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Analysis of Drug Use in Non-Ventilator Covid-19 Patients at Bangil Hospital

Vincentina Yenny Triamyanti[1], Fauna Herawati[2], Rika Yulia[2*], Abdul Kadir Jaelani[3]
[1]Master of Pharmacy Study Program, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia
[2]Department of Clinical and Community Pharmacy, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia
[3]Pharmacy Installation Training Unit, Bangil Regional General Hospital, Pasuruan, Indonesia

*Corresponding author: rika_y@staff.ubaya.ac.id

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Abstract

Background*: Coronavirus Disease 2019 (Covid-19) is an infectious disease. Common signs and symptoms of Covid-19 infection include acute respiratory distress such as fever, cough and shortness of breath. Analysis of drug use in Non-Ventilator Covid-19 patients needs to be carried out to provide an overview of drug therapy currently being used based on the Covid-19 Management Guidelines Edition 3rd because so far, there has not been a single type of drug that has received marketing authorization for Covid-19 therapy.* ***Objectives****: This study aims to determine patient profiles, therapeutic outcomes, suitability of drug use with Covid-19 Management Guidelines 3rd edition, the quantity of antibiotic use using the DDD/100 patient-days method and antivirals.* ***Methods****: The method used in this study is an observational design study which was analyzed descriptively with retrospective data collection.* ***Result****: Based on the profile of drug use in COVID-19 patients, there are 31 types of drug classes. The most consumed drugs were antibacterial (91%) and analgesics (91%), followed by vitamins (89%) and supplements (85%). Based on the DDD/100 patient-days value, the most widely used antibiotics were Azithromycin.* ***Conclusion****: The patient's profile at the time of admission to the hospital was 44% moderate and 56% severe. The condition of patients at the time of discharge from the hospital with a moderate degree using antivirals and antibiotics were more recovered and returned home with improvements with percentages of 84.1% and 88.64%, respectively.*

Keywords*: covid-19, non-ventilator patients, antibiotic, antiviral*

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INTRODUCTION

Infectious disease is a disease that often occurs throughout the world. The cause of this infection is a new type of virus called Severe Acute Respiratory Syndrome Coronavirus-2 or SARS-CoV-2. WHO named the disease Coronavirus Disease 2019 or Covid-19 through consultation and collaboration with the World Organization for Animals (OIE) and the Food and Agriculture Organization of the United Nations (FAO). Common signs and symptoms of Covid-19 infection include acute respiratory distress such as fever, cough, and shortness of breath. The average incubation period is 5-6 days, with the most prolonged incubation period being 14 days. Severe cases of Covid-19 can lead to pneumonia, acute respiratory syndrome, kidney failure, and even death.

Transmission of the Covid-19 virus can occur through respiratory droplets (aerosol), direct contact with contaminated objects and surfaces from sufferers, and both asymptomatic and symptomatic (WHO, 2021). On January 30th, 2020, this virus spread rapidly and caused an exponential increase in the number of patients until July 9th, 2020. WHO reported 11,840,226 confirmed cases with 545,481 deaths worldwide (Case Fatality Rate/CFR 4.6%) (WHO, 2021). Based on the condition and severity of Covid-19 cases, they are divided into several categories: asymptomatic, mild, moderate, severe, and critical. Based on an earlier study, from the profile of Covid-19 patients for the period January to April 2021 at RSU Haji Surabaya from 100 patients, the results showed that 61% were Covid-19 patients in the moderate category and 39% were in a severe category. Among patients in moderate category, 90.16% recovered while 9.84% died. From the profile of drug use in COVID-19 patients for the period January to April 2021 at RSU Haji from 100 patients, the results showed 99% of patients used mucolytic drugs by 99%, and the second most used was vitamin class drugs, which was 98%, then followed by the use of antibiotics class of drugs by 97%, and the fourth is antiviral drugs by 96% (Isna, 2021).

