

SYSTEMATIC REVIEW

Melatonin as adjuvant treatment in COVID-19 patients. A meta-analysis of randomized and propensity matched studies

Krisztina Tóth¹, Eros Pilia², Giovanni Landoni^{3,4,*}, Davide Oreggia³, Salvatore Giacomarra³, Rosario Losiggio³, Giacomo Maiucci³, Iliyan Vlasakov³, Andrey Yavorovskiy⁵, Valery Likhvantsev^{5,6}, Andrea Székely⁷, Remo Daniel Covello⁸

¹Doctoral School of Theoretical and Translational Medicine, Semmelweis University, 1089 Budapest, Pest, Hungary

²Department of Medical Sciences and Public Health, University of Cagliari, 09124 Cagliari, Italy

³Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy

⁴Faculty of Medicine, Vita-Salute San Raffaele University, 20132 Milan, Italy

⁵I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991 Moscow, Russia

⁶Federal Research and Clinical Center of Resuscitation and Rehabilitation, 107031 Moscow, Russia

⁷Department of Anesthesia, Semmelweis University, 1082 Budapest, Pest, Hungary

⁸Anesthesia and Intensive Care Unit, Emergency Department, Busto Arsizio Hospital, ASST Valle Olona, 21052 Busto Arsizio, Varese, Italy

***Correspondence**

landoni.giovanni@hsr.it
(Giovanni Landoni)

Abstract

Melatonin is a neurohormone well-known as sleep disorder treatment. A few clinical trials have recently pointed out the biological plausibility of utilising melatonin in the treatment of coronavirus disease 2019 (COVID-19, SARS-CoV-2) patients. Melatonin wide range of activities include anti-inflammatory, antiviral and antioxidant effects. Our meta-analysis aimed to investigate the effect of melatonin on mortality in COVID-19 patients with different disease severity. We searched PubMed, EMBASE, Web of Science with no language restrictions updated on February 2023 for randomized and propensity matched studies, comparing melatonin plus standard COVID-19 therapy vs. standard COVID-19 therapy alone. Patients had to be hospitalised with a confirmed diagnosis of SARS-CoV-2 infection. Primary outcome was mortality at the longest follow-up available. We included 7 randomized and 1 propensity matched studies enrolling 1155 overall patients with a mean age of 61 ± 19.5 years. We found a reduced mortality rate in the overall population (127/575 (22%) vs. 209/580 (36%) Relative Risk: 0.62 (confidence interval (CI): 0.40, 0.96), $I^2 = 86\%$ $p = 0.03$, with the results confirmed when pooling the 5 studies which administered melatonin in non-intensive-care-unit patients (26/423 (6.1%) vs. 69/419 (16%) Relative Risk 0.30 (CI: 0.10, 0.86), $I^2 = 40\%$ $p = 0.02$). According to recent randomized and propensity matched evidence, melatonin might be a life-saving adjuvant therapy in COVID-19 patients. This effect was mainly driven by non-intensive care unit patients.

Keywords

Melatonin; COVID-19; SARS-CoV-2; Mortality; Critical care; Intensive care unit

1. Introduction

Since the COVID-19 pandemic started, many drugs were studied to counteract COVID-19. Vaccine research played and still has a fundamental role, albeit undermined by the reluctance of some fringes of the population, the emergence of new variants and the difficult path towards vaccine immunization in the poorest countries [1]. The high costs, side effects, interaction with concomitant medications and comorbidities-related exclusion criteria of the latest antiviral therapies represent a limit to their widespread use [2]. Concomitantly with the quest for novel specific drugs, existing drugs approved for different conditions, with established pharmacokinetics, pharmacodynamics and safety profile, were repurposed in this scenario beyond their conventional use, with the aim of preventing and limiting the consequences of COVID-19 in infected patients [3, 4].

