

02. Therapy for patients with asymptomatic and mild cases

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RESEARCH ARTICLE

Therapy for patients with asymptomatic and mild cases of COVID-19 in Indonesia [version 1; peer review: awaiting peer review]

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Abstract

Background: Though coronavirus disease (COVID-19) has been designated as a global pandemic, its nature as a viral infection means that it is essentially a self-limiting disease. We studied the application of symptomatic, isolation, relaxation, nutrition and observation (SIRNO) therapy in patients with asymptomatic and mild symptoms of COVID-19 at a rescue hospital in Indonesia.

Methods: This is a retrospective cohort study involving 2122 patients who were admitted to Indrapura Field Hospital in Surabaya from 28 May 2020 to 20 September 2020. We analyzed demographic data, clinical signs and symptoms, laboratory data, therapy and clinical outcomes.

Result: The total sample of 2122 patients consisted of 1403 male patients (66.12%), and 719 female patients (33.88 %). The most

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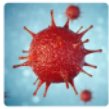
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common age range was 26-45 years, at 52.54% (1115 patients). The clinical symptoms of 1121 patients (52.8%) were asymptomatic, 977 patients (46%) had mild symptoms, and 24 patients (0.1%) had moderate symptoms. All patients received the SIRNO therapy method. From a total of 2122 patients, 1930 patients (90.9%) were cured, 181 patients (8.5%) are still being treated, seven patients (0.03%) were referred for indications of desaturation (SpO₂ <94%), and four patients (0.01%) were moved to a referral hospital. Until 20 September 2020, the final date studied, there were no patient deaths.

Conclusion: The SIRNO method provides excellent results in the management of COVID-19 at a rescue hospital for patients with asymptomatic and mild symptoms. Economic pharmacological research can initiate a follow-up study in order to objectively measure the effectiveness and efficiency of SIRNO treatment methods in patients with asymptomatic, mild symptoms of COVID-19, and the small number of 24 patients (0.1%) with moderate symptoms.

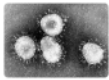
Keywords

Symptomatic, Isolation, Relaxation, Nutrition, Observation, COVID-19



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Introduction

Coronavirus disease (COVID-19) is a global public health issue that was confirmed as a pandemic in March 2020. Defined by the World Health Organization (WHO), COVID-19 is caused by a new coronavirus called the 2019-novel coronavirus (2019-nCoV)¹. However, the International Committee on Taxonomy of Viruses named the novel coronavirus as "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2)².

On September 21, 2020, a total of 30,675,675 confirmed COVID-19 cases were reported in more than 216 countries, including 954,417 deaths, resulting in a mortality rate of 3.1%. In Indonesia, the total number of cases was 248,852 with a death rate of 9,677, while in East Java the total number of cases was 40,708 (16.35%) with a mortality rate of 7.28 %, or 2,695 patients³. As the number of COVID-19 sufferers in some countries continues to increase, as well as the deaths resulting from it, epidemiological studies are very important in order to determine the source of transmission and devise effective and efficient therapeutic methods⁴. Although the understanding of COVID-19 epidemiology continues to develop, it is assumed that SARS-CoV-2 is primarily transmitted through droplets and close contact with a person that is carrying the virus⁴ and the likelihood of death strongly depends on the methods of therapy and comorbidities found in patients.

COVID-19 has a very wide clinical output, from asymptomatic to severe and critical symptoms; more than 75% cases are asymptomatic cases⁵. Among those symptomatic patients, clinical presentations of this include fever, non-productive cough, dyspnea, myalgia, fatigue, normal or decreased leukocytes count, and radiography evidence of pneumonia⁶. Severe complications can include organ dysfunction, including shock, acute respiratory distress syndrome (ARDS), acute heart injury and acute kidney injury. These manifestations may continue and lead to death⁷. The WHO recommended therapies for asymptomatic and mild symptomatic COVID-19 cases are symptomatic, isolation, and observation, related to complaints as well as the monitoring of vital signs and the progress of the disease. In addition, highly nutritional therapy⁸ and relaxation are also needed in the form of light exercise, communication with fellow patients, a psychological approach and calming of the patient with spiritual lectures and studies into religion, as well as a relaxed atmosphere in the hospital⁹. This approach was based on the nature of viral infection which is a self-limiting disease. Viruses that enter the body will be countered by our body's defense system, either naturally via non-specific defences, or specific antibodies.