Following the Covid-19 therapy guidelines from WHO, Indonesia has recommended supportive therapy for handling Covid-19, such as symptom therapy, supplemental oxygen, antibiotics, fluid therapy, vasopressors, and medical measures (including installing a ventilator) to save the patient's life (Setiadi et al., 2020). Repurposing drugs is the use of drugs that already exist and are not officially indicated for Covid-19 but are used as therapy through an efficient approach. (Singh et al., 2020). According to the guidelines for managing Covid-19 therapy in Indonesia, which refers to the WHO, empirical antibiotics are given as therapy for Covid-19 patients to overcome secondary bacterial infections (Burhan et al., 2020). Data on the use of antibiotics in Covid-19 patients shows that antibiotics rank first in the treatment of Covid-19 with a percentage of 90.83% (Gutiérrez et al., 2020). The most widely used antibiotics are ceftriaxone 69.28%, azithromycin 67.93%, and levofloxacin 15.2%. Other therapies used for Covid-19, among others, are antimalarials by 44.37%, with the use of hydroxychloroquine ten times greater than chloroquine (64.95%: 6.13%), the use of steroids by 44.37%, and the use of the antiviral lopinavir-ritonavir by 42.63% and tocilizumab by 9.37% (Gutierrez et al., 2020). Analysis of drug use in Non-Ventilator Covid-19 patients needs to be carried out to provide an overview of drug therapy currently being used based on the Covid-19 Management Guidelines 3rd Edition because so far, there has not been a single type of drug that has received marketing authorization for Covid-19 therapy. Reminding the high cases of Covid-19 and the efforts of all parties to obtain the best therapeutic data in perfecting the management of Covid-19 therapy, this study aims to determine patient profiles, therapeutic outcomes, suitability of drug use with Covid-19 Management Guidelines 3rd edition, the quantity of antibiotic use using the DDD/100 patient-days method, and the use of antivirals at Bangil Hospital.

METHOD

This research was an observational research design which used a retrospective descriptive design. The data sources were medical records and records of drug use from the Department of Hospital Pharmacy. The population in this research were Covid-19 patients with moderate or severe categories of hospitalization who received treatment at Bangil Hospital. The sample size was taken using the purposing sampling method, namely 100 COVID-19 patients who met the inclusion and exclusion criteria from all confirmed COVID-19 patients in the isolation room without a ventilator (moderate or severe).

Assessment and evaluation of the quantity of antibiotic use is carried out using the Defined Daily Dose. The calculation of the Defined Daily Dose was as follows:

$$\frac{DDD}{100} Patient - Days: \frac{Medicine\ in\ grams\ used\ by\ all\ patient\ x\ 100}{DDD\ WHO\ standard\ in\ grams\ LOS}$$

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The reliability and accuracy of drug use in percentage units compared with the Covid-19 Management Manual 3rd Edition 2020. This research used ICD-10 and ATC codes to shorten the presentation table by grouping. This research also received an Ethics Certificate from the Bangil Hospital Ethics Number 445.1/026/424.072.01/2021.

RESULTS AND DISCUSSION

Coronavirus disease has been identified since 2019 (Covid-19) and is associated with the cause of many deaths. It has been reported that the most susceptible to Covid-19 are elderly patients with a 6-fold higher risk. Based on the severity of cases, Covid-19 is divided into 5 levels: asymptomatic, mild, moderate, severe and critical. This shows that the treatment or therapy given must be different for each so as not to worsen the patient's condition (PDPI et al., 2020). In this situation, it is necessary to conduct a drug analysis for non-ventilator Covid-19 patients.

Samples were classified by their severity. Each level of severity was further classified based on age, sex, and length of hospitalization. The sample data showed that most of the moderate Covid-19 patients were 36-45 years old (late adulthood) and 46-55 years old (early elderly), with a percentage of 22%. Moreover, most patients with the severe category were 56-65 years old (elderly), with 17%. Based on the length of hospitalization, the severe category takes longer than moderate severity.

Based on the demographic data, the sample was divided according to age and gender. The result showss that the highest percentage is at 36-45 years (late adulthood). This age group is the most affected by Covid-19 because of the frequent contact with patients. Meanwhile, based on gender, the most affected by Covid-19 are males. This is due to hormonal and immune conditions, and viral receptor enzymes are more commonly found in the male. The enzyme in question is Angiotensin-Converting Enzyme 2 (ACE 2) (Esmaeil et al., 2022).

Based on the demographic data, there were 100 samples. 44 samples (44%) were in the moderate category, and 56 samples (56%) were in a severe category. Moderate Covid-19 patients required hospitalization for 456 days, while patients with severe category of Covid-19 need 797 days for hospitalization. Factors that can affect the length of hospitalization are complications experienced by the patient. Patients with comorbidities may experience complications that prolong hospitalization (Hiroyuki et al., 2021).

The results of the research samples in the moderate patient category indicated that there were 24 samples (24%) of male infected with Covid-19 and this number was more than female who only had 20 samples (20%). The results of the research sample for severe patient category based on gender showed that there were 32 samples of male patients (32%) infected with Covid-19, and this number was more than female patients who only had 24 samples (24%). This is in line with a study entitled Pandemic Covid-19 in a Demographic Perspective which stated that there were 51.5% male Covid-19 patients and only 48.5% female (Laura et al., 2021). Other studies have also found different behavior between males and females in maintaining their health. Females tend to care more about their health than males. In general, this behavior shows that females comply more with health protocols such as wearing masks, washing hands and keeping a distance (Goncalves et al., 2020).

