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Research Article

Description of Leukocytes in Patients who are Positive for COVID-19 Infection

Marliana Nurprilinda[1]*, Erica Gilda Misnawati Simanjuntak[2]

[1.] *Department of Pathology, Faculty of Medicine, Universitas Kristen, Jakarta, Indonesia*

[2.] *Department of Anesthesiology, Faculty of Medicine, Universitas Kristen Indonesia*

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*Address for Correspondence:

Marliana Nurprilinda, Department of Pathology, Faculty of Medicine, Universitas Kristen, Jakarta, Indonesia

Abstract

In December 2019, the first mysterious pneumonia case was reported in Wuhan, Hubei Province. Based on the obtained information, the first case was associated with a fish market in Wuhan, and five cases were found with *Acute Respiratory Distress Syndrome* (ARDS). These cases continue to rise from December 31, 2019, to January 3, 2020, with 44 cases found. This research aims to know the description and the correlation between the levels of leukocytes and the value of the rRT-PCR COVID-19. This research uses descriptive design linear regression analysis, bivariate with a cross-sectional approach using patients' medical records. Researchers obtained 77 samples of patients who examined the rRT-PCR COVID-19 at one hospital in East Bekasi, West Java. The results of this study showed a significant correlation between the levels of leukocytes with the results of the examination of the rRT- PCR COVID-19 (P=0.01) and decreased levels of leukocytes at the beginning of the examination of the rRT-PCR (R= -2, 92).

Keywords: COVID-19, Leukocytes

INTRODUCTION

In December 2019, a mysterious pneumonia case was first reported in Wuhan, Hubei province. Based on the information obtained, this case was first linked to the fish market in Wuhan, and there were 5 cases with Acute Respiratory Distress Syndrome (ARDS). This case continues to increase starting from December 31, 2019, with 44 cases as of January 3, 2020. [1]

The samples obtained from this patient showed infection with coronavirus. It is a new type of betacoronavirus; this disease was initially named the 2019 novel Coronavirus (2019-nCoV). [2] WHO finally announced a new name for this disease, namely Coronavirus Disease (COVID-19), on February 11, 2020. This disease is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus. [3]

Leukocytes or white blood cells are part of the composition of human blood cells, which play a role in the immune system or kill germs and germs that enter the human bloodstream. Each person's normal leukocyte levels will be different, influenced by several factors. Normal levels of leukocytes in healthy people are between 4,000 to 11,000 per microliter of blood. [4]

Calculating total leukocyte levels can be used as a diagnostic tool for disease in patients. Changes in total leukocyte values can decrease below normal values (leukopenia) or increase above normal values (leukocytosis). Both of these things can indicate the presence of a disease that is attacking the patient's body. [5]

The problem in this research is "What is the profile of leukocyte examination in COVID-19 patients? And is there a relationship between the patient's leukocyte levels and the COVID-19 rRT-PCR value? The research aims to determine the profile picture of the COVID-19 leukocyte examination and the correlation between the patient's leukocyte levels and the COVID-19 rRT-PCR value.

LITERATURE REVIEW

After the first case was reported on December 18, 2019, cases of Coronavirus Disease (COVID-19) caused by SARS-COV-2 continue to increase every day. On January 2, 2020, in China, 41 hospitalized patients had been identified as having positive results for COVID-19 infection. Nearly half of the patients have underlying diseases, such as diabetes, hypertension, and cardiovascular disease. It is believed that 41 patients were infected with COVID-19 in a hospital or nosocomial infection. [6]

The first reported case of COVID-19 in Indonesia occurred on March 2, 2020, with a total of 2 cases. [7] As of December 31, 2021, the Indonesian government informed that 743,198 patients were positive for COVID-19. There were 22,138 deaths from patients who tested positive for COVID-19 and 611,097 positive patients who have recovered. [8] Globally, 88,828,387

cases of positive COVID-19 patients have been confirmed, and the total number of deaths from COVID-19 is 1,926,625 cases recorded on January 3, 2021. [9] For the prevalence of the number of cases based on type gender, women and men both have equal cases. But in terms of mortality, men outnumber women. It is influenced by the smoking habits of men and women who are more likely to protect themselves from contracting the COVID-19 disease, such as (washing their hands, not leaving the house, and gathering in crowded places). [10]

CoVs are single positive RNA viruses; when viewed from an electron microscope, they will appear like a "crown-like" crown because there are glycoprotein spikes on the envelope/surface. This virus belongs to the Orthocoronavirinae subfamily and the Coronaviridae family, which is divided into four groupings: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV) and Gammacoronavirus (gammaCoV). [11] These CoVs have four structural proteins consisting of protein S (spike), protein M (membrane), protein E (envelope), and protein N (nucleocapsid). [12]

