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International Immunopharmacology 107 (2022) 108689

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Comparing efficacy and safety of tocilizumab and methylprednisolone in the treatment of patients with severe COVID-19

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ARTICLE INFO

Keywords:
Methylprednisolone
Tocilizumab
COVID
Dexamethasone

ABSTRACT

Objectives: This study was designed to compare the efficacy and safety of methylprednisolone and tocilizumab in the treatment of patients with severe COVID-19.
Methods: During a prospective cohort study, hospitalized patients with severe COVID-19 received intravenous methylprednisolone (250–500 mg daily up to three doses), weight-based tocilizumab (maximum 800 mg, one or two doses as daily interval) or dexamethasone (8 mg daily). The primary outcome was time to onset of clinical response. Secondary outcomes were improvement rate of oxygen saturation and CRP, need for ICU admission, duration of hospitalization and 28-day mortality. During study, adverse events of the treatments were recorded.
Results: Although the difference was not statistically significant ($p = 0.090$), clinical response occurred faster in the tocilizumab group than other groups (10 vs. 16 days). Clinical response was detected in 74.19%, 81.25%, and 60% of patients in the methylprednisolone, tocilizumab, and dexamethasone groups respectively ($p = 0.238$). Based on the Cox regression analysis and considering dexamethasone as the reference group, HR (95% CI) of clinical response was 1.08 (0.65–1.79) and 1.46 (0.89–2.39) in the methylprednisolone and tocilizumab groups respectively. Improvement rate of oxygen saturation and CRP was not significantly different between the groups ($p = 0.791$ and $p = 0.372$ respectively). Also need for ICU admission and 28-day mortality was comparable between the groups ($p = 0.176$ and $p = 0.143$ respectively). Compared with methylprednisolone, tocilizumab caused more sleep disturbances ($p = 0.019$). Other adverse events were comparable among patients in the groups.
Conclusion: When or where access to tocilizumab is a problem, methylprednisolone may be considered as an alternative for the treatment of patients with severe COVID-19,

1. Introduction

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have raised hopes to reach the end of Coronavirus Disease 2019 (COVID-19) pandemic, following the emergence of new variants especially Delta and Omicron, it is now unpredictable [1–3]. The vaccines showed strong protection against previous variants such as Alpha (B.1.1.7) and Beta (B.1.351) [4]. However, the advent of new Omicron variants has affected the vaccine effectiveness even in the fully vaccinated people [5]. Therefore, it is essential to continue the investigations to find an effective drug for hospitalized patients with COVID-19.

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https://doi.org/10.1016/j.intimp.2022.108689
Received 2 February 2022; Received in revised form 2 March 2022; Accepted 7 March 2022
Available online 17 March 2022

Although corticosteroids had been proposed for hospitalized patients with COVID-19 from the beginning of the pandemic, their usage has been established following the release of RECOVERY trial results [6]. After that, corticosteroids have been used as a component of the standard of care in patients with COVID-19 who require supplemental oxygen. Despite some studies indicated the benefits of high doses of corticosteroids, the recommended dose is still 6 mg daily of dexamethasone or equivalent doses of methylprednisolone, prednisolone, or hydrocortisone for up to 10 days [7–8]. Some primary studies showed survival benefits of methylprednisolone pulse (MPP) 250 mg daily as intravenous infusion for up to three days in patients with severe COVID-19 [9–10]. However, some studies did not support these findings [11–12].

In the early studies, survival benefit of tocilizumab was not found [13–14], but in the subsequent trials such as REMAP-CAP and RECOVERY, it significantly decreased mortality in patients with COVID-19 [15–16]. These positive effects were demonstrated in the later systematic reviews and meta-analyses [17–18]. Then tocilizumab has been included in the management protocols of COVID-19. The extensive use of this product created a financial burden for healthcare systems particularly in the limited resources countries. Considering cost and availability of tocilizumab, this study was designed to compare the efficacy and safety of MPP and tocilizumab in the treatment of patients with severe COVID-19.

2. Methods

2.1. Study design

In this prospective cohort study (from June 24 to December 24, 2021), the efficacy and safety of MPP and tocilizumab were compared in patients with severe COVID-19 who were admitted to Imam Khomeini Hospital Complex, one of the referral teaching hospitals for managing patients with COVID-19 in Tehran, Iran. Eligible patients who provided the consent form of study were included. The Ethics Committee of Tehran University of Medical Sciences approved the protocol (ID: IR.TUMS.MEDICINE.REC.1400.322).

2.2. Eligibility criteria

Adult patients (≥18 years old) with severe COVID-19 who required supplemental oxygen were included. Severe COVID-19 was defined as peripheral oxygen saturation (SpO2) less than 90% and C- reactive protein (CRP) ≥ 75 mg/dl. The diagnosis of COVID-19 was based on positive Real-Time Polymerase Chain Reaction (RT-PCR) of nasopharyngeal sample or the highly suggestive signs/symptoms and compatible lung involvement on chest computed tomography (CT). For RT-PCR, viral nucleic acid was extracted from each sample using high pure viral nucleic acid extraction kit (Roche-Germany). Then, nucleic acid diagnostic kit (Sansure Biotech-China) was applied to detect the viral RNA. PCR-fluorescence probing was used in this process.

Patients with history of hypersensitivity to methylprednisolone, dexamethasone and tocilizumab or any component of the formulations, uncontrolled diabetes mellitus (random blood sugar ≥ 300 mg/dl), uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in the patients receiving antihypertensive medications) and cardiovascular diseases, acute massive thromboembolic events, active bacterial, fungal, parasitic and viral infections other than SARS-COV-2, active tuberculosis, angle-closure glaucoma, history of myopathy, acute or uncontrolled psychiatric disorders, history of corticosteroids or tocilizumab use, history of immunodeficiency disorders, active malignancy, chemotherapy within the previous three months, pulmonary emboli before or during the treatment and pregnant or lactating women were excluded.

