Survival of COVID-19 Patients Who Received Antiviral and Antiviral Therapy Combined with Anti-inflammation Therapy in a National Referral Hospital, Indonesia

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Abstract

BACKGROUND: COVID-19 has infected and spread over the whole earth. For the time being, there is no cure for COVID-19. Although several medications have the potential to be utilized at various stages of the disease, no therapy has yet been demonstrated to be completely successful.

AIM: This study aims to determine survival of COVID-19 patients who received antiviral and antiviral therapy combined with anti-inflammation therapy in a National Referral Hospital, Indonesia.

METHODS: COVID-19 patients treated at Dr. M Djamil General Hospital in Padang, Indonesia were the subject of an analytic investigation using a retrospective cohort design. From January to June 2021, data were gathered from patient medical records. Independent sample T test and Chi-square test were used to analyze subject characteristics data. The median survival and survival rates were calculated using Kaplan–Meier survival analysis. It is also subjected to cox-regression analysis to answer the study hypothesis.

RESULTS: The mean age of the subjects who received antiviral and anti-inflammatory medication was 60.95 12.11 years, while the average age of those who received antiviral therapy was 56.72 17.80 years, with the highest sex being male in both groups (59.3% and 50.6%). Antiviral and antiviral medication, as well as anti-inflammatory therapy, had no effect on the length of stay of COVID-19 patients (p > 0.05). Antiviral and antiviral therapy, as well as anti-inflammatory therapy, play a role in the outcome of COVID-19 patients (p < 0.05), with patients receiving antiviral and anti-inflammatory therapy being a preventive factor in the final outcome of patients compared to patients receiving antiviral therapy HR = 0.69 (95% CI 0.48–0.99).

CONCLUSION: When compared to patients who just got antiviral medication, the patients who received antiviral plus anti-inflammatory therapy had a better outcome.

Introduction

COVID-19 infections have been reported in 213 countries and territories outside of mainland China [1]. COVID-19 infection has had a considerable impact in the United States, Europe, and Asia. COVID-19 had infected over 109.21 million individuals globally and killed over 2.4 million people as of February 2021 [2]. The number of cases among people aged 65 and up is extremely significant. There is no discernible distinction between males and women. Incubation lasts an average of 5.2 days. In a Wuhan study of 85 severe COVID-19 patients with a median age of 65 years, the majority of patients died from multiorgan failure, including respiratory failure (94%), shock (81%), and acute respiratory distress syndrome (ARDS) (74%), which are consistent with the high prevalence of multiorgan failure, high levels of d-dimer, fibrinogen, and prolonged thrombin time [3].

The majority of modern medical care is not standardized. Several medicines have been investigated in clinical trials, including lopinavir-ritonavir, remdesivir, hydroxychloroquine, and azithromycin, but none have yet been proven to be effective [4]. Finding medications to control and treat COVID-19 infection are difficult. Several prospective medications are now being utilized at various stages of the illness, but no therapy has yet been demonstrated to be completely successful. Colchicine, a chemical often used to treat gout and several autoinflammatory diseases such as adult onset illness, Behçet's disease, Mediterranean fever, and cardiac issues, is one medicine that might be useful [5].

Colchicine has been used for more than a decade to treat the symptoms of iatrogenic allogenosis (IA), a condition caused by allogeneic chemicals that enter the body, such as modeling agents or foreign biopolymers. Colchicine lowers arthralgia, headaches, and lung infiltrates, as well as other inflammatory symptoms and clinical presentations. The

patients' clinical condition improved and the frequency of their complaints decreased [6].

