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Role of Melatonin in Management of COVID-19: A Systematic Review

Authors: Ghada Essam El-Din Amin[1,a], Salwa Mostafa Mohammad Abdel Rahman[2], Rehab Mohamed Ali Mohamed[3], Mohamed Farouk Allam[4,b]

Abstract

Background: the COVID-19 pandemic has significantly impacted global healthcare and economic systems. The clinical manifestation of the disease varies from flu-like symptoms to severe pneumonia and, in some cases, death. Melatonin and its metabolites play a crucial role in immunomodulation and possess anti-oxidative properties, capable of directly and indirectly scavenging reactive oxygen species. **Objective**: the aim of the present systematic review was to assess the effectiveness of melatonin in the management of COVID-19 patients and its role in expediting the return of patients to their baseline health. **Methodology**: the literature review was conducted up to August 2022, resulting in the identification of 533 articles after sorting them by authors and year of publication. Following the removal of 223 duplicate articles, 310 abstracts were screened, leading to the exclusion of 281. Subsequently, 29 full-text studies were evaluated for eligibility, with 22 being excluded. Finally, seven studies met the inclusion criteria and were included for further qualitative and quantitative analyses. **Results**: the findings revealed a noteworthy reduction in hospital stay among patients who received melatonin compared to those who received a placebo (standardized mean difference: -0.50, Standard error: 0.15, 95% CI: -0.80, -0.20, P value: 0.001). Melatonin was associated with a significant decrease in mortality in COVID-19 patients when compared to the placebo (Pooled RR: 0.21, 95% CI: 0.08, 0.56, P value: 0.002). However, there were no significant differences between melatonin and placebo regarding the need for hospitalization, ICU admission, artificial ventilation, and the requirement for oxygen therapy. **Conclusion**: melatonin may decrease the mortality rate among patients with COVID-19. Melatonin may reduce the duration of hospital stay in patients with COVID-19. Melatonin had no effect on the following outcomes in COVID-19 patients: the need for hospitalization, ICU admission, artificial ventilation and the need for oxygen therapy.

Key word: coronavirus disease 2019, severe acute respiratory syndrome, Middle East respiratory syndrome.

[1]Department of Family Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
[2]Department of Community, Environmental and Occupational Medicine, Faculty of Medicine,
[3]Department of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University,

[a]https:/orcid.org/0000-0001-7738-6392
[b]https:/orcid.org/0000-0001-5954-8909

Corresponding author:
Mohamed Farouk Allam
Address: Department of Family Medicine, Faculty of Medicine, Ain Shams University, 11566 Abbasia, Cairo, Egypt. Phone/Fax: +(202) 24346888, Mobile: +(2) 01143559946.
E-mail: farouk.allam@med.asu.edu.eg

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Introduction

Coronaviruses (CoVs) constitute a diverse group of RNA viruses, potentially posing significant health risks. Currently, they are responsible for an outbreak of respiratory illness referred to as CoV disease 2019 or COVID-19. Alongside Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), these viruses are recognized as causing severe respiratory illnesses in humans (1).

Similar to SARS-CoV, SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) cell receptors as a pathway for entering host cells. Various cellular proteases, including cathepsins, transmembrane protease serine 2 (TMPRSS2), and human airway trypsin-like protease (HAT), play a role in cleaving the spike protein, facilitating the virus's entry. This step is crucial for the coronavirus to penetrate host cells. Following receptor engagement, a conformational change in the spike protein promotes the fusion of the viral envelope with the cell membrane through the endosomal route. Subsequently, the viral RNA is translated, and viral mRNA guides the production of proteins. The process of exocytosis is then employed for viral replication and the assembly of new virions. These newly formed virions are released into surrounding cells or blood vessels. A 20-kb replicase gene encodes a large protein complex responsible for the replication of the virus (2).

Proteins are synthesized at the cell membrane, and the genomic RNA becomes incorporated as the mature viral particle buds from the inner cell membrane (3). The multiplication of CoV within host cells leads to various effects such as cellular necrosis, lysis, apoptosis, and cell fusion, ultimately resulting in the formation of syncytia (4).