2.3. Procedures

According to the hospital protocol, remdesivir, dexamethasone and oxygen support were the standard of care for all hospitalized patients with severe COVID-19. However considering clinical conditions of patients and availability of drugs, some patients also received either MPP or tocilizumab. Patients were categorized in three groups. Patients in the MPP group received methylprednisolone (250–500 mg daily up to three doses) along with the standard of care. Each dose of methylprednisolone was diluted in 100 ml of normal saline and infused intravenously over one hour. If the oxygen saturation dropped or CRP did not reduce by at least 25% compared with the previous days, the second or third dose of methylprednisolone was administrated. Patients in the tocilizumab group received a single dose of tocilizumab based on the body weight (BW): BW < 70 kg → 400 mg, 70 kg ≤ BW ≤ 90 kg → 600 mg, and BW > 90 kg → 800 mg. Each 400 mg of the product was diluted in 100 ml of normal saline and infused intravenously over one hour. If the desired response (as mentioned for the methylprednisolone group) did not achieve, the second dose of tocilizumab was prescribed. Patients in the dexamethasone group received 8 mg dexamethasone once daily as intravenous injection based on the hospital protocol.

Patients in the tocilizumab group also concomitantly received 8 mg dexamethasone once daily. In the MPP group, the treatment was followed with dexamethasone 8 mg once daily. In all groups, dexamethasone was continued for up to 10 days or hospital discharge.

According to the hospital protocol, all patients also received supportive care including oxygen therapy, fluid and electrolyte management, prophylaxis against stress ulcer and deep vein thrombosis, nutritional support and antibiotics (if needed).

At the time of recruitment, demographic features of patients, baseline diseases, past drug history, initial symptoms, symptoms' onset to hospitalization, baseline vital signs and laboratory data were collected. Patients were visited daily during the hospital stay. After discharge from the hospital, a 28-day follow-up was considered by telephone call.

2.4. Efficacy measures

The primary outcome was time to onset of clinical response. Each patient had a research sheet and patient's chief complaints were recorded at the time of hospital admission. Patients were daily visited and clinical response was considered when patient's primary complaints resolved.

Secondary outcomes were improvement rate of oxygen saturation and CRP, need for ICU admission, duration of hospitalization and 28-day mortality.

The rate of improvement was defined as:

$$\text{Oxygen saturation improvement rate} = \frac{oxygen\ saturation\ at\ discharge - oxygen\ saturation\ at\ inclusion}{duration\ of\ hospital\ stay}$$

$$\text{CRP improvement rate} = \frac{initial\ CRP - final\ CRP}{duration\ of\ hospital\ stay}$$

Table 1
Baseline characteristics of patients.

Variable	Methyl prednisolone group(n = 31)	Tocilizumab group (n = 32)	Dexamethasone group (n = 30)	P-value
Mean age ± SD (year)	50 ± 15	52 ± 14	56 ± 12	0.223
Sex: n (%)				
Male	14 (45.16)	19 (59.37)	13 (43.33)	0.379
Female	17 (54.84)	13 (40.63)	17 (56.67)	
Comorbid conditions: n (%)				
Hypertension	8 (25.81)	6 (18.75)	10 (33.33)	0.423
Obesity	6 (19.35)	8 (25.00)	4 (13.33)	0.509
Diabetes mellitus	5 (16.13)	6 (18.75)	8 (26.66)	0.569
Hypothyroidism	2 (6.45)	0	2 (6.66)	0.334
Liver diseases	2(6.45)	0	0	0.130
Rheumatoid Arthritis	1 (3.22)	0	1 (3.33)	0.585
Hyperlipidemia	0	3 (9.37)	2 (6.66)	0.239
Malignancy	0	2 (6.25)	1 (3.33)	0.373
Renal diseases	0	1 (3.12)	2(6.66)	0.347
Respiratory diseases	0	1 (3.12)	0	0.382
Ischemic heart disease	0	0	3 (10.00)	0.039
Cerebrovascular accident	0	0	2(6.66)	0.117
Drug history: n (%)				
ARBs	5 (16.13)	3 (9.37)	5 (16.66)	0.649
Aspirin	4 (12.90)	2 (6.25)	6 (20.00)	0.272
Beta-blockers	2 (6.45)	3 (9.37)	2 (6.66)	0.887
Metformin	2 (6.45)	2 (6.25)	7 (23.33)	0.060
Levothyroxine	2 (6.45)	1 (3.12)	2 (6.66)	0.784
PPIs	2 (6.45)	1 (3.12)	0	0.362
Azithromycin	1 (3.22)	2 (6.25)	1 (3.33)	0.798
Hydroxychloroquine	1 (3.22)	1 (3.12)	1 (3.33)	0.999
Methotrexate	1 (3.22)	0	0	0.364
Azathioprine	1 (3.22)	0	0	0.364
Sulfasalazine	1 (3.22)	0	0	0.364
H_2-receptor blockers	1 (3.22)	0	0	0.364
Statins	0	4 (12.50)	2 (6.66)	0.130
Insulin	0	1 (3.12)	2 (6.66)	0.338
Clopidogrel	0	0	2 (6.66)	0.117
NSAIDs	0	0	1 (3.33)	0.346
Doxycycline	0	0	1 (3.33)	0.346
Supplements	0	0	1 (3.33)	0.346
Symptoms at admission: n (%)				
Dyspnea	19 (61.29)	21 (65.62)	18 (60.00)	0.891
Cough	18 (58.06)	21 (67.74)	22 (73.33)	0.548
Fatigue	17 (54.84)	16 (50.00)	18 (60.00)	0.732
Myalgia	13 (41.93)	19 (59.37)	18 (60.00)	0.270
Fever	12 (38.71)	15 (46.87)	10 (33.33)	0.547
Chills	9 (29.03)	10 (31.25)	5 (16.66)	0.373
Anorexia	9 (29.03)	9 (28.12)	7 (23.33)	0.865
Nausea	9 (29.03)	5 (15.62)	5 (16.66)	0.345
Headache	7 (22.58)	6 (18.75)	8 (26.66)	0.758
Chest discomfort	7 (22.58)	5 (15.62)	1 (3.33)	0.090
Vomiting	6 (19.35)	4 (12.50)	3 (10.00)	0.549
Diarrhea	3 (9.67)	4 (12.50)	3 (10.00)	0.925
Insomnia	2 (6.45)	3 (9.37)	2 (6.66)	0.887
Pharyngitis	2 (6.45)	2 (6.25)	2 (6.66)	0.998
Dizziness	1 (3.22)	5 (15.62)	3 (10.00)	0.250
Abdominal pain	1 (3.22)	0	1 (3.33)	0.585
Anosmia	0	1 (3.12)	4 (13.3)	0.055
Ageusia	0	0	4 (13.33)	0.012
Lung involvement, mean (%) ± SD				
Right upper and middle lobe	24 ± 17	29 ± 23	24 ± 17	0.669
Right lower lobe	16 ± 12	23 ± 19	15 ± 17	0.261
Left upper lobe and lingula	31 ± 19	36 ± 23	29 ± 23	0.612
Left lower lobe	29 ± 23	32 ± 23	21 ± 23	0.445

