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The Relationship Between IgG and IgM Anti-SARS-CoV-2 Antibody Levels With Severity of Disease in Adult COVID-19 Patients in Bengkulu City in 2020

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ABSTRACT

Coronavirus disease (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) and was declared a pandemic by WHO in 2020. When the human body is infected with a virus, it will respond by forming antibodies such as IgM and IgG. In forming antibodies, the body will show clinical manifestations that can be grouped according to degree. The degree of clinical manifestations in the course of the disease affects the antibody response produced, so this study aims to determine the relationship between clinical manifestations and the level of IgG Anti-SARS-Cov-2 antibodies in COVID-19 patients confirmed to have recovered in Bengkulu City in 2020. This study used an observational analytic research method in the form of a Cross-Sectional study. The number of research samples was 24 people. The sampling technique was non-probability sampling with a consecutive sampling method. Assessment of the degree of clinical manifestations using the classification of the severity of COVID-19 disease by WHO in 2022. The relationship between the two variables was analyzed using the Pearson correlation test. The results showed that the age of COVID-19 patients was dominated by the age range of 45-54 years in as many as 12 research subjects (50%), with the majority of patient manifestations of fever, as many as 17 research subjects and the distribution of patients based on the severity of the disease, the most being moderately ill 41.7% as many as ten research subjects. Based on statistical analysis, it was found that there was no relationship between IgG and IgM Anti-SARS-CoV-2 antibody levels on the severity of disease in COVID-19 patients (IgG p = 0.149, IgM p = 0.780, both p = > 0.05). There is no relationship between IgG and IgM Anti-SARS-CoV-2 antibody levels on the severity of disease in COVID-19 patients in Bengkulu City.

KEYWORDS : COVID-19, Severity, IgG, IgM

INTRODUCTION

Coronavirus disease 2019 (COVID-19) appears for the first time in Wuhan, China and has spread rapidly worldwide (del Rio, Carlos; Malani, 2020; Khan, Haleem and Javaid, 2020). The World Health Organization (WHO) states that this disease is a pandemic that has spread worldwide (WHO, 2020). COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Member of the Betacoronavirus genus like two other viruses, namely SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERS- CoV) (Peterhoff et al., 2020).

Based on the WHO report on 13 April 2021, there were 136,291,755 cases COVID-19 confirmation with numbers 2,941,128 deaths and a Case Fatality Rate (CFR) of 2.2% worldwide consisting of of the Americas with cases confirmed the most, namely 58,571,081 cases, followed by the European region with 48,148,670 cases, the Southeast Asian region with 16,732,227 cases, the Eastern Mediterranean region with 8,220,531 cases, the African region with 13,194,684 cases and the Western Pacific region with 2,128,426 cases. (WH0, 2020). According to The Indonesian Ministry of Health on 13 April 2021 recorded 1,577,526 cases confirmed, with numbers 42,782 deaths (CFR 2.7%) which spread to various regions, including DKI Jakarta, with cases confirmed cumulative the most, namely 394,118 cases and the North Maluku region with cases cumulative the fewest, namely 4,360 cases (RI Ministry of Health, 2020).

It is known that the main transmission of SARS-CoV-2 is via droplets; however, its possible through faecal-oral (Fitriani, 2020). Research conducted by Xiao et al. (2020) on 73 patients caring for COVID-19 shows that 53.42% of patients were positive for SARS-CoV-2 ribonucleic acid (RNA) in faeces. Research further proves that there is the expression of angiotensin-converting enzyme 2 (ACE2) in gastric, duodenal and epithelial glandular cells rectum as well as SARS-CoV-2 virus nucleocapsid protein was found in the epithelium stomach, duodenum and rectum (Xiao et al., 2020). It shows that COVID-19 can infect channel digestion and allows transmission in a manner faecal - oral. In addition, based on the report of one case of SARS-CoV-2 infection in Germany, this virus can be transmitted through contact with patients without symptoms (Gou; Yan-Rong et al., 2020). Infected individuals without symptoms can become source transmission of SARS-CoV-2 and experience fast progress even ending Acute Respiratory Distress Syndrome (ARDS) with high CFR (Fitriani, 2020)

