Length of hospital stay and Oseltamivir in mild or moderate degree COVID-19 patients in North Sumatra, Indonesia.

ABSTRACT

Background Coronavirus disease 2019 is caused by a new strain of corona virus that affect the human respiratory tract.
Aims: The aim of the study is to retrogressively review the use of antivirals on COVID-19 patients on their length of hospital stay (LoS) with mild and moderate degree of symptoms.
Study design: This cross-sectional study used medical records of confirmed COVID-19 patients, hospitalized, and achieved recovery during May-November 2020.
Place and Duration of Study: Data were collected retrospectively at a General Hospital, Deli Serdang, North Sumatera, Indonesia.
Methodology: Convenient sampling technique was used to select 185 patient's results who met the inclusion and exclusion criteria.
Results: The result showed that Oseltamivir was the only antiviral agent prescribed for COVID-19 patients. Oseltamivir was given to 80% of the patients and no antiviral agents for the rest 20%. The median LoS of COVID-19 patients with Oseltamivir was 11 days (ranged 2-34 days), whereas of those without antiviral agent was 12 days (ranged 4-29 days) at p = 0.049. Also, there were significant differences observed in group of mild and moderate degree with number of symptoms, i.e. less symptoms associated with less length of hospital stay (adjusted p=0.0003). In COVID-19 patients group with mild degree and one symptom, again, Oseltamivir treatment had shorter LoS (median 5, ranged 3-9 days) than those not on Oseltamivir treatment (median 12, ranged 6-20 days) at p = 0.0725. In moderate degree of COVID-19 patients with one symptom who were treated with Oseltamivir, LOS shortened (median 5 days) when compared to those without oseltamivir (median 12 days) (p= 0.0342).
Conclusion: In this study, the administration of oseltamivir was observed to shorten the length of stay of COVID-19 patients in the hospital.

Keywords: COVID-19; Antiviral; Oseltamivir; Length of Stay; Indonesia

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a new strain of corona virus that acutely infects the human respiratory tract [1]. Based on the clinical spectrum, COVID-19 patients are classified into several levels, namely: asymptomatic, mild, moderate, severe, very severe or critical illness [2, 3]. Despite no specific treatment to treat COVID-19 [4], recommendation on therapeutics were described in national and international guidelines, including antivirals for those with mild and moderate degrees [5-7]. Mild-degree patients have clinical findings in the form of mild clinical symptoms or lower or upper respiratory tract infections while moderate-grade patients are patients with lobar or multilobar pneumonia with or without the need for supplemental oxygen, or are refractory to initial treatment [2].

Treatment is one of the factors that affect the length of stay in the hospital. Length of hospital stay (LoS) is one of the important indicators of medical services used to assess the efficiency of hospital management, quality of patient care, and functional evaluation or evaluation of hospital management/administrators [8]. There is limited publication whether antivirals used in COVID-19 cases reducing the length of stay of patients in a hospital. Decreased length of stay has been associated with a reduced risk of opportunistic infections and treatment side effects, as well as improved treatment outcomes and lower mortality rates [8].

This study looked in a real setting whether the length of hospital stay for mild to moderate COVID-19 patients related to the type of antiviral used. The present study was conducted specifically in Deli Serdang Regency, North Sumatra, Indonesia. The hospital chosen was one of public hospital run by the government of Indonesia and served as one of referral health facilities for COVID-19 patients outside Java. Previous report on the use of drugs for COVID-19 in Indonesia, not specifically addressing length of hospital stay, was conducted in a private hospital in Jakarta, Java [9]. As comparison, as of July 2021, Jakarta represents the highest incidence of total ~ 2,615,529 cases for COVID-19, i.e.~26. 2%, whereas North Sumatra ~1.5% [10]. Since publication of the report, there were several changes on guidelines especially on recommendations, access and availability of antivirals for COVID-19 [6, 7]. The most current guideline released by Indonesian Asssociation of Internist in 2022 stated that the antivirals recommended for mild to moderate degrees of COVID-19 are Favipiravir, Molnupiravir, Nirmatrelvir/Ritonavir, and Remdesivir [7]. However, the present study was conducted prior 2022, when the specific antivirals and their clinical efficacy for SARS-COV-2 were less clear. The COVID-19 Management Guideline used during this study recommended Oseltamivir, Favipiravir, Remdesivir, and Lopinavir/Ritonavir as antivirals used for mild to moderate degrees of COVID-19.

2. MATERIAL AND METHODS

2.1 Study design and setting

The present cross-sectional study used medical records of confirmed COVID-19 patients by PCR, hospitalized, and achieved recovery during May-November 2020. Data were collected retrospectively at a General Hospital, Deli Serdang, North Sumatera, Indonesia. Total sampling was used to select patients who met the inclusion and exclusion criteria, i.e., age was 18-year-old or more; diagnosed as mild or moderate degrees completed with PCR and other relevant laboratory and clinical findings; with oseltamivir, favipiravir, lopinavir-ritonavir and/or remdesivir or without any antiviral agent. Patients having comorbid HIV/AIDS or cancer and pregnant patients were excluded from the study.