If the body's non-specific defenses are unable to prevent the virus, then the virus will enter the cell, damage the cell and replicate itself. Antiviral drugs specifically for SARS-COV-2 are still in clinical trials, the administration of antiviral side effects damages the body's cells, so the type, time and dosage of its administration must be precise. In addition the effectiveness of virusidal against the virus that causes COVID-19 has not yet been empirically proven. A review of the economic pharmacology also needs to be considered, the efficiency and

effectiveness of therapy is key to the success of the therapy method¹⁰.

Kogabwilhan II Indrapura Field Hospital is a specialized hospital that treats COVID-19 patients, which is confirmed by swab results with positive PCR (polymerase chain reaction) examination infected with SARS-COV-2. The hospital was established for the treatment and isolation of COVID-19 patients without symptoms and with mild symptoms, in an effort to support COVID-19 services in existing referral hospitals. The initiator of the establishment of Indrapura Field Hospital was the COVID-19 Control Task Force of East Java Province, with financing from the National Disaster centre and fully supported by the Provincial Government of East Java, military regional command V Brawijaya, East Java regional police, the Ministry of Health and the Commander of Joint Command Region II.

The purpose of this study is to describe application of symptomatic, isolation, relaxation, nutrition, and observation (SIRNO) therapy for asymptomatic and mild symptomatic patients at rescue field hospital.

Methods

Study design

This study is a retrospective cohort study of COVID-19 patients who were admitted at Kogabwilhan II Indrapura Field Hospital from 28 May 2020 to 20 September 2020 in Surabaya, East Java Indonesia. This date range was chosen as the opening date of service of the Indrapura Field Hospital for COVID-19 patients. The obtained data was downloaded from the hospital electronic medical records, including demographic data, clinical signs and symptoms, laboratory data, therapy and clinical outcomes (24).

Patient criteria

All patients with COVID-19 enrolled in this study diagnosed according to the guidelines for diagnostic criteria from *Clinical management of COVID-19: interim guidance* (World Health Organization, 27 May 2020). All patients suffered from the infection of SARS-CoV-2, ascertained in the laboratory (the results of RT-PCR [reverse-transcription polymerase chain reaction] specific for SARS-CoV-2 was positive). Diagnosis of mild case patients is made based on the criteria of symptomatic patients and meets the definition of COVID-19 cases without evidence of viral pneumonia or hypoxia, and moderate cases of patients with clinical symptoms of pneumonia (fever, cough, dyspnea, rapid breathing) but no sign of severe pneumonia, including SpO₂ ≥ 90% in the air of the room. All patients treated in Indrapura field hospital according to the criteria constitute the sample of the study.

Data characteristics

Data demographic characteristics of patients were obtained with form collection from the electronic medical record. The collected information included age, gender, occupation, and domicile.

The patients' clinical data were data related to current and past patient medical history. Current signs and symptoms were fever, cough, shortness of breath, fatigue, anorexia, muscle pain, headache, chills, nausea and vomiting, diarrhea, and confusion. Patients' past history included hypertension, heart disease, diabetes, obesity, chronic obstructive pulmonary disease, liver disease. Serial vital signs included blood pressure, pulse, respiratory rate, body temperature, oxygen saturation, and body mass index. The date of onset of the disease is defined as the day when symptoms are first known. Determination of COVID-19 positivity was based on RT-PCR SARS-CoV-2 from naso/oropharyngeal swabs which were collected on the day of admission and evaluated when patients were discharged. Clinical outcome data, including recovery rates, length of treatment, referred cases and death cases, were also analyzed in this study.

SIRNO therapy

Symptomatic by providing therapy according to the complaints felt by the patient, such as the administration of antipyretics, anti diarrhea, decongestan, antitussive and so on.

