



Frequency of receiving antiviral medications in patients who died following COVID-19 disease

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ABSTRACT

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Various antiviral medications have been used during the Coronavirus disease 2019 (COVID-19) pandemic, however, there is no promising result on the effectiveness of many of these medications, their side effects, and their association with death in patients. This study aimed to investigate the frequency of receiving antiviral medications in patients who died due to COVID-19 disease. In this cross-sectional study, the demographical data and clinical characteristics of 1477 deceased patients with COVID-19 who were referred to Razi Hospital, Rasht, Iran, from 2018 to 2019, were collected from the hospital archive. The data included age, gender, medical insurance, hospitalization in the intensive care unit (ICU), O₂ saturation, a history of underlying disease, and antiviral medications (Remdesivir, Oseltamivir, IFN- β -1a, and Lopinavir/Ritonavir). Due to our results the mean age of deceased patients was 64.8 years old. A total number of 764 patients were males. About 664 patients received Remdesivir, 388 patients received Interferon-beta-1a (IFN- β -1a), 186 patients received Oseltamivir, 169 patients received Lopinavir/Ritonavir, and 475 patients did not take any antiviral medications. Also, 609 people (41.2%) received one, 381 people (25.8%) received two, and 12 people (8%) received three antiviral medications. The results of the present study showed that in one-third of the cases, no antiviral medications were taken and the most frequent antiviral medication among patients was Remdesivir.

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1. Introduction

On February 2020, the World Health Organization (WHO) officially called the new coronavirus disease COVID-19 [1] and the International Committee on Classification of Viruses (ICTV) changed the name of the virus from nCoV-2019 to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. This novel virus engaged the whole world with health crisis. Various health organizations in the world have stated different incubation periods for the COVID-19 disease. WHO, National Health Commission of China, and USA Centers for Disease Control and Prevention stated it 2-10, 10-14, and 2-14 days, respectively [3].

According to the result of a meta-analysis study on 50466 patients with COVID-19, the mortality rate due to this virus was reported at 4.3%. However, most of the dead patients had underlying diseases such as hypertension, chronic pulmonary disease, diabetes, and cardiovascular diseases that weakened their immune systems [4]. The co-existence of the above-mentioned underlying disease upsurges the severity condition of patients with COVID-19 that results in death outcomes [5-7]. On the other hand, another reason for death among patients with COVID-19 was excessive immune responses directed toward cytokine storm with a low chance of recovery [8].

While there is not any specific effective antiviral treatment for COVID-19, some effective antiviral treatments for COVID-19 were being used all over the world based on either *in vitro* or extrapolated evidence or observational studies [9]. Among various antiviral medications, some were more famous that commonly were used by physicians. It has been shown that Remdesivir was superior to a placebo in reducing the time to recovery in hospitalized COVID-19 patients with lower respiratory tract infection [10]. Moreover, various studies on some antiviral medications for COVID-19 disease reported controversial results, in which some demonstrated that administration of Oseltamivir was associated with less length of duration of hospitalization and earlier recovery, and a lower mortality rate [11, 12], while others reported that Oseltamivir is not effective for the patients with COVID-19 [13].

A result of a systematic review illustrated that for COVID-19 patients with a severe condition, Lopinavir/Ritonavir might play a role in improving outcomes [14]. On the other hand, in another study, it was reported that the use of Lopinavir/Ritonavir in COVID-19 patients represented no significant clinical improvement [15]. Interferon-beta (IFN- β) is another antiviral medication that was a candidate to treat COVID-19 in various clinical trials [16, 17]. The use of IFN- β -1a in combination with hydroxychloroquine and Lopinavir/Ritonavir was successful in the management of COVID-19 [18], while IFN- β -1a plus Remdesivir was not superior to Remdesivir alone and patients who required high-flow oxygen at baseline had severe outcomes after receiving IFN- β -1a compared with those given placebo [19]. In this regard, further study is

required to achieve an accurate antiviral medication to treat patients with COVID-19 to decrease the rate of morbidity and mortality. In this current study, we investigate the frequency of received some antiviral medications in patients who died following COVID-19 disease.

2. Materials and Methods

2.1 Study design

In this cross-sectional study, the samples were collected through the census method. The demographical data and clinical characteristics of 1477 patients who died following COVID-19 disease were collected from the hospital archive. All the deceased patients with COVID-19 referred to Razi Hospital, Rasht, Iran, in a period of three years (from 1398 to 1401) with complete data were included and the patients with incomplete data were excluded from the study. The data included age, gender, medical insurance, hospitalization in the intensive care unit (ICU), O₂ saturation, a history of underlying disease (hypertension, diabetes, gastrointestinal disease, cardiovascular disease, kidney disease, and pulmonary disease), and antiviral medications (Remdesivir, Oseltamivir, IFN- β -1a, and Lopinavir/Ritonavir). The study design was approved by the ethical committee at the Guilan University of Medical Science [IR.GUMS.REC.1401.272]. Because of using medical records, the local ethics committee waived the necessity of taking informed consent. All personal records kept confidential.

