



SYSTEMATIC REVIEW CHILDREN'S IMMUNITY RESPONSE TO COVID-19 INFECTION

Yuly Peristiwati^{1*}, Semi²

¹Department of Nursing, Institut Ilmu Kesehatan STRADA Indonesia, Jl. Manila No.37, Tosaren, Kec. Pesantren, Kota Kediri, Jawa Timur 64133, Indonesia

²Faculty of Public Health, Institut Ilmu Kesehatan STRADA Indonesia, Jl. Manila No.37, Tosaren, Kec. Pesantren, Kota Kediri, Jawa Timur 64133, Indonesia

*yulystikes@gmail.com

ABSTRACT

Immunity is resistance from infection and the immune response is the coordination of cells in the body and other molecules against infection. Corona Virus is a positive chain Ribonucleic acid (RNA) virus whose transmission occurs more often from infected closest relatives with the main route through inhalation. direct respiratory droplets from coughing and sneezing. This systematic review aims to identify the immune response of children infected with Covid-19. Search articles using 4 databases, namely Scopus, ProQuest, Pubmed, and Science Direct using keywords and Boolean operators. Strategy to find articles using PICO. The results obtained 14 articles, assessment using PRISMA checklist. The results of the review show that SARS-CoV-2 infection in children triggers non-specific and specific immune responses. The non-specific immune response begins with an increase in white blood cells and triggers a specific immune response, namely T and B cells that will produce antibodies. There are increased levels of CRP, IL-6, IL-10, IFN- γ , TNF- α and IP-10 which can be an independent predictor of disease severity. Excessive levels of mediators can cause a cytokine storm that damage the human body and increased D-dimer in severe cases. The specific immune response will mediate the formation of antibodies. B cells are assisted by T cells to differentiate into plasma cells, which then produce specific antibodies for viral antigens, in the form of IgM which is detected early and is then replaced by IgG. To improve the performance of the immune system, there needs to be an increase in nutrition, adequate rest, support and family motivation.

Keywords: children; COVID-19; immune response

INTRODUCTION

Children are the biggest investment in the family. Children are the best hope as the next generation of the nation. During the Corona virus disease 19 (Covid-19) pandemic, children are very vulnerable to decreased immunity (Shi et al., 2020). Based on the number of cases of Covid-19 in children according to the report of the Chinese Center for Disease Control and Prevention from January 16, 2020 to February 8, 2020 with a total of 2135 cases, with an age range of 2-13 years with a total of 1208 (56.6% in male children) (Dong et al., 2020). Meanwhile, on March 2, 2020, the first case was detected in Indonesia, data until May 18, 2020, the number of children who were positive for Covid-19 in Indonesia reached 584 cases. Meanwhile, the number of patients under supervision (PDP) for children was \pm 3,400. The number of positive confirmed cases that died was 14 children. The PDP who died as many as 129 children. Eighty million children in Indonesia (about 30% of the entire population) have the potential to experience serious impacts from COVID-19 (UNICEF, 2020). Indonesia before the Covid-19 pandemic was a country with 3 burdens of malnutrition (non-optimal care, nutrition and care, high infectious diseases). In Indonesia, more than 2 million children experience weight that is not in accordance with their height and 2 million other children are overweight or obese. Parenting that is not optimal, nutritional fulfillment and high infectious diseases are circles that greatly affect immunity in children (UNICEF, 2020).

Immunity status in children during the COVID-19 pandemic is certainly related to the immune response in their bodies. The immune response that occurs in children during a pandemic, depends on the environment and the amount of exposure to the COVID-19 virus. The immune response in children against COVID-19 infection consists of non-specific and specific immune responses. This immune system will respond starting from the entry of the virus to the formation of specific antibodies against the virus. In children with mild clinical symptoms will cause an increase in T cells (activated), especially CD8 T cells on days 7-9. There was an increase in antibody secreting cells (ASCs) and follicular helper T cells. Progressively increased IgG/IgM, decreased monocyte, natural killer (NK), monocyte chemoattractant protein-1 (MCP- 1). While in clinical weight monocytes, eosinophils, and basophils are lower. Pro-inflammatory cytokines such as TNF-, IL-1, IL-6 and infection markers such as procalcitonin, ferritin and C-reactive protein (CRP) showed higher results, decreased CD4 and CD8 T lymphocytes (Thevarajan et al., 2020).

After the pandemic ends, children throughout Indonesia will continue to feel the impact of the decline in immunity for years to come. Alternative solutions must be sought immediately, both at the central and lower levels of government. The alternative to regional quarantine (lockdown) can disrupt the stability of family income, so that it will affect the purchasing power of daily food. As a result, the lack of nutritional needs slowly or quickly will affect the child's weight to fall rapidly (wasting), so that it will affect the immunity of children during the Covid-19 pandemic (Jayawardena et al., 2020). We must move together with sustainable and continuous action by investing in nutrition and reducing the impact of the Covid-19 crisis as soon as possible. The root of the problem must be immediately addressed with financial assistance to overcome the social and economic impacts, so that nutritional improvements can be resolved immediately, because it will indirectly have an impact on the sustainability of immunity in children. In this millennial era parents are also expected to be able to seek related information. increase immunity by searching the internet. In this study, because the COVID-19 pandemic is still entering the new normal era, the researchers conducted a systematic review as an update of the literature that will be used as reference material for clinical research related to the immune response of children to Covid-19 infection.

METHODS

The stages in a systematic review include:

1. Literature Search Strategy

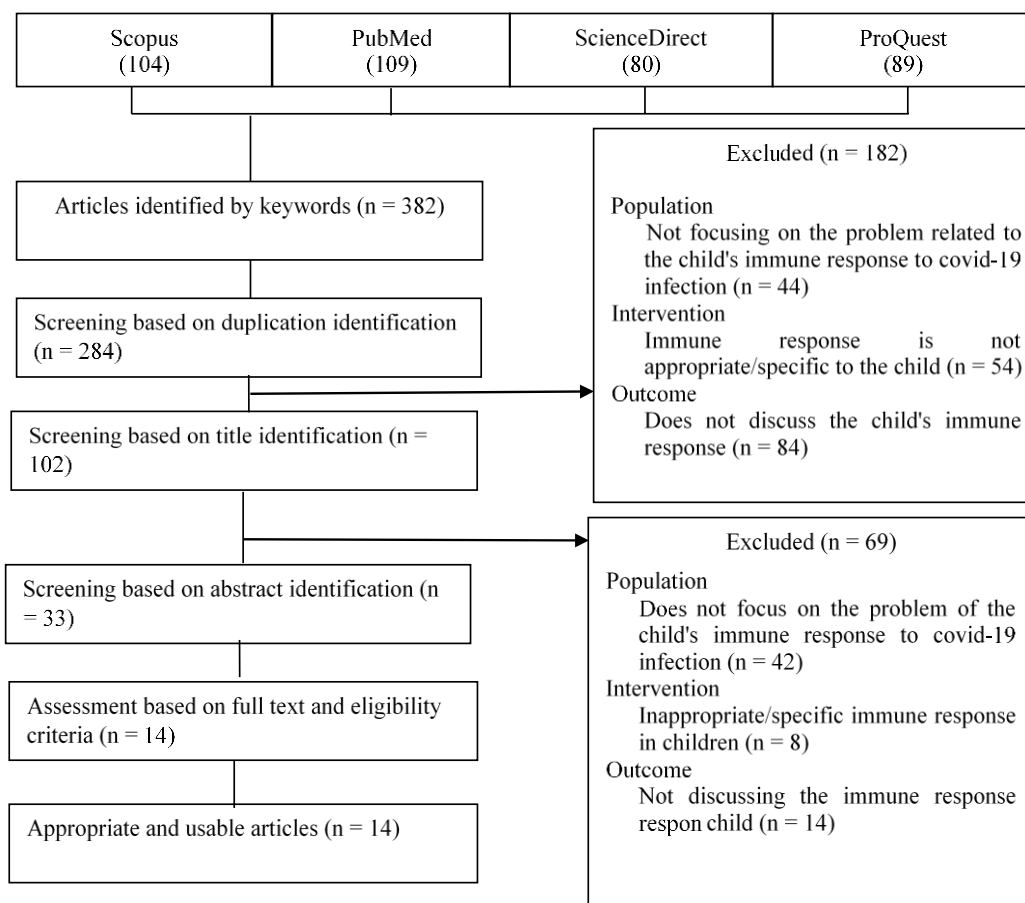
Table 1.

