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The Association between Kidney Function and the Severity of COVID-19 in Children

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Abstract

BACKGROUND: Kidney manifestations are life-threatening conditions, such as end-stage kidney disease, notably when caused by viral infections. The severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), is an emerging global health problem, potentially affecting all organs, including the kidney. Most reports on kidney manifestations were focused on the adult and elderly population but limited on children.

AIM: This study aims to analyze the association between kidney function and the severity of the disease of pediatric patients suffering from COVID-19.

METHODS: From March 2020 to March 2021, an observational analytic study was conducted in Hasan Sadikin General Hospital, Bandung, Indonesia. The demographic data, clinical signs, laboratory results, and notable kidney function were analyzed, and based on its clinical appearance the disease was classified as severe and non-severe. Subsequently, the Mann–Whitney test for nonparametric was used to analyze the collected data.

RESULTS: In this study, 40 COVID-19 children were selected as the subjects, and the median estimated glomerular filtration rate (eGFR) value in the severe group was discovered to be lower (88.2 mL/min/1.73 m^2) compared to the non-severe (124.4 mL/min/1.73 m^2), it was statistically significant ($p = 0.041$). There was no difference in hemoglobin and leukocyte values between the two groups ($p > 0.05$). Furthermore, the CRP and NLR results showed no difference between the groups ($p > 0.05$).

CONCLUSION: A severe SARS-CoV-2 infection correlates with kidney function, which was manifested by a lower median eGFR value in the severe compared to the non-severe group.

Introduction

Since the emergence of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in December 2019, the world in both developed and developing countries has been hunted due to the fast spread of the disease. As a result, in 2020, the WHO declared the disease a pandemic. COVID-19 was first reported on March 2, 2020, and treated at Hasan Sadikin Hospital, Bandung on March 17, 2020, which was the case of a 17-year-old girl that had close contact with her father that died of the disease in Indonesia. Furthermore, it is known to be caused by SARS-CoV-2 [1], and results in the rapid activation of innate immune cells, especially in patients with severe infection. This novel disease primarily manifests as an acute respiratory illness accompanied by interstitial and alveolar pneumonia, but also affects multiple organs, such as the heart, digestive tract, blood, central nervous system, and kidney [2], [3], [4], [5]. In addition, COVID-19 raises the levels of various pro-inflammatory effector cytokines, especially in critically ill patients with acute kidney injury (AKI) [5], [6].

Besides the respiratory system, the kidneys (urinary system) are the most frequently involved in the COVID-19 process [3], [7], [8], [9], [10], [11]. The various kidney involvement in children with this disease ranges from mild, such as proteinuria or asymptomatic hematuria, to severe forms, such as AKI [5], [11], [12].

This study aims to analyze the various characteristics and to determine the correlation of kidney function and severity of the disease in children with clinical and radiological features of pneumonia and/or hypoxemia (SpO_2 < 90% on room air). Furthermore, this study was conducted on pediatric patients suffering from COVID-19 who were hospitalized in the pediatric intensive care unit (PICU) at Hasan Sadikin Hospital in Bandung, Indonesia.

Material and Methods

This was an observational and analytical study on pediatric patients suffering from COVID-19, treated

at Hasan Sadikin Hospital in Bandung between March 2020 and March 2021. After receiving clearance from the Health Research Ethical Committee, Hasan Sadikin Hospital, Bandung (No.1159/UN6.KEP/EC/2019), the data were obtained from medical records. Furthermore, COVID-19 children with complete data on general characteristics, such as age, gender, treatment date, and underlying disease were the inclusion criteria for the study subjects. The clinical features and possible infection of the respiratory system were also noted, with laboratory and radiological features recorded including routine blood tests, serum urea, creatinine, CRP, Neutrophil-Lymphocyte Ratio (NLR), and chest radiograph. Subsequently, the patients were classified into two groups based on the severity of the disease. Children with clinical and radiological features of pneumonia and/or hypoxemia (SpO_2 < 90% on room air) and/or those hospitalized in the PICU as the severe, and without pneumonia or hospitalized as the nonsevere. Based on the serum creatinine, the estimated glomerular filtration rate (eGFR) value was calculated using the Schwartz formula. The data which included the platelets, CRP, NLR, and eGFR, were presented descriptively using tabulations and analyzed using different tests. When the data were normally distributed, the independent t-test was used, and when not normal, the Mann–Whitney method was utilized. Furthermore, the Shapiro–Wilk test was used to analyze the numerical data normality.

