Early Results of the Persian Registry of Cardiovascular Disease/Congenital Heart Disease (PROVE/CHD) in Isfahan

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Abstract

Background: In 2016, a prospective registry for pediatric patients with congenital heart disease (CHD) was established in Isfahan, Iran. Data on pediatric CHD in Iran are scant; accordingly, we aimed to report the early results of the Persian Registry Of cardioVascular diseaseE (PROVE/CHD) Registry in Isfahan.

Methods: All patients with CHD and associated defects diagnosed by pediatric cardiologists were assessed via echocardiography for inclusion in the present study between late 2016 and August 2019. The participants’ sociodemographic characteristics, maternal history, birth history, medical history, current clinical presentations in the clinic or hospital, paraclinical data, cardiac diagnoses based on the International Classification of Diseases, 10th Revision (ICD-10), disease management plans, and medications were entered into a questionnaire by the subjects’ parents/legal custodians and physicians and then transferred to the PROVE/CHD Registry.

Results: The PROVE/CHD registry encompasses 1252 patients with CHD (49.9% male) at a mean age of 6.50±6.36 years. The most frequent cardiac diagnoses were ventricular septal defect (39.3%), atrial septal defect (29.7%), patent ductus arteriosus (25.4%), pulmonary stenosis (11.0%), tetralogy of Fallot (6.1%), coarctation of the aorta (5.4%), and aortic stenosis (5.1%), respectively. The most frequent interventions were patent ductus arteriosus closure (4.3%), atrial septal defect closure (3.6%), pulmonary valvuloplasty (2.2%), coarctation of the aorta angioplasty (1.9%), and ventricular septal defect closure (1.1%), correspondingly. The approximate corresponding rates of corrective and palliative surgeries were 32.0% and 13.1%. The corrective surgeries were mainly comprised of ventricular septal defect closure (7.8%), patent ductus arteriosus closure (7.3%), atrial septal defect closure (5.1%), and tetralogy of Fallot repair (3.8%), respectively. The palliative surgeries mainly consisted of the Glenn shunt (9.0%) and pulmonary artery banding (3.6%).

Conclusion: The PROVE/CHD Registry collects data on pediatric patients with CHD. The results of this registry can provide epidemiological data and a set of homogeneously defined cases for further studies.

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Introduction

Congenital heart disease (CHD) is the leading cause of infant mortality among birth defects. The reported prevalence rate of CHD is approximately 4 to 10 per 1000 live births. Various etiological factors have been identified; however, the exact reasons for these abnormalities have remained unclear. CHD is now believed to have multifactorial etiologies in the form of a combination of both environmental and genetic factors. The early detection and use of new techniques in the surgical repair and treatment of CHD has dramatically improved patients’ outcome, with the disease now deemed treatable with improved survival. Although interventions and surgical repair are beneficial to most patients with CHD and improve their quality of life, by no means has a “cure” been found yet. Children with repaired complex CHD and with unrepaired cyanotic defects are at risk for long-term complications and mortality during adulthood. It is well known that the identification of CHD risk factors, in conjunction with national registries and local data collection, is crucial.

Iran lacks reliable data on CHD risk factors and long-term outcomes because of the absence of a large, national registry. To address this deficiency, the first registry program of CHD in Iran was begun in the Iranian city of Isfahan, in 2016, under the title of “The Persian Registry Of cardioVascular disease” (PROVE/CHD). The objectives of the PROVE/CHD Registry are as follows: 1) to define the incidence of CHD in the city of Isfahan in 5 outpatient clinics (2 private clinics and 3 university outpatient clinics), 2) to determine the known risk factors of CHD, 3) to enhance the quality of care, and 4) to pilot register patients with CHD and determine problems regarding further national CHD registrations. This registry is the first national CHD registry in Iran and is almost unique among Middle Eastern countries. This paper is a report of the early results of the PROVE/CHD Registry in Isfahan.

Methods

PROVE/CHD is a registry of data on patients with CHD from 5 outpatient clinics (2 private clinics and 3 university clinics) in the Iranian city of Isfahan. The data used in this study were collected between late 2016 and August 2019. The study protocol was approved by the Ethics committee of Isfahan University of Medical Sciences (Code: IR.MUI.MED.RED.1398.085). A questionnaire was designed by pediatric cardiologists and validated by the institutional quality control committee experts. The questionnaire consisted of 7 different sections collecting information on demographic characteristics (eg, National Identity Number, registry location, parents’ occupation, and family history of CHD), birth history (eg, birth condition and birth weight), maternal history (eg, registry location, history of diseases, addictions, medications during pregnancy, and exposure to chemical substances and X-ray during pregnancy), medical history (eg, time of first CHD diagnosis, genetic congenital abnormalities, and history of cardiac catheterization, cardiac surgery, and medications), current clinical presentations in the clinic or hospital (eg, height, weight, and associated diseases), paraclinical data (eg, electrocardiography, chest X-ray, echocardiography, angiography, computed tomography angiography, and cardiovascular magnetic resonance imaging), cardiac diagnosis (based on the International Classification of Diseases, 10th Revision [ICD-10]), and disease management plans.