Keyword Systematic Review of Children's Immunity Response to Covid-19 infection 9	
Covid-19	Immunity Response
Covid-19 of children	Immunity
OR	O R
Corona virus disease 2019	Children immunity
OR	O R
Wuhan covid-19	Children immunity during covid-19
OR	
Wuhan coronavirus disease 2019	

The protocol in the systematic review uses the Preferred Reporting Items For Systematic Reviews and Meta Analyses (PRISMA) checklist to determine the selection of studies that have been found and adapted to the purpose of the systematic review (Nursalam, 2020). The

literature search was carried out from August to September 2020. The data used in this study were secondary data obtained from the results of previous research. Databases used in these literature searches include Scopus, ProQuest, Pubmed, and Science Direct. Search articles or journals using keywords and Boolean operators (AND, OR NOT or AND NOT), while the keywords in this systematic review are adjusted to the Medical Subject Heading (MeSH) presented on Table 1.

Flowcart for searching publication literature in four databases, namely *Scopus*, ProQuest, Pubmed, and Scient Direct and using keywords that have been adjusted to the Medical Subject Heading (MeSH) presented in Figure 1



Picture 1. Flowchart Search Systematic Review Response Children's immunity to covid 19 infection

Based on Figure 1, it is known that the results of the search for publication literature in four databases obtained 382 articles that match these keywords. These results are then checked for duplication and exclusion according to the established criteria. Thus, 14 articles were obtained which as a whole matched the eligibility criteria. The fourteen articles came from the databases: Scopus (3 articles), PubMed (6 articles), ScienceDirect (2 articles), and ProQuest (3 articles).

2. Inclusion and Exclusion Criteria

The strategy used to search for articles uses the PICOS framework, which is presented in Table

Table 2.

PICOS Systematic Review Format Children's Immunity Response to Covid-19 infection

PICOS Framework	Inclusion Criteria	Exclusion Criteria
Population	Children infected with COVID-19	Not focusing on children infected with COVID-19 –
Intervention	A study that examines the immune response of children to COVID-19 infection	Studies that do not discuss the child's immune response to covid 19 infection
Comparison	No comparison	No exclusion criteria
Outcomes	Children's immune response to covid-19 infection	Does not discuss the child's immune response to covid 19 infection
Study Design and Population type	Research design used in reviewed articles	No exclusion criteria
Publication years	2019 and beyond	Before 2019
Language	English and Indonesian	Apart from English and Indonesian

3. Quality Rating

Evaluation of the quality of the systematic review using the PRISMA checklist to determine theselection of studies that have been found and adapted to the purpose of the systematic review that has been collected and analyzed for the quality of the methodology in each study with the PRISMA checklist assessment list with several questions to assess the quality of the study.

RESULT

In the 14 journal article analyized. the median age of 1,314 patients dying from COVID-19 was Childrents > 1 mounth < 15 years, male and female genders.

Characteristis Respondent

Characteristics of study respondents include the number of respondents, gender, and age range of respondents. The number of respondents in the study of Y. Wang et al.(2020) as many as 43 children, divided into 8 children with severe Covid-19 infection and 35 children with mild Covid-19 infection. The number of male respondents was 27 children and female respondents were 16, with the mean age in severe cases being 5 years and the average age in mild cases being 6.8 years. In severe cases there were two children with comorbidities, and in mild cases there were eight children with comorbid cases. Respondents in the study of Sun et al. (2020) as many as 8 child patients infected with Covid-19 are being treated in the ICU, three of them are in critical condition and five patients are seriously ill. Male respondents were 6 patients and 2 patients were female respondents. The age range of respondents was two months to 15 years. All respondents lived in Wuhan during the Covid-19 pandemic period. The next study, in the research of Li et al. (2020) using respondents as many as 22 child patients infected with Covid-19, which were divided into 12 male and 10 female patients. The mean age of the patients was 8 years.

Respondents in the study of W. Du et al. (2020) as many as 67 patients consisting of 53 adult patients and 14 pediatric patients. Adult patients consisted of 26 male patients and 27 female patients. The mean age of adult patients was 41.47 years. Pediatric patients had a mean age of 6.2 years and consisted of 6 male patients and 8 female patients. Respondents in the study of Zhang et al. (2020) as many as three cases, all of which were male at the age of 9, 6, and 8

years. All three cases had a history of close contact with their adult relatives diagnosed with COVID-19.

The number of respondents in the study of Diorio et al. (2020) as many as 20 patients, the respondents were divided into two groups, namely the group with Multisystem Inflammatory Syndrome in Children (MIS-C) and the non-MIS-C group (severe and mild Covid-19) with details: 9 suffered from severe Covid-19, 5 had mild Covid-19 and 6 had MIS-C. The age range of the respondents is 5- 18 years. Respondents consisted of 9 men and 11 women. Respondents in the research of Xia et al. (2020) as many as 20 pediatric patients, consisting of 13 male patients and 7 female patients. The age range of respondents used is one day to 14 years 7 months, with an average age of 2 years and 1.5 months. Thirteen pediatric patients (13/20, 65%) had a history of close contact with a family member diagnosed with Covid-19.

Respondents in the study of Xu et al. (2020) as many as ten pediatric patients, consisting of six boys and four girls. The mean age of the patients was two months to 15 years. Four pediatric patients had a history of close contact with patients who were confirmed to be infected with Covid-19. Respondents in the study of Su et al. (2020) 9 pediatric patients (three boys and six girls) and 14 family members were treated at the Jinan Infectious Disease Hospital of Shan Dong University. The youngest of the 9 patients was a pair of twins aged eleven months and the oldest nine years and 9 months (mean age 4.5 years, median age 3.5 years). There were 14 adults included in the study (two patients were admitted to another hospital), consisting of 8 men and 6 women with a mean age of 42.9 years.