COVID-19 is important in medicine because of its rapid deployment and potential to cause collapse system health, but also because manifestation clinical in patients. SARS-CoV-2 attacks target organs expressing ACE2, such as the lung, kidney, heart, cell brain and gastrointestinal tract, so the manifestation clinical from COVID-19 varies greatly, starting from asymptomatic until failure breath severe and requires a ventilator (Gou; Yan-Rong et al., 2020). Research conducted by Huang et al. (2020) states that the manifestation of clinical COVID-19 most often happens with fever (98%), cough (76%), myalgia or fatigue (44%) (Huang et al., 2020). Manifestation and other clinical can occur in other organs, such as congested breath, pain throat, nose congestion, dizziness, chills, pain in muscles, arthralgia, production of excessive mucus with expectoration, hemoptysis, pain, headache, diarrhoea, pain in the stomach, vomiting, chest pain and rhinorrhea (Baj et al., 2020). Every COVID-19 patient can experience more than one manifestation (Baj et al., 2020).

Along with increasing cases confirmed by COVID-19, high CFR and ongoing research on COVID-19 continues until then. Therefore it required enforcement predictive and appropriate handling to be able to lower CFR. At this point still available diagnostic form assessment of IgG and IgM levels. Research conducted by Cecilie Bo Hansen et al. (2021) showed that patients with high IgG and IgM levels correlated with level severity symptoms, in which the IgG level is elevated for 11 weeks First after symptom onset, while IgM and IgA levels remain constant and stable for a period same time. This research illustrates that symptom light during SARS-CoV-2 infection will increase the response to more antibodies low compared to patients symptom medium and heavy (Wu et al., 2007; Jacofsky, Jacofsky and Jacofsky, 2020; Hansen et al., 2021).

In contrast, research by Length et al. stated that seroconversion to IgG and IgM coincides with both peaks six days after seroconversion (Pang et al., 2021). In addition, a study by Zhang et al. on patients infected with COVID-19 occurred enhanced IgG and IgM antibody levels on days of a possible end

of infection, which is helpful in the diagnosis of infection (Ozma et al., 2020). Dynamics response humoral immunity determines the speed of elimination of viruses (Xiang et al., 2020). More virus clearance fast associated with response antibodies previously when the initial low RNA SARS-CoV-2 detected in patients without S IgG showed that induction adaptive humoral response possibly depends on the strength of viral replication (Pang et al., 2021). Therefore, researchers _ will conduct related research connections between IgG and IgM anti-SARS-CoV-2 antibody levels with degrees of severity disease in patients of COVID-19 adults in Bengkulu City in 2020.

MATERIALS AND METHODS

Types and Research Design

The type of research uses analytical research methods observational with form studies cross-sectional. Research location to detect IgG and IgM antibodies against SARS-CoV-2 in the laboratory serology the Prodia City of Bengkulu and the research subjects come from hospitalized COVID-19 patients hospital stay Regional General Hospital (RSUD) M. Yunus Bengkulu and Hospital Regional General Hospital (Hospital) Harapan dan Doa Bengkulu City so this also be research location.

This study's population is hospitalized COVID-19 patients at M.Yunus Bengkulu Hospital and Harapan dan Doa Hospital in Bengkulu City. The sample in this study is part of the population that has fulfilled the research criteria. The sample used in this study uses the sample formula single for the estimation proportion of a population (Sastroasmoro, 2014).

$$n1 = n2 = \frac{(Za^2)\ X\ P\ X\ Q}{(d)^2}$$

$$n = \frac{1,96^2\ X\ 0,50\ X\ (1 - 0,50)}{(0,2)^2}$$

$$n = \frac{0,96}{0,04} = 24\ \text{subjects}$$

Information :

n = Sample Size

Z a 2 = Significance level (1.96)

P = Proportion of previous research (if unknown 0.50)

Q = 1-P (0.50)

d = Desired degree of population deviation (20% = 0.2)

Based on the formula above, a total sample is required _ in this research of as many as 24 people.

