

Compare of Early Medicated Mild Symptomatic Covid-19 Patients from Emergency Room

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ORIGINAL RESEARCH ARTICLE

Abstract

Purpose: This research aimed to determine the impacts of early medication of hydroxychloroquine, favipiravir, or both drugs from the emergency room (ER) on hospitalization, mortality, and length of stay (LoS) in hospital.

Material-method: This research is a retrospective, cross-sectional and descriptive study that includes the period between 01.11.2020 and 30.11.2020. The patients were divided into three groups according to the drugs they used.

Results: During the study period, 34299 cases applied to the ER with Covid-19 symptoms. The Covid-19 reverse transcription polymerase chain reaction (Rt-PCR) test of 14469 (42.2%) patients was positive. Rt-PCR was positive in 3724 (60.1%) of 6202 medicated patients in the ER; moreover, 99 (1.6%) of them were hospitalized at their subsequent admission. Of inpatients, 21 (21.2%) died, 78 (78.8%) were discharged. There was no significant difference between hospitalized patients in terms of service or intensive care admission, mortality status, LoS in hospital. Mortality rate was; 0.2% in Group 1, 0.7% in Group 2, 1.1% in Group 3. The LoS in hospital according to the groups was 5.6 days, 7.9 days, and 7 days, respectively.

Conclusion: Among the mildly symptomatic Covid-19 patients, the group using hydroxychloroquine alone was less hospitalized than the patient groups using other drugs. According to their drugs, there was no significant disparity between hospitalized patient groups in terms of mortality status or LoS in hospitals.

Keywords: Emergency room, Covid-19, pandemic, hydroxychloroquine, favipiravir

I. INTRODUCTION

Covid-19 is an infectious disease that first appeared in China at the end of 2019, then expanded to the world, causing it to be declared a pandemic by the World Health Organization (WHO) in March 2020 [1]. Varied programs and drugs have been tried to fight against this infectious disease, which was unknown in the first days. For example, remdesivir, favipiravir, ribavirin, lopinavir, loraquine/hydroxychloroquine, ivermectin, tocilizumab, and dexamethasone were some of these drugs [2].

Chloroquine is a drug that has been produced since 1934 and used in the treatment and prophylaxis of malaria [3]. It is

also used today to treat rheumatic diseases due to its anti-inflammatory properties [4]. Hydroxychloroquine, a chloroquine derivative, was thought to be used in treating the Covid-19 disease in the early days of the pandemic due to its anti-inflammatory effects, preventing the virus's entry into the host cell in the early days of the pandemic [2]. Admittedly, at the beginning of the pandemic, publications showing that hydroxychloroquine was advantageous in attending Covid-19 disease have attracted attention [5], [6]. However, the drug's effectiveness has become controversial, as the publications proving that it did not contribute any advantage for Covid-19 patients entered the literature in the following periods [7], [8].

On the other hand, Favipiravir is an antiviral agent that prevents replication of influenza virus with RNA-dependent RNA polymerase inhibition, and its use against certain viruses such as; Ebola, yellow fever, chikungunya, norovirus, and enterovirus was discussed in 2002 [9], [10]. Based on its RNA-dependent RNA polymerase inhibition feature, it has been suggested that Favipiravir can be used in the treatment of Covid-19 cases and was later inserted in the Covid-19 treatment [10].

This research aimed to determine the impacts of early administration of hydroxychloroquine, favipiravir, or both drugs from the ER on parameters such as hospitalization, mortality, and length of stay (LoS) in hospital.

II. MATERIAL AND METHODS

Research Type

This research is a retrospective, cross-sectional and descriptive study that includes the period between 01.11.2020 and 30.11.2020.

The study sample was patients with mild Covid-19 symptoms and who were started on medication from the Sakarya Training and Research Hospital (SEAH) Pandemic ER. The population of the research is cases with Covid-19 symptoms and admitted to ER.

Definitions

Pandemic ER is the hospital unit where only outpatient and mild symptoms of Covid-19 suspect cases are examined, diagnosed, and treated. There is only one Pandemic ER in ... Province.

The following findings were accepted as mild symptoms of Covid-19: Fever, dry cough, fatigue, loss of taste or smell, nasal congestion, conjunctivitis, sore throat, headache, muscle or joint pain, different types of skin rash, nausea or vomiting, diarrhea, chills or dizziness [11].

In the pandemic ER, reverse transcription polymerase chain reaction (Rt-PCR) was performed for all patients with Covid-19 symptoms. In line with the Ministry of Health's Covid-19 Guideline, patients could be treated with hydroxychloroquine, favipiravir, or both drugs [12].

