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Original Article

Status of adult outpatients with congenital heart disease in Japan: The Japanese Network of Cardiovascular Departments for Adult Congenital Heart Disease Registry☆

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ABSTRACT

Background: The Japanese Network of Cardiovascular Departments for Adult Congenital Heart Disease (JNCVD-ACHD) was founded in 2011 for the lifelong care of adult patients with congenital heart disease (ACHD patients). This network maintains the first Japanese ACHD registry.
Methods and results: From 2011 to 2019, the JNCVD-ACHD registered 54 institutions providing specialized care for ACHD patients in 32 of the 47 prefectures in Japan. The registry collected data on the disease profile for 24,048 patients from 50 institutions and the patient characteristics for 9743 patients from 24 institutions. The most common ACHDs were atrial septal defect (20.5 %), ventricular septal defect (20.5 %), tetralogy of Fallot (12.9 %), and univentricular heart (UVH)/single ventricle (SV; 6.6 %). ACHD patients without biventricular repair accounted for 37.0 % of the population. Also examined were the serious anatomical and/or pathophysiological disorders such as pulmonary arterial hypertension (3.0 %) including Eisenmenger syndrome (1.2 %), systemic right ventricle under biventricular circulation (sRV-2VC; 2.8 %), and Fontan physiology (6.0 %). The sRV-2VC cases comprised congenitally corrected transposition of the great arteries without anatomical repair (61.9 %) and transposition of the great arteries with atrial switching surgery (38.1 %). The primary etiology (86.4 %) for Fontan physiology was UVH/SV. In addition, developmental/chromosomal/genetic disorders were heterotaxy syndromes (asplenia, 0.9 %; polysplenia, 0.7 %), trisomy 21 (4.0 %), 22q11.2 deletion (0.9 %), Turner syndrome (0.2 %), and Marfan syndrome (1.1 %).
Conclusions: Although the specific management of ACHD has systematically progressed in Japan, this approach is still evolving. For ideal ACHD care, the prospective goals for the JNCVD-ACHD are to create local networks and provide a resource for multicenter clinical trials to support evidence-based practice.

Introduction

In Japan, the number of adult patients with congenital heart disease (CHD) in 2007 was >400,000, which accounts for >50 % of all Japanese patients with CHD [1]. However, only few cardiologists specialized in adult CHD (ACHD), and these patients were thus primarily treated by pediatric cardiologists. Until around 2010, this care model resulted in pediatric cardiologists caring for most ACHD patients, particularly those with complex CHD and/or severe comorbidities, such as residual cyanosis, critical arrhythmias, heart failure, pulmonary arterial hypertension (PAH), and Fontan physiology [2]. Furthermore, in many cases outpatient care may be discontinued for ACHD patients because of improper transfer to this care setting. In an ideal setting, the care for ACHD patients would be provided at ACHD-specialized and well-equipped institutions with a multidisciplinary team comprising ACHD specialists or experienced physicians, including adult cardiologists, cardiac surgeons, pediatric cardiologists, and interventionists, and other medical staff such as mental health specialists and nurses specializing in ACHD [3].

Because the lack of cardiologists interested in ACHD was a critical problem [3], we undertook a project to provide cardiologists specialized in ACHD. To meet this goal, we founded the Japanese Network of Cardiovascular Departments for ACHD (JNCVD-ACHD, https://www.jncvd-achd.jp/ and https://www.jncvd-achd.jp/english/?l=en_US) in 2011 with 8 institutions, which has since grown to 54 member institutions by 2019 (Fig. 1). All member institutions complete the uniform registry file to provide their data on ACHD patients. This article summarizes these data.

Materials and methods

JNCVD-ACHD institutions

The criterion to become a member institution of the JNCVD-ACHD is that the institution should aim to provide a multidisciplinary care system for ACHD patients with care provided by cardiologists who are willing to specialize in ACHD and cooperate with pediatric cardiologists.

Registry file and data

Each JNCVD-ACHD member institution received and maintained an original registry file (FileMaker Pro, Apple Japan, Tokyo, Japan) that is used for the collection of their data for ACHD patient age 15 years and older (Online Fig. 1). The 18 categories for CHD diagnosis were: 1) aortic stenosis (AS); 2) atrial septal defect (ASD); 3) atrioventricular septal defect/endocardial cushion defect (AVSD/ECD); 4) bicuspid aortic valve (BAV); 5) congenitally corrected transposition of the great arteries (ccTGA); 6) coarctation of aorta/interrupted aortic arch (CoA/IAA); 7) Ebstein disease (Ebstein); 8) mitral valve disease (MV); 9) pulmonary atresia with intact ventricular septum (PA-IVS); 10) pulmonary atresia with ventricular septum defect (PA-VSD); 11) patent ductus arteriosus (PDA); 12) pulmonary stenosis (PS); 13) persistent truncus arteriosus (PTA); 14) total anomalous pulmonary venous return (TAPVR); 15) transposition of the great arteries (TGA); 16) tetralogy of Fallot (TOF); 17) univentricular heart/single ventricle (UVH/SV); and 18) ventricular septal defect (VSD); and others. Patients with previously diagnosed double-outlet right ventricle (DORV) were recategorized into one of the 18 CHD categories or others because DORV comprises several anomalies such as UVH/SV, ccTGA, TGA, TOF, and VSD.

