Review

Efficacy of melatonin in non-intensive care unit patients with COVID-19 pneumonia and sleep dysregulation

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ABSTRACT

The association of sleep disruption with a higher vulnerability to COVID-19 infection is a subject of major clinical importance. In patients with pneumonia associated with COVID-19 admitted to non-intensive care unit (NICU) several factors, like the disrupting influence of respiratory distress, medication, greater stress due to social isolation, and lack of appropriate exposure to environmental light can be instrumental to disrupt sleep/wake cycle. The therapeutic potential of melatonin to counteract the consequences of COVID-19 infection has been advocated. Because of its wide-ranging effects as an antioxidant, anti-inflammatory, and immunomodulatory compound, melatonin could be unique in impairing the consequences of SARS-CoV-2 infection. Melatonin is also an effective chronobiotic agent to reverse the circadian disruption of social isolation and to control delirium in severely affected patients. Properly administered, melatonin may restore the optimal circadian pattern of the sleep-wake cycle and improve clinical condition in pneumonia associated with COVID-19 patients. The present review article discusses the importance of maintaining normal sleep and circadian rhythmicity in NICU patients and provides preliminary data suggesting the efficacy of melatonin (9 mg/day) to reduce length of stay of pneumonia patients associated with COVID-19 in NICU.

Key words: Chronotherapy, COVID-19 pandemic, melatonin, pneumonia, respiratory distress, sleep.

1 INTRODUCTION

In pneumonia associated with COVID-19 patients admitted to non-intensive care unit (NICU) several factors, like the disrupting influence of respiratory distress, medication, greater stress due to social isolation and erratic exposure to environmental light are instrumental to disrupt the sleep/wake cycle. Sleep deprivation and abnormal melatonin excretion are associated with the occurrence of delirium, a frequently encountered dysfunction in critically ill patients (1). Delirium is a consciousness disorder with cognitive change (hyperactive, hypoactive, or mixed form) and is a well-known risk factor for prolonged duration of intensive care unit (ICU) stay, higher mortality, greater risk of cognitive sequelae, and more hospital costs (1).

The potentiality of melatonin, a molecule of unusual phylogenetic conservation present in all known aerobic organisms, to serve as a preventive and therapeutic agent in COVID-19 pandemic has been advocated (2, 3). Melatonin (a) may prevent SARS-CoV-2 infection; (b) is suitable as an effective anti-inflammatory/immunoregulatory/antioxidant agent; (c) counteracts chronodisruption; (d) combats several comorbidities such as diabetes, metabolic syndrome, and ischemic and non-ischemic cardiovascular diseases, which aggravate COVID-19 disease; (e) exerts a neuroprotective effect in acutely and chronically affected SARS-CoV-2 patients; and (f) can be an adjuvant to potentiate anti-SARS-CoV-2 vaccines (see for ref. (4). This multifactorial therapeutic potential is unique to melatonin and is not shared by any other therapeutic drug candidate for the COVID 19 pandemic.

As a chronobiotic agent, melatonin may restore the optimal circadian pattern of the sleep/wake cycle and improved clinical condition in individuals with COVID-19 pneumonia admitted to NICU. We hereby discuss the importance of sleep and circadian rhythm regulation in pneumonia associated with COVID-19 patients in ICU and provide preliminary data suggesting the efficacy of melatonin (9 mg/day) to reduce NICU length of stay in those patients.

2. SLEEP / WAKE CYCLE IN NON-INTENSIVE AND INTENSIVE CARE UNIT

Human sleep is organized by the interaction of homeostatic and circadian processes that are carried out independently, but in a complementary way. The homeostatic component (process S, for “sleep”) leads to sleep approximately one third of each 24-hour cycle, and the circadian component (process C) links the desire to sleep with the daily fluctuations of hormones programmed by the body clock. This two-process model of sleep, first proposed by Borbély in 1982, explains how homeostatic and circadian factors regulate the quantity and timing of sleep (5). According to this model, the requirement for sleep increases during wakefulness because of homeostatic process S in the brain (“sleep debt”) while circadian process C reflects circadian modification of vigilance. Borbély’s theory states that the likelihood of wakefulness and sleep are traded off against one another in a circadian mode. Homeostatic process S is defined as a homeostatic sleep-promoting process, which continuously escalates during wakefulness. Process S is related to decreased intellectual performance and vigilance, and an increase in sleepiness/fatigue while awake. During sleep, particularly slow wave sleep, process S continuously decreases (i.e., sleep pressure disintegrates). In contrast, the circadian scheduled process C (also known as the circadian pacemaker) is best seen as a nearly 24 h endogenous oscillatory variation for sleep propensity (5).