Isolation by dividing into red zones for patients, which are not mixed between patients and service providers. The room includes a bed space, space for rest and a field for outdoor activities, as well as a garden.

Relaxation by doing gymnastics activities on the field, as well as deep breathing exercises. In addition, there are karaoke activities while still using masks and keeping distance, and regular spiritual and religious lectures and stress management.

Nutrition provided is adjusted to the patient's caloric needs and comorbidity. The type of food provided should also meet the balance of macro nutritional needs such as carbohydrates, proteins, fats, vitamins, and minerals.

Observations are divided into three shifts, each shift will enter the isolation zone for 3 hours to observe the patient's vital signs, complaints and progress. During observation, patients can also consult both physical and mental complaints such as sleep difficulty and restlessness. Patients can also contact the care team at any time online.

All patients are not given antiviral therapy or antibiotics.

Statistical analysis

Statistical analysis was performed using SPSS Version 24. All continuous data is presented as a mean \pm standard deviation (SD) or median \pm interquartile range (IQR). Categorical data is presented as numbers and percentages.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Dr. Soetomo Teaching Hospital (Surabaya, Indonesia), and Universitas Airlangga Faculty of Medicine (Surabaya, Indonesia). All participants have provided written consent for the usage of their data for research purposes.

Results

Clinical characteristics

From the research period of 28 May to 20 September 2020, a total of 2122 patients were found to fit the research criteria. Of these, 1403 patients (66.12%) were men, with the most common age range of study subjects being 26–45 years of age at 52.54% (1115 patients), while 27.33% were 46–65 years, 17.58% were 12–25 years, 1.51% were 6–11 years and 1.03% were over 65 years. In total, 1656 patients were treated without comorbidities (78%) and 466 patients had comorbidities (21.9%). The most common comorbidities were hypertension, at 286 patients (13.47%), diabetes mellitus at 84 patients (3.95%), while 59 patients (2.78%) were obese. A small number of patients also had various comorbidities such as bronchial asthma, hypertensive heart disease, and coronary heart disease. In terms of patient occupation demographics, 946 patients (44.58%) worked as a private employee, followed by 219 patients (10.3%) as military and police, 130 patients (6.1%) as civil servants, and 73 patients (3.4%) as medical personnel, with details of 68 nurses (3.20%), four doctors (0.18%), and one midwife (0.04%) (Table 1).

Signs and symptoms

Of the COVID-19 patients that were treated at Indrapura field hospital, there were 1121 patients (52.8%) without complaint, 977 patients (46%) with mild symptoms, and 24 patients (0.1%) with moderate symptoms. The most common symptoms of COVID-19 were coughing in 325 patients (15.3%), followed by a cold in 132 patients (6.2%), anosmia in 110 patients (5.1%), fever in 93 patients (4.3%), nausea in 47 patients (2.2%), headaches in 46 patients (2.1%), and shortness of breath in 39 patients (1.8%). There were also other symptoms that patients complained about such as abdominal pain and diarrhea in 38 patients (1.7%) (Table 2).

Swab RT-PCR SARS-CoV-2 results

All RT-PCR SARS-CoV-2 swab results were positive for patients treated at Indrapura field hospital. Recovered patients are patients with missing or mildly tolerated clinical symptoms after treatment without symptomatic drugs, and for whom swabs have been negative as much as two times. After leaving the hospital, 181 patients (8.5%) gave feedback related to post-treatment re-swab examination. Of these 181 patients, there were 52 patients (28.7%) who re-examined after exiting the Indrapura field hospital, while 129 patients (71.3%) did not do the re-swab. A total of 19 patients (37.3%) did the re-examination after more than 15 days of returning home, followed by eight patients (15.3%) on the 14th day, and the rest did the examination on the 6th day. Of the 52 patients who did the re-swab, we found 43 patients (82.8%) with negative results, and 9 patients (17.2%) with positive results (Table 2).

Therapy

All patients treated in Indrapura field hospital received SIRNO therapy which was symptomatic (such as antitussive, expectorant, antipyretic, decongestan, bronchodilator), and involved isolation, relaxation, nutrition, and observation. In addition,

Table 1. Demographic characteristics of patients at Indrapura Region II Joint Command Field Hospital.