Registry protocol

The original registry file data were created by retrospectively collecting the data on new patients. To transfer the data, PDF and Excel files were created from the original registry file. The PDF file data (Table 1) contained only information on the number of adult outpatients in each CHD category and were transferred annually to the JNCVD-ACHD secretariat at the University of Tokyo, Japan. After obtaining approval from the ethics committee of each institution, password-locked Excel file data containing anonymized patient information (Online Table 1) were also transferred to the JNCVD-ACHD secretariat via the internet. These data collected until 2020 were used for analyses in the present study.

IRB approval

This study (reference no. 10680) was approved by the Ethics Committee of the Office for Human Research Studies, Graduate School of Medicine and Faculty of Medicine, the University of Tokyo, Japan.

Statistical analysis

The statistical software Origin Pro 2019 (LightStone Corp. Tokyo, Japan) was used to determine mean age differences between the groups. Because the Kruskal–Wallis test did not show Gaussian distribution in all the analyses performed, a p-value of <0.05 by Mann–Whitney test indicated significance.

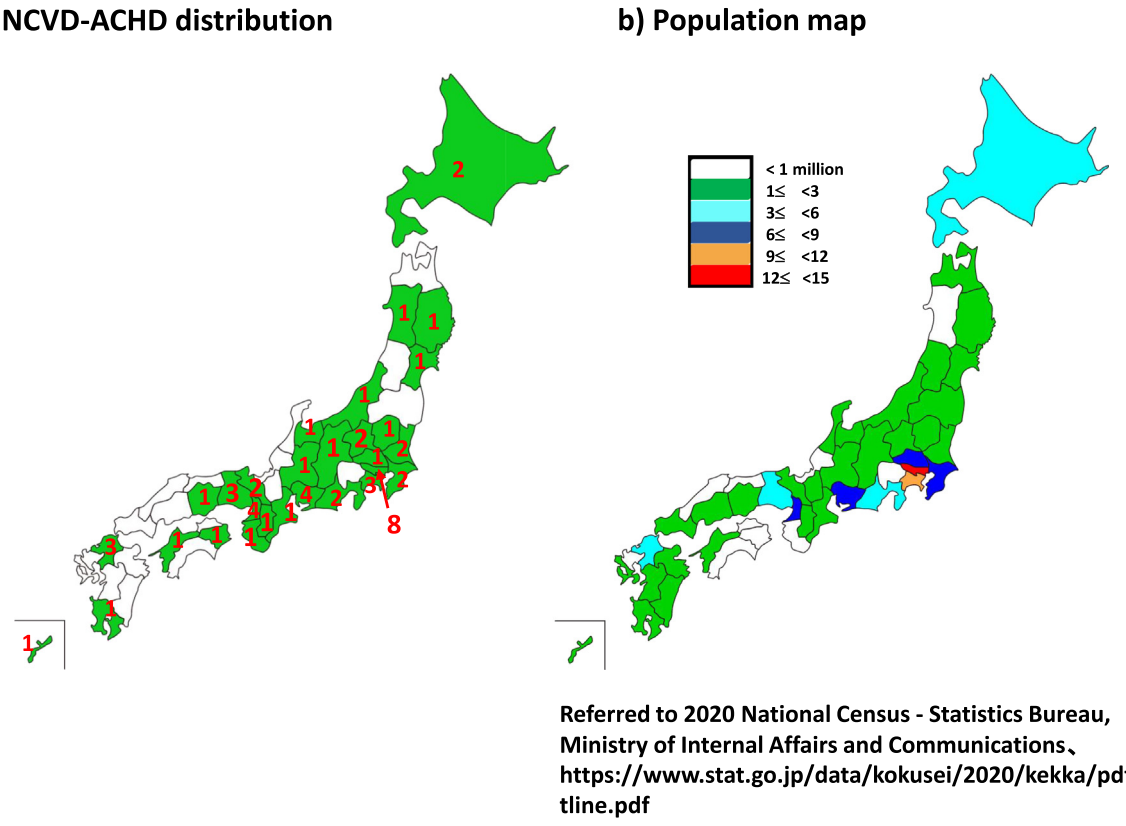

Fig. 1. Distribution of the 54 Japanese Network of Cardiovascular Departments for Adult Congenital Heart Disease (JNCVD-ACHD) institutions. (a) The 29 of 47 prefectures in Japan with JNCVD-ACHD institutions are shown (green), implying the lack of an ACHD-specialized institution in 18 prefectures (white). The number of JNCVD-ACHD institutions is in red. (b) The population for each area is shown as colored. The 29 areas with one or more institutions shown in panel (a) covered all densely populated (≧3 millions) areas, whereas the other 18 areas had <3 million people in each.

