ORIGINAL ARTICLE

The effect of Fingolimod on patients with moderate to severe COVID-19

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Abstract

Hyper-inflammation, cytokine storm, and recruitment of immune cells lead to uncontrollable endothelial cell damage in patients with coronavirus disease 2019 (COVID-19). Sphingosine 1-phosphate (S1P) signaling is needed for endothelial integrity and its decreased serum level is a predictor of clinical severity in COVID-19. In this clinical trial, the effect of Fingolimod, an agonist of S1P, was evaluated on patients with COVID-19. Forty patients with moderate to severe COVID-19 were enrolled and divided into two groups including (1) the control group ($n = 21$) receiving the national standard regimen for COVID-19 patients and (2) the intervention group ($n = 19$) that prescribed daily Fingolimod (0.5 mg) for 3 days besides receiving the standard national regimen for COVID-19. The hospitalization period, re-admission rate, intensive care unit (ICU) administration, need for mechanical ventilation, and mortality rate were assessed as primary outcomes in both groups. The results showed that re-admission was significantly decreased in COVID-19 patients who received Fingolimod compared to the controls ($p = .04$). In addition, the hemoglobin levels of the COVID-19 patients in the intervention group were increased compared to the controls ($p = .018$). However, no significant differences were found regarding the intubation or mortality rate between the groups ($p > .05$). Fingolimod could significantly reduce the re-admission rate after hospitalization with COVID-19. Fingolimod may not enhance patients' outcomes with moderate COVID-19. It is necessary to examine these findings in a larger cohort of patients with severe to critical COVID-19.

KEYWORDS
COVID-19, cytokine storm, Fingolimod, sphingosine 1-phosphate

1 | INTRODUCTION

A growing body of evidence recommends that the main reason for disease severity in coronavirus disease 2019 (COVID-19) is cytokine storm.[1] Hyper-inflammation, cytokine storm, and recruitment of immune cells lead to uncontrollable endothelial cell damage, and consequently, acute lung injury (ALI)/Acute respiratory distress syndrome (ARDS).[2,3] Multiorgan vascular endothelial dysfunction and its connection with poor prognosis among patients with COVID-19 are attributed to SARS-CoV-2-induced microvascular endothelial pathology and endotheliitis.[4] Alteration in endothelial permeability and function also occurs in COVID-19 disease.[5]

Sphingosine 1-phosphate (S1P) is a bioactive lipid and a regulator of various physiological and pathophysiological procedures. The signaling pathway related to S1P and its receptor (S1PR1) is critical for the improvement of endothelial barrier function in the lung.[6-8] RNA viruses including SARS-1, mouse pulmonary virus, and Influenza H1N1 2009 during their invasion modulate the S1P signaling[9] and S1P1 receptor agonist treatment could suppress global cytokine storm.[10] In line with those studies, it could be speculated a mechanistic connection between serum S1P level as a severity predictor and the progression to a severe inflammatory phase of COVID-19. Accordingly, it is reported that low serum level of S1P/ high-density lipoproteins (HDL) has a prognostic value for intensive care unit

(ICU) administration and mortality in COVID-19.[11] Hence, different S1P analogs can inhibit alveolar exudation by stabilizing cell-matrix adherence, maintaining the integrity of the endothelial cytoskeleton, and tightening the inter-cellular junction.[12-14]