Pathological examinations of lungs from patients with CoV reveal characteristics such as edema, proteinaceous exudates containing globules, patchy inflammatory cellular infiltration, and bilateral widespread alveolar injury. Additionally, findings may include edema, pneumocyte desquamation, and the significant development of hyaline membranes (5). SARS-CoV, MERS-CoV, and SARS-CoV-2 are all known to have these pathogenic characteristics. SARS-CoV-2 infections are generally significantly more severe than SARS-CoV and MERS-CoV infections in terms of symptoms and illness severity (6).

Melatonin is a pineal hormone that is predominantly produced and released at night from the amino acid tryptophan (7). Other tissues that synthesize it include heart, liver and spleen, thymus, bone marrow cells and lymphocytes, stomach and intestines, muscles and epithelial cells (8).

Melatonin is produced by mitochondria, which also control G protein-coupled receptors (GPCR) signaling to prevent cytochrome c release (9). Melatonin is promptly released into the cerebrospinal fluid and circulation once it is produced in the pineal gland (7). Melatonin was first discovered as a skin-lightening agent in amphibians, but later research revealed that it influences circadian rhythms and seasonal reproduction, as well as protecting the placenta, fetus, and mother from oxidative damage caused by a variety of toxic oxidizing events associated with pregnancy (10).

Melatonin and its metabolites are also important in immunomodulation, and they have anti-oxidative properties due to their capacity to scavenge reactive oxygen species (ROS) both directly and indirectly (11). Melatonin has now been discovered to be a very resourceful, versatile pleiotropic substance that orchestrates a wide range of physiological activities (12). Specific functions are regulated by membrane-bound MT1 and MT2, as well as broadly dispersed G protein-coupled receptors (GPCR) (13). Other effects, such as direct free radical scavenging, appear to be receptor-independent. The MT3 receptor, a third cytosolic receptor, protects against oxidative stress by preventing quinone electron transfer processes (8).

Delirium has been reported in as many as 50% of hospitalized elderly patients and up to 80% of critically ill patients in ICU who require mechanical ventilation (14).

COVID-19 can result in altered levels of consciousness in approximately 15% of hospitalized patients, manifesting as a spectrum from somnolence to disorientation, delirium, stupor, and even coma. Various factors contribute to the development of delirium in COVID-19 patients, including imbalances in neurotransmitters, the presence of pro-inflammatory cytokines, hypoxia, and sleep deprivation (15).

In intensive care unit (ICU) patients, melatonin or melatonin receptor agonists (MRAs) decreased delirium and increased sleep quality (16). Moreover, melatonin can decrease central respiratory depression, help alleviate infection-induced acute respiratory distress, and act as its anti-inflammatory, anti-oxidative, and immune-enhancing agent (17).

Melatonin supplementation can counteract SARS-COV-2 infections by reversing aerobic glycolysis via suppression of both HIF-1 and mTOR, allowing pyruvate dehydrogenase complex (PDC) activity to be suppressed and acetyl-coenzyme A to be produced (10).

The combination of mitochondrion-produced and parenteral melatonin has been observed to reduce the cytokine storm and alleviate damage induced by COVID-19 infection (18). Melatonin could be a promising anti-coronavirus agent, and notably, it does not seem to have harmful effects on fertility (18,19).

The aim of the present systematic review was to assess the effectiveness of melatonin in the management of COVID-19 patients and its role in expediting the return of patients to their baseline health.

Methodology

Criteria for considering studies

Types of studies: the review was restricted to Clinical Trials, which investigated the melatonin administration and standard treatment in COVID-19 patients, versus standard treatment with placebo.

Types of participants: participants were adult patients with the diagnosis of COVID-19. Patients were considered to have a definite diagnosis of COVID-19 if they were laboratory-confirmed using reverse transcription polymerase chain reaction (RT-PCR) and/or high-resolution CT chest with CO-RADS 4 or 5. All healthcare settings (community/primary care, hospital outpatient, or long-stay institutional) were considered eligible.

Types of interventions: clinical trials were included. Melatonin was administered in COVID-19 patients in addition to standard treatment, versus standard treatment and placebo.

Types of outcome measures: at least one of these outcome measures will be considered: Duration of COVID-19 illness till recovery, need for hospitalization, need for O2 therapy, need for ICU admission, need for artificial ventilation and mortality.

