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RESEARCH ARTICLE

Clinical use of antiviral, antibiotic and immunomodulatory drugs in hospitalized COVID-19 patients: a retrospective study in Bandung, Indonesia [version 1; peer review: 1 not approved]

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Abstract

Background: Evidence of highly effective repurposed drugs for coronavirus disease 2019 (COVID-19) is insufficient. However, empirical therapy using antiviral, antibiotic and immunomodulatory drugs is massive. Studies evaluating the clinical use of these drugs in Indonesia are sparse.

Methods: We performed a retrospective study using medical records of hospitalized COVID-19 patients from July 2020 to March 2021 in Bandung, Indonesia. Data were collected at relevant timelines: age, sex, comorbid condition, peripheral oxygen saturation (SpO₂), and hematology at admission; antiviral, antibiotic, and immunomodulator treatment during hospitalization; length of stay hospitalization (LOS) and death at discharge. Clinical use of the drug regimens included dose, frequency, and duration of therapy. The main outcome of hospitalization care was LOS and death.

Results: Out of 249 patients, 43.3% had a comorbid condition, 74.7% had non-severe COVID-19 (SpO₂ ≥ 90%), and almost all received antiviral or antibiotic agents. Remdesivir was the most frequent drug composing various antiviral regimens. Patients receiving a combination of remdesivir and favipiravir had lower SpO₂ compared to those receiving oseltamivir (p=0.01). The short LOS was associated with remdesivir alone (p=0.03), the combination of favipiravir and oseltamivir (p=0.01), and the combination of intravenous levofloxacin and ceftriaxone (p<0.0001). Immunomodulatory drugs (methylprednisolone, dexamethasone, tocilizumab) were used in 47.1% of patients with low SpO₂ (p=0.001). Its use was associated with

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prolonged LOS ($p=0.0043$). The increased risk of death in patients treated with the combination of remdesivir and favipiravir (OR 4.1; 95%CI 1.4-12.2), and immunomodulatory drugs (OR 6.2; 95%CI 1.7-23.3) was confounded by the baseline characteristics of older age, comorbid condition, SpO_2 level, and low lymphocyte number.

Conclusions: Some treatment regimens were associated with short LOS, but there were drug regimens which might increase the risk of death. Further study should control the clinical conditions of COVID-19 patients at admission to confirm the outcome of death following drug therapy.

Keywords

antibiotic, antiviral, COVID-19, immunomodulators, levofloxacin, remdesivir.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had caused at least 240 million cases of coronavirus disease 2019 (COVID-19) and more than 4.8 million deaths worldwide until 18 October 2021.¹ At that time, Indonesia has reported 4.2 million confirmed COVID-19 cases with over 140 thousand deaths.² The management of COVID-19 using repurposed drugs has been authorized since the beginning of the pandemic³ to rapidly control the mortality and morbidity of this new disease in the absence of evidence of clinical trial results.

Exploration on the effectiveness of repurposed drugs for COVID-19 in the first year of pandemic remains inconclusive. For example, a clinical trial on the most promising antiviral remdesivir showed its benefit on the clinical improvement at day 15.⁴ However, the interim report of the World Health Organization's (WHO) Solidarity trial showed the lack of benefit of remdesivir on the reduction of mortality and hospitalization duration.⁵ Similarly, the Indonesian national guideline for COVID-19^{6,7} recommends the antiviral favipiravir. However, this drug is not part of the recommendation from the WHO guideline based on the evidence from clinical trials evaluating remdesivir and favipiravir for COVID-19 therapy.⁸ The latest version of the WHO guidelines for COVID-19 therapy provides strong recommendation for systemic corticosteroid in severe and critical COVID-19, and conditional recommendation against remdesivir in hospitalized COVID-19.⁹ Corticosteroid and tocilizumab are drugs modulating the immune response that plays a critical role in the pathogenesis of severe COVID-19. As pneumonia is the main clinical manifestation of COVID-19, the use of antibiotics for COVID-19 patients regardless of the evidence of bacterial infection is concerning.¹⁰

The report on the pharmacological therapy of COVID-19 in Indonesia is not as extensive as that in other Asian countries with high cases of COVID-19, such as China and India. This retrospective study aimed to investigate the clinical use of antiviral, antibiotic and immunomodulatory agents in hospitalized COVID-19 patients during the first year of the pandemic. The treatment using these drugs were considered common based on the pathogenesis of infection and inflammation on COVID-19 disease. These drugs are also listed in the Indonesian national guideline for COVID-19.^{6,7} We also evaluated the outcome of length of stay (LOS) and death following hospitalization to understand the benefit of pharmacological therapy of antiviral, antibiotic and immunomodulators.

