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RESEARCH ARTICLE

The Results of Echocardiography Applied to Heart Murmurs in Two Different Centers: is Geography Destiny?

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ABSTRACT

Objective: Heart murmurs in childhood are the most common reason for pediatric cardiology consultations worldwide. The aim of this study is to investigate the frequency and etiology of congenital heart disease (CHD) in two different centers possessing significant differences in factors such as geography, climate, and sociocultural conditions.

Methods: The study involves patients who'd been referred to the pediatric cardiology outpatient clinic due to heart murmurs between November 2022-October 2023. All patients were evaluated by echocardiograph to investigate the causes of the murmur.

Results: The study includes 2,127 patients (1,452 from Şırnak and 675 from Giresun; median age = 1.95 years). The gender distributions were similar in both regions. Pathological heart murmurs were more prevalent in Şırnak (21.6%) compared to Giresun (7.7%), while Giresun had a higher percentage of innocent murmurs (92.3%). Cyanotic conditions were rare. Surgery was required for 3.7% of patients overall (4.5% in Şırnak; 1.9% in Giresun). Normal echocardiograms were found in 46% of the total population, with variations being 41% in Şırnak and 56% in Giresun. Pathological murmurs were more common in females. Patients with pathological murmurs were more likely to require surgery. Şırnak had more pathological echocardiography results and a higher need for surgery. Neonates were the age group most frequently requiring surgery in both centers.

Conclusions: Educating society and fostering awareness are imperative steps for preventing consanguineous marriages and encouraging appropriate birth intervals. Swift public education is particularly crucial in developing nations marked by elevated consanguinity rates and limited financial resources, highlighting the potential detrimental consequences of inbreeding.

Keywords: Child, echocardiography, cardiac murmur

INTRODUCTION

Congenital heart defects (CHDs) represent a significant share of clinically notable birth abnormalities and are a crucial aspect of pediatric cardiovascular conditions, with an estimated occurrence of 6–9 CHD cases per 1,000 live births [1,2]. Heart murmurs are one of the most common warning signs for pediatricians in the diagnosis of CHD. Heart murmurs are sounds created by turbulent blood flow in the heart and vascular structures and are transmitted to the chest wall between 20-2,000 Hz. Heart murmurs in the childhood age group are the most common reason for pediatric cardiology consultations worldwide. Innocent heart murmurs can be heard in 70-85% of healthy children. This type of murmur develops due to increased blood flow rate without any cardiac pathology and occurs in cases where cardiac output increases, such as fever, anemia, and thyrotoxicosis. Innocent murmurs are defined as short-term, single, soft, non-propagating rhythmic sounds systolic in nature that change character with breathing and position. Heart murmurs can also occur as a sign of congenital or acquired heart disease. A child with a heart murmur needs to be evaluated with a history and a systemic examination, as well as a detailed cardiovascular system examination. Therefore, having pediatricians distinguish between innocent and pathological murmurs is of great importance. In this way, incorrect diagnoses, unnecessary referrals, and loss of money and time can be prevented [3–5].

This study's objective is to assess the frequency and complexity of CHD alongside echocardiographic findings in patients presenting to one of two pediatric cardiology outpatient clinics

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with heart murmurs. The study has chosen two cities in pursuit of this, one being Şırnak, a mountainous region that has a lower sociocultural level, higher fertility rates, and a greater number of consanguineous marriages. The other is Giresun, a coastal area with lower fertility rates where consanguineous marriages are relatively less common. Based on the 2022 data from the Turkish Statistical Institute (TURKSTAT), the crude birth rate in Şırnak is 23.7 per thousand, which is significantly higher than that of Giresun, which stands at 8.3 per thousand. Additionally, Şırnak has a 14.5% rate of consanguineous marriages, while Giresun's is 8.5%. Both of these differences have been found to be statistically significant ($p < 0.005$) through the chi-squared test. The aim is to explore the etiology of CHD in two distinct centers that differ significantly in terms of such factors as geography, climate, and sociocultural conditions.

MATERIAL AND METHODS

This retrospective study was conducted between November 2022-October 2023 at two medical centers, one in Şırnak and the other in Giresun. The study focuses on patients who'd been referred to the pediatric cardiology clinic due to the presence of heart murmurs. All patients who presented during this period were included in the study, and their demographic characteristics and echocardiographic findings are analyzed retrospectively. The study received ethical approval from the Şırnak University Faculty of Medicine Ethics Committee (Approval No: 71172 dated 8/10/2023) and was conducted in accordance with the principles outlined in the Helsinki Declaration.