The tricyclic alkaloid colchicine is derived from the colchicum autumnale plant. Colchicine is a potent tubulin polymerization inhibitor. The high affinity of colchicine for attaching to the tubulin subunit, which prevents it from accumulating and so preventing microtubule polymerization, is the most researched mechanism. Microtubules are a component of the cytoskeleton that play a role in a variety of cellular functions, including cell shape maintenance, intracellular substance transfer, cytokine and chemokine secretion, cell migration, ion channel regulation, and cell division. Colchicine also affects the chemotaxis of inflammatory cells such as neutrophils and monocytes, as well as intracellular vesicle movement such as endosomes and exosomes. Colchicine also reduces the production of E-selectin, an adhesion molecule required for leukocyte adherence to endothelial cells and monocyte and neutrophil recruitment to inflamed tissues. Finally, colchicine inhibits the generation of neutrophils by free radicals such as superoxide. After that, inflammasome activity is inhibited, preventing caspase-1 activation and the production of IL-1 and IL-18 [7].

SARS-CoV-1 infection has been linked to calcium ion transport activation, which results in IL-1 overproduction, direct caspase-1 activation, or increased potassium excretion. Colchicine is 40% bound to albumin in the circulation. Based on intra-leukocyte accumulation, peak concentrations occur 1 h after injection and the greatest anti-inflammatory impact develops over 24–48 h. Colchicine reaches substantially larger amounts in leukocytes than it does in plasma, and it stays there for days after intake [8], [9].

Several studies have recently suggested that cytokine release syndrome (CRS) may affect a subset of individuals with severe COVID-19. CRS is a potentially fatal toxicity characterized by a rise in tumor necrosis factor (TNF), followed by increases in interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, and interferon-γ (IFN-γ). IL-2, IL-7, IFN, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1, and TNF were all shown to be high in COVID-19 and IL-6 was used as a predictor of death. All provided findings may be regarded evidence, demonstrating the inflammatory process' activation and the incidence of CRS in COVID-19-positive critically sick patients [10].

Colchicine may be a potential therapy option in the battle against the COVID-19-induced cytokine storm, according to the Papadopoulus *et al*. It is a more appealing alternative due to its relatively inexpensive cost and ample availability. However, due of the risk of drug-drug interactions (DDI), vigilance should be maintained. Early reports on effectiveness are promising, but there is still a lot of work to be done. A study including 105 individuals who were randomly assigned to receive either regular therapy or normal treatment with colchicine [10].

Methods

Study design and research samples

This is a retrospective cohort research with an analytical study. All COVID-19 patients treated in the COVID-19 isolation room at Dr M Djamil Hospital Padang from January to December 2021 were included in this research. The patients above the age of 18 were eligible for the study, as were COVID-19 patients taking antiviral and antiviral medication, as well as anti-inflammatory medicines. Incomplete medical record data are an exclusion criterion.

Operational definitions

Antiviral and antiviral and anti-inflammatory medication was the independent factors in severe and critical clinical COVID-19 patients. In this study, the antiviral in question is remdesivir. Colchicine is the anti-inflammatory drug mentioned in this study. The analysis of COVID-19 patients' survival is the dependent variable.

Research procedure

The researchers started by gathering information from the medical records of COVID-19 patients who got antiviral medication together with anti-inflammatory medicines (Group A), which included 81 subjects, and antiviral therapy only (Group B), which included 83 subjects.

Data analysis

Computerized data processing and statistical analysis were carried out. The independent sample T test and the Chi-square test were used to examine the subject's characteristics. Furthermore, Kaplan–Meier survival analysis was used to calculate the median survival and survival rate for the study hypothesis. If $p < 0.05$ is significant and the hazard ratio (HR) is known, the following study will use cox-regression to answer the research hypothesis, with the interpretation that HR> 1 is a risk factor and HR 1 is a preventative factor. SPSS version 18.0 was used to analyze the data.

Results

Subject characteristics (Table 1).

Table 1 showed in COVID-19 patients receiving antiviral and antiviral treatment with anti-inflammatories, there are variations in concomitant hypertension, diabetes mellitus, and chronic kidney disease, as well as outcomes ($p < 0.05$).

