COVID-19 Detection in Limited Hospital Facilities: The Role of Monocytes

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COVID-19 Detection in Limited Hospital Facilities: The Role of Monocytes

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ABSTRACT

***INTRODUCTION** COVID-19 is an emerging infectious disease with etiology severe acute respiratory syndrome corona virus-2 (SARS-COV-2) which is causing various clinical manifestations not only in the respiratory tract. COVID-19 declared as a pandemic that causes high mortality worldwide. Simple examination modalities are needed to help diagnose COVID-19. This descriptive case report has aims to show the role of monocyte count to help establish the diagnosis of COVID-19.*

***METHODOLOGY** This is a case report from confirmed COVID-19 cases in RS Bhayangkara Brimob. Data will be presented according to the descriptive method.*

***RESULTS**52 confirmed cases from April 2020 until May 2020 were used in this research, consist of 42 (81.13%) male patients and 10 (16.87%) female patients. 34 (65,38%) patients had an increase in monocyte count. Of 45 symptomatic patients, 29 of them (64.44%) were known to have monocytes> 7. Of 17 confirmed positive patients who shown unilateral and bilateral infiltrate, 13 of them had an increase in monocyte count, 1 patient(100%), and 12 (26,67%) patients, respectively.*

***CONCLUSIONS** From the data, we conclude that simple laboratory result parameters such as lymphocyte, sedimentation rate, particularly monocyte, help to establish the diagnosis of COVID-19. This is based on increasing monocyte in mostly all confirmed COVID-19 patients involved in this study.*

***Key words:**Role of monocytes; detection of COVID-19 parameters; Limited hospital facilitie*

***Running Title:**The Role of Monocytes in COVID-19 Detection*

Introduction

In December 2019, there were a lot of reported cases of COVID-19 in Wuhan, Hubei Province. This COVID-19 case then spread around the world. At first, this new disease was called as 2019 novel coronavirus (2019-nCov), after that WHO declared a new name called coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2).1 As August 2020, COVID-19 has caused approximately 784,000 deaths worldwide.[2] There were many inaccuracies in detecting this virus due to inadequate equipment. This disease can be seen with clinical symptoms by looking at the exposure history of patients who visit certain areas that have been infected or are in contact with people who have contracted cases of COVID-19 in certain time.[3] This virus infects animals and passes to humans so it is called zoonosis. Various clinical symptoms such as respiratory and systemic complaints and unclear patient history will make it difficult for early detection of patients.[4]

The most clinical manifestation that common to be seen in COVID-19 in severe degree is pneumonia with fever, cough, and dyspnea. Chinese Center for Disease Control and Prevention reported that there were 44,500 confirmed infections, most of the infected patients (80%) had mild disease (without or only mild pneumonia), 14% developing into severe pneumonia (with dyspnea, hypoxia, or more than 50% involvement of lung in the radiology examination), and 5% developed into critical disease (marked by respiratory failure, systemic shock, and multi organ failure).[5] About 20-30% of patients who have been hospitalized with COVID-19-related pneumonia need intensive care for respiratory support.Acute respiratory distress syndrome (ARDS) is a common complication from severe viral pneumonia, included pneumonia that caused by coronavirus that is highly pathogenic like in the severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS).[6,7]Therefore there is a need to collect data from simple laboratory and radiology examinations, adjusted to the available facilities in the setting or the workplace. After observing the patient's journey from the start to the examination with a swab, several parameters can be obtained which are expected to help detect the direction of the diagnosis of COVID-19. Apart from the fact that currently the transmission area is not very helpful in diagnosis because of the rapid spread to other areas. This case report demonstrates the role of inflammatory cells such as monocytes that are easily detected in simple laboratory tests in helping diagnose COVID 19.

Methodology

Study Design and Subjects

The study design in this study is observation study. The data were collected from patients that admitted to hospital through Emergency Room (ER). We collected clinical data, the laboratory and radiology examination result from 52 patients that hospitalized in a COVID-19 referral hospital that did not have PCR examination facility, so that the sample must be sent to be examined in a special laboratory appointed by the government. Patient data between April and May 2020. All patients with positive PCR results were included in this case study.