The recruitment technique for the sample used in this study is non-probability sampling by technique consecutive sampling. The researcher takes subject patient care for COVID-19 at the M. Yunus Bengkulu Hospital and the Harapan dan Doa Hospital in Bengkulu City.

Criteria inclusion in this study are : (a) Registered as a patient confirmed COVID-19 being treated at the M. Yunus Bengkulu Hospital and the Harapan dan Doa Hospital in Bengkulu City; (b) COVID-19 patients aged ≥ 18 years; (c) Willing agrees to participate in the research informed consent sheet to be taken blood as an antibody serum sample. Criteria Exclusions in this study are : (a) COVID-19 patients co-infected with urinary tract infections, another breath; (b) COVID-19 patients who experience reinfection. The criteria for dropout in this study are : (a) Respondents with secondary data, namely records of incomplete medical; (b) Research respondents withdrew themselves from the research; (c) Research respondents did not follow taking samples at least three times.

Research Data Collection

The study was conducted by collecting secondary data from laboratory results of IgG and IgM Anti-SARS-CoV-2 antibody levels in patients of COVID-19 adults and medical record data containing

manifestation clinical will grouped based on degrees of severity of COVID-19 disease (Table1). The researcher will analyze the results obtained and analyzed manifestation clinical patient adults based on COVID-19 degrees severity disease to know the relationship between anti-SARS-CoV-2 IgM and IgG antibody levels and degree severity disease in patients COVID-19 adults in Bengkulu City in 2020.

Data Analysis

Secondary data in the form of laboratory results level IgG and IgM antibodies and manifestations of clinical COVID-19 patients were analyzed using a statistical software program for social science (SPSS). Data analysis in this study was used to analyze two variables, the severity degrees of disease in patients COVID-19 adults and IgG and IgM antibody levels, using a correlation test Pearson to see the connection between two variables using the categorical (ordinal) and numeric data.

Table 1 Degrees Severity COVID-19 disease according to the Ministry of Health of the Republic of Indonesia

Degrees Disease	**Manifestation clinical**	**Explanation**
Without Symptom	Nothing _ symptom clinical	The patient does not show symptoms.
Sick light	Sick light without complications	Patients with non-specific symptoms include fever, cough, throat pain, nose congestion, malaise, headache, and muscle pain. Need to be wary of age advanced and *immunocompromised* Because atypical signs and symptoms _
Moderate Pain	Mild pneumonia	Patient Teen or Adult with signs of clinical pneumonia (fever, cough, dyspnea, rapid breathing) and absent sign of severe pneumonia Children with mild pneumonia experience cough or trouble breathing + rapid breathing: respiratory rate :
Sick Heavy	Pneumonia Weight / ARI	Patient adolescent or adult with fever or deep respiratory infection surveillance, plus One from respiratory rate > 30 x/ minute, respiratory distress weight, or saturation oxygen (SpO2) <90% in the air room A patient child with cough or difficulty breathing, plus at least one of the following : • cyanosis central or SpO2 <90% • Distress breathing heavy (e.g. snoring, pulling heavy chest wall). • The signs of severe pneumonia are inability to breastfeed or drink, lethargy or decline of consciousness, or seizures.