Corticosteroids were the first drugs shown to decrease mortality in critically ill COVID-19 patients [5]. The

initial concerns of the scientific community on the usage of corticosteroids in treatment of patients with a viral disease were overcome by data from clinical trials that demonstrated their role in regulating inflammation-coagulation-fibroproliferation pathways, which led to their recommendation for severe and critical illness. Among other drugs, melatonin seems to deserve particular attention. Psychological alterations such as stress, insomnia, sleep disturbances and delirium are in fact well described in COVID-19 patients and can be variously linked to each other. Stress can cause in fact sleep deprivation and sleep deprivation can increase stress itself. Moreover, psychological stress is a known predisposing factor for oxidative stress, which can endanger the immune system. If on one hand melatonin could improve therefore psychological aspects due to its role in regulating circadian rhythms, on the other side its anti-inflammatory, antioxidant and immunomodulatory effects are increasingly emerging, making melatonin a plausible drug against COVID-19 (Fig. 1) [6]. Biological plausibility of melatonin as a drug against

MELATONIN AS ADJUVANT TREATMENT IN COVID-19 PATIENTS

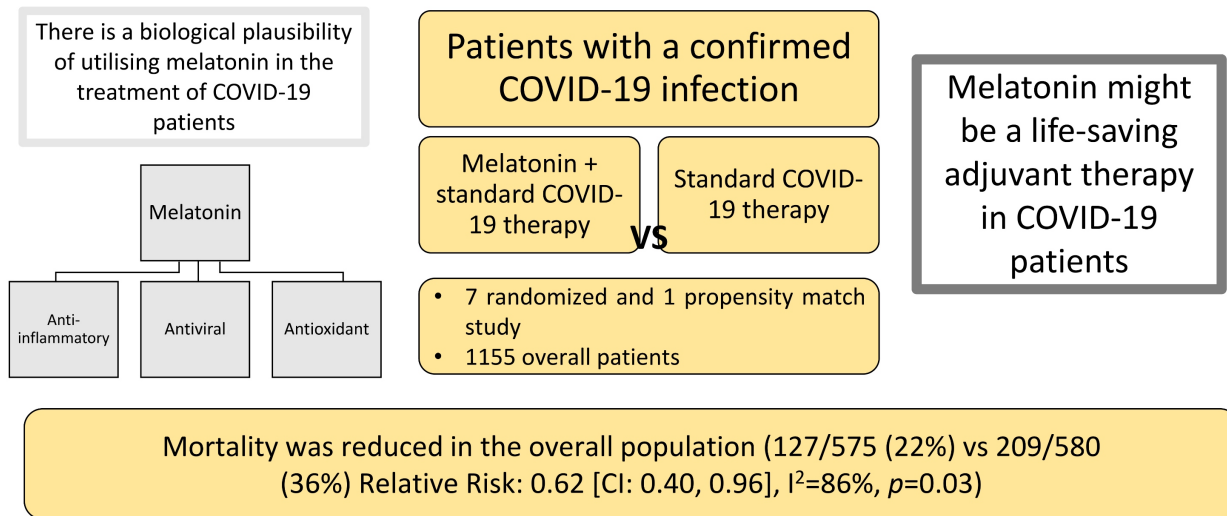


FIGURE 1. Visual abstract. COVID-19: coronavirus disease 2019; CI: confidence interval.

COVID-19 is reinforced by the results of new combined system biology and artificial intelligence-based approaches which predicted that melatonin would have high clinical benefits for COVID-19 patients and should be prioritized for further investigation [7]. Moreover, the clinical role of melatonin in COVID-19 patients might be inferred from pre-clinical and clinical trials performed in bacteria-related sepsis and sepsis triggered by other viral infections [8]. Melatonin was tested in clinical studies, including randomized controlled trials in patients affected by COVID-19 [9–18]. Two meta-analyses of randomized controlled trials (RCTs) were published on standard therapy with the addition of melatonin in comparison to standard therapy alone in COVID-19 patients [19, 20]. These studies showed a significant improvement in clinical recovery rate, but no difference in mortality.

A significant reduction of mortality in melatonin-receiving group has arisen in our preliminary analysis [21]. Evidence is accumulating and several other studies were published to support these promising findings. Furthermore, even if it is intuitive that melatonin could be effective during the early stages of the disease, previous meta-analyses did not differentiate between patients with different disease severity.

In the hypothesis that melatonin can be beneficial in improving survival in COVID-19 patients and that this effect can be more pronounced in early stages of the disease we conducted a systematic review and meta-analysis of RCTs and propensity matched studies on this topic.