The Alphacoronavirus and Betacoronavirus groups can infect mammals and cause respiratory and digestive disorders. [13] Alphacoronavirus itself consists of several types of viruses (HCoVs, HCoV-229E, and NL63), while Betacoronavirus itself consists of (MERS-CoV, SARS-CoV, HCoV-OC43, and HCov-HKU1). [14] MERS-COV and SARS-CoV infection can cause Acute lung injury and Acute Respiratory Distress Syndrome (ARDS), which can cause lung failure and ultimately cause death. [15]

According to phylogenetic analysis, SARS-Cov2 is included in the Betacoronavirus genus, which has the same receptor-binding domain as SARS-CoV. [16] Scientists in China discovered that this similarity lies in binding to the Angiotensin Converting Enzyme (ACE 2) receptor to enter host cells. [17]

For the transmission of CoVs, there are still no definite details about how to infect humans. But based on the first case in the Huanan seafood market, Wuhan. Transmission of viruses from animals to humans was considered the main infection mechanism at that time. But as cases continue, animal-to-human exposure is no longer considered the primary mechanism. However, the virus is transmitted from human to human, especially people who have symptoms and can spread it easily to other people. [18]

Transmission of SARS-CoV-2 through a human-to-human mechanism. It can occur due to direct contact of respiratory fluid droplets and aerosol particles when an infected person (talks, breathes, and sneezes) to another infected person nearby. These droplets and aerosol particles will directly enter the respiratory system through the nose and mouth and cause problems with the respiratory system. [19]

SARS-CoV-2, contained in aerosol particles released when an infected person speaks, can remain in the air for 3 hours. Apart from that, this virus can survive for 72 hours on the surface of plastic and stainless steel objects. So, it can be concluded that transmission of SARS-CoV-2 can be through direct contact with droplets and aerosol particles, as well as contact with the surface of objects. [20]

There are five stages of the virus life cycle in cells: attachment, penetration, biosynthesis, maturation, and release. In the process (attachment), the virus will bind to the host cell's receptor, after which the virus will enter (penetrate) by endocytosis and membrane fusion. The viral RNA will enter the host cell nucleus and start the replication process (biosynthesis). Then, the new virus particles will (mature) and be (released). [21]

For SARS-CoV-2 itself, in the attachment process, it will bind to the receptor for ACE 2. The receptor for ACE 2 is located in the nasal mucosa, bronchi, lungs, heart, esophagus, kidneys, stomach, bladder, and ileum. [22] SARS-CoV-2 has an S protein (spike), which has an important role in the attachment process to host cells. Because this S protein has an affinity/binding to the ACE-2 receptor, it can make the virus attach to host cells. [23]

After the S protein in the virus attaches to the host cell, the S protein will undergo protease cleavage. This protease cleavage divides the S protein into 2, namely S1 and S2. It is where the function of S2 is to initiate the process of membrane fusion (penetration) to enter the host cell, while S1 plays a role in stabilizing the position of the virus while remaining attached to the host cell when the membrane fusion process occurs. [24]

A virus that has entered the host cell will immediately release the viral RNA genome into the cytoplasm and begin to be translated into 2 polyproteins and a structural protein; the viral genome will begin to replicate. [25] The glycoproteins in the newly formed viral envelope will enter the endoplasmic reticulum membrane or Golgi apparatus, and a combination of genomic RNA and nucleocapsid protein will form the nucleocapsid. The virus particles will grow into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), and finally, the vesicles containing the virus particles fuse with the plasma membrane to release the virus.

When the virus enters the host cell, the antigen on the virus will be presented by APC (antigen presentation cells). This APC is part of the immune center in the body; apart from that, peptides from antigens will be presented by MHC (major histocompatibility complex). This specific virus will be recognized by cytotoxic T lymphocytes (CTLs). [26]

The results of the presentation of viral antigens will stimulate the body's humoral and cellular immunity, such as B cells and T cells, against that specific virus. Just like acute viral infections in general, the profile of IgM and IgG in SARS-CoV has its specific pattern. [27] IgM can be detected until the 12th week, and after that, it will disappear. Meanwhile, IgG will last for a long time.