Inclusion criteria: randomized controlled trials. Studies conducted on adult human subjects. Studies conducted on patients diagnosed with COVID-19 confirmed with positive reverse transcription polymerase chain reaction (RT-PCR) and/or high-resolution CT chest with CO-RADS 4 or 5. Studies conducted in all healthcare settings (community/ primary care, hospital outpatient or long-stay institutional). Studies published in Arabic, English, French or Spanish languages.

Exclusion criteria: observational studies. Ecological studies. Studies conducted on animals.

Information Sources and Search Strategy

Published studies and abstracts on the role of melatonin in the management of COVID-19 were identified through a comprehensive search of electronic databases that included PubMed (https://pubmed.ncbi.nlm.nih.gov/), ScienceDirect (www.sciencedirect.com), Scirus (www.scirus.com/srsapp), ISI Web of Knowledge (http://www.isiwebofknowledge.com), Google Scholar (http://scholar.google.com) and CENTRAL (Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.htm), using a combination of the following keywords: "Melatonin, COVID-19, Clinical Trail".

Methods of the review

Locating and selecting studies

Abstracts of articles identified using the search strategy above mentioned were viewed, and articles that appeared to fulfill the inclusion criteria were retrieved in full. Data on at least one of the outcome measures was included in the study. Each article identified was reviewed and categorized into one of the following groups:

Included: RCT that met the described inclusion criteria and those where it was impossible to tell from the abstract, title or MESH headings.

Excluded: non RCT, observational studies.

When there was a doubt, a second reviewer (MFA) assessed the article, and a consensus was reached.

The literature was reviewed till August 2022 and yielded 533 articles after ranking the articles according to authors and year of publication. Only articles fulfilling the inclusion criteria were included (total 7 articles) for further steps of data collection, analysis, and reporting.

The studies that met our inclusion criteria were **Gholamreza et al. (2021), Mousavi et al. (2021), Hosseini et al. (2021), Irene et al. (2022), Davoodian et al. (2021), Alizadeh et al. (2022)** and **Hasan et al. (2022)**. All were in English and there were no available studies published in Arabic, French or Spanish language.

Data extraction

A copy of each identified paper was obtained, and relevant data was abstracted by the first reviewer for a quantitative overview. We extracted the following study data from full-text articles: first author name, year of publication, study design, study location, eligibility criteria, sample size, age, sex, description of intervention and control groups, primary and secondary outcomes. In case of discrepancies or when the information presented in a study was unclear, abstraction by a second reviewer (MFA) was sought to resolve the discrepancy.

Statistical considerations: Data were abstracted from every study in the form of a risk estimate and its 95% confidence interval. When a risk estimate and its 95% confidence interval (95%CI) were not available from the article, we calculated unadjusted values from the published data of the article, using the Epi Info 6 computer program version 6.04d. Pooled estimates of relative risks were obtained by weighing each study by the inverse variance of the effect measure on a logarithmic scale. This approach to pool the results assumed that the study populations being compared were similar and hence corresponded to a fixed effect analysis. The validity of pooling the relative risks was tested (test of homogeneity) using chi square test. A violation of this test suggested that the studies being pooled differed from one another. In the presence of significant heterogeneity of the effect measure among studies being compared, we performed a random effect analysis that was based on the method described by DerSimonian and Laird. The random effect analysis accounted for the interstudy variation. Because the test of homogeneity had low power, we reported the figures of the random effect analysis even with the absence of significant heterogeneity. All statistical analyses for pooling the studies were performed on the MetaXL Software.

Ethical Considerations: systematic reviews and Meta-analysis are exempted from Ethical Committees Approvals.

Results

Figure 1

Shows the selection of studies (PRISMA chart of included studies)