Methods

Study design

This study was conducted in two main hospitals affiliated with the Faculty of Medicine Universitas Islam Bandung, Indonesia. One of the hospitals was a private hospital located in the Eastern of Bandung City, whereas another hospital was a referral government hospital for the West Java Province area located in Bandung Suburb. We performed a retrospective study using medical records of patients who were hospitalized during the first year of the COVID-19 pandemic from July 2020 to March 2021. The inclusion criteria for the subjects of this study were ≥ 18 years old, had confirmed COVID-19 and had peripheral oxygen saturation (SpO_2) at admission. The minimum sample size of 172 patients was calculated to compare two independent means¹¹ using the standard deviation of LOS from a previous study.¹² The sample was collected based on a non-probability sampling procedure resulting in 249 patients. A confirmed COVID-19 patient was proven by a laboratory result for positive detection of the nucleic acid of SARS-CoV-2 virus using a reverse transcription-quantitative polymerase chain reaction (RT-qPCR) test from the nasopharyngeal and oropharyngeal sample. The severity of COVID-19 disease was categorized as severe ($\text{SpO}_2 < 90\%$) and non-severe ($\text{SpO}_2 \geq 90\%$).

The main antiviral drugs evaluated in this study were remdesivir, favipiravir, and oseltamivir. Azithromycin, levofloxacin, and ceftriaxone were the main antibiotics assessed. Immuno-modulators included methylprednisolone, dexamethasone, and tocilizumab. We evaluated the LOS and death as two main outcomes of therapy. An additional outcome evaluated was the use of a mechanical ventilator indicated by intensive care unit (ICU) admission. As the mortality in hospitalized COVID-19 was also associated with sociodemographic characteristics and laboratory result at admission,¹³ we also addressed these potential confounder factors.

Clinical data

The data on medical records were collected based on three relevant timelines. Baseline data at admission time were demographic characteristics (age, sex), comorbid disease (diabetes mellitus, hypertension, asthma, other conditions), SpO_2 measurement, and hematology results. Data during the hospitalization period were pharmacological therapy using antiviral, antibiotics, and immunomodulatory drugs. The outcome of therapy was evaluated at the end of hospitalization. To validate the evaluation of therapy, the subjects were excluded if the duration of hospitalization was shorter than three days regardless of the causes. This period is suggested for clinical evaluation of community-acquired pneumonia (CAP) in adults.¹⁴ This approach is to minimize the bias on data collection for evaluating the outcome of therapy.

Statistical methods

The numeric data was first analyzed for normality using the Kolmogorov-Smirnov test for further relevant parametric or non-parametric analysis. Statistically significant difference of SpO₂ or LOS between two groups of therapies was analyzed by Mann-Whitney test, unless otherwise stated, whereas for more than two groups Kruskal-Wallis with Dunn's multiple comparison test was used. The association of pharmacological therapy with the death was analyzed using Fisher's exact test. The screening for potential confounding factors that are comorbidity, age and laboratory results was analyzed by Fisher's exact, student t-test and Mann-Whitney, respectively. The difference was considered statistically significant if the p-value was less than 0.05. A multivariable logistic regression model was constructed for all variables reached p-value <0.25 in the screening to determine the odd ratio and identify confounding factors for the outcome of death. A confounding factor was defined as a variable that changed the odds ratio of the pharmacological therapy >10% after the adjustment for the relevant variable. The statistical analysis and data display was performed using **GraphPad Prism** V.8 software (La Jolla, CA). The logistic regression was performed using **SPSS** version 23 (Armonk, NY: IBM Corp).

Ethical considerations

The protocol of this study was approved by the Institutional Review Board and Health Research Ethics Committee of Al Islam Hospital No.001/KEPPIN-RSAI/02/2021. The data collection, management and storing ensured patient privacy.

Results

Patient characteristics at admission

The demographic and clinical characteristics of 249 patients are shown in **Table 1**.³⁶ Most of the patients were aged 40-60 years (54.2%) and categorized as having non-severe COVID-19 (74.7%). Slightly more patients were male (55.4%) than female (44.6%). Almost half of patients had comorbid conditions (43.3%) with hypertension (12.5%) and diabetes mellitus (9.2%) as the two most frequent single comorbidities.

Clinical use of antiviral, antibiotic and immunomodulatory drugs in COVID-19 patient

Pharmacotherapy of main drugs in the management of hospitalized confirmed COVID-19 patients is shown in **Table 2**. All patients received antiviral drugs and almost all patients were treated with antibiotic agents. Patients who were treated

Table 1. Demographic and clinical characteristics of patients at admission. COVID-19 = coronavirus disease 2019, SpO₂ = peripheral oxygen saturation.