Fingolimod (FTY720), an analog of S1P, is an FDA-approved therapy for multiple sclerosis (MS), 2010.[15] Fingolimod binds to S1P1R on the endothelium and improves the integrity of the endothelial barrier and restricts the lymphocytes' recruitment toward the inflamed organs and tissues and alveolar space.[16,17] Fingolimod by diminishing the cytokine storm and stabilization of pulmonary endothelial integrity can decline the migration of inflammatory immune cells into the lung and prevent pulmonary exudation.[17] This clinical trial aimed to evaluate the effect of Fingolimod on the primary outcomes of COVID-19 patients.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This single-center, non-randomized controlled clinical trial was conducted on patients with moderate to severe COVID-19 admitted to the Infectious Disease Wards of Tabriz University of Medical Sciences (TUOMS), Imam Reza teaching hospital between May to September 2021. Forty patients with COVID-19 were enrolled and divided into two groups (intervention
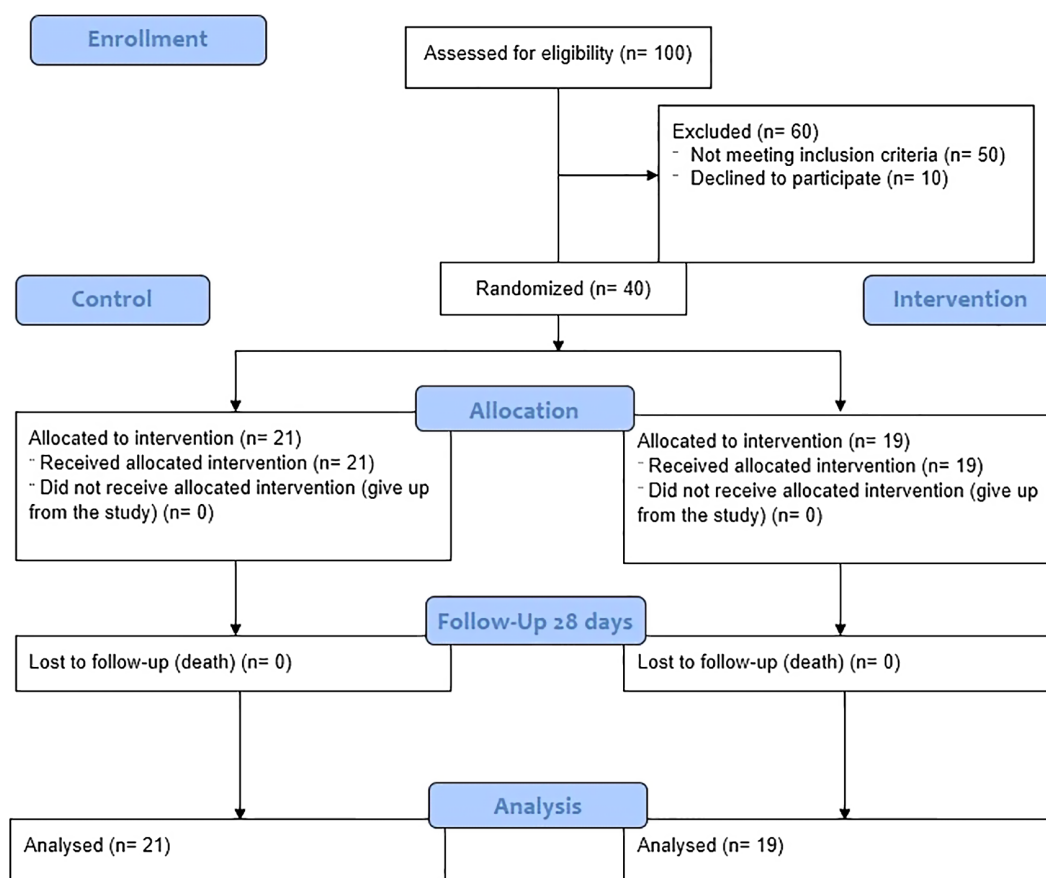

FIGURE 1 CONSORT diagram 2010

and control). Inclusion criteria were; patients with moderate to severe SARS-COV-2 infection, aged between 18 and 80 years, and positive PCR test for coronavirus. Patients with higher liver enzymes (threefold higher than normal range), active pulmonary tuberculosis, definite fungal and bacterial infections, breast-feeding and pregnant, severe kidney failure (glomerular filtration rate (GFR) <30 ml/min/1.73 m^2), active thrombosis, severe respiratory failure, and immediate need for intubation were excluded from the study. Patients with expected survival duration <24 h who were already enrolled in other clinical trials were excluded as well (Figure 1). This project was approved by the Ethics Committee of TUOMS, Tabriz, Iran (Ethical code: IR.TBZMED.REC.1399.001) and registered at the Iranian Registry of Clinical Trials on 2020-04-03 (Registration number: IRCT20200317046797N2).

Patients in the control group received the national standard regimen for moderate COVID-19 infection including Dexamethasone 6 mg daily, Remdesivir 200 mg on the first day, and then 100 mg daily (600 mg in total 5 doses). Moreover, some patients received Famotidine 40 mg twice a day. The intervention group received Fingolimod (0.5 mg) for 3 days in addition to the standard national regimen for COVID-19. The hospitalization period, re-admission rate, ICU administration, need for mechanical ventilation, and the mortality rate were assessed as the primary outcomes in both groups.