Results

JNCVD-ACHD registry outlines

Fifty-four JNCVD-ACHD institutions were located in 32 of the 47 prefectures in Japan, covering all densely populated areas in Japan (Fig. 1). Datasheets provided as PDF files for 24,048 adult outpatients with CHD (ACHD outpatients) were collected from 50 (92.6 %) of the 54 JNCVD-ACHD institutions (Table 1). On average, 480.8 ± 626.4 (37–4021; median 319.5) ACHD outpatients received care in each institution. For the anonymized patient information provided as Excel files, although the collection rate of 44.4 % among 24 institutions was much lower than

Table 1
Profiles of adult outpatients with congenital heart disease in the Japanese Network of Cardiovascular Departments for Adult Congenital Heart Disease.

Main diagnostic name	(Abbreviation)	PDF files	Excel files				
		All N (%)	All N (%)	Female N (%)	Age (Dec 31st,2020)		
					All	Male	Female
Aortic stenosis	(AS)	503 (2.1)	108 (1.1)	44 (40.7)	29.9 ± 12.2	28.6 ± 8.2	31.8 ± 16.4
Atrial septal defect	(ASD)	4941 (20.5)	1978 (20.3)	1273 (64.4)	47.4 ± 21.6	46.2 ± 22.2	48.1 ± 21.2***
Atrioventricular septal defect/endocardial cushion defect	(AVSD/ECD)	1089 (4.5)	366 (3.8)	228 (62.3)	35.8 ± 15.4	33.8 ± 13.8	37.1 ± 16.2
Bicuspid aortic valve	(BAV)	951 (4.0)	381 (3.9)	147 (38.6)	44.7 ± 20.0	44.5 ± 20.3	44.9 ± 19.6
Congenitally corrected transposition of the great arteries	(ccTGA)	589 (2.4)	219 (2.2)	102 (46.6)	39.0 ± 14.8	37.5 ± 14.1	40.8 ± 15.4
Coarctation of aorta/interrupted aortic arch	(CoA/IAA)	807 (3.4)	343 (3.5)	162 (47.2)	29.8 ± 10.8	29.3 ± 11.6	30.4 ± 9.9***
Ebstein disease	(Ebstein)	390 (1.6)	187 (1.9)	105 (56.1)	42.2 ± 17.9	40.6 ± 18.1	43.5 ± 17.8
Mitral valve disease	(MV)	287 (1.2)	116 (1.2)	76 (65.5)	30.8 ± 9.7	29.3 ± 10.1	31.6 ± 9.5
Pulmonary atresia with intact ventricular septum	(PA-IVS)	334 (1.4)	124 (1.3)	68 (54.8)	28.0 ± 6.8	26.4 ± 6.5	29.3 ± 6.7**
Pulmonary atresia with ventricular septum defect	(PA-VSD)	599 (2.5)	260 (2.7)	131 (50.4)	31.1 ± 9.8	31.1 ± 10.2	31.2 ± 9.3
Patent ductus arteriosus	(PDA)	599 (2.5)	256 (2.6)	192 (75.0)	44.1 ± 21.9	30.3 ± 13.3	48.7 ± 22.3*
Pulmonary stenosis	(PS)	630 (2.6)	282 (2.9)	161 (57.1)	32.6 ± 14.2	31.1 ± 14.4	33.8 ± 13.9***
Persistent truncus arteriosus	(PTA)	91 (0.4)	22 (0.2)	9 (40.9)	29.9 ± 6.5	29.5 ± 5.2	30.4 ± 8.2
Total anomalous pulmonary venous return	(TAPVR)	292 (1.2)	98 (1.0)	46 (46.9)	29.5 ± 9.7	28.2 ± 6.8	31.0 ± 12.0
Transposition of the great arteries	(TGA)	993 (4.1)	414 (4.2)	132 (31.9)	30.1 ± 8.7	29.8 ± 8.0	30.8 ± 9.9
Tetralogy of Fallot	(TOF)	3093 (12.9)	1360 (14.0)	662 (48.7)	36.4 ± 13.2	36.0 ± 13.2	36.9 ± 13.1
Univentricular heart/single ventricle	(UVH/SV)	1592 (6.6)	619 (6.4)	275 (44.4)	29.5 ± 8.7	29.4 ± 8.7	29.6 ± 8.7
Ventricular septal defect	(VSD)	4920 (20.5)	2135 (21.9)	1178 (55.2)	35.1 ± 14.7	34.2 ± 15.1	35.8 ± 14.5*
Others		1348 (5.6)	475 (4.9)	247 (52.0)	37.8 ± 16.9	35.7 ± 16.4	39.7 ± 17.1**
Total		24,048 (100)	9743 (100)	5238 (53.8)	37.6 ± 17.1	35.8 ± 16.3	39.1 ± 17.5*

N: the number of patients, The Kolmogorov-Smirnov test did not showed Gaussian distribution in the data of age. * $p < 0.001$, **$p < 0.01$, *** $p < 0.05$ vs Male by Mann-Whitney test.

that for the PDF files, disease categorization was similar between the Excel and the PDF files.