Characteristics	Number (%) (N = 249)
Sex	
Male	138 (55.4)
Female	111 (44.6)
Age (years)	
>60	70 (28.1)
40-60	135 (54.2)
<40	44 (17.5)
Comorbid condition	
No comorbidities	141 (56.6)
Comorbid condition	108 (43.3)
Single comorbidity	85 (34.1)
Diabetes mellitus	23 (9.2)
Hypertension	31 (12.5)
Asthma	1 (0.4)
Others	30 (12.1)
Double comorbidity	23 (9.2)
Severity of COVID-19	
Non-Severe (SpO ₂ ≥ 90%)	186 (74.7)
Severe (SpO ₂ < 90%)	63 (25.3)

Table 2. Pharmacological therapy of antiviral, antibiotic and immunomodulatory agents during hospitalization of coronavirus disease 2019 (COVID-19) patients.

Drugs	Number (%) (N=249)	Route	Doses (mg)	Freq/day	Duration of therapy (day) Mean (min-max)
Antiviral					
<i>Single drug</i>	138(55.4)				
Remdesivir (RDV)	91 (36.3)	IV	100 ^a	1	7 (1-13)
Favipiravir (FAV)	32 (12.9)	Oral/IV	600 ^b	2	8 (1-14)
Oseltamivir (OST)	15 (6)	Oral	75	2	7 (1-14)
<i>Double combination</i>	84 (33.7)				
RDV + FAV	55 (22.1)	IV+Oral/IV	100 ^a + 600 ^b	1 + 2	7(1-14) + 6(1-21)
RDV + OST	15 (6)	IV + Oral	100 ^a + 75	1 + 2	8(5-11) + 1(1-2)
FAV + OST	14 (5.6)	Oral + Oral	600 ^b + 75	2 + 2	5 (1-6) + 2 (1-7)
<i>Triple combination</i>					
RDV + FAV + OST	6 (2.4)	IV+Oral+ Oral	100 ^a + 600 ^b + 75		7(4-12) + 5(2-6) + 3(1-7)
<i>Others</i>	15 (6)				
Lopinavir/Ritonavir	7 (2.8)		400/100	2	6 (3-10)
Isoprinosine	14 (5.6)	Oral	1000-3000	4	11 (7-16)
Antibiotics					
<i>Single drug</i>	20 (8)				
Azithromycin (AZI)	9 (3.6)	Oral	500	1	10.8 (8-15)
Levofloxacin (LVX)	9 (3.6)	IV	500/750	1	5.6 (1-12)
Ceftriaxone (CRO)	2 (0.8)	IV	1000-3000	sd ^c /1	5.5 (1-10)
<i>Double combination</i>	218(86.9)				
AZI + LVX	41 (16.5)	Oral+Oral/IV	500 + 750	1 + 1	10.4 (5-16) + 9 (1-14)
AZI + CRO	1 (0.4)	Oral + IV	500 + 1000	1 + 3	19 + 8
LVX + CRO	179 (71.9)	IV + IV	500/750 + 2000	1 + sd ^c /1	6.1 (1-21) + 4.2 (1-19)
<i>Triple combination</i>					
AZI+ LVX + CRO	4 (1.6)	Oral+ IV + IV	500 + 750 + 1000	1 + 1 + 3	12(5-21) + 7.3(1-12) + 8.3(6-10)
<i>Others</i>	1 (0.4)				
Amoxicillin	1 (0.4)	Oral	500	3	5
<i>No Antibiotics</i>	3 (1.2)	NA	NA	NA	NA
Immuno-modulator					
<i>Single drug</i>	91(36.3)				
Dexamethasone (DEX)	29 (11.6)	IV	1-6	1-3	2.2 (1-10)
Methylprednisolone (MP)	60 (24.1)	IV/oral	6.25/125	1/3	2.2 (1-13)
Tocilizumab (TCZ)	2 (0.8)	IV	200	1	1
<i>Double combination</i>	5 (2)				
MP + DEX	2 (0.8)	Oral/IV + IV	4/62.5 + 5	2/1 + 5	4.3 (1-11) + 2 (1-4)
MP + TCZ	3 (1.2)	IV + IV	6.25/125+200	1	1 (1)+4.7(1-9)
<i>Triple combination</i>					
MP + DEX + TCZ	1 (0.4)	IV + IV + IV	125 +5 + 400	1+2+1	1 + 2 + 2
<i>No immuno-modulator</i>	152(52.9)	NA	NA	NA	NA

IV: intravenous, NA: not applicable.

^aloading dose: 200 mg.^bloading dose: 1600 mg.^csd: single dose.

using antiviral drugs were more likely to receive a single (55.4%) or double combination (33.7%) of drugs. Remdesivir was the most frequent drug used in antiviral regimens for single drug (36.3%), and double combination with favipiravir (22.1%) or with oseltamivir (6%). A triple combination of these drugs was prescribed to a few patients (2.4%). Remdesivir was used via the intravenous (IV) route with a loading dose of 200 mg and maintenance dose of 100 mg once daily. Favipiravir was used orally or IV with a loading dose 1600 mg and maintenance dose of 600 mg twice

daily. Oseltamivir was given orally with the dose 75 mg twice daily. The same dose for these drugs was used in different regimens of the drug combination. The duration of antiviral therapy varied from 1 day to 21 days at the most prolonged period. The mean duration of remdesivir and favipiravir was about 7 days in various regimens. The mean duration of oseltamivir as a single drug therapy was 7 days, however the duration was shorter in the combination regimens.

