Cohort Study

Melatonin as adjunctive therapy in patients admitted to the Covid-19

Elahe Karimpour-razkenari [a], Fahimeh Naderi-Behdani [a], Ali Salahshoor [b], Fatemeh Heydari [c,*],
Abbas Alipour [d], Afshin Gholipour Baradari [e]

[a] Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[b] Department of Anesthesiology and Critical Care Medicine, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran
[c] Department of Anesthesiology and Critical Care Medicine, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran
[d] Community Medicine Department, Medical Faculty, Mazandaran University of Medical Sciences, Sari, Iran
[e] Professor of Anesthesiology and critical care, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

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ABSTRACT

Objective: Coronavirus has disrupted the natural order of the world since September 2019 with no specific medication. The beneficial effects of melatonin on sepsis and viral influenza were demonstrated previously, but its effects on covid-19, especially COVID -19 ICU, is unclear. Therefore, our aim was to determine the effects of melatonin in COVID-19 ICU patients.
Methods: This is a retrospective cohort study in which the records of patients admitted to COVID -19 ICU of (XXX) during March to June 2020 were reviewed. According to inclusion criteria, patients who received 15 mg of melatonin daily were called MRG and the rest were called NMRG.
Results: Thirty-one patients were included and analyzed, of which twelve patients were in MRG. Demographic and clinical characteristics, and laboratory data were similar between two groups at ICU admission. Melatonin had no significant effect on ICU duration, CRP and ESR, also the trend of changes was in favor of melatonin. Nevertheless, melatonin significantly reduced the NLR (OR = −9.81, p = 0.003), and also declined mortality marginally (p = 0.09). Melatonin was well tolerated with no major adverse effects, moreover the thrombocytopenia occurrence was significantly lower in MRG (p = 0.005). In MRG, survival increased and mortality risk decreased, although the difference between groups wasn't significant (p = 0.37), which might be related to the small sample-size.
Conclusion: Our study showed that melatonin is unlikely to reduce mortality among COVID19 patients and with no significant effect on disease-specific biochemical parameters.

Author contribution

Please specify the contribution of each author to the paper, eg study concept or design, data collection, data analysis or interpretation, writing the paper, others, who have contributed in other ways should be listed as contributors. Elahe Karimpour-razkenari and Dr. Abbas Alipour: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Fahimeh Naderi-Behdani and Afshin Gholipour Baradari: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Ali Salahshoor and Fatemeh Heydari: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

1. Introduction

Respiratory infections associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impressed the world since September 2019. SARS-CoV-2 is a member of beta coronavirus family, with high similarity in pathological parameters, and main effect such as oxidative stress and inflammation [1]. As well as other member of this family, it is a respiratory virus and caused fetal pneumonia with lung destruction [2]. However the mortality rate is lower than other family members [3].

Melatonin (5-methoxy-N-acetyltryptamine) is a natural neuroendocrine which is synthesized and released by the pineal gland, it has various vital functions such as effective antioxidant, free radical scavenging and anti-inflammatory activity through its normal and

pathophysiological circumstances [4–6]. Moreover, it might aroused the messenger RNA (mRNA) levels of several antioxidant enzymes, increase anti-inflammatory capacity and improve the immune system of human [7]. Melatonin effects several cell signaling pathways, including the ERK and MAPK pathways which play an important role in regulating the immune system [8–10]. In addition, by affecting the Erk/Akt/NFkB pathway, H2O2-induced oxidative stress is reduced [11]. Also, a randomized double-blind controlled trial of melatonin in patients with hemorrhagic stroke found anti-inflammatory and endothelial stabilizing functions with an acceptable safety profile [12]. as well, other studies showed high biological safety for melatonin, even the high dose of melatonin can be used without serious side effects [13,14].

Consequently, antioxidants are used to reduce oxidative stress and proinflammatory mediators in patients infected with covid-19, and readjustment of the immune system is required in these patients. In this regard, melatonin would be a good choice to improve the immune system against covid-19 infection and related side effects. In this study we retrospectively surveyed the benefit and adverse effects of high dose melatonin in COVID-19 intensive care unit (COVID-19 ICU).

2. Methods

This retrospective cohort study was performed to evaluate the effects of melatonin in patients with covid-19 infection and admitted to the COVID-19 ICU (XXX).There was no need for the informed consent of patients or their caregivers because the study was retrospective and patients' information was anonymous.