Results

Only 40 children met the inclusion criteria during the study period, from March 2020 to March 2021, out of 64 who had positive PCR results for COVID-19. There were 31 children with COVID-19 without kidney disease, and the resulting data were not normally distributed.

Demographic data and epidemiological characteristics of research subjects are presented in Table 1.

Based on Table 1, the median age of the study subjects was 8.12 years, with a range of 27 days (0.08 years) and 17.42 years. A ratio of 1.10:1 was noted with more boys 21 (52.5%) than girls 19 (47.5%). Out of the 40 study subjects, nine had kidney disease (22.5%), five had cancer, and four (10%) had congenital abnormalities. Meanwhile, two were suffering from Tetralogy of Fallot, one with complete atrioventricular septal defect, and one had intrahepatic cholestasis and jaundice accompanied by microcephaly and diaphragmatic hernia. Other epidemiological data revealed that two patients traveled to the COVID-19 area, 11 patients had contact with an infected person, while 27 had no contact.

Table 1: Characteristics of children with COVID-19

Characteristic	n_1 (40)	%	n_2 (31)	
			Non-severe	Severe
Age (years old)				
<2-year-old	9	22.5	2	6
2–6-year-old	6	15	5	0
>6-year-old	25	62.5	15	3
Median (range): 8.12 (0.08–17.42)				
Gender				
Boys	21	52.5	10	6
Girls	19	47.5	12	3
Underlying disease/Comorbid				
Healthy	15	37.5	13	2
Congenital	4	10	2	2
Tuberculosis	3	7.5	1	2
Obesities	1	2.5	1	0
Kidney Diseases	9	22.5	0	0
Tumor/Cancer	5	12.5	3	2
Others	3	7.5	2	1
Epidemiologic history				
Traveling history	2	5	1	0
Contact history with confirmed COVID-19 patient	11	27.5	9	1
Family cluster	0	0	0	0
Unknown	27	67.5	13	7

n_1: all children with COVID-19, n_2: children with COVID-19 without Kidney Diseases.

Clinical characteristics of children with COVID-19

The subjects in this study experienced various symptoms and signs are shown in Table 2.

Table 2: Clinical characteristics of children with COVID-19

Characteristic	n	%
Clinical signs		
Asymptomatic	7	17.5
Fever	12	30.0
Cough	10	25.0
Vomit/diarea	3	7.5
Breathless	8	20
Clinical classification		
Severe/Bronchopneumonia	11	27.5
Non-severe/ Non Bronchopneumonia	29	72.5

Table 2 shows that, out of the 40 children, 7 (17.5%) had no symptoms, while the rest had fever (12 or 30%), cough (10 or 25%), vomit/diarrhea (3 or 7.5%), and breathlessness (8 or 20%). However, based on the severity of the disease, two patients were critically ill and needed treatment at the PICU, while nine patients with bronchopneumonia were treated in the Pediatric wards.

Laboratory investigation and outcome of COVID-19 patients

To analyze the correlation between kidney function of pediatric patients suffering COVID-19, 9 with kidney diseases of the 40 patient subjects were excluded from the study. The complete laboratory results included the hemoglobin, leukocyte, platelet, C-reactive protein (CRP), NLR, and serum creatinine values, which were converted to eGFR using the Schwartz formula. Furthermore, chest radiographs were taken on all the subjects. Out of the 31 subjects, two required PICU treatment, and one died. Table 3 shows the laboratory, radiological, and outcomes of the study subjects.