Antibiotic therapy occurred in most patients (86.9%) using a regimen consisting of two drugs. A combination of levofloxacin and ceftriaxone was the main regimen given to 71.9% of patients (Table 1). Levofloxacin and ceftriaxone were delivered intravenously once daily, and ceftriaxone was often used as a single dose. Levofloxacin had a standard dose of 500 mg with some patients receiving 750 mg, whereas ceftriaxone had the common dose of 2000 mg. There were 16.5% of patients receiving a combination of levofloxacin and azithromycin in which the oral route favoured. Azithromycin 500 mg once daily was the main oral antibiotic for COVID-19 in various regimens and had the longest mean of duration therapy in the single (10.9 days), double (10.7 days) and triple (12 days) combinations. Thus, the main antibiotic therapy was the combination of IV levofloxacin and ceftriaxone, while azithromycin was the main antibiotic for oral delivery.

Fewer than half (47.1%) of patients were treated with immunomodulatory drugs which were mainly used in a single regimen (36.3%) (Table 1). Methylprednisolone was the most frequent (24.1%) immunomodulatory drug used, followed by dexamethasone (11.6%). The mean duration of immunomodulatory drugs (2-4 days) was generally shorter than that of the previous antiviral and antibiotic therapy.

Drug regimens indicated by baseline peripheral oxygen saturation

Peripheral oxygen saturation is one of the indications of drug therapy in the Indonesian guideline of COVID-19 management. We evaluated whether different combinations of antiviral and antibiotic drugs or immunomodulatory

Figure 1. Peripheral oxygen saturation (SpO₂) at the initial pharmacological therapy. (A) Baseline SpO₂ and the antiviral therapy using remdesivir, favipiravir, and oseltamivir in the various drug combinations. (B) Initial SpO₂ and antibiotic combination of relevant azithromycin, levofloxacin, and ceftriaxone. (C) Immunomodulatory therapy using methylprednisolone, dexamethasone, and tocilizumab. Data are presented as median and interquartile range (IQR). Statistical differences were analyzed by Kruskal-Wallis and Dunn's multiple comparisons (A, B) or Mann-Whitney test (C).

therapy were associated with the baseline of SpO₂ recorded at admission (Figure 1). The level of SpO₂ in the group of patients receiving the double combination of remdesivir and favipiravir or other antivirals (lopinavir/ritonavir and isoprinosine) was significantly lower than that when receiving oseltamivir alone ($p = 0.01$ or $p = 0.034$, respectively) (Figure 1A). Among the antibiotic drug regimens, Figure 1B shows that patients receiving the combination of levofloxacin and ceftriaxone had higher levels of SpO₂ than those receiving combination of azithromycin and levofloxacin ($p = 0.019$). However, few patients with a very low level of SpO₂ were found in both of groups as shown by plots below 80% of SpO₂ in Figure 1B. In contrast, the treatment of immunomodulatory drugs was very likely indicated by the level of SpO₂ as shown by Figure 1C that the patients receiving immune-modulators were strongly associated with the lower level of SpO₂ ($p = 0.001$) compared to those not treated with immune-modulators (Figure 1C).

The outcome of hospitalization following regimens of pharmacology therapy

The efficacy of pharmacological therapy in hospitalized COVID-19 patients was evaluated by the LOS and the death as the main outcome, and the use of mechanical ventilator as the additional outcome. Out of 249 patients in this study, there were 22 deaths (8.8%) and three patients required mechanical ventilators (Table 3). The median of LOS from all patients was 7 days with interquartile range (IQR) 5-10 days. Patients who were treated with remdesivir or the combination of favipiravir and oseltamivir had a shorter LOS compared to those who were treated with the other antiviral drugs ($p = 0.03$ and $p = 0.01$, respectively). However, treatment with the combination of remdesivir and favipiravir was associated with the deaths ($p < 0.0001$).

Table 3. The outcome of hospitalization following therapy regimen using antiviral, antibiotic and immunomodulatory agents. SD = standard deviation; IQR = interquartile range.