All patients records who are admitted to COVID-19 ICU from 13-march-2020 to 30-may-2020 were reviewed, and the patients were less than 18 years old, pregnant, participating in other study, had severe leukocytosis (more than 50000), severe thrombocytopenia (less than 50000) at admission, negative reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal secretions for COVID-19, undergoing chemotherapy or radiotherapy and using melatonin before admitting to ICU were excluded from the study. Demographic characteristics of patients including age, sex, weight, cause of hospitalization, acute physiology and chronic health evaluation II (APACHE II) score and National Early Warning Score (NEWS2), white blood cell count (WBC), lymphocytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and clinical manifestations upon ICU admission, course of symptoms during hospitalization, daily ventilation and the severity of the disease info as well as standard care and medicine were extracted from patients' documentations.

The Kidney Disease Improving Global Outcomes criteria was used to determined Acute kidney injury (AKI) [15]. Liver dysfunction was defined when abnormal lab test seen such as: hepatic enzyme levels elevated >3 times the upper limit of normal amount or serum total bilirubin higher than 2 mg/dl [16]. The definition of WHO were used for anemia [17], the platelet count less than 100000/μL defined as thrombocytopenia, and electrolytes abnormality were considered when abnormal concentration was observed in lab test.

The primary outcomes were considered as ICU duration, and death during hospitalization. The effect on laboratory test and inflammatory factors, requiring and duration of mechanical ventilation (MV), and any adverse effect were reflected the secondary outcomes.

After collecting information, to investigate the effects of melatonin in patients who received melatonin during hospitalization and those who did not receive melatonin, SPSS version 24 was used. We report the categorical variables as percentage and frequency, and continuous variables as median (interquartile). Due to abnormal distribution of the data comparison of continuous variables between groups was performed using the Mann-Whitney U tests and Chi-square tests were used for categorical variables. Repeated measured ANOVA, multivariant regression, EEG model, Kaplan-Meier method and The Log Rank Test were used to compare the correlation between the variables and survival time. Two-sided P value < 0.05 was considered statistically significant.

Unique identifying number is: research registry:7486.

The methods were written in compliance with STROCSS 2021 guidelines [18].

3. Results

During this period, 45 patients were admitted to COVID-19 ICU, but 14 files were not analyzed due to exclusion criteria. Twelve of these patients had received melatonin (high-dose melatonin, 15 mg daily), which were considered as melatonin receiving group (MRG) and the rest of the patient were defined as non-melatonin receiving group (NMRG).

Analyses showed approximately 50% of patient were female and median of age was over 60 years in both groups. Patients demographics and clinical characteristics were comparable in baseline, and there was no statistically significant difference between the two groups (Table 1). hypertension and diabetes were there the most common comorbidity in both groups. In addition, dyspnea and loss-of-consciousness in both groups were the most common symptoms; however, the difference was not statistically significant (Table 1).

Vital signs and laboratory data at admission to ICU are shown in Table 1, and were not significantly different in the two groups. Although oxygen saturation at ICU admission was marginally significant (85.0 ($\pm$11.28) and 89.0 ($\pm$10.47) for MRG and NMRG respectively, p = 0.077).

Almost all of patients received lopinavir/ritonavir and interferon beta-1a with no statistically difference between two groups. It should be noted that this was based on national COVID-19 guideline of that time. Additionally, corticosteroids especially dexamethasone, vitamin C, atorvastatin and heparin were used with same protocol for all the patient.

The efficacy and safety evaluation of melatonin is described in Table 2. Melatonin had no effect on ICU duration, requiring, mortality, and duration of MV in compare to NMRG.

The melatonin has no beneficial effect on NEWs2, but repeated measured ANOVA showed that variation in news2 score was significant over the time, however the interaction between melatonin and time was not significant (Table 4). Melatonin has significant effect on CRP, P = 0.05 but was insignificant in terms of ESR, P = 0.06 and NLR, P = 0.08, (Table 4). Regarding to Platelet, the interaction and time effect were significant (p = 0.049, 0.00 respectively) (Table 4).

It should be mentioned that the safety concern analysis with ANOVA showed no significant deference between two groups in terms of adverse effects including: LFT abnormality, electrolyte abnormality, anemia, and thrombocytopenia (Table 3).

