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Association Analysis between Cyanotic Congenital Heart Disease and Nephropathy in Children

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Summary

Cyanotic congenital heart disease (CCHD) causes chronic hypoxia in several organs, especially kidneys. The association between CCHD and nephropathy has been known although the mechanism is not yet completely understood. This study was aimed to investigate the association between CCHD and the incidence of nephropathy in children.

This case-control study was conducted at the Pediatric Outpatient Installation of the Integrated Heart Service Center (IHSC) and Children's Inpatient Room, Dr. Soetomo General Hospital Surabaya from January to May 2021. The inclusion criteria included children with CCHD and normal children aged 1-18 years who visited IHSC and Pediatric Clinic. Informed consent was signed by the parents. Demographic data, proteinuria, and hematuria were analyzed to find the association with the incidence of CCHD in children.

Eighty-five participants participated in the study, of which seven were excluded, leaving 78 eligible participants. Forty-four CCHD patients and 34 control patients had a difference in oxygen saturation (67.70 ± 11.21 to 94.94 ± 0.98%). Sixty-four percent of the participants were diagnosed with tetralogy of Fallot (TOF), while 29.5% were diagnosed with double outlet right ventricle (DORV). There was a significant association between CCHD with proteinuria and hematuria ($p = 0.001$, $r = 0.481$; $p = 0.001$, $r = 0.375$). Significant associations was also found in proteinuria and hematuria with CCHD with a diagnosis of DORV and TOF ($p = 0.014$, $p = 0.002$).

As a conclusion, a significant association was found between CCHD with the incidence of proteinuria and hematuria. Nephropathy screening is needed in patients suffering from CCHD to detect renal damage.

Key Words: congenital heart disease, cyanotic congenital heart disease, hematuria, nephropathy, proteinuria

Introduction

Cyanotic Congenital Heart Disease (CCHD) causes chronic hypoxia in several organs in the body, including the kidneys[1]. Chronic hypoxia can lead to nephropathy, such as proteinuria and hematuria[2]. In overcoming this case, technological advances in surgery have a crucial impact on the life expectancy of children with CCHD, but the emergence of one of the complications, namely nephropathy, will increase mortality and morbidity in the next decade of life[3]. This mortality and morbidity occur in CCHD children who experience nephropathy, although improvements have been made in children with CCHD. So, the early detection of im-

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paired kidney function in children is important to prevent kidney dysfunction[2]. Generally, nephropathy occurs in 70% of CCHD patients above ten years old. Most patients will develop chronic kidney disease[3].

Congenital heart disease (CHD) is clinically divided into cyanotic and non-cyanotic CHD. CCHD occurs in 30% of all congenital abnormalities, with an incidence of 6-10 per 1000 live births. Data from Dr. Soetomo General Hospital showed that the incidence of CCHD occurred in 80 patients per year[4]. Premature babies are twice as likely to suffer from CHD than normal babies, where about 16% of them have CCHD[5]. The most common CCHD prevalence is tetralogy of Fallot (TOF) which accounted about 5-10% and Transposition of the Great Artery around 5%. Otherwise, non-cyanotic CHD are ventricular septal defects (VSD) around 30-50%, atrial septal defects (ASD) around 7-10%, persistent ductus arteriosus (PDA) around 10%[6]. CCHD is generally recognized by hypoxemic conditions, namely oxygen saturation in arterial blood that is less than 90%. Prolonged hypoxia causes several consequences in the lives of CCHD sufferers and causes some difficulties in the treatment of CCHD sufferers[7]. Several studies have shown an association between kidney dysfunction and CCHD. Most researchers state that chronic hypoxia in CCHD causes damage to the glomerulus, which in the long term causes structural and functional damage to the kidneys[8,9]. Early detection of nephropathy in children with cyanotic CHD can be done by examining proteinuria and hematuria. Proteinuria and hematuria are the first signs that appear and are most easily recognized before the onset of decreased kidney function or other symptoms. The presence of proteinuria and hematuria indicates that there has been dysfunction in the layers of the glomerulus with varying degrees of severity. Progressive and long-term damage will cause more massive damage, causing chronic kidney disease[10,11]. Therefore, this study analyzed the relationship between CCHD and the incidence of nephropathy in children.

Methods

This present investigation is a case-control study design to assess the relationship between CCHD and the incidence of nephropathy assessed by the presence of proteinuria, hematuria, in patients with CCHD. The study was conducted at the Integrated Heart Service Center (IHSC) Poly and Children's Inpatient Room, Dr. Soetomo General Hospital Surabaya from January 2021-May 2021. The participants of this study consisted of two groups, namely pediatric patients with CCHD as the Case Group and normal children as the control group. Written consent was obtained from each pediatric patient with CCHD, child control participants and their parents or guardians. The ethical feasibility of research was issued by the Clinical Research Unit Ethics Commission, Dr. Soetomo General Surabaya Number 0155/102/VIII/2020.