Drugs	Length of stay (days)		Death		Mechanical ventilator
	Mean (SD)/ Median (IQR)	p-value	n	p-value	
All (N=249)	7 (5-10)		22 (8.8%)		3
Antiviral					
Remdesivir (RDV) (n = 91)	5 (5-9)	0.03 ^{1,a}	7		1
Favipiravir (FAV) (n = 32)	8.7 (3.7)		1		0
Oseltamivir (OST) (n = 17)	7.1 (3.3)		0		0
RDV + FAV (n = 55)	9 (5-10)		13	<0.0001 ^b	2
RDV + OST (n = 15)	7.6 (2.9)		0		0
FAV + OST (n = 14)	5.5 (1.6)	0.01 ^{1,a}	0		0
RDV+FAV+OST (n = 6)	9.8 (5.8)		0		0
Others (n = 21)	9.8 (4.2)		1		0
Antibiotic					
Azithromycin (AZI) (n = 9)	10 (2.3)		0		0
Ceftriaxone (CRO)(n = 2)	7.5 (6-9)		0		0
Levofloxacin (LVX)(n = 9)	8 (2.9)		0		0
AZI + LVX (n = 41)	11 (3.4)		1		1
LVX + CRO (n = 179)	5 (5-9)	<0.0001 ^{2,a}	21	0.0018 ^b	2
AZI + CRO (n = 1)	20		0		0
AZI + LVX + CRO (n = 4)	12 (9.5-18)		0		0
No Antibiotics (n = 3)	6 (4-9)		0		0
Immunomodulator					
Immuno-modulator (n = 97)	9 (5-10)	0.0043 ^c	19	<0.0001 ^b	3
No Immuno-modulator (n = 152)	6 (5-9)		3		0

¹ versus others; ² versus AZI + LVX; p value was analyzed by ^a Kruskal-Wallis with Dunn's multiple comparisons or ^b Fisher's Exact or ^c Mann-Whitney test.

Patients who were treated with the combination of levofloxacin and ceftriaxone had significantly shorter LOS ($p < 0.0001$) compared to those receiving the combination of azithromycin and levofloxacin. However, the combination of levofloxacin and ceftriaxone was also associated with the outcome of death ($p = 0.0018$). The use of immunomodulatory drugs was associated with a longer LOS ($p = 0.0043$) and death ($p < 0.0001$) compared to the patients who were untreated with immunomodulatory drugs. Thus, regimen therapies associated with shorter LOS were remdesivir alone, the combination of favipiravir and oseltamivir, and the combination of levofloxacin and ceftriaxone. However, the outcome of death was associated with the combination of remdesivir and favipiravir, the combination of levofloxacin and ceftriaxone, and the immunomodulatory drugs.

The outcome of death was affected by the baseline clinical characteristics

Table 4 showed the baseline characteristics of patients that were statistically associated with death. Compared to patients who were discharged alive, death patients had older age ($p = 0.0115$), comorbid conditions (0.0058), lower lymphocyte number ($p = 0.0061$) and higher neutrophil to lymphocyte ratio (NLR) ($p = 0.004$). To note, the group of discharged alive had no data of hematology (lymphocyte, thrombocyte, and NLR) for seven patients.¹⁵ This screening suggests baseline clinical characteristics were potential confounding factors for the outcome of death following hospitalization.

To confirm the confounding factors of pharmacological therapy, we performed multivariable analysis for the outcome of death but not for the LOS, because the data of LOS was not normally distributed. Patients treated with the combination of

Table 4. Clinical characteristics at admission associated with the outcome of death. SD=standard deviation; SpO₂ = peripheral oxygen saturation; IQR = interquartile range.

Characteristics	Death (n = 22)	Discharged alive (n = 227)	p-value
Age (year) mean (SD)	59.4 (10.2)	51.7 (13.8)	0.0115 ^a
Sex, n (%)			0.115 ^b
Female	6 (5.4)	105 (94.6)	
Male	16 (11.6)	122 (8.4)	
Comorbid condition, n (%)			0.0058 ^{a,b}
No comorbid	6 (4.3)	135 (95.7)	
Comorbid	16 (14.8)	92 (85.2)	
SpO ₂ (%), median (IQR)	90.5 (88-93.5)	94 (90-97)	0.0285 ^{a,c}
Lymphocyte (10 ⁹ /L), median (IQR)	1.1 (0.7-1.2)	1.3 (0.9-1.8)	0.0061 ^{a,c}
Thrombocyte (10 ⁹ /L), median (IQR)	218 (144-261)	226 (178-289)	0.4083 ^c
Neutrophil to Lymphocyte ratio (NLR) median (IQR)	6.2 (3.9-10.3)	3.7 (2.4-6.3)	0.004 ^{a,c}

^aStudent t-test.

^bFisher's Exact test.

^cMann-Whitney test.

* $p < 0.05$.

** $p < 0.01$.

Table 5. Multivariable analysis adjusted on clinical characteristics at admission. SpO₂ = peripheral oxygen saturation.