The children’s parents/legal custodians received comprehensive explanations about the objectives of the registry so that informed consent could be obtained for the commencement of data collection. The PROVE/CHD questionnaires were completed by parents/legal custodians and physicians, and the information of the patients was confirmed by pediatric cardiologists. The data were thereafter transferred to the PROVE/CHD Registry.

The inclusion criteria consisted of all patients with CHD diagnosed by pediatric cardiologists and confirmed via echocardiography in 3 state-run outpatient pediatric cardiology clinics and 2 private outpatient pediatric cardiology clinics. Patients were excluded if they had a diagnosis of mitral valve prolapse or a patent foramen ovale. During the 3-year period (ie, 2016 to 2019), data collection was performed in 1252 pediatric patients with CHD. The data were subsequently processed and analyzed using the SPSS software, version 23.0 (IBM Corp, Armonk, NY, USA). The qualitative variables were presented as frequencies and percentages, and the quantitative variables were expressed as the mean ± the standard deviation.

Results

From late 2016 to August 2019, the registry enrolled 1252 patients, of whom 625 (49.9%) were male. There were 292 (23.3%) neonates, 301 (24.0%) infants, 299 (23.9%) patients between 3 and 6 years old, 314 (25.1%) patients aged between 7 and 18 years, and only 46 (3.7%) patients aged
above 18 years.
Among the 1252 patients, 275 (22.0%) had low birth weights (<2500 g), 959 (76.5%) had appropriate weights for gestational age (2500–4000 g), and 18 (1.4%) were large for gestational age (>4000 g). The mother’s age in 843 (67.4%) patients was between 18 and 35 years. In regard to parents’ occupation, 1136 (90.7%) patients had homemaking mothers, and the fathers of 456 (36.4%) patients were workers (Table 1).

| Table 1. Sociodemographic characteristics of the participants’ |
|---------------------------------|-----------------|-----------------|
| **Sex**                         | **Male**        | **Female**      |
| **Age of the Patients**         | **<1 mon**      | **1 mon to 2 y**|
| **Birth Weight of the Patients**| **SGA (<2500 g)**| **AGA (2500–4000 g)**| **LGA (>4000 g)**|
| **Age of the Mother (y)**       | **<18 y**       | **18–35 y**     | **>35 y**       |
| **Mother’s Occupation**         | **Homemaker**   | **Employee**    | **Worker**      |
| **Father’s Occupation**         | **Laborer**     | **Self-employed**| **Employee**    |
| **Birth Place**                 | **Isfahan Province**| **Another Province**|

The results showed that the parents of 31.6% of the study population had consanguineous marriages. Of all the diseases investigated among the patients’ mothers, hypothyroidism (n=106, 8.5%) and diabetes mellitus (n=48, 3.8%) were the most common. These mothers used levothyroxine and metformin, respectively.

A total of 1252 (4.0%) patients had CHD associated with syndromes. For instance, 44 (3.5%) patients had Down syndrome. The time of first CHD diagnosis in 621 (49.6%) patients was in the neonatal period. Cardiac murmurs were auscultated in 1121 (89.5%) patients, and respiratory distress was reported in 86 (6.8%) patients in the physical examinations (Table 2).

| Table 2. Baseline characteristics of the participants’ |
|---------------------------------|-----------------|-----------------|
| **Consanguineous Marriages**     | No relation     | Third-degree relation |
| **Maternal Illness During Pregnancy** | Hypothyroidism | Diabetes mellitus |
| **Syndromes**                   | Down syndrome (Trisomy 21) | Williams syndrome |
| **Time of CHD Diagnosis**       | Prenatal        | Neonatal        |
| **Clinical Findings in CHD (data of the first examination)** | Murmur | Respiratory distress |
| **VSD, Congenital heart disease** | Cyanosis | Asymptomatic |

With respect to CHD lesions, 765 (61.1%) patients had a single lesion, while 487 (38.8%) had more than 1 lesion. CHD subtypes were classified in 4 categories: 1) acyanotic with left-to-right shunts (n=1206, 96.3%), 2) obstructive (n=275, 21.9%), 3) cyanotic with decreased pulmonary flow (n=110, 8.7%), and 4) cyanotic with increased pulmonary flow (n=29, 2.3%). Table 3 presents the list of CHD subtypes.