Data Collection

The whole data were collected from medical record in BhayangkaraBrimob Hospital. We also collected epidemiological exposure history 14 days before complaints of disease onset, for example: having a

history of exposure to a patient who is positive for COVID-19 and having close contact with this patient or having traveled to a place where many patients have tested positive for COVID-19. The data in this study were the first to be taken from the hospital based on the clinical judgment of the doctor and the medical burden considerations of the absence of a CT scan due to limited hospital costs and facilities. Types of data collected were patient characteristics, age, gender, complaints, history of exposure, basic vital signs, laboratory results, signs of pneumonia.

Laboratory Confirmation

Laboratory confirmation used real time reverse transcription-polymerase chain reaction (RT-PCR) based on the protocol that established by WHO. CT Scan examination was not done, only using a simple radiology chest x-ray examination.

Statistical Analysis

All variables were reported in frequency, percentage (%), and mean±standard deviation (SD) if data distribution was normal. If the distribution was not normal, then it will be written median with range (minimum and maximum). Normality distribution was checked using Kolmogorov-Smirnov test. The laboratory results mentioned before were actual data and assessed whether the results were in normal range or not. All the data were analyzed with IBM SPSS version 21 with descriptive methods.

Results

Patients Characteristics

Fifty-two confirmed COVID-19 patients involved in this study had a mean age of 41.9 ± 9.80 years (Table 1), consisting of 42 (81.13%) male patients and 10 (16.87%) female patient. A total of 37 patients (71.2%) had a history of contact with exposure from various clusters, including dormitories, families, and clusters of their respective activities. Of the 52 patients, it was found that 45 were symptomatic (86.54%). Symptoms that appeared in patients included sore throat (30.8%), cough (34.6%), runny nose (1.9%), fever (34.6%), malaise (5.8%), abdominal pain (1.9%), muscle pain (1.9%), and no complaints (13.5%). From vital signs, the mean value was within normal limits. For saturation, it is known that 3 (5.77%) people have an oxygen saturation below 95% without using oxygen.

Laboratory Result

As many as 13 (25%) patients had leukocytes above normal (leukocytosis) and 4 (7.55%) patients had leukocytes below normal with a mean value of 8121.73 ± 2673.07 /uL. A total of 10 patients (19.23%) and 5 patients (9.62%), respectively, had neutrophils above and below normal values. As many as 3 (5.77%) people had lymphocyte values above normal, while 18 (34.62%) had lymphocytopenia. From the calculation of lymphocytes and neutrophils, the mean value of neutrophil-lymphocyte-ratio (NLR) was 3.42 ± 2.90, and from the entire population, 17 patients (32.69%) had an increase in NLR. As many as 3 (5.77%) people had platelet values below normal. As many as 35 people (66.04%) had monocyte values above normal. Hb value below 9 is 1 person. A total of 28 (52.83%) people had a sedimentation rate above normal.

Comparison between Lymphocyte Count, Erythrocyte Sedimentation Rate (ESR), and Monocyte Count

From the various examinations above, it was found that several parameters were found to be experienced by people with COVID-19. Among them are the parameters of lymphocyte reduction (lymphocytopenia), increased ESR, and increased monocytes. In Table 3, it was found that the number of patients and the percentage ratio between the three parameters were 34.62% of patients had lymphocytopenia, 40.38% of patients had an increase in ESR, and 65.38% of patients had an increase in the number of monocytes.

In terms of these three parameters, it was found that 4 (7.69%) patients experienced lymphocytopenia, increased ESR, and increased monocytes and were accompanied by varied symptoms. So that evidence of COVID-19 is not obtained from the necessity of diagnostic criteria for these three parameters but one. From this study, in Table 3, it was found that an increase in monocytes was one of the parameters experienced by many COVID-19 patients.

Comparison of the Results of Monocyte Count with the Presence of Symptoms

From the data obtained, it is known that the average patient with monocytes above 7 has a tendency to develop COVID-19 symptoms compared to patients with monocyte counts in the normal range. As previously known, out of 52 patients involved in this study, 45 patients were symptomatic. In terms of the number of monocytes, it was found that 21 of them (65.38%) had monocytes> 7. Symptoms that appear include sore throat (10 people, 22.22%), cough (11 people, 24.44%), fever (9 people, 20%), nausea (6 people, 13.33%), shortness of breath (4 people, 8.89%), malaise (4 people, 8.89%), muscle pain (1 person, 2.22%), chest pain (2 people, 4.44%), abdominal pain (1 person, 2,22%), and colds (1 person, 2.22%). This result shows that populations with monocytes that are higher than normal have a positive tendency for COVID-19 to be accompanied by symptoms, in which the symptoms that appear are also varied.