According to the classical view, the preoptic area (POA) and the posterior hypothalamus are thought to be the sleep and wake centers, respectively (6). More recently, new brain areas and

neurons involved in the regulation of the sleep/wake cycle have been uncovered. For example, GABAergic neurons in the medullary parafacial zone located in the brain stem and the ventral tegmental area (7) and adenosine expressing neurons in the nucleus accumbens are involved in the regulation of rapid eye movement (REM) sleep, whereas the MT_2 receptors selectively increase non-REM sleep (8). While the POA contains not only sleep-promoting neurons but also wake-promoting neurons (9), noradrenergic neurons in the locus coeruleus, serotonergic neurons in the dorsal raphe, and histaminergic neurons in the tuberomammillary nucleus are only implicated in regulation of wakefulness (10). Orexin/hypocretin neurons in the lateral hypothalamus play a crucial role to maintain wakefulness by orchestrating the activity of these monoaminergic neurons (11).

Sleep deprivation and poor sleep quality are problems in patients admitted in NICU, as reported in a study of 100 patients with low levels of sleep quality from Canadian general or family practice wards (12). In this type of patients, most studies reported difficulties during night sleep, even without previous sleeping problems at home (13–15).

These disorders worsen in ICU patients. The therapeutic procedures and medication and inappropriate lighting conditions contribute to disruption of the normal sleep / wake cycle in ICU (16–18). Increased pain sensitivity, reduced respiratory capacity, impaired immunity, and changes in neuroendocrine and metabolic functions have been reported in ICU patients (see for ref. (19). Additionally, consequences of sleep deprivation like memory impairment and mood deficits and delirium occur (20). Therefore, normalization of sleep in pneumonia associated with COVID-19 patients is instrumental to improve secondary outcomes including ICU length of stay and post-ICU recovery and functioning (18).

A mixture of medications including analgesic, sedative and hypnotic agents are often used in the ICU to reduce patients' pain or awareness of their environment, reduce responses to external stimulation, and eventually facilitate endotracheal tube tolerance and mechanical ventilator synchrony. Approximately 25% of ICU patients were prescribed eight or more medications concurrently and, of those patients, the average number prescribed was more than 13 (21). However, many negative side-effects emerge with the use of these medications, including impaired cognitive function, risk of dependency, depressed ventilation, and disrupted sleep patterns.

By measuring blood and urine melatonin levels the abolition of the circadian rhythm of physiologic melatonin release was documented in sedated ICU patients (22). This may be due to the exposure to artificial light and limited natural light exposure, greater severity of illness compared with the general wards, and universal application of sedative and narcotic drugs, which may further contribute to a compromised quality of sleep. About 15% of hospitalized COVID-19 patients have impaired consciousness including somnolence, confusion and delirium (23). Indeed, about 50% of hospitalized elderly patients and 80% of critically ill patients under mechanical ventilation shows sleep disturbances and delirium (17, 24). All these indicate a profound alteration in the duration and organization of sleep.

Circadian disruption by sleep loss, like that observed in COVID-19 patients admitted to ICU, affects every major system in the human body. Several epidemiologic studies have reported associations between sleep/wake cycle disruption and cardiometabolic disease (25, 26). Shortened sleep and poor sleep quality have also been identified as risk factors for cognitive decline, neurodegenerative disease, mood changes and depression, as well as other neuropsychiatric conditions (27, 28). There is also mounting evidence linking sleep disruption to immune function and cancer (29–31).