Respondents used in the study of Chen et al. (2020) as many as 12 pediatric patients, consisting of 6 boys and 6 girls. The mean age of pediatric patients was 14.5 years (ranging from 7 months to 17 years). Three patients are local residents of Wuhan, one patient has traveled to Wuhan within fourteen days, eight patients were contacted with confirmed cases of COVID-19. Respondents in the study of Yonker et al. (2020) as many as 192 children (with an average age of 10.2 ± 7.0 years) which were divided into three groups. The first group was 125 who were not infected with Covid-19 consisting of 67 boys and 58 girls with an age range of less than 1 year to 22 years, which consisted of 7 Asian race children, 5 Black or American American children, 43 children. white race and 26 children of unknown race. The second group is a group infected with Covid-19 as many as 49 children (23 boys and 26 girls), who come from 1 child of Asian race, 4 children of Black or American race, 7 children of white race and 10 children of a different race. not known. The third group was patients with Multisystem Inflammatory Syndrome in Children (MIS-C) with 18 children (14 boys and 4 girls), from 1 Asian race, 2 Black or American American children, 9 white children and 2 children of unknown race.

Respondents used in the Peng et al., (2020) study were 38 patients who were divided into two groups, namely the re-detectable positivity (RP) group, namely the group with positive RT-PCR results after recovering and leaving the hospital and the control group, namely non-RP. The control group consisted of 24 children consisting of 11 boys and 13 girls with an average age of 7.6 years. The RP group consisted of 14 children consisting of 5 boys and 9 girls with an average age of 7.2 years. Respondents in the study of Ozsurekci et al. (2020) as many as 30 cases of children (14 boys and 16 girls) with an average age of 10.5 years and 30 adult cases (14 boys and 16 girls) with an average age of 62.5 years. Child respondents were divided into 3 groups: mild case group (11 children), moderate case group (10 children), and severe/critical case group (9 children). Adult respondents were divided into 3 groups: mild case group (4 children), moderate case group (15 children), and severe/critical case group (11 children).

Each case of children and adults has a control group that does not suffer from Covid-19, with a total of 15 respondents). The number of respondents in the study of H. Du et al. (2020) as many as 182 children consisting of 62 girls and 120 boys. Respondents were divided into two groups: the group with allergies (43 children) and the group without allergies (139 children). The mean age of the patients was 6 years, ranging from 3 days to 15 years and most of the children were infected by family members.

Laboratory Analyzed

White blood cell count was performed in 11 studies, 8 studies showed normal (Chen et al., 2020; H. Du et al., 2020; Ozsurekci et al., 2020; Su et al., 2020; Sun et al., 2020; W. Duet al., 2020; Xia et al., 2020; Xu et al., 2020) and 3 studies showed improvement (Peng et al., 2020; Y. Wang et al., 2020; Zhang et al., ., 2020). Normal/increased lymphocytes were described in 2 studies (Peng et al., 2020; Sun et al., 2020) while normal/decreased lymphocytes were described in 1 study (Sun et al., 2020). In the study of Li et al. (2020) there is an increase in the rate of erythrocyte sedimentation. Elevated CRP was described in 6 studies and 3 studies showed normal amounts of CRP. Procalcitonin levels were described in 4 studies, 75% normal (3/4 studies) and 25% elevated (1/4 studies).

Interleukin levels were carried out in 5 studies, 1 study showed normal interleukin levels (IL-6 (Zhang et al., 2020) and 4 studies showed an increase in interleukins (IL-6 and IL-10 (Y. Wang, et al. , 2020); IL-6 and IL-10 (Sun et al., 2020); IL-6, IL-8, and IL-10 (Dioroet al., 2020); IL-6, IL-17 and IL -22 (Xu et al., 2020)). Elevated levels of IFN γ were explained by 2 studies (Diorio et al., 2020; Sun et al., 2020). Elevated levels of TNF α were described in 1 study (Diorio et al., 2020). Immunoglobulin levels were described in 4 studies, 1 study showed normal immunoglobulin (IgM, IgA, and IgG) levels (Zhang et al., 2020) and 3 studies showed increased immunoglobulin (IgG, IgM and IgA) levels (Peng et al., 2020); IgG and IgM (Yonker et al., 2020); and IgE (H. Du et al., 2020)). There was an increase in D-dimer in 2 studies (H. Du et al., 2020; Y. Wang, et al., 2020).

Table 3.
Journal review results

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
1	Wang et al.,(2020)	Children Hospitalized With Severe COVID-19 in Wuhan, The Pediatric Infectious Disease Journal, Volume 39 (7) 2020	Design: retrospective case-control study Sample: Eight children with severe SARS-Cov-2 infection and 35 children with mild SARS-Cov-2 infection at Wuhan Children's Hospital. Variable: Dependent Variable: risk factors for Covid-19 infection Independent Variable: clinical laboratory results in Covid-19 patients Instrument: Medical records which include:epidemiology, symptoms, clinical features, laboratory tests, chest CT scan image data Analysis: Univariate and Multivariate logistic regression with 95% confidence level	Based on laboratory results, white blood cell counts were significantly higher in severe children compared to mild children. Levels of inflammatory biomarkers such as hsCRP, IL-6, IL-10 and D-dimer were increased in children with severe cases compared with children with mild cases at the time of hospital admission.	An overactive immune response to SARS-Cov2, especially an increase in IL-6 and in severe cases an increase in D-dimer. Organ damage such as intravascular and hepatobiliary coagulation dysfunction can lead to multi-organ dysfunction. Age Sampel : 2 bulam sd 15 tahun , total sampel 8, 6 boy , 2 girl Sampel age : mean 6 years ,

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
2	Sun et al. (2020)	Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study, World Journal of Pediatrics, Volume 16, 2020	<p>Design: <i>Single center's observational study</i></p> <p>Sample: Eight seriously ill patients with COVID-19 admitted to the Intensive Care Unit (ICU)</p> <p>Variable: - Dependent variable: patient's SARS-Cov-2 infection severity condition Independent variable: clinical laboratory results</p> <p>Instrument: Medical records and Laboratory results (complete blood count, serum biochemistry, lymphocyte subset analysis tests, cytokine detection tests, and identification of other respiratory pathogens) Analysis: Descriptive analysis</p>	<p>Laboratory results showed normal or elevated whole blood counts (7/8), elevated C-reactive protein, procalcitonin and lactate dehydrogenase (6/8), and abnormal liver function (4/8). Other findings included decreased CD16 + CD56 (4/8) and Th/Ts (1/8), increased CD3 (2/8), CD4 (4/8) and CD8 (1/8), IL-6 (2/8), IL-10 (5/8) and IFN-γ (2/8). And a high increase in D-dimer (2/5)</p>	<p>In conclusion, for severely ill or critically ill pediatric patients who remain in intensive care, an exaggerated immune response occurs in the form of increased plasma cytokines and can lead to long-term lung damage and severe health complications. Therefore, early identification of the specific features of severe pediatric patients and timely treatment is essential.</p>
3	Li et al. (2020)	Radiographic and Clinical Features of Children With Coronavirus Disease (COVID-19) Pneumonia, Indian Pediatrics, Volume 57, 2020	<p>Design: <i>Retrospective study</i></p> <p>Sample: Involved 22 pediatric patients with confirmed COVID-19 from January to March 2020.</p> <p>Variable: - Dependent variable: pneumonia in Covid-19 patients - Independent variables: chest CT image and clinical condition</p> <p>Instrument: Chest CT images, clinical data, and laboratory results Analysis: Descriptive analysis</p>	<p>The most common symptoms were fever (64%) and cough (59%), and the mean level of elevated C-reactive protein (CRP) was 11.22 (11.06) and the erythrocyte sedimentation rate was 18.8 (15.17). The main CT abnormalities observed were ground-glass opacity white patches and consolidation lesions (36%), consolidation (32%), and ground-glass opacity white patches (14%). Peripheral distribution (45%) of the pulmonary lesions was dominant. Most of the lesions were multilobar (68%), with an average of three lung segments involved.</p>	<p>There is an increase in C-reactive protein (CRP) and an increase in the erythrocyte sedimentation rate on blood tests. The presence of inflammation in the lungs causes CT scan images of lung abnormalities in Covid-19 patients with pneumonia. So that CT scans play an important role in the management of Covid-19 infection with pneumonia and children.</p>
4	W. Du et al. (2020)	Clinical characteristics of COVID-19 in children compared with adults in Shandong	<p>Design: <i>retrospective descriptive clinical study</i></p> <p>Sample:</p>	<p>Laboratory results in children with normal white blood cell counts with a slight</p>	<p>Most cases in children are mild and conventional cases, with mild</p>

