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Correlation Cycle Threshold (Ct) values and clinical symptoms of pediatric patients with COVID-19

Andrew Partogi Hamonangan Hutabarat[1], Sabar Hutabarat[2*], Wahyu Indah Dewi Aurora[3]

[1]Faculty of Medicine, Universitas Kristen Indonesia, Indonesia
[2]Faculty of Medicine, Universitas Adiwangsa Jambi, Indonesia
[3]Faculty of Medicine, Universitas Jambi, Indonesia

*Corresponding:
Sabar Hutabarat; Faculty of Medicine, Universitas Adiwangsa Jambi, Indonesia
haisayaaurora@gmail.com

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ABSTRACT

Introduction: The COVID-19 pandemic has affected individuals of all age groups, including children. Understanding the correlation between cycle threshold values and clinical symptoms in pediatric patients with COVID-19 is crucial for accurate diagnosis and management of the disease. This research aims to determine the correlation of Cycle Threshold (CT) Values with Clinical Symptoms Of Pediatric Patients With COVID-19.

Methods: This research uses quantitative design with a cross sectional study approach. The population in this study was all children diagnosed with COVID-19 at hospitals in Jambi City in 2021. The data for this study were collected by reviewing the medical records of children registered at Jambi City Hospital who were diagnosed with confirmed cases of COVID-19. Data analysis of this study used univariate and bivariate analysis.

Result: From the characteristics of respondents, it was found that the majority of respondents were aged 11-18 years (58%) and male (58%). From the distribution of clinical symptoms, it was found that some receptors had milder symptoms (48%). The results of this study show that clinical symptoms are significantly associated with low CT values in pediatric patients with COVID-19 ($p = 0.000$).

Conclusion: CT values show a positive correlation with clinical symptoms in pediatric patients with COVID-19. A rising Ct value might suggest a declining viral load, potentially indicating recovery.

Keywords: Cycle threshold (CT), Clinical Symptoms, Pediatric, COVID-19.
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INTRODUCTION

In 2020, the World Health Organization (WHO) declared a global pandemic due to the spread of COVID-19. The COVID-19 pandemic is a considerable threat to the world.[1] Millions of people around the world are affected by this COVID-19 virus.[2] Until the end of the pandemic in 2023, there were 772,166,517 confirmed cases of COVID-19, including 6,981,263 deaths.[3] Indonesia itself is included in the top 3 countries in Southeast Asia and is among the top 20 in the world on the spread of COVID-19.[4] As of November 2023, Indonesia has recorded 6,814,111 positive cases of COVID-19 and 161,920 deaths, which is the 8th highest in Asia.[5]

COVID-19 cases have indeed subsided, and the WHO has also lifted the pandemic status in October 2023.[3] However, COVID-19 still exists in some regions of the world and tends to become endemic.[6] COVID-19 Vaccine effectiveness has saved many lives.[7] The disadvantage of administering vaccines is that due to clinical symptoms that appear milder than some time ago, the spread of COVID-19 is still ongoing.[8,9] Not only adults but there are also many children affected by COVID-19 with respiratory problems that interfere with activities and are even feared to cause severe illness.[9]

Clinical disorders found vary from mild to can cause death.[10] *Person-to-person transmission (human-to-human)* is predicted to occur through droplets and contact with the virus released in droplets, as shown by subsequent data developments.[11] The virus spreads through droplets and direct contact, after which it can infiltrate the mucosa. The virus will cause clinical disorders. Clinical disorders that occur include Fever, Cough, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Sore throat, loss of taste or smell, Headache, Congestion or runny nose, Nausea or vomiting, Diarrhea, and other clinical symptoms.[12] Clinical symptoms can range from mild to severe, and some individuals infected with the virus may remain asymptomatic, showing no noticeable symptoms at all.