Patients with pre-existing cardiac diagnoses who were under follow-up, as well as those who presented with symptoms unrelated to heart murmurs (e.g., chest pain, syncope, palpitations) or for obtaining a sports medical certificate were excluded from the study. The remaining patients were categorized into two groups (i.e., innocent heart murmurs, pathological heart murmurs) based on the referral made by pediatric physicians. Comprehensive medical histories were obtained from all patients. Two-dimensional, M-mode, and color Doppler echocardiography techniques were employed to evaluate the patients, and the examination findings were compared with the results from their echocardiography.

Statistical analysis

The data were analyzed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented in terms of the number of units (*n*), percentages (%), and median values. The study assesses the normality of the single numerical variable of age using the Shapiro-Wilk normality test. Categorical variables such as gender, the child cardiology center to which the patient belonged, the need for surgery, the presence of cyanosis, and type of murmur are evaluated using the chi-squared test. A p-value less than 0.05 is considered statistically significant.

RESULTS

The study involves a total of 2,127 patients, with 1,452 patients being from Şırnak and 675 from Giresun. The median age of the patients is 1.95 years (Range: 1 d - 18 yrs.). Figure 1 shows the patients' age distributions. Of the total cohort of cases, 45.3% are girls and 54.7% are boys. Similarly, both Şırnak and Giresun have similar gender distributions. Regarding the presence of pathological or innocent heart murmurs, a higher percentage of patients in Şırnak had pathological murmurs (21.6%) compared to Giresun (7.7%), resulting in an overall average percentage of 17.2% for the total population. Meanwhile, Giresun had a higher percentage of innocent murmurs (92.3%) compared to Şırnak (78.4%). Cyanotic conditions were rare in both centers, with only a small percentage of the total cohort of patients presenting with cyanosis. The need for surgery was present in a small proportion of cases, with 3.7% of patients in the total cohort requiring surgery (4.5% in Şırnak; 1.9% in Giresun). Finally, when assessing the echocardiography results, 46% of the total population had normal echocardiograms. Şırnak had a slightly lower percentage of normal echocardiograms (41%), while Giresun had a higher percentage (56%) of normal echocardiography findings (Table 1).

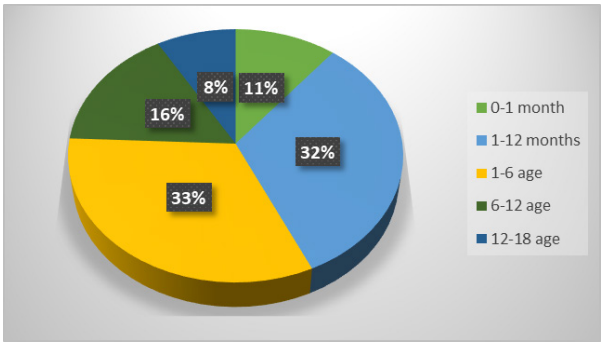

Figure 1: Distribution of patients by age groups.

A significant statistical difference was observed when examining the relationship between heart murmurs and gender. Pathological heart murmurs were found to be more prevalent among females ($p = 0.017$). However, no significant dependence was observed between gender and the need for surgery ($p > 0.05$). Additionally, the patients with pathological heart murmurs were observed to require surgery more often ($p < 0.001$). Additionally, an approximately 42% correlation was found between type of heart murmur and the need for surgery. When comparing the echocardiography results from both centers, pathological echocardiography results were found more often in patients in Şırnak ($p < 0.001$). When evaluating the center where the patients were located alongside the need for surgery, the patients in Şırnak were determined to require surgery more often ($p = 0.005$; Table 2). No significant dependence was observed between the center where the patients were located and their diagnosis of cyanotic heart disease ($p = 0.443$).

A significant difference was observed between the groups based on whether the patients were referred for surgery and their age. When evaluating each center internally, the neonatal age group was the age group most frequently in need of surgery in both centers ($p < 0.05$; Table 3).