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
		ProvinceChina, Infection, Volume 48, (3), 2020	A total of 67 cases including 53 adult cases and 14 children infected with Covid-19. Variable: Dependent variable: Covid-19 infection in children and adults Independent variables: Clinical characteristics of Covid-19, biochemical indicators, and cytokine measurements Instrument: Patient medical records, laboratoryresults Analysis: <i>Student's t-test</i> (for numerical data)orChi-square/ χ^2 test(for categorical data with 95%confidence level	decrease in the number of neutrophils and an increase in the number of lymphocytes compared to adults. There is a lower increase in CRP in children compared to adults.	clinical signs and symptoms. This is due to the lower inflammatory response, seen from the insignificant increase in CRP and white blood cells.
5	Zhang et al.,(2020)	Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia, Journal of Medical Virology, Volume 92, (7), 2020	Design: <i>Retrospective study</i> Sample: Three children during the recoveryperiod of COVID-19 pneumonia Variable: Dependent variable: clinical, radiographic and laboratory features of Covid19 Independent variable: viral RNA in feces Instrument: Medical records and laboratoryresults Analysis: Descriptive analysis	The three patients in this case experienced mild symptoms. Amongthe three children, Case 1 had a complicated purulent tonsillitis, with an increase in leukocytes and C-reactive protein (CRP) of 64.7 mg/L, and this index reduced to normal levels after anti-infective treatment. Cases 2 and Case 3 showed normal ranges of white blood cell (WBC), CRP, and lymphocyte counts.Hemoglobin and platelets were normal in three children. Serum procalcitonin, blood lactate dehydrogenase, and interleukin-6were normal in three patients. Immunological tests (IgG, IgM, IgA,C3, and C4) were all within the normal range, and the lymphocyte subsets (T cells, B cells, and NK cells) were essentially normal.	There was no increase in the number of white blood cells, CRP and lymphocytes in patients with mild symptoms and there was an increase in CRP and leukocytes in children with purulent tonsillitis. Recovered pediatric patients may become carriers for the virus, so it is necessary to re-evaluate the criteria for discharge from the hospital or termination of quarantine and ongoing patient management. And itis necessary to watch out for the possibility of transmission of SARS-CoV-2 infection through feces-oral.
6.	Diorio et al.(2020)	Multisystem inflammatory syndrome in childrenand COVID-19 are distinct presentationsof SARS-CoV-2, The Journal of Clinical Investigation, Volume	Design: <i>Prospective cohort study</i> Sample: Twenty patients with details: 9suffering from severe Covid-19, 5mild Covid-19 and 6 sufferingfrom Multisystem InflammatorySyndrome in	Five cytokines (IFN- γ , IL-10, IL-6, IL-8, and TNF- α) contributed to the analysis. Identical TNF- α and IL-10 were found in patients with MIS-C	Pediatric patients with SARS-CoV-2 are at risk for critical illness with severe COVID-19 and MIS-C. Cytokine profiling and peripheral

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
		130, (11), 2020	Children (MIS-C) Variable: Dependent variable: Covid-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) Independent variable: cytokine examination Instrument: Medical records, laboratory results of immunological examinations Analysis: Univariate and multivariate logistic regression with 95% confidence level <i>Mann-Whitney</i>	compared with COVID-19. The presence of spine cells on the blood smear was found in patients with MIS-C and patients with severe Covid-19, whereas in patients with mild Covid-19 they were not found.	blood smear examination can differentiate between patients with MIS-C and patients with severe COVID-19.
7	Xia et al. (2020)	Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults, Pediatric Pulmonology, Volume 55, (5), 2020	Design: <i>Retrospective study</i> Sample: Twent hospitalized pediatric patients were infected with COVID-19 confirmed by a COVID-19 pharyngeal swab nucleic acid test from January 23 to February 8 at the Wuhan Children's Hospital. Variable: - Dependent variable: Covid-19 infection in children and adults - Independent variables: clinical features and chest CT in pediatric patients with Covid-19 infection Instrument: Clinical and laboratory data were obtained from inpatient records. Analysis: Descriptive Analysis	Laboratory findings showed that the white blood cell count was normal in 14 cases (14/20, 70%), decreased in 4 cases (4/20, 20%), and increased in 2 cases (2/20, 10%). The decreased percentage of lymphocytes occurred in 7 cases (7/20, 35%) and increased in 3 cases (3/20, 15%). Alanine aminotransferase was elevated in 5 cases (5/20, 25%); creatine kinase - MB increased in 15 cases (15/20, 75%); C-reactive protein (CRP) was increased in 9 cases (9/20, 45%); and procalcitonin (PCT) was elevated in 16 cases (16/20, 80%). Eight patients were coinfecting with other pathogens (8/20, 40%), including influenza A and B viruses, mycoplasma, respiratory syncytial virus, and cytomegalovirus. Subsequently, four cases had abnormal electrocardiogram events. Two patients had a history of atrial	The results of the white blood cell and CRP counts were mostly normal. On average there is an increase in procalcitonin and changes in CT scan images in patients with mild pneumonia Sample Age : , 1 month sd >6 year. 13 boy, 7 girl