The cases in the study were classified into three groups:

Group 1: Patients with Covid-19 symptoms and medicated with hydroxychloroquine (5 days treatment at a dose of 2x200 mg/day)

Group 2: Patients who were medicated with Favipiravir. The first day was started at a dose of 2x1600 mg/day and continued at a dose of 2x600 mg/day for a total of five days.

Group 3: Patients who were medicated on both hydroxychloroquine and favipiravir. Drug doses were as described above.

Inclusion Criteria

- Patients aged 18 and over
- Patients with a positive Rt-PCR test
- Patients who have applied to the pandemic ER
- Patients with mild symptoms
- Patients whose treatment was started in the ER
- Discharged patients from the ER
- Cases whose data could be accessed entirely through the hospital automation system were included in the study.

Exclusion Criteria

- Patients younger than 18 years old
- Patients with negative Rt-PCR tests
- Pregnant patients
- Patients with severe symptoms
- Patients applying by ambulance
- Patients whose treatment was started outside the ER (by filiation teams or another healthcare facility)
- Patients who were hospitalized or transferred to another institution on their first application
- Patients whose data could not be accessed entirely through the hospital automation system were excluded from the study.

Data Collection

The patients' demographic data (age, gender), comorbidities, the drug given from the ER, need for hospitalization, hospital unit where the patients were hospitalized, LoS in the hospital, and mortality status were

retrospectively scanned from the patient files and hospital automation system.

Statistical Analysis

The data were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) version 21 program. Skewness and Kurtosis values were expected to be in the range of -2 / + 2 for the data's normal distribution (13). Chi-square test was applied for comparison of categorical data, and results with $p < 0.05$ were realized as statistically significant.

An independent t-test was utilized to compare two independent data groups that were normally distributed. Furthermore, a one-way ANOVA test was used to compare more than two independent data groups normally distributed. Results with $p < 0.005$ were considered statistically meaningful. The Mann-Whitney U test was applied to compare two independent data groups that were not normally distributed; moreover, the Kruskal Wallis Test was used to analyze more than two independent data groups. Similarly, results with $p < 0.05$ were considered significant.

Permissions

Permission was obtained from the chief physician of SEAH on 30.04.2021.

III. RESULTS AND DISCUSSION

A. Results

During the study period, 34299 people applied to the SEAH Pandemic ER with Covid-19 symptoms. The Covid-19 Rt-PCR test of 14469 (42.2%) patients was Rt-PCR positive. Medication was started in 6202 patients (18.1%) from the ER. Furthermore, of the patients who were started on medication, 3724 (60.1%) were Covid-19 Rt-PCR positive, and 99 (1.6%) of them were hospitalized at their subsequent admission.

Out of 99 patients hospitalized, 63 (63.6%) were male, and 36 (36.4%) were female. The mean age of the patients was 58.1 (\pm 13.7), the median value was 58 years, and the age range was 24-84 years.

Hypertension, diabetes, and coronary artery disease, respectively, were seen to be the most common comorbidities in hospitalized patients. See Table 1 regarding patients' comorbidity conditions.

Table 1. Comorbidity of inpatients

Comorbidity	Count	Percent %
Hypertension	49	49.5
Diabetes	35	35.4
Coronary artery disease	20	20.2
Cerebrovascular disease	10	10.1
Chronic lower respiratory disease	9	9.1
Mental disorders	8	8.1
Other diseases	35	35.4

Of the patients who were later hospitalized, 25 (25.3%) had only hydroxychloroquine, 61 (61.6%) only favipiravir, and 13 (13.1%) both hydroxychloroquine and favipiravir were given from the ER at their first admission. Patients were hospitalized following an average of 9 days (± 6 , between 3-42 days) after being discharged from the ER. Seventy-three of the cases (73.7%) were hospitalized in the service and 26 (26.3%) in the intensive care unit (ICU). While 21 of the sufferers (21.2%) died in the hospital, 78 (78.8%) were discharged. The status of Rt-PCR test positivity, hospitalization, and mortality of the cases are shown in Table 2.

Table 2. Distribution Data of Drug Groups

Drugs	Medicated patients		Rt-PCR positivity		Hospitalized patients		Mortality status	
	n	% ^a	n	% ^a	n	% ^b	n	% ^b
Group 1	2003	5.8	1091	3.2	25	2.3	2	0.18
Group 2	3761	11	2361	6.9	61	2.6	16	0.68
Group 3	438	1.3	272	0.8	13	4.8	3	1.1
Total	6202	18.1	3724	11	99	2.7	21	0.6

^aThe ratio of all patients admitted to the pandemic ER during the study period,

^bThe ratio of Rt-PCR positive and within the drug group

The statistical analysis of our findings presented no significant difference between the three groups of hospitalized patients in terms of service or intensive care admission ($\chi^2=5.774$, $SD=2$, $p = 0.056$). Moreover, there was no meaningful distinction between the mortality status of these groups ($\chi^2=3.557$, $SD=2$, $p = 0.169$), and a significant association was not observed in terms of hospital stay ($H=1.656$, $SD=2$, $p = 0.437$). See Table 3.