Laboratory data including lactate dehydrogenase (LDH), neutrophil-lymphocyte ratio (NLR), liver enzymes [alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT)], bilirubin, serum calcium, sodium, potassium, magnesium, creatine phosphokinase (CPK), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), CPK-MB, partial thromboplastin time

TABLE 1 Demographic features and clinical symptoms of COVID-19 patients

Features	Control (n = 21)	Intervention (n = 19)	Total (n = 40)	p-value*
Sex				
Male	14 (67%)	10 (53%)	24 (60%)	.36
Female	7 (33%)	9 (47%)	26 (40%)	
Age (years)	61.88 ± 19.35	58.59 ± 18.93	60.18 ± 18.91	.62
Asthma				
Negative	14 (66.7%)	18 (94.7%)	32 (80%)	.10
Mild	4 (19%)	1 (5.3%)	5 (12.5%)	
Moderate	2 (9.5%)	0 (0%)	2 (5%)	
Severe	1 (4.8%)	0 (0%)	1 (2.5%)	
Dry cough				
Negative	17 (81%)	18 (94.7%)	35 (87.5%)	1.00
Mild	2 (9.5%)	1 (5.3%)	3 (7.5%)	
Moderate	1 (4.8%)	0 (0%)	1 (2.5%)	
Severe	1 (4.8%)	0 (0%)	1 (2.5%)	
Productive cough				
Negative	19 (90.5%)	19 (100%)	38 (95%)	1.00
Mild	1 (4.8%)	0 (0%)	1 (2.5%)	
Moderate	0 (0%)	0 (0%)	0 (0%)	
Severe	1 (4.8%)	0 (0%)	1 (2.5%)	
Anorexia				
Negative	17 (81%)	17 (89.5%)	34 (85%)	1.00
Mild	2 (9.5%)	2 (10%)	4 (10%)	
Moderate	1 (4.8%)	0 (0%)	1 (2.5%)	
Severe	1 (4.8%)	0 (0%)	1 (2.5%)	
Anosmia				
Negative	20 (95.2%)	19 (100%)	39 (97.5%)	1.00
Mild	0 (0%)	0 (0%)	0 (0%)	
Moderate	0 (0%)	0 (0%)	0 (0%)	
Severe	1 (4.8%)	0 (0%)	1 (2.5%)	
Fatigue				
Negative	14 (66.7%)	14 (73.7%)	28 (70%)	.26
Mild	3 (14.3%)	5 (26.3%)	8 (20%)	
Moderate	3 (14.3%)	0 (0%)	3 (7.5%)	
Severe	1 (4.8%)	0 (0%)	1 (2.5%)	

The table has a "Participants" header spanning the Control, Intervention, and Total columns.

*Chi-square or fisher's exact test was used and p-value <.05 was considered statistically significant. The severity of symptoms was determined by physicians based on national protocols.

(PTT), prothrombin time (PT), international normalized ratio (INR), urea, O_2 saturation, and serum creatinine were also recorded. The duration of the fever period and the day of hospital discharge were studied as secondary outcomes.

2.2 | Statistical analysis

The Shapiro–Wilk test was used for checking the normality of the data distribution. Quantitative variables were presented as mean ± standard deviation (SD) or median [interquartile range (IQR)]. Differences between the groups were compared respectively by independent t-test or Mann–Whitney U test. SPSS software version 21.0 was used for statistical analysis. p-values < .05 were considered statistically significant.

3 | RESULTS

3.1 | Demographic features and clinical symptoms

A total of 19 patients received Fingolimod and 21 patients were in the control group. About 67% of patients in the control group and 53% of patients in the intervention group were males (p = .36). The mean age of all patients was 60.18 ± 18.91 years old and there was not a significant difference between the groups (58.59 vs. 61.88, p = .62). The most common clinical symptom among all patients was cough. However, there was no significant difference between the two arms in terms of clinical symptoms, including; asthma, dry or productive cough, anorexia, anosmia, and fatigue (p > .05). Demographic features and clinical symptoms of patients are shown in Table 1.

The median admission days of the patients was 7 and 5 days in the control and Fingolimod groups, respectively (p = .42). Only two patients in each group needed ICU admission. Prescription of additional therapies including hemoperfusion (×3), interferon 1-β, and Methylprednisolone (500 mg) was not significantly different between the groups (p > .05). None of the patients needed intubation and mechanical ventilation. Patients in the Fingolimod group did not need re-admission but 5 patients (23.8%) in the control group were re-admitted after their first hospitalization which was statistically significant (p = .04). None of the included patients died because of COVID-19 infection during the study, and only one patient in the control group died because of his underlying cardiovascular problems. The primary outcomes of patients are shown in Table 2.