The most frequent main cardiac diagnoses were ventricular septal defect (VSD) (n=493, 39.3%), atrial septal defect (ASD) (n=372, 29.7%), patent ductus arteriosus (PDA) (n=318, 25.4%), pulmonary stenosis (n=138, 11.0%), tetralogy of Fallot (ToF) (n=76, 6.1%), coarctation of the aorta (CoA) (n=68, 5.4%), and aortic stenosis (n=64, 5.1%). Regarding CHD subtypes, ASD and PDA were more frequent in female patients, whereas VSD, pulmonary stenosis, ToF, aortic stenoses, and CoA predominated in males (Figure 1). The CHD diagnosis was coded based on the ICD-10 (sections Q20–Q26) (Table 4).

**Data are presented as n (%).**

**SGA, Small for gestational age; AGA, Appropriate for gestational age; LGA, Large for gestational age.**
Table 3. Congenital heart defects subtypes in the PROVE/CHD Registry

| Congenital Heart Defects Type | Subtype                                      | Count (Percentage) |
|------------------------------|----------------------------------------------|--------------------|
| **Single Lesions**           |                                              | 765 (61.0)         |
| Multiple Lesions (n=487)     | Two                                          | 304 (24.3)         |
|                              | Three                                        | 120 (9.6)          |
|                              | Four                                         | 41 (3.3)           |
|                              | Five                                         | 17 (1.4)           |
|                              | Six                                          | 5 (0.4)            |
| **Acyanotic Lesions**        |                                              |                    |
| Left-to-right shunt (n=1206) | Ventricular septal defect                    | 493 (39.3)         |
|                              | Atrial septal defect                         | 372 (29.7)         |
|                              | Patent ductus arteriosus                    | 318 (25.4)         |
|                              | Atroventricular septal defect               | 23 (1.8)           |
| Obstructive Lesions (n=275)  | Aortic stenosis                              | 69 (5.5)           |
|                              | Pulmonary valve stenosis                     | 138 (11.0)         |
|                              | Coarctation of the aorta                    | 68 (5.4)           |
| **Cyanotic Lesions**         |                                              |                    |
| Decreased pulmonary flow (n=110) | Tetralogy of Fallot                        | 76 (6.1)           |
|                              | Pulmonary atresia                           | 32 (2.6)           |
|                              | Tricuspid atresia                           | 2 (0.2)            |
| Increased pulmonary flow (n=29) | Transposition of the great arteries         | 18 (1.4)           |
|                              | Total anomalous pulmonary venous return     | 11 (0.9)           |

*Data are presented as n (%).

There were some lesions of CHD (eg, acyanotic and cyanotic) in a single patient simultaneously.

Table 4. Cardiac diagnoses based on the ICD-10 (Sections Q20–Q26) for the patients with CHD

| Cardiac Diagnosis | Count (Percentage) |
|-------------------|--------------------|
| Q20. Chambers and Connections |                  |
| Double-outlet right ventricle | 14 (1.1) |
| Double-outlet left ventricle | 1 (0.1) |
| Discordant ventriculoatrial connection | 18 (1.4) |
| Double-inlet ventricle | 1 (0.1) |
| Discordant atroventricular connection | 3 (0.2) |
| Isomerism of atrial appendages | 2 (0.2) |
| Other | 3 (0.2) |
| Unspecified | 33 (2.6) |
| Q21. Cardiac Septa |                  |
| Ventricular septal defect | 493 (39.3) |
| Atrial septal defect | 372 (29.7) |
| Atroventricular septal defect | 23 (1.8) |
| Tetralogy of Fallot | 76 (6.1) |
| Other malformations of the cardiac septa | 8 (0.6) |
| Malformation of the cardiac septum, Unspecified | 19 (1.5) |
| Q22. Pulmonary and Tricuspid Valves |                  |
| Pulmonary valve atresia | 32 (2.6) |
| Congenital pulmonary valve stenosis | 138 (11.0) |
| Other congenital pulmonary valve insufficiencies | 2 (0.2) |
| Congenital tricuspid stenosis | 3 (0.2) |
| Hypoplastic right heart | 2 (0.2) |
| Other congenital malformations of the tricuspid valve | 5 (0.4) |
| Q23. Aortic and Mitral Valves |                  |
| Congenital stenosis of the aortic valve | 64 (5.1) |
| Congenital insufficiency of the aortic valve | 16 (1.3) |
| Congenital mitral stenosis | 8 (0.6) |
| Congenital mitral insufficiency | 8 (0.6) |
| Hypoplastic left heart syndrome | 1 (0.1) |
| Other cardiac malformations of the aorta and the mitral valve | 15 (1.2) |
| Cardiac malformations of the aorta and the mitral valve, Unspecified | 14 (1.1) |
| Dextrocardia | 10 (0.8) |
| Pulmonary infundibular stenosis | 4 (0.3) |
| Other specified cardiac malformations of the heart, Unspecified | 10 (0.8) |
| Malformations of the heart, Unspecified | 11 (0.9) |
| Patent ductus arteriosus | 318 (25.4) |
| Coarctation of the aorta | 68 (5.4) |
| Supravalvular aortic stenosis | 5 (0.4) |
| Other cardiac malformation of the aorta | 4 (0.3) |
| Atriaesi of the pulmonary artery | 2 (0.2) |
| Coarctation of the pulmonary artery | 2 (0.2) |
| Congenital pulmonary arteriovenous malformations | 1 (0.1) |
| Malformations of the great arteries, Unspecified | 3 (0.2) |
| Total anomalous pulmonary venous return | 11 (0.9) |
| Partial anomalous pulmonary venous connection | 7 (0.6) |
| Other cardiac malformations of the great veins | 12 (1.0) |
| Malformations of the great veins, Unspecified | 11 (0.9) |