Table 3. Hospitalized patient features

Parameter		Group 1		Group 2		Group 3		p-value
		n	%	n	%	n	%	
Gender	Male	13	13.1	38	38.4	12	12.1	0.047 ^a
	Female	12	12.1	23	23.2	1	1	
Unit	Service	21	1.9 ^b	40	1.7 ^c	12	4.4 ^d	0.056 ^a

	ICU	4	0.4 ^b	21	0.9 ^c	1	0.4 ^d	
Mortality Status	Ex	2	0.2 ^b	16	0.7 ^c	3	1.1 ^d	0.169 ^a
	Alive	1089	99.8 ^b	2345	99.3 ^c	269	98.9 ^d	
Comorbidity	Yes	14	14.1	51	51.5	9	9.1	0.025 ^a
	No	11	11.1	10	10.1	4	4	
The average age		50.8 years		60.5 years		61 years		0.007 ^e
LoS in the hospital		5.6 days		7.9 days		7 days		0.437 ^f
Time to hospitalization		9.5 days		8.9 days		8.4 days		0.815 ^f

^a Pearson Chi-Square, ^b It is the ratio of all Group 1 patient, ^c It is the ratio of all Group 2 patients, ^d It is the ratio of all Group 3 patients, ^e ANOVA test, ^f Kruskal Wallis Test

When we investigated the effect of comorbidity on the groups, there was no significant difference between comorbidity and the hospital unit where the patients were hospitalized ($\chi^2 = 0.667$, $SD = 1$, $p = 0.410$). On the other hand, there is a meaningful association between comorbidity and patient groups ($\chi^2 = 7.401$, $SD = 2$, $p = 0.025$). Hence, it is recognized that emergency physicians mostly medicate the only favipiravir for patients with comorbidities.

It was found that the ages of the patients admitted had a significant effect on the mortality of the patients [$t(44) = -5.925$, $p = 0.001$]. Accordingly, the average age of the patients who died was 69.8 years, while the surviving patients were 55 years. A statistically significant relationship was observed between the presence of comorbidity and mortality status ($\chi^2 = 5.929$, $SD = 1$, $p = 0.015$), and at least one comorbidity was found in 20 (95.2%) of 21 cases who died. However, it was remarked that the presence of comorbidity did not have a significant influence on the LoS in hospital ($U = 769.000$, $p = 0.154$, $z = -1.424$, $r = -0.14$).

B. Discussion

When the hospitalization and mortality rates of Covid-19 disease are examined in general, it has been reported that 81% of the patients had the disease with mild symptoms, and 2.3% of them had a severe course and ended in death [13]. WHO reported that there were 148,329,348 cases of Covid-19 identified worldwide as of 28.04.2021, of which 3,128,962 (2.1%) died [14]. According to the Turkish Ministry of Health data, the total number of cases in Turkey as of 28.04.2021 was 4.751.026, and 39.398 patients (0.8%) died [15]. In SEAH, it was reported that 85 patients with Covid-19 died between 13.03.2020-09.05.2020 [16]. Our study determined that 99 of

3724 patients admitted to the SEAH Pandemic ER and who were medicated at the first admission in the ER were later hospitalized, and 21 of them (0.6%) were dead.

In a study conducted in France, Covid-19 patients who were hospitalized in intensive care were examined, and no significant difference was observed in terms of prognosis between patients who were started with hydroxychloroquine after admission to the hospital and patients who were not [17]. In another study, Joshua Geleris et al. reported that initiating hydroxychloroquine in patients after hospitalization does not significantly reduce intubation or mortality [18, p. 19]. On the contrary, it has been reported that low-dose hydroxychloroquine significantly reduces the fatality rates in critically ill patients [19]. There are also publications showing that using hydroxychloroquine alone or combining it with azithromycin significantly reduces mortality in Covid-19 patients [20]. In the literature, there is limited information about the effects of initiating hydroxychloroquine when patients have mild symptoms before a hospitalization indication develops. In a prospective study, initiation of hydroxychloroquine in patients with mild symptoms has been shown to increase Rt-PCR negativity in throat swab (5) significantly. In contrast to these positive effects of hydroxychloroquine, Milena et al. concluded that there was no change in hospitalizations due to Covid-19 in patients using hydroxychloroquine for rheumatic diseases [21]. This situation causes discussion of the use of hydroxychloroquine in terms of its prophylactic effect and its therapeutic effect.