Complications of ARDS are a condition where the lungs do not get enough oxygen into the body's circulation. This incident is very life-threatening for the patient if it continues to occur. The incidence of ARDS in patients infected with SARS-CoV-2 is caused by severe cytokine inflammation. The cytokines involved are IL-6, IL-8, IL-10, Tumor Necrosis Factor (TNF), and Vascular Endothelial Growth Factor (VEGF). [28]

An excessive and irregular immune response in COVID-19 patients causes damage to the patient's organs. In the case of COVID-19, this excessive immune response causes ARDS and damage to the lung organs.

This excessive and irregular immune response is characterized by releasing excessive amounts of cytokines and chemokines. The cytokines are (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGF-β), while the chemokines are (CCL2, CCL3 , CCL5, CXCL8, CXCL9, CXCL10). So, many proinflammatory cytokines cause the inflammatory process to continue in the lung tissue, causing damage to the lung tissue and various other organs. [29]

Apart from causing lung failure, this cytokine storm can also cause failure of other organs/multiple extrapulmonary organ failure. Some signs that there is extrapulmonary multi-organ failure are an increase in enzymes in the liver and creatinine. These two signs can be seen in some patients with symptoms without respiratory failure, indicating that this cytokine storm can also occur in organs other than the lungs.

The risk factors for contracting COVID-19 are having close

contact with COVID-19 patients, such as living together in the same house as the patient and having a history of traveling to infected areas. Medical personnel have a high risk of infection because they have more frequent close contact with COVID-19 patients. Several risk factors for COVID-19 can develop, causing the severity of the patient's illness to increase, such as older age from 65 years old, smoking habits, hypertension, diabetes, cardiovascular disease, and respiratory system disease. Apart from that, there is also speculation that ACE inhibitors (ACEI) and Angiotensin II receptor blockers (ARB) drugs can make the risk of COVID-19 more severe. However, there are no results and strong evidence to confirm that the use of ACEI and ARB drugs can worsen COVID-19 disease with comorbid hypertension who receive ACE1 and ARB therapy. [30]

In this COVID-19 disease, which has a virus incubation time of around five days, there will be initial symptoms that are not very specific, making it difficult to diagnose at first. Non-specific symptoms consist of (fever, dry cough, and fatigue). But then it will start to attack several organ systems in the body, such as respiratory (coughing, shortness of breath, sore throat, hemoptysis, rhinorrhea, and chest pain), digestive (diarrhea, nausea, and vomiting), musculoskeletal (myalgia) and neurological (headaches and confusion). [31]

There is a classification of clinical manifestations for COVID-19 disease based on severity: [32]

Mild illness: a) Children, adolescents, and adult patients may have non-specific symptoms such as cough, fever, fatigue, malaise, muscle aches, sore throat, diarrhea, nausea, and vomiting; b) In adolescent and adult patients there are mild clinical symptoms of pneumonia such as (fever, cough, and dyspnea/shortness of breath) without symptoms of severe pneumonia and do not require oxygen assistance; c) in pediatric patients there are clinical symptoms of mild pneumonia such as coughing, difficulty breathing, rapid breathing (for ages <2 months the respiratory frequency is > 60 times/minute; for ages 2-11 months the respiratory frequency is > 50 times/minute; while those aged 1-5 years have a respiratory frequency > 40 times/minute) and without symptoms of severe pneumonia.

Severe illness: a) In adolescent and adult patients there are clinical symptoms of severe pneumonia/severe ARI such as (fever, severe respiratory tract distress, respiratory frequency >30 times/minute, and oxygen saturation (SpO2) <93%; b) In patients children have clinical symptoms of severe pneumonia/severe ARI such as (coughing, shortness of breath, central cyanosis, oxygen saturation (SpO2) <90%, severe respiratory tract distress such as snoring and rapid breathing frequency. For respiratory frequency (for ages <2 months, respiratory frequency > 60 times/minute; for those aged 2-11 months, have a respiratory frequency > 50 times/minute; while for those aged 1-5 years have a respiratory frequency > 40 times/minute) without symptoms of severe pneumonia.

Critically ill: a) Adolescent and adult patients may experience ARDS, respiratory system failure, septic shock, and multi-organ failure. Criteria for ARDS in adults include: b) The patient has had disease onset for seven days, with new or worsening respiratory tract symptoms; c) CT scans, radiographs and ultrasonography of the lungs show bilateral opacities that cannot be explained based on excess volume, lobe or lung collapse, presence of nodules in the lungs, and infiltrates in the lungs; d) mild ARDS: 200 mmHg < PaO2 / FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O, or not ventilated) moderate ARDS: 100 mmHg < PaO2 / FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O, or without ventilation).