Chest X-ray Examination Results

All patients underwent a chest X-ray on admission. As many as 17 people (32.69%) had bilateral infiltrates. There were no nodules, effusions and reticular features. A total of 10 (19.23%) patients had cardiomegaly which may be associated with comorbid hypertension. All patients who were included in the criteria were patients with mild symptoms.

Comparison between Chest X-Ray Result with Monocyte Count

From the data, it was found that there was an increase in monocytes in COVID-19 patients accompanied by findings of chest X-ray infiltrates.

Discussion

In this study case, we reported clinical data, laboratory, and chest X-Ray examination results in a COVID-19 referral hospital. The mean patient age was 41.90 ± 9.80 (male and female) who had the same risk factors for getting COVID-19. Several studies have shown that the severity and mortality of COVID-19 is related to age, comorbidities such as diabetes and hypertension. The respiratory

symptoms of COVID-19 are very similar to those of upper respiratory tract disease. Recently, digestive and musculoskeletal disorders include vomiting and an inability to smell. The prominent abnormal laboratory parameters were lymphocytes, ESR, and monocytes. A low lymphocyte count below 20% is an indicator of the severity of a COVID-19 patient. The finding of an above normal sedimentation rate in the majority of patients indicates that this parameter can complement the signs that these patients may have COVID-19. NLR values (Neutrophils, Lymphocytes, Ratio) above 2.8-3.0 indicate suspicion of COVID-19. In the previous study that has been reported, it is known that lymphopenia and increasing in ESR are two of the laboratory results that indicate COVID-19.[8] From this study, the results of the monocyte count found by most of the patients showed an increase above the normal average, so it is believed that monocytes can be one of the strong parameters that can guide diagnose COVID-19. When viewed from the symptoms, in this case report, it was also found that most of the symptomatic cases were also marked by an increase in the number of monocytes. With various variants that involve various organ systems and are not typical, it is hoped that this increase in monocytes can help in establish the diagnosis towards COVID-19.

The factors driving the severity of individuals infected with SARS-CoV-2 are not fully understood and disease progression does not appear to be associated with viral load. This excessive inflammatory response of the COVID virus was determined to be the main cause of disease severity and death in COVID-19 patients and was associated with circulating levels of cytokines, lymphopenia and mononuclear cell infiltration in the lungs, heart, spleen, lymph nodes and kidneys as observed in the post mortem analysis. The mortality and morbidity of COVID19 are associated with excessive inflammation. A better understanding of immunology needs to be studied in order to identify better therapeutic targets.[9]

Almost all COVID-19 patients show pulmonary involvement by radiological examination and there is a risk of serious complications such as ARDS and death. Several observational studies have reported that age and comorbid risk factors can increase the severity of COVID-19 patients. Increased levels of inflammatory markers in the blood including CRP, ferritin, D dimer and NLR, and increased levels of several inflammatory cytokines and chemokines were associated with disease severity and mortality. The systemic cytokine profile observed in COVID-19 patients shows similarities to the macrophage activation syndrome accompanied by increased production of cytokines IL-6, IL-7 and Tumor Necrosis Factor (TNF). The irregular activation of mononuclear phagocytes contributes to and is associated with the hyperinflammation of COVID-19. On examination of the bronchoalveolar fluid of patients with severe COVID-19, Mononuclear Phagocytes (MNP) content was found to be 40-80%. This condition suggests that the pathogenicity of macrophage infiltration can spread and cause acute inflammation and is in line with the fibrotic complications observed in patients using mechanical ventilation. In patients with mild COVID-19, the infiltration of inflammatory cells monocytes in bronchoalveolar fluid is minimal.[9]