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
				septal defect surgery and one with epilepsy as sequelae of previous viral encephalitis. For laboratory findings, an increase in procalcitonin (16/20, 80%) should be noted, which is not common in adults. A total of 6 patients with unilateral lung lesions (6/20, 30%), 10 with bilateral lung lesions (10/20, 50%), and 4 cases showed no abnormality on chest CT (4/20, 20%).	
8	Xu et al. (2020)	Characteristic of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding, Nature Medicine, Volume 26, 2020	<p>Design: <i>Prospective observational study</i></p> <p>Sample: Ten pediatric patients infected with SARS-CoV-2</p> <p>Variable:</p> <ul style="list-style-type: none"> - Dependent variable: Covid-19 infection in children - Independent variables: characteristics of SARS-CoV-2 infection from laboratory examinations and CT scans in children <p>Instrument: Medical records, laboratory results, rectal and nasopharyngeal swab results</p> <p>Analysis: Descriptive Analysis, Chi Square</p>	<p>Complete blood count, urine and stool analysis, coagulation function, blood biochemistry and biomarkers of infection were tested on admission. Almost all test results were normal in patients except patient 9. Some cases had leukopenia, leukocytosis, lymphopenia or elevated transaminases, which are otherwise often seen in adult patients.</p> <ul style="list-style-type: none"> • Of the nine patients (the tenth patient was transferred from another hospital who did not perform a cytokine test on admission), seven showed an increase in interleukin (IL)-17 and five of these 	<p>Most blood cell count laboratory test results show normal numbers. There is an increase in the inflammatory mediator interleukin. There were positive rectal swab findings in eight children despite negative nasopharyngeal swab results. However, we do not have evidence of a virus competent for replication in faecal swabs, which is necessary to confirm the potential for fecal-oral transmission.</p>

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
				patients had a concomitant increase in IL-22. Five patients had elevated IL-6	
9	Su et al., (2020)	The different clinical characteristics of corona virus disease cases between children and their families in China – the character of children with COVID-19, <i>Emerging Microbes & Infections</i> , Volume 9, 2020	Design: <i>Retrospective study</i> Sample: Nine children and 14 adult family members Variable: - Dependent variable: index of Covid-19 in children and their families - Independent variable: clinical laboratory results Instrument: Medical records and laboratory results Analysis: Descriptive analysis	Eight of the nine children (88.9%) had normal or decreased white blood cell counts, one child had a slight increase in white blood cells. All inflammatory indicators, including CRP, PCT, ESR and IL-6 were within normal range. All adult patients had normal (10/14, 71.4%) or decreased (4/14, 28.6%) white blood cell counts and 10 (71.4%) had lymphopenia. There were 4 (28.6%) patients experienced an increase in CRP, PCT, Serum amyloid A (SAA), D-dimer and IL-6.	The results of blood laboratory examinations showed that the white blood cell counts and indicators of inflammation in the patients in this study were within the normal range. However, their PCR results in feces showed a longer time than their families. Because the clinical process is mild or asymptomatic, it is difficult to recognize early by pediatricians and public health staff.
10	Chen et al. (2020)	The clinical and immunological features of pediatric COVID-19 patients in China, <i>Genes & Diseases</i> , Volume 7, 2020	Design: <i>Cross sectional study</i> Sample: Twelve patients were under 18 years of age and 20 were adults. Variable: - Dependent variable: Covid-19 infection - Independent variables: immunological features and clinical outcomes Instrument: Laboratory Results Analysis: Test t-test / Mann Whitney Uji	The immunological profile of the child showed a normal white blood cell count and biochemical tests. Due to the mild symptoms, a comparison of the immunological profile of children with adults was carried out. Children had higher total T-cell, CD8 β T-cell and B-cell counts but lower levels of CRP and IL-6 than adults ($P < 0.05$). The mean level of IL-6 in pediatric patients was lower than in adults.	Children infected with COVID-19 had different immune profiles with higher T cell counts than adults and low levels of inflammatory factors, which may be due to mild clinical symptoms. Sample age : median 14,5 th, 20 pasien
11	Yonkers et al. (2020)	Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses, <i>The Journal of Pediatrics</i> , Volume 227, 2020	Design: <i>Retrospective study</i> Sample: A total of 192 children Variable: - Dependent variable: SARS-CoV-2 and Multisystem Inflammatory Syndrome in Children (MIS-C) - Independent variables: clinical outcome and	Children with acute SARS-CoV-2 infection were more likely to have elevated IgM to RDB than those with MIS-C. IgG levels increased in acute SARS-CoV-2 infection with increasing duration of	The study revealed that children had milder disease or less symptoms. There is an increase in IgM and IgG in patients with severe Covid-19 and MIS-C

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
			immune response Instrument: Medical records and laboratory results Analysis: <i>Mann Whitney & Kruskal-Wallis</i>	symptoms (Spearman correlation, $r = 0.44$; $P = .02$). Children with severe MIS-C were more likely to have increased SARS-CoV-2 IgM and IgG responses than those with mild MIS-C. SARS-CoV-2 IgM and IgG levels in mild MIS-C were below the threshold of 0.5 mg/ml.	Sampel age , 18 year, 38 pasien
12	Peng et al. (2020)	Risk factors for redetectable positivity in recovered COVID-19 children, Pediatric Pulmonology, Volume 55 (12), 2020	Design: <i>retrospective study</i> Sample: Thirty-eight pediatric patients diagnosed with COVID-19. Divided into groups that were detected back positive (Redetectable positivity / RP) of 14 patients and non-RP of 24 patients. Variable: - Dependent variable: Covid-19 risk factors - Independent variables: Immunological features of the RP group and the non RP group (control) Instrument: Medical records and laboratory results Analysis: Chi square	The RP group had a relatively higher white blood cell (WBC) count and a longer plasma prothrombin time (PT), while the percentage and number of neutrophils, lymphocytes, hb, platelets, erythrocyte sedimentation rate, CRP, IL-6, showed no difference. Likewise, the humoral immune system seen in the form of IgM, IgG, IgA, C3c, C4 showed no significant differences between the two groups. Subclassification of T lymphocytes was observed at five time points: the first test after admission, 2 weeks, and 1, 2, and 3 months after discharge. The RP group had higher CD8+ T lymphocyte percentages and counts and lower CD4+/CD8+ ratios at 2 weeks, whereas lower CD4+ T lymphocyte	Familial cluster infection, higher WBC counts, and longer PT are early risk factors for RP in recovered COVID-19 children. Dynamic changes in the number and ratio of CD4+ and CD8+ T lymphocytes may be involved in the prolonged recovery of SARS-CoV-2. Nasopharyngeal swab sampling during onset and anal swab sampling during recovery can increase RT-PCR positivity rates

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
				percentages and counts and lower CD4+/CD8+ ratios at 2 months. Positive rate of nasopharyngeal swab by RT-PCR is higher during onset, whereas anal swab is higher during COVID-19 recovery	
13	Ozsürekcı et al. (2020)	Predictive value of cytokine/chemokine responses for the disease severity and management in children and adult cases with COVID-19, Journal of Medical Virology, Volume 93, 2020	<p>Design: <i>Experiment study</i></p> <p>Sample: Thirty pediatric patients and 30 adult patients infected with Covid-19</p> <p>Variable: - Dependent Variable: Covid-19 disease severity in children and adults - Independent Variable: Cytokine/chemokine response</p> <p>Instrument: Blood laboratory results and cytokine examination</p> <p>Analysis: <i>Chi-Square</i> and the Mann-Whitney test</p>	<p>The average number of white blood cells, lymphocytes, neutrophils and platelets in adult cases is lower than in children. Meanwhile, the mean CRP level was significantly higher in adult patients and the PCT level was significantly higher in pediatric patients. MDC, MIP-1α, MIP-3β and IL-17A were significantly higher in children than in adults. Interferon gamma-induced protein 10 (IP-10) and macrophage inflammatory protein (MIP) -3β levels were significantly higher in pediatric and adult patients with COVID-19 when compared to the control group (p 0.001 in each). Moreover, IP-10 is an independent predictor of disease severity, especially in children and interleukin-6 appears to be a relatively good predictor of disease severity in adults. IP-10 and MIP 3β appear to be good research candidates for</p>	<p>Cytokines IP-10 and MIP-3β are biomarkers with significant changes in disease severity in children. As activation of viral antigen-specific Th1 immune responses is critical for COVID-19 protection, chemokines, such as MIP-1α, and MIP-3β appear to be promising immunopositive candidates for further vaccine studies.</p> <p>Sample age : median 20,5 year, 30 pediatric, 14 male, 16 female.</p>

