



Correspondence

Does melatonin reduce mortality in COVID-19?

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To the editor:

Coronaviruses (CoVs) usually affect the respiratory system of mammals causing mild to severe infections. In the past two decades pathogenic human CoVs with high morbidity and mortality such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) emerged from animal reservoirs. The current global coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), lead to death over 6 million of people worldwide. It represents a challenge for all healthcare systems and for the countries that have dealt with unprecedented social and economic consequences [1]. Since the COVID-19 pandemic began, numerous drugs have been proposed to treat or prevent COVID-19. Along with the search for new drugs, existing drugs with known pharmacokinetics/dynamics and safety profiles have been repurposed beyond traditional use. In fact, compared to de novo drug discovery, drug repurposing could be an effective research strategy to shorten time and reduce costs. A retrospective cohort study by Karimpour-Razkenari et al. on the effects of melatonin in COVID-19 ICU patients has been recently published in this journal [2]. Authors showed only marginal effect on disease-specific biochemical parameters and a non-statistically significant reduction in mortality in melatonin-receiving group (41%) vs non melatonin-receiving group (72%).

Melatonin is a neurohormone released by the pineal gland with a regulatory effect on the circadian rhythm and exogenous melatonin is used to manage sleep disorders. A few reviews have recently pointed out the biological plausibility of melatonin in treating COVID-19 patients because of its wide-ranging effects. Some effects are expected, such as reversing circadian rhythm disruption, chronic stress of social isolation, hospital and ICU stay, control of delirium in frail and critically ill patients, and the prevention/treatment of post-COVID-19 cognitive impairment (long COVID) [3]. Some other effects are less obvious but reflect the known pleiotropic complexity of melatonin: possible antiviral action by interfering with SARS-CoV2/angiotensin-converting enzyme 2 association; antioxidant/anti-inflammatory/immunoregulatory activities [4]; cytoprotective effects on medical conditions such as diabetes, metabolic syndrome and ischemic cardiovascular diseases which are associated to worse outcomes in COVID-19 patients; potential adjuvant

of anti-SARS-CoV2 vaccines. New network-based medicine methodologies support the biological plausibility of melatonin in COVID-19 and also the Cleveland Clinic suggested that melatonin, alone or in association with other drugs, may help preventing SARS-CoV2 infection or aid in treating COVID-19 [5].

What do randomized controlled trials say about melatonin in COVID-19 and its effect on mortality? We investigated PubMed/Medline, Cochrane Central Register of clinical trials and Clinicaltrials.gov for recently completed or not published studies and we identified three RCTs that reported mortality rates in hospitalized COVID-19 patients receiving melatonin in addition to standard therapy compared to patients treated with standard therapy alone [6–8].

Even if few events occurred, a reduction in mortality at the longest follow-up available can be observed: 1.3% (2/154) among patients treated with melatonin plus standard therapy compared to 11.1% (16/144) in those that received standard therapy alone. Our pooled analysis of three RCTs, as shown in the forest plot, confirmed a significant reduction in mortality at the longest follow-up available in melatonin-receiving group (risk ratio [RR], 0.12; 95% CI = 0.03–0.50; $p < 0.01$; $I^2 = 7\%$) [9]. (Fig. 1).

It is important to note that all reported RCTs were open-label, single-center, small sample size studies with a short follow-up, evaluating melatonin at different doses in different stages of the disease and with variable exclusion criteria. These limitations should bring caution in interpreting these RCTs and we recommend high quality RCTs with a larger number of patients or to include melatonin in registered adaptive platform trials to better clarify its role in COVID-19 patients. If more evidence about melatonin beneficial effect in COVID-19 is confirmed there will be a further confirmation of the importance of network-based medicine methodologies and artificial intelligence-based approach in the identification of drug treatments. Melatonin could become a low cost adjuvant in the therapy against SARS-CoV-2 infection available in a short time and rapidly producible.

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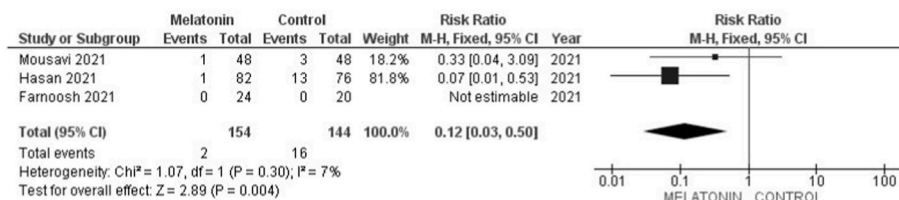


Fig. 1. Forest plot of the rate of mortality at the longest follow-up available.

Ethical approval

None to declare.

Consent

None to declare.

Registration of Research Studies

1. Name of the registry: None to declare.
2. Unique Identifying number or registration ID: None to declare.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): None to declare.

Author contribution

Pilia Eros - writing the paper and performed data analysis. Ettore Alborino - data collection. Remo Daniel Covello – study design and writing the paper.

Guarantor

Pilia Eros. Ettore Alborino. Remo Daniel Covello

Declaration of competing interest

None to declare.

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