Patient characteristics

The mean patient age was 37.6 ± 17.1 years, and female patients were significantly older (Table 1). Slightly more than half of the patients were female (53.8 %), and female predominance (>55 %) was observed in ASD, AVSD/ECD, Ebstein, MV, PDA, PS, and VSD, whereas male predominance was noted in AS, BAV, PTA, TGA, and UVH/SV (Table 1).

Two simple CHDs, VSD and ASD, and two complex CHDs, TOF and UVH/SV, were the four most common ACHD, in approximately 60 % of all patients (Table 1), followed by TGA, BAV, AVSD/ECD, CoA/IAA, PS, PA-VSD, PDA, and ccTGA, ranging from 4.2 % to 2.2 %; biventricular intracardiac repair (2V-ICR) was performed in 62.9 %. Almost all patients underwent 2V-ICR for cyanotic complex CHDs (87.7 %–99.0 %), including AVSD/ECD, PA-VSD, PTA, TAPVR, TGA, and TOF, but not UVH/SV and PA-IVS (Table 2).

Serious anatomical and pathophysiological disorders

Pulmonary arterial hypertension

PAH, including Eisenmenger syndrome (ES, Online Fig. 1), was observed in 292 (3.0 %) patients, including 101 patients with 2V-ICR (1.6 % of 2V-ICR) and 191 with non-2V-ICR (5.3 % of non-2V-ICR; Table 2). Most (58.2 %) of those with PAH had ASD (102 patients) or VSD (68 patients). In 114 patients (1.2 %), ES was observed, primarily VSD, ASD, and AVSD/ECD. Among 54 patients with unrepaired VSD-PAH, 46 (85.1 %) had ES. In contrast, among 69 patients with unrepaired ASD-PAH, 20 had ES (29.0 %).

Systemic right ventricle under biventricular circulation

Of all patients, 2.8 % had a systemic right ventricle under biventricular circulation (sRV-2VC), comprising ccTGA without anatomical repair (ccTGA-sRV, 76.3 % of ccTGA; 61.9 % of sRV-2VC) and TGA with atrial switching surgeries (24.9 % of TGA; 38.1 % of sRV-2VC; Table 2). Patients with ccTGA-sRV consisted of those with classical 2V-ICR (functional repair, 29.2 % of ccTGA) and with no significant surgery required (47.0 % of ccTGA).

Fontan circulation

Fontan circulation was observed in 580 (6.0 %) of all patients (Table 2): 501 cases (80.9 %) with UVH/SV and 53 (42.7 %) with PA-IVS (Table 2). Of the ccTGA cases, 20 (9.1 %) underwent Fontan surgery.

Developmental/chromosomal/genetic disorders

We investigated the incidence of heterotaxy syndromes (asplenia, polysplenia), trisomy 21 (Down syndrome), 22q11.2 deletion, Turner syndrome, and Marfan syndrome. The mean age was significantly younger in patients with versus without asplenia, polysplenia, trisomy 21, and 22q11.2 deletion, whereas patients with Marfan syndrome were significantly older (Table 3).

More than 90 % (76 of 83) of asplenia cases (0.9 % of all ACHD patients) were categorized with UVH/SV, representing 12.3 % of UVH/SV cases (Table 3). Polysplenia was most common in UVH/SV (48.6 %), representing 5.7 % of UVH/SV cases. Of those with UVH/SV, 17.9 % had a heterotaxy syndrome. Less frequent but noted were asplenia (0.8 %) and polysplenia (4.9 %) among AVSD/ECD cases.

Among the studied chromosomal/genetic disorders, trisomy 21 was the most common (388 patients, 4.0 %) (Table 3), especially in AVSD/ECD (114 patients, 31.1 %), whereas most (128 patients) had VSD (6.0 % of VSD cases). Moreover, trisomy 21 had a high prevalence in patients with PDA (9.4 %), PTA (4.5 %), TOF (4.1 %), Ebstein (3.7 %), and ASD (2.0 %). The presence of 22q11.2 deletion was most frequent in TOF (43 patients), with the highest prevalence (11.2 %) in PA-VSD, both of which accounted for 79.1 % of the patients with 22q11.2 deletion-ACHD, whereas VSD and CoA/IAA accounted for 9.9 % and 7.7 %, respectively. Turner syndrome was not often observed (19 patients, 0.2 %). This syndrome mainly influenced the incidences of BAV and CoA/IAA (Table 3). Patients with Marfan syndrome accounted for 1.1 % of the total population (Table 3). These patients were mostly categorized into others.