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
				understanding the severity of COVID-19 in pediatric and adult populations and for investigating possible pathophysiological mechanisms of COVID-19.	
14	H. Du et al.(2020)	Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status, Allergy, Volume 76, 2021	<p>Design: <i>Retrospective study</i></p> <p>Sample: 182 children with Covid-19 patients who will be divided into groups with allergies and without allergies</p> <p>Variable: - Dependent variable: severity and allergy status - Independent variables: clinical and laboratory characteristics</p> <p>Instrument: Electronic medical records, laboratory and immunological results, and radiological images.</p> <p>Analysis: <ul style="list-style-type: none"> • <i>Two-tailed t test</i> and Mann-Whitney : to compare data from two groups • Chi-square and Fisher's tests: used to compare levels of categorical parameters in the two groups <i>Spearman's correlation test</i> : used to calculate the correlation coefficient</p>	Laboratory results showed mostly within the normal range, and only a slight ratio of lymphopenia (3.9%) and eosinopenia (29.5%) was observed. The most common types of allergies are rhinitis, atopic dermatitis, food allergies, asthma, urticaria, and drug allergies. There were no significant differences in demographics and clinical signs between the allergic and nonallergic groups. The blood cell count and blood biochemistry showed similar results, except for the presence of low eosinophil counts, serum PCT levels, D-dimer and AST in the allergy group. Total serum IgE in allergic patients is higher. Allergic patients showed less increase in acute phase reactant, procalcitonin, D-dimer, and aspartate aminotransferase levels compared to all patients. The majority (97.8%) of the	Pediatric COVID-19 patients tend to have a mild clinical course. Patients with pneumonia had a higher proportion of fever and cough and elevated inflammatory biomarkers than patients without pneumonia. There were no differences between allergic and non-allergic COVID-19 children in disease incidence, clinical features, as well as laboratory and immunological findings. Allergy is not a risk factor for the development and severity of SARS-CoV-2 infection and hardly affects the course of COVID-19 disease in children. Sampel Age : mean 6 years , , 1 th sd 15 years

No	Author	Title, Journal Name, Vol, No, Year	Method (Design, sample, variable, instrument, analysis)	Systematic review results	Conclusion
				infected children were not seriously infected, and 24 (13.2%) of them had asymptomatic infection. Children with pneumonia had a higher percentage of comorbid history, fever and cough symptoms, and elevated serum procalcitonin, alkaline phosphatase, and serum interleukin (IL)-2, IL-4, IL-6, IL-10, and IL-10 levels. TNF- α . The immunological profile including circulating subsets of T, B, and NK lymphocytes, total and complement immunoglobulin levels, and serum cytokines did not show any difference in the allergy and pneumonia groups.	

DISCUSSION

Immunity is resistance from infection and immune response is the coordination of cells in the body and other molecules against infection. Corona virus (CoV) is a positive chain ribonucleic acid (RNA) virus whose transmission occurs more often from infected closest relatives with the main route through direct inhalation of respiratory droplets from coughing and sneezing. The immune response of children with COVID-19 consists of specific and non-specific immune responses.

Covid-19 virus infection in children will activate the non-specific and specific immune system both cellularly, humorally and through the release of biochemical and inflammatory mediators in the form of cytokines. The first step in infection is the binding of the virus to the host cell via its target receptor. SARS-CoV principally targets airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lung, all of which express the target receptor for angiotensin- converting enzyme 2 (ACE2) used by SARS- CoV. SARS-CoV-2 infection triggers a non- specific immune response by recruiting macrophages and monocytes that respond to infection, releasing cytokines and triggering T and B cells that will produce antibodies that match the virus (Tay et al., 2020).

Non-specific immune response in children with Covid-19 infection

Activation of immune cells due to viruses will trigger an increase in the number of white

blood cells, CRP, and the activation of IL-6, IL-10 and other cytokines. The results of the study showed that 27% had an increase in white blood cells in patients infected with Covid-19 (Peng et al., 2020; Y. Wang et al., 2020; Zhang et al., 2020), while 73% showed white blood cell count results within normal limits (Chen et al., 2020; H. Du et al., 2020; Ozsurekci et al., 2020; Su et al., 2020; Sun et al., 2020; W. Du et al., 2020; Xia et al., 2020; Xu et al., 2020). A total of 67% had an increase in the number of lymphocytes (CD4+ and CD8+) (Peng et al., 2020; Sun et al., 2020), while 33% experienced a decrease in the number of lymphocytes (Sun et al., 2020). An increase in white blood cells is an indication of the severity of the disease. Most pediatric patients have mild/asymptomatic symptoms. In a study conducted by Ozsurekci et al. (2020) 21/30 children had mild symptoms (70%), as did the study Su et al. (2020) all respondents (9 children) had mild symptoms.

Levels of C reactive protein (CRP) increased in 67% of the study results, and 33% of the study results showed normal values. CRP is a response of the liver during infection in which the liver synthesizes large amounts of acute phase protein (APP). This acute inflammatory protein is a highly sensitive biomarker for inflammation, tissue damage, and infection. CRP levels can increase phagocytosis and activate the complement system. In other words, CRP binds to microorganisms and promotes their elimination through phagocytosis. The current study revealed significantly higher CRP levels in severe cases than in non-severe patients suggesting that CRP levels are a marker of disease severity and progression in patients with COVID-19 (Zavareh et al., 2021). Study conducted by Li et al. (2020) showed the average level of increase in C-reactive protein (CRP) was 11.22. W. Du et al. (2020) reported that the increase in CRP was significantly higher in adult patients than in pediatric patients.

A rapid and well-coordinated non-specific immune response is the first line of defense against viral infections. However, an irregular and excessive immune response can cause immune damage to the human body. Furthermore, tissue damage caused by viruses can lead to overproduction of proinflammatory cytokines, recruitment of macrophages and proinflammatory granulocytes. This can cause a cytokine storm called Macrophage Activation Syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis. Cytokine storm is the main mechanism of acute respiratory distress syndrome (ARDS) due to uncontrolled systemic inflammation induced by proinflammatory cytokines (IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF-) and chemokines (Rumende et al., 2020).