EEG model was used to adjust the heterogenicity between two groups. The factors which differed between groups such as O2sat, nausea and vomiting were adjusted, and the result are shown in Table 4. Among the factors that were considered as an outcome, NLR was significant factor after adjustment (−9.81(−16.20–3.42), p = 0.003). Also, in the case of mortality, the difference between two groups was marginally significant, which may be due to small sample size. The EEG model for thrombocytopenia showed that melatonin could reduce the risk for thrombocytopenia (0.02(0.00–0.32), p = 0.005).

Finally, the survival analyses with Kaplan Mayer equation (Fig. 1), demonstrated median survival was 19.00 (95% CI:13.23–24.76) in all patients, which was 18.00 (95% CI: 9.05–26.95) for MRG group, and 21.00(95% CI: 13.52–28.48) for NMRG, however, this difference was not statistically significant (p = 0.35). The analysis showed that the probability of survival increases significantly in MRG (p = 0.37 HR = 0.61, 0.21–1.76).

4. Discussion

Melatonin is reported to have anti-inflammatory, antioxidant and immuno-modulating effects [19,20], and high dose melatonin have valuable effects on severe viral influenza and sepsis, when used as

Table 1

Baseline Demographics and characteristics, Vital signs, clinical conditions and Laboratory data of patients infected with COVID-19 at ICU admission.

Variable	Melatonin (n = 12)	Control(n = 19)	P-value
Age, years, median (IQR)	64.50(40.75–75.50)	61.50(40.75–75.50)	0.783
Gender, Female, n(%)	7(58.3)	9(50.0)	0.65
Body mass index, kg/m2; median (IQR)	27.00(23.57–33.23)	25.08(22.99–29.17)	0.512
Smoking and opioid addiction, n(%)	1(8.3)	5(27.8)	0.19
Comorbidity, n(%)			
Diabetes	4 (33.3)	7(38.9)	0.76
Respiratory disease	1(8.3)	4(22.2)	0.32
Hypertension	4 (33.3)	8(44.4)	0.37
Cardiovascular disease	3(25.0)	5(27.8)	0.87
Renal disease	4 (33.3)	4 (22.2)	0.5
Malignancy	4(33.3)	3(16.7)	0.29
Immunosuppressive agent use	3(25.0)	4(22.2)	0.86
Stork	1(8.3)	5(27.8)	0.19
Symptoms at the time of hospital admission, n (%)			
Dyspnea	9(75.0)	11(61.1)	0.43
Cough	4(33.3)	5(27.8)	0.75
Fever	4(33.3)	5(27.8)	0.75
Chills	4(33.3)	3(26.7)	0.29
Fatigue	4(33.3)	6(33.3)	0.99
Weakness	1(8.3)	4(22.2)	0.32
Nausea and Vomiting	0(0.0)	3(16.7)	0.14
Headache	0(0.0)	1(5.6)	0.41
Confusion	4(33.3)	5(27.8)	0.75
LOC	9(75.0)	14(77.8)	0.34
Vital signs and clinical conditions			
Temperature, °C, mean (SD)	37.5 (0.7)	37.32(0.67)	0.682
Respiratory rate (breaths/minute) mean (SD)	22.0(5.74)	20.72 (3.95)	0.798
spo2, mean (SD)	88(11.48)	92.0(10.08)	0.092
O2 saturation,%, mean (SD)	85.0(11.28)	89.0(10.47)	0.077
NEWS2, median (SD)	8.50(2.72)	8.00(2.68)	0.55
Acute kidney injury, n(%)	7(58.3)	7(38.9)	0.30
Liver dysfunction, n(%)	3(25.0)	6(33.3)	0.63
Thrombocytopenia, n(%)	0(0.0)	1(5.6)	0.41
abnormality in electrolyte, n(%)	5(41.7)	6(33.3)	0.64
Anemia, n(%)	2(16.7)	7(38.9)	0.19
Laboratory data			
procalcitonin, mean (SD)	2.79(6.58)	0.94(1.49)	0.723
Interleukin-6, mean (SD)	22.98(24.35)	17.00()	0.77
Creatine phosphokinase; median (IQR)	188.00(41.50–448.50)	113.00(53.00–246.50)	0.55
erythrocyte sedimentation rate, mm/h; median (IQR)	39.50(29.50–57.00)	35.00(13.75–65.00)	0.48
C-reactive protein; median (IQR)	46.35(34.47–84.62)	37.90(7.17–96.65)	0.37
white blood cell, cells/μl; median (IQR)	9050.00(7375.00–15800.00)	13550.00(8675.00–19525.00)	0.33
Lymphocyte, %, median (IQR)	10.45(5.80–15.25)	13.45(6.90–22.92)	0.41
NLR base, median (IQR)	7.69(5.29–15.66)	6.05(3.10–12.47)	0.42
Platelet, cells/μl; median (IQR)	211000.00(186750.00–392500.00)	247500.00(151500.00–314500.00)	0.72
Alanine transaminase, U/l; median (IQR)	17.00(13.00–27.75)	26.00(10.00–113.50)	0.36
Aspartate aminotransferase, U/l; median (IQR)	31.00(16.75–80.75)	39.50(24.50–133.25)	0.20
Alkaline phosphatase, U/l; median (IQR)	211.50(184.25–257.75)	241.00(205.75–353.00)	0.17