Severe ARDS: PaO2 / FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O, or not ventilated); e) In pediatric patients, there are ARDS criteria such as: a) The patient has had disease onset for seven days; b) There is pulmonary edema with symptoms of unexplained respiratory failure which may be caused by heart failure or excess fluid in the lungs; c) The radiological image shows a new infiltrate consistent with acute lung disease; d) mild ARDS (invasive ventilation): 4 ≤ OI <8 or 5 ≤ OSI <7.5; e) moderate ARDS (invasive ventilation): 8 ≤ OI <16 or 7.5 ≤ OSI <12.3; e) Severe ARDS (invasive ventilation): OI ≥ 16 or OSI ≥ 12.3. However, on April 1, 2020, the Chinese government provided information that several new cases of COVID-19 that occurred in China had asymptomatic symptoms. COVID-19 sufferers with asymptomatic symptoms can also spread the virus to other humans.

The diagnosis of COVID-19 patients has an operational definition that has been set, namely suspect case, probable case, confirmed case, close contact, traveler, discarded, completed isolation, and death. 26 A person who has the following criteria: a) Person with a respiratory tract infection Acute Respiratory Respiratory Syndrome (ARI) and in the last 14 days before symptoms appeared, had a history of travel or lived in a country/territory of Indonesia that reported local transmission; b) People with one of the symptoms/signs of ARI and in the last 14 days before symptoms appeared had a history of contact with a confirmed/probable case of COVID-19; c) People with severe ARI/severe pneumonia who require hospital treatment and there is no other cause based on a convincing clinical picture. Suspected cases with severe ARI/ARDS/Died with a convincing clinical picture of COVID-19 and no rRT laboratory test results -PCR. A person who has tested positive for infection with the COVID-19 virus, as proven by. People with a history of contact with probable cases or confirmed cases of COVID-19.

The contact history referred to includes a) Face-to-face/close contact with probable cases or confirmed cases within a radius of 1 meter and a period of 15 minutes or more; b) Direct physical contact with probable or confirmed cases (such as shaking hands, holding hands, etc.; c) People who provide direct care to probable or confirmed cases without using standard PPE (personal protective equipment); d) Other situations that indicate contact based on the local risk assessment determined by the local epidemiological investigation team.

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without using standard PPE (personal protective equipment); d) Other situations that indicate contact based on the local risk assessment determined by the local epidemiological investigation team.

Someone who has traveled from within the country (domestic) or abroad in the last 14 days. Discarded if one of the following criteria is met: a) vA person with suspect case status with two negative rRT-PCR examination results for two consecutive days with an interval of > 24 hours; b) Someone with close contact status who has completed the 14-day quarantine period.

Isolation is complete if one of the following criteria is met: A) Confirmed cases without symptoms (Asymptomatic) who did not undergo a follow-up rRT-PCR examination with an additional ten independent days since taking the confirmation diagnostic specimen; b) Probable cases/confirmed cases with symptoms (symptomatic) that do not undergo a follow-up rRT-PCR examination are counted ten days from the date of onset plus a minimum of 3 days after no longer showing symptoms of fever and respiratory problems; c) Probable cases/confirmed cases with symptoms (symptomatic) who receive negative rRT-PCR follow-up examination results once, with a minimum of 3 days after no longer showing symptoms of fever and respiratory problems. COVID-19 deaths for surveillance purposes are confirmed cases /probable COVID-19 who died.

To diagnose a patient, a rRT-PCR (real-time Reverse Transcription Polymerase Chain Reaction) diagnostic test is required using a specimen from a nasal swab. This method can be done by taking samples from the patient's upper respiratory system via the nasopharyngeal and oropharyngeal respiratory tract. This method is most often used for taking samples from patients because it does not cause contamination for service staff and patients. [27] The diagnostic test using rRT-PCR is by amplifying viral nucleic acid and sequencing. The results will be positive if at least 2 SARS-CoV-2 genomes are detected, namely (N, E, S, or RdRP) or the results of the rRT-PCR show positive for betacoronavirus which is SARS-CoV-2, which is supported by the results of sequencing part or all of the genome.

A negative rRT-PCR test result on a single specimen collection (especially if the specimen is taken from the upper respiratory tract) does not indicate that an infection has not occurred in that patient. So, it is necessary to repeat the sample collection and testing; this could be done by changing the sample collection from the lower respiratory tract. Several things can cause negative results in infected patients, including a) Poor specimen quality because it only contains a small amount of viral material; b) Inappropriate timing of specimen collection because the specimen was taken at the end of the infection or very early stages of COVID-19; c) Poor specimen management and specimen transportation; d) There are clinical obstacles that hinder the RT-PCR examination, such as mutations in the virus.