Table 2
Clinical Status of adult outpatients with congenital heart disease in JNCVD-ACHD.

Dx	Total	PAH	2V-ICR		Non 2V-ICR (palliations, Fontan, no cardiovascular repair)				sRV
	N (%)	N (% of Dx)	N (% of Dx)	PAH (% of 2V-ICR)	N (% of Dx)	PAH (% of non 2V-ICR)	ES (% of Dx)	Fontan (% of Dx)	N (% of Dx)
AS	108 (1.1)	1 (0.9)	73 (67.6)	0 (0.0)	35 (32.4)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
ASD	1978 (20.3)	102 (5.2)	1282 (64.8)	33 (2.6)	696 (35.2)	69 (9.9)	20 (1.0)	0 (0.0)	0 (0.0)
AVSD/ECD	366 (3.8)	17 (4.6)	333 (91.0)	4 (1.2)	33 (9.0)	13 (39.4)	12 (3.3)	0 (0.0)	0 (0.0)
BAV	381 (3.9)	1 (0.3)	143 (37.5)	0 (0.0)	238 (62.5)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
ccTGA	219 (2.2)	4 (1.8)	116 (53.0)	1 (0.9)	103 (47.0)	3 (2.9)	1 (0.5)	20 (9.1)	167 (76.3)
CoA/IAA	343 (3.5)	6 (1.7)	317 (92.4)	4 (1.3)	26 (7.6)	2 (7.7)	2 (0.6)	0 (0.0)	0 (0.0)
Ebstein	187 (1.9)	0 (0.0)	60 (32.1)	0 (0.0)	127 (67.9)	0 (0.0)	0 (0.0)	5 (2.7)	0 (0.0)
MV	116 (1.2)	1 (0.9)	41 (35.3)	1 (2.4)	75 (64.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PA-IVS	124 (1.3)	1 (0.8)	4 (3.2)	1 (25.0)	120 (96.8)	0 (0.0)	0 (0.0)	53 (42.7)	0 (0.0)
PA-VSD	260 (2.7)	23 (8.8)	228 (87.7)	10 (4.4)	32 (12.3)	13 (40.6)	7 (2.7)	0 (0.0)	0 (0.0)
PDA	256 (2.6)	11 (4.3)	187 (73.0)	2 (1.1)	69 (27.0)	9 (13.0)	7 (2.7)	0 (0.0)	0 (0.0)
PS	282 (2.9)	1 (0.4)	162 (57.4)	1 (0.6)	120 (42.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PTA	22 (0.2)	0 (0.0)	22 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TAPVR	98 (1.0)	3 (3.1)	97 (99.0)	3 (3.1)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TGA	414 (4.2)	14 (3.4)	373 (90.1)	10 (2.7)	41 (9.9)	4 (9.8)	6 (1.4)	1 (0.2)	103 (24.9)
TOF	1360 (14.0)	17 (1.3)	1337 (98.3)	13 (1.0)	23 (1.7)	4 (17.4)	3 (0.2)	0 (0.0)	0 (0.0)
UVH/SV	619 (6.4)	10 (1.6)	3 (0.5)	0 (0.0)	616 (99.5)	10 (1.6)	7 (1.1)	501 (80.9)	0 (0.0)
VSD	2135 (21.9)	68 (3.2)	1119 (52.4)	14 (1.3)	1013 (47.4)	54 (5.3)	46 (2.2)	0 (0.0)	0 (0.0)
Others	475 (4.9)	12 (2.5)	234 (49.3)	4 (1.7)	236 (49.7)	8 (3.4)	3 (0.6)	0 (0.0)	0 (0.0)
Total	9743 (100.0)	292 (3.0)	6131 (62.9)	101 (1.6)	3604 (37.0)	191 (5.3)	114 (1.2)	580 (6.0)	270 (2.8)

AS, aortic stenosis; ASD, atrial septal defect; AVSD/ECD, atrioventricular septal defect/endocardial cushion defect; BAV, bicuspid aortic valve; ccTGA, congenitally corrected transposition of the great arteries; CoA/IAA, coarctation of aorta/interrupted aortic arch; Ebstein, Ebstein disease; MV, mitral valve disease; PA-IVS, pulmonary atresia with intact ventricular septum; PA-VSD, pulmonary atresia with ventricular septum defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; PTA, persistent truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH/SV, univentricular heart/single ventricle; VSD, ventricular septal defect; Dx, diagnostic name of congenital heart disease; ES, Eisenmenger syndrome; N, the number of patients; PAH, pulmonary arterial hypertension; sRV, systemic right ventricle; 2V-ICR, two ventricular intracardiac repair.
2 patients with residual shunt-associated ES after 2V-ICR for TGA were included in 6 TGA-ES patients, while other ES-patients were composed with those with non-2V-ICR.