LOC: loss of consciousness; NEWS2: National Early Warning Score 2; NLR: neutrophile to lymphocyte rate; IQR: interquartile; SD: standard deviation.

adjuvant therapy [19,21]. In COVID-19, cytokine storms are caused by excessive inflammation and uncontrolled oxidation, and eventually acute respiratory distress syndrome occurs [22,23]. High-dose melatonin can be effective in preventing this by modulating the immune response [19,24]. In addition, some studies have shown that the incidence of COVID-19 in outpatients consuming melatonin decreases [25, 26]. A pilot study conducted with Alizadeh et al. showed that melatonin improved recovery rate in outpatients with mild to moderate COVID-19, as well as decreases CRP level [27]. Farnoosh et al. study also showed that adjuvant treatment with low dose melatonin has a beneficial effect on clinical symptoms and earlier recovery in hospitalized COVID-19 patients [28]. Another study showed melatonin administration has significant beneficial effects on vital signs and inflammatory parameters [29]. Till now, one clinical trial is currently working on the effect of melatonin in ICU admitted patients [30]. This cohort study retrospectively was investigated and analyzed the effects of high dose melatonin in patients admitted to ICU.

In our study, there were no differences in characteristic, demographic and laboratory factors between the two groups at ICU admission. The analysis with the GEE model showed high dose

melatonin could reduce mortality in critical patient with COVID-19 in compare with standard care however, this difference was not significant, which could be due to the small sample size of our study. Moreover, the Kaplan Meyer survival analysis in our study displayed that the

Table 2

Efficacy and safety outcomes.

Parameter	Melatonin (n = 12)	Control(n = 19)	P
Efficacy outcomes			
ICU stay duration, day; mean (SD)	10.08 (4.12)	10.28(5.60)	0.85
Mechanical ventilation duration, days; median (IQR)	4.00 (0.00–6.75)	7.00 (2.00–13.25)	0.13
Death; n(%)	5.00(41.7)	13.00(72.2)	0.09
Safety outcomes n(%)			
Acute kidney injury	3(25.0)	5(27.8)	0.98
Liver dysfunction	5(41.7)	3(16.7)	0.13
Abnormal electrolytes	2(16.7)	5(27.8)	0.48
Thrombocytopenia	7(38.9)	5(35.3)	0.07
Anemia	10(83.3)	15(83.3)	0.99

IQR: interquartile; SD: standard deviation.

Table 3
Clinical outcomes in repeated meagered ANOVA model.

