Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.4(2023). p.267-73 DOI: https://doi.org/10.14238/pi63.4.2023.267-73

Original Article

Accuracy of NADAS criteria to establish diagnosis in children with suspected congenital heart disease

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Abstract

Background The majority of congenital heart disease is diagnosed during evaluation of a murmur detected either during a routine follow-up or while assessing an intercurrent illness. NADAS criteria might be useful as a screening test to differentiate pathologic from innocent murmurs.

Objective To assess the accuracy of NADAS criteria in diagnosing pathology in children with suspected congenital heart disease.

Methods This diagnostic study included children aged 1 month - 12 years who visited the Outpatient Pediatric Cardiology Clinic at Haji Adam Malik General Hospital, Medan, North Sumatera. Inclusion criteria from history and physical examination were recurrent acute respiratory illness (ARI), poor nutritional status, failure to thrive, cardiac murmurs, and/or a history of cyanosis.

Results Seventy children underwent NADAS screening, of whom 60 had CHD. In the <5-year age group, 63.3% had heart disease. All CHD patients had poor nutritional status and abnormal electrocardiogram (ECG), while 88.33% had a history of recurrent ARI, 80% had abnormal chest x-ray, and 55% had abnormal S2 heart sound on auscultation. A grade 3 or higher systolic murmur was found in 78.33% of patients who had CHD. There were 55 children who had a NADAS score of 3 or higher, of which 53 children with CHD and 2 children non CHD (1 of the 2 children non CHD showed only 3 minor criteria of the NADAS score and had infantile fibrosarcoma). The other 15 children had a NADAS score of less than 3 with 7 children with CHD and 8 children without CHD.

Conclusion The NADAS criteria can be used as a screening test to diagnose disease in children suspected of having CHD for cut-off score at 3 (1 major + 2 minor), with 87.14% accuracy, 88.33% sensitivity, 80% specificity, and 0.883 AUC value. **[Paediatr Indones. 2023;63:267-73; DOI: https://doi.org/10.14238/pi63.4.2023.267-73**].

Keywords: *CHD; NADAS criteria; cardiac murmur; children*

Congenital heart disease (CHD) is defined as an abnormality in the cardiocirculatory structure present since birth.[1] The clinical manifestations of this disorder vary from mild to severe. In mild cases, there are often no clinical signs or symptoms. In severe CHD, clinical signs and symptoms are observed from birth and often require immediate action.[2] Cardiovascular signs and symptoms can be non¬specific (e.g., poor feeding and failure to thrive) or specific (e.g., chest pain and palpitations), and can help identify children who are likely to have structural heart disease.[3] In infants, feeding difficulties may be the first sign of congestive heart failure, and is present in approximately one-third of infants and children with CHD.[4] The most common symptoms in children presenting to the emergency department with acute heart failure, include dyspnea, nausea, vomiting, fatigue, and cough.[5]

The prevalence of congenital heart disease is approximately 8/1,000 live births.[6] The majority of them are diagnosed during evaluation of a murmur

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Submitted March 29, 2022. Accepted August 14, 2023.

detected either during a routine follow-up or while assessing an intercurrent illness.[7] Murmurs are abnormal heart sounds due to changes in blood flowing into the heart chambers through defective valves.[8]

It is important to clinically differentiate significant murmurs from innocent murmurs to avoid unnecessarily investigating children with innocent murmurs. The majority of murmurs detected in the pediatric age group are innocent. They are usually found in children aged 3 to 7 years. Innocent murmurs usually do not radiate, and the intensity may change with the child's position or respiration.[7]

Due to the high sensitivity and specificity values from several previous studies that used the NADAS criteria to distinguish between pathological murmurs and innocent murmurs, NADAS criteria might be used as one of the criteria in establishing a diagnosis of disease in children suspected of having congenital heart disease.[7] This study was aimed to assess the accuracy of NADAS criteria in diagnosing pathology in children with suspected CHD.

Methods

This diagnostic study with a cross-sectional approach included children aged 1 month to 12 years who visited the Outpatient Cardiology Pediatric Clinic at Haji Adam Malik General Hospital, Medan, North Sumatera, between January and July 2021. Inclusion criteria were recurrent acute respiratory infection (ARI), poor nutritional status, failure to thrive, cardiac murmurs, and/or cyanosis from history and physical examination. Exclusion criteria were children with syndromes such as Down's syndrome, Noonan syndrome, Turner's syndrome, or children who previously underwent treatment by a cardiologist or a pediatric cardiologist. All children underwent chest x-ray, ECG, and echocardiogram. Significance of NADAS criteria for detection of CHD was analyzed.