Table 3
Developmental/chromosomal/genetic disorders of adult outpatients with congenital heart disease.

	All ACHD	Heterotaxy		Chromosomal/genetic disorders			
	Total	Asplenia	Polysplenia	Trisomy 21	22q11.2 deletion	Turner	Marfan
Total (%)	9743 (100.0)	83 (0.9)	72 (0.7)	388 (4.0)	91 (0.9)	19 (0.2)	103 (1.1)
Female (%)	5238 (53.8)	42 (49.4)	39 (54.2)	178 (45.9)	46 (50.5)	–	58 (56.3)
Mean age (yrs)							
All	37.6 ± 17.1	26.9 ± 7.6†	28.8 ± 7.8 †	30.4 ± 9.9†	26.6 ± 5.3†	30.5 ± 9.4	40.9 ± 15.0† †
Male	35.8 ± 16.3	26.0 ± 6.9	28.8 ± 8.2	30.2 ± 9.3	27.1 ± 5.4	–	38.7 ± 15.0
Female	39.1 ± 17.5*	27.8 ± 8.2	28.7 ± 7.5	30.7 ± 10.6	26.2 ± 5.1	–	42.6 ± 15.0
	N	N (% of each Dx)	N (% of each Dx)	N (% of each Dx)	N (% of each Dx)	N (% of each Dx)	N (% of each Dx)
AS	108	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
ASD	1978	0 (0.0)	3 (0.2)	40 (2.0)	0 (0.0)	2 (0.1)	2 (0.1)
AVSD/ECD	366	3 (0.8)	18 (4.9)	114 (31.1)	0 (0.0)	0 (0.0)	0 (0.0)
BAV	381	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	6 (1.6)	0 (0.0)
ccTGA	219	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CoA/IAA	343	0 (0.0)	1 (0.3)	2 (0.6)	7 (2.0)	5 (1.5)	0 (0.0)
Ebstein	187	0 (0.0)	0 (0.0)	7 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
MV	116	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	4 (3.4)
PA-IVS	124	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PA-VSD	260	1 (0.4)	0 (0.0)	3 (1.2)	29 (11.2)	1 (0.4)	0 (0.0)
PDA	256	0 (0.0)	0 (0.0)	24 (9.4)	1 (0.4)	0 (0.0)	0 (0.0)
PS	282	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PTA	22	0 (0.0)	0 (0.0)	1 (4.5)	1 (4.5)	0 (0.0)	0 (0.0)
TAPVR	98	1 (1.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TGA	414	0 (0.0)	2 (0.5)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
TOF	1360	0 (0.0)	2 (0.1)	56 (4.1)	43 (3.2)	2 (0.1)	1 (0.1)
UVH/SV	619	76 (12.3)	35 (5.7)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
VSD	2135	1 (0.0)	2 (0.1)	128 (6.0)	9 (0.4)	2 (0.1)	2 (0.1)
Others	475	0 (0.0)	5 (1.1)	3 (0.6)	1 (0.2)	1 (0.2)	93 (19.6)

AS, aortic stenosis; ASD, atrial septal defect; AVSD/ECD, atrioventricular septal defect/endocardial cushion defect; BAV, bicuspid aortic valve; ccTGA, congenitally corrected transposition of the great arteries; CoA/IAA, coarctation of aorta/interrupted aortic arch; Ebstein, Ebstein disease; MV, mitral valve disease; PA-IVS, pulmonary atresia with intact ventricular septum; PA-VSD, pulmonary atresia with ventricular septum defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; PTA, persistent truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH/SV, univentricular heart/single ventricle; VSD, ventricular septal defect; Dx, diagnostic name of congenital heart disease; N, the number of patients.
†$p < 0.001$, † †$p < 0.01$ vs all other ACHD by Mann-Whitney test; *$p < 0.001$ vs Male by Mann-Whitney test.

Discussion

This study presents data from the first national ACHD registry in Japan, including diagnostic profiles and clinical characteristics of outpatients treated for ACHD at JNCVD-ACHD member institutions, which can be a resource for ACHD clinical studies. Based on the CHD diagnosis, even patients with severe ACHD, including complex or cyanotic CHDs, Fontan circulation, and developmental/chromosomal/genetic disorders, were transferred to the outpatient setting without restriction for treatment by adult cardiologists in cooperation with pediatric cardiologists. Now that a Japanese national resource for ACHD care has been created, the next step is to assess JNCVD-ACHD for points of improvement.