Table 1: Subject characteristics

Variables	Therapy		p-value	HR (95% CI)
	Group A (n = 81)	Group B (n = 83)		
Age, mean ± SD	60.95 ± 12.11	56.72 ± 17.80	0.077[a]	2.37 (0.46–8.92)
Sex, f (%)			0.339[b]	
Male	48 (59.3)	42 (50.6)		1.42 (0.77–2.63)
Female	33 (40.7)	41 (49.4)		Ref
Comorbidity, f (%)				
Hypertension	13 (16.0)	1 (1.2)	0.002[b]*	15.68 (2.00–122.89)
Diabetes mellitus	19 (23.5)	6 (7.2)	0.008[b]*	3.93 (1.48–10.45)
Overweight	2 (2.5)	0	n/a[b]	n/a
Chronic kidney disease	11 (13.6)	1 (1.2)	0.006[b]*	12.89 (1.62–102.30)
Heart disease	2 (2.5)	0	n/a[b]	n/a
Outcome, f (%)			<0.001[b]*	
Death	74 (91.4)	47 (56.6)		8.09 (3.33–19.69)
Life	7 (8.6)	36 (43.4)		Ref
Length of stay (hari), mean ± SD	9.31 ± 6.21	8.29 ± 6.59	0.310[a]	1.02 (0.99–2.99)

[a]Independent sample T test; [b]Chi-square test; *p<0,05 considered significant; Group A: Antiviral and anti-inflammatory therapy; Group B: Antiviral therapy; HR: Hazard ratio; Ref: Reference.

The impact of antiviral, antiviral, and anti-inflammatory medication on COVID-19 patients' length of stay (Table 2).

Table 2: The impact of antiviral, antiviral, and anti-inflammatory medication on COVID-19 patients' length of stay

Length of stay	Therapy		p-value	HR (95% CI)
	Group A (n = 81)	Group B (n = 83)		
>21 days	3 (3.7)	3 (3.6)	1.000[b]	1.03 (0.20–5.24)
≤21 days	78 (96.3)	80 (96.4)		Ref

[b]Chi-square test; *p < 0.05 considered significant; Group A: Antiviral and anti-inflammatory therapy; Group B: Antiviral therapy; HR: Hazard ratio; Ref: Reference.

Table 2 reveals that antiviral and antiviral medication, as well as anti-inflammation, had no effect on the length of stay of COVID-19 patients (p > 0.05).

The role of antiviral, antiviral, and anti-inflammatory medication in COVID-19 patients' outcomes (Table 3 and Figure 1).

Table 3: The role of antiviral, antiviral, and anti-inflammatory medication in COVID-19 patients' outcomes

Outcome	Rate (%)	Median follow-up (day) (95% CI)	p-value	HR (95% CI)
Group A	91.4	9.00 (7.33–10.67)	0.046*	0.69(0.48–0.99)
Group B	56.6	11.00 (3.02–18.98)		

*p < 0.05 considered significant; Group A: Antiviral and anti-inflammatory therapy; Group B: Antiviral therapy; HR: Hazard ratio.

Table 3 shows that patients receiving antiviral and anti-inflammatory medication had a greater death rate (91.4%) than those receiving antiviral therapy (56.6%). Individuals receiving antiviral and anti-inflammatory medication had a shorter median follow-up length of stay, 9 days, compared to patients receiving antiviral therapy, which was 11 days. According to the results of statistical test analysis, there is a significant relationship between antiviral and antiviral therapy, as well as anti-inflammation, and the outcome of COVID-19 patients (p 0.05), where patients who receive antiviral and anti-inflammatory therapy have a lower final outcome than patients who do not, HR = 0.69 (95% CI 0.48–0.99).