Activation of pulmonary parenchymal monocytes into the inter-alveolar space to fight infection and inflammatory response as incases of pneumonia.Monocytes will penetrate the bone marrow and are able to migrate into the lungs. In cases of pneumonia due to COVID-19, high levels of monocytes are of course related to their function as a response to the immune system. Therefore, of about 18 patients who had chest X-rays of pneumonia, 9 had an increase in monocytes. In other words, the monocyte

count parameter may be used to detect pneumonia due to COVID-19 with pneumonia caused by other causes.[10]

Infiltration of monocytes and lymphocytes of the lungs, heart, kidneys, liver, and muscles, can cause spleen necrosis and vocal necrosis of lymph. There is still a question about the exact contribution of viruses to the activation of macrophages and cytokines, their effect on infection, epigenetic remodeling events in monocyte responses, the contribution of tissue or bone marrow inflammation to macrophage activation, and the contribution of tissue macrophages in response to tissue damage.[11]

The factors causing the severe lung damage caused by COVID-19 are still not fully understood. Potential mechanisms including high viral replication may be responsible for cytolysis and the production of highly inflammatory cytokines and chemokines due to infected epithelial cells as well as the delayed antiviral response to interferon. This can lead to excessive accumulation of monocytes, macrophages and neutrophils in the lungs.[9] Animal studies of the acute lung injury (ALI) viral model induce several proinflammatory pathways including monocyte infiltration.[12] Low platelet count, increased fibrin degradation (D-dimer) and coagulation abnormalities associated with a poor prognosis of COVID, can be major causes of organ failure and patient death.[13] Monocyte activation contributes to the emergence of the COVID-19 cytokine storm by releasing a number of proinflammatory cytokines. The pathology of macrophages is mostly from circulating monocytes infiltrating the lungs and other organs.[9] Although the antiviral activity of hydroxychloroquine is still unclear, the immunomodulatory activity in chronic inflammatory disease is well known and this could contribute, although it is controversial that this drug has clinical benefits in COVID-19 patients.[14] Various factors, limited facilities, the length of the results of the PCR examination, made the clinician face the delay in making intervention decisions to reduce morbidity and mortality. We hope that finding parameters with simple laboratory tests can help clinicians to strongly predict cases of COVID-19 and treat these patients comprehensively with limited resources.

Conclusion

The characteristic data, laboratory, and radiology results from COVID-19 patients in mild to moderate degree shows that simple laboratory parameters such as level of lymphocyte, sedimentation rate, and monocyte can guide in establishing he diagnosis. Particularly, the increment of monocyte level found in the majority of the patients that were confirmed with COVID-19, therefore we conclude this parameter has a possibility used as an early screening for COVID-19 detection more cheaply and simply. This method might help primary facility health care in deciding referrals and guide establishing the diagnosis in limited-resources hospitals.

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References

1. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it (Internet). Geneva : World Health Organization; 2020 (cited : August 26, 2020). Available from :https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza?gclid=CjwKCAjwkJj6BRA-EiwA0ZVPVnoogdGM7zr2NwLnsdrolgfXxPdWJooBKVmu54yphtIe4Q8NIqugTBoCzMwQAvD_BwE
2. World Health Organization. Estimating mortality from COVID-19 (Internet). Geneva L World Health Organization; 2020 (cited : August 27, 2020). Available from : https://www.who.int/news-room/commentaries/detail/estimating-mortality-from-covid-19
3. Leung K, Wu JT, Liu Di, Leung GM. First wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second wave scenario planning: a modelling impact assessment. *Lancet*2020;395:1382-93.
4. D Gennaro F, Pizzol D, Marotta C, Antunes M, Racalbuto V, Veronese N, Smith Lee. Coronavirus Disease (COVID-19) current status and future perspective: a narrative review. *Int. J. Environ.Res.Public Health* 2020,17,2690;doi:3390/ijerph17082690.
5. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020;180(7):934–943. doi:10.1001/jamainternmed.2020.0994
6. Chen N et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*2020;395:507-513.
7. Huang C.et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. Lancet 2020;395:497-506.
8. Zhang, Z. L., Hou, Y. L., Li, D. T., & Li, F. Z. (2020). Laboratory findings of COVID-19: a systematic review and meta-analysis. Scandinavian journal of clinical and laboratory investigation, 2020 1-7.
9. Merad, M., & Martin, J. C. (2020). Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nature Reviews Immunology*, 1-8.
10. Channappanavar R, Perlman. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin. Immunopathol2017;39:529-39.
11. Ding Y et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol2003;200:282-289.
12. Channappanavar R et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016;19:181-193.
13. Tang N et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J ThrombHaemost 2020
14. Gandhi, R. T., Lynch, J. B., & del Rio, C. (2020). Mild or moderate COVID-19. *New England Journal of Medicine*.