Ethical approval was sought from and granted by the Ethical Medical Committee of the Faculty of Medicine of Universitas Sumatera Utara, Indonesia (Approval Letter 220/KEP/USU/2021).

2.2 Data collecting and handling

Patient medical record data from May – November 2020 were collected, sorted, and annotated then analyzed statistically (GraphPad Prisma 9). Differences were compared by Mann-Whitney U non-parametric test, $p<0.05$ was considered significant for all tests. Data were expressed as median or percent of patients. Linear regression was performed to find the parameter significant for length of hospital stay for patients with mild and moderate degree of COVID-19.

3. RESULTS AND DISCUSSION

3.1 Patient characteristics

Total 185 patient medical records met the inclusion and exclusion criteria were analyzed in this study. The baseline characteristics of the patients are shown in Table 1. Overall, 100 patients were male (54%), with a median age of 40 years. Less than half had underlying diseases (16, 8.5%), including hypertension (5, 2.7%), diabetes (7, 3.7%) and tuberculosis (TB) lung (4, 21.1%).

Table 1. Patient characteristics

Variable	Total (N=185)	No antivirus (N=37)	Oseltamivir (N=148)	P value
Age, years (median, min-max)	40 (18-82)	40 (18-82)	40 (18-77)	0.435
Sex (N,%)				0.065
Male	100 (54)	15 (8)	85 (46)	
Female	85 (46)	22 (12)	63 (34)	
Degree of COVID-19 (N, %)				0.003*
Mild	89 (48)	26 (14)	63 (34)	
Moderate	96 (52)	11 (6)	85 (46)	
SaO2	98±0.7	98±1	98±0.5	1.000
Signs/symptoms (N, %)				
Fever	61(33)	17(9)	44(24)	0.078
Cough	91(49)	28(15)	63(34)	0.000*
Sore throat	18(9.7)	5(2.7)	13(7)	0.365
SOB	22(12)	9(5)	13(7)	0.019*
Rhinorrhea	20(10.8)	2(1.1)	18(9.7)	0.375
Anosmia	8(4.3)	1(0.5)	7(3.8)	1.000
Headache	16(8.6)	3(1.6)	13(7)	1.000
Vomit	13(7)	3(1.6)	10(5.4)	0.726
Diarrhea	6 (3.2)	0(0)	6(3.2)	0.601
Abdominal pain	4(2.2)	1(0.5)	3(1.6)	1.000
Number of Symptoms (N, %)				0.006*
0	47(25.4)	3(1.6)	44(23.8)	
1	23(12.4)	10(5.4)	13(7)	
2	51(27.6)	11(6)	40(21.6)	
3	45(24.3)	7(3.8)	38(20.5)	
4	15(8.1)	5(2.7)	10(5.4)	
5	3(1.6)	1(0.5)	2(1.1)	
6	1(0.5)	0(0)	1(0.5)	
Comorbidities (N,%)				1.000
Hypertension	5(2.7)	1(0.5)	4(2.2)	
DM	7(3.7)	1(0.5)	6(3.2)	

TB lung	4(2.1)	1(0.5)	3(1.6)	
Medication (N, %)				
Acetaminophen	57(30.8)	16(8.6)	41(22.2)	0.076
Corticosteroid	6(3.2)	0(0)	6(3.2)	0.601
Vitamin C	182(87)	36(9)	146(78.9)	0.491
Antibiotic (Azythromycin, levofloxacin or cefixime)	171(92.5)	31(16.8)	140(75.7)	0.037*
LOS, days (median, CI 95%)	11 (9-12)	12 (11-15)	11 (10-12)	0.049*

3.1 Antiviral agents and length of hospital stay

Despite several antiviral agents allowed to be administered for mild or moderate degree of COVID-19 at that time [6], the only antiviral agent prescribed as observed in patient medical records was oseltamivir. Oseltamivir was used in majority of patients (148, 80%). No antiviral agent prescribed for 37 patients (20%) with mild-degree (26, 29%) and moderate-degree (11, 11%) patients. Almost all patients (171, 92.5%) were prescribed also antibiotics for the possibility of bacterial coinfection, vitamin C (182, 98.4%) as supplement, whereas other drugs for symptomatic reliever (Table 1). This study result differs with the previous report which describe many kinds of antivirals used [9], which probably due to the released guideline at that time, access, and availability of drugs, health facility type (public versus private hospital) and geographical location (non-capital city, out side Java versus capital city, in Java).