Subjects' murmurs were graded according to Levine's criteria in 1933:[7]

- Grade 1 was a barely audible murmur and required several cycles to detect
- Grade 2 was a soft murmur that could be readily heard
- Grade 3 was a moderately loud murmur without a thrill
- Grade 4 was a loud murmur with a thrill
- Grade 5 was a loud murmur that could be heard with edge of stethoscope touching the chest wall
- Grade 6 was a loud murmur that can be heard without the stethoscope touching the chest wall.

The NADAS criteria had 4 major and 5 minor components. Major criteria included systolic murmur of grade 3 or more, diastolic murmurs, cyanosis, and congestive cardiac failure. Minor criteria included systolic murmur of grade less than 3, as well as abnormal second sound, ECG, x-ray, and blood pressure. Scores of 2 points and 1 point were given to major and minor criteria, respectively.

Abnormalities of the aortic and pulmonary components were assessed, including intensity, timing, and wide splitting of aortic and pulmonary components. Abnormalities in size and shape of heart, situs, pulmonary blood flow and other associated anomalies were assessed by chest x-ray. A cardiothoracic ratio >55% and >50% were defined as cardiomegaly in infants and other children, respectively. Cardiothoracic ratio was calculated by dividing the largest horizontal measurement of the heart by the largest internal diameter of the chest in a postero-anterior view. A 14-lead ECG revealed evidence of pressure and volume overload, chamber hypertrophy, as well as PR and QRS abnormalities. Subjects' blood pressure was taken for all children using an appropriately-sized cuff.

This study was approved by the Health Research Ethics Committee, Medical Faculty of Sumatera Utara and Haji Adam Malik Hospital, Medan. Subjects' parents provided written informed consent. The initials of the study subjects were used to ensure the confidentiality of the study subjects' identity. Data was used exclusively for scientific purposes only. Data and ROC curve were analyzed and created using the IBM *SPSS Statistics version 25* software.

Results

Seventy pediatric patients met the inclusion criteria. **Table 1** shows the demographic characteristics of subjects. Sixty children were detected to have CHD. Over half of the subjects (51.67%) were female in the CHD group. There were 38 (63.33%) patients aged

below 5 years and 22 (36.67%) patients aged 5-12 years with CHD. All patients had poor nutritional status, both CHD and non-CHD patients. All CHD patients had an abnormal electrocardiogram (ECG); 53 (88.33%) patients had a history of recurrent ARI; 48 (80%) patients had abnormal chest X-ray; 33 (55%) patients had abnormal second heart sound (S2); 3 (5%) patients had diastolic murmur, 9 (15%) patients had cyanosis, and 8 (13.33%) patients had congestive cardiac failure. A grade 3 or higher systolic murmur was found in 47 (78.33%) patients with CHD.

Table 2 shows type of CHD from the echocardiography results. Sixty children were detected to have CHD, consisting of 21 (30%) patients with patent ductus arteriosus (PDA), 19 (31.67%) patients with ventricular septal defect (VSD), 10 (16.67%) patients with atrial septal defect (ASD). These three dominant events were included in the acyanotic CHD with shunts category. Acyanotic CHD without shunt was found in 1 (1.67%) patient with aortic stenosis and 1 (1.67%) patient with pulmonary stenosis. Cyanotic CHD was present in only 5 (8.33%) patients with TOF and 3 (5%) patients with TGA. About 86% of screened subjects suffered from acyanotic CHD.

Table 3 shows that the lowest NADAS score of 1 (major criteria 0 + minor criteria 1) was found in 5 (7.14%) patients, but their echocardiograms revealed no CHD. However, echocardiography revealed CHD in 7 (10%) patients with NADAS score of 2 (major criteria 0 + minor criteria 2). We used **Table 3** as a guide to decide cut-off points for optimal sensitivity and specificity. The comparison of the NADAS scores with sensitivity and specificity values is shown in **Table 4** and **Figure 1**. NADAS score ≥ 1 had 100% sensitivity but 0% specificity; NADAS score ≥ 2 had 100% sensitivity and 50% specificity; NADAS score ≥ 3 had 88.33% sensitivity and 80% specificity; NADAS score ≥ 4 had 66.67% sensitivity and 100% specificity; and NADAS score ≥ 5 had 20% sensitivity and 100% specificity. Thus, total NADAS score ≥3 (1 major + 2 minor) was the optimal cut-off point for the best sensitivity and specificity values. The cut-off point between sensitivity and specificity is shown in **Figure 1**.