From Table 3, the platelet levels in the severe group were lower than those in the non-severe ($p = 0.881$). There was no difference in hemoglobin and leukocyte values between the two groups ($p > 0.05$). Furthermore,

Table 3: Laboratory and radiologic findings in children with COVID-19 according to disease severity without kidney diseases

Variable	Overall (n = 31)	Disease severity		p
		Nonsevere (n = 22)	Severe (n = 9)	
Laboratoric findings				
Leucocyte (×10^3/mm^3)	9.43 (4.04–27.55)	8.76 (4.04–26.78)	10.52(5.37–27.55)	0.374
Limphocyte (×10^3/mm^3)	2.50 (0.42–11.57)	2.50 (1.90–7.28)	2.22 (0,42–11.57)	0.628
Thrombocyte (×10^3/mm^3)	265 (2–792)	279 (2–589)	212 (33–792)	0.881
Hemoglobin (g/dL)	11.0(5.2–24.5)	11.4 (5.2–24.5)	10.0 (8.7–14.7)	0.498
CRP (mg/L)	0.47 (0.06–29.0)	0.46 (0.06–18.58)	0.47 (0.06–29.0)	0.493
NLR	1.72 (0.04–31.6)	1.91 (0.25–31.6)	1.19 (0.04–22.75)	0.915
eGFR (mg/dL)	113 (28–798)	124.4 (65–231)	88.2 (27.9–798)	0.041
Radiologic findings				
Normal	22	22	0	
Local infiltrate	1	0	1	
Bilateral infiltrates	8	0	8	
Outcome				
Discharge	12	12	0	
Pediatric ward	16	10	6	
PICU	2	0	2	
Death	1	0	1	

CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, PICU: Pediatric intensive care unit. Data presented as median and range from minimum-maximum. The Mann–Whitney test was significant at $p < 0.05$.
NLR: neutrophil lymphocyte ratio

the CRP and NLR results showed no difference between the two groups ($p > 0.05$). The eGFR value in the severe group was lower (88.2 mL/min/1.73 m^2) compared to the non-severe (124.4 ml/min/1.73 m^2), which was statistically significant ($p = 0.041$). There were no data on the amount of urine or urinalysis results in the study subjects. Meanwhile, radiological findings revealed that 22 from the non-severe group were normal and from the severe group, one had local infiltrate and eight had bilateral infiltrates.

Discussion

The subjects of this study were 40 children ranging in age from 27 days to 17.42 years, and nine patients under the age of 2. Another study conducted in Korea revealed that out of 201 children confirmed with COVID-19, the youngest infected was 45 days, and the oldest was 15 years [3], [13]. According to some studies, infants and children under age 2 were more susceptible to COVID-19 infection [7], [14]. Therefore, they showed severe symptoms, especially with comorbidities, accompanied by decreased kidney function, indicated by increased serum creatinine levels. In this study, the kidney function was different between the severe and non-severe groups. This is seen from the results of median and range from minimum-maximum eGFR of severe disease, which were 88.2 (27.9–798), while non-severe disease were 124.4 (65–231) and statistically significant.

Most COVID-19 patients who experienced severe and critical illness or were hospitalized at the PICU, were diagnosed with comorbid diseases, such as hypertension, cardiovascular infection, or diabetes mellitus [3], [8], [9], [10], [11], [15]. In this study, the comorbid factors obtained included several congenital disorders, such as Tetralogy of Fallot, complete atrioventricular septal defect, and intrahepatic jaundice cholestasis with microcephaly, diaphragmatic hernia, cancer, and tuberculosis.

When SARS-CoV-2 enters the body, the innate immune cells, which are the first line of defense, respond to virus immunity, and anti-infection immune tolerance. This response is designed to identify coronavirus, while anti-infection immune tolerance is a mechanism that regulates the immune response to avoid overreaction of the body. Furthermore, the imbalance between the immune response and tolerance can lead to anti-infection immune intolerance. This causes organ injury by pro-inflammatory cytokines and impaired adaptive immune responses. Moreover, SARS-CoV-2 infection through angiotensin-converting enzyme 2 (ACE2) can cause local and systemic pathological changes, such as cellular immune disorders, cytokine storms, deposition of immune compounds, endothelial cell injury, thrombus formation, impaired glucose, lipid metabolism, and hypoxia. This will aggravate the injury of the organs including the kidneys [16]. One of the severe complications of COVID-19 is AKI and this pathophysiology is multifactorial such as direct viral injury, dysregulated inflammation with cytokine storm, and vascular injury. The other hypothesis of AKI is that several pro-inflammatory are released in the clinically severe COVID-19 manifestation, resulting in podocyte collapse, apoptosis, and even glomerular fibrosis [3], [5], [8], [17]. The AKI aggravate the proteinuria by releasing transforming growth factor beta (TGF-β) [18].

