






IGSCPS SPECIAL EDITION

RESEARCH ARTICLE

Antihypertensive profile in COVID-19 patients at emergency field hospital Surabaya, Indonesia

Didik Hasmono¹ , Samirah¹ , Sandra Junita Parambang² , Ririn Dwi Cahyani² , Erwin Astha Triyono³ , Halim Priyahau Jaya⁴

¹ Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

² Master of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

³ Department of Internal Medicine, RSUD Dr. Soetomo, Surabaya, Indonesia

⁴ Hospital Pharmacy Installation, RSUD Dr. Soetomo, Surabaya, Indonesia

Keywords

Antihypertensive drug
Covid-19
Hypertension
Length of stay

Correspondence

Didik Hasmono
Department of Pharmacy Practice
Faculty of Pharmacy
Universitas Airlangga
Surabaya
Indonesia
didik-h@ff.unair.ac.id

Abstract

Background: Case fatality rates for COVID-19 patients with hypertension have reached up to 14%. Using ACEi and ARB reduces ACE and increases ACE2 expression, which theoretically can mediate SARS-CoV-2 invasion and infection. **Objective:** This study examines the profile of hypertension therapy, time to reduce blood pressure, and length of stay. **Method:** A retrospective cross-sectional observational study was undertaken. Data were collected from patients' medical records using a consecutive and time-limited sampling method. **Result:** 222 patients were involved in this study. The most widely used antihypertensive monotherapy is oral amlodipine (1x5 mg) 51.35%, and combination therapy with oral amlodipine (1x10 mg) plus candesartan (1x8 mg) 8.11%. The mean time to reduce blood pressure was 5.96 and 6.67 days, and the mean length of stay was 5.99 and 6.67 days. Correlation analysis on the rate of decrease in blood pressure with length of stay showed significance ($p = 0.000 < 0.05$) with a positive Spearman correlation (0.992), which showed a very strong correlation. **Conclusion:** Antihypertensive therapy in this study was following existing guidelines. The time to reduce blood pressure was proportional to the length of stay, so hypertension is vital to control to support the improvement of the patient's clinical condition.

Introduction

SARS-CoV-2, which causes COVID-19, is a coronavirus that causes severe acute respiratory syndrome. The epidemic of severe acute respiratory syndrome (SARS) in the early 2000s was brought on by severe acute respiratory coronavirus one (SARS-CoV-1), which shares genetic similarities with SARS-CoV-2 (Lai *et al.*, 2020). On 19 January 2023, the total number of confirmed COVID-19 infections worldwide was 663,001,898 people in 235 infected countries, with 6,707,959 deaths (a case fatality rate (CFR) of 1.01%) (World Health Organisation, 2023). The number of confirmed COVID-19 infections in Indonesia reaches 6,727,317 cases, with 160,764 deaths (CFR 2.39%) in 34 provinces, and confirmed cases of COVID-19 in East Java are up to 637,348 cases, with 32,277 deaths (CFR

5.06%) (Ministry of Health of the Republic of Indonesia, 2023; World Health Organisation, 2023).

By attaching to the angiotensin-converting enzyme II receptor (ACE2), which affects the renin-angiotensin-aldosterone system (RAAS), one of the causes of high blood pressure, SARS-CoV-2 invades and infects human cells. Hypertension is one of the most prevalent comorbidities seen in COVID-19 patients. A study in China involving 1,099 patients with COVID-19 showed hypertension prevalence data of 23.4% (Guan *et al.*, 2020). Approximately 30% of SARS-CoV-2 patients had comorbid hypertension, with an increase in mortality rate (CFR) of up to 14% (Zhang *et al.*, 2020). Another study in China found that the case death rate (CFR) for all COVID-19 patients was 2.3% but increased to 6.0% for COVID-19 patients with hypertension with COVID-19 (Clark *et al.*, 2021).

The expression of ACE is decreased, and ACE2 is increased by using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). The propagation of the virus and deterioration of the lungs may result from this, serving as a factor in the entrance and infection. This function causes damage by activating the angiotensin II type one receptor (AT1R). However, research has indicated that ACE2 protects against lung injury (Kai & Kai, 2020). ACE2 converts angiotensin II into angiotensin one to seven, which has more anti-inflammatory properties. This reduces the pro-inflammatory effects of angiotensin II. As a result, the severity of lung damage is reduced, and acute respiratory distress syndrome (ARDS) is avoided (Huang *et al.*, 2020). There is no evidence that ACEIs or ARBs should be discontinued due to concerns about COVID-19. These drugs continue to be recommended to treat COVID-19 and its complications, treat high blood pressure, and improve the quality of life (PERKI, 2020).