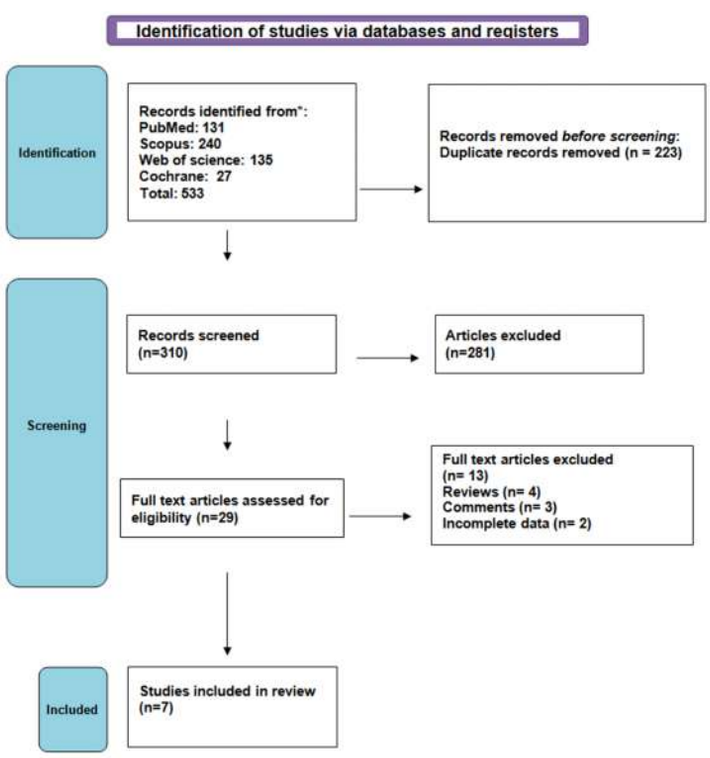


Table 1

Characteristics of included studies evaluating the efficacy of melatonin in COVID-19 management

Author, year	Study design	Study sites	Study population	Regimen of melatonin	No of patients	
					Study group	Control group
Gholamreza et al., 2021	Randomized, controlled double-blind clinical trial	Iran	Mild to moderate COVID-19	Melatonin at 3 mg three times daily for 14 days	24	20
Mousavi et al., 2021	Randomized open-label, active-controlled clinical trial	Iran	Hospitalized patients with COVID-19	Melatonin at 3 mg before bedtime for 7 days	48	48
Hosseini et al., 2021	Randomized controlled clinical trial	Iran	Hospitalized patients with COVID-19	Melatonin at 9 mg Oral dose for 14 days	20	20
García-García et al., 2022	A multicentre, randomised, parallel, 2-arm, double-blind controlled clinical trial	Spain	Not having a previous COVID-19 diagnosis and having a negative serologic rapid test (IgM/IgG) result before randomization	Melatonin at 2 mg Oral before bedtime for 12 weeks	160	148
Davoodian et al., 2021	A randomized controlled double-blind clinical trial	Iran	Hospitalized patients with COVID-19	Melatonin at 3 mg tablet orally three times a day for 2 weeks	42	39
Alizadeh et al., 2022	A single-center, double-blinded, randomized controlled trial	Iran	Patients with COVID-19 who were admitted to the intensive care unit (ICU) and had undergone invasive ventilation	The intervention group received 21 mg melatonin daily (i.e., seven crushed tablets of 3 mg melatonin)	34	33
Hasan et al., 2022	A single-center, controlled, randomized clinical trial	Iraq	Patients with severe COVID-19	10 mg melatonin	82	76

Table 2

Comparison between melatonin and standard treatments groups regarding the duration of COVID-19 illness till recovery (time until recovery)

Study	Year	Melatonin group		Control group		Study weights	SDM (95%CI)
		N	Mean (SD)	N	Mean (SD)		
Hosseini et al.	2021	20	12.80 (10.37)	20	23.88 (17.55)	22.08%	-0.75 (-1.40, -0.10)
Farnoosh et al.	2022	24	15.09 (8.69)	20	29.60 (21.12)	23.27%	-0.91 (-1.55, -0.28)
Mousavi et al.	2022	48	6.12 (2.01)	48	6.58 (2.13)	54.65%	-0.22 (-0.63, 0.19)
Fixed effects model							
Pooled standardized mean difference: -0.50							
Standard error: 0.15							
95%CI: -0.80, -0.20							
P value: 0.001*							
Random effects model							
Pooled standardized mean difference: -0.58							
Standard error: 0.23							
95%CI: -1.03, -0.12							
P value: 0.01*							
Heterogeneity							
Q: 4.27							
df: 2							
I^2: 53.13%							
P value: 0.12							

SDM: Standardized Mean Difference, CI: Confidence Interval, df: degree of freedom, *Statistically significant at P value <0.05.