Apart from that, specimens can also be collected using bronchoalveolar lavage and tracheal aspirate. However, this method can only be done if the examination results from nasopharyngeal/oropharyngeal sampling are negative and can be done for patients who have used intubation. This method is also rarely used because it can potentially cause the risk of medical personnel contracting infection when taking samples.

This diagnostic test functions to detect the SARS-CoV-2 virus antigen, but because there is no amplification of the target to be detected, this test is less sensitive than the rRT-PCR test. [33] However, this test can still be carried out if the rRT-PCR test is unavailable or there are conditions where the test completion time is long, preventing diagnostics.

This test only takes 30 minutes to complete, but the results of this rapid antigen test can give false positive results which can occur because the antibodies on the test strip detect other viral antigens besides SARS-CoV-2 (another type of coronavirus). [29] So, the WHO also recommends that the use of rapid antigen tests can be used for epidemiological or other research purposes.

This diagnostic test detects IgG, IgM, and IgA antibodies in the patient's blood. However, the formation of antibodies in each patient's body varies greatly depending on the host response. In the COVID-19 disease, most patients' antibodies will form on days 7 to 14 after exposure to the SARS-CoV-2 virus. This test can also give false positive results because this test can cross-react with other pathogenic viruses (other types of human coronavirus) and other conditions that already exist in the patient's body, such as (pregnancy and autoimmune diseases).

Because this test has a low sensitivity of 36.4% and specificity of 88.93%, this test is not recommended for screening in the community. The use of this test is only used to investigate ongoing extraordinary events (ongoing outbreaks) and retrospective examination of the attack rate of these extraordinary events. On complete blood tests, these patients had varying results depending on the stage of the disease. During the incubation period (1-14 days) or at the beginning of the disease phase, which appears in the appearance of non-specific symptoms, the results of the leukocyte and lymphocyte counts are low or within normal limits. [34]

But after 7-14 days of symptoms, there begins to be an increase in inflammatory mediators along with cytokines and chemokines which we know is a "cytokine storm". Then, there will be a change in the number of lymphocytes, which becomes very low (lymphopenia), and there will also be an increase in the number of leukocytes (leukocytosis). However, leukopenia can also occur in some cases, so the value of the number of leukocytes during a "cytokine storm" has different results. Apart from that, COVID-19 patients who have comorbid heart diseases also show an increase in total leukocyte levels (leukocytosis). Differential leukocyte calculations found that the highest increase was in neutrophils, while lymphocytes experienced a decrease (lymphopenia).

Imaging examinations that can be carried out are by doing a chest X-ray and a thoracic Computed Tomography Scan (CT-scan). The image most often found in COVID-19 patients is bilateral ground-glass opacification (GGO), which is distributed towards the periphery and posterior of the lungs. Other rare features can be found, such as pleural effusion, pericardial effusion, lymphadenopathy, cavities, and CT halo sign. [35]

CT-scan images are divided into four groups, namely: a) Group 1 (preclinical group): CT-Scan images ranging from unilateral, multifocal, ground-glass opacification, can also rarely see images of intralobular septal thickening, thickening of the adjacent pleura, and pleural effusion; b) Group 2 (first-week group after onset): Diffuse bilateral appearance, and predominantly ground-glass opacification. However, features of pleural effusion and lymphadenopathy can be found but are very rare in this group; c) Group 3 (second-week group after onset): Dominant picture of ground-glass opacification, there is a consolidation pattern; d) Group 4 (third-week group after onset): Remains predominantly ground-glass opacification and with a reticular pattern. You can also find bronchiolectasis, thickening of the pleura, pleural effusion, and lymphadenopathy.

Leukocytes or white blood cells are still cellular components of blood that do not have hemoglobin, have a nucleus, can move, and can defend the body against infection and disease. These

leukocytes have several ways to defend the body from infections that attack the body, such as swallowing foreign materials and cellular debris (debris), destroying infectious substances, and producing antibodies. Leukocytes consist of several cells with different nuclei, starting from different shapes, textures, and sizes. Microscopically, leukocytes are divided into three large parts: granulocytes, monocytes and lymphocytes

Granulocytes are white blood cells that can phagocytose/engulf bacteria, viruses, and parasites. These cells have visible granules in the cytoplasm, and the cell nucleus is elongated/lobed. The cell diameter ranges between 12-20 µ, and the nucleoli are absent. These granulocytes are divided into three sub-granulocytes: A) Neutrophils: Neutrophils are granulocyte cells that come first to the area of infection and immediately carry out the phagocytosis process on foreign microorganisms. Neutrophils have nuclei of various types, such as rods and segmented. Segment neutrophils in peripheral circulation have a nucleus of 2-5 segments, while rod neutrophils will have a nucleus shaped like a horse's horseshoe. The basophil granules contain heparin, histamine, chondrotin sulfate, and several chemotactic factors, all fighting hypersensitivity reactions in the bloodstream. c) Eosinophils: These eosinophils have a two-glazed nucleus and a cytoplasm with large acidophil granules. These eosinophils can secrete toxins from their granules to kill pathogenic foreign substances in the body, such as parasites and worms.