2. Materials and methods

Our research was registered on 23 May 2022 in Open Science Framework Registries (OSF registration DOI:

10.17605/OSF.IO/7P4VG). We searched PubMed, EMBASE, Web of Science for “melatonin AND COVID-19” and “melatonin AND SARS-CoV-2” (last updated 23 February 2023). The search results were independently reviewed by two independent trained investigators. Inclusion criteria were: RCTs or propensity score matched trials; ≥18 years in age with a confirmed diagnosis of COVID-19 infection by Reverse Transcription Polymerase Chain Reaction, antigen testing or computer tomography findings irrespective of gender or ethnicity; comparing melatonin (any dosage) and standard therapy versus standard therapy alone. Exclusion criteria were: melatonin used for prophylaxis of SARS-CoV-2 infection; and studies that did not report mortality. Disagreements about articles inclusion or exclusion were resolved by discussion. In cases where the methodology of the article was appropriate, but no mortality data was available, we contacted the corresponding authors by e-mail to ask them for further data. None of the corresponding authors we contacted replied to our enquiries. The primary outcome was all cause mortality at the longest follow-up available. Secondary outcomes were length of hospital stay, ICU admission and C-Reactive Protein (CRP) levels after treatment.

2.1 Risk of bias

The included studies’ risk of bias were assessed with the Cochrane Handbook for Systematic Reviews of Interventions and the RoB 2 version of the Cochrane risk-of-bias tool [22]. We evaluated the potential risk of bias as “Low”, “Some concerns” or “High” for each trial separately. The propensity score matched study was ranked by using ROBINS-I tool (Risk Of Bias In Non-randomized Studies-of Interventions)

[23]. The potential risk of bias could be “Low”, “Moderate”, “Serious” or “Critical”.

Small study effect and publication bias were assessed for primary endpoint by visual inspection of the funnel plot. Funnel plot asymmetry was determined with Egger’s linear regression method carried out with STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. StataCorp LP, College Station, TX, USA).

2.2 Statistical analysis

We used Review Manager (RevMan) Version 5.4.1 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 13.0 (Stata Corporation, College Station, TX, USA) to analyse data. Heterogeneity of results was assessed using Cochran’s Q test and I^2 statistic. An $I^2 \geq 50\%$ was considered as high statistical heterogeneity. In case of low heterogeneity, we utilized a fixed-effects model, while in case of high heterogeneity the random-effects was used. Mantel-Haenszel statistical method was used to calculate pooled risk ratios (RRs) for dichotomous outcomes and RR was presented with 95% confidence intervals (CI). p -value < 0.05 was considered statistically significant. We then determined mean difference (MD) or standardized mean difference (SMD) with the remaining 95% CIs for continuous variables. Continuous variables reported as median, interquartile range or range were converted into mean and standard deviation using the method by Wan *et al.* [24].

3. Results

The primary search identified 761 records from PubMed ($n = 221$), EMBASE ($n = 355$) and Web of Science ($n = 185$) (Fig. 2). Thirteen reports were assessed for eligibility and five [7, 12, 25–27] were excluded due to reasons detailed in **Supplementary Table 1**. The analysis was therefore performed on 1155 patients from 8 studies (7 RCTs, 1 propensity score match study) [10, 11, 13–18].

All studies were single centre (Table 1); five studies were performed outside the ICU; length of follow up was heterogeneous as well as melatonin dosing regimen (total daily dose, number of administrations per day and length of treatment) and only 3 studies had mortality as a primary endpoint. The pooled mean age was 61 ± 19.0 versus 61 ± 20.0 years in the melatonin and comparator group. Males represented 54% of the patients in both groups.

Mortality was 127/575 (22%) in the melatonin group vs. 209/580 (36%) in the control group RR: 0.62 (CI: 0.40, 0.96), $I^2 = 86\%$ $p = 0.03$) with 8 studies and 1155 patients included (Fig. 3) (**Supplementary Fig. 1**). Mortality reduction remained significant when restricting the analyses to the 5 studies (4 RCTs and 1 propensity matched study) which administered melatonin in patients at an early stage of the disease (non-ICU patients): 26/423 (6.1%) vs. 69/419 (16%) relative risk 0.30 (CI: 0.10, 0.86), $I^2 = 40\%$ $p = 0.02$). This significant mortality reduction in non-ICU patients receiving melatonin was confirmed when excluding the propensity matched study (**Supplementary Fig. 2**). The funnel plot of mortality rate did not identify small study bias in favour of melatonin.

We found no difference in length of hospital stay (**Supplementary Fig. 3**), need for new ICU admission (**Supplementary Fig. 4**), and CRP levels (**Supplementary Fig. 5**) between groups. Only one trial [10] reported interrupting treatment with the study drug due to “hypersensitivity” in one patient, but did not specify if the patient belonged to the treatment or study group and did not report details of the reaction.