Pooled analysis shows there is a reduction in duration of hospital stay in patients treated with melatonin supplementation as compared to others without melatonin treatment (Pooled standardized mean difference: -0.50, Standard error: 0.15, 95%CI: -0.80, -0.20, P value: 0.001). Fixed effect model was considered as heterogeneity was noted as per I2 statistics (53.13%; P-value 0.12).

Figure 2

Comparison between melatonin and standard treatments groups regarding the duration of COVID-19 illness till recovery

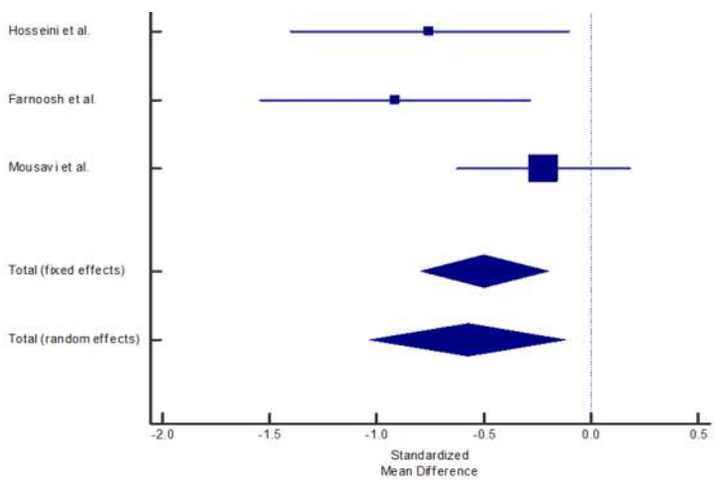


Table 3

Comparison between melatonin and standard treatments groups regarding the need for ICU admission

Study	Year	Melatonin group		Control group		Study weights	RR (95%CI)
		N	N requiring ICU	N	N requiring ICU		
Farnoosh et al.	2022	24	0 (0%)	20	2 (10%)	11.27%	0.15 (0.007, 3.34)
Mousavi et al.	2022	48	6 (12.5%)	48	10 (20.8%)	88.73%	0.54 (0.18, 0.16)
Fixed effects model							
Pooled RR: 0.45							
95%CI: 0.16, 1.25							
P value: 0.13							
Random effects model							
Pooled RR: 0.47							
95%CI: 0.17, 1.33							
P value: 0.15							
Heterogeneity							
Q: 0.59							
df: 1							
I^2: 0%							
P value: 0.44							

RR: Relative Risk, CI: Confidence Interval, df: degree of freedom.

Pooled analysis showed that Melatonin didn't reduce the need for ICU admission in patients treated with melatonin supplementation as compared to others without melatonin treatment (Pooled RR: 0.45, 95%CI: 0.16, 1.25, P value: 0.13). Random effect model was considered as no heterogeneity was noted as per I2 statistics (0% P value: 0.44)

Figure 3

Comparison between melatonin and standard treatments groups regarding the need for ICU admission

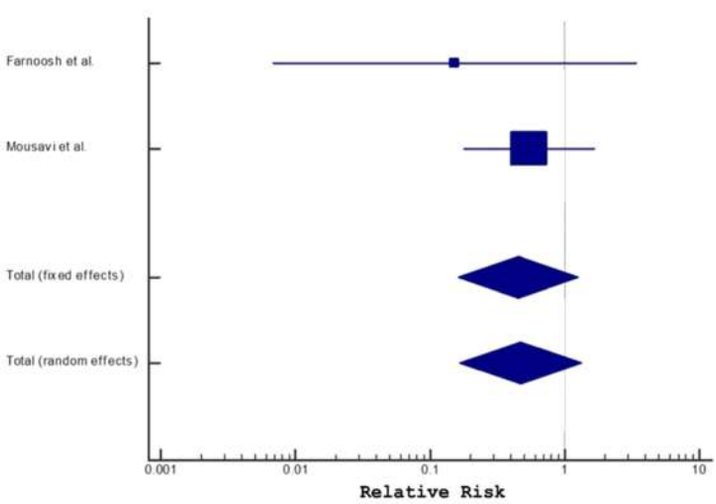


Table 4

Comparison between melatonin and standard treatments groups regarding the need for artificial ventilation

Study	Year	Measure	Melatonin group	Control group	Total= 66
		N	33	33	
Alizadeh et al.	2022	N (%) needed	7 (21.2%)	3 (9.1%)	RR (95%CI)= 0.43 (0.10, 1.80)
		Mean (SD) ventilation time	26.64 (13.17)	34.51 (17.80)	Mean difference (SD)= 7.87 (15.66) 95%CI= 0.17, 15.57

SD: Standard Deviation, CI: Confidence Interval.