*Data are presented as n (%).

ICD-10, International Classification of Diseases, 10th; CHD, Congenital heart
Better devised professional education programs

Corrective surgeries were performed on 401 (32.0%) patients and palliative surgeries on 165 (13.1%). Further, 291 (23.2%) patients had 1 surgery, 54 (4.3%) patients had 2 surgeries, and 14 (3.7%) patients had 3 or more surgeries. The most frequent corrective surgeries were VSD closure (7.8%), PDA closure (7.3%), ASD closure (5.1%), and ToF repair (3.8%), respectively. The most frequent palliative surgery was the Glenn shunt (9.0%), followed by pulmonary artery banding (3.6%). Table 5 lists the cardiac medications, the most frequent interventions, and corrective and palliative surgeries.

Table 5. Medications and different cardiac procedures of the patients

| Heart Failure (n=264) |   |
|----------------------|--|
| Furosemide           | 88 (7.0) |
| Captopril            | 83 (6.6) |
| Digoxin              | 71 (5.7) |
| Spironolactone       | 22 (1.8) |
| Anticoagulants (n=92)|   |
| Acetylsalicylic acid | 58 (4.6) |
| Warfarin             | 18 (1.4) |
| Plavix               | 16 (1.3) |
| Treatment for Pulmonary Hypertension (n=58) |   |
| Sildenafil           | 49 (3.9) |
| Tadalafil            | 5 (0.4)  |
| Bosentan             | 4 (0.3)  |
| Antiarrhythmics (n=17)|   |
| Propranolol          | 12 (0.1) |
| Amiodarone           | 4 (0.3)  |
| Sotalol              | 1 (0.1)  |
| Cardiac Procedures   |   |
| Congenital Catheterization | 229 (18.2) |
| Interventional Catheterization (n=185) |   |
| PDA closure          | 55 (4.3) |
| ASD closure          | 46 (3.6) |
| Pulmonary valvuloplasty | 28 (2.2) |
| CoA angioplasty      | 25 (1.9) |
| VSD closure          | 13 (1.1) |
| Other                | 18 (1.4) |
| Corrective surgery (n=401) |   |
| VSD closure          | 98 (7.8) |
| PDA closure          | 92 (7.3) |
| ASD closure          | 65 (5.1) |
| ToF repair           | 48 (3.8) |
| COA repair           | 22 (1.7) |
| PS repair            | 18 (1.4) |
| Other                | 58 (4.6) |
| Palliative surgery (n=165) |   |
| Glenn shunt          | 113 (9.0) |
| PA banding           | 46 (3.6) |
| Other                | 6 (0.4)  |

Data are presented as numbers (%).

ASD, Atrial septal defect; VSD, Ventricular septal defect; PDA, Patent ductus arteriosus; ToF, Tetralogy of Fallot; CoA, Coarctation of the aorta; PS, Pulmonary stenosis; PA, Pulmonary atresia

Discussion

In the first Iranian registry of CHD, which was initiated in the city of Isfahan in 2016, within 3 years, 1252 patients with CHD were registered.