Variable	Odds ratio	(95% CI)	p value
Remdesivir+Favipiravir (RDV+FAV)	4.1	1.4-12.2	0.01
Levofloxacin+Ceftriaxon (LVX+CRO)	2.96	0.4-20.5	0.271
Immunomodulatory drugs	6.2	1.7-23.3	0.007
Age	1.1	0.9-1.1	0.06
Sex	1.6	0.5-4.7	0.06
Comorbid	1.9	0.6-5.9	0.248
SpO ₂	0.9	0.9-1	0.411
Lymphocyte count (number)	1	1-1	0.6

remdesivir and favipiravir or treated with immunomodulatory drugs had increased risk of death (odds ratio [OR] 4.1; 95% confidence interval [CI] 1.4–12.1 or OR 6.3; 95% CI 1.7–23.5, respectively) before adjustment. This remained significant after adjustment for age, sex, gender, comorbid, and lymphocyte count (OR 4.1; 95% CI 1.4–12.2 or OR 6.2; 95% CI 1.7–23.3, respectively) (Table 5). However, all the clinical characteristics at admission, except for the NLR, were confounding factors for the risk of death following therapy using combination of remdesivir and favipiravir or immunomodulatory drugs.

Discussion

Our study evaluated the clinical use of antiviral, antibiotic and immunomodulatory drugs for hospitalized patients confirmed with COVID-19. We found that antivirals and antibiotics were the standard treatment delivered to almost all the patients, whereas the immunomodulator treatment was an additional therapy. We assessed the clinical use of these drugs with SpO₂ for the indication of therapy, and with LOS and death for the outcome of therapy.

The results showed that remdesivir is the primary drug composing various antiviral regimens. Remdesivir was recommended conditionally for COVID-19 patients who required oxygen supplementation¹⁶ and severe COVID-19 patients defined by a low level of SpO₂.⁸ However, treatment with remdesivir alone in our study did not correlate significantly with the level of SpO₂ compared to favipiravir or oseltamivir. Patients with more severe COVID-19 were more likely to receive the combination of remdesivir and favipiravir or other antiviral drugs (lopinavir/ritonavir or isoprinosine). On the other hand, oseltamivir seems to be the first antiviral choice for the non-severe COVID-19. The initial SpO₂ was not the main indication for the choice of the rest antiviral regimens.

Remdesivir in this study was used intravenously with a loading dose of 200 mg followed by 100 mg/day for a mean duration of 7 days. This dose provides an effective conversion of its metabolite into intracellular adenosine triphosphate analogue that selectively inhibits viral RNA polymerase.¹⁷ The same dose of remdesivir was used in other studies,^{5,18,19} however, some studies used remdesivir for 5 days^{18,20} or 10 days.^{18,19} The 5-day remdesivir was associated with better outcome at day 11,¹⁸ but another study found no differences.²⁰ A meta-analysis revealed that the 5-day remdesivir provided similar benefit but fewer adverse events than the 10 day.²¹ Favipiravir in our study was given with a loading dose of 1200 mg and a daily dose of 600 mg. This dose was half of that used in several studies on COVID-19,¹⁶ but the same dose as a recent study evaluating favipiravir in recurrent COVID-19.²² Favipiravir (Avigan®) selectively inhibits viral RNA polymerases of influenza viruses and has a broad-spectrum antiviral activity for neglected and emerging RNA viruses.^{23,24} Treatment with favipiravir alone was considered safe and effective to shorten viral shedding in recurrent positive COVID-19 patients.²² Few studies showed the benefit of combined therapy of favipiravir with methylprednisolone.¹⁶ Combination of remdesivir and favipiravir was the most common antiviral regimen in our study, however, this was not available on the list of drug therapy used in clinical trials of COVID-19.^{16,25} Therefore, the safety and the efficacy of the combination of remdesivir and favipiravir is unknown. Indeed, clinical judgement to guide management decisions is part of WHO's conditional recommendation.⁹ Further studies should evaluate clinical symptoms for comprehensive evidence for clinical judgement.

The empiric antimicrobial therapy for COVID-19 patients in our study was very high (98.2%). This proportion is higher than that reported in the United Kingdom (UK) (85.2%),²⁶ Netherland (60.1%),¹⁰ and Surabaya Indonesia (75.3%).²⁷ In fact, microbiological testing showed that the bacterial infection and co-infection among hospitalized COVID-19 patients was infrequent.¹⁰ Several studies reported 1.25 % of 925 patients,¹⁰ 19.7% of 218 patients,²⁷ 1107 of 48902 patients were confirmed bacterial co-infection. In COVID-19 patients in the UK, the most frequent etiology of respiratory co-infection was *Staphylococcus aureus* and *Haemophilus influenza*, of secondary respiratory infection was Enterobacteriaceae and *S aureus*, and in bloodstream infection was *Escherichia coli* and *S aureus*.²⁶ In the Indonesian setting, Gram-negative was the common causative agents of bacterial infection in COVID-19 patients.²⁷ These findings suggested that the choice for empirical antimicrobial should be treated for Gram-negative bacteria and *S aureus* until the results of culture available.