3. MELATONIN AND SLEEP

The circadian rhythm in synthesis and secretion of pineal melatonin is closely associated with the sleep rhythm (32). The onset of nighttime melatonin secretion is initiated approximately 2 h in advance of an individual's habitual bedtime and has been shown to correlate with the onset evening sleepiness. Several studies implicate endogenous melatonin in the physiological regulation of the circadian mechanisms ruling sleep propensity (33). Melatonin reduces the need for sedation in ICU patients (34–39). Thus, in the context of COVID-19 pandemic the therapeutical utility of melatonin emerges.

Melatonin is a prototype chronobiotic that plays a major function in the coordination of circadian rhythmicity (40). Drugs that directly affect the circadian phase, and thus the output of the biological clock, are called chronobiotics. This term was introduced in the early 1970s and has been used to broadly define a drug that affects the physiological regulation of the structure of biological time and, specifically, is capable of therapeutically recovered desynchronized circadian rhythms in the short or long term, or prophylactically avoiding its interruption after an environmental attack (41). The magnitude and direction of phase changes depend on the circadian phase in which these compounds are administered, which in turn produces pronounced phase changes in behavioral rhythms. For example, melatonin given in the morning delays the phase of circadian rhythms while when given in the evening it advances the phase of circadian rhythms. For most part of the day, melatonin administration is unable to modify the phase of the clock (phase response curve).

During the day-to-night transition, melatonin exposure advances neural activity rhythms in the central circadian pacemaker located at the hypothalamic suprachiasmatic nuclei (SCN) via the activation of protein kinase C. Melatonin induces an increase in the expression of two SCN clock genes, Period 1 (*Per1*) and Period 2 (*Per2*). This effect occurs at circadian time (CT) 10, when melatonin advances SCN phase, but not at CT 6, when it does not. Using anti-sense oligodeoxynucleotides to *Per1* and *Per2*, as well as to E-box enhancer sequences in the promoters of these genes, it was shown that their specific induction is necessary for the phase altering effects of melatonin on SCN neural activity rhythms (42).

Melatonin secretion is an "arm" of the biologic clock in the sense that it responds to signals from the SCN and that the timing of the melatonin rhythm indicates the status of the clock, both in terms of phase (i.e., internal clock time relative to external clock time) and amplitude (43). From another point of view, melatonin is also a chemical code of night: the longer the night, the longer the duration of its secretion. In most vertebrate species, this pattern of secretion serves as a time cue for seasonal rhythms (44).

Pineal melatonin production is controlled by a complex neural system originating in the SCN and terminating in the high levels of the thoracic spinal cord – the superior cervical ganglion sympathetic system. The postganglionic sympathetic nerve terminals of the superior cervical ganglion release norepinephrine into the pineal gland that triggers melatonin synthesis by its interaction with β- (mainly) and α-adrenoceptors on the membrane of pineal cells. Melatonin, due to its high diffusibility, is not stored inside the pineal and is released as soon as it is produced (45). The structures which regulate circadian rhythms have been described as the SCN-melatonin loop (45). This loop includes melanopsin-containing retinal ganglion cells, the retino-hypothalamic tract, SCN, paraventricular nucleus, intermediolateral cell column, the sympathetic cervical ganglia, the pineal gland, and the melatonin rhythm which feedback impacts the SCN.

As a result, the melatonin production, and consequently its cerebrospinal fluid and blood levels, are circadian in nature and tightly synchronized with the environmental light/dark cycle. Indeed, the circadian pineal production of melatonin is restricted to the dark phase of the light/dark cycle in all mammalian species. It is noteworthy that melatonin is always produced during the night independent of the daily pattern of activity/rest of the species, indicating its strong relationship with the external photoperiod. Additionally, melatonin is produced during the night provided there is no light in. Given the regularity of the daily melatonin production that is associated with high and low or absent blood concentrations during the night and day, respectively, melatonin is able to synchronize the circadian rhythms of several organs and their functions (43)

Daily timed administration of melatonin to rats shifts the phase of the circadian clock, and this phase shifting may explain the effect of melatonin on sleep in humans. Indirect support for such a physiological role derives from clinical studies on blind subjects (who show free running of their circadian rhythms) treated with melatonin (46). More direct support for this hypothesis was provided by the demonstration that the phase response curve for injected melatonin was opposite (i.e., about 180 degrees out of phase) to that of light (47).