In this study, 275 (21.8%) pediatric patients with CHD had a birth weight of less than 2500 g, and 405 (32.3%) mothers were aged above 45 years. Previous research has shown that birth weight and maternal age during pregnancy can meaningfully increase the risk of CHD. According to our results, the parents of 395 (31.6%) of our pediatric patients were consanguineously married. There is a substantial body of evidence indicating the existence of a relationship between consanguineous parents and congenital defects. Hypothyroidism (8.5%) and diabetes mellitus (3.8%) were the most common diseases during pregnancy in our investigation, which is consistent with a large number of studies confirming the association between maternal diseases in pregnancy and CHD such as those conducted by Grattan et al., Pastor-Garcia et al., and Ahmadi et al.

CHD has a significant association with Down syndrome. The data analysis in the current study revealed that 44 (3.5%) patients with CHD had Down syndrome.

In our study, only 2.8% of the patients were diagnosed prenatally; this rate is lower than the European average of 25.5%. Better devised professional education programs for prenatal sonographers can increase the prenatal diagnosis of CHD. The time of the first CHD diagnosis in 49.6% of our study population was in the neonatal period, compared with 17.1% in Pakistan and 24.9% in Saudi Arabia.

Since almost half of deaths from CHD occur in infancy and some untreated patients with CHD do not survive their first year, the early detection and correction of CHD during the first year of life is vitally important.

Heart murmurs were detected in 1121 (89.5%) of our patients. According to Mirzarahimi et al., 51.6% of the neonates with cardiac murmurs in their investigation had CHD.

In the current study, 765 (61.1%) patients had only a single lesion, and the acyanotic type of CHD was more frequent than the cyanotic type. In terms of obstructive lesions, left-to-right shunting was the most frequent (96.3%) lesion. Cyanotic CHD with decreased pulmonary flow was more frequent than lesions with increased pulmonary blood flow. This finding is in agreement with the results of Yanji et al. in China, Pastor et al. in Spain, and Calzolari et al. in Italy.

The most frequent subtypes of CHD based on the ICD-10 codes were VSD, ASD, PDA, pulmonary valve stenoses, ToF, CoA, and aortic valve stenoses. Many CHD registries in other countries have reported similar results concerning the frequency of CHD types; that is, VSD and ASD comprise the most frequent types of CHD. In the Québec Registry, VSD and ASD had the highest prevalence, which is compatible with the current study. In contrast, in
the CONCOR Registry, ToF was demonstrated as the most prevalent main diagnosis. A possible explanation for this difference may be the age of the registered population and the role of environmental and genetic factors. Some instances of CHD such as VSD tend to close spontaneously in the first years of life; accordingly, studies with a later registration age do not include this item in their registration.

In our study, a history of treatment with cardiac medications for heart failure was reported in 264 (21.0%) subjects. The most frequently consumed drugs were furosemide (7.0%) and captopril (6.6%). Additionally, anticoagulants, medications for pulmonary hypertension, and antiarrhythmic medications were consumed by 92 (7.3%), 58 (4.6%), and 17 (1.3%) patients, respectively. In 2 registries of patients with adult CHD, the consumption of antiarrhythmic medications was reported in 15.0% of the subjects in the CHALLENGE Registry and 18.0% of the subjects in the CONCOR Registry.

In our study, 229 (18.2%) patients underwent congenital catheterization and 185 (14.7%) had interventional catheterization. Moreover, 401 (≈32.0%) patients had corrective surgeries and 165 (13.1%) had palliative surgeries.

The most frequent interventions in this study were PDA and ASD closure. The rate of VSD closure was lower because of the frequency of PDA and ASD in our population and the accessibility of devices for their closure in our center.

Previous studies have shown that major developments in the diagnosis of complex CHD, in tandem with its medical care, treatment options, surgical techniques, and postoperative care, have conferred decreased morbidity and mortality and enhanced quality of life in children with CHD.

To our knowledge, the PROVE/CHD Registry is the first of its kind for patients with pediatric CHD in Iran and the Middle East. In addition, this study is a part of limited registration studies in the entire world on pediatric CHD that aim to provide epidemiological data and a set of homogeneously defined cases for further studies. However, there are some limitations to our study. Most of the patients enrolled in this registry were those referred to pediatric cardiologists in private clinics and university outpatient clinics, but not all children with a congenital heart defect from birth. Therefore, some of the results of the current study such as the prevalence of congenital heart defects cannot be generalized to the general population of Iran.

**Conclusion**

The registration of pediatric patients with congenital heart disease in the Iranian city of Isfahan can provide a valuable data pool with a view not only to improving management, prevention, and treatment plans but also to contributing to local, national, and international research.

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