The epidemiology of AKI in children infected with SARS-CoV-2 reported was variable. In a cohort of 52 children in the UK, 46% had a serum creatinine level above the normal upper limit, while 29% met the definition of AKI, but none required RRT [19], [20]. In another multicenter study, 18% of the critically ill children with COVID-19 had AKI [20]. A strong link between AKI and Multisystem Inflammatory Syndrome in Children was reported in these two studies. This is a severe form of COVID-19 presentation that usually occurs few weeks after the initial (usually milder) symptoms [21].

This present study revealed that fever and respiratory symptoms predominated in the symptomatic children with COVID-19 with gastrointestinal symptoms coming as the next common manifestations. Moreover, other observational studies have reported similar frequency of symptoms [22]. According to Li *et al*.

(2020), cough and fever were common symptoms in COVID-19. In addition, a systematic review of 27 studies showed that fever was present in half of the subjects (41–58%), followed by cough (39–51%) and rapid breathing (6–17%). Gastrointestinal symptoms, particularly diarrhea was noted in 6–13% of children [22]. In this study, clinical symptoms revealed that, out of the 40 COVID-19 children, fever (30%), and respiratory symptoms (cough 25% and breathless 20%) predominated. Gastrointestinal symptoms (7.5% and 17.5%) were also present but did not express any symptoms. Symptoms and severity of COVID-19 pneumonia in children are the same as for other viral pneumonias [22], [23].

COVID-19 pneumonia imaging findings in the pediatric population may differ from adults. In diagnosis, chest X-ray should be preferred, while CT scan should be requested if there is a pathologic finding on radiography that merits further evaluation and if clinically indicated [24], [25]. Adult COVID-19 pneumonia has been associated with typical findings on chest CT imaging. The most common findings are multifocal peripherally located ground-glass appearance starting from the lower lobes, with thickening in the interlobular septa, prominent vascular structures, halo, and inverted halo signs. In advanced cases, crazy paving appearance and fragmented consolidation are observed [25]. The ground-glass appearance observed especially in chest CT is thought to be caused by alveolar edema, exudation, and bleeding secondary to inflammation [23], [24]. Chest X-ray imaging is mostly preferred for the diagnosis of pneumonia in children. However, there are few studies on the use of chest X-ray in COVID-19 pneumonia in literature. In our chest X-ray examinations, abnormal findings were observed in 46% of cases diagnosed with COVID-19 pneumonia. The most common findings in chest X-ray was a unilateral increase in density and the lower zones were the most affected area [25]. Ground-glass opacity (GGO) was the most common radiographic presentation of children with COVID-19 pneumonia, while the proportion of cases with consolidation was lower in the cohort as compared to the viral pneumonia cohort [23]. Other radiographic presentations of COVID-19 pneumonia included tiny nodules, consolidation combined with GGO, cable shadow, light shadow, streak shadow, and hydrothorax. There were no significant differences found between the cohort and the viral pneumonia cohort [25], [26].

COVID-19 cases were mild not only in clinical symptoms but also in laboratory examination results which included lymphocyte, CRP, PCT, and D-dimer levels in the children under 5 years. Imaging results were more commonly presented as ground-glass opacity in COVID-19 patients [25], [26]. Furthermore, the number of cases and literature on the imaging of COVID-19 pneumonia, its findings, contribution to diagnosis, its correlation with RT-PCR, and its differences in pediatric patients are limited. There have been few studies, evaluating the findings in chest X-rays [24], [25], [26]. However, COVID-19 pneumonia is clinically mild in children; hence, chest X-ray is usually performed in pediatric patients. Chest CT scan is performed when there is a pathologic finding on radiography that merits further evaluation and if clinically indicated. Imaging findings have been reported to be different from adults and may be atypical [24], [25], [26].