About 21.2 % participants in the melatonin group need artificial ventilation compared to 9.1% participants in the control arm. The mean ventilation time is 26.64 (SD 13.17) and 34.51 (SD 17.8) in the intervention and control arm, respectively which means melatonin supplementation helped to reduce ventilation time needed compared to control group, but there is no effect of melatonin supplement on need for artificial ventilation in patients treated with melatonin supplementation as compared to others without melatonin treatment

Table 5

Comparison between melatonin and standard treatments groups regarding oxygen saturation

Study	Year	Melatonin group		Control group		Study weights	SDM (95%CI)
		N	Mean (SD)	N	Mean (SD)		
Davoodian et al.	2021	42	96.0 (1.54)	39	93.65 (2.31)	49.27%	1.19 (0.72, 1.67)
Mousavi et al.	2022	48	92.85 (5.29)	48	92.19 (3.92)	50.73%	0.14 (-0.26, 0.54)
Fixed effects model							
Pooled standardized mean difference: 0.58							
Standard error: 0.16							
95%CI: 0.28, 0.87							
P value: <0.001*							
Random effects model							
Pooled standardized mean difference: 0.66							
Standard error: 0.53							
95%CI: -0.38, 1.70							
P value: 0.21							
Heterogeneity							
Q: 11.28							
df: 1							
I^2: 91.14%							
P value: 0.008*							

SDM: Standardized Mean Difference, CI: Confidence Interval, df: degree of freedom.

Pooled analysis showed that there is no effect of melatonin supplement on need for oxygen therapy in patients treated with melatonin supplementation as compared to

others without melatonin treatment (Pooled standardized mean difference: 0.66, Standard error: 0.53, 95%CI: 0.38, 1.70, P value: 0.21). Random effect model was considered as heterogeneity was noted as per I2 statistics (91.14%, P value: 0.008).

Figure 4

Comparison between melatonin and standard treatments groups regarding oxygen saturation