We used echocardiography as the gold standard to assess the accuracy, sensitivity, and specificity of using NADAS as screening criteria for CHD (**Table 5**). Accuracy was 87.14%, sensitivity 88.33%, and specificity 80% for a NADAS score of >3 (1 major + 2 minor) as the optimal value. When the NADAS score was 3 (0 major + 3 minor), they were found to have febrile sarcoma, which is not a CHD. From these results, NADAS criteria can be useful as a screening test to diagnose disease in children suspected of having congenital heart disease.

Table 1. Subjects' characteristics

Characteristics	CHD (n=60)	Non-CHD (n=10)	P value*
Gender, n (%)			
Male	29 (48.3)	6	0.495
Female	31 (51.7)	4	
Age, n (%)			
< 5 years	38 (63.3)	6	0.840
5-12 years	22 (36.7)	4	
Nutrition, n (%)			
Poor	60 (100	10	1
History ARI recurrent, n (%)	53 (88.3)	7	0.125
Major Criteria, n (%)			
Systolic murmur < 3	47 (78.3)	1	<0.001
Diastolic murmur	3 (5)	0	0.470
Cyanosis	9 (15)	0	0.190
Congestive cardiac failure	8 (13.3)	0	0.220
Minor criteria, n (%)			
Systolic murmur < 3	10 (16.7)	5	0.017
Abnormal second sound	33 (55.0)	0	0.001
Abnormal ECG	60 (100)	5	<0.001
Abnormal X-ray	48 (80.0)	1	<0.001
Abnormal blood pressure	7 (11.7)	4	0.023

Figure 2 shows the receiver-operator characteristic (ROC) curve of a NADAS cut-off score of 3. The sensitivity was 0.88, specificity was 0.8 (**Table 5**), and the area under the curve was 0.883 (**Table 6**).

Table 2. Type of CHD from echocardiogram

Type of CHD	(N=70)
PDA, n (%)	21 (30)
VSD, n (%)	19 (27.14)
ASD, n (%)	10 (14.29)
TOF, n (%)	5 (7.14)
TGA, n (%)	3 (4.29)
AS, n (%)	1 (1.43)
PS, n (%)	1 (1.43)
Normal, n (%)	10 (14.29)

PDA=patent ductus arteriosus , VSD=ventricular septal defect, ASD=atrial septal defect, ToF=Tetralogy of Fallot, TGA=Transposition of the great arteries, AS=aortic stenosis; PS=pulmonary stenosis

Discussion

We found no association between gender and suspicion of having CHD in our subjects, nor was there an association between age of the child and CHD (**Table 1**). As age advances, the chance of the murmur being innocent increases.[7] Previous studies revealed that 68-84.8% children with CHD were below 5 years of age.[7,10] In our study, 63.3%of children with CHD were below 5 years.

Physical examination revealed that all patients had poor nutritional status. Children with CHD have a high prevalence of difficulty eating and nutritional disorders.[9] A cross-sectional study was carried out in children aged 0-2 years old in Jakarta reported prevalences of 51.1% malnutrition and 22.3% severe malnutrition in children with CHD, with the prevalence of failure to thrive higher than problems with nutritional disorders.[11] The difference in nutritional status results may be due to differences

Table 3. Score NADAS criteria

NADAS criteria			Echocardiogram results	
Major score	Minor score	Total score	CHD	Non-CHD
0	1	1	-	5
0	2	2	7	3
0	3	3	-	1
1	2	3	13	1
1	3	4	22	-
1	4	5	5	-
2	2	4	6	-
2	3	5	7	-
Total patients			60	10