All RCTs had some methodological concern as far as the risk of bias is concerned (**Supplementary Fig. 6**) and the propensity score matched study had moderate concerns. Seven of the included studies considered some concerns of risk of bias, while for one study high risk of bias was identified.

4. Discussion

In this meta-analysis of 7 RCTs and one propensity matched study we found that melatonin decreased mortality in COVID-19 patients. These findings were mainly driven by non-ICU patients and confirmed in this setting when considering RCTs only. We found no difference in secondary outcomes (hospital stay, need for ICU, and levels of CRP).

The COVID-19 pandemic embodies the largest global crisis faced by public health worldwide. In addition to vaccines and newly-developed antiviral medications, repurposing of existing drug beyond their traditional use may offer potential prevention and treatment options for COVID-19 by reducing research times and costs [4, 28]. Results of molecular modelling techniques, experimental studies in cells, previous studies on other viral infections, network medicine and large-scale data analyses from patient registries predicted that melatonin would be a safe and potentially valid agent for preventing and/or treating COVID-19 [8, 29]. Melatonin is a neuro-hormone secreted from the pineal gland with a regulatory action on the sleep-wake cycle. External administration of synthetic melatonin is typically indicated in the treatment of insomnia and circadian sleep disturbances and is safe and tolerable for most of the patients [30].

Melatonin has been therefore proposed for the prevention and treatment of sleep disturbances, associated psychological stress and post-COVID-19 cognitive impairment caused by the virus in direct or indirect ways. The circadian rhythm strengthening of melatonin might be even more useful in hospitalized patients in whom circadian disruption is associated with delirium and likely contributes to the pathophysiology of COVID-19 acute illness [31]. Biological plausibility of melatonin against COVID-19 disease goes beyond its regulatory effect on the sleep-wake cycle and reflects its pleiotropic complexity as evinced by extensive literature [6]. Melatonin may have direct antiviral action by blocking the cellular entrance and replication of SARS-CoV-2 [29]. It is a potent free radical scavenger, antioxidant and antiapoptotic molecule [32]. Furthermore, it is an excellent anti-inflammatory molecule with immunoregulatory activity [33] and may enhance innate immunity [34]. Melatonin curtails the exaggerated response of the innate immune system in the case of a viral infection (COVID-19 “cytokine storm”).