Monocytes: Monocyte cells are leukocytes with the largest shape compared to other types, with a diameter of around (10-30) µ. Monocytes contain only one nucleus, which is rarely lobulated, and usually, the nucleus is shaped like a kidney or horseshoe. The cytoplasm will be pale blue-gray in color. These cells function to phagocytose foreign microorganisms and clean debris in the area of infection. Two cells can differentiate from this monocyte form: a) [36] Macrophages: Phagocytic cells with a single, large nucleus often shaped like a kidney. These cells are also capable of acting as APCs (Antigen-presenting Cells); b) Dendritic Cells: Cells that have a small and round nucleus, but when they are mature, the nucleus will become large with an irregular star-like shape and cytoplasmic protrusions (dendrites) appear.

Lymphocytes: lymphocytes are leukocytes that have varying sizes and shapes. Small lymphocytes have a diameter of (6-9) µ, a large nucleus, and are surrounded by pale blue cytoplasm. For large lymphocytes, the diameter will be (12-15) µ, and the nucleus is larger and slightly paler with more cytoplasm. Lymphocytes are the only type of leukocyte that do not have phagocytic abilities but can produce antibodies in response to foreign objects phagocytized by macrophages. Lymphocytes are classified into 2, namely: [36]

B Lymphocytes: Cells that will differentiate into plasma cells to play a role in the humoral immune response to produce antibodies; and b) T lymphocytes: Cells that produce proteins called cytokines, which help to provide an inflammatory response to other cells. Leukocyte counts are very important to determine the presence of an indicator of the severity of the disease process. Several specific leukocyte response patterns are found in several diseases, such as total leukocyte values and differential values, which decrease and increase in several diseases. This leukocyte count can be a diagnostic tool for a disease until the results are related to the patient's clinical status. For normal values for calculating total leukocytes based on the University of Rochester Medical Center (UMRC) per microliter of blood (mcL) can be seen in the following table. If the total leukocyte count shows higher than normal values (leukocytosis), it indicates that there are several causes, such as an increase in leukocyte production to fight infections in the body such as viral infections.

Table 1. Normal leukocyte levels in humans

Age	Normal Leukocyte Value (per.mcL blood)
Newborn baby	9.000 – 30.000
Children < 2 years old	6.200 - 17.000
Children > 2 years and adults	5.0 – 10.000

If the total leukocyte count is higher than the normal value (leukocytosis), it indicates the presence of several causes, such as [5] a) There is an increase in leukocyte production to fight infections in the body. Such as Virus infection; b) increases leukocyte production. Such as After using steroids and epinephrine. Diseases in the bone marrow that cause abnormally increased leukocyte production. Such as Leukemia, myelofibrosis; and c) There is a disturbance in the body's immune system, which increases the production of leukocytes. Such as rheumatoid arthritis

RESEARCH METHOD

The research design used was a descriptive design research method, bivariate linear regression analysis with a cross-sectional approach using patient medical record data to determine the correlation between the patient's leukocyte levels and the results of the COVID-19 rRT-PCR examination. This research was conducted at a private hospital in Bekasi Timur. This research was conducted from May to November 2020. All patients were in one of the private hospitals in East Bekasi. All patients underwent real-time reverse transcription polymerase chain reaction (rRT-PCR) as a diagnostic test for COVID-19. The minimum number of samples used is 25 samples. The research instrument used in this study was medical record data from patients who underwent rRT-PCR diagnostic examinations for COVID-19 and completed blood tests. This study used secondary data from the rRT-PCR and complete blood examination results. Then, the data will be processed using the SPSS for Windows 24.0 program. Data processing is carried out in the following steps: Data editing, data coding, tabulation, and entry. Entering data already in the form of statistical variables into the SPSS for Windows 24.0 program. This research data analysis will use bivariate analysis to explain the characteristics of each variable to be studied. Then, the data will be processed using the SPSS for Windows 24.0 program and entered in table form. According to the Central Statistics Agency, the projected population in Indonesia in 2020 is 271,066,400, and as of 29-05-2020, according to data from the Task Force for the Acceleration of Handling COVID-19 on May 20, 2020, there were 19,189 positive cases of COVID-19. Therefore, the Lemeshow formula is used to determine The number of samples that need to be used in this research. In this study, to find the prevalence of COVID-19 in Indonesia, it is necessary to use the Prevalence Rate formula to determine the prevalence value. After calculating using the Lemeshow formula, it is known that the minimum number of samples required in the study "Leukocyte Figures in Patients Positively Infected with COVID-19" is 25 samples.