Overall median hospital stay was 12 days (CI 95% 11-15, ranged 4-29) without oseltamivir, and 11 days (CI 95% 10-12, ranged 2-34) with oseltamivir ($p<0.049$), regardless the mild or moderate degree of COVID-19 (Table 1). Thus, oseltamivir shorthened the length of hospital stays. This finding is in line with a study reported earlier, that oseltamivir administration lowers the duration of symptom when it is used in combination with antibacterial therapy [11].

When length of hospital stay was analyzed further using Mann-Whitney multiple comparison, based on degree of COVID-19 and/or number of symptoms, the results showed that difference on length of hospital stay was mainly in group of patients with one symptom (Figure 1). In group of COVID-19 patients with mild degree and one symptom, oseltamivir shortened the length of hospital stay (median 5, ranged 3-9 days) compared to without oseltamivir (6-20 days, median 12 days), however adjusted p value is not significant ($p=0.0725$). In moderate degree COVID-19 and one symptom, administration of oseltamivir shorthened n the length of hospital stay (median 5, ranged 4-11 days) compared to without oseltamivir (median 12 days), with adjusted p value 0.0342. The linear regression analysis results also indicate that less symptoms associated with less length of hospital stay (adjusted $p=0.0003$), as well as concurrent use of antibiotics (adjusted $p=0.013$).

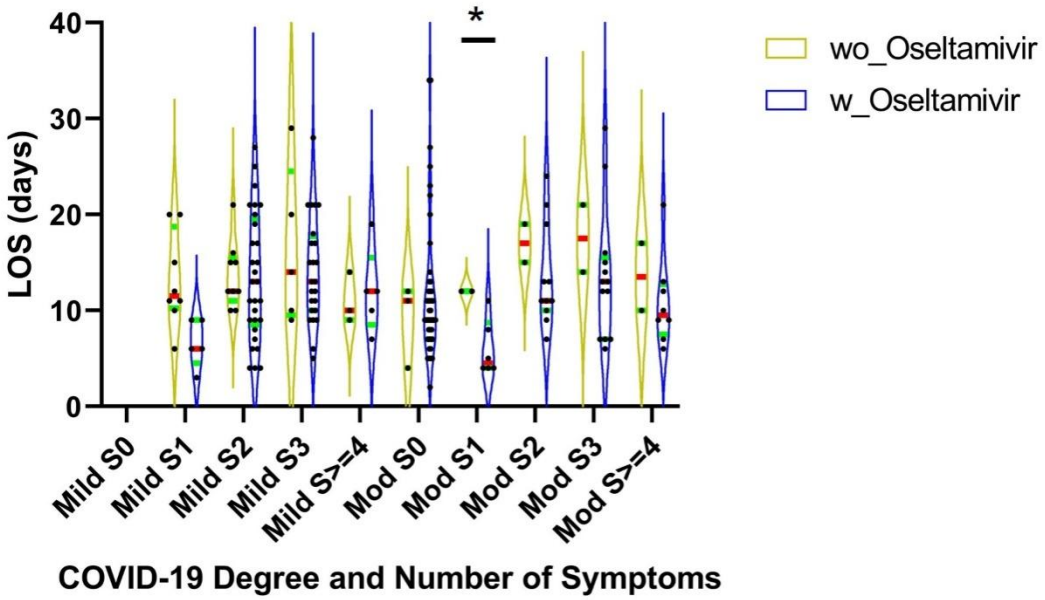

Fig. 1. Length of hospital stay (LOS), oseltamivir use, and COVID-19 degree and number of symptoms. *The violin plot shows that significant difference (asterisk) is in group of Covid-19 patients with moderate degree and one symptom (Mann-Whitney multiple comparison, adjusted p=0.0342). Administration of oseltamivir shorthen the length of stay (median 5 days) compared to without oseltamivir (median 12 days).*

The wide range of length of hospital stay in this patient population was not due to drugs used or comorbidities. It may be due to variation of the genetic of the virus [12], patients [13] and/or interaction with microbiome of the patients [14] which affect the overall speed of clinical response of the patients. Unfortunately, such probabilities could not be tested as there is no sophisticated facilities such as DNA/RNA sequencing for the virus and patients in the studied hospital.

4. CONCLUSION

Length of hospital stay of mild and moderate degree COVID-19 patients may be shortened with the use of oseltamivir.

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AUTHORS' CONTRIBUTIONS

IL, VY and DL designed the study, IL collected the data, IL, DL performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

CONSENT

This study used medical record and did not require patient consents.

ETHICAL APPROVAL

Ethical approval was sought from and granted by the Ethical Medical Committee of the Faculty of Medicine of Universitas Sumatera Utara, Indonesia (Approval Letter 220/KEP/USU/2021).

COMPETING INTERESTS DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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