Patient Demographics (n = 2122)	Value (%)
Gender	
Male	1403 (66.12%)
Female	719 (33.8%)
Age	
6–11 years	32 (1.51%)
12–25 years	373 (17.58%)
26–45 years	1115 (52.54%)
46–65 years	580 (27.33%)
> 65 years	22 (1.03%)
Occupation	
Private Employee	946 (44.58%)
Military and Police	219 (10.3%)
Civil Servant	130 (6.1%)
Student	123 (5.8%)
Company Employee	94 (4.43%)
Housewife	85 (4%)
Nurse	68 (3.2%)
Teacher	64 (3%)
Doctor	4 (0.18%)
Midwife	1 (0.04%)
Others (Retired, Unemployment)	388 (18.3%)
Comorbidity	
No comorbid	1656 (78%)
Hypertension	286 (13.47%)
Diabetes mellitus	84 (3.95%)
Obesity	59 (2.78%)
Asthma	12 (0.56%)
Hypertension Heart Disease	7 (0.33%)
Others (CHD, stroke, HIV)	18 (0.85%)

CHD: Coronary Heart Disease; HIV: Human Immunodeficiency Virus.

patients also received therapy for comorbidities. Until 20 September 2020, 1907 patients (89.87%) received multivitamin therapy (Becefot), 337 patients (15.8%) received N-acetyl cystein therapy 200mg (NAC), 227 patients (10.6%) received decongestant therapy (such as Tremenza and Flutrop), 171

Table 2. Clinical characteristics of patients at Indrapura Region II Joint Command Field Hospital.

Characteristics (n = 2122)	Value (%)
Severity	
No Symptoms	1121 (52.82%)
Mild	977 (46.04%)
Moderate	24 (1.13%)
Severe	0 (0%)
General Symptoms	
Cough	325 (15.3%)
Cold	132 (6.2%)
Anosmia	110 (5.1%)
Fever	93 (4.3%)
Nausea	47 (2.2%)
Headache	46 (2.1%)
Dyspnea	39 (1.8%)
Others (Abdominal pain, diarrhea)	38 (1.7%)
Swab RT-PCR SARS-CoV-2	
Positive	2122 (100%)
Feedback post-treatment	181 (8.5%)
Didn't do the re-swab	129 (71.3%)
Did the re-swab	52 (28.7%)
Re-swab >15 days	19 (37.3%)
Re-swab on day 14	8 (15.3%)
Re-swab on day 6	25 (48%)
Negative	43 (82.8%)
Positive	9 (17.2%)

RT-PCR SARS-CoV-2: Reverse-Transcriptase Polymerase Chain Reaction Severe Acute Respiratory Syndrome Coronavirus 2

patients (8%) received paracetamol, and 97 patients (4.5%) received lorazepam for anxiety disorders. For hypertensive comorbid therapy, 197 patients (9.28%) received Amlodipine therapy 10mg and 190 patients (8.95%) received Amlodipine 5mg, while 26 patients (1.2%) received candesartan therapy 16mg and 21 patients (0.98%) received Candesartan 8mg. Patients with comorbid diabetes (as many as 37 patients, or 1.74%) received metformin therapy 500mg, Glimperide therapy 2mg was received by 43 patients (2%), and 16 patients (0.75%) received insulin (Apidra, Novorapid, and Levemir). All patients in Indrapura field hospital had no antiviral therapy, nor corticosteroids (Table 3).

Table 3. Characteristics of therapy and clinical outcomes of patients at Indrapura Region II Joint Command Field Hospital.