Table 1. Severity Profile

Variable of Covid-19 Patients			
		Moderate	**Severe**
Age	17 – 25	7%	3%
	26 – 35	7%	5%
	36 – 45	12%	14%
	46 – 55	10%	13%
	56 – 65	7%	17%
	65 – over	1%	4%
Gender	Male	24%	32%
	Female	20%	24%
Length of stay		456 days	797 days
Mean		10	14

The sample data of severity affects the condition of patients out of the hospital. The exposure data can be seen in Table 2. The data showed that patients with moderate severity had no death cases, while 19 (33.93%) patients died in severe severity. The profile of the study sample based on the condition of discharge from the hospital was influenced by the severity. Patients with symptoms who were discharged from the hospital in a recovered state were more than those who were discharged in an improved state. None of the Covid-19 patients with moderate symptoms died. More patients with severe symptoms of Covid-19 returned home in a recovered state than in an improvement state. An improvement state means that the patients are still given drugs to support their recovery. Meanwhile,

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patients with severe symptoms died. Thus, it can be concluded that the number of patients with recovered outcomes is greater than the number of deaths (Kim et al., 2020).

This study is in accordance with a study in Korea which stated that the study's total sample was 5621 patients, with a total of 5387 patients recovered and 234 patients died. The study also explained that most Covid-19 patients who died were due to worsening conditions and respiratory failure in the ICU (Luis et al., 2022). The criteria for recovered patients are asymptomatic, mild symptoms, moderate symptoms, or severe/critical symptoms, provided that the patients have met the criteria for the issuance of a warning letter based on the assessment of the doctor at the health facility where it is carried out or by the DPJP. The criteria consist of a thorough clinical study that includes improved radiological and blood examination carried out by the DPJP, stating that the patient is allowed to go home. There is no action/treatment required by the patient, either related to COVID-19 or other health problems experienced by the patient (PDPI et al., 2020).

Complication regarding Covid-19 is mainly associated with pneumonia (Table 3). This can occur because Covid-19 attacks the respiratory tract, where there are many ACE2 receptors, causing the respiratory tract to weaken as Covid-19 takes host (Naoyuki et al., 2022). Inflammation of the lungs can trigger infection and worsen the inflammatory condition (Tsamrotul et al., 2020). Inflammatory conditions of the lungs due to infection can be categorized as pneumonia. Inflammation of the airways can lead to respiratory failure in patients. Respiratory failure can cause the patient's condition to worsen and even cause death. This condition needs to be considered so that Covid-19 patients do not experience a much worse condition (Somers et al., 2020).

Table 2. Profile of Research Samples Based on Severity and Outcome Patient

Severity	Outcome Patient			
	Healed	Repatriation	Died	Total
Moderate Category Covid-19 Patients (44%)	56.82%	43.18%	0%	100%
With antibiotics	50.00%	38.64%	0%	
Without antibiotics	6.81%	4.55%	0%	100%
Appropriate antibiotics	38.47%	25.64%	0%	
No appropriate antibiotics	20.51%	15.38%	0%	100%
With antivirals	54.55%	29.55%	0%	
Without antivirals	2.26%	13.64%	0%	100%
Appropriate antivirals	43.24%	32.44%	0%	
No appropriate antivirals	21.62%	2.70%	0%	100%
Severe Category Covid-19 Patients (56%)	53.57%	12.5%	33.93%	100%
With antibiotics	48.21%	10.71%	33.93%	
Without antibiotics	5.36%	1.79%	0%	100%
Appropriate antibiotics	38.46%	7.69%	29.92%	
No appropriate antibiotics	11.54%	5.77%	9.62%	100%
With antivirals	46.43%	12.50%	30.36%	
Without antivirals	7.14%	0%	3.57%	100%
Appropriate antivirals	44.00%	14.00%	32.00%	100%
No appropriate antivirals	8.00%	0%	2.00%	

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Table 3. Profile of Research Samples Based on Diagnosis of Comorbidities