The inclusion criteria for this study were: 1) Children aged 1 to 18 years, 2) Children with CCHD whose diagnosis had been confirmed using echocardiography with saturation below 90%, 3) Parents were willing to sign an informed consent to participate in the study. In addition, the other control group had the following inclusion criteria. Children aged 1 to 18 years who were controls to the general pediatric clinic of Dr. Soetomo General Hospital without impaired kidney function and impaired heart function (normal children) and informed consent signed by parents or legal guardians. Exclusion criteria in this study were 1) children who were experiencing infection, namely with a fever of 38.5℃ or higher and the results of blood tests showed white blood cell count (WBC) >15 × 10^3/μl and/or the urine sediment showed WBC >5/hpf with found bacteria, 2) children with cyanotic CHD receiving drugs that affect urinary protein excretion, such as the Angiotensin-converting enzyme inhibitor (ACEI) (captopril), angiotensin II receptor antagonists (losartan), 3) patients with renal structural abnormalities, such as diabetic nephropathy, IgA nephropathy, lupus nephritis, and other glomerulonephritis and nephrotic syndrome, 4) children who experienced strenuous activity in the 24 hours prior to the examination, 5) their parents/legal guardians refused to participate in the study.

The data accumulation of the characteristics of the clinical participants used a data collection sheet. The sheet contained basic patient information and interviews with the patient's parents, as well as data from medical records. The tool needed for urine sampling is a 30 ml urine pot with a minimum of 10 ml of urine for each patient. The urine pot is then labeled and examined for urinalysis and urine sediment. Urine examina-

Table 1 The clinical characteristic of participants (N = 78)

Characteristic	CCHD Group (N = 44)	Control Group (N = 34)	*p*
Gender, N (%)			
Male	16 (36.4)	16 (47.1)	0.341[a]
Female	28 (63.6)	18 (52.9)	
Age (year), Mean ± SD, N (%)	6.68 ± 4.56	7.59 ± 3.07	0.123[b]
< 5	18 (40.9)	6 (17.6)	0.027[a]*
≥ 5	26 (59.2)	28 (82.4)	
Blood Pressure (mm Hg), Mean Systolic/Diastolic			
Children < 5 years old	82.8/46.4	96.7/55.8	
Children ≥ 5 years old	103.1/65.4	104.1/64.1	
Blood Pressure (mm Hg), N (%)			
Normal	33 (75)	34 (100)	0.002[a]*
Below 80/50	11 (25)	0 (0)	

[a]Chi-square test; [b]Mann-whitney test; *a p value < 0.05 was considered significant statistically
CCHD: Critical Congenital Heart Disease

tion was carried out at the Integrated Diagnostic Center Building (IDCB) laboratory, Dr. Soetomo General Hospital Surabaya.

Descriptive analysis was performed to assess the characteristics of CCHD group and control group. The data were analyzed using the Chi-Square test ($\chi 2$) to assess the association between CCHD and the incidence of nephropathy (proteinuria and hematuria). The data normality test was tested using the Kolmogorov-Smirnov test. The Mann-Whitney test was used to test for differences in data that were not normally distributed. We also analyzed the relationship between proteinuria, hematuria, and the type of CCHD with the diagnosis of double outlet right ventricle (DORV) and TOF. Data processing used IBM Statistic SPSS Version 25 software (IBM., Corp., Armonk, NY, USA).

Results

A total of 85 research participants were enrolled in this study consisting of 45 children with CCHD and 40 control groups. There were four children excluded from the control group due to a fever and two children of the control group were excluded because of urinary tract infection (UTI). One pediatric patient with CCHD was excluded due to the use of ACEI. Thus, 78 eligible research participants consisted of 44 children with CCHD and 34 control subjects. The fundamental clinical characteristics, namely age, and sex are presented in Table 1. Female were more prevalent in CCHD with 63.6%, but the distribution of sex in the CCHD group and the control group was not significantly different. It was found that over 5 years old (59.2%) were more than those under 5 years old. The mean oxygen saturation in the CCHD group was 67.70 ± 11.21, while 94.94 ± 0.98 in the control group. There was an obvious difference in the mean SpO_2 level in the CCHD group and the control group (p = 0.001). CCHD group which consists of a few diagnoses, namely TOF and DORV, are shown in Table 2.