Characteristics (n = 2122)	Value (%)
Symptomatic Therapy	
Multivitamins	1907 (89.87%)
N-acetylcystein 200mg	337 (15.8%)
Decongestants	227 (10.6%)
Paracetamol	171 (8%)
Lorazepam	97 (4.5%)
Comorbid Therapy	
Amlodipine 10mg	197 (9.28%)
Amlodipine 5mg	190 (8.95%)
Candesartan 16mg	26 (1.2%)
Candesartan 8mg	21 (0.98%)
Metformin 500mg	37 (1.74%)
Glimepiride 2mg	43 (2%)
Insulin	16 (0.75%)
Antiviral Therapy	0 (0%)
Corticosteroids Therapy	0 (0%)
Clinical Outcomes	
Cured	1930 (90.9%)
Being Treated	181 (8.5%)
Referred	7 (0.03%)
Died	0 (0%)
Length of Treatment	
< 7 days	1399 (72.48%)
8–14 days	417 (21.6%)
15–21 days	91 (4.71%)
22–28 days	20 (1.04%)
> 28 days	3 (0.15%)

Clinical outcomes

From a total of 2122 patients, 1930 patients (90.9%) were cured, and 181 patients (8.5%) are still being treated. There were seven patients (0.03%) referred for indications of desaturation (SpO₂ <94%), and four patients (0.01%) moved to a referral hospital. No patient died or returned home on their own request (0%). The highest number of patients treated in the Indrapura field hospital based on average length of stay (LOS) was in the group with a LOS of less than 7 days, which was 1399

patients in total (72.48%), followed by the group with a LOS of 8–14 days with 417 patients (21.6%), the group with a LOS of 15–21 days with 91 patients (4.71%), and the group with a LOS of 22–28 with 20 patients (1.04%). Additionally, three patients (0.15%) were treated with a LOS of more than 28 days (Table 3).

Discussion

COVID-19 has been reported to have caused the deaths of more than one million people, and the nature of viral infection remains a concern of many medical doctors worldwide. As for the asymptomatic and mild symptom cases, isolation and supportive therapy is the recommended approach¹¹. The clinical outcome was mainly affected by patient comorbidities, including old age, chronic metabolic diseases, obesity and long term viral exposure¹². Our data showed various medical comorbidities, with the most common being hypertension and diabetes mellitus. In addition, occupation-based analysis showed most patients were private employees, followed by military and police and civil servants. These occupations were occupations with high risk for contact with other people and high risk for COVID-19 infection³.

In this study, there were 1238 patients without complaint (58.3%), 325 patients complained of coughing (15.3%), followed by 132 flu patients (6.2%), 110 anosmia patients (5.1%), and 93 fever patients (4.3%). Complaints of nausea, headache, tightness, abdominal pain, and diarrhea were less common. Gastrointestinal complaints were not found in COVID-19 patients in this study. Based on previous research by Ge *et al.* in 2019, we conducted retrospective research on confirmed patients for 10 months and obtained clinical manifestations of patients infected with SARS-CoV-2, ranging from mild non-specific symptoms to severe pneumonia with damage to organ function¹³. Common symptoms are fever (77.4–98.6%), cough (59.4–81.8%), fatigue (38.1–69.6%), dyspepsia (3.2–55.0%), myalgia (11.1–34.8%), sputum production (28.2–56.5%), and headaches (6.5–33.9%)¹³. Sore throat, rinorhea, chest pain, hemoptysis, conjunctiva congestion, diarrhea, nausea, and vomiting were less frequent¹⁴. One study showed that 39.6% of the 140 confirmed COVID-19 patients had gastrointestinal symptoms, and 10.1% of patients experienced gastrointestinal discomfort at the onset¹³. SARS-CoV-2, SARS-CoV, and MERS-CoV (Middle East respiratory syndrome coronavirus) infections have many similar clinical symptoms, including fever, cough, myalgia, and dyspnea¹⁵. However, patients with SARS and MERS had more gastrointestinal symptoms (about a third) than COVID-19 patients¹⁶.