Supplementary files legends

Figures

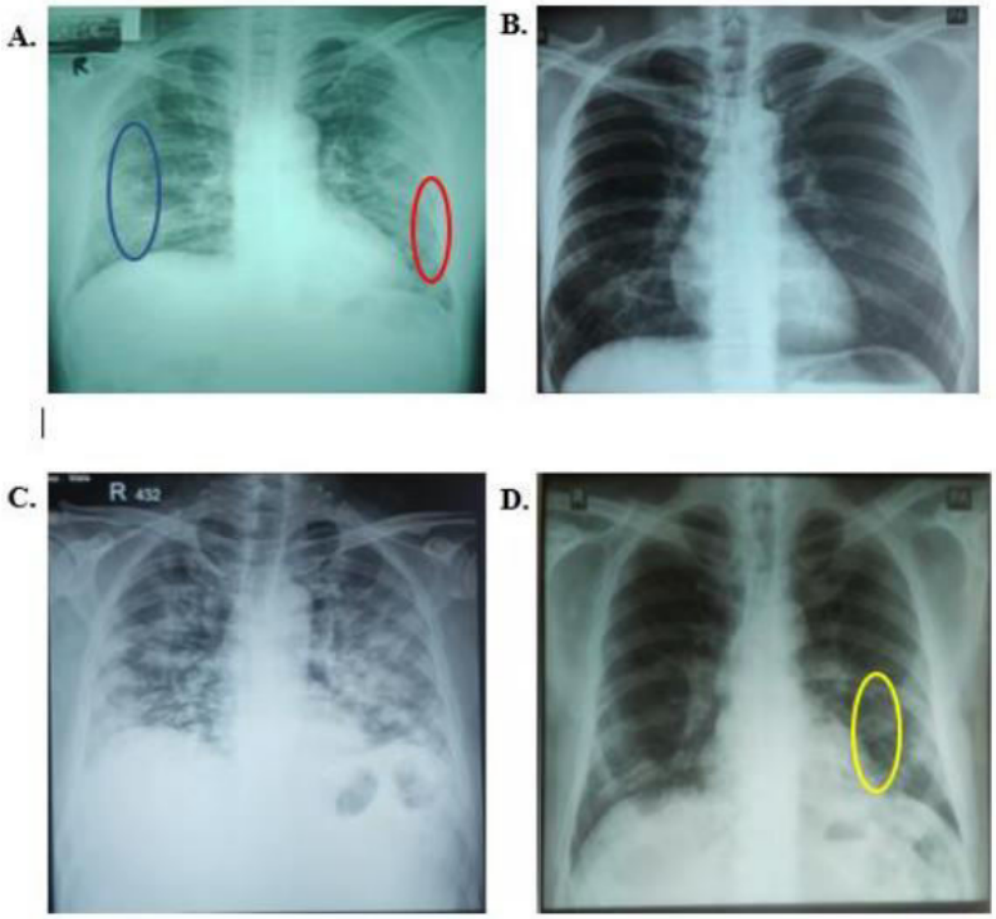

Figure 1. Chest Radiology Examination in Several COVID-19 Patients
(A) Subpleural Consolidation (blue) and infiltrate (red). (B) Normal CXR in a male patient aged 39 years with complaints of sore throat. (C) Male patients 47 years old with cough, shortness of breath and fever, showed ground glass opacity in both lower and middle lung fields. (D) 55 years old male with left subpleural consolidation (yellow)