It was revealed that the laboratory measurements were not significantly different between the studied groups (p > .05). Laboratory measurement after the intervention revealed that total WBC, neutrophil count, and CPK, CPK-MB, and ALP levels were decreased and platelet levels were increased in COVID-19 patients who received Fingolimod compared to the control group. However, none of the observed differences was statistically significant (p > .05). Hemoglobin levels of patients who received Fingolimod were significantly increased in the intervention group compared to the controls (p = .01). Other biochemical tests are shown in Table 3.

4 | DISCUSSION

Fingolimod could significantly reduce the re-admission rate of hospitalized COVID-19. The results suggest that the use of Fingolimod in hospitalized patients with moderate to severe COVID-19 does not affect the patients' outcomes and the disease prognosis.

TABLE 2 Primary outcomes of the COVID-19 patients

	Participants			
Primary outcomes	**Control (n = 21)**	**Intervention (n = 19)**	**Total (n = 40)**	***p*-value***
Admission days[1]	7 (4)	5 (6)	5.5 (5)	.42
ICU				
No	19 (90.5%)	17 (89.5)	36 (90%)	p > .05
Yes	2 (9.5%)	2 (10.5%)	4 (10%)	
Additional therapies				
Hemoperfusion (×3)	1 (4.8%)	0	1 (2.5%)	.46
Interferon 1-β	0	1 (5.3%)	1 (2.5%)	
Methylprednisolone (500 mg)	0	1 (5.3%)	1 (2.5%)	
Intubation				
No	21 (100%)	19 (100%)	40 (100%)	—
Yes	0	0	0	
Re-admitted patients				
No	16 (76.2%)	19 (100%)	35 (87.5%)	.04
Yes	5 (23.8%)	0	5 (12.5%)	

[1]Data are shown as median [interval quartile (IQR)], *Chi-square or fisher's exact test was applied and p-value<.05 was considered statistically significant.

TABLE 3 Laboratory findings of the COVID-19 patients

Laboratory data	Admission	Patients			p-value
		Control (n = 21)	Intervention (n = 19)	Total (n = 40)	
The percentage of O_2 Saturation	Early	91 (4)	90 (6)	90 (88–92)	1.00
	Middle	94 (5)	90 (7)	92 (5)	.10
	Late	93 (8)	92 (5)	93 (6)	.18
WBC (10^9/L)	Early	7.1 (5.8)	7.1 (5.9)	7.1 (5.7)	.91
	Middle	7.55 (6.8)	4.85 (3.5)	5.75 (4.9)	.24
	Late	9.4 (5.1)	5.8 (5.2)	7.7 (5.6)	.34
Neutrophil (10^9/L)	Early	77.22±10.36	70.53±13.91	74.27±12.33	.11
	Middle	72.01±16.55	70.77±6.26	71.56±13.53	.80
	Late	75.21±10.92	69.48±15.16	72.51±13.0	.38
Hemoglobin (mg/dl)	Early	13.63±1.79	14.34±2.15	13.97±1.98	.26
	Middle	12.64±1.75	14.42±1.7	13.32±1.91	.01
	Late	12.56±1.71	13.19±1.53	12.83±1.63	.37
Lymphocyte (10^9/L)	Early	18.82±10.24	19.78±11.22	19.26±10.55	.79
	Middle	19.24±14.25	22.8±7.22	20.53±12.09	.44
	Late	17.75±9.67	20.87±8.04	19.13±8.87	.47
Platelet (10^9/L)	Early	159 (94)	190 (107)	168 (102)	.59
	Middle	181 (128)	130.5 (199)	156.5 (149)	.58
	Late	186 (194)	214.5 (245)	192 (228)	.69
LDH (U/L)	Early	539 (301)	457 (168)	486.5 (201)	.76
	Middle	526 (365)	517 (322)	521.5 (346)	.80
	Late	1219 (–)	410 (–)	580 (901)	.40
Urea (mg/dl)	Early	36 (31)	35 (24)	35.5 (24)	.37
	Middle	32 (15)	38 (33)	33 (20)	.45
	Late	37 (22)	27 (35)	34 (26)	.20
Creatinine (mg/dl)	Early	1.15±0.29	1.22±0.42	1.18±0.35	.55
	Middle	1.08±0.27	1.24±0.36	1.14±0.31	.35
	Late	1.12±0.24	1.06±0.25	1.09±0.24	.56
Sodium (mmol/L)	Early	137.5 (6)	138 (2)	138 (5)	.98
	Middle	136.5 (5)	137.5 (3)	137 (4)	.30
	Late	138 (5)	139 (3)	138.5 (4)	.44
Potassium (mmol/L)	Early	4.1 (0.5)	4.1 (0.4)	4.1 (0.5)	.61
	Middle	4.1 (0.7)	4.35 (0.6)	4.15 (0.6)	.27
	Late	4.5 (1.2)	4.5 (0.6)	4.5 (1.1)	.58
Ionized calcium (mg/dl)	Early	1.06±0.06	1.05±0.05	1.05±0.058	.53
	Middle	1.06±0.06	1.08±0.07	1.07±0.07	.55
	Late	1.07±0.07	1.11±0.03	1.09±0.04	.38
Total calcium (mg/dl)	Early	8.1 (1.3)	8.55 (1.1)	8.5 (1.2)	.50
	Middle	8.25 (–)	—	8.4 (–)	.14
Magnesium (mg/dl)	Early	1.86±0.29	1.97±0.2	1.93±0.23	.39
	Middle	2.01±0.2	1.98±0.23	2.0±0.21	.81
	Late	2.2±0.42	2.17±0.15	2.18±0.22	.94
Phosphorus (mmol/L)	Early	2.7±1.12	2.93±1.02	2.81±1.03	.71
	Middle	2.8±0.45	2.95±0.41	2.91±0.4	.60
	Late	3.0	2.67±0.43	2.74±0.4	.55