COVID-19 can also attack pediatric patients and is feared to cause severe clinical disorders as experienced by adults. Additionally, there have been instances of a post-viral condition in children called Multisystem Inflammatory Syndrome in Children (MIS-C), which can occur weeks after COVID-19 infection.[13] MIS-C involves inflammation in different body parts and can cause fever, abdominal pain, vomiting, diarrhea, neck pain, rash, bloodshot eyes, or feeling extra tired. However, while rare, severe cases and

fatalities can still occur in children. The reasons behind COVID-19-related deaths in children caused Underlying Health Conditions, Multisystem Inflammatory Syndrome in Children (MIS-C), Complications from Severe Infection, and Immune Response Variability.[14]

To detect whether someone has COVID-19 or not, an accurate examination is needed, such as real-time PCR with a cycle threshold (CT) value indicator. The Cycle Threshold (Ct) value is a parameter used in PCR (Polymerase Chain Reaction) testing, including tests for COVID-19. It's a measurement that indicates the number of cycles needed for the PCR machine to detect the virus in a given sample.[15] During a PCR test, genetic material from a patient's sample (such as a nasal swab) is amplified through a series of cycles. The Ct value represents the number of cycles required for the fluorescent signal to cross a specific threshold, indicating the presence of the virus in the sample.[16] A lower Ct value indicates a higher viral load in the sample, suggesting that the virus was more prevalent and easier to detect. Conversely, a higher Ct value implies a lower viral load, meaning the virus was less abundant in the sample and might be at a stage where it's harder to detect.[17]

In fact, children have a lower risk of contracting COVID-19 compared to adults. Children are generally less susceptible to severe illness and death from COVID-19 compared to adults. Children infected with COVID-19 might remain asymptomatic or show very mild symptoms, which can make it harder to detect the infection.[12]

Clinical symptoms of COVID-19 that attack children also generally have mild ones. However, pediatric patients with weakened immune systems are at higher risk for severe disease.[18] From several studies, the value of *Cycle Threshold* (CT) also affects the clinical symptoms caused.[17]

This research is important because the severe symptoms experienced by pediatric patients with COVID-19 are also influenced by the cycle threshold (CT) value. In addition, it is to assess what clinical symptoms are most experienced by children with COVID-19. Therefore, this research aims to determine the correlation of Cycle Threshold (CT) Values with Clinical Symptoms Of Pediatric Patients With COVID-19.

METHOD

This research uses quantitative design with a cross sectional study approach. The population in this study was all children diagnosed with COVID-19 at hospitals in Jambi City in 2021. The sampling method uses a total sampling technique. The data in this study was collected by looking at the medical records of children registered at Jambi City Hospital who were diagnosed with confirmed cases of COVID-19. Inclusion criteria for this study are children aged 1-18 years diagnosed with confirmed COVID-19 using RT-PCR testing and children with complete medical records, including CT values and documented clinical symptoms. Exclusion criteria for this study are children with incomplete medical records and children with pre-existing chronic conditions that could influence clinical outcomes, such as cancer or congenital heart disease.

This study employed a total sampling technique in which all eligible pediatric COVID-19 patients during the specified period were included in the sample. Data were collected by reviewing medical records of children registered at Jambi City Hospital, focusing on RT-PCR results with CT values and associated clinical symptoms. Data analysis was conducted using both univariate and bivariate analysis. Univariate analysis used descriptive statistics to summarize the demographic characteristics of the participants (e.g., age, gender) and the distribution of clinical symptoms. For bivariate analysis, the correlation between CT values and clinical symptoms was assessed using an independent t-test to compare CT values across different symptom categories (asymptomatic, mild, moderate-to-severe). A p-value of less than 0.05 was considered statistically significant.

RESULT

The characteristics of respondents showed that the majority of respondents were aged 58% of respondents were aged 11-18 years, and 58% were male (Table 1). From the distribution of clinical symptoms, it was found that some receptors had milder symptoms (48%), as shown in Table 2.

From the result, this study shows

Table 1. Characteristics of Respondents

Characteristic	Count	Percentage (%)
Age		
1 – 5 year	9	18
6 – 10 year	12	24
11 – 18 year	29	58
Gender		
Female	21	42
Male	29	58

Source: Primary Data

Table 2. Clinical Symptoms and Clinical Manifestations of Respondents

Variable	Count	Percentage (%)
Clinical symptoms		
Asymptomatic	6	12
Mild	24	48
Medium-heavy	20	40
Clinical Manifestation		
Cough	22	44
Shortness	1	2
Fever	10	20
Runny Nose	17	34
Anosmia	9	18
Sore Throat	2	4
Indigestion	8	16

Source: Primary Data

clinical symptoms are significantly associated with low CT values in the study of COVID-19 pediatric patients at Abdul Manap Hospital Jambi City (p = 0.000) (Table 3).