ICD-10 Code Grouping	Code	Percentage of Patients (%)	Diagnosis	ICD-10 Code	Percentage (%)
A00-B99	A	47	Gastroenteritis	A08.4	12
			Tuberculosis	A15	3
			Sepsis	A41.9	34
	B	2	Hepatitis C	B17.9	2
D50-D89	D	14	Anemia	D64.9	2
			Hypercoagulation	D68.69	11
			Thrombocytopenia	D69.6	1
E00-E90	E	22	Diabetes mellitus	E10	19
			Hypoglycemia	E16	1
			Dyslipidemia	E78.5	3
			Hyponatremia	E87.1	1
			Hyperkalemia	E87.5	1
			Hypoalbumin	E88.9	2
H60-H95	H	2	Vertigo	H81.399	2
I00-I99	I	11	Hypertension	I10	2
			Acute Coronary Syndrome/ACS	I24.9	3
			Heart Failure / HF	I50.9	1
			Stroke / CVA	163.9	3
			Atherosclerosis	I70.9	2
J00-J99	J	73	Pneumonia	J12.82	69
			Bronchitis	J40	12
			Chronic Obstructive Pulmonary Disease (COPD)	J44.9	3
			Acute Respiratory Distress Syndrome	J80	1
K00-K93	K	7	Peptic Ulcer	K27	2
			Dyspepsia	K30	5
			Hematemesis	K92.2	1
L00-L99	L	1	Drug Eruption	L27	1
N00-N99	N	4	Chronic Kidney	N18	1
			CKD Stage 5	N18.5	1
			Kidney Insufficiency	N19	1
			Urinary tract infection	N39	1
R00-R99	R	36	Haemoptysis	R04.2	1
			Anosmia	R43.0	35
			Ageusia	R43.2	32
U00-U99	U	100	Covid-19	U00	100

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Table 4. Drug Use Profile

No	Drug Type	ATC Code	Percentage of Patients (%)	Drugs Used	Percentage of Drug Use (%)
1	Antiviral	J05AB16	83	Remdesivir	47
		J05AX27		Favipiravir	25
		J05A0H02		Oseltamivir	15
2	Antibacterial	J01FA10	91	Azithromycin	37
		J01MA14		Moxifloxacin	49
		J01MA12		Levofloxacin	40
		J01DC02		Cefuroxime	2
		J01DD02		Ceftazidime	11
		J01DD04		Ceftriaxone	29
		J01DD12		Cefoperozone	1
		J01DH02		Meropenem	36
3	Analgesic	N02BB02	91	Metamizole	18
		R05DA04		Codeine	53
		N02BE01		Paracetamol	32
		N05BA01		analysis	8
		N02AA01		Morphine	3
		N01AH02		Fentanyl	2
4	Antihistamine	R06AE07	37	Setirizin	37
		R06AA11		Dimenhydrinate	2
5	Corticosteroids	A01AC03	70	Hydrocortisone	40
		A01AC02		Dexamethasone	32
		D07AA01		Methylprednisolone	27
6	Mucolytic	R05CB01	83	Acetylcysteine	83
7	5-HT3 Antagonist	A04AA01	20	Ondansetron	20
8	Diuretic	C03CA01	36	Furosemide	36
9	Antihypertensive	C09CA06	35	Candesartan	15
		C07AB07		Bisoprolol	22
		C08CA05		Nifedipine	1
		C08CA01		Amlodipine	14
				nicardipine	1
		C09CA03		Valsartan	1
10	Anticoagulants	B01AF01	45	Rivaroxaban	3
		B01AB01		Heparin	35
		B01AB05		Enoxaparin	14
		B01AX05		Fondaparinuks	11
11	Hypnosis and Anesthesia	N05BA12	47	Alprazolam	27
		N05BA01		Diazepam	15
		N05CD08		Midazolam	5
12	Antiplatelet	B01AC04	14	Clopidogrel	13
				aspirin	3
13	Antianginal	C01DA08	11	ISDN	11
		C08CA04		nicardipine	1
		C01EB15		myozidine	1
14	Hypolipidemic	C10AA05	33	Atorvastatin	9
		C01AA07		Rosuvastatin	23
		C10AB04		Gemfibrozil	3
		C10AB05		Fenofibrate	2
15	Antidiabetic		9	Levemir	9
		A10BF01		Acarbose	2
16	Anti-ulcer	A02BC03	76	Lansoprazole	8
		A02BC02		Pantoprazole	62
		A02BC01		Omeprazole	11
		A02BX02		Sucralfate	9
17	Supplement		85	Gabaxa/Amino acids	8