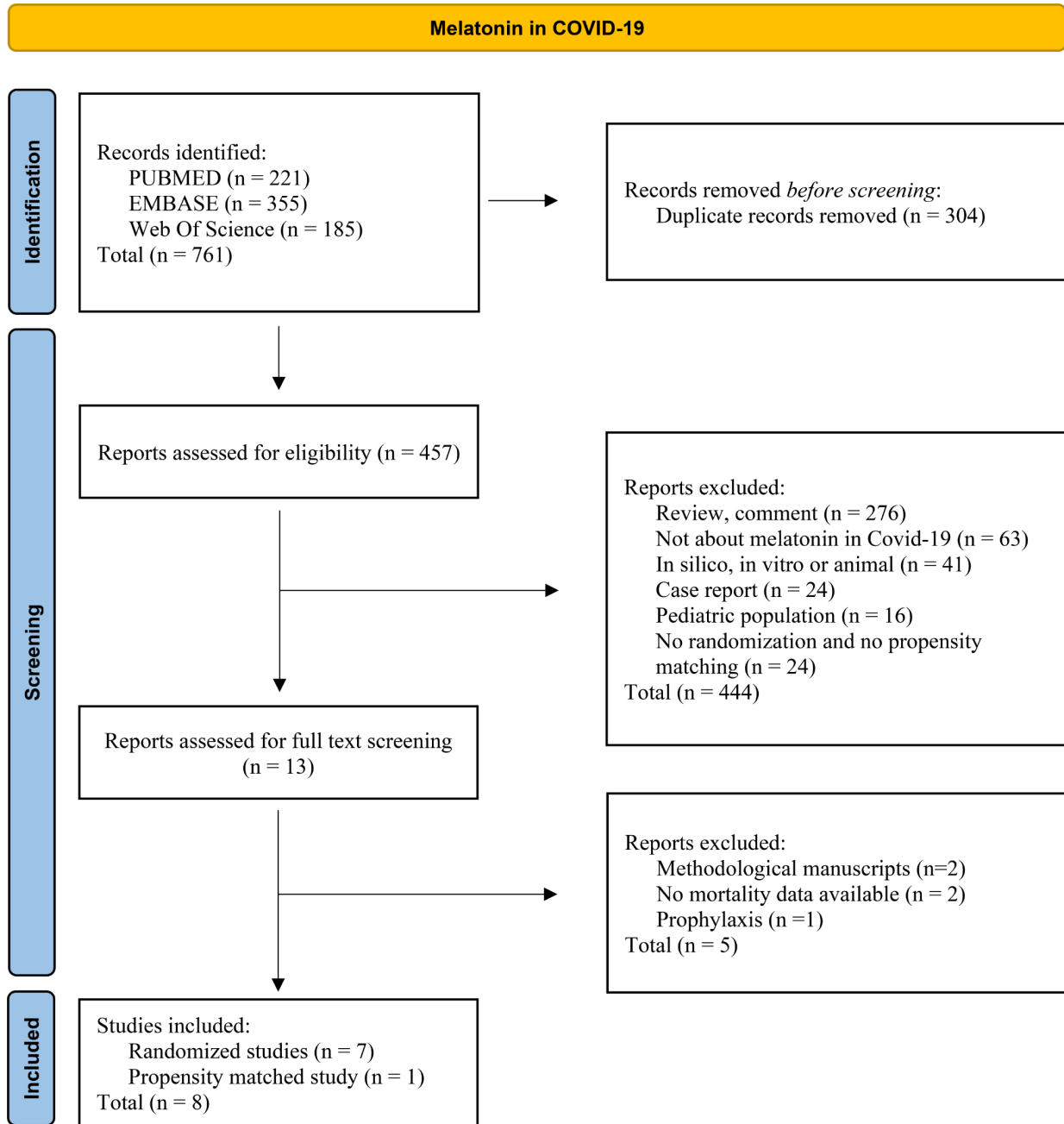


FIGURE 2. Flow chart of studies identification. COVID-19: coronavirus disease 2019.

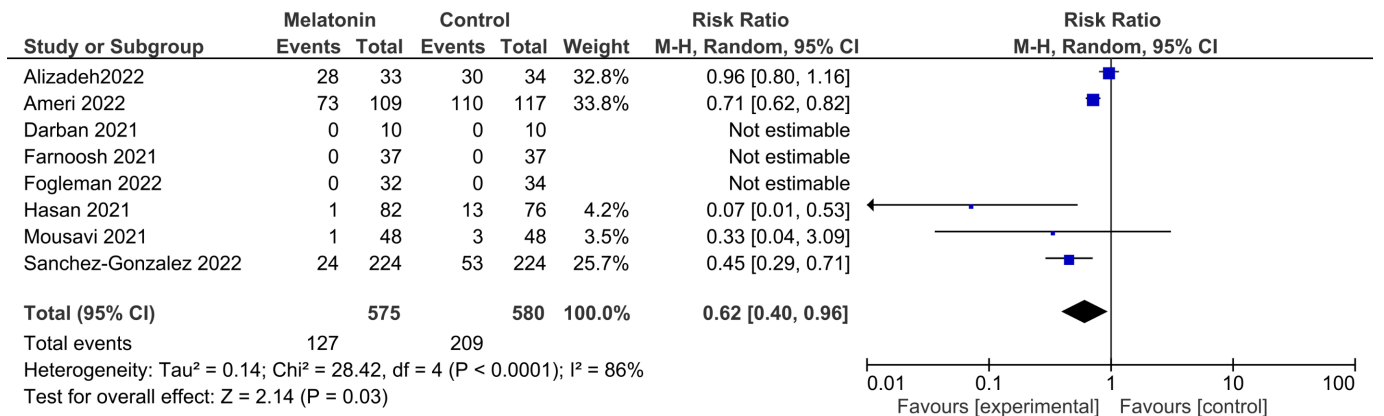


FIGURE 3. Forest plot of mortality. CI: confidence interval.