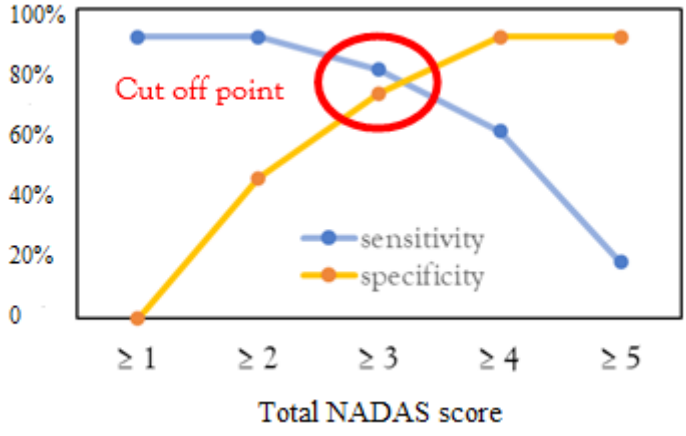

Figure 1. Graphic comparison of NADAS scores' sensitivity and specificity

Table 4. Comparison of NADAS scores on sensitivity and specificity

NADAS score	Sensitivity, %	Specificity, %
≥1	100	0
≥2	100	50
≥3	88.33	80
≥4	66.67	100
≥5	20	100

Table 5. Comparison of NADAS criteria to echocardiography results

NADAS score	Echocardiography results		
	CHD	Non-CHD	Total
≥3	53	2	55
<3	7	5	16
Total	60	10	70

Accuracy 87.14%; sensitivity 88.33%; specificity 80%; positive predictive value (PPV) 96.36%; negative predictive value (NPV) 53.33%; ratio of false negativity 0.15; ratio of false positivity 4.42.

Table 6. Area under the curve (AUC) of NADAS score

Area	Std. error[a]	Asymptotic sig.[b]	Asymptotic 95%CI	
			Lower bound	Upper bound
0.88342	0.076	0.000	0.734	1.000

The test result variable(s): NADAS score has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a]under the bi-negative exponential distribution assumption; [b]null hypothesis: true area = 0.5;

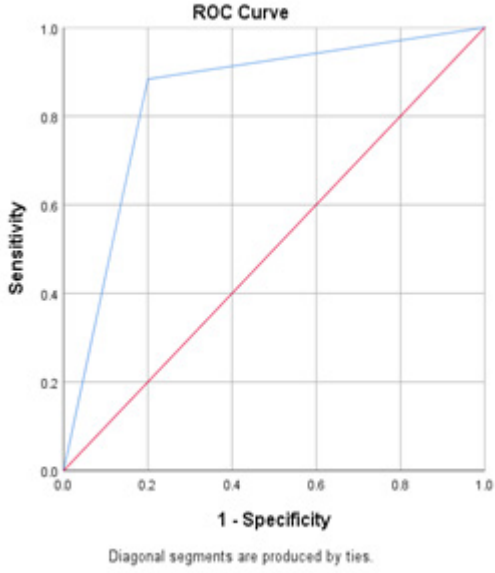

Figure 2. ROC curve in diagnostic test research

in age in the study which is only up to 2 years where children may get adequate nutrition from breast milk. Nutritional disorders in children with CHD are caused by many factors and arise because the need and loss of energy is greater than food intake.[12] The etiology of nutritional disorders in children with CHD can generally be grouped into three categories: inadequate food intake, absorption and inefficient utilization, as well as increased energy requirements.[13]

We also found history of recurrent ARI in 88.33% of patients with CHD. In acyanotic CHD, the volume load and pressure load on the heart increase, causing an increase in blood flow to the heart. The increased volume of blood in the lungs reduces pulmonary flexibility and increases the work of breathing. Increased intravascular pressure in the pulmonary capillaries causes pulmonary edema, leading to ARI symptoms in children.[14] In cyanotic CHD with a right-to-left shunt, hypoxemia is often found because the degree of pulmonary stenosis increases over time, increasing the risk of hypercyanotic attacks. Patients will also experience decreased lung volume, airway hypoplasia, and impaired ventilation perfusion. All of these can damage the airway mucosa, impair immunity,

and ultimately, increase the risk of respiratory tract infections.[15]

In CHD, cyanosis due to low systemic blood saturation. Cyanosis is easily seen in the buccal mucosa, but not around the mouth. Cyanosis due to central cyanosis needs to be distinguished from peripheral cyanosis, which is often seen in children who are feeling cold. Peripheral cyanosis is more clearly seen in the fingertips.[16] In our study, only 9 patients with CHD had cyanosis (5 TOF, 3 TGA, and 1 aortic stenosis).