RESULT AND DISCUSSION

The data obtained for this research was obtained from medical record data on patients who had undergone the rRT-PCR test for COVID-19 for the first time. This medical record data was obtained in May 2020 – November 2020, and a sample of 77 patients was obtained. From the data obtained, 43 (55.8%) patients were positive for COVID-19, and 34 (44.2%) patients were negative for COVID-19.

Table 2. Sample Characteristics Based on Age.

Vulnerable Age	Negative for COVID-19	Positive for COVID-19	Total
< 10 years	1 (1.3%)	0 (0%)	1 (1.3%)
11-20 years	1 (1.3%)	0 (0%)	1 (1.3%)
21-30 years	2 (2.6 %)	3 (3.9%)	5 (6.5%)
31-40 years	7 (9.1%)	10 (13.0%)	17 (22.1%)
41-50 years	11 (14.3%)	13 (16.9%)	24 (31.2%)
51-60 years	7 (9.1%)	10 (13.0%)	17 (22.1%)
61-70 years	3 (3.9%)	6 (7.8%)	9 (11.7%)
71-80 years	1(1.3%)	1 (1.3%)	2 (2.6%)
>80 years	1(1.3%)	0 (0%)	1(1.3%)

Table 2 shows that the average age of all samples in this study was 46.82 years, for the sample of patients who were negative for COVID-19 was 45.91, and for the sample of patients who were positive for COVID-19 was 47.53. Vulnerable ages 21-30 years, 31-40 years, 41-50 years, 51-60 years, and 61-70 years had more samples that were positive for COVID-19 compared to samples that were negative for COVID-19.

Table 3. Sample Characteristics Based on Gender

Gender	**OVID-19**	**OVID- 19**	**Total**
Male	19 (24.7%)	23 (29.9%)	42 (54.5%)
Female	15 (19.5%)	20 (26.0%)	35 (45.5%)

The data in Table 3 shows that the number of male samples was 42 (54.5%), and for women, it was 35 (45.5%).

Table 4. Sample Characteristics Based on Age.

Leukocyte Levels	**- for COVID-19**	**+ for COVID-19**	**Total**
Low (<5000 sel/µL)	3 (3.9%)	9 (11.7%)	12 (15.6%)
Normal (5000 cells/ µL – 10000 sel/µL)	19 (24.7%)	28 (36.4%)	47 (61.0%)
High (> 10000 cells/µL)	12 (15.6 %)	6 (7.8%)	18 (23.4%)
Total	34 (44.2%)	43 (55.8%)	77 (100 %)

Based on data from Table 4, it shows that of the 34 (44.2%) patients who were negative for COVID-19, 3 (3.9%) patients had low leukocyte levels, and 12 (15.6%) patients had high leukocyte levels. With normal leukocyte levels, the number of patients was greater, namely 19 (24.7%), compared to low and high leukocyte levels. The average value of leukocytes in patients who are negative for COVID-19 is 10282.06 cells/µL, while the lowest value is 4320 cells/µL and the highest value is 25320 cells/µL.

Meanwhile, of the 43 (55.8%) patients who were positive for COVID-19, 9 (11.7%) patients had low leukocyte levels, and 6 (7.8%) patients had high leukocyte levels. The number of patients with normal leukocyte levels was 28 (36.4%) higher than those with low and high leukocyte levels. The average value of leukocytes in patients who are positive for COVID-19 is 7234.19 cells/µL, while the lowest value is 3890 cells/µL, and the highest value is 14470 cells/µL. So, of the total number of patients who had both negative and positive results for COVID-19, the highest number had normal leukocyte levels, 47 (61.0%) out of the total number of patients, 77 (100%).

This bivariate analysis test was carried out to see the relationship between the independent and dependent variables in this study. The independent variable in this study is patients who have positive results for COVID-19 using the rRT-PCR diagnostic examination. In contrast, the dependent variable is patients who have positive results for COVID-19 using the results of total leukocyte levels from the patient's complete blood examination. To carry out this bivariate analysis, researchers used the Spearman correlation test. However, before carrying out the Spearman correlation test, the researcher first carried out a normality test to determine the residual value of this data.