COVID-19 was found to be more lethal in men than women, with a mortality rate of 2.8% and 1.7%, respectively [27], [28]. Data from several European countries showed a similar number of cases between men and women, but, more severe in males [28]. In addition, mortality rate was higher in those with cardiovascular disease, and the reason this mechanism being more in women was unclear [27], [28]. The mechanism and role of ACE2 and transmembrane serine protease 2 (TMPRSS2) receptors, sex hormones' role in responding to adaptive and natural (innate) immune responses, and a specific lifestyle regarding gender, health patterns, psychological stress, and socioeconomic conditions were investigated [1], [27], [28]. TMPRSS2 was the second protein for the invasion of SARS-CoV-2 into cells and was mostly found in the prostate epithelium [1]. Meanwhile, the androgenic ligands and androgen receptors regulated the TMPRSS2 transcription [1]. To enter cells, the SARS-CoV-2 virus binds to the ACE2 receptor and the TMPRSS2 cellular serine protease. In various tissues, including the lungs and kidneys, ACE2 was the membrane-based protein expressed. Furthermore, various reports have shown that the circulating ACE2 levels were higher in men than women with kidney disease. The solute ACE2 was enzymatically active and had modest inhibitory effects on viral infection efficiency. However, no relationship was found between circulating ACE2 levels and COVID-19 involving epigenetic factors [5].

Several data that supported the role of gender in the incidence and severity of COVID-19 were mostly performed in adults [27], [28], while, it was limited in children. In this study, nine children experienced severe COVID-19 manifestation, six of them were male and three were female, and this result matched theoretically. The mechanism underlying the higher mortality rate for men than women was still unclear. Nonetheless, the role of the ACE2 receptor, the TMPRSS2 cellular serine protease, and sexual hormones in response to innate and adaptive immune responses was suggested. To enter cells, the SARS-CoV-2 virus binds to the ACE2 and TMPRSS2 receptors [1]. Various reports showed higher levels of circulating ACE2 in men than women with kidney disease [13], [27], [28]. However, several preclinical trials have shown that ACE2 had a protective effect against lung disease [29], [30]. However, presently, this role is still unclear when compared based on gender. According to a study conducted in China by Qiu *et al*. (March 2020), the majority out of 36

children below 16 years infected with COVID-19 were 3.8-years-old [31].

Some COVID-9 patients with AKI come to the hospital with complaints of vomiting and diarrhea. In these cases, there was an assumption that this was due to pre-renal problems [8]. In addition to these reasons, the incidence was suspected to be caused by an accompanying comorbid or direct invasion of the viral material into the kidney parenchyma [7], [9]. Moreover, in this study, there were 3 (7.5%) cases with vomiting and diarrhea complaints, which was one of the symptoms of AKI. However, AKI occurrence in patients with these complaints is still unknown. Some postmortem histopathology findings indicated interference or damage to the kidney tissue of COVID-19 patients that were not previously detected through routine examination (increased levels of urea or creatinine), indicating the possibility of subclinical AKI [11].

Furthermore, this study revealed a higher CRP, lower thrombocyte count, and lower NLR in the severe group but statistically not significantly different. This condition correlated with the advanced cytokine storm process that increased pro-inflammatory mediators, such as interleukin (IL)-6, TGF-β, tumor necrosis factor-α, vascular endothelial growth factor, platelet-derived growth factor, IL-10, and soluble urokinase plasminogen activator receptor [5]. The release of pro-inflammatory and anti-inflammatory mediators disrupted clotting cascades, causing thrombus in the later stages, and plasminogen stimulation with antithrombin-III activation took place in the fibrinolytic system [32]. As a result, fibrinolytic and fibrinogen substances were depleted, while clot formation and bleeding associated with disseminated intravascular coagulation also occurred concurrently. Cases with inflammatory and biochemical indicators related to organ or tissue damage, D-dimer, and secondary bacterial infection were also lower in COVID-19 pneumonia [16], [23].

Conclusion

Although children have fewer ACE2 receptors, the severe form of COVID-19 was found at their age. The severity of this disease was associated with kidney function, even at a childhood age. Therefore, the pediatric nephrologist should be aware of kidney involvement for those with severe clinical manifestations.

Data Availability

In this study, the data used to support the findings were included in the manuscript.

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