Elevated levels of interleukin (IL) occurred in 80% of studies (Y. Wang, et al., 2020; Sun et al., 2020; Dioro et al., 2020; Xu et al., 2020). The interleukins observed in the studies were IL-6 in 4 studies, IL-10 in 3 studies and IL-8 in 1 study. IL-6 is produced by stromal cells and almost all cells of the immune system in the lung and its secretion is stimulated by proinflammatory cytokines, particularly interleukin 1 β (IL-1 β) and tumor necrosis factor (TNF α). In the early stages of infection, IL-6 is produced by lung macrophages (Sabaka et al., 2021). Plasma levels of IL-6, which is considered a significant cytokine contributing to MAS, are elevated in patients with severe COVID-19 infection (Rumende et al., 2020). IL-6 increases pulmonary capillary permeability which promotes the development of ARDS and also stimulates the coagulation pathway that leads to microthrombi in the pulmonary circulation and increases the risk of thrombotic events. A study by Giamarellos-Bourboulis et al. (2020) demonstrated that patients with severe respiratory failure in Covid-19 suffer from a type of immune dysregulation mediated by upregulation of IL-6. (Sabaka et al., 2021). On study Sun et al. (2020) there was a significant increase in IL-6 and IL-10 levels in critically ill pediatric patients admitted to the ICU. This is confirmed by studies conducted Huang et al. (2020) that Covid-19 patients admitted to the ICU have levels of IL-2, IL-7, IL-10 and TNF-

α higher plasma levels than patients who were not admitted to the ICU.

Interferon levels γ (IFN- γ) in patients with very high Covid-19 infection, including in children with mild infections (Diorio et al., 2020). A study conducted by Sun et al (2020) showed that an increase in IFN- γ in pediatric patients admitted to the ICU. In the study conducted Diorio et al. (2020) Some patients with both mild and severe symptoms have elevated IFN- γ . IFN- γ is produced by NK cells and T lymphocytes, although cells with different phases of the immune response (non-specific and specific), this cytokine is important in all phases of the immune response. The IFN- γ system is important for antiviral defense. IFN- γ decreases viral replication and activates the production of cytokines by T cells, increasing the activity of cytotoxic T lymphocytes. However, persistently high levels of IFN- γ exacerbate systemic inflammation, and increase tissue injury and organ failure (Gadotti et al., 2020). On study Ozsurekci et al. (2020), levels of gamma interferon-induced protein 10 (IP-10) and macrophage inflammatory protein (MIP)-3 significantly higher in pediatric and adult patients with COVID-19. IP-10 levels were significantly higher in both children and adults. IP-10 is an independent predictor of disease severity, especially in children. In addition, in the study of Y. Wang et al. (2020) and Sun et al. (2020) there is an increase in D-dimer in severe cases.

Specific immune response in children with Covid-19 infection

The immune response to the virus will mediate the formation of antibodies. B cells are assisted by T cells to differentiate into plasma cells, which then produce antibodies specific to viral antigens. Antibodies help block viruses from entering the host cell to limit infection and play a very strong protective role in the later stages of infection and prevent recurrence of infection. Chowdhury et al. (2020). During Covid-19 virus infection, the production of virus-specific antibodies was consistent in most patients, except in immunocompromised patients. IgM can be detected as early as 3 days after infection and provides the first line of defense of humoral immunity, after which a high-affinity IgG response is initiated and plays a key role in long-term immune memory. (Shah et al., 2021). There was an increase in immunoglobulin in 75% of the study results and 25% of the studies showed normal immunoglobulin levels. In a study conducted by Peng et al. (2020) there was no significant difference in immunoglobulin (IgG, IgM, IgA) levels between the group of pediatric patients who were detectable positivity (RP) and non-RP patients. Study conducted by Yonkers et al. (2020) showed that children with severe Covid-19 infection were more likely to have elevated IgM to RDB than patients with MIS-C (Multisystem Inflammatory Syndrome in Children). IgG levels increased in patients with severe COVID-19 infection with increasing duration of symptoms (Spearman correlation, $r = 0.44$; $P = .02$). Children with severe MIS-C were more likely to have increased SARS-CoV-2 IgM and IgG responses than those with mild MIS-C. SARS-CoV-2 IgM and IgG levels in mild MIS-C were below the threshold of 0.5 mg/ml.

This is very in line with the theory that the child's immune system is natural / physiologically non-specific, where when there are microbes that enter, the child's physical defense will immediately work, especially the respiratory tract with cilia and mucous membrane protection which produce mucus to catch incoming viruses, If the virus enters the stomach, it will be destroyed by stomach acid. If the physical defenses are not able to provide resistance, then the humeral defenses found in extracellular body fluids will be activated, including complement (lectins, interferons, C-reactive protein) and acute phase proteins (cytokin, TNF- α), IL-1, IL-6 Cellular defenses can be found in the circulation (neutrophils, eosinophils, basophils, monocytes, T cells, B cells, NK cells, red blood cells and platelets and tissues (eosinophils, mast cells, macrophages, T cells, NK cell plasma cells (Rengganis, 2018).

Specific immune defense works without the help of non-specific immunity, when it recognizes objects that are considered foreign in the body, the humeral immune system / body fluids will activate, which consists of B lymphocytes or B cells from the bone marrow, B cells stimulated by foreign objects will proliferate, differentiate and develop into plasma cells that will produce antibodies, the released antibodies will be found in the serum. In their development, B cells first produce immunoglobulin M (IgM) IgG, IgA, IgE which mature or remain as memory cells, the next defense is the immune system. Specific cellular systems in T lymphocytes or T cells are formed in bone cells but proliferate and differentiate in the thymus gland, T cells consist of CD4 + and CD8 + (Rengganis, 2018). Based on the analysis of researchers after studying literature from journals that matched facts and theories, a new theory emerged related to laboratory results in patients with Severe Acute respiratory coronavirus 2 (SARS-Cov-2) apart from laboratory results of the body's immune response, namely an increase in D-dimer yield > than 0.5 mg/L. D-dimers are protein fragments that appear when a blood clot dissolves in the body. In normal body conditions, the body has a mechanism to carry out the process of clotting and thinning blood. Blood clots occur when there is an injury to a part of our body, so to prevent continuous bleeding D-dimer is used to check for abnormalities or disorders in blood clotting. The condition of the reaction of the patient's immunity with SARS-Cov-2 as one of the causes of the reaction to blood clotting. When an infection occurs, there is an elevation of the body's immune system, the SAR-C0v-2 virus will cause blood clotting disorders or coagulopathy. Conditions like this can cause blood clots or thrombosis in the veins that flow to the heart, besides that it can block the blood vessels from the heart to the lungs, this can cause death. D-dimer is also associated with the release of excessive cytokines so that the immune system will attack the body itself. This can cause interference with blood coagulation. The higher the D-dimer result, the higher the risk of SAR-Cov-2 patients experiencing blockage. Blood clots in SAR-Cov-2 can cause pulmonary embolism and thromboembolic embolism that lead to severity and death (Yao et al, 2020).

CONCLUSIONS

The results of this review can be concluded that Covid-19 infection in children triggers non-specific and specific immune responses. The non-specific immune response begins with an increase in white blood cells by recruiting macrophages and monocytes that respond to infection, releasing cytokines and other inflammatory mediators and triggering a specific immune response, namely T and B cells that will produce antibodies that match the virus. There are increased levels of CRP, IL-6, IL-10, IFN- γ , and TNF- α in studies conducted on pediatric patients. In addition, there is an increase in IP-10 levels which can be an independent predictor of disease severity, especially in children. Excessive levels can cause immune damage to the human body because it causes a cytokine storm that causes organ damage. The non-specific immune response of the virus will mediate the formation of antibodies. B cells are assisted by T cells to differentiate into plasma cells, which then produce specific antibodies for viral antigens, in the form of IgM which is detected early and then replaced by IgG. This immune response is related to the severity of the disease.