The Kogabwilhan II Indrapura Field Hospital Surabaya is a hospital that explicitly treats patients infected with COVID-19, regardless of whether they have comorbidities, and the highest comorbidity rate is hypertension, followed by diabetes and chronic obstructive pulmonary disease (COPD). Taking into account this, a study was conducted on COVID-19 patients with hypertension to examine their profile of hypertension therapy, time to reduce blood pressure, and length of stay.

Methods

Design

This study's design was retrospective, observational, and cross-sectional, using a consecutive time-limited sampling technique. The Faculty of Medicine of Universitas Airlangga Health Research Ethics Committee approved this study under ethics approval number 37.EC/KEPK/FKUA/2021 for ethical suitability.

Assessment

The sample in this study was electronic medical record data for patients at Kogabwilhan II Indrapura Field Hospital Surabaya from July to November 2020, all ages diagnosed with COVID-19 with hypertension comorbidity, excluding patients with a combination of other comorbidities and patients with incomplete medical record data.

Medical records that have been collected based on inclusion criteria are examined to obtain patient data, including 1) patient characteristic data: gender, age,

and medical history; 2) patient clinical data: clinical symptoms experienced by the patient, time from symptom onset to recovery, complete laboratory and RT-PCR examination data, and patient's vital signs; 3) data regarding the patient's drug history: treatments performed, duration of treatment, and length of stay. Statistical analysis was performed using the chi-square test to analyse the relationship between symptom categories and length of stay, and the Spearman correlation test was used to determine the correlation between the obtained data. Analysis of differences in the median length of stay for patients in the categories of asymptomatic and mild symptoms with the Kolmogorov-Smirnov normality test was not normally distributed ($p = 0.035$), so the median difference test was continued with Mann-Whitney U and showed significance ($p = 0.006$).

Results

In this study, a total of 222 patient data was collected. Men patients (Table I) predominated concerning patient characteristics, with 141 patients (63.51%). Most cases were between the ages of 46 and 55, and 94 patients (42.34%) had a mean age of 46.54. 37 patients (56.06%) reported having a cough, 14 reported having a fever, and 14 reported having a headache as their most frequent symptoms. Of the 222 patients, 65 (29.28%) accomplished the target of controlled hypertension, while 157 (70.72%) did not reach the aim of treatment, that is, uncontrolled hypertension at discharge. Data on patient length of stay in this study showed a majority of one to five days in 122 patients (54.95%), with a mean length of stay of 6.39 days.

Analysis of the relationship between symptom categories and length of stay using the Chi-square test (Table II) showed a significant relationship with a p -value of 0.030. Analysis of the mean length of stay difference in patients with asymptomatic and mildly symptomatic symptoms using the Mann-Whitney U mean difference test showed significance with a p -value of 0.006. The median stay of patients with COVID-19 and hypertension in the asymptomatic group was five days, and the mild symptoms group was eight days. Thus, it can be concluded that symptoms of COVID-19 infection affect the length of stay.