Table 1: Demographic characteristics of the patients, murmur types, cyanosis status and main diagnoses detected after echocardiography

Variables	Total (n=2127)	Şırnak (n=1452)	Giresun (n=675)
Median Age (years)	1.95 (1 day-18 years)	2.23 (1 day-17.6 years)	1.29 (1 day-18 years)
Female/Male	964/1163 (45.3%/54.7%)	663/789 (45.7%/54.3%)	301/374 (44.6%/55.4%)
Pathological/Innocent Murmur	365/1762 (17.2%/82.8%)	313/1139 (21.6%/78.4%)	52/623 (7.7%/92.3%)
Cyanotic/Non-Cyanotic	7/2120 (0.3%/99.7%)	6/1446 (0.4%/99.6%)	1/674 (0.1%/99.9%)
Need for Surgery	78 (3.7%)	65 (4.5%)	13 (1.9%)
Echocardiographic results			
Normal	979 (46%)	600 (41%)	379 (56%)
Patent foramen ovale	486 (22.8%)	398 (27.4%)	88 (13%)
Atrial septal defect	195 (9.2%)	120 (8.3%)	75 (11.1%)
Mitral regurgitation	105 (4.9%)	77 (5.3%)	28 (4.1%)
Ventricular septal defect	99 (4.6%)	75 (5.2%)	24 (3.6%)
Patent ductus arteriosus	98 (4.6%)	89 (6.1%)	9 (1.3%)
Pulmonary stenosis	49 (2%)	24 (1.6%)	15 (2.2%)
Aortic regurtitation	37 (1.7%)	25 (1.7%)	12 (1.8%)
Peripheral pulmonary stenosis	25 (1.1%)	10 (0.6%)	15 (2.2%)
Coronary fistula	11 (0.5%)	3 (0.2%)	8 (1.2%)
Aortic coarctation	7 (0.3%)	3 (0.2%)	4 (0.6%)
Atrioventricular septal defect	6 (0.2%)	5 (0.34%)	1 (0.2%)
Aortic stenosis	6 (0.2%)	3 (0.2%)	3 (0.4%)
Ascending aortic dilatation	8 (0.4%)	0	8 (1.2%)
Tetralogy of Fallot	5 (0.2%)	4 (0.3%)	1 (0.2%)
Other	21 (1%)	16 (1.1%)	5 (0.7%)

Table 2: Comparison of Echocardiography Results by Centers when Evaluated as Normal-Pathological

Center	Normal (n, %)	Pathological (n, %)	p-value	Need for surgery	No-need for surgery	p-value
Şırnak	600 (41.3%)	852 (58.7%)	**<0.001**	65 (%4,5)	1387 (%95,5)	**0,005**
Giresun	379 (56.1%)	296 (43.9%)		13 (%2)	662 (%98)	

Table 3: The comparison of patients' referral for surgery based on age groups at the * and **** centers**

Center	Age Groups	p-value	0-1 month (n, %)	1-12 months (n, %)	1-6 years (n, %)	6-12 years (n, %)	12-18 years (n, %)
Şırnak	No Surgery	**<0.001**	117 (88%)	438 (94.2%)	427 (96.8%)	257 (98.5%)	148 (97.4%)
	Surgery		16 (12%)	27 (5.8%)	14 (3.2%)	4 (1.5%)	4 (2.6%)
Giresun	No Surgery	**<0.05**	90 (93.8%)	220 (98.7%)	248 (98.8%)	78 (100%)	26 (96.3%)
	Surgery		6 (6.3%)	3 (1.3%)	3 (1.2%)	0 (0%)	1 (3.7%)

DISCUSSION

Cardiovascular malformations affect 0.4-1.4% of live births, and a quarter of these cases require specialized cardiac treatment in infancy. However, delayed or unsuccessful diagnoses occur in 20-30% of cases, despite prenatal CHD screening being successful and widely available. Over 10% of severe CHD cases currently still experience delayed identification [6]. Therefore, accurate detection of cardiac murmurs protects patients with innocent murmurs from the fear of heart disease, unnecessary medication, and physical activity restrictions while ensuring that patients with pathological murmurs are quickly diagnosed and given the necessary intervention and treatment. To distinguish between innocent and pathological murmurs, a suitable environment must be provided for the examination, and the physician performing the examination must be experienced. Yıldız et al. [7] observed that valve insufficiency and atrial septal defects that may require follow

up were detected in the echocardiograms of patients who were thought to have had innocent murmurs. They emphasized that echocardiographic examinations may also be required for innocent heart murmurs.