Table 2 The diagnosis of CCHD group (N = 44)

Diagnosis	N (%)
Tetralogy of Fallot (TOF)	28 (63.6)
Dextro -Transposition of the great arteries (DTGA)	1 (2.3)
Double outlet right ventricle (DORV)	13 (29.5)
Trunkus arteriosus	1 (2.3)
TGA + Ventricular septal defect (VSD)	1 (2.3)

CCHD: Critical Congenital Heart Disease

Differences in characteristics between the two types of CCHD disorders in this study, namely DORV and TOF, are shown in Table 3. In this study, there were significant differences in mean age (p = 0.004) and oxygen saturation (p = 0.009) between DORV and TOF groups. The association between CCHD on proteinuria, hematuria, and subjects diagnosed with proteinuria and hematuria is presented in Table 4. A total of 24% of all participants were diagnosed with proteinuria. Forty-one percent of patients with proteinuria were

Table 3 The characteristics of CCHD participants who had dignosed TOF and DORV

Characteristic	DORV (N = 13)	TOF (N = 28)	*P*
Gender, N (%)			
Male	6 (46.2)	8 (28.57)	0.269[a]
Female	7 (53.8)	20 (71.43)	
Age (year), Mean ± SD	4.23 ± 3.49	8.21 ± 4.56	0.004[b]*
SpO_2 (%), Mean ± SD	60.38 ± 13.85	70.54 ± 8.82	0.009[b]*

[a]Chi-square test; [b]Mann-whitney test; *a *p* value < 0.05 was considered significant statistically
CCHD: Critical Congenital Heart Disease; DORV: Double Output Right Ventricle; TOF: Tetralogy of Fallot

Table 4 The association analysis of proteinuria, hematuria, and participants who diagnosed both proteriuria and hematuria

	CCHD Group N = 44	Control Group N = 34	*p*
Proteinuria			0.001*
Positive	18 (40.9)	0 (0)	
Negative	26 (59.1)	34 (100)	
Hematuria			0.001*
Positive	12 (27.27)	0 (0)	
Negative	32 (72.73)	34 (100)	
Proteinuria and/or Hematuria			0.001*
Positive	20 (45.45)	0 (0)	
Negative	24 (54.55)	34 (100)	

Chi-square test were used; *a *p* value < 0.05 was considered significant statistically; CCHD: Critical Congenital Heart Disease

found in the CCHD case group. The association test revealed a significant association in the incidence of proteinuria between the CCHD group and the control group with p = 0.001, with a fairly strong association coefficient of 0.481 (Table 4). Hematuria was also associated with the incidence of CCHD (p = 0.001, r = 0.375). From the case group, 45% of the participants were diagnosed with proteinuria and/or hematuria. Table 4 displays the association between CCHD and the incidence of proteinuria and hematuria in general (p = 0.001, r = 0.516). In the control group, there was no incidence of proteinuria and/or hematuria in this study. The saturation of subjects displayed a significant difference in the DORV and TOF groups, so further analysis of proteinuria was carried out in the two study group subjects. Table 5 presents the relationship between the type of CCHD (DORV and TOF) with the incidence of proteinuria and/or hematuria (p = 0.014, p = 0.002).

Table 5 Association between CCHD types with proteinuria and hematuria

	DORV N = 13	TOF N = 28	*p*
Proteinuria			0.001*
Positive	9 (69.23)	8 (28.57)	
Negative	4 (30.74)	20 (71.43)	
Hematuria			0.001*
Positive	8 (61.54)	4 (14.29)	
Negative	5 (38.46)	24 (85.71)	

Chi-square test were used; *a *p* value < 0.05 was considered significant statistically
CCHD: Critical Congenital Heart Disease; DORV: Double Output Right Ventricle; TOF: Tetralogy of Fallot

Discussion

In the case group, a total of 45 patients were collected in the 5-month study period. One child with CCHD was excluded from the study due to taking an ACEI. Angiotensin-converting enzyme inhibitor (ACEI) has been shown to reduce proteinuria in patients with CCHD. ACEI has an anti-proteinuria effect through their direct influence on glomerular hemodynamics by their efferent arteriolar vasodilating effect. An Italian study reported that the combination of ACEIs with angiotensin II type 1 receptor antagonists in children with proteinuria due to major kidney problems reduced proteinuria significantly compared to the separate administration of these drugs alone[12].

Based on the results of the analysis, more female (63.6%) than male children suffered from CCHD. This is in line with research in Baramulah, North Kashmir, and India which found more CCHD prevalence in women[13]. This is different from what happened in Nigeria where CCHD is more common in men than women[14]. The age distribution in the CCHD group in the age group above 5 years was more (59.1%) compared to those aged under 5 years (40.9%). In a study in Manado, it was also found that the most CHD sufferers were in the 4-year-old or less[15,16].