Table I: Basic characteristics

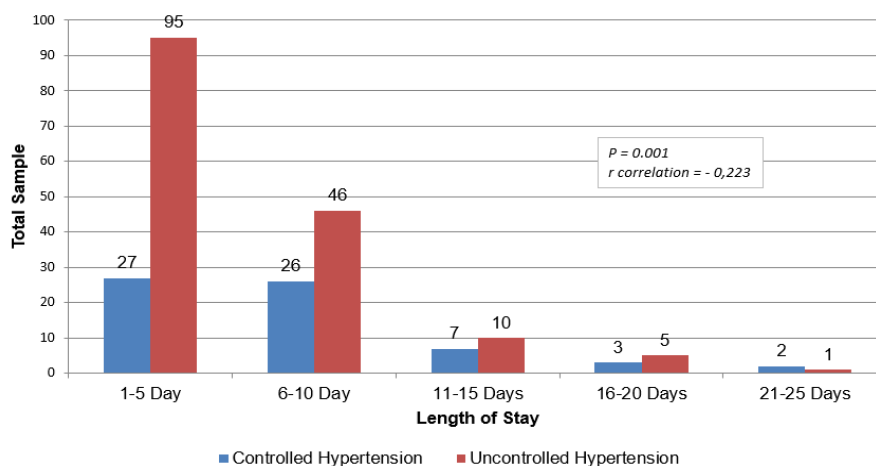
Characteristics	N (%), n=222	Average ± SD
Age (years old)		
≤ 17	0 (0.00)	
18-25	5 (2.25)	
26-35	28 (12.61)	
36-45	61 (27.48)	46.54 ± 10.09
46-55	94 (42.34)	
56-65	29 (13.06)	
≥ 66	5 (2.25)	
Gender		
Women	81 (36.49)	
Men	141 (63.51)	
Clinical symptoms		
Asymptomatic	156 (70.27)	
Mild symptoms	66 (29.73)	
Fever	14 (21.21)	
Cough	37 (56.06)	
Fatigue	4 (6.06)	
Anorexia	0 (0.00)	
Anosmia	8 (12.12)	
Congested	8 (12.12)	
Myalgia	2 (3.03)	
Sore throat	11 (16.6)	
Nasal congestion	10 (15.5)	
Headache	14 (21.21)	
Diarrhoea	5 (7.58)	
Nauseous/vomiting	5 (7.58)	
Hypertension category		
Controlled hypertension	65 (29.28)	
Uncontrolled hypertension	157 (70.72)	
Length of stay (days)		
1-5	122 (54.95)	
6-10	72 (32.43)	
11-15	17 (7.66)	
16-20	8 (3.60)	
21-25	3 (1.35)	

Table II: Correlation between the symptom category and length of stay

Length of stay (days)	Symptom category		p-value [†]	
	Asymptomatic (n = 156)	Mild symptoms (n = 66)		
1-5	95	27		
6-10	45	27		
11-15	9	8	0.030	
16-20	4	4		
21-25	3	0		
Differences in the median length of stay (days)		5	8	0.006

[†]Analysis of the relationship between the symptom categories and length of stay using the Chi-square test and analysis of the differences in median length of stay in patients with no symptom and mild symptom categories using the Mann-Whitney U median difference test

The correlation analysis between the type of hypertension and the length of stay using Spearman’s bivariate correlation rho test (Figure 1) showed a significant correlation with a p-value of 0.001. The Spearman correlation value is negative (-0.223), indicating an inversely variable relationship with a very low correlation.



*Analysis of the correlation between hypertension category and length of stay using bivariate correlation Spearman's rho test

Figure 1: Correlation between hypertension category and length of stay

Based on the observations of 222 patients, antihypertensive treatment was administered according to the patient's medication history, as the American College of Cardiology/American Heart Association (ACC/AHA) recommended. The research results (Table III) show that the most commonly used hypertension treatment was monotherapy of class CCB in 185 patients (83.33%) and combination therapy of CCB and ARB in 24 patients (10.81%).

Oral amlodipine (1x5 mg) was the most commonly used monotherapy in 114 patients (51.35%), while oral

amlodipine (1x10 mg) plus candesartan (1x8 mg) was the most widely used combination therapy in 18 patients (8.11%). When bivariate correlation was used to examine the relationship between the rate time of reduction in blood pressure and length of stay, Spearman's rho test (Table III) revealed a correlation with a *p*-value of 0.000 > 0.050. The Spearman correlation value is positive (0.992), indicating a strong correlation. The patient's average time reduction in blood pressure was 6.34 days.