Heart failure is a clinical syndrome due to heart abnormalities such that the heart is unable to meet the body's metabolic needs. The heart pumps blood with normal strength, but the blood flowing to the peripheral arterial system is ineffective, due to most of the blood leaving the heart flowing to the lungs by an anatomical defect, causing a left-to-right shunt. The heart and lungs are no longer able to cope with the hemodynamic changes. This mechanism often occurs in infants and children with left-to-right defects, namely ASD, VSD, or PDA.[17] In our study, congestive heart failure occurred only in 13.33% patients with CHD (4 large VSD, 3 large PDA, and 1 large ASD).

In our study, 55% of patients with CHD had an abnormal second heart sound (S2). In a normal heart, the second heart sound (S2) during expiration is usually single, and during inspiration the second heart sound (S2) consists of the closure of the aortic valve (A2), which occurs first, and the closure of the pulmonary valve (P2), which occurs second. The A2 sounds broad across the chest. When one hears S2 in the mitral area, A2 will still be heard. The P2 is usually soft and heard only in the pulmonary area (left parasternal, 2nd intercostal space), but even in this area A2 is louder. There are several causes of physiological separation of S2. Both A2 and P2 close when the pressure above each valve is greater than the pressure in the ventricle below. Given the lower vascular resistance of the pulmonary arteries, during inspiration, the pulmonary arteries are able to tolerate more blood volume before the pressure above the valve increases. In addition, during inspiration, more blood fills the right ventricle causing a slightly longer ejection time, adding to the delayed closure of the pulmonary valve. Several techniques are used in testing the second heart sound (S2) such as: separation is best heard in the left 2nd intercostal space (close to the sternal border), the second heart sound (S2) is best heard when the patient is in a semi-supine position (30-40 degrees vertical) and in quiet inspiration, and the intensity of P2 is determined relative to A2. The intensity of P2 is considered to be increased if P2 is louder than A2 in the pulmonary area (left parasternal, 2nd intercostal space).[18] James *et al.*[7] also showed that all of their 21 pediatric subjects with an abnormal second heart sound (S2) had structural heart disease.

In our study, all children with CHD were described with abnormal ECG conditions. These ECG abnormalities included disturbances in P waves and axis (atrial enlargement), QRS and T axes (axis deviation and strain), R height in S and R/S ratio and T waves in the precordial lead (ventricular hypertrophy), QRS waves (RV volume overload and RV pressure overload), and rhythm (arrhythmia). There was left ventricular hypertrophy (LVH) in PDA, VSD, and AS, as well as right ventricular hypertrophy (RVH) in ASD and PS. A previous study showed that the number of children who had an abnormal ECG was significantly higher in children with CHD.[7]

Chest X-ray revealed that 80% of our CHD subjects had cardiomegaly. James et al. showed that all children with cardiomegaly had CHD and 72% of children with abnormal chest X-rays had CHD.[7] In addition, there was an increased pulmonary vascular pattern in patients with PDA, VSD and ASD. Pulmonary vascular markings describe the flow of small blood vessels in the lungs. An increase in pulmonary vascular markings can indicate a number of possibilities, including congestive heart failure, lung infections, chronic bronchitis, and asthma.[7] In addition, there was 1 patient without CHD who suffered from infantile fibrosarcoma, resulting in an abnormal chest X-ray.

The most common minor criteria found in our subjects were abnormal ECG and abnormal chest X-ray. Although S2 and ECG were considered to be minor in the NADAS criteria, all children with abnormal S2 and abnormal ECG in our study had CHD. A false diagnosis of cardiomegaly can be made in children with a large thymus or poor inspiratory effort, which further lowers the x-ray value.[7]

Although a score of 2 or more indicates CHD according to NADAS criteria, in our study a score of 3 and above indicated definite CHD, with optimal

sensitivity and specificity values. This assessment was also in agreement with that of James et al. in which of all children at murmur grade 2, only 26% had structural heart disease while of those at murmur grade 3, almost 71% had structural heart disease.[7]

In conclusion, NADAS criteria can be used as a screening test to diagnose disease in children with suspected CHD, with 87.14% accuracy, 88.33% sensitivity, 80% specificity, at a cut-off score of 3 (1 major + 2 minor).

Conflict of interest

None declared.

Funding acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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