ARB: angiotensin receptor blockers, NSAID: non-selective anti-inflammatory drugs, PPI: proton pump inhibitor.

2.5. Safety measures

During the hospitalization, adverse events of the treatments including acute kidney injury (AKI), acute hepatic injury (AHI), dermatologic, gastrointestinal, hematologic [leukocytosis (white blood cell count > 10,000 cells/μL) and thrombocytosis (platelet count > 450,000 cell/μL)], electrolyte disturbances, arrhythmia, myocardial infarction (MI), rise in blood pressure (systolic blood pressure more than 140 mmHg or diastolic blood pressure more than 90 mmHg), peripheral edema, heart failure (HF), thrombosis, elevated blood sugar (blood sugar more than 180 mg/dl), mood changes, anxiety, agitation, delirium, sleep disturbances, myopathy, weakness, oral candidiasis, and secondary infections were investigated.

The definition of AKI was based on the KDIGO guideline [19]. In addition, AHI was defined as an increase of more than three times the upper limit of aminotransferases or total bilirubin > 2 mg/dl [20]. MI, HF, and thrombosis were diagnosed according to the last updated guidelines of the European Society of Cardiology (ESC) [21–23]. Secondary infections were considered according to the signs and symptoms of infection, radiological findings or microbial culture.

Table 2
Vital signs and laboratory data at the time of hospital admission.

Variable (Mean ± SD)	Methyl prednisolone group(n = 31)	Tocilizumab group (n = 32)	Dexamethasone group (n = 30)	P-value
Vital signs				
Temperature (°C)	37.08 ± 0.90	36.79 ± 0.55	36.74 ± 0.53	0.138
Heart rate (beats /minute)	88 ± 13	85 ± 10	89 ± 14	0.391
Respiratory rate (breaths /minute)	28 ± 11	23 ± 6	22 ± 4	0.012
SBP (mm Hg)	121 ± 16	114 ± 12	116 ± 12	0.180
SPO_2 (%)	85 ± 4	84 ± 6	85 ± 5	0.477
Laboratory data				
WBC (cells /μl)	6080 ± 3155	6337 ± 3455	7373 ± 3760	0.313
ALC (cells /μl)	686 ± 287	808 ± 598	1075 ± 430	0.008
Hemoglobin (g/dl)	12.98 ± 1.78	13.24 ± 1.98	13.57 ± 1.64	0.461
Platelet count (cells × 10^3/μl)	199 ± 89	174 ± 51	200 ± 68	0.284
BUN (mg/dl)	36 ± 16	42 ± 21	43 ± 32	0.517
Creatinine (mg/dl)	0.97 ± 0.27	1.03 ± 0.40	1.03 ± 0.52	0.766
Sodium (meq/l)	137 ± 3	138 ± 3	136 ± 4	0.030
Potassium (meq/l)	4.07 ± 0.53	4.06 ± 0.71	4.35 ± 0.73	0.160
Calcium (mg/dl)	8.15 ± 0.44	8.30 ± 0.64	8.39 ± 0.80	0.354
Phosphorus (mg/dl)	3.38 ± 0.72	3.33 ± 0.48	3.45 ± 0.84	0.824
Magnesium (mg/dl)	2.21 ± 0.24	2.26 ± 0.31	2.16 ± 0.36	0.476
Blood sugar (mg/dl)	160 ± 58	179 ± 96	169 ± 86	0.692
AST (u/l)	51 ± 26	51 ± 32	61 ± 40	0.431
ALT (u/l)	46 ± 37	43 ± 33	47 ± 32	0.925
ALP (u/l)	230 ± 155	157 ± 60	193 ± 72	0.026
Total bilirubin (mg/dl)	0.69 ± 0.27	0.76 ± 0.34	0.75 ± 0.34	0.655
CRP (mg/dl)	126 ± 33	136 ± 29	100 ± 44	0.001
ESR (mm/h)	65 ± 23	52 ± 25	60 ± 27	0.120
LDH (u/l)	797 ± 206	816 ± 341	821 ± 315	0.808

ALC: absolute lymphocyte count, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, SBP: systolic blood pressure, SPO_2: peripheral oxygen saturation, WBC: white blood cell.

2.6. Statistical analysis

The quantitative variables were shown as mean ± standard deviation (SD) and qualitative variables as frequency (percentage). One-way ANOVA and Chi-square test were used to compare the quantitative and qualitative data, respectively.

The Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of the primary and secondary outcomes. The dexamethasone group was considered as the reference group. Time to onset of clinical response and 28-day mortality was estimated using Kaplan-Meier analysis and compared with a log-rank test. P-value < 0.05 was considered as statistical significance. All statistical analyses were performed by SPSS software (version 26.0).

Table 3
Medications during hospitalization.