The latest guidelines for the treatment of COVID-19 patients indicate that suspected and confirmed cases should be treated in isolated hospitals with effective isolation and protection conditions¹⁷. As for asymptomatic and mild COVID-19 cases, the WHO recommends that COVID-19 patients are given symptomatic treatments such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration⁷. In this study, it was found that all patients treated at Indrapura field hospital did not receive antiviral therapy. The procedures were provided

in the form of isolation, observation, and supportive therapy, symptomatic therapy, multivitamins, nutrition, **therapies for comorbidities** and randomized control trials such as amlodipine for hypertension, then therapy to reduce symptoms such as N-acetyl cystein (NAC), decongestants, and paracetamol. Indeed, there were several anti-viral drugs available for treating COVID-19 patients. Of the three clinical cohort studies, oseltamivir was used for antiviral therapy in 35.8% of patients, 89.9% of patients, and 92.7% of patients¹⁸. Another study involved 99 COVID-19 patients, of which 76% received antiviral treatment, including oseltamivir, ganciclovir, and lopinavir and ritonavir tablets, with the duration of antiviral treatment being 3–14 days. Although oseltamivir was widely used in early cohort studies, its effectiveness in treating COVID-19 has not been so clear¹³. To date, there is no evidence to recommend any specific anti-COVID-19 treatment. Large-scale RCT (randomized controlled trial) COVID-19 drugs are still ongoing. The current use of chloroquine, hydroxychloroquine, oseltamivir, lopinavir/ritonavir, favipiravir, and remdesivir in COVID-19 management is currently based on small-scale clinical studies, which are not enough to draw strong conclusions about its efficacy and safety. Based on clinical pharmacological reviews, the decision to use this drug during the COVID-19 pandemic should consider its potential benefits and risks for patients, as the drug is likely to be effective, available and affordable, with the lowest risk to patients and the public¹⁹. Therefore, the administration of antivirals is not recommended for infections with no symptoms. To date, isolation and close observation are still considered as better options for asymptomatic patients²⁰.

With this procedure, in this study, the obtained clinical outcome is 1399 patients (72.48%) with a LOS of less than 7 days, followed by 417 patients (21.6%) with a LOS of 8–14 days, 91 patients (4.71%) with a LOS of 15–21 days, 20 patients (1.04%) with a LOS of 22–28 days, and three patients (0.15%) were treated with a LOS of more than 28 days. In addition, eight patients were referred for clinical worsening indications, two patients moved hospitals, and one patient was in self-isolation. After leaving the hospital, there were 181 patients (8.5%) which gave feedback related to post-treatment re-swab examination. Of these 181 patients, there were 52 patients (28.7%) who were re-examined after exiting the Indrapura field hospital, while 129 patients (71.3%) did not do the re-swab. A total of 19 patients (37.3%) did re-examination after more than

15 days of returning home, followed by eight patients (15.3%) on the 14th day, and the rest did the examination on the sixth day. Of the 52 patients who did the re-swab, we found 43 patients (82.8%) with negative results, and nine patients (17.2%) with positive results.

There were several limitations to this study. Firstly, the included subjects in this study were asymptomatic and mild symptom patients without any comparison between the treated and untreated groups, hence we could not generate a good conclusion. Secondly, this study only covers one location with mostly Javanese patients. Since Indonesia does not only consist of Javanese people, a multi-center study involving more patients will give a more comprehensive understanding of the management of COVID-19 patients in Indonesia.

Conclusion

The conclusion of this study is that SIRNO method provides excellent output in the management of COVID-19 at Indrapura field hospital. Economic pharmacological research can perform a follow-up study in order to objectively measure the effectiveness and efficiency of SIRNO treatment methods in asymptomatic and mild symptomatic infections of COVID-19.

Data availability

Figshare: Demographic Information Indrapura Field Hospital Surabaya, Indonesia 2122.xlsx. <https://doi.org/10.6084/m9.figshare.14412464.v2>²¹

The project contains the following underlying data:

- Demographic Information Indrapura Field Hospital Surabaya, Indonesia 2122.xlsx (This is part of the article Therapy for Asymptomatic and Mild Cases of COVID-19 Patients in Indonesia)

Data are available under the terms of the **Creative Commons Attribution 4.0 International license (CC-BY 4.0)**.

The full data are not publicly available due to restrictions for ethical reasons, as the information could compromise the privacy of research participants. The datasets used and/or analysed during the current study are available from the corresponding author (Erwin Astha Triyono, erwintriyono@yahoo.com) on reasonable request.

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