2.2 Statistical analysis

The qualitative variables were reported as a percentage; the quantitative variables are reported as mean \pm standard deviation (SD) and interquartile range (IQR) and median. The data was analyzed using SPSS version 16 software with a significance level of less than 0.05.

3. Results

The mean age of patients was 64.8 \pm 14.8 years (16-99 years). The median age of patients was 65 years (IQR: 56-76), of which 75% of deceased patients were older than 56 years, 50% were older than 65 years, and 25% were older than 76 years. About 51.7% of cases were male and 90.8% of patients had insurance. The O₂ Saturation of deceased patients was 86.7% (83-93.0%). The median O₂ saturation of the patients was 86% (IQR: 84-89), of which 75% of the patients had an O₂ saturation less than 89%, 50% had O₂ saturation less than 86%, and 25% had O₂ saturation less than 84%. About 252 patients (17.1%) had no disease, 389 patients (26.3%) had one disease, 421 patients (28.5%) had two diseases, and 415 patients (28.1%) were suffering from three diseases and more. Hypertension and diabetes were the most frequent underlying disease among the cases, 39.1% and 33.3%, respectively.

Table 1: Frequency of data of patients who died following COVID-19 disease.

Variables		Number	Percentage
Gender	Male	764	51.7
	Female	713	48.3
Medical insurance	Yes	1341	90.8
	No	136	9.2
Hospitalization in ICU	Yes	469	31.8
	No	1008	68.2
Underlying disease	Hypertension	578	39.1
	Diabetes	492	33.3
	Gastrointestinal disease	524	35.5
	Cardiovascular disease	459	31.1
	Pulmonary disease	437	29.6
	Kidney disease	183	12.4
Antiviral medications	Remdesivir	664	45.0
	IFN- β -1a	388	26.3
	Oseltamivir	186	12.6
	Lopinavir/Ritonavir	169	11.4

The most frequently received antiviral medications were Remdesivir (45%), IFN- β -1a (26.3%), Oseltamivir (12.6%), and Lopinavir/Ritonavir respectively (11.4%), respectively. About 475 patients (32.2%) received no antiviral medication, 609 patients (41.2%) received one antiviral medication, 381 patients (25.8%) received two antiviral medications, and 12 patients (8%) received three antiviral medications, Table 1.

4. Discussion

Antiviral therapy for SARS-CoV-2 infection is still controversial due to the different outcomes and no promising medication has been demonstrated for COVID-19 patients. In the current study, the investigation of the frequency of different antiviral medications in patients who died following COVID-19 disease illustrated that most of the patients received at least one antiviral medication and Remdesivir was the most frequent antiviral medication. Different studies reported that some antiviral medications such as Remdesivir and Favipiravir were more effective than others such as Lopinavir/Ritonavir [15, 20].

Studies illustrated that Remdesivir accelerated the time of recovery in patients with COVID-19 and limited the spread of the virus to the patient's lungs [10]. *In vitro* examinations showed that Remdesivir can inhibit diseases caused by SARS-CoV and MERS-CoV. The experiments using primary human respiratory tract epithelial cells demonstrated that Remdesivir was effective against Bat-CoVs and human-CoVs in human lung cells. This study showed that Remdesivir was superior to Lopinavir/Ritonavir and IFN- β *in vitro* and an animal model of MERS-CoV [21-23].

Dastan et al reported that administrating IFN- β -1a in combination with hydroxychloroquine and Lopinavir/Ri-

tonavir in the management of COVID-19 disease could be effective in reducing the symptoms of the patient [18]. Sodeifian et al reported that it is critical to note the best time for IFNs' administration. While IFNs have many antiviral actions, more clinical trials are required to find the best timing for administrating IFN- β -1a for patients with various COVID-19 modalities [24].

Among many suggested antiviral medications, Remdesivir, Lopinavir/Ritonavir, hydroxychloroquine, etc., only Remdesivir has been approved by the FDA for the treatment of patients with COVID-19 [25], though its clinical efficacy is still debatable. In this regard, to face the current and future global challenges and prevent other pandemic, developing specific antiviral medication is required.

The cross-sectional nature of the current investigation is one of the limitations of this study. Since this study was conducted in one educational and medical center, the generalizability of the findings may not completely possible. In this regard, further multicentral investigations is recommended.

The results of the present study showed that in one-third of the patients who died following COVID-19 disease, no antiviral medications were prescribed, and the patients who received antiviral medication were mostly treated with one type, which was often Remdesivir.

Authors' contributions

Supervision and conceptualization: EH, HAB, KD, MR. Data collection and analysis: ZT, SM, MD, MP. Original draft preparation: EH, HAB, MR, ZT, SM, MD, MP. Critical revision and editing: EH, KD. All authors read and approved the final version of manuscript.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Ethical declarations

This was approved by the ethical committee at the Guilan University of Medical Science [IR.GUMS.REC.1401.272].

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