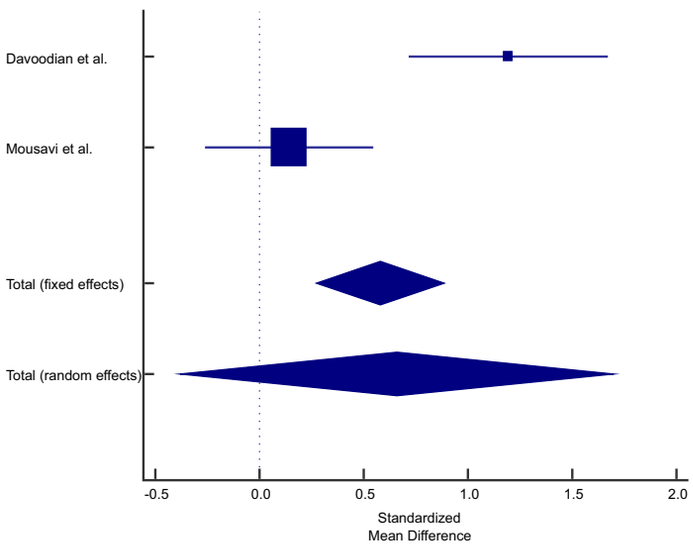


Table 6

Comparison between melatonin and standard treatments groups regarding mortality

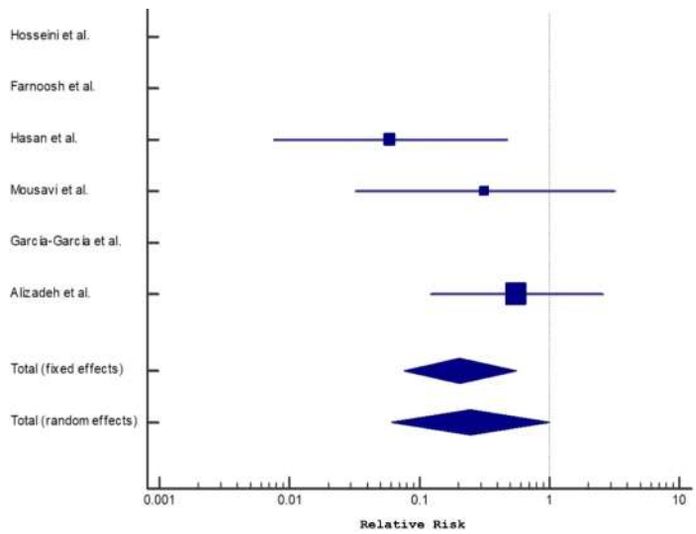
Study	Year	Melatonin group		Control group		Study weights	OR (95%CI)
		N	N (%) died	N	N died		
Hosseini et al.	2021	20	0 (0%)	20	0 (0%)	-	-
Farnoosh et al.	2022	24	0 (0%)	20	0 (0%)	-	-
Hasan et al.	2022	82	1 (1.2%)	76	13 (17.1%)	27.49%	0.06 (0.008, 0.48)
Mousavi et al.	2022	48	1 (2.1%)	48	3 (6.2%)	22.07%	0.32 (0.03, 3.18)
García-García et al.	2022	119	0 (0%)	113	0 (0%)	-	-
Alizadeh et al.	2022	33	28 (84.8%)	33	30 (90.9%)	50.44%	0.56 (0.12, 2.56)
Fixed effects model							
Pooled RR: 0.21							
95%CI: 0.08, 0.56							
P value: 0.002*							
Random effects model							
Pooled RR: 0.25							
95%CI: 0.06, 0.996							
P value: 0.0049*							
Heterogeneity							
Q: 3.19							
Df: 2							
I^2: 37.21%							
P value: 0.20							

RR: Relative Risk, CI: Confidence Interval, df: degree of freedom. *Statistically significant at p value <0.05.

Pooled analysis showed that there is reduction in mortality prognosis in patients treated with melatonin supplementation as compared to others without melatonin treatment (Pooled RR: 0.21, 95%CI: 0.08, 0.56, P value: 0.002). Fixed effect model was considered as heterogeneity was noted as per I2 statistics (I2: 37.21%, P value: 0.20).

Figure 5

Comparison between melatonin and standard treatments groups regarding mortality



Need for hospitalization

Patients in all studies were hospitalized, except ***García-García et al. (2022)*** where none of the subjects was hospitalized (prophylaxis).

Discussion

This meta-analysis encompassed seven randomized controlled trials (20-26), all published up to August 2022. Five of these studies originated from Iran (20-25), one from Spain (23), and one from Iraq (26). Among them, three were conducted in hospital wards, three in ICU settings, and one focused on prophylaxis for non-hospitalized individuals.

Concerning the duration of COVID-19 illness until recovery, three studies (20-22) evaluated recovery time, with the study by Mousavi et al. reporting the shortest recovery time (21). The meta-analysis revealed a reduction in hospital stay duration among patients treated with melatonin supplementation compared to those without (Pooled standardized mean difference: -0.50; Standard error: 0.15; 95% CI: -0.80, -0.20; p-value: 0.001). A fixed-effect model was applied due to noted heterogeneity based on I2 statistics (53.13%; p= 0.12). Our findings were corroborated by the systematic review and meta-analysis conducted by Lankarani et al., which included five RCTs with 272 patients examining the efficacy of oral melatonin compared to placebo in mild to moderate COVID-19 cases (27). Their analysis demonstrated a reduction in discharge time with melatonin compared to placebo (WMD=-0.93 days; 95% CI: -2.94. 1.07; p= 0.36; I2= 56.78%).

Regarding the need for ICU admission, two studies (20, 21) were analyzed, revealing no significant reduction in relative risk (Pooled RR: 0.45; 95% CI: 0.16, 1.25; p= 0.13). A random-effects model was applied as no heterogeneity was observed based on I2 statistics (0%; p= 0.44). In line with our findings, a meta-analysis by Lan et al. investigated the effect of melatonin on clinical outcomes in COVID-19 patients, showing a numerically lower risk of ICU admission in the melatonin group, albeit not statistically significant (OR: 0.45; 95% CI: 0.16 1.25; I2= 0%; p= 0.13) (28).