Table 3. The relationship of clinical symptoms with CT values

Clinical Symptoms	CT value (Mean)	P value
Asymptomatic	32,6	
MIld	28,79	0,000*
Medium-heavy	24,16	

Note: *significant at p<0.05 by independent t-test

DISCUSSION

COVID-19 is diagnosed in fewer children than adults, and most cases of children are mild or asymptomatic.[19] In addition, hospitalization rates in children are significantly lower than hospitalization rates in adults with COVID-19, thus supporting the theory that states that children have milder illness from COVID-19 compared to adults. Children generally have more robust and adaptable immune systems. Their immune responses might be more efficient in fighting off the virus or controlling its replication, leading to milder symptoms or asymptomatic cases.[20]

Children are less likely to have underlying health conditions such as heart disease, diabetes, or compromised immune systems, which are risk factors for severe COVID-19 symptoms. The virus responsible for COVID-19, SARS-CoV-2, enters cells via ACE2 receptors.[12] Some studies suggest that children might have lower expression levels of these receptors in their respiratory tracts compared to adults, potentially reducing the virus's ability to infect and replicate.[21]

Children are regularly exposed to respiratory viruses and tend to develop better innate immune responses to these types of infections. This might contribute to a more controlled response to SARS-CoV-2.[14]

Adults are more prone to an exaggerated immune response, including cytokine storms, which can lead to severe complications. Children often have more balanced and controlled cytokine responses, reducing the risk of severe inflammation and organ damage. However, it's important to note that while children tend to experience milder symptoms, they are not immune to severe cases or complications from COVID-19.[8] Some children, especially those with underlying health conditions or specific inflammatory conditions like MIS-C, can develop severe illness. Monitoring children for any unusual symptoms and seeking medical attention if necessary is crucial to ensuring their well-being, particularly if they've been exposed to the virus.[22]

As is known that COVID-19 is a disease caused by Sars-coV-2, which attacks the respiratory system. This virus is a single-strain RNA virus, has encapsulation, and is also not well segmented.[23] Variants of this virus are increasingly adjusting the mutase process of the virus.[24] one of the variants that cause severe clinical symptoms in COVID-19 patients is coronarius alfa, beta, delta, gamma, omicron, etc.[24]

Sars-cov-2 is shaped like a cube, and the S protein is externally exposed.[25] The S protein (also called spike protein) is the primary viral antigen protein that provides the structural foundation for viral DNA transcription. Due to its interaction with specific receptors on the host cell, the S protein facilitates the attachment and entry of viruses.[26] The Sars-cov-2 virus requires a host cell to replicate.[8] SARS-CoV's S protein interacts with the host cell's ACE-2 (angiotensin-converting enzyme 2) enzyme. ACE-2 is found in brain smooth muscle cells, arterial and venous vascular endothelium, pulmonary alveolar epithelium, and small intestinal enterocytes. The nasal cavity, skin, thymus, bone marrow, spleen, liver, kidneys, and brain all contain ACE-2.[8]

Once inside, the RNA of the viral genome is translated into new copies of the viral genes. In addition, transcription and translation involve complex assembly of viral replication and viral RNA translation, respectively.[16] The infected person will then make the virus enter their upper respiratory tract, where it will replicate in the epithelial cells lining that area.[27] After that, the chest and lungs will be in the next row.[27] The virus leaves the body through the respiratory system during acute infection and can replicate latently within digestive tract cells long after the wound has healed.[28] After a 3-7 day incubation period of the virus, symptoms of the disease begin to appear.[28] Symptoms of the disease that appear attack the respiratory system and several other systems.

Clinical symptoms of COVID-19 that attack children are also generally milder than adults, even without symptoms. The results of this study show that Most children with COVID-19 suffer from cough, runny nose, and fever (Table 2.) COVID-19, caused by the SARS-CoV-2 virus, commonly leads to coughing due to its impact on the respiratory system. The virus primarily affects the respiratory tract, and coughing is one of the body's natural defense mechanisms to clear irritants or pathogens from the airways.[29]

SARS-CoV-2 infects the cells lining the respiratory tract, particularly the upper respiratory tract (nose, throat), and sometimes progresses to the lower respiratory tract (lungs). This infection causes irritation and inflammation, triggering the body's reflex to clear the airways, resulting in a cough. The virus replicates in the respiratory tract, leading to damage and cell death. As the body works to clear the virus, the immune response causes inflammation, further irritating the airways and provoking a cough. COVID-19 coughs are often described as dry and persistent. Unlike coughs associated with the common cold that might produce mucus, COVID-19 coughs tend to be non-productive, meaning they don't typically bring up phlegm. Coughing is one of the ways the virus spreads from an infected person to others. When an infected person coughs, the virus-containing respiratory droplets can be released into the air, potentially infecting those nearby.[2,30]

COVID-19 can cause fever as part of the body's immune response to the infection.