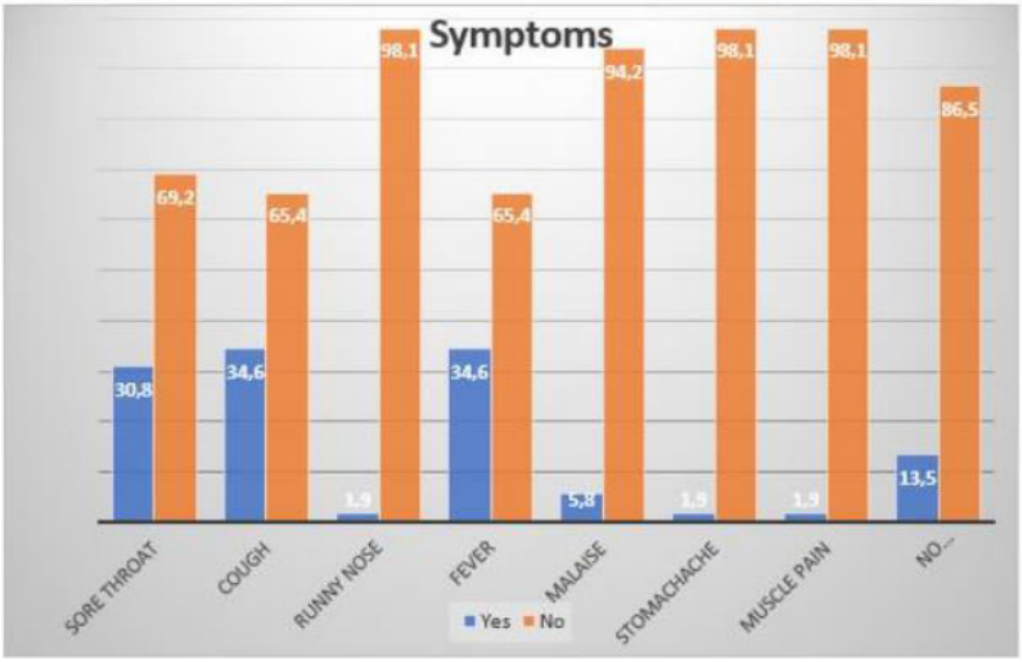

Figure 2. Symptoms Percentage of COVID-19 Patients

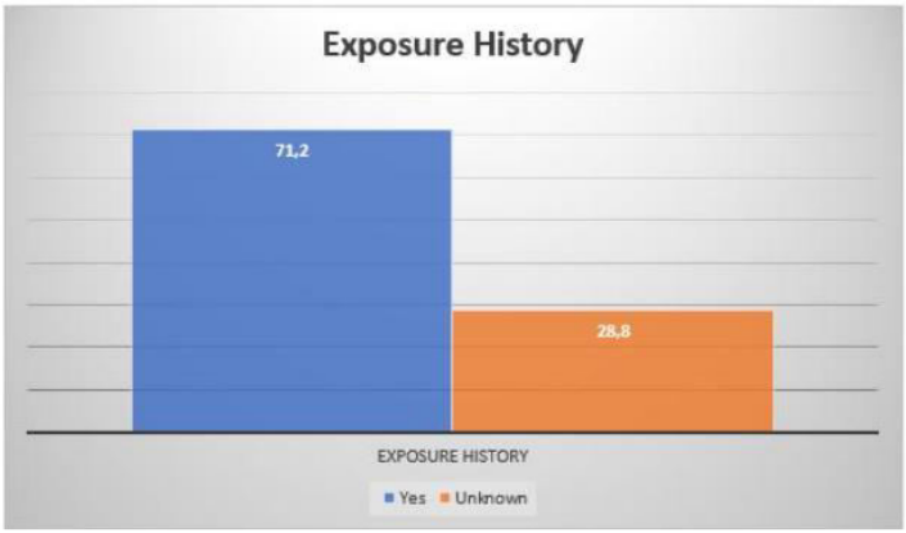

Figure 3. Exposure History Percentage of COVID-19 Patients

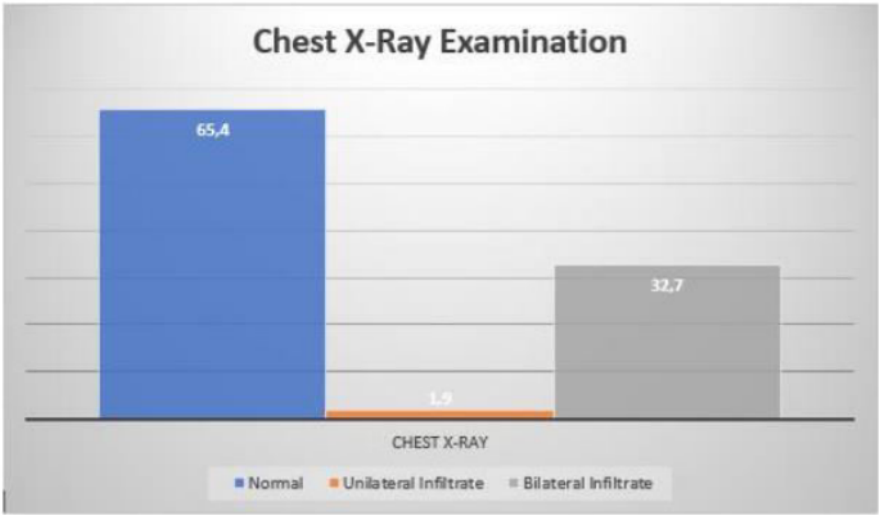

Figure 4. Chest X-Ray Percentage of COVID-19 Patients

Tables

Table 1. Clinical Characteristic of COVID-19 Patients

Patient Characteristic	**N = 52 (%) Mean ± SD, Median (min-max)**
Age	41,90 ± 9,80
Gender	
Male	42 (80,8%)
Female	10 (19,2%)
Temperature	37,04 ± 0,39
Respiration rata	21,75 ± 2,00
Saturation	95,90 ± 1,51
Pulse	81,10 ± 9,57
Symptoms	
Sore throat	16 (30,8%)
Cough	18 (34,6%)
Runny nose	1 (1,9%)
Fever	18 (34,6%)
Malaise	3 (5,8%)
Abdominal pain	1 (1,9%)
Muscle pain	1 (1,9%)
No complaints	7 (13,5%)
Exposure history	37 (71,2%)

Table 2. Laboratory Result of COVID-19 Patients

Laboratory Result	**N = 52 (%) Mean ± SD, Median (min-max)**
White blood cell count, x 10^3/uL; normal range 4-10	8,12 ± 2,67
Increase	13 (25%)
Decrease	4 (7,55%)
Neutrophil percentage; normal range 50-70	62,50 (36-83)
Increase	10 (19,23%)
Decrease	5 (9,62%)
Lymphocyte percentage; normal range 25-40	26,40 ± 9,08
Increase	3 (5,77%)
Decrease	18 (34,62%)
Neutrophil/Lymphocyte Ratio; normal range 3,13	3,42 ± 2,90
Increase	17 (32,69%)
Monocyte percentage; normal range 2-7	8,52 ± 2,45