JNCVD-ACHD and other registries

According to a report by Shiina et al. [1] the number of Japanese ACHD patients was approximately 530,000 in 2020, including 175,000 moderate to severe cases, such as the outpatients in the current study. Based on these data, approximately 26,000 ACHD outpatients, representing 0.02 % of the Japanese population, are cared for in 54 JNCVD-ACHD institutions (Table 1), suggesting that the national registration data are sufficient to represent the profile of all moderate to severe cases. However, in terms of transfer to the outpatient setting, only 1/7 (14.7 %) of patients with moderate to severe CHD have been transferred to the JNCVD-ACHD institutions. This estimated low rate of transfer cannot be explained by the lack of JNCVD-ACHD institutions in 18 of the 47 prefectures in Japan (Fig. 1). As previously reported [4], the referral relationship between regional ACHD centers, such as the JNCVD-ACHD institutions, and local facilities in each prefecture (a local network) is thought to be relatively important for the proper transfer of ACHD patients in each prefecture.

The Netherlands CONCOR registry, founded in 2002, has similar criteria for voluntary participation as the JNCVD-ACHD registry. The CONCOR registry has collected data for 17,198 ACHD patients from 107 hospitals till date in 2020, approximately 0.1 % of the total population (https://concor.net/en/). This registration rate (0.1 %) and the number of voluntarily participating hospitals (107) were five times higher and two times larger than those in the JNCVD-ACHD registry, respectively, suggesting that the JNCVD-ACHD registry has much room for improvement.

In this context, the next step is to encourage the JNCVD-ACHD institutions to make a locally suitable network for CHD care in cooperation with local facilities in each prefecture, in addition to establishing more JNCVD-ACHD institutions in the areas of need.

Patient characteristics

The mean patient age was 37.6 ± 17.1 years, with younger patients who had AVSD/ECD, CoA/IAA, or complex/cyanotic CHDs often requiring 2V-ICR/Fontan surgeries (rather difficult open heart surgeries), such as for PA-IVS, PA-VSD, PTA, TAPVR, TGA, TOF, and UVH/SV (Table 1), especially among those with an additional developmental/genetic/chromosomal disorder, such as a heterotaxy syndrome, 21 trisomy, and 22q11.2 deletion (Table 3). This young mean age of the ACHD outpatients may reflect recent (these 40 years) advance of medicine and surgical technique to allow most of infants and children to expect for their adult lives. In another word, it was quite difficult for newborn babies with CHDs before 1980, especially those with complex CHDs, to survive in adulthood.

Regarding ACHD outpatients with 2V-ICR, it is understandable that those with complex/cyanotic CHDs and/or valvular CHDs require ACHD-specialized care for postoperative concerns and various comorbidities that occur later throughout their lifespan. Notable, however, is

the large number of ACHD outpatients requiring treatment for simple CHDs, such as ASD and VSD, who visited the ACHD-specialized institutions (Table 2). This rate may simply reflect the high birth rates of VSD (30 %–40 %) [5,6] and ASD (4 %–35 % of large variance caused by a large ascertain bias due to low disease detectability) [5–8] (35.2 % and 19.3 %, respectively, in Japan, Online Table 2). For those with repaired ASD, we speculate that they may have had, in addition to PAH (Table 1), other conditions such as RV dysfunction, symptomatic arrhythmias, or stroke in adulthood [9]. Concerning VSD, the infundibular/conus/subarterial VSD type that typically does not close naturally [10] may account for 30 % or more of VSD cases in Japan [11], an extremely high rate compared with the Caucasian population (approximately 7 %) [12]. Also in this type of VSD, residual or postoperative aortic valve disorders may require medical follow-up, contributing to the large number of adult outpatients with repaired as well as unrepaired VSD in this study.

Pulmonary arterial hypertension

Epidemiologic data are lacking on the prevalence of PAH in ACHD patients. A European survey reported a range of 5 %–10 % [13]. However, the data were based on echocardiograms as well as hemodynamic studies; thus, overestimation was inevitable. Our rate of PAH was based on PAH/ES diagnosed by hemodynamic criteria (mean pulmonary arterial pressure ≧25 mm Hg and mean pulmonary arterial wedge pressure < 15 mm Hg, Online Fig. 1) and clinically diagnosed ES, guaranteeing the reliability (3.0 % and 1.2 %, respectively) for PAH/ES and for ES only. Until adulthood, unrepaired post-tricuspid shunts represented by VSD was a more likely cause of ES (46 of 54 patients; Table 2) than unrepaired pre-tricuspid shunts represented by ASD (20 of 69 patients). Based on an estimated 175,000 patients with moderate to severe CHD, approximately 5000 ACHD patients with PAH/ES and 2000 with ES may exist in Japan.

Systemic right ventricle

A CHD-specific pathophysiology is sRV, and these patients are at high risk of heart failure and serious arrhythmias [14]. In this study, sRV-2VC was observed in 2.8 % of all patients, including those with ccTGA without anatomical repair (61.8 %) and TGA after atrial switching surgery (38.1 %). These rates may correspond to the estimation of nearly 5000 adult patients with sRV-2VC in Japan, strongly supporting the need for a treatment algorithm specific for sRV failure in this population.