		Another sign of pneumonia is: pulling chest wall, tachypnea : • <2 months ≥ 60 x/ minute • 2-11 months, ≥ 50 x/ min • 1-5 years, ≥ 40 x / min • >5 years , ≥30x/ minute This diagnosis is based on clinical; chest imaging can help diagnose and eliminate complications.
Sick Critical	ARDS	Onset: recent or worsening in time One week. Imaging (thoracic CT scan, or ultrasound Lungs): bilateral opacity, pleural effusion that cannot explain cause, collapse lung, collapse lobes or nodules. Cause of oedema: respiratory failure that is not a consequence of a failing heart or extra liquid. Need inspection objective (e.g. echocardiography) to rule out that the cause of the oedema is not consequence hydrostatic if not found factor risk. ARDS criteria in adults : • Mild ARDS: 200 mmHg <$PaO_2/FiO_2 \leq$ 300 mmHg (with PEEP or *continuous positive airway pressure* (CPAP) ≥ 5 cmH_20, or not ventilated • Moderate ARDS: 100 mmHg <$PaO_2/FiO_2 \leq$ 200 mmHg with PEEP ≥ 5 cmH_20, or non-ventilated • Severe ARDS: $PaO_2/FiO_2 \leq$100 mmHg with PEEP ≥ 5 cmH_20, or not ventilated When PaO_2 is not available, $SpO_2 / FiO_2 \leq 315$ indicates ARDS (incl non-ventilated patient) ARDS criteria in children : • Age: Excluded patients with disease lungs perinatal • Time: within seven days since disease onset • Cause of oedema: failed unable to breathe explained by failed heart or extra fluid *(fluid overload)* • Radiological: new infiltrate consistent with disease lungs I • Oxygenation: ventilation mechanical non-invasive, ventilation invasive mechanics PARDS Light Moderate Severe Full face mask bi-level ventilation or CPAP ≥ 4 ≤ OI ≤8 8 ≤ OI ≤ 16 OI ≥ 16

Source: RI Ministry of Health, 2020.

RESULTS

Characteristics Subject COVID-19 research

Based on Table 2, the research data results show characteristics based on the subject's gender and age. Type male and female amounted to the same as 12 research subjects (50%); meanwhile, age dominated in the 45-54 years as many as 12 research subjects (50%).

Table 2 Frequency Distribution of Characteristics Research Subjects

Characteristic Data		Frequency		Total
		n	%	
Age	25-34 years	1	4.16%	24
	35-44 years	3	12.5%	
	45-54 years	12	50%	
	55-64 years	6	25%	
	65-74 years	2	8.33	
Type Sex	Male	12	50%	24
	Female	12	50%	

Spread Manifestation Clinical Patient Adult COVID-19

Based on the results of data collection, obtained distribution manifestation clinical patient COVID-19 adults can see in Table 3.

Table 3 Frequency Distribution of Manifestation Clinical Patient Adult COVID-19

Manifestation Clinical	F(n)	%
Cough	13	20.63 %
Fever	17	26.98%
Weak	5	7.93 %
Shortness of breath	7	11.11%
Anosmia	3	4.76%
Diarrhoea	4	6.34%
Vomit	3	4.76%
Sick Throat	5	7.93%
Sick Head	2	3.17 %
Heartburn _	1	1.58%
muscle pain	2	3.17 %
Unconscious _	1	1.58%
Amount	63	100

Based on Table 3 frequency manifestation, The fewest clinical subjects in the study were unconsciousness and heartburn (1.58%) in 1 subject. Frequency manifestation The most frequent clinical disease was fever (26.98%) in 17 research subjects.

Spread Degrees Severity Patient Adult COVID-19

Research obtained data from 24 patient sera take care inpatient COVID-19 at the M.Yunus Bengkulu

Hospital and the Harapan and Prayer Hospital in Bengkulu City, which checked on the day first. Distribution degrees manifestation clinical according to the Ministry of Health in 2022 got seen in Figure 1.