Treatment; n (%)	Methyl prednisolone pulse(n = 31)	Tocilizumab (n = 32)	Dexamethasone (n = 30)	P-value
Antiviral agents				
Remdesivir	31 (100)	32 (100)	30 (100)	–
Antibiotic therapy: n (%)				
Clindamycin	1 (3.22)	0	2 (6.66)	0.332
Meropenem	0	3 (9.37)	0	0.177
Piperacillin-tazobactam	0	2 (6.25)	0	0.143
Vancomycin	0	2 (6.25)	0	0.143
Ciprofloxacin	0	1 (3.12)	3 (10.00)	0.145
Levofloxacin	0	1 (3.12)	0	0.382
Symptomatic treatments: n (%)				
Diphenhydramine	11 (35.48)	11 (34.37)	12 (40.00)	0.889
Dextromethorphan	8 (25.81)	15 (46.87)	7 (23.33)	0.090
Acetaminophen	8 (25.81)	14 (43.75)	9 (30.00)	0.286
NSAIDs	4 (12.90)	5 (15.62	3 (10.00)	0.804
Anti-emetics	4 (12.90)	2 (6.25)	0	0.122
Stress ulcer prophylaxis: n (%)				
H_2 receptor antagonists	21 (67.74)	22 (68.75)	22 (73.33)	0.880
PPIs	10 (32.26)	10 (31.25)	8 (26.67)	0.880
Deep vein thrombosis prophylaxis: n (%)				
Heparin	29 (93.55)	28 (87.50)	30 (100)	0.135
Enoxaparin	2 (6.45)	4 (12.50)	0	0.135
Cardiovascular drugs: n (%)				
Statins	4 (12.90)	5 (15.62)	5 (16.66)	0.913
ARBs	4 (12.90)	4 (12.50)	6 (20.00)	0.654
Aspirin	3 (9.67)	7 (21.87)	2 (6.66)	0.164
Beta-blockers	2 (6.45)	4 (12.50)	2 (6.66)	0.624
CCB	2 (6.45)	2 (6.25)	0	0.369
ACEIs	0	2 (6.25)	1 (3.33)	0.373
Anti-diabetic agents: n (%)				
Insulin	5 (16.13)	8 (25.00)	9 (30.00)	0.433
Psychotropic drugs: n (%)				
Melatonin	11 (35.48)	18 (56.25)	7 (23.33)	0.026
Benzodiazepines	4 (12.90)	7 (21.87)	3 (10.00)	0.391
Antidepressants	1 (3.22)	3 (9.37)	0	0.179
Antipsychotics	0	2 (6.25)	0	0.143
Supplements: n (%)				
Multivitamins	7 (22.58)	4 (12.50)	3 (10.00)	0.344
Vitamin C	7 (22.58)	3 (9.37)	2 (6.66)	0.137
Vitamin D	4 (12.90)	0	0	0.015

ACEI: angiotensin converting enzyme inhibitor, CCB: calcium channel blocker.

3. Results

3.1. Participants

In this study, 31, 32, and 30 patients were included in the MPP, tocilizumab, and dexamethasone groups, respectively. The mean age of patients was 50 years in the MPP group, 52 years in the tocilizumab group, and 56 years in the dexamethasone group. The most common comorbidities were hypertension, diabetes mellitus, and obesity. Except for ischemic heart disease, no significant difference was noted between the groups. The patients' comorbidities (hypertension, diabetes mellitus and ischemic heart disease) were stable at the time of recruitment. The most commonly used drugs were angiotensin receptor blockers, aspirin and metformin. The common complaints of patients at the time of hospital admission were cough, dyspnea, and fatigue (Table 1). Except for respiratory rate, there was no significant difference between the groups. Absolute lymphocyte count (ALC), sodium level, alkaline phosphatase, and CRP were different among the baseline laboratory data (Table 2).

The mean ± SD days from onset of the symptoms to the hospital admission was 9 ± 2, 8 ± 2, and 9 ± 3 in the MPP, tocilizumab, and