TABLE 1. Characteristics of included studies.

| First author, Publication year | Study design | Severity/setting | Sample size (N) | Melatonin dose, duration | Standard therapy | Longest follow-up available | Primary outcome |
|--------------------------------|--------------------|---------------------|-----------------|--|--|-----------------------------|---|
| Alizadeh, 2022 [12] | RCT, single centre | intensive care unit | 67 | through nasogastric tube 21 mg (for 5 days) | -remdesivir (200 mg on the first day and 100 mg daily for 4 days thereafter) -corticosteroids -anticoagulant (prophylactic dose) -sometimes tocilizumab | 6 days | -mortality rate -duration of mechanical ventilation -changes in oxygenation indices -changes in C-reactive levels |
| Ameri, 2022 [17] | RCT, single centre | intensive care unit | 226 | oral 2 × 5 mg (7 days) | - | 28 days | -mortality rate -need for invasive mechanical ventilation |
| *Darban, 2021 [10] | RCT, single centre | intensive care unit | 20 | oral 6 mg (q6 hr) | -azithromycin (250 mg/day) -lopinavir/ritonavir (100 mg/25 mg/day) -glucocorticoids -necessary oxygen | 10 days | changes in severity of hypoxemia (PaO ₂ /FiO ₂ ** ratio) |
| Farnoosh, 2021 [13] | RCT, single centre | mild to moderate | 44 | 3 × 3 mg (14 days) | -discretion of treating physicians -according to national COVID-19*** treatment protocol | 28 days | clinical improvement of symptoms and laboratory parameters including neutrophil-lymphocyte ratio, erythrocyte sedimentation rate and C-reactive protein |
| Fogleman, 2022 [18] | RCT, single centre | mild to moderate | 66 | oral 1 × 10 mg (14 days) | -oral placebo (cornstarch) | 14 days | |

TABLE 1. Continued.

| First author, Publication year | Study design | Severity/setting | Sample size (N) | Melatonin dose, duration | Standard therapy | Longest follow-up available | Primary outcome |
|--------------------------------|--------------------|-----------------------|-----------------|--|--|-----------------------------|-----------------|
| Hasan, [14] | RCT, single centre | severe | 158 | oral 1 × 10 mg (14 days following diagnosis) | -oxygen therapy -remdesivir (day 1, 200 mg intravenous infusion over 1 hour, then 100 mg intravenous infusion over 1 hour on days 2, 3, 4 and 5) -levofloxacin 500 mg/day intravenously was used empirically for secondary bacterial infections -dexamethasone 24 mg/day intravenously -anticoagulants: enoxaparin 6000 units once daily for prophylaxis and twice daily for treatment of thrombosis | 17 days | thrombosis |
| Mousavi, 2021 [15] | RCT, single centre | hospitalized patients | 96 | oral 1 × 3 mg (7 days or until death) | -hydroxychloroquine -atazanavir -methylprednisolone -azithromycin -naproxen -lopinavir/ritonavir for 7 days or until death | 10 days | sleep quality |
| Sanchez-Gonzalez, 2022 [16] | PSM, single centre | hospitalized patients | 448 | oral 2–6 mg (during admission) | - | not specified | mortality |

Abbreviations: RCT—Randomized controlled trial; PSM—propensity matched study.

*in this study the treatment group also received intravenous vitamin C (2 g, q6 hr), oral melatonin (6 mg, q6 hr), and oral zinc sulphate (220 mg containing 50 mg elemental zinc, q6 hr) for 10 days.

PaO₂/FiO₂: arterial oxygen partial pressure/fractional inspired oxygen; * COVID-19: coronavirus disease 2019.

In opposition to downregulating the overactivation of the innate immune response, melatonin promotes an adaptive immune response, augmenting antibody formation and it has been suggested as a potential adjuvant of anti-SARS-CoV2 vaccines [35, 36]. It is important to emphasize the extremely high safety profile of melatonin. No side effects are generally noticed even when melatonin is administered at high dose (e.g., 1 g a day for a month) and, if present, they are usually limited to nausea, headaches, dizziness and drowsiness [6]. Finally, the cytoprotective capability of melatonin towards medical conditions such as metabolic syndrome, diabetes, ischemic cardiovascular diseases and nephrotoxicity, which are correlated to worse outcomes in COVID-19 patients, have also been well documented [37]. It is interesting to note that melatonin levels decline considerably with aging. This is associated with several age-related diseases and could partially explain age-related vulnerability to COVID-19 [38].