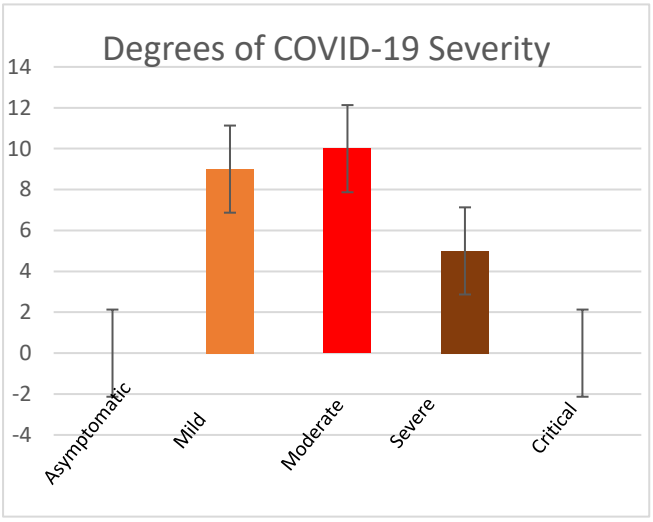

Figure 1. Chart Distribution Degrees Severity COVID-19 disease

The chart shows that the lowest severity is severe (20.8%) in as many as five research subjects, and the most research subjects have degrees of severity of COVID-19 disease is mild (41.7%) in as many as ten research subjects.

Distribution of Antibody Levels in COVID-19 Patients

Figure 2 shows a comparison of mean IgG antibody levels based on the degrees of severity of COVID-19 disease, and results obtained that IgG antibody level values in the disease light majority from range 0.9 – 16.57 (median 6.21), while in the sick currently majority antibody level value from range 0.20 – 132.62 (median 9.25) and illness heavy majority antibody level value from range 19.59 – 65.66 (median 37.96).

Figure 3 shows a comparison of mean IgM antibody levels based on degrees of severity of COVID-19 disease, and results obtained that IgM antibody level values in disease light majority from range 0.06 – 0.285 (median 0.08), while in the sick currently majority antibody level value from range 0.027 – 0.43 (median 0.27) and illness heavy majority antibody level value from range 0.025 – 0.61 (median 0.15).