In our study, three groups of patients with only mild symptoms and their medications were started at the first admission from the ER. It was observed that only 25 (2.3%) of 1091 patients included in Group 1 were hospitalized after an average of 9.5 days. This rate was determined as 2.6% for Group 2 patients and 4.8% for Group 3 patients. In the study of Brian Procter et al., it was concluded that only 1.9% of the patients medicated with multidrug in the early period were hospitalized; moreover, 0.3% of them died. [22]. This result is consistent with the results of our study, and it can be interpreted as the low rate of hospitalization in patients with mild symptoms who were started on medication in the early period.

Studies conducted on favipiravir have notified that favipiravir reduced mortality and shortened LoS in hospitals [10]. On the contrary, Vijayvargiya et al. reported that Covid-19 patients did not show the desired effect, so further studies should be done [23, p. 19]. In our study, no significant difference was observed between three Groups of hospitalized patients regarding LoS in hospital, mortality, and the unit the patients were hospitalized in. However, considering that 0.7% of Group 2 patients and 0.2% of Group 1 patients died, the mortality rate was higher in patients using favipiravir than Group 1 patients. The fact that favipiravir was started more in patients with comorbidity may be one factor affecting this result. Another factor affecting this result may be that the average age of Group 1 patients was 50.8 years, and the average age of Group 2 patients was 60.5 years. Supporting this, the USA Center of Disease Control (CDC) has shown

that hospitalization and mortality rates of Covid-19 patients increase with age [24].

In the randomized study conducted by Hany M et al., no statistically significant difference was found between the groups using hydroxychloroquine and favipiravir in LoS in hospital and mortality [25]. The result of this study coincides with the results of our study in this aspect.

Richardson et al. reported that 21% of Covid-19 patients hospitalized were dead [26]. Giacomo et al. found that 26% of Covid-19 patients hospitalized in intensive care were dead [27]. Also, Docherty et al. stated that it was found that 26% of Covid-19 patients hospitalized were dead in England [28]. Wenjie et al. stated in a meta-analysis that the mortality rate of Covid-19 patients hospitalized was around 25% [29]. Although the first application symptoms of the patients in our study were mild and the medication was started in the early period, the mortality rate of the patients who required hospitalization was similar to these studies.

When all drug-initiated patients were analyzed, the mortality rate for Group 1 was 0.2%, Group 2 was 0.7%, and Group 3 was 1.1%. It is concluded that these rates are lower than the worldwide mortality rate of 2.2% [14]. The mortality rate in Turkey is 0.8%; it was observed that the mortality rate of Group 1 patients remained below the overall Covid-19 mortality rate, the rate of Group 2 patients was similar, and Group 3 was above the average [15]. In Turkey, the vast majority of Rt-PCR positive outpatients are medicated by fillation teams with the only favipiravir. Therefore, the mortality rate of Group 2 can be expected to be close to Turkey's mortality rate.

Although it was not statistically significant, the mortality rate appears to be higher in Group 3 patients. In addition, there was no significant difference between the other group patients in terms of hospital stay, hospital unit, and mortality status. These results can be interpreted as starting favipiravir, and hydroxychloroquine together does not provide any extra benefit.

It was found that the LoS in hospital according to the groups was 5.6 days, 7.9 days, and 7 days, respectively. In a meta-analysis examining the hospital stay of Covid-19 patients, it was reported that the average hospital stay in Chinese hospitals was 14 days (IQR 10–19), and 5 days (IQR 3–9) outside of China [30]. However, in this meta-analysis, no information was given about the patients' treatment. Ming Li et al. asserted that the LoS in hospital patients taking chloroquine was 28.75 days [31]. Our study defined that all three groups of patients had shorter LoS than China in terms of average hospital stay. It is impracticable to evaluate this issue in this study since there is limited information about the duration of hospital stay in Turkey of those who takes these drugs and those who do not.

LIMITATION

The fact that the study was limited only to the SEAH pandemic ER is a limitation. Because, among the medicated patients, those who applied to another health institution could not be included in the study. The patients were generally

evaluated in terms of drugs used, hospitalization rates, and comorbidities. Blood test results and imaging test information of the patients were not examined.

IV. CONCLUSION

Among the mildly symptomatic Covid-19 patients, the group using hydroxychloroquine alone was less hospitalized than the patient groups using other drugs. According to their drugs, there was no significant disparity between hospitalized patient groups in terms of mortality status or LoS in hospitals. It should be appropriate to support these results with a more extensive patient series.

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