Clinical studies testing melatonin in COVID-19 patients are consistent with experimental information. Case series, retrospective analyses with control groups and RCTs mostly demonstrate the efficacy of melatonin in aiding the recovery of COVID patients, demonstrated by any endpoint and parameter considered, with no significant side-effects [9, 10, 12–16]. A meta-analysis of three RCTs of standard therapy with the addition of melatonin in comparison to standard therapy alone in COVID-19 patients, has been recently published by Lan *et al.* [19]. Melatonin treatment significantly improved the recovery rate (94.2% (81/86) *vs.* 82.4% (70/85), OR: 3.67; 95% CI: 1.21–11.12; $I^2 = 0\%$, $p = 0.02$) with no difference in requirement for intensive care (8.3% (6/72) *vs.* 17.6% (12/68) $p = 0.13$) and mortality (1.4% (1/72) *vs.* 4.4% (3/68) $p = 0.33$). Another meta-analysis including six RCTs found similar results: it did not pool mortality data, but detected a higher recovery rate in patients receiving melatonin *vs.* patients receiving standard therapy alone (odds ratio = 3.05, 95% CI = 1.47, 6.31; $p = 0.003$) [20] with no difference in terms of CRP (weighted mean difference (WMD) = -0.36 , 95% CI = -3.65 , 2.92 , $p = 0.83$), arterial oxygen saturation (WMD = 1 , 95% CI = -1.21 , 3.22 , $p = 0.37$) and white blood cells (WMD = -1.07 , 95% CI = -2.44 , 0.30 , $p = 0.13$) [20]. Our meta-analysis, by including a larger number of studies, confirmed our preliminary results [21] and showed a statistically significant reduction in mortality in the overall population and in non-ICU COVID-19 hospitalised patients with melatonin plus standard therapy *vs.* standard therapy alone. By contrast there were no differences in mortality in patients who were already in ICU.

These data support the use of melatonin to lower mortality in hospitalized COVID-19 patients who are not admitted to the ICU. These data confirm what is usually known *i.e.*, that identifying drugs that have a clear impact on the mortality of ICU patients is very difficult given the complexity of mechanisms underlying critical illness. These data also show that the effect of melatonin on COVID-19 patients may depend on disease stage and/or severity and suggest that an early administration of melatonin in the initial phases or in mild disease conditions, which are prevalent in the whole COVID-19 population, may have a significant impact on mortality.

In this regard a comparison with corticosteroids might be interesting. Corticosteroids decrease mortality in critically ill

COVID-19 patients [5] but are likely detrimental in the early stages of the disease [39].

If we compare these data with those we have reported about melatonin we could picture a pharmacological strategy in which melatonin and corticosteroids might be used in a sequential and complimentary manner. Melatonin for early treatment in mild/early phases of COVID-19 disease, whereas corticosteroids could play their role (supported by melatonin) in COVID-19 patients who require oxygen therapy.

Nevertheless our study is not without limitations. First, the number of studies included is relatively low and all studies are open label and single-center. Second, there is a wide variety in melatonin administration regimen among the studies. In particular differences can be found in total daily dose administered (range from 2 mg up to 21 mg), number of administrations per day (one to four) and length of treatment. These limitations warrant therefore caution in interpreting our analysis, which would benefit from higher-quality RCTs with a larger pool of patients and a lower risk of bias. Other RCTs investigating the usefulness of melatonin as a treatment for COVID-19 patients in different clinical settings are already on their way [25–27]. As in the case of corticosteroids, the inclusion of melatonin in registered adaptive platform trials would allow rapid evidence generation, thus clarifying the role of melatonin as a potentially timely, safe, self-administered, affordable and widely available adjunctive treatment for COVID-19 patients.

5. Conclusions

In this meta-analysis of RCTs and propensity matched studies we found that melatonin seems to decrease mortality in COVID-19 patients although dosing regimen and length of therapy is still unclear. According to our analysis the reduction in mortality still remained significant when considering only patients who were not admitted to ICU. We found instead no differences in term of hospital stay, need for ICU and CRP levels in patients treated with melatonin.

AVAILABILITY OF DATA AND MATERIALS

Upon reasonable request, the corresponding author will provide the data analysed in this current study. The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper. No financial or non-financial interests were in this current research. Our research was registered on 23 May 2022 in Open Science Framework Registries (OSF registration DOI: 10.17605/OSF.IO/7P4VG).

AUTHOR CONTRIBUTIONS

GL, RL, AY, VL and AZ—have given substantial contribution to the acquisition, analysis and interpretation of data for the work. GL and RDC—Covello revised it critically. All authors have given substantial contributions to the conception and design of the work. All authors have participated to drafting the manuscript. All authors read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as one of the Editorial Board members of this journal. We declare that Giovanni Landoni had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.signavitae.com/mre-signavitae/article/1691722790965526528/attachment/Supplementary%20material.docx>.

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