Table 5. Description of normality test results from COVID-19 rRT-PCR results with leukocyte levels.

One-Sample Kolmogorov-Smirnov Test

		Unstandardized Residual
N		68
Normal Parameters[a,b]	Mean	.0000000
	Std. Deviation	.47739719
Most Extreme Differences	Absolute	.350
	Positive	.273
	Negative	-.350
Test Statistic		.350
Asymp. Sig. (2-tailed)		.000[c]

a. Test distribution is Normal.
b. Calculated from data.
c. Lilliefors Significance Correction.

Table 5 shows that the residual value is not normally distributed because the significance value in this data is P=0 (P<0.05). After obtaining a significance value of <0.05, the researcher will continue the correlation coefficient test using the Spearman correlation method.

Table 6. Spearman correlation test of COVID-19 rRT-PCR results with leukocyte levels.

Correlations			Leukocytes	PCR code
Spearman's rho	Leukocytes	Correlation Coefficient	1.000	-.292**
		Sig. (2-tailed)	.	.010
		N	77	77
	PCR code	Correlation Coefficient	-.292**	1.000
		Sig. (2-tailed)	.010	.
		N	77	77
**. Correlation is significant at the 0.01 level (2-tailed).				

Table 5 shows a relationship between the results of rRT-PCR for COVID-19 and leukocyte levels with a value of (P= 0.010). The results of the Spearman correlation analysis show a weak correlation coefficient (R= -2.92) with a negative pattern, which indicates that patients who are positive for COVID-19 have lower leukocyte values than patients who are negative for COVID-19.

The research results show that based on age prevalence, the number of people with the most positive COVID-19 results is those aged 41-50 years (16.9%), while the age prevalence who have the least negative results for COVID-19 are those aged 0-20 and > 80 years old. Hidayati D's research also has appropriate results for the percentage of ages susceptible to being infected with COVID-19, namely 31-45 years old, while for those aged 0-5 years vulnerable, it has the lowest results for COVID-19 cases. It happens because, at a productive age, a person will do activities outside the home more often and meet others.

From the results of this research, it was also found that men had higher positive cases of COVID-19 compared to women. The same research from Hidayati D shows that based on gender, men have more cases than women. It is due to men having more activities outside the home, namely working, and coupled with the lifestyle of men who tend to be smokers, the respiratory tract condition in men is worse than in women.

Based on the results of this study, from a total of 77 patients who underwent rRT-PCR COVID-19 examination, 43 (55.8%) patients were positive for COVID-19, and 34 (44.2%) patients were negative for COVID-19. In describing the leukocyte levels of patients positive for COVID-19, this research shows that the results of normal leukocyte levels have the highest cases 28 (36.4%) compared to low leukocyte levels/leukopenia 9 (11.7%) and high leukocyte levels/leukocytosis 6 (7.8%). It is possible because the data taken are laboratory results from patients who were checking into the hospital for the first time, and the data was only taken once, so researchers do not know when the patient was first infected with COVID-19. These results also followed research by Terpos E et al., which showed that during the incubation period (7-14 days) or in the early phase of the COVID-19 disease, leukocyte levels were low or within normal limits, and the patient also did not show any symptoms. [38]

In research conducted by Zhao, Kaochang et al., leukocytosis results were found in COVID-19 patients who were older, had fever, and had underlying chronic diseases. An increase in the number of neutrophils in the peripheral blood also characterizes the results of leukocytosis. This increase in neutrophils can cause a cytokine storm and cause tissue damage to multiple organs, especially the lungs, which can lead to death. [39]

Based on analysis tests using the Spearman correlation method from the SPSS version 24.0 statistical program, it was found that there was a relationship between the results of rRT-PCR for COVID-19 and leukocyte levels with a value of (P= 0.010). The results of the Spearman correlation analysis show a weak correlation coefficient (R= -2.92) with a negative pattern, which indicates that patients who are positive for COVID-19 have

lower leukocyte values than patients who are negative for COVID-19.

CONCLUSION

From the results of the research and discussion presented in the previous chapter, the following conclusions were obtained: a) An overview of the leukocyte levels of COVID-19-positive patients in this study showed that the results of normal leukocyte levels had the highest cases 28 (36.4%) compared to low leukocyte levels/leukopenia 9 (11.7%) and high leukocyte levels/leukocytosis 6 (7.8%); b) It was found that there was a significant relationship between the results of rRT-PCR for COVID-19 and leukocyte levels with a negative pattern, indicating that patients who were positive for COVID-19 had lower leukocyte values than patients who were negative for COVID-19.

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