The difference in the proportion of sex in patients

with CCHD can be caused by variations in research methods between studies, study locations, and inequality sample selection between studies based on inclusion and exclusion criteria. Children cases of CCHD in this study had two major groups of CCHD abnormalities that predominated, namely 63.6% (28/44) with TOF and 29.5% (13/44) with a diagnosis of DORV. Several studies found that the most common diagnoses of children with CCHD were TOF, tricuspid atresia, and VSD[13,17-19]. In contrast, DORV was only found in 0.5% of study subjects. Another study by Namuyonga[20], which collected retrospective data over seven years from the Uganda Heart Institute and summarized 4621 study subjects with CHD. Similar to this study, TOF was the most common case in the CCHD group (247 cases; 7% of all CHD cases), but the second most common cyanotic CHD case was slightly different, namely Truncus Arteriosus (165 cases; 5% of all CHD cases). DORV occupies the third position with as many as 104 cases (3% of all CHD cases). For age characteristics between TOF and DORV cases, similar to this study, TOF age at diagnosis was higher than DORV.

The causes of chronic hypoxia in the kidneys are multifactorial. Concerning CCHD, hypoxia can play a role in the early stages. Chronic hypoxia can affect kidney function, either directly or through secondary effects, namely polycythemia and blood hyperviscosity. In CCHD chronic hypoxia will cause erythrocytosis stimulation through erythropoietin, ultimately causing an increase in blood viscosity (hyperviscosity). Hyperviscosity can cause an increase in glomerular efferent arteriolar resistance, hydraulic pressure in the glomerulus, and filtration fraction, which will increase oncotic pressure in the glomerulus[21]. A review describes how CHD can cause long-term changes in kidney function[22]. In addition to cyanosis which indicates chronic hypoxia in subjects with cyanotic CHD, other factors that also play a role in changes in renal function are polycythemia, changes in blood flow to the kidneys, intraglomerular hemodynamic changes, and neurohormonal activation. The abnormality of the hydrostatic pressure will lead to pathological changes in the kidneys, including glomerulosclerosis[22].

Table 4 reported that hematuria is more prevalent in the CCHD group than in the control group. Hematuria in the urine indicates a breakdown of the glomerular filtration barrier (GFB). GFB consists of five components, namely endothelial surface coated with glycosaminoglycans, endothelial cells, glomerular basement membrane, podocytes, and subpodocyte spaces. The specific mechanism by which red blood cells can penetrate the GFB is still unknown. In children with CCHD, erythrocytosis is found which will be accompanied by an increase in blood viscosity and an increase in intraglomerular endothelial shear stress, which will disrupt the integrity of the GFB and cause hematuria[23].

In the present study, the incidence of proteinuria was significantly higher in DORV (69.23%) than in TOF (28.57%). The condition of polycythemia which also plays a role in causing damage to the basement membrane is also caused by chronic hypoxic conditions. Furthermore, the difference in oxygen saturation was statistically significantly lower in DORV. Polycythemia is a form of adaptation of cyanotic CHD patients to low oxygen saturation. Polycythemia also poses a risk of thromboembolism in patients with cyanotic CHD, including thromboembolism in the kidneys[24]. The relationship between the severity of polycythemia and proteinuria is not clear, but this study can show that lower oxygen saturation in DORV may be one of the factors why proteinuria is more common in the DORV group. The absence of hematocrit data is one of the weaknesses of this study so that this study cannot show that polycythemia secondary to chronic hypoxia in cyanotic CHD has a relationship with proteinuria through basement membrane proliferation.

Table 5 reports that there are 12 children with CHD experiencing hematuria. Cyanotic congenital heart disease can cause damage to the glomerulus and produce structural abnormalities in the form of glomerulomegaly, capillary dilatation, capillary wall thickening, the focal and diffuse proliferation of mesangial and segmental cells, and even global glomerulosclerosis, which can manifest as hematuria[25].

Amornchaicaroensuk's study was conducted on older children and adults with CHD by assessing kidney function by calculating the glomerular filtration rate (GFR), urinary protein to creatinine ratio and urinary albumin to creatinine ratio. Although very different from this study, Amornchaicharoensuk's study proved that the prevalence of impaired renal function

and biochemical markers indicating impaired renal function was higher in the CCHD group than in the acyanotic CHD group[26].

Conclusion

This study proved a significant relationship between CCHD and the incidence of nephropathy, such as the incidence of proteinuria and/or hematuria in children. In addition, the results showed a difference in the incidence of proteinuria and hematuria between the CCHD types, DORV and TOF. Nephropathy screening needs to be done in CCHD patients by conducting urinalysis, to detect damage to the kidneys so that the progression of kidney damage can be inhibited. In addition, hematocrit and renal function (serum creatinine and glomerular filtration rate) should be examined to evaluate further kidney damage. Administration of ACEI is also necessary to reduce intraglomerular pressure and proteinuria through their directly vasodilating effects on the efferent arteriole in CCHD patients.

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Competing Interest Statement

The authors declare no conflict of interest.

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