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				Vipalbumin	10
				Sancoidan	2
				Curcuma	57
				Methylcobalamin	5
				Hepamax	11
				Synbiotic	20
				Prorenal	3
18	Vitamin	A11GA		Vitamin C	78
		A11CC		Vitamin D	26
			89	Furamin	12
				Zegavit	62
				Becom C/Z	23
19	Anti-Guat	M04AA01	4	Allopurinol	4
20	Vertigo		2	Betahistine Melisat	2
21	Psychosis and Similar Disorders	N05AD01	1	Haloperidol	1
22	Hemostatic and Antifibrinolytic	B02AA02	6	Tranexamic Acid	6
23	Anesthetic	L01XX11	6	Tramus	6
24	Urinary and Genital System	V03AE07	2	Aminoral	2
25	Shock and Hypotension	C01CA07	2	Dobutamine	2
26	Tricyclic Antidepressants	N06AA09	2	Amitriptyline	2
27	Nausea and vertigo	C10AB05		Fenofibrate	2
		A03FA01	2	Metoclopramide	5
		A03FA03		Domperidone	1
28	Laxative	A06AB02	8	Dulcolac	8
29	Cardiac Glycoside		2	Fargoxin	2
30	Antiasthma and Bronchodilators	A07EA06	8	Symbicort	1
				Ventolin	3
		R03DA05		Aminophylline	5
31	Immunoglobulins		3	IVIG	2
		J06BA		Intract	3

Table 5. Profile of DDD/100 Days of Hospitalization

ATC Code	Antibiotics	DDD in WHO	Number of grams	DDD/100 days in patient	Length of Days of Antibiotic Use (Days); Mean
J01FA10	Azithromycin	0,3	99,5	26,26	185; 5
J01MA14	Moxifloxacin	0,4	98,8	19,56	98; 2
J01DD04	Ceftriaxone	2	248	9,82	73; 2,5
J01DD12	Cefoperazone	4	8	0,16	8; 8
J01MA12	Levofloxacin	0,5	159,75	25,30	213; 15,3
J01DD02	Ceftazidime	4	138	2,73	69; 6,3
J01DH02	Meropenem	3	510	13,46	170; 4,7
J01DC02	Cefuroxime	3	6	0,16	6; 6
	Total		1268,05	97,44	822

Antibiotics are a class of drugs used in the treatment of COVID-19 patients. The antibiotics use activity was assessed from the accuracy of the antibiotic's selection. According to the 3rd Edition of Covid-19 Management Manual, it is explained that the recommended antibiotic therapy is Azithromycin or Levofloxacin when there is an indication of bacterial infection (PDPI et al., 2020). The assessment of accuracy in the antibiotic's selection refers to the initial diagnosis of Covid-19 patients. Therefore, if there are no discrepancies such as the addition of other types of antibiotics, additional antibiotic therapy is maybe aimed at complications. According to the manual, the range of antibiotic use is 5-7 days (Gennaro et al., 2020).

The choice of antiviral therapy according to the Manual is Favipiravir and Remdesivir. Favipiravir is prescribed for the treatment of Covid-19. The use of this antiviral is limited to the treatment of cases that do not

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improve with other antivirals. This drug is currently used as a test drug for Covid-19 (Lapostolle et al., 2020). The use of antivirals as therapy is used to suppress the virus development, not to destroy the entire virus. The correct choice of antiviral depends on the patient's diagnosis and the choice of the antiviral prescribed. Antiviral selection profiles were compared with those listed under the Covid-19 Management Manual 3rd Edition. The appropriate antivirus, according to the Manual, was Favipiravir or Remdesivir (PDPI et al., 2020).

CONCLUSION

Data shows that men are more exposed to Covid-19 than women. The condition of patients at the time of hospital admission was 44% moderate and 56% severe. Meanwhile, the condition of patients with moderate degree using antivirals and antibiotics at the time of hospital discharge was 84.1% recovered and 88.64% in improvement state. Meanwhile, the condition of patients with severe degrees using antivirals and antibiotics was 58.93% recovered and 58.92% in improvement state.

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AUTHOR CONTRIBUTIONS

Conceptualization, R.Y.; Software, V.Y.T.; Methodology, F.H.; Validation, F.H., R.K.; Formal Analysis, V.Y.T.; Investigation, F.H., R.K.; Resources, V.Y.T., A.K.J.; Data Curation, V.Y.T.; Writing - Original Draft, V.Y.T.; Writing - Review & Editing, F.H., R.K., A.K.J.; Visualization, V.Y.T.; Supervision, F.H., R.K., A.K.J.; Project Administration, V.Y.T., A.K.J.; Funding Acquisition, V.Y.T.

CONFLICT OF INTEREST

The authors report no conflict of interest in this study.

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