Studies have reported the prevalence of innocent murmurs in patients admitted with a cardiac murmur to range from 63-80% [3,5]. The current study found this rate to be 82.8% over the entire patient group. Of the echocardiographic evaluations of patients presenting with heart murmurs, 46% resulted in normal cardiac findings. Of the patients presenting with murmur, the most common abnormal cardiac findings were patent foramen ovale (PFO), atrial septal defect (ASD), and mitral regurgitation (MR). Similar to this study, two other studies conducted in Turkey found the order of frequency (highest to lowest) to be PFO, ASD, and pulmonary stenosis [5,7], while another study instead found mitral valve prolapse and mitral regurgitation to come after ASD [3].

The echocardiographic evaluations of patients presenting with heart murmurs in the current study reveal abnormal cardiac findings in 54% of the entire group. However, these data show significant differences between the two centers, with the patients living in Şırnak having a greater number of abnormal cardiac findings. At the same time, the patients living in Şırnak were also determined to require cardiac operations more frequently. Several reasons for this situation have been considered. According to 2022 TURKSTAT data, 14.3% of marriages in Şırnak are consanguineous, while this rate is 8.5% in Giresun [8]. Previous investigations have explored the connection between consanguinity and various diseases in children. The findings indicate that, despite higher fertility rates in consanguineous marriages compared to non-consanguineous ones, the percentage of living children is similar in both groups. This is attributed to the increased child mortality rate in consanguineous marriages. The results underscore the impact of homozygous recessive genes in causing different types of CHD, suggesting a potential multi-factorial genetic pattern. Consanguinity among parents enhances the accumulation of recessive genes in their offspring, consequently elevating the likelihood of congenital malformations, including heart anomalies. Consequently, raising awareness within communities, particularly in countries with high consanguinity rates and an elevated disease burden, about the adverse effects of inbreeding is crucial [9,10].

Of course, the presence of genetic influences in the development of CHD is very crucial. The recent advancements in genetic and genomic techniques have facilitated the discovery of over 100 genes linked to CHD. Despite these significant breakthroughs, only one-third of CHD cases have been attributed to straightforward genetic causes. This is due to the complex nature of CHD, where factors such as oligogenic influences, environmental elements, and gene-environment interactions also play pivotal roles. One of these is hypoxia, a secondary effect of living in high altitudes. In the early 1950s, the initial reports highlighted an elevated incidence of atrial septal defect and patent ductus arteriosus cases among infants born at high altitudes. Maternal exposure to varying levels of reduced oxygen during mid-gestation, even for brief periods, has been identified as a factor causing conotruncal heart defects [11]. Other studies have demonstrated an 8%-14% exposure to hypoxia midgestation to reduce the levels of the cardiac transcription factor Nkx2-5, leading to heart defects [12]. This interaction between the environment and a gene may offer insight into the intriguing clinical observation that populations at high altitudes exhibit significantly higher rates of complex CHD compared to those at sea level [13]. These observations align with the findings from the current study, indicating a lower frequency of abnormal cardiac findings in the coastal province of Giresun (altitude = 14 meters) compared to the mountainous region of Şırnak (altitude = 1,700 meters). However, importance is had in noting that this association should be interpreted cautiously and that the need exists for more extensive investigations to establish a direct link between altitude and the development of CHD. Additionally, the potential influence of other factors such as the duration of maternal residence in these regions during pregnancy requires further exploration.

In addition, evidence exists that a mother's decreased intake of vital nutrients may increase her offspring's risk of developing CHD [11]. The decrease in essential nutrients in mothers can be attributed to various factors. Firstly, maintaining a well-balanced diet that prevents deficiencies is crucial and requires both nutritional knowledge and the financial means to afford such dietary support when necessary. Achieving this demands a favorable socioeconomic status. In the Southeastern Anatolia region (SAR) where Şırnak is located, however, 41.5% of the population falls into the lowest welfare category. In contrast, in the Eastern Black Sea region (EBR) that is represented by Giresun, 25.5% of the population is categorized as having the lowest welfare level [14].