Concerning the need for artificial ventilation, Alizadeh et al. reported a ventilation requirement of 21.2% in the melatonin group compared to 9.1% in the control arm. Although melatonin supplementation reduced ventilation time compared to the control group, no significant effect on the need for artificial ventilation was observed (25). This aligns with a mini systematic review by Gholizadeh et al., which indicated that melatonin supplementation reduced the severity of COVID-19, leading to shorter ventilation periods and decreased lung damage (29).

In terms of oxygen saturation, the meta-analysis included two studies (21, 24), showing no significant effect of melatonin supplementation on the need for oxygen therapy (Pooled standardized mean difference: 0.66; Standard error: 0.53; 95% CI: 0.38, 1.70; p= 0.21). A random-effects model was applied due to observed heterogeneity (I2= 91.14%; p= 0.008). In agreement, a meta-analysis by Wang et al. involving six eligible studies with 338 participants found no significant difference in SaO2 between the melatonin treatment group and the control group (WMD= 1; 95% CI= –1.21, 3.22; p= 0.37) (30). However, Lankarani et al. reported a significant increase in SaO2 with melatonin compared to placebo (WMD= 1.38%; 95% CI: 0.09 to 2.68; p= 0.04; I2= 49.82%), attributing it to melatonin's influence on oxygen transport and tissue usage (27). This discrepancy may stem from variations in inclusion criteria and sample sizes among the studies.

Regarding mortality rate, six studies (20, 21, 22, 23, 25, 26) were analyzed, showing a significant reduction in the risk of fatal prognosis with melatonin supplementation (Pooled RR: 0.21; 95% CI: 0.08, 0.56; p= 0.002). A fixed-effect model was applied due to observed heterogeneity (I2: 37.21%; p= 0.20). This finding was supported by a systematic review and meta-analysis by Faridzadeh et al., which included ten RCTs and suggested that melatonin could be a potential adjuvant in treating COVID-19 patients, reducing recovery time, mortality rate, and the likelihood of coagulopathy or sepsis (31). However, Lankarani et al. reported a nonsignificant effect of melatonin on mortality risk (RR=0.72; 95% CI: 0.25, 2.13; p= 0.56; I2= 0.0% [with 4 RCTs]), although they observed a significant decrease in CRP levels (WMD=-7.24 mg/l; 95% CI: -11.28, -3.21; p<0.001) (27). Moreover, Lan et al. found a numerically lower mortality risk and higher clinical recovery rate in the melatonin group compared to controls (OR: 0.32; 95% CI: 0.03 , 3.18; I2= 0%; p= 0.33) (28). Similarly, Wang et al. reported no significant difference in mortality between the melatonin and control groups, along with no significant differences in CRP levels or white blood cell counts (WMD: –0.36; 95% CI: –3.65, 2.92; p= 0.83 for CRP; WMD: –1.07; 95% CI: –2.44, 0.30; p= 0.13 for WBC) (30). Additionally, Wang et al. suggested that melatonin can reduce the generation of reactive oxygen species and free metal ions, preventing harmful conditions such as DNA damage, protein oxidation, and lipid peroxidation, and inhibiting oxidative stress and cell apoptosis to prevent lung inflammation caused by COVID-19, with higher antioxidant capacity than other active oxygen scavengers.

While various mutant strains of COVID-19, such as Alpha, Beta, Gamma, Delta, and Omicron, exhibit diverse effects on the host, melatonin appears to possess inhibitory and blocking effects in the process of suppressing virus replication and maturation. However, long-term research is crucial to verify and further understand.

Conclusion

Melatonin may decrease the mortality rate among patients with COVID-19. Melatonin may reduce the duration of hospital stay in patients with COVID-19. Melatonin had no effect on the following outcomes in COVID-19 patients: the need for hospitalization, ICU admission, artificial ventilation and the need for oxygen therapy.

Author contributions

Ghada Essam El-din Amin: field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft. **Salwa Mostafa Mohammad Abdel Rahman**: field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft. **Rehab Mohamed Ali Mohamed**: field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft. **Mohamed Farouk Allam**: field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft.

Ethics statement

Not applicable.

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None.

Conflicts of interest

No competing interests.

Availability of data

Our study is a Systematic Review/Meta-analysis. The datasets analyzed during the current study are available in the published pooled study. Also, the datasets used and analyzed during the current study available from the corresponding author on reasonable request.

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