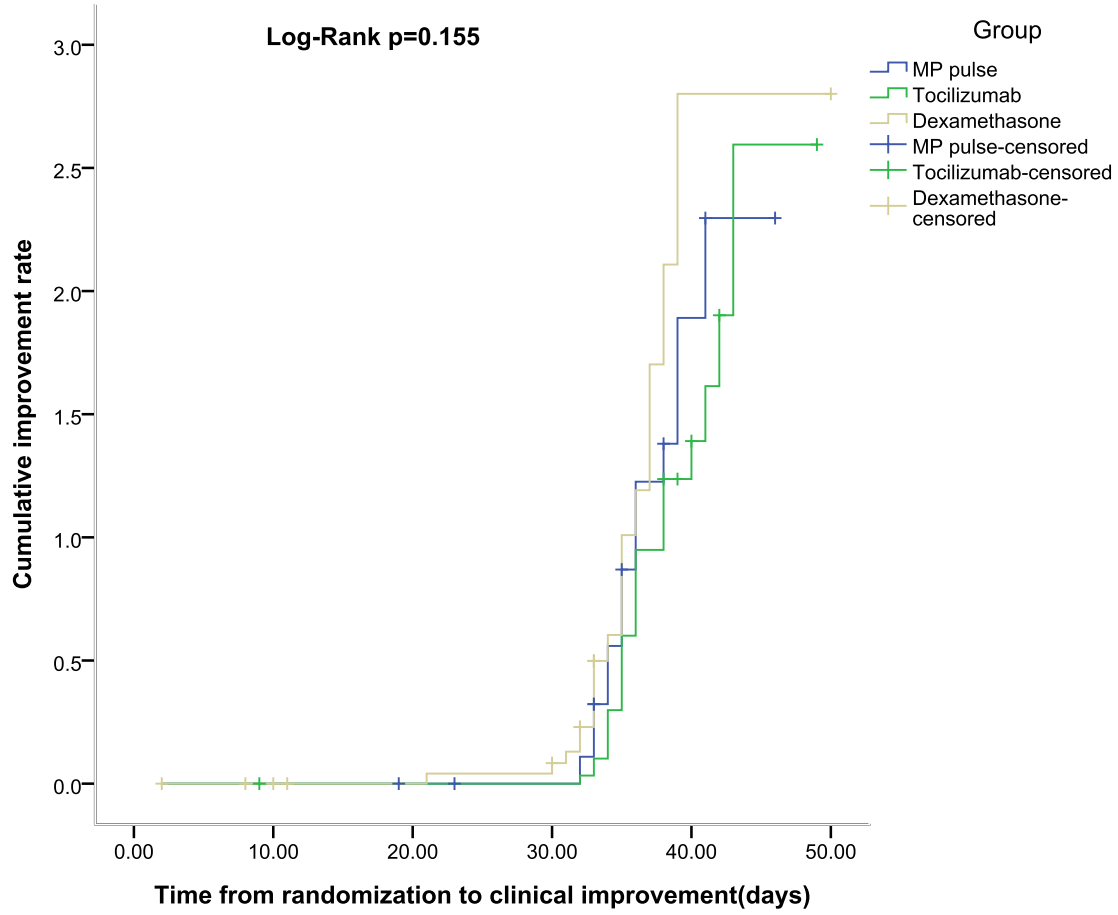

Fig. 1. Estimation of cumulative clinical response by Kaplan-Meier plot. Legend: Clinical response occurred faster in patients in the tocilizumab group than other groups but estimated cumulative clinical response was not different between the groups (p = 0.155).

dexamethasone groups respectively (p = 0.904).

RT-PCR test was performed and in 19 (79.16%), 23 (92%), and 23 (79.31%) patients in the MPP, tocilizumab, and dexamethasone groups were positive respectively. The lung involvement location was not statistically different between the groups (Table 1).

Respiratory support modalities were comparable among the patients. The nasal cannula was used for one patient in each group. Respiratory support was applied through simple face mask or face mask with reservoir bag in 28, 29, and 25 patients in the MPP, tocilizumab, and dexamethasone groups respectively. Non-invasive ventilation was applied for three patients (two patients in the MPP group and one in the tocilizumab group). One patient in the tocilizumab group and four patients in the dexamethasone group required invasive mechanical ventilation.

Although no significant difference was detected between the groups regarding the rate of antibiotic administration, more patients in the tocilizumab group received antibiotic. In addition, there was no significant difference between the groups in terms of symptomatic treatments, stress ulcer and deep vein thrombosis prophylaxis, cardiovascular drugs, anti-diabetic agents, psychotropic medications (apart from melatonin), and supplements (apart from vitamin D) during hospitalization (Table 3).

Mean administered dose of MPP and tocilizumab were 658 ± 372 and 1088 ± 349 mg respectively.

3.2. Efficacy

Although the difference was not significant (p = 0.090), clinical response occurred faster in the tocilizumab group than other groups (10 vs. 16 days). Clinical response was observed in 74.19%, 81.25%, and 60% of patients in the MMP, tocilizumab, and dexamethasone groups, respectively (p = 0.238). Based on the Cox regression analysis and considering dexamethasone group as the reference group, HR (95% CI) of clinical response was 1.08 (0.65–1.79) and 1.46 (0.89–2.39) in the MPP and tocilizumab groups respectively. Since baseline respiratory rate, ALC and CRP were different between the groups, their effects as the confounders were examined by adjusted Cox regression hazards model. Adjusted HR (95% CI) of clinical response for the MPP and tocilizumab groups was 1.40 (0.76–2.60) and 1.47 (0.84–2.59) respectively. Estimation of time to onset of clinical response by Kaplan-Meier analysis is shown in Fig. 1. The improvement rate of oxygen saturation and CRP were not statistically different between the groups (p = 0.791 and p = 0.372 respectively). During study, six patients were transferred to ICU and five of them were intubated. Duration of hospital stay were comparable between the groups (p = 0.095). During hospitalization, four patients died in the dexamethasone group while only one patient died in each of the MPP and tocilizumab groups [HR (95% CI): 0.41 (0.05–3.55) and HR (95% CI): 0.30 (0.04–2.56) in the MPP and tocilizumab groups respectively]. During the 28-day follow-up, only two patients died that

Table 4
Efficacy measures.

Measure; mean	Methyl prednisolone pulse(n = 31)	Tocilizumab (n = 32)	Dexamethasone (n = 30)	P-value
Clinical response: n (%)	23 (74.19)	26 (81.25)	18 (60.00)	0.238
Mean time to onset of clinical response (days) ± SD	16.04 ± 10.58	10.38 ± 9.55	16.67 ± 12.05	0.09
Oxygen saturation improvement rate	0.69 ± 0.84	0.85 ± 0.94	0.81 ± 0.74	0.791
Improvement rate of CRP	17 ± 5	15 ± 6	18 ± 7	0.372
Need for ICU admission: n (%)	1 (3.22)	1 (3.12)	4 (13.33)	0.176
Need for mechanical ventilation: n (%)	0	1 (3.12)	4 (13.33)	0.055
Mean duration of hospital stay (days) ± SD	8.00 ± 3.89	8.97 ± 3.60	6.83 ± 3.98	0.095
In-hospital mortality: n (%)	1 (3.22)	1 (3.12)	4 (13.33)	0.176
28-day mortality: n (%)	2 (6.45)	1 (3.12)	5 (16.66)	0.143

were in the MPP and dexamethasone groups (Table 4). The Kaplan-Meier analysis of 28-day mortality is demonstrated in Fig. 2.

3.3. Safety

Although was not statistically different, leukocytosis was more common in the tocilizumab group than the MPP and dexamethasone groups. Compared with the MPP and dexamethasone groups, more patients in the tocilizumab group complained from the sleep disturbances ($p = 0.019$). Thrombocytosis was more common in the dexamethasone group than other groups ($p = 0.018$). Interestingly, number of elevated blood sugar episodes in the MPP group was less than other groups. The incidence of oral candidiasis was comparable between the groups. Unexpectedly, mood changes and agitation were less frequent in patients in the MPP group than patients in the tocilizumab group. However, secondary infections occurred more frequently in the tocilizumab group than other groups ($p = 0.422$). Rise in blood pressure was reported in two patients of each group ($p = 0.998$). Three patients in the dexamethasone group experienced peripheral edema ($p = 0.039$). Other safety outcomes are shown in Table 5.