A new theory was found of the reaction of the immunity of patients with Covid-19 as one of the reasons for the reaction to blood clotting, when an infection occurs, an elevation of the body's immune system occurs, the Covid-19 virus will cause blood clotting disorders or coagulopathy, conditions like this can cause blood clots or thrombosis in the veins that flow to the heart, otherwise it can block the blood vessels from the heart to the lungs. this can cause death, the D-dimer examination must be carried out related to the release of excessive cytokines so that the immune system will attack the body itself and the D-dimer can cause interference with blood clotting. When a child is infected with the Covid-19 virus, the specific

and non-specific immune systems are already working, to improve the performance of the immune system, it is necessary to increase adequate nutrition, adequate rest, support and family motivation.

REFERENCES

- Chen, G. et al. (2020) 'Clinical and immunological features of severe and moderate coronavirus disease 2019', *The Journal of clinical investigation*. Am Soc Clin Investig, 130(5).
- Chowdhury, MA et al. (2020) 'Immune response in COVID-19: A review', *Journal of Infection and Public Health*. King Saud Bin Abdulaziz University for Health Sciences, 13, pp. 1619–1629. doi: 10.1016/j.jiph.2020.07.001.
- Diorio, C. et al. (2020) 'Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2', *Journal of Clinical Investigation*, 130(11), pp. 5967–5975. doi:10.1172/JCI140970.
- Dong, Y. et al. (2020) 'Epidemiology of COVID-19 among children in China', *Pediatrics*. Am Acad Pediatrics, 145(6).
- Du, H. et al. (2020) 'Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status', *Allergy: European Journal of Allergy and Clinical Immunology*, 76(2), pp. 510–532. doi: 10.1111/all.14452.
- Du, W. et al. (2020) 'Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China', *Infection*. Springer Berlin Heidelberg, 48(3), pp. 445–452. doi:10.1007/s15010-020-01427-2.
- Gadotti, AC et al. (2020) 'IFN- γ is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection', *Virus Research*, 289(198171), pp. 1–7.
- Giamarellos-Bourboulis, EJ et al. (2020) 'Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure', *Cell Host and Microbe*. Elsevier Inc., 27(6), pp. 992–1000. doi: 10.1016/j.chom.2020.04.009.
- Huang, C. et al. (2020) 'Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China', *The Lancet*, 395(10223), pp. 497–506.
- Jayawardena, R. et al. (2020) 'Enhancing immunity in viral infections, with special emphasis on COVID-19: A review', *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. Elsevier.
- Kloc, M. et al. (2020) 'Development of child immunity in the context of the COVID-19 pandemic', *Clinical Immunology*. Elsevier, 217(June), p. 108510. doi: 10.1016/j.clim.2020.108510.
- Li, B. et al. (2020) 'Radiographic and Clinical Features of Children With Coronavirus Disease (COVID-19) Pneumonia', *Indian Pediatrics*, 57, pp. 423–426.

- Nursalam (2020) *Writing Literature Review and Systematic Review on Health Education*. Surabaya: Faculty of Nursing Universitas Airlangga.
- Ozsurekci, Y. et al. (2020) 'Predictive value of cytokine/chemokine responses for the disease severity and management in children and adult cases with COVID- 19', *Journal of Medical Virology*, 93(5), pp. 2828–2837. doi:10.1002/jmv.26683.
- Peng, D. et al. (2020) 'Risk factors for redetectable positivity in recovered COVID-19 children', *Pediatric Pulmonology*, 55(12), pp. 3602–3609. doi: 10.1002/ppul.25116.
- Rengganis, I. (2018) *'Basic Immunology'*. Publishing Agency of the Faculty of Medicine, University of Indonesia.
- Rumende, CM, Susanto, EC and Sitorus, TP (2020) 'The Management of Cytokine Storm in COVID-19', *Acta medica Indonesiana*, 52(3), pp. 306–313.
- Sabaka, P. et al. (2021) 'Role of interleukin 6 as a predictive factor for a severe course of Covid-19: retrospective data analysis of patients from a long-term care facility during Covid-19 outbreak', *BMC Infectious Diseases*, 21(308), pp . 4–11. doi:10.1186/s12879-021-05945-8.
- Shah, J. et al. (2021) 'IgG and IgM antibody formation to spike and nucleocapsid proteins in COVID-19 characterized by multiplex immunoblot assays', *BMC Infectious Diseases*. *BMC Infectious Diseases*, 21(325), pp. 1–8.
- Shi, Y. et al. (2020) 'COVID-19 infection: the perspectives on immune responses', *Cell Death and Differentiation*. Springer US, 27(5), pp. 1451–1454. doi:10.1038/s41418-020-0530-3.
- Su, L. et al. (2020) 'The different clinical characteristics of corona virus disease cases between children and their families in China—the character of children with COVID-19', *Emerging Microbes and Infections*, 9(1), pp. 707–713. doi: 10.1080/22221751.2020.1744483.
- Sun, D. et al. (2020) 'Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study', *World Journal of Pediatrics*. Springer Singapore, 16(3), pp. 251–259. doi:10.1007/s12519-020-00354-4.
- Tay, MZ et al. (2020) 'The trinity of COVID- 19: immunity, inflammation and intervention', *Nature Reviews Immunology*, 20(6), pp. 363–374. doi:10.1038/s41577-020-0311-8.
- Thevarajan, I. et al. (2020) 'Breadth of concomitant immune responses prior to patient recovery: a case report of non- severe COVID-19', *Nature medicine*. Nature Publishing Group, 26(4), pp. 453–455
- UNICEF (2020) 'COVID-19 and Children in Indonesia Action Agenda to Overcome Socio-Economic Challenges', in *Journal of education, psychology and counseling*. Jakarta: UNICEF. Available at: www.unicef.org.
- Wang, Y. et al. (2020) 'Children Hospitalized With Severe COVID-19 in Wuhan', *The*

Pediatric infectious disease journal. LWW, 39(7), pp. e91--e94.

Xia, W. et al. (2020) 'Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults', *Pediatric Pulmonology*. John Wiley & Sons, Ltd, 55(5), pp. 1169–1174. doi:10.1002/ppul.24718.

Xu, Y. et al. (2020) 'Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding', *Nature Medicine*, 26(4), pp. 502–505. doi:10.1038/s41591-020-0817-4.

Yonker, LM et al. (2020) 'Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses', *Journal of Pediatrics*, 227, pp. 45-52.e5. doi:10.1016/j.jpeds.2020.08.037.

Zavareh, MS-H. et al. (2021) 'C-Reactive protein as a prognostic indicator in hospitalized patients with COVID-19', *Interdisciplinary Perspectives on Infectious Diseases*, 15, pp. 1–5. doi: 10.1371/journal.pone.0242400.

Zhang, T. et al. (2020) 'Detectable SARS- CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia', *Journal of Medical Virology*, 92(7), pp. 909–914. doi:10.1002/jmv.25795