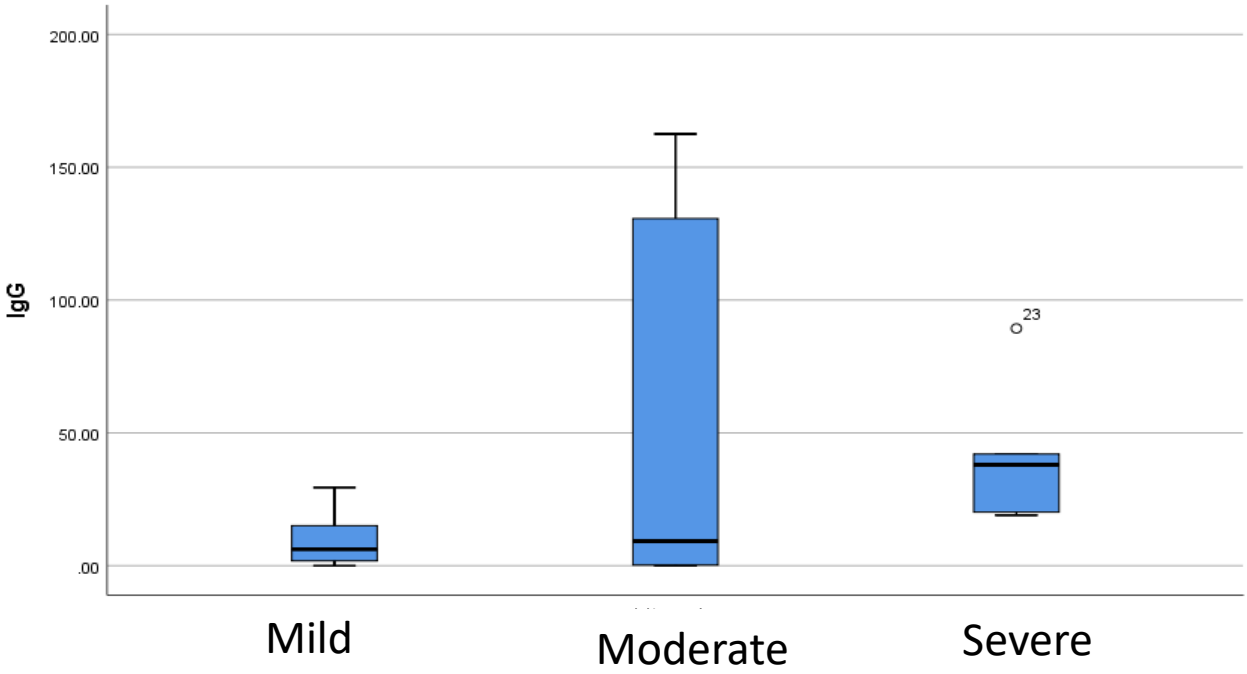

Figure 2 Graph Comparison Mean IgG Antibody Level According to Degrees Severity COVID-19 disease

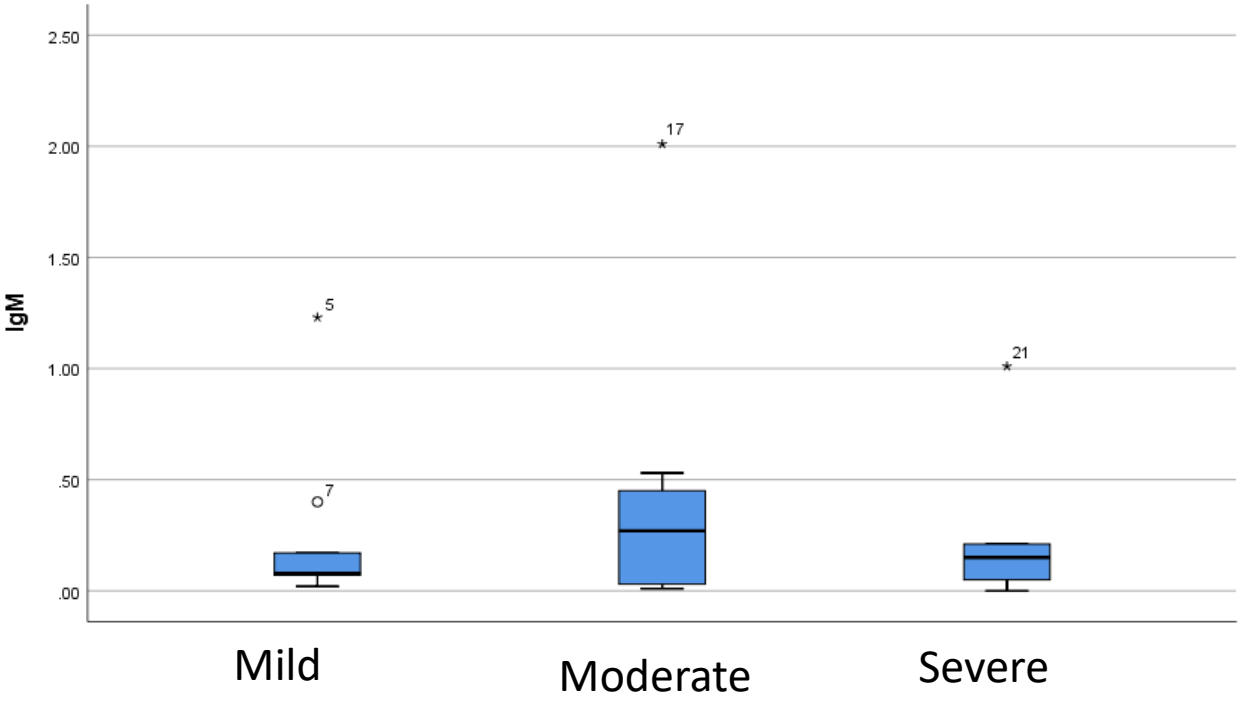

Figure 3 Graph Comparison Mean IgM Antibody Level According to Degrees Severity COVID-19 disease

Relationship between IgG and IgM Antibody Levels and Degree Severity Disease COVID-19 Patient Adult COVID-19

Testing hypothesis correlation Pearson, it has done test prerequisites to meet correlation test conditions Pearson namely normality and linearity tests can see in the attachment so that the normality test results obtained p> 0.005 means that the data is distributed normally. The linearity test using ANOVA obtained p = 0.672, p> 0.05 means a linear relationship, so fulfill prerequisite correlation test.