Increase	34 (65,38%)
Decrease	0 (0%)
Platelet count; x 10^3/uL ; normal range 150-440	302,90 ± 104,12
Increase	1 (1,92%)
Decrease	3 (5,77%)
Haemoglobin; g/dL normal range 13,5 - 17,5	13,62 ± 1,54
Decrease	21 (40,38%)
Erythrocyte sedimentation rate; mm/hour; normal range 0-30	37,50 ± 32,10
Increase	21 (40,38%)

Table 3. Comparison of Lymphocytopenia, ESR, Monocyte Count on the Number of Positive PCR Patients

Positive PCR patients; n (%)	Lymphocytopenia; n (%)	Increasing ESR ; n (%)	Increasing Monocyte Count; n (%)
52 (100%)	18 (34,62%)	21 (40,38%)	34 (65,38%)

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Table 4. Comparison of Symptomatic Patients in Patients with Normal Monocyte Group with Monocytes > 7

Monocyte count	Symptomatic Patients n (%); (45; 100%)
2-7 (normal)	16 (35,56%)
>7	29 (64,44%)

Table 5. Comparison of Chest X-Ray Examination

Positive PCR patients; n (%)	Unilateral Infiltrate; n (%)	Bilateral Infiltrate; n (%)	Normal Chest X-Ray; n (%)
52 (100%)	1 (1,92%)	17 (32,69%)	34 (65,38%)

Table 6. Comparison between Chest X-Ray and Monocyte Range

Chest X-Ray Infiltrate	Monocyte Range	n (%)
Unilateral Infiltrate	2-7	0 (0%)
	>7	1 (100%)
Bilateral Infiltrate	2-7	5 (11,11%)
	>7	12 (26,67%)

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