Our study showed that IV levofloxacin (500/750 mg), IV ceftriaxone (200 mg), and oral azithromycin (500 mg) were the common antibiotic therapy used in COVID-19 patients. The combination of intravenous levofloxacin and ceftriaxone was the most frequent antibiotic regimen prescribed. The choice of levofloxacin for COVID-19 patients is probably because fluoroquinolone antibiotic has a broad-spectrum activity. Fluoroquinolone antibiotic is used in severe CAP, and has the potency of antiviral and immune-modulator.²⁸ Ceftriaxone is a broad-spectrum beta-lactam antibiotic that has been one of the choices for treating community-onset pneumonia (COP). The dose of 1000 mg has a similar cure rate to 2000 mg.²⁹ Azithromycin is a macrolide antibiotic that is effective against Gram-positive, Gram-negative, and atypical bacteria. It has primarily been used as a treatment for upper and lower respiratory infection with its potential application for COVID-19 due to its effect of antiviral and immune-modulator.³⁰ A systematic review and meta-analysis study reported the prevalence of antibiotic use in COVID-19 patients was 24.5% azithromycin, 10% fluoroquinolone, and 9%

ceftriaxone.³¹ However, the study found the lack of data on the specific indication and specific name antibacterial agents. The standard broad-spectrum antibiotics in our study were not supported by the type of bacteria found in most studies.^{26,27,31} However, our study has added value in providing the name of antibacterial agents used.

The latest version of living WHO guideline recommends both corticosteroid and IL-6 receptor blocker (tocilizumab) for severe and critical COVID-19 patients.⁹ Our study found that patients who were treated with immunomodulatory drugs (methylprednisolone, dexamethasone, and tocilizumab) had a significantly lower level of SpO₂ compared to those who were untreated with these drugs ($p = 0.001$). Systemic corticosteroid such as 6 mg of oral or intravenous dexamethasone or 50 mg of intravenous hydrocortisone was strongly recommended for severe and critical COVID-19, but not for the non-severe COVID-19 because of the low certainty evidence on the increased risk of death.³² Similarly, the RECOVERY clinical trial showed the efficacy of dexamethasone on reducing the incidence of death was for the severe and critical, but not on the non-severe COVID-19.³³ Interestingly, in our study, the use of immunomodulators was associated with prolonged LOS ($p = 0.0043$) and a higher number of deaths ($p < 0.0001$) compared to the non-immunomodulatory drug user. Thus, the treatment of more severe COVID-19 patients with immunomodulatory drugs did not improve the outcome.

Our study evaluated the LOS and death as the outcome for clinical use of antiviral, antibiotic, and immunomodulatory therapy. Our study found that remdesivir alone was associated with shorter LOS than therapy using other antiviral drugs (lopinavir/ritonavir or isoprinosine). This is in line with a recent review updating the results of randomized clinical trials (RCT) on antiviral agents which showed that remdesivir could increase clinical improvement but lacked benefit on preventing death.²⁵ A study in Surabaya reported that COVID-19 patients confirmed with bacterial infection had longer LOS and higher mortality than those without bacterial infection.²⁷ However, the study did not evaluate the outcome of antibiotic therapy as we did. Multivariable analysis in our study found concerning safety issues for two regimen therapies. Patients who were treated with the combination of remdesivir and favipiravir had a four times higher risk of death compared to those receiving antiviral drugs other than this regimen. Similarly, patients treated with immunomodulatory drugs had a six times higher risk of death compared to those untreated with immune-modulators. However, several baseline clinical characteristics including age, gender, sex, comorbid condition, SpO₂ level, and lymphocyte contributed to this risk and became confounding factors. It has been known from the beginning of COVID-19 pandemic that older age and comorbid disease, in particular hypertension and diabetes mellitus, were associated with higher death rate.³⁴ Lower lymphocyte count was also associated with the severity of COVID-19.^{27,35} Further confirmation studies should control the baseline clinical characteristics of COVID-19 patients to validate the increased risk of death following the treatment with the combination of remdesivir and favipiravir or immunomodulatory drugs.

This study has several limitations. The non-probability sampling may affect the ability to generalize of the result to a broader population. Our study did not include data on the clinical symptoms of COVID-19 patients and the microbiological testing that would provide more comprehensive clinical judgment for antiviral and antibiotic therapy. However, to our understanding, this is among the first retrospective study reporting the details on the specific name of drugs and drug combination of antiviral and antibiotic for COVID-19 patients. Further prospective study to ensure the drug interaction and safety profile of combination drug regimens is warranted.

Conclusions

Clinical use of antiviral drugs and antibiotics in our study were very likely the standard therapy applied to almost all hospitalized COVID-19 patients. On the other hand, the treatment of COVID-19 patients using the immunomodulatory drugs was an additional therapy. The most common antiviral regimen was the combination of remdesivir and favipiravir, whereas the most frequent antibiotic regimen was the combination of levofloxacin and ceftriaxone. Treatment of hospitalized COVID-19 with remdesivir alone, the combination of favipiravir and oseltamivir, and the combination of levofloxacin and ceftriaxone was associated with short LOS. There was increased risk of death in patients treated with the combination of remdesivir and favipiravir and the immunomodulatory drugs. However, clinical characteristics at admission including age, sex, comorbid condition, SpO₂ level, and lymphocyte count contributed to this risk.