Based on the Pearson correlation test showed that there is not a significant relationship between IgG and IgM anti-SARS-CoV-2 antibody levels with degrees of severity disease in patients with adult COVID-19 (IgG p = 0.149, IgM p = 0.780, both p = > 0.05).

DISCUSSION

Manifestation clinical patient COVID-19 adults predominate with manifestations clinically, namely fever of 26.98% in 17 research subjects, resulting in clinical diversity from asymptomatic to non-specific symptoms. Fever is caused by a response physiological complex immune system-mediated cytokines innate and adaptive involving _ track stimulation adrenergic (Gul, Htun and Inayat, 2021). Research conducted by Huang et al. (2020) shows that the most frequent symptoms were fever (98%), cough (76%), and myalgia (44%). This result supports that most clinical manifestations of fever, followed by coughing (20.63%) in 13 research subjects, will be grouped based on degrees of severity according to the COVID-19 disease Ministry of Health (2020).

Based on research results, degrees of severity, the most common disease of COVID-19 is moderate 41.87% of as many as ten subjects followed by mild 37.5% of as many as nine research subjects and severe 20.8% of as many as five research subjects. This result aligns with research conducted by Zhao et al. (2020) which shows that as much as 60-80% of cases experiencing COVID-19 patients manifest clinical light until the clinical condition is moderate (Zhao et al., 2020). In previous studies, degrees of manifestation The clinical consequences for COVID-19 patients in Bengkulu City are varied, according to previous studies showing that most manifestations found at the Regional General Hospital M.Yunus, Harapan dan Doaer Hospital, Bengkulu City are case by degree manifestation moderate or mild pneumonia 54 cases and degrees manifestation clinical others each reached 13 cases for cases mild to, 21 cases to degrees manifestation clinical weight and 17 cases for degrees manifestation clinical severe (Rizqoh et al., 2022).

Difference manifestation of COVID-19 results from the interaction between vulnerable individuals with the virus's ability (good quality or quantity)o infect, as well as How dynamics interact with ACE2 and SARS-CoV-2 receptors (Ikawaty, 2020). Manifestation of existing clinical connected with a place where he found ACE2 receptors, view clear that ACE2 expression is distributed across a wide range of body tissues and organs and, as a result, happened interaction between SARS-CoV-2 and ACE2 receptors in specific tissues or organs, so that involvement of other organs can influence degrees severity COVID-19 disease.

Kwon et al. (2020) research identified factor severity in COVID-19 patients, namely concentration cytokines or chemokines, viral load and response antibodies. The result was that concentration cytokines or chemokines are no different in a manner significantly higher in the group severe and critical. Among the 21 cytokines, only MCP-1 correlated with viral load (p = 0.034 (Kwon et al., 2020). A study by Lu Qingqing et al. (2020) stated that enhancement of MCP-1 expression is associated with the inhibition of IFN and IRF3 signals and correlated increase in MCP-1 positive against IgG and IgM (Lu et al., 2020).

Based on the analysis correlation Pearson connection between Anti-SARS-CoV-2 IgG antibody level and degree severity disease in patients COVID-19 adults found that there was no result connection between antibody level and degree severity (IgG p=0.149, IgM=0.780, p>0.05). Besides degree severity, deep matter this, many possible factors influence the kinetics response of IgG and IgM antibodies, such as factor age, sex, obesity, disease accompaniments, and results in laboratory COVID-19 patients(Vanshylla et al., 2021). Low level of IgG also can influence a reinfection case of COVID-19 (Nugraheni et al., 2022). The community should continue to implement health protocols and practice clean and healthy living behaviors (PHBS) to control COVID-19 infection (Rizqoh,

Djatmiko, et al., 2023).