Table III: Antihypertensive therapy profile

Regimen of antihypertensive therapy	Frequency	N (%), n=222	Average rate time of decrease in blood pressure (Days)	Average length of stay (days)	* <i>p</i> -value	* <i>r</i> correlation value
Monotherapy						
CCB						
Amlodipine 5 mg		114 (51.35)	5.96	5.99		
Amlodipine 10 mg	once daily	70 (31.53)	6.79	6.87		
Nifedipine 10 mg		1 (0.45)	9	9		
ARB						
Candesartan 8 mg	once daily	1 (0.45)	6	7		
Candesartan 16 mg		5 (2.25)	8	8		
Beta Blocker (BB)						
Bisoprolol 5 mg	once daily	1 (0.45)	9	9		
Combination therapy						
CCB						
Amlodipine 5 mg + Nifedipine 10 mg	once daily	1 (0.45)	6	6		
CCB + ARB						
Amlodipine 10 mg + Candesartan 8 mg		18 (8.11)	6.67	6.67	0.000	0.992
Amlodipine 10 mg + Candesartan 16 mg	once daily	5 (2.25)	6.60	6.60		
Nifedipine 10 mg + Candesartan 16 mg		1 (0.45)	8	8		
CCB + BB						
Amlodipine 10 mg + Bisoprolol 5 mg	once daily	2 (0.90)	5.50	5.50		
Amlodipine 5 mg + Bisoprolol 5 mg		1 (0.45)	7	7		
ARB + BB						
Candesartan 8 mg + Bisoprolol 5 mg	once daily	1 (0.45)	3	3		
CCB + ARB + BB						
Amlodipine 10 mg + Candesartan 8 mg + Nifedipine 10 mg + Bisoprolol 5 mg	once daily	1 (0.45)	2	2		
Total		222 (100.00)	6.34	6.39		

**p*-value and *r*-correlation value were analysed using bivariate correlation Spearman's rho test

Discussion

The essential patient characteristics in Table I show that COVID-19 patients with hypertension are dominated by men, with 141 patients (63.51%). Previous studies in COVID-19 sufferers with high blood pressure comorbid confirmed a men's presentation of 56.90% (Huang *et al.*, 2020). SARS-CoV and SARS-CoV-2 attack cells through the same receptor, ACE2. An early 2003 study of SARS-CoV patients found that high expression of the ACE2 receptor in specific organs correlated with organ failure, and this was demonstrated with relevant clinical parameters in SARS-CoV patients. Circulating ACE2 levels were higher in men than women and patients with diabetes and cardiovascular disease. (Jin *et al.*, 2020). Hypertension is more common in men than women in their working years because they have the hormone oestrogen, which can protect against high blood pressure and its complications. Oestrogen is responsible for increasing high-density lipoprotein (HDL) levels. At the onset of menopause, the prevalence of high blood pressure tends to be the same in women and men as oestrogen levels drop (Riyadina, 2019).

Data on the frequency distribution of symptoms and clinical conditions (Table I) show that the proportion of COVID-19 patients with hypertension was 70.27% in the asymptomatic category and 29.73% in the mild category. The most common symptom among patients in the mild category was cough (56.06%), followed by fever (21.21%) and headache (21.21%). These results were consistent with a study by Zhou and colleagues, which showed that the main symptoms of COVID-19 patients with hypertension were fever at 83.30% and cough at 72.20% (Zhou *et al.*, 2020). Regardless of age or other risk factors, patients with hypertension have a terrible prognosis, according to COVID-19. Still, no concrete evidence exists that this condition increases the chance of developing new infections or suffering adverse outcomes (Kario *et al.*, 2020).

Analysis of the relationship between symptom categories and length of stay using the Chi-square test (Table II) showed a significant relationship with a *p*-value of 0.030. The Mann-Whitney U median difference test was used to analyse differences in median length of stay between patients with asymptomatic and mild symptoms. The results were significant, with a *p*-value of 0.006. For COVID-19 patients with comorbid hypertension, the median stay was five days for those with asymptomatic symptoms and eight days for those with mild symptoms. Based on the two analyses, the group with symptoms had a longer stay than the group without symptoms. This is because the prevalence of bilateral pneumonia is

significantly lower than in the asymptomatic group (Wu *et al.*, 2020).

Analysis of the correlation between hypertension category and length of stay (Figure 1) showed a significant relationship based on the results of the bivariate correlation statistical tests of Spearman's rho test *p*-value of 0.001 with Spearman correlation value -0.223, which indicated that the variables have an opposite relationship with a very weak correlation. The hypertension category affects the length of stay. However, the higher the value of one variable will reduce the relationship with other variables. The study conducted by Chen and colleagues found that the hypertension category did not correlate with length of stay. Patients with managed and uncontrolled hypertension did not have significantly different stay durations. The significance value of the study was $0.066 > 0.05$ (Chen *et al.*, 2020). Uncontrolled hypertension can be caused, among other things, by not complying with medication, consuming excess salt, or consuming substances and drugs that can increase blood pressure or reduce the effect of antihypertensive drugs such as alcohol and non-steroidal anti-inflammatory drugs (NSAID) (Williams *et al.*, 2018). The study by Pristianty and colleagues showed that patient adherence to hypertension medication is influenced by the patient's knowledge and attitude (Pristianty *et al.*, 2023).