Data availability

Underlying data

Figshare: Clinical use of antiviral, antibiotic and immunomodulatory drugs in hospitalized COVID-19 patients: a retrospective study in Bandung Indonesia.

<https://doi.org/10.6084/m9.figshare.16530615>.³⁶

This project contains the following underlying data:

- Clinical characteristics, therapy of antiviral, antibiotic and immunomodulatory drugs, hematology results for all patients

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Harapan Harapan

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In this article, authors reporting the use of antiviral, antibiotic and immunomodulatory drugs and the effects on the outcomes (LOS and mortality) among hospitalized COVID-19 patients in Bandung. Although the number of the patients is relatively small the information are important in particular with limited data from Indonesia.

Abstract

I have some suggestions to improve the article: I cannot see the objective in the Abstract section.

Abstract: " Patients receiving a combination of remdesivir and favipiravir had lower SpO₂ compared to those receiving oseltamivir (p=0.01)." Was it compared to oseltamivir alone?

"The short LOS was associated with remdesivir alone (p=0.03), the combination of favipiravir and oseltamivir (p=0.01), and the combination of intravenous levofloxacin and ceftriaxone (p<0.0001)." This statement should have comparison in order to able to understand this text correctly: treatment with remdesivir had short LOS compared to what?

"Immunomodulatory drugs (methylprednisolone, dexamethasone, tocilizumab) were used in 47.1% of patients with low SpO₂ (p=0.001)" This is unclear. The use of immunomodulatory drugs associated with low SpO₂? I think this is only the nature of the data where the severe COVID-19 were treated with dexamethasone for example. This is similar with "Its use was associated with prolonged LOS (p=0.0043)."

"The increased risk of death in patients treated with the combination of remdesivir and favipiravir (OR 4.1;95%CI 1.4-12.2), and immunomodulatory drugs (OR 6.2; 95%CI 1.7- 23.3) was confounded by the baseline characteristics of older age, comorbid condition, SpO₂ level, and low lymphocyte number." This text indicates that the treatment with remdesivir and favipiravir or immunomodulatory drugs increased the mortality of the patients. Such interpretation might not be true.

In short I believe authors should re-write the manuscript and interpret the findings very carefully.

Introduction

"We also evaluated the outcome of length of stay (LOS) and death following hospitalization" I think the better way is "We also evaluated the length of stay (LOS) and the outcome of COVID-19 following hospitalization..." This because the authors assessed both outcomes of COVID-19 (death and survival).

Methods

Statistical methods

There is no consistency between the objective and the analysis that was conducted.

"Statistically significant difference of SpO2 or LOS between two groups of therapies was analyzed by Mann-Whitney test, unless otherwise stated, whereas for more than two groups Kruskal-Wallis with Dunn's multiple comparison test was used." Sp.O2 (or severity of COVID-19) was not mentioned as the outcome in this study.

Authors did not adjust their analyses based on severity of the disease (or did sub-group analysis based on diseases severity) and this could misleading the interpretation of the study. Authors should do this otherwise the findings might not be genuine.

Results

Table 1, the abbreviation should be on the bottom of the table.

Table 2. Such significant variations of therapy duration could cause significant bias of the finding. I am afraid the finding could be misleading and this potentially have consequence on COVID-19 treatment.

Drug regimens indicated by baseline peripheral oxygen saturation

"We evaluated whether different combinations of antiviral and antibiotic drugs or immunomodulatory therapy were associated with the baseline of SpO2 recorded at admission".

This analysis is misleading. The authors measured the SpO2 at admission (method) and here authors assessed the association with the treatment of antiviral and antibiotic drugs or immunomodulatory that given later during the hospitalisation and concluded "The level of SpO2 in the group of patients receiving the double combination of remdesivir and favipiravir or other antivirals (lopinavir/ritonavir and isoprinosine) was significantly lower than that when receiving oseltamivir alone ($p = 0.01$ or $p = 0.034$, respectively)" I am afraid this is interpretation is not appropriate: how have authors assessed that SpO2 was associated with the treatments that were given later during the treatment.

Table 3. The positions of the p-values are confusing. The position of the p-value should be on the

first row such $<0.0001^b$ should be on on row with "Antiviral" if this for who whole group. The p-values on LOS are consuming either. Why only some have p-values. If the p-value is not available due to unable to be calculated please indicate as NA or something that is easy to understand not blank. Also the p-value should be consistent (preference 0.000 if less write <0.001 . Please do not mix the p-values 0.03, 0.01, 0.0043 (Table 3). This is true for all tables. The last column "Mechanical ventilator" is confusing, why is this column here. This is one of my major concern.

Table 4. Why there is no p-value on Sex?

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology and Public Health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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