Variables; median (IQR)	Groups	Time			P-value		
		T1	T3	T7	Time effect	Group effect	Time*Group effect
NEWs; mean(SD)	MRG	10.33(3.24)	6.92(2.57)	6.58(3.85)	**0.002**	0.106	0.923
	NMRG	9.06(2.69)	7.72(2.16)	8.46(2.33)			
CPK	MRG	248.00(87.50–622.5)	140.00(79.00–380.00)	222.00(79.00–1261.00)	**0.055**	0.956	0.561
	NMRG	114.00(53.00–344.00)	285.00(84.75–945.00)	161.5(65.25–325.50)			
ESR	MRG	51.50(23.00–80.75)	42.50(31.00–60.50)	32.00(15.00–66.00)	0.312	0.058	0.764
	NMRG	28.50(13.75–53.00)	56.00(25.75–71.75)	51.90(31.75–71.75)			
CRP	MRG	40.40(28.37–80.70)	48.50(28.37–80.70)	24.10(18.90–45.60)	0.932	0.053	0.389
	NMRG	56.10(17.07–101.00)	69.00(42.60–99.00)	82.00(21.30–101.00)			
WBC	MRG	9900.00(7325.00–20050.00)	10950.00(7450.00–17700.00)	10400.00(8475.00–12350.00)	0.096	0.950	0.728
	NMRG	16200.00 (10025.00–19250.00)	11950.00(9750.00–17225.00)	11900.00(8100.00–16600.00)			
Lymphocyte	MRG	8.20(4.575–16.32)	8.25(5.70–17.825)	8.00(5.25–13.27)	**0.023**	0.149	0.797
	NMRG	7.70(2.65–15.60)	6.60(2.70–10.00)	5.10(4.00–12.50)			
NLR	MRG	10.26(4.83–20.38)	10.32(4.32–16.05)	11.03(6.29–17.08)	**0.033**	0.080	0.091
	NMRG	10.99(5.03–335.26)	12.58(8.65–33.89)	18.09(6.51–23.12)			
Platelet	MRG	205000.00 (167500.00–366750.00)	215000 (149000.00–333500.00)	203000.00 (122750.00–297750.00)	**0.000**	**0.049**	0.091
	NMRG	207500.00 (145000.00–291000.00)	150500.00 (136250.00–176250.00)	136000.00 (70000.00–172000.00)			
ALT	MRG	30.50(16.00–40.75)	29.50(15.50–40.50)	32.00(18.00–54.00)	0.535	0.205	0.549
	NMRG	26.00(11.75–178.75)	31.00(12.75–82.00)	29.00(11.50–37.50)			
AST	MRG	46.00(28.50–65.25)	40.50(27.00–89.75)	55.00(25.00–79.00)	0.417	0.352	0.467
	NMRG	45.50(31.75–205.00)	46.00(28.00–120.50)	43.00(23.50–61.00)			
ALP	MRG	235.50(158.75–343.00)	–	204.00(152.00–394.00)	0.816	0.950	0.331
	NMRG	241.00(205.00–348.75)	–	281.50(211.00–405.00)			

ALT: Alanine transaminase; median; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; NLR: neutrophil to lymphocyte rate; WBC: wight blood cell, ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CPK: Creatine phosphokinase; NEWS2: National Early Warning Score 2; IQR: interquartile; SD: standard deviation.

Table 4
Association between melatonin consumption and outcomes after adjustment for GEE model.

Safety	SE	OR (95% CI)	P-value
Electrolyte	0.62	0.60 (0.06–6.05)	0.66
Thrombocytopenia	0.03	0.02(0.00–0.32)	**0.005**
Anemia	0.27	0.33(0.07–1.63)	0.17
Outcome	SE	Regression coefficient (95% CI)	P
NEWs2	0.79	−0.49(-2.04-1.05)	0.53
ESR	14.49	15.20 (−13.20–43.59)	0.294
CRP	10.66	−5.84 (−26.74–15.06)	0.584
NLR	3.26	−9.81(-16.20–3.42)	**0.003**
Platelet	52976.13	77737.16 (−26094.14–181568.5)	0.142

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NLR: neutrophil to lymphocyte rate; NEWS2: National Early Warning Score 2; OR; odd ratio; CI: confidence interval; SE: effect size.

Fig. 1. Survival analyses with Kaplan Mayer equation.

probability of survival in the MRG was higher than NMRG. Nevertheless, high dose melatonin had no effect on ICU duration and mechanical ventilation need. Castillo et al. study demonstrated high dose melatonin as adjuvant therapy could shorten clinical improvement time, less need for intubation and mechanical ventilation, and reduce hospital stay [31]. They reported that the effect of melatonin for all patients with COVID-19, however, our study included the high dose melatonin as adjuvant therapy in critical care patients, so the severity of the patients may because of the difference. Also another study found that the administration of melatonin was associated with positive outcomes in intubated patients with COVID-19 [32], which was not observed in our study.