Research conducted by Vanshylla et al. (2021) analyzed factor age and found that advanced person age, namely individuals aged 60 years and over, has a higher severity. It is suspected due to competence system immune somebody will the more reduce along increase age caused by the degeneration decline quantity from cellular (cell neutrophils, cells T lymphocytes and dendritic cells), decrease in the number of receptors involved in the immune response system (TLR receptors and receptors surface cell monocytes and macrophages), decreased ability to differentiate (cell B lymphocytes) on the component system immune.

COVID-19 patients who have rate lymphocytes low at age >60 years compared to age <60 years. Lymphocytes show as a response to viral infection. Low lymphocyte levels _ can indicate degrees of severity of COVID-19 disease (Liu et al., 2020). Aged COVID-19 patients □60 years experienced respiratory organ failure taller compared to those aged <60 years, so aged COVID-19 patients □60 years need time longer treatment and healing compared to those aged <60 years. It shows that age □60) experience more COVID-19 heavy and have more inadequate respons during the treatment period (Li et al., 2020).

Research by Liu et al. (2020) discusses the correlation between disease accompanying chronically infected individuals with levels of the severity of COVID-19 infection, indicating that that person has disease accompaniments, especially those that are chronich disease, more prone to infected with COVID-19 and have more possibilities high to raise manifestation severe clinically (Liu H.2020). As an example, diabetes mellitus is one of comorbid disease that can influence IgG level (Rizqoh, Haloho, et al., 2023).

Leulseged et al. (2021) research regarding marker laboratory can predict the disease's severity level. The research results show that there is a significant difference in a manner statistics on the level severity of COVID-19 disease among classified groups based on exists disease heart disease, hypertension, type II diabetes mellitus and laboratory biomarkers NLR, platelet count, SGPT, SGOT, ALP, Na, K.With thus, NLR, elevated SGOT and abnormal Na and K levels (state hypo and hyper) are found as predictor significant to develop severe COVID-19 disease (Leulseged et al., 2021). This data is supported by research conducted by Mouchia et al. (2020) on severe or critical groups associated with improvement marker response immune default such as neutrophil count, NLR, IL-6, CRP, and serum ferritin; decline marker response immune adaptive such as the number of lymphocytes, CD4 and CD8; and improvement marker damage primary tissue and organ failure including D-dimer LDH, Troponin I, CK-MB, AST, ALT, urea, and creatinine. Based on the meta-analysis results, markers significant laboratory against-risk disease critical are NLR, IL-6, serum ferritin, lymphocyte count and CD4, D-dimer and troponin (Moutchia et al., 2020).

There are several limitations moment do this research. The researcher only used sample data from blood patients on the day they first stated positive for COVID-19, so we can not compare antibody levels by day next, like days seventh and 14th. Researchers only analyze the severity of COVID-19 on IgG and IgM anti-SARS-CoV-2 antibody levels, so it does not involve Other factors affecting antibody levels like comorbidity. Researchers do not consider the examination results to support patient COVID-19 adults, so it describes the condition of patients due to limitations of research data obtained by researchers. The number of samples used in this research is also minimal, and the research subject is only in space the scope of two hospitals in Bengkulu, so it cannot describe the degrees of severity of COVID-19 disease against IgM and IgG antibody levels in COVID-19 patients in Bengkulu City.

CONCLUSIONS

Based on the results of data analysis and discussion, it can be concluded that the most common clinical manifestation was fever 26.98% in 17 research subjects. The most severe degree of COVID-19 disease is moderate illness 41.7% in 10 research subjects. IgG and IgM antibody levels have no relationship to the Severity of COVID-19.

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Conflict of Interest

Author declared that there is no conflict of interest.

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