(Continues)

TABLE 3 (Continued)

Laboratory data	Admission	Patients Control (n = 21)	Intervention (n = 19)	Total (n = 40)	p-value
CPK (U/L)	Early	142 (657)	91.5 (145)	121 (144)	.12
	Middle	185 (900)	54 (114)	116 (159)	.41
	Late	37.5		38 (–)	.66
CPK-MB (U/L)	Early	36 (38)	27 (26)	33 (22)	.19
	Late			18 (–)	1.00
ALT (U/L)	Early	21.5 (19)	27.5 (29)	24.5 (22)	.60
	Middle	23.5 (24)	40 (45)	27 (41)	.43
	Late	48 (101)	53.5 (–)	53.5 (59)	.82
AST (U/L)	Early	33 (25)	40.5 (35)	36.5 (27)	.62
	Middle	36 (17)	46 (63)	39 (47)	1.00
	Late	71 (166)	81 (–)	81 (107)	.87
ALP (U/L)	Early	216 (83)	156 (77)	177 (90)	.05
	Middle	216 (279)	140.5 (68)	145.5 (141)	.13
	Late	154 (–)	129 (–)	130 (81)	.78
ESR (mm/h)	Early	16 (–)	21 (–)	21 (23)	1.00
	Middle		16 (–)	21 (44)	.07
INR	Early	1.08 (0.17)	1.09 (0.16)	1.08 (0.16)	.88
	Middle	1.13 (0.71)	1.1 (3.03)	1.1 (0.18)	.79
	Late	1.43 (0.4)		1.3 (0.39)	.34
PTT (seconds)	Early	31 (12)	33.5 (15)	32 (11)	.48
	Middle	38 (24)	40 (35)	40 (24)	.93
	Late	37 (38)		36.5 (35)	1.00
PT (seconds)	Early	14.4 (32.1)	14.5 (2.2)	14.4 (2.2)	.81
	Middle	16 (15.9)	15.2 (17.7)	15.8 (12.6)	.90
	Late	19.2 (5.4)	0.6 (–)	17.45 (5.2)	.34
NLR	Early	4.81 (7.63)	4.09 (4.73)	4.09 (5.58)	.42
	Middle	5.73 (9.37)	3.41 (1.78)	3.65 (6.52)	—
	Late	5.52 (7.42)	4.04 (3.45)	4.9 (5.57)	.32
Total bilirubin (µmol/L)	Early	0.66±0.2		0.95±0.59	—
	Middle		1.35±0.63	1.3±0.63	.58
Direct bilirubin (µmol/L)	Early	0.33±0.057		0.42±0.18	.52
	Middle		0.55±0.21	0.55±0.21	.27

Note: Data are shown as median [interval quartile (IQR)] or mean±standard deviation (SD). p-value is calculated using the Mann–Whitney U test or independent T-test in variables with non-normal or normal distributions, respectively.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; CPK, creatine phosphokinase; CRP: C-reactive protein; Early, at the onset of admission; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; Late, at the end of admission; Middle, at the middle of the admission; NLR, neutrophil leukocyte ratio; PLT, platelets; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white-blood cell.