In this study, news2 scoring was used to evaluate the severity of the disease during hospitalization, and the analyses showed that the severity of the disease in the two groups had a downward trend, but the MRG had a steeper downward trend than the NMRG, although this difference was not significant. Similar to other study, melatonin could improve clinical characteristics, when used as adjuvant therapy [28,31,32]. It is also
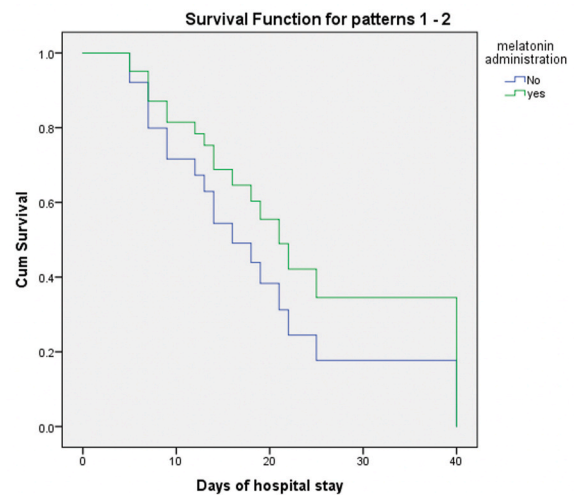
noteworthy that the trend of changes in ESR and CRP in our study was not statistically significant, but the trend of changes in the two groups were completely different, which was downward in the MRG and upward in the NMRG.

In the case of NLR, it was decreasing during treatment in both groups and the difference between them was not significant. Additionally, when the variables were adjusted by GEE model, it shows that the downward trend for NLR in the MRG group which was significantly comparable with NMRG, showing that high dose melatonin could reduce 9.81 unit NLR. This more effective reduction in NLR reflects the positive effects of melatonin on increasing lymphocyte counts and thus reducing inflammations. NLR displayed a disproportion of the inflammatory response in COVID-19 patients, and some studies found that high NLR is

independently related with disease severity and mortality [33,34]. Also, serial NLR measurements in hospitalized patient with COVID-19 is a good predictor for mortality, as well as, some studies found that increase in NLR is associated with mortality [35–39]. Our findings showed that high dose melatonin significantly reduced NLR when added to standard treatment and ultimately decline mortality risk.

Activated platelets and neutrophils had important effects on the thrombo-inflammatory phase of COVID-19 [35]. Studies have confirmed that lower total platelets count and decrease in platelets was detected in severe COVID-19 cases and non-survived group [35,36]. Our study showed that there is a significant difference between the two groups in terms of platelet depletion. The platelet count decreased in both groups during treatment, but the downward trend in MRG had slower slope, which could indicate beneficial effects of high dose melatonin for thrombo-inflammatory phase of COVID-19.

In case of safety concerns, there was no statistically significant difference between the two groups. The occurrence of impaired liver enzymes, electrolytes abnormality and anemia were similar between the two groups in our study. However, it should be note that, 6 patients in the NMRG developed thrombocytopenia and 1 patient in the MRG.

This is a retrospective cohort study of a limited clinical database; more information was unfortunately not available. We suggest double-blinded clinical trial in this regard to achieve more definite result.

Our study displayed high doses melatonin as an adjuvant therapy may have valuable effects in COVID-19 patients, however, findings of our study did not find any significant difference in this regard.

Provenance and peer review Not commissioned, externally peer-reviewed.

Ethical approval

Research studies involving patients require ethical approval. Please state whether approval has been given, name the relevant ethics committee and the state the reference number for their judgement.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Please state any sources of funding for your research

All sources of funding should be declared as an acknowledgement at the end of the text. Authors should declare the role of study sponsors, if any, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should so state.

No funding was secured for this study.

Please state any conflicts of interest

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

The authors deny any conflict of interest in any terms or by any means during the study.

Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish a case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, the Editor in Chief must be made aware of all such conditions.

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Not applicable.

Registration of research studies

In accordance with the Declaration of Helsinki 2013, all research involving human participants has to be registered in a publicly accessible database. Please enter the name of the registry and the unique identifying number (UIN) of your study7486.

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1. Name of the registry: N/a.

2. Unique Identifying number or registration ID: IR.MAZUMS. REC.1399.7405.

3. Hyperlink to the registration (must be publicly accessible): N/A.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Dr. Fatemeh Heydari.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103492.

The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

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