Fontan circulation

The proportion of ACHD patients with Fontan circulation was 6.0 %, about 1600 of those among all 54 JNCVD-ACHD institutions and approximately 10,000 in Japan. Most patients (86.4 %) with Fontan circulation were in UVH/SV, resulting in the fourth highest composite rate (6.6 %, Table 1) of UVH/SV in this study, despite a low birth rate of UVH/SV (1 %–2 %) [5–8,15] (Online Table 2). These patients may develop Fontan-associated liver disease in adulthood and are at high risks for heart failure, valvular disorders, serious arrhythmias, venous thrombosis, congestive organ failure, and protein-losing enteropathy [16]. Finally, some patients become candidates for heart and/or liver transplantation. To date, no surgeries have replaced Fontan surgeries, so effective treatment strategies must be developed to address such adverse events in adult patients after Fontan surgery.

Developmental/chromosomal/genetic disorders

Heterotaxy syndromes

The heterotaxy syndromes of asplenia and polysplenia are strongly associated with complex CHDs [17], represented by DORV, including UVH/SV [17]. Although UVH/SV accounted for most asplenia cases, only 50 % of the study patients with polysplenia also had UVH/SV (Table 3). Because we did not include DORV as a diagnostic category, as described in Materials and methods, the high prevalence of heterotaxy syndromes in UVH/SV is understandable based on previous reports [17].

Trisomy 21

Trisomy 21 is the most common chromosomal disorder, approximately 1 of 800 births worldwide [18], with CHD found in 44 %–66 % of these infants [18,19]. The highest rate of trisomy 21 in this study was in patients with AVSD/ECD (31.1 %), followed by PDA, VSD, PTA, TOF, Ebstein, and ASD. These findings are consistent with the previously reported prevalence [18,19].

22q11.2 deletion

As a rare disease, 22q11.2 deletion is estimated to occur in 1 in 4000–6000 live births, frequently with a cardiac malformation (60 %–80 %), most often a subset of conotruncal malformations (TOF, PTA, or IAA), VSD or ASD, and aortic arch anomalies [20]. In this study, patients with TOF and PA-VSD—which are developmentally similar—were 79.1 % of 22q11.2 deletion cases, whereas those with VSD and CoA/IAA were 9.9 % and 7.7 %, respectively. Thus, the distribution of 22q11.2 deletion in ACHD likely takes over its characteristics at birth.

Turner syndrome

Turner syndrome is rare, with a reported birth rate of approximately 50 in 100,000 girls [21]. Determining the precise prevalence of CHD is challenging because Turner syndrome itself is difficult to diagnose before elementary school. The most common CHD comorbidity is BAV, and CoA is the second most common comorbidity [21]. These rates are consistent with our findings.

Marfan syndrome

Marfan syndrome is also rare, with a prevalence of 1 in 3000–5000 individuals. It is commonly associated with an aortopathy syndrome due to a genetically malfunctioning transforming growth factor-β signaling cascade [22], and reported to not accompany any CHD except mitral prolapse (approximately 50 % of cases) [22] In this study, patients with Marfan syndrome were mostly in the "other diagnoses (others)" category, whereas 4 patients had an MV diagnosis. One reason for the low prevalence of MV may be because the physicians ignored the mitral disease as a minor comorbidity. Based on these findings, it is important to recognize that patients with Marfan syndrome in Japan, regularly receive care in general cardiovascular or Marfan syndrome-specific outpatient clinics but not in ACHD-specialized clinics.

Study limitations

This study had several limitations. The JNCVD-ACHD registry data were collected through December 2020 and do not include the survival and mortality information. Therefore, we calculated patient ages as of December 31, 2020, assuming that all were alive. Although the numeric data for each study variable are not as precise as would be provided by a transverse survey at the specific time point, the prevalence for each condition and comparison among ACHD patients most likely reflects the real-world setting.

Another concern is the possibility of multiple counts of one person reported by different institutions, although no cases showed the same birth year and month, sex, and diagnosis in the Excel file data (9743 patients) of patient characteristics, suggesting that even in the PDF files (24,048 patients) of the diagnoses, the number of duplicate cases is negligible.

Finally, the diagnoses of genetic disorders were based on not genetic tests but instead on the physician's choice of the listed diagnoses.

Conclusions

The JNCVD-ACHD registry data represent ACHD patients in Japan who require specialist care and have been transferred from pediatric physicians to outpatient clinics operated by cardiology departments for adults. These data may represent the diagnoses and patient characteristics for moderate to severe cases of ACHD, including PAH, sRV, Fontan circulation, and developmental/chromosomal/genetic disorders. Although the JNCVD-ACHD system still needs to incorporate local networks for CHD care, in addition to adding more institutions in areas of need, it is ready to serve as a resource for national multicenter clinical trials for various challenges in ACHD, thereby contributing to establishment of the Japanese evidence-based guidelines for ACHD.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.07.019.

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