4. Discussion

In this study, the efficacy and safety of MPP and tocilizumab were compared in patients with severe COVID-19 who had evidence of hyperinflammation (CRP $\geq$ 75 mg/dl) within the first 24 h of hospital admission. Although occurred faster in the tocilizumab group, time to onset of clinical response as the primary outcome of study was not statistically different among the patients treated with MPP or tocilizumab. Also, two groups were comparable in terms of clinical response, improvement rate of oxygenation and CRP, need for ICU admission, duration of hospital stay, 28-day mortality and incidence of adverse events (except sleep disturbances).

Comparable efficacy and safety of MPP and tocilizumab in this primary study are remarkable and interesting that have to be confirmed in future randomized clinical trials. The results may be considerable for developing countries particularly those with limited resources. The average cost of a 400 mg vial of tocilizumab (Temziva®, ArioGen Pharmed Pharmaceutical Co., Iran) is about $100 while a 500 mg vial of methylprednisolone succinate is less than $1. So, MPP may be considered as a cheap and available alternative in the treatment of patients with severe COVID-19.

Role of corticosteroid therapy in patients with COVID-19 was established. In RECOVERY trial, 6 mg dexamethasone daily for up to 10 days reduced 28 days mortality by 17% compared with the usual care in patients with COVID-19 who required supplemental oxygen. This effect was more pronounced among patients who were receiving mechanical ventilation (rate ratio: 0.64) [6]. Consequently, IDSA, NIH, and WHO included corticosteroids for the treatment of hospitalized patients with COVID-19 who are hypoxemic and require supplemental oxygen [7–8,24]. The recommended dose and duration are consistent with the RECOVEY trial. Higher doses of corticosteroids are not recommended or suggested in these guidelines.

However, higher doses of corticosteroids showed favorable results in a number of clinical trials. Tomazini et al. examined the efficacy of dexamethasone with a dose of 20 mg daily for five days, followed by 10 mg daily for additional five days in patients with moderate to severe COVID-19. The number of days alive and free from the ventilator significantly increased following treatment with high-dose dexamethasone [25]. The efficacy of high-dose dexamethasone (20 mg daily for five days and then 10 mg daily for additional five days) was compared with the low dose (6 mg daily for ten days) in hospitalized patients with moderate to severe COVID-19. Clinical deterioration within 11 days from the randomization reduced by 57% with high-dose dexamethasone [26]. The effect of MPP as 250 mg daily for three days was assessed among patients with severe COVID-19 before intubation. Mortality was significantly lower in patients treated with MPP than the standard of care (HR: 0.29, 95% CI: 0.15–0.56) [9].

It should be noted that these beneficial effects have not been repeated in other studies. The COVID STEROID 2 trial was designed to compare the efficacy of high-dose dexamethasone (12 mg daily) with low-dose dexamethasone (6 mg daily) in COVID-19 patients with severe hypoxemia. The number of days alive without life support was the primary endpoint. The adjusted mean difference between the groups was 1.3 days ($p = 0.07$). Also 28-day and 90-day mortality were not significantly different between the groups. However, the authors concluded that the power of the study might not be enough to detect a significant difference [27]. In another RCT, high-dose dexamethasone improved the ventilator-free days same as the low-dose dexamethasone, although the hazards of successful discontinuation from ventilator significantly increased by high-dose dexamethasone [28].

The efficacy of MPP and dexamethasone was compared in patients with severe COVID-19. Pinzon et al examined the inflammatory biomarkers and clinical outcomes of 105 patients who received MPP (250 to 500 mg daily for three days followed by prednisolone 50 mg daily for 14 days) versus 111 patients who were treated by dexamethasone (6 mg daily for 7 to 10 days). At the end of study, serum levels of inflammatory biomarkers, requirement for ICU admission and recovery time were significantly reduced following treatment with MPP compared with