Fever is a common symptom of various infections, including COVID-19, and it serves as a defense mechanism to fight off the invading virus. When the SARS-CoV-2 virus enters the body, it triggers the immune system to respond. Immune cells release signaling molecules called cytokines, which play a role in fighting the virus. This immune response can stimulate the hypothalamus in the brain, which regulates body temperature, leading to an increase in body temperature—resulting in fever. As the virus replicates within the body, it causes damage to the cells it infects. This damage and the subsequent immune response can contribute to the release of cytokines, further inducing fever as part of the body's attempt to combat the infection. COVID-19 can cause inflammation in the respiratory system and potentially other organs. Inflammatory responses are often associated with fever as the body attempts to control and eliminate the infection.[30]

A runny nose (rhinorrhea) is not typically considered one of the primary symptoms of COVID-19, although it can occur in some cases. The SARS-CoV-2 virus primarily affects the respiratory system, causing symptoms such as cough, fever, and difficulty breathing. However, some individuals infected with COVID-19 might experience a runny or stuffy nose, though it's more commonly associated with other respiratory illnesses like the common cold.[31]

Strutner's (2021) study, which found a correlation between low CT scores and clinical symptoms of COVID-19 in children, is in line with current research findings.[32] The Cycle Threshold (Ct) value in COVID-19 testing, which indicates the number of PCR cycles required to detect the virus in a sample, can offer some insights into the clinical manifestation and severity of the disease, but it's not the sole determinant. Lower Ct values usually correspond to higher viral loads in a patient's sample, indicating a higher concentration of the virus. Higher viral loads have been associated with increased infectivity, implying that individuals with lower Ct values might be more contagious.[9]

Some studies suggest a potential correlation between lower Ct values (higher viral loads) and more severe clinical manifestations of COVID-19. Patients with lower Ct values might be more likely to develop severe symptoms or complications due to the higher amount of virus present. On the other hand, individuals with higher Ct values (lower viral loads) might be asymptomatic or experience milder symptoms. Higher Ct values could indicate a lower concentration of the virus, potentially resulting in less severe disease manifestations.[28]

However, it's essential to note that while there might be correlations between Ct values and clinical outcomes, it's not a direct or consistent relationship. Clinical manifestations of COVID-19 can vary significantly among individuals, and other factors like the immune response, underlying health conditions, and individual variability can significantly influence the disease course and severity.[33]

Ct values have been linked to tissue and organ damage in recent post-mortem analyses of deceased COVID-19 patients. However, the magnitude of organ damage was not significantly associated with Ct values. RT-PCR and Ct values have been implicated in obtaining a more comprehensive picture of viral dynamics in deceased COVID-19 patients. Higher Ct values indicate a low viral RNA load and a lower risk of infection transmission. On the other hand, recent studies have shown that Ct values through successful virus isolation in cell cultures indicate that patients with Ct values above 33-34 no longer appear to be infectious.[34]

CONCLUSION

This study has several limitations. First, the sample size was relatively small and limited to a single geographic area, which may affect the generalizability of the findings to broader populations. Second, the retrospective nature of the study, relying on medical records, may have led to missing or incomplete data, particularly concerning the clinical symptoms experienced by pediatric patients. Third, we did not account for potential confounding factors, such as underlying health conditions or the presence of other respiratory infections, which could have influenced the relationship between CT values and clinical symptoms. Finally, the study only analyzed data from a specific period (2021), and given the evolving nature of the COVID-19 virus, future research should examine how different variants may impact pediatric patients and CT values.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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ETHICAL APPROVAL

The protocol of the study was approved by The Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Andalas (No. 157/UN.16.2/KEP-FK/2020).

AUTHOR CONTRIBUTIONS

- **Sabar Hutabarat**: Conceptualization, methodology, and.
- **Wahyu Indah Dewi Aurora**: Data collection, analysis, and interpretation of data.
- **Andrew Partogi Hamonangan Hutabarat**: Writing draft preparation, Reviewing, editing, and supervision.
- **All authors**: Approved the final version of the manuscript for publication.

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