According to the 2022 TURKSTAT data, Şırnak is the province in Turkey with the second highest fertility rate (23.7 per thousand), while Giresun has the fourth lowest fertility rate (8.3 per thousand; Figure 2) [8]. Şırnak's high number of patients with heart murmurs may be attributed to its high birth rate and child population. Given the need to avoid missing diagnoses, especially in the newborn and young child group, many patients in Şırnak are inevitably directed to pediatric cardiology for heart murmur diagnosis. Although women are known to have many children with little time in between births in Türkiye, especially in the SAR, the 2018 Turkey Population and Health Survey (TNSA) states the median birth interval of women to have been 33 months in the SAR, while this value was 50 months in the EBR [14]. Previous publications have determined low birth weight to also be an independent risk factor [9]. While the rate of children born smaller than average and very small in SAR is 26.7%, this rate is 21.8% in EBR [14].

This study has limitations that are secondary to its retrospective character. Importance is had in noting that the specific consanguinity statuses of the individual cases included in the

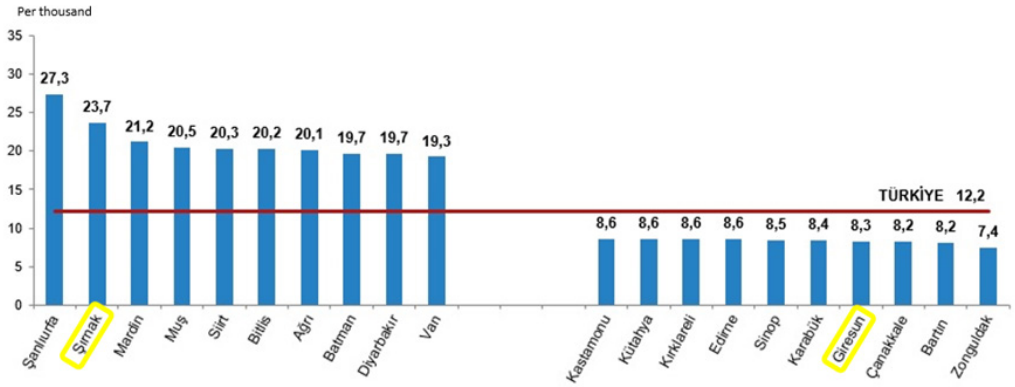

Figure 2: The 10 provinces with the highest and lowest crude birth rates, 2022[8].

analysis were unavailable and that the study had to use the 2022 TURKSTAT data to compare consanguinity situations in the two regions. Despite efforts to obtain this information, its absence limits the study's comprehensiveness. Other factors that have been found to have an impact in the literature regarding the prospective design can also be examined, such as mothers' drug and cigarette use. Nevertheless, this study is believed to be able to contribute to the literature by being a heart murmur etiology study with a large population and by shedding light on the realities in Türkiye.

CONCLUSION

In conclusion, this study had delved into the prevalence and complexity of CHD among pediatric patients presenting with heart murmurs in two distinct regions with varying sociocultural, geographical, and climatic conditions. The findings underscore the significance of distinguishing between innocent and pathological murmurs, as incorrect diagnoses can lead to unnecessary referrals and resource expenditures. The study's results reveal a higher prevalence of pathological murmurs in the mountainous region of Şırnak, which might possibly be attributable to factors such as consanguinity rates, altitude-related hypoxia, and socioeconomic conditions. The need for cardiac surgery was also more pronounced in this region, emphasizing the importance of early detection and intervention. This study highlights the impact consanguinity has on CHD, with Şırnak exhibiting higher rates of both compared to Giresun. Despite these limitations, the large population size and comprehensive analysis contribute valuable insights into the heart murmur etiology landscape in Türkiye. Prospective studies that consider additional factors such as maternal habits and a broader range of socioeconomic indicators will be able to further enrich the world's understanding. In essence, this research underscores the intricate interplay of genetic, environmental, and sociocultural factors in shaping the prevalence and complexity of CHD. Awareness of these factors is crucial for healthcare practitioners, policymakers, and communities in implementing targeted preventive measures and ensuring timely and accurate diagnoses for pediatric patients with heart murmurs.

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Ethics Committee Approval: The study received ethical approval from the Şırnak University Faculty of Medicine Ethics Committee (Approval No: 71172 dated 8/10/2023) and was conducted in accordance with the principles outlined in the Helsinki Declaration.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- M.M.A.; Data Acquisition- M.M.A., B.Y., V.T.; Data Analysis/Interpretation- B.Y.; Drafting Manuscript-M.M.A., V.T. ; Critical Revision of Manuscript-M.M.A., B.Y.; Final Approval and Accountability- M.M.A., B.Y., V.T.

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