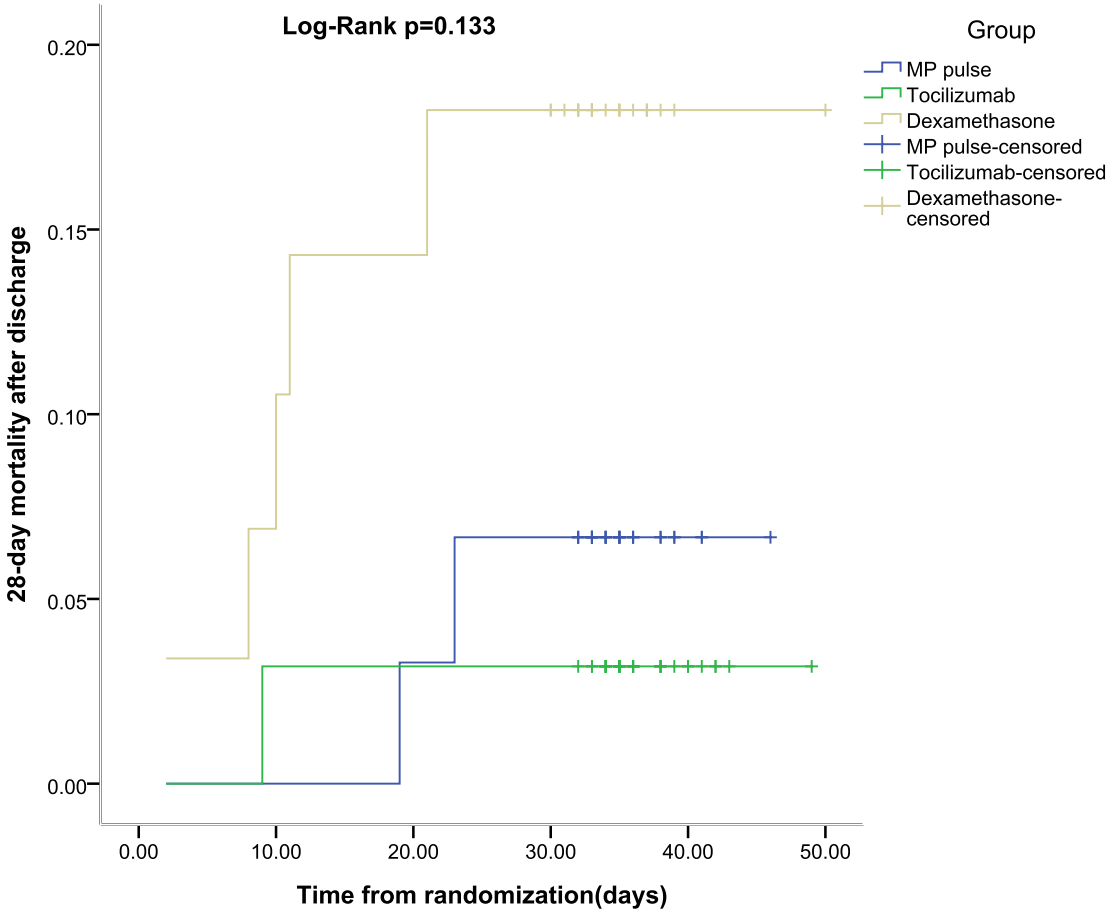

Fig. 2. Estimation of 28-day survival by Kaplan-Meier plot. Legend: Estimated 28-day mortality was not different between the tocilizumab, MPP and dexamethasone groups ($p = 0.133$).

dexamethasone [29]. In favor of better clinical outcomes of patients with COVID-19 following MPP treatment versus dexamethasone, we can refer to Ranjbar et al study. In this RCT, patients were randomly assigned to either methylprednisolone group (2 mg/kg/day) or dexamethasone group (6 mg daily). Clinical status at days 5 and 10 and 28-day all-cause mortality were the primary outcomes. Need for ICU admission and invasive mechanical ventilation were secondary outcomes. Although mortality did not change significantly, patients who were received methylprednisolone experienced significantly better clinical status at days 5 and 10 and need for invasive mechanical ventilation was less than patients who were treated with dexamethasone [30].

The results of early RCTs in terms of the efficacy of tocilizumab in patients with COVID-19 were not promising. However, criticisms were later made about the administration time of tocilizumab, severity of the disease, different phases of the inflammatory responses and heterogenicity of patients. In the COVACTA trial, the efficacy and safety of tocilizumab were tested among patients with severe COVID-19 who had baseline oxygen saturation $< 93\%$ or arterial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO_2) < 300 mmHg. Approximately 40% of patients were intubated at baseline. The primary outcome was clinical status at day 28, which was not significantly different in patients who received tocilizumab compared with placebo ($p = 0.31$). Also, 28-day mortality was comparable between the groups (19.7% vs. 19.4%) [13]. In another RCT, which included patients with moderate COVID-19 (97% of them were in medical wards at the time of randomization), tocilizumab did not reduce need for invasive mechanical ventilation or death (HR: 0.83, 95% CI: 0.38–1.81). Also, it did not change disease progression at day 14 (HR: 1.11, 95% CI: 0.59–2.10) [14].

However, subsequent RCTs showed positive effects and survival benefits of tocilizumab in patients with COVID-19. In the EMPACTA trial, patients with baseline oxygen saturation less than 94% and lung involvement in chest imaging were randomly assigned to tocilizumab plus the standard of care group or the standard of care alone group. The patients who required non-invasive or invasive mechanical ventilation at the time of randomization were excluded. Tocilizumab significantly decreased the probability of progression to intubation or death (HR: 0.56, 95% CI: 0.33–0.97). It is necessary to mention that all-cause mortality at day 28 was not significantly different between the groups [31]. These beneficial effects were also demonstrated in the REMAP-CAP trial. In this trial, patients received tocilizumab within 24 h of the initiation of organ support in ICU. Respiratory and cardiovascular organ support-free days were the primary endpoint. The median adjusted cumulative odds ratio was 1.64 (95% CI: 1.17–2.91). In contrast to the previous trial, tocilizumab improved survival [15]. Finally, the positive effects of tocilizumab were approved in the RECOVERY trial with adequate sample size. During this study, 4116 patients were randomly assigned to standard of care group or standard of care plus tocilizumab group. The major inclusion criteria were oxygen saturation below 92% and CRP ≥ 75 mg/dl. The primary endpoint was 28-day mortality. Finally, 31% of the patients who received tocilizumab died compared with 35% in the standard of care group (rate ratio: 0.85, 95% CI: 0.76–0.94). Tocilizumab significantly reduced the probability

Table 5
Safety measures.

Measure; n (%)	Methyl prednisolone pulse(n = 31)	Tocilizumab (n = 32)	Dexamethasone (n = 30)	P-value
Leukocytosis	12 (38.71)	16 (50.00)	10 (33.33)	0.393
Sleep disturbances	9 (29.03)	20 (62.50)	11 (36.66)	0.019
Elevated blood sugar	9 (29.03)	12 (37.50)	9 (30.00)	0.733
Oral candidiasis	6 (19.35)	5 (15.62)	5 (16.66)	0.922
Gastrointestinal	5 (16.13)	6 (18.75)	1 (3.33)	0.157
Electrolyte disorders	4 (12.90)	8 (25.00)	7 (23.33)	0.439
Mood changes	3 (9.67)	8 (25.00)	3 (10.00)	0.151
Agitation	3 (9.67)	5 (15.62)	2 (6.66)	0.509
Secondary infections	3 (9.67)	4 (12.50)	1 (3.33)	0.422
Thrombocytosis	3 (9.67)	1 (3.12)	8 (26.66)	0.018
Anxiety	2 (6.45)	6 (18.75)	2 (6.66)	0.197
Rise in blood pressure	2 (6.45)	2 (6.25)	2 (6.66)	0.998
Thrombosis	2 (6.45)	0	1 (3.33)	0.350
Dermatologic	1 (3.22)	0	0	0.364
Acute kidney injury	0	3 (9.67)	5 (16.66)	0.066
Arrhythmia	0	2 (6.25)	3 (10.00)	0.215
Acute hepatic injury	0	2 (6.25)	2 (6.66)	0.351
Weakness	0	1 (3.12)	2 (6.66)	0.338
Peripheral edema	0	0	3 (10.00)	0.039
Heart failure	0	0	2 (6.66)	0.117
Myocardial infarction	0	0	2 (6.66)	0.117
Delirium	0	0	1 (3.33)	0.346

of progression to intubation (risk ratio: 0.84, 95% CI: 0.77–0.92) [16].

