiile congenitale la copii. Conferința națională Bienala Chișinău-Sibiu, ediția a III-a „Interdisciplinaritate în bolile infecțioase pediatrice". Chișinău, Republica Moldova, 16-18 mai, 2019 (raport).
25. **Gavriliuc N.,** Palii I., Revenco N., Eșanu V. ș.a. Implicații genetice în aortopatiile congenitale la copii. Congresul de Cardiologie pediatrică. Iași, România, 17-19 mai, 2018 (raport).
26. **Gavriliuc N**., Palii I. Paterrnul diametrelor aortice la copiii cu aortopatii congenitale. Conferința națională Zilele USMF "Nicolae Testemițanu". Chișinău, Republica Moldova, 15-19 octombrie 2018.
27. **Gavriliuc N**., Palii I. Substratul genetic în aortopatiile congenitale la copii. Al VII-lea Congres Național de Pediatrie cu participare internațională „Urgențele pediatrice și managementul actului medical". Chișinău, Republica Moldova, 14-15 septembrie 2018.
28. **Gavriliuc N.** Aortopatiile congenitale la copii. Conferința Națională de Pediatrie cu participare internațională „Probleme și căi de soluționare în asistența medicală a copiilor". Chișinău, 9-10 septembrie 2016 (raport).

  - ✓ **National events**

29. **Gavriliuc N.,** Eșanu V., Palii I. Interferența dintre aortopatiile congenitale și sindromul metabolic la copil. Conferința Națională de Pediatrie „Progrese în Pediatrie". București, România, 21-24 martie 2018. 30 P

- **Participations at poster sessions within scientific forums:**

  - ✓ **International events**

30. **Gavriliuc N.,** Palii I., Eșanu V., Pîrțu L., Caraman A. Aortopatiile congenitale la copii. Conferința Națională de Pediatrie. Progrese în Pediatrie. România, București, 21-24 martie, 2018 (poster).
31. **Gavriliuc N**., Palii I., Eșanu V., Zahariuc T. ș. a. Formarea aneurismului gigant în aorta descendentă asociată cu coarcatarea aortică la copil – raport de caz. Congresul de Cardiologie Pediatrică. Iași, România, 17-19 mai 2018 (poster).
32. **Gavriliuc N.,** Palii I., Eșanu V., Ciubotaru A., Pîrțu L. O combinație de aortopatii congenitale cu multiple implicații terapeutice. Prezentare de caz. Conferința Națională de Pediatrie. Progrese în Pediatrie. România, București, 21-24 martie 2018 (poster).
33. **Gavriliuc N.** The Impact on Aorta Geometry After Surgical Repair of Aorta Coarctation in Children. In: ICHA-abstracts. 1st International Congress of Hypertension in Children and Adolescents (ICHCA). Valencia, Spain, February 9-11, 2018 (poster).
34. **Gavriliuc N**., Esanu V., Pîrțu L., Ciubotaru A., ș.a. *Pattern-ul* diametrelor aortice la copii cu aortopatii congenitale. Al 57-lea Congres Național de Cardiologie, Sinaia, România, 19-22 septembrie 2018 (poster).
35. **Gavriliuc N**., Palii I., Eșanu V., Zahariuc T. ș.a. Formarea aneurismului gigant în aorta descendentă asociată cu coarcatarea aortică la copil – raport de caz. Congresul de Cardiologie Pediatrică, Iași, România, 17-19 mai, 2018 (poster).