Numerous studies have been done to examine the benefit of different medications that were allocated based on their mechanism of action to improve the outcomes of patients with COVID-19.[18] Li and colleagues reported that lopinavir/ritonavir (LPV/r) or arbidol monotherapy exerted little benefit in enhancing the clinical outcomes of mild/moderate COVID-19 patients.[19] In another randomized clinical trial in COVID-19 patients with mild-to-moderate pneumonia, it has been shown that anakinra (a recombinant human

IL-1 receptor antagonist) could not enhance patients' outcomes and was not effective in reducing the need for non-invasive or mechanical ventilation or death.[20] Furthermore, it has been reported that aerosol inhalation of interferon kappa (IFN-κ) and trefoil factor family member 2 (TFF2), a small secreted polypeptide that diminishes inflammatory responses and improves the repair of mucosal injury, in combination with standard treatment effectively could suppress SARS-CoV-2 invasion. Moreover, these treatments could improve

clinical manifestations in all clinical samples of patients with moderate COVID-19.[21]

The SP1-S1PR1 signaling pathways are needed for preserving endothelial integrity by mediating the localization of Beta-catenin and vascular endothelial (VE)-cadherin at adherent junction sites of endothelial cells.[22] It has been also proposed that the rearrangement of adherents' junction proteins and phosphorylation of intracellular myosin light chain by S1P can improve the endothelial barrier function of the lung.[23-26] S1P by disturbing the activation and recruitment of lymphocytes can reduce the cytokine storm in viral infection.[27]

Since some immunosuppressive therapies have been recommended for COVID-19 patients, we proposed that Fingolimod (an S1P analog) could positively affect the clinical outcome of COVID-19. Through its potential effects on tightening the endothelial junction and preventing vascular leakage,[28,29] Fingolimod inhibits the trans-endothelial passage of immune cells.[30-32] Fingolimod could also decrease lipopolysaccharide (LPS)-induced pulmonary damage[12] and necrotizing pancreatitis in animal models.[33] Likewise, Fingolimod could prevent airway inflammation[34] and inflammatory cell recruitment in vivo.[35] The advantageous effect of Fingolimod has been also reported in MS patients with COVID-19 and its discontinuation during the infection period could induce a worsening of SARS-CoV2 infection.[36] Fingolimod can decrease cytokine storm, improve endothelial cell integrity in the lung[37,38] and reduce mortality[38] in MS patients infected by SARS-COV-2. A case report study did report that there were no statistically significant differences in the frequency of COVID-19 between MS patients who received Fingolimod or Siponimod and the general population.[39] In the present study, Fingolimod could significantly prevent re-admission of patients; however, it had no significant effects on the hospitalization period, ICU administration, need for mechanical ventilation, and the mortality rate of patients with moderate to severe COVID-19. Several studies have evaluated approaches to lessen early re-admission rates and evaluate the risk factors for re-admission of patients hospitalized with COVID-19.[40] Reducing the re-admission rate will help the clinic to provide better care for patients and decrease burdens on medical services.

The small sample size was the main limitation of this study; hence, the result cannot be generalized to the whole population. Moreover, it is suggested to perform this trial on patients with severe to critical COVID-19 who require ICU admission. More extensive clinical trials with a large sample size are needed. Moreover, since Fingolimod has a widespread effect on S1PR1 and S1PR3–5, to minimize off-target effects, more specific S1P analogs such as CYM5542 or RP-002 are needed to be examined in the future.[41]

5 | CONCLUSION

It can be concluded that the use of Fingolimod could reduce the re-admission and increase hemoglobin levels. Fingolimod in hospitalized patients with moderate to severe COVID-19 does not significantly affect the patients' outcomes and the disease prognosis.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL STATEMENT

This project was approved by the Ethics Committee of TUOMS, Tabriz, Iran (Ethical code: IR.TBZMED.REC.1399.001).

PATIENT CONSENT STATEMENT

Informed consent was obtained from all included patients in this study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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