The treating clinician determined hypertension therapy in this study. Based on observations of 222 patients, antihypertensive therapy was given following the patient's previous treatment history, according to the American College of Cardiology/American Heart Association (ACC/AHA) recommendations. The data of the antihypertensive therapy profile in Table III shows that the most widely used high blood pressure remedy is monotherapy for the CCB class in 185 patients (83.33%) and combination therapy for the CCB + ARB class in 24 patients (10.81%). This aligns with the hypertension management algorithm (James *et al.*, 2014). Oral amlodipine (1x5 mg) was the most commonly used monotherapy in 114 patients (51.35%), while oral amlodipine (1x10 mg) plus candesartan (1x8 mg) was the most commonly used combination therapy in 18 patients (8.11%). A study by Yang *et al.* (2020) showed that hs-CRP ($P=0.049$) and procalcitonin ($P=0.008$) are reduced in COVID-19 patients with hypertensive comorbidities treated with ACEI/ARB. The parameters of the inflammatory markers were shown to increase significantly in patients receiving non-ACEI/ARB therapy (Yang *et al.*, 2020). Another study conducted by Zhang and colleagues showed that COVID-19 patients with hypertension comorbid who were treated with amlodipine had significantly lower mortality rates

(CFR) than non-amlodipine ($p = 0.037$) (Zhang *et al.*, 2020).

Data on the distribution of length of stay (Table III) showed that the average patient's total length of stay was 6.39 days. A study conducted at the Wuhan Fourth Hospital in China in COVID-19 patients with hypertension showed an average length of stay of 11.1 days (Zhou *et al.*, 2020). The mean blood pressure reduction rate for patients receiving oral amlodipine (1 x 5 mg) was 5.96 days. For patients receiving oral amlodipine (1 x 10 mg) plus candesartan (1 x 8 mg), it was 6.67 days. The analysis of the correlation between the rate time of decrease in blood pressure and the length of stay using bivariate correlation Spearman's rho test (Table III) was $0.000 < 0.050$. This is supported by the positive Spearman correlation (0.992), which shows a very strong correlation. The overall rate of decline in blood pressure in patients averaged 6.34 days. A study by Chen *et al.* showed that poor blood pressure control resulted in higher levels of hs-CRP and procalcitonin, enhanced inflammatory responses, and worse clinical outcomes (Chen *et al.*, 2020).

This study has limitations because the pathogenic mechanisms linking hypertension to the severity and prognosis of COVID-19 infection have not yet been investigated. Therefore, more research is required to determine how SARS-CoV-2 enters and infects human cells by interacting with the ACE2 receptor, which affects RAAS, one of the factors contributing to hypertension. The use of ACEIs and ARBs decreases ACE and increases ACE2 expression. Theoretically, this could be a vector for the entry and infection, leading to viral spread and worsening lung damage.

Conclusion

This study concludes that symptoms in COVID-19 patients with hypertension comorbid are often experienced as coughing, fever, and headache. Antihypertensive therapy in this study was following existing guidelines. The most widely used monotherapy is oral amlodipine (1x5 mg), and the combination therapy is oral amlodipine (1x10 mg) plus candesartan (1x8 mg) with mean blood pressure reduction rates of 5.96 and 6.67 days and mean length of stay was 5.99 and 6.67 days, respectively. The rate of decline in blood pressure was proportional to the length of stay, so hypertension is vital to control to support the improvement of the patient's clinical condition.

Acknowledgement

The authors thank Kogabwilhan II Indrapura Field Hospital Surabaya for providing the data needed to complete this study. This article was presented at the 2023 International Graduate Student Conference on Pharmaceutical Sciences.

Conflict of interest

The authors declare that they have no conflicts of interest with respect to this study and the publication.

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