Our study results should be compared with studies which compared the efficacy of MPP and tocilizumab in patients with COVID-19. Aslan et al designed a prospective observational study to compare the efficacy of MPP (≥250 mg daily for three days) and tocilizumab (8 mg/kg single dose or 400 mg daily for two days). The patients were divided into MPP group, tocilizumab group and combination (MPP + tocilizumab) group. In contrast to our study, critically ill patients in ICU were included. Similar to our patients, participants received standard dose of corticosteroid for 7–10 days. The definition of hyperinflammation in that study was different with our study. The age of patients in the tocilizumab group was significantly lower than other two groups. Also, proportion of the patients with high fever (temperature > 38) was statistically different among patients in the groups. The primary outcome was 28-day mortality in ICU. In the MPP, tocilizumab and combination groups, 55%, 60% and 50% of the patients died during ICU stay [32]. The high mortality was predictable considering the included population. In consistent with our study, the efficacy of MPP and tocilizumab was not statistically different.

Kumar et al. compared the efficacy of MPP (1 g daily for three days) and tocilizumab (8 mg/kg as a single dose, maximum 800 mg) in TAME-COVID, a multicenter retrospective cohort study. All patients received the standard of care including low-dose methylprednisolone (1 mg/kg twice daily). Patients with severe COVID-19 who had oxygen saturation ≤ 93% or PaO2/FiO_2 < 300 were included. Intubation rate was the primary outcome of study. Although patients in the tocilizumab group had more poor prognostic factors (frequent baseline coronary artery disease, higher respiratory rate, heart rate, and CRP, and a higher proportion of severe ARDS) than the MPP group, intubation rate was significantly lower among patients who were treated with tocilizumab. However, 30-day mortality was comparable between the groups (34% in the MPP group vs. 36% in the tocilizumab group) [33]. As characteristics of patients were not matched and the incidence of the primary outcome was not adjusted based on the confounding factors, the results should be interpreted with caution. Apart from the different design, patients with critical conditions (hypotension and organ failure) were included in this study. However, compared with our study, it seems that the sample size of Kumar et al. study was enough to identify differences between the groups.

In another retrospective cohort study, the efficacy of MPP (500 mg daily for three days) and tocilizumab (two 400 mg fix doses) was compared in patients with mild ARDS induced by COVID-19. Dosing of MPP and tocilizumab was relatively similar to our study but the inclusion and exclusion criteria were different among the studies. Although the details of the baseline characteristics and applied supportive care were not addressed, no significant difference in mortality, need for ICU admission, intubation and duration of ICU or hospital stay was detected between the groups [34]. In line with our suggestion, MMP therapy was considered as a cheap and available alternative for treatment of severe COVID-19.

SAM-COVID-19 was a multicenter retrospective cohort study that compared the effects of corticosteroids and tocilizumab on intubation rate or death in patients with COVID-19. The patients were enrolled into either tocilizumab, intermediate to high-dose of a corticosteroid, MPP or combination group. At least one clinical and laboratory criteria indicating hyperinflammation was considered for eligibility and patients who required invasive mechanical ventilation at baseline were excluded. The rate of intubation or death was main outcomes of study. Since the study was retrospective and patients had different baseline characteristics, various adjusted analyses including propensity score and inverse probability of treatment weights (IPTW) were used for case matching. In all analyses (crude and adjusted) tocilizumab reduced rate of intubation or death. Only in IPTW analysis, the use of MPP was associated with lower incidence of intubation or death. Use of intermediate to high dose of corticosteroid and combination therapy did not change risk of intubation or death. Tocilizumab significantly reduced the mortality and improved survival [35]. These results were in favor of tocilizumab and to some extent MPP in the treatment of COVID patients with evidence of hyperinflammation. Although this study was retrospective but large sample size is considerable.

Our study was a prospective cohort but non-randomization design and small sample size were main limitations.

5. Conclusion

In patients with severe COVID-19, although tocilizumab caused faster clinical response but showed comparable efficacy with MPP in terms of clinical response, improvement rate of oxygenation and CRP, need for ICU admission, duration of hospital stay and 28-day mortality. Except sleep disturbances, adverse events were not statistically different among patients in the tocilizumab and MPP groups. When or where access to tocilizumab is a problem, MPP may be considered as an

alternative in the treatment of hospitalized patients with severe COVID-19. These findings should be examined in future randomized clinical trials.

CRediT authorship contribution statement

Ladan Abbasian: Investigation, Writting - review and editing. **Negar Toroghi:** Investigation, Data curation. **Hamid Rahmani:** Formal analysis, Writing original draft. **Hossein Khalili:** Conceptualization, Methodology, Editing. **Malihe Hasannezhad:** Data curation, Investigation. **Fereshteh Ghiasvand:** Data curation, Investigation. **Sirous Jafari:** Data curation, Investigation. **Mohammadreza Salehi:** Data curation, Investigation. **Faeze Salahshour:** Data curation, Investigation. **Mahsa Azadbakhsh Kanaf Gorabi:** Data curation, Investigation. **Fateme Alizade:** Data curation, Investigation. **Sara Ghaderkhani:** Data curation, Investigation. **Maryam Nakhostin:** Data curation, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to thank the nurses and other staffs of Imam Khomeini Hospital Complex for their kind supports. No grant was received regarding this work.

Funding

The authors did not receive any fund for this work.

Availability of data and materials

Available per request.

Ethics approval

The Ethics Committee of Tehran University of Medical Sciences approved the protocol of study (ID: IR.TUMS.MEDICINE.REC.1400.322).

Consent to participate

Inform consent was obtained from all participants or from a responsible first-degree family member.

Consent for publication

Patients signed informed consent regarding publishing their data.

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