Discussion

According to the findings, antiviral and antiviral medication had no effect on the duration of stay of COVID-19 patients (p > 0.05). When the length of stay of patients on antiviral therapy was compared to the length of stay of patients on antivirals and anti-inflammatories, the results revealed that the longest length of stay was 21 days, with 80 (96.4%) in antiviral therapy subjects and 78 (96.3%) in antiviral therapy and anti-inflammatory therapy subjects. COVID-19 patients taking colchicine had a faster time to clinical improvement, according to the research by Deftereos et al. [11]. The use of colchicine reduced the time spent on supplementary oxygen treatment and hospitalization [12].
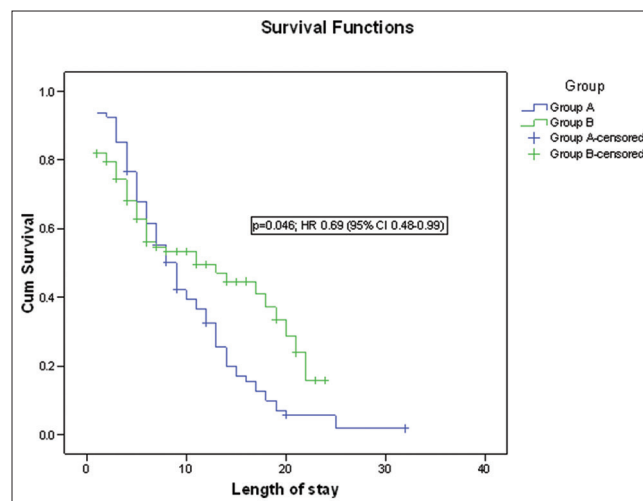

Figure 1: The role of antiviral, antiviral, and anti-inflammatory medication in COVID-19 patients' outcomes

At 21 days of the treatment, COVID-19 patients who received colchicine showed a higher survival rate than those who received conventional therapy (84.2% vs. 63.6%, p = 0.001) [13]. Colchicine is predicted to reduce the patient's auto-inflammatory response when given at the start of the COVID-19 phase [13]. Meanwhile, the previous study found that the death rate in COVID-19 patients was lower in the colchicine group than in the usual treatment group (OR 0.2, 95% CI, 0.05–0.80; p = 0.023). The patients on colchicine were 5 times more likely to be outpatient at the conclusion of the study (p = 0.023) than those on conventional treatment [14].

The patients who received colchicine used less oxygen and were more likely to be discharged

on day 10. Colchicine dramatically improved tissue oxygenation (PaO_2/FiO_2) and decreased lung inflammation. The rate of serious problems was observed to be lower in COVID-19 patients who were given colchicine than in those who were given a placebo [15], [16].

According to the findings, the patients receiving antiviral and anti-inflammatory medication had a greater death rate (91.4%) than individuals receiving antiviral therapy (56.6%). Individuals receiving antiviral and anti-inflammatory medication had a shorter median follow-up length of stay, 9 days, compared to patients receiving antiviral therapy, which was 11 days. According to the results of statistical test analysis, there is a significant relationship between antiviral and antiviral therapy, as well as anti-inflammation, and the final outcome of COVID-19 patients ($p < 0.05$), where the patients who receive antiviral and anti-inflammatory therapy have a lower outcome than patients who do not, HR = 0.69 for antiviral (95% CI 0.48–0.99).

A prior research compared standard medication (hydroxychloroquine and/or dexamethasone iv, and/or lopinavir/ritonavir) with the addition of colchicine 1 mg/day to normal therapy in instances of COVID-19 with pneumonia and ARDS and showed the patients who received colchicine lived longer. Compared to normal care, there was superior healing (84.2% vs. 63.6%, p = 0.001) and a decreased death rate (p < 0.0001). Death is associated with advanced age, low PaO_2/FiO_2, and high ferritin levels at the time of admission to the hospital [15].

Another research comparing the effects of colchicine 0.5 mg twice daily for 3 days followed by once daily for 30 days on outpatients with COVID-19 found that the patients receiving colchicine had greater mortality, length of stay, and lower hospital rates than placebo [16].

Conclusion

In comparison to patients getting antiviral medication only, this study demonstrates that the patients receiving antiviral and anti-inflammatory therapy are a preventative factor in the patient's final prognosis. Based on additional factors that contribute to COVID-19 patients' poor results, more study is needed to look at the influence of antiviral and antiviral as well as anti-inflammatory medication on the final outcome of COVID-19 patients.

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