Melatonin is a pleiotropic signal that has to be analyzed at different levels, from the sites of synthesis and local dynamics, distribution of receptors and other binding sites in target organs, cell-specific differences in signaling as related to the presence of G protein variants, and intracellular effects – with a particular focus on mitochondrial actions – to numerous secondary changes induced by influencing other hormones, neurotransmitters, neurotrophins and further signal molecules (48). In functional terms, melatonin exerts a host of effects that can be under the control of the SCN and has also direct effects in numerous peripheral organs. In particular, melatonin is involved in sleep initiation, vasomotor control, adrenal function, antiexcitatory actions, immunomodulation including anti-inflammatory properties, antioxidant actions, and energy metabolism, influencing mitochondrial electron flux, the mitochondrial permeability transition pore, and mitochondrial biogenesis (48, 49).

The chronobiotic action of melatonin is mediated via the melatonin receptors, which have been identified both in the central nervous system and in the periphery (50). Melatonin MT_1 and MT_2 receptors, all belonging to the superfamily of membrane receptors associated with G proteins (G-protein coupled receptors, GPCR), have been cloned. More recently, another member, GPR50, was included in the melatonin receptor subfamily. GPR50 shows high sequence homology to MT_1 and MT_2 but does not bind to melatonin or any other known ligand. Ligand-independent functions for GPR50 such as the allosteric regulation of other proteins/receptors through their interaction with GPR50 in common protein complexes have been proposed. In the case of the molecular complex of GPR50 with the melatonin MT_1 receptor, GPR50 negatively regulates the function of MT_1 (51).

Circulating melatonin is loosely bound to albumin (52) and in the liver, it is first hydroxylated and then conjugated with sulfate and glucuronide (53). In human urine, 6-sulfatoxymelatonin has been identified as the main metabolite. In the brain and most peripheral cells melatonin is metabolized into kynurenine derivatives. In mammals, circulating melatonin is derived almost exclusively from the pineal gland. In addition, melatonin is synthesized locally in most cells, tissues and organs, including lymphocytes, bone marrow, thymus, gastrointestinal tract, skin and eyes, where it can play an autocrine or paracrine role (54). Indeed, there is now strong evidence that melatonin is produced in every animal cell that has mitochondria (55). In both animals and humans, melatonin participates in diverse physiological functions that indicate not only the

duration of the night, but also improve the elimination of free radicals and the immune response, showing relevant cytoprotective properties.

Concerning the sleep/cycle, melatonin is a powerful chronobiotic with very slight hypnotic capacity. Daily doses of 2-5 mg melatonin, timed to advance the phase of the internal clock by interaction with MT_1 receptors in the SCN, maintains synchronization of the circadian rhythms to a 24-h cycle in sighted persons who are living in conditions likely to induce a free-running rhythm (47). Melatonin synchronizes the rhythm in persons after a short period of free running. In blind subjects with free-running rhythms, it has been possible to stabilize, or entrain, the sleep/wake cycle to a 24-h period by giving melatonin, with resulting improvements in sleep and mood (46). The phase shifting effect of melatonin is also sufficient to explain its effectiveness as a treatment for circadian-related sleep disorders, such as jet lag or delayed phase sleep syndrome (56, 57). Recent advances using selective MT_1/MT_2 receptor ligands and MT_1/MT_2 receptor knockout mice have suggested that the activation of the MT_1 receptors is mainly implicated in the regulation of REM sleep, whereas the MT_2 receptors selectively increase non-REM sleep (58).

Several meta-analyses support the view that the chronobiotic/hypnotic properties of melatonin are useful in patients with primary sleep disorders to decrease sleep onset latency and to increase total sleep time, with little if any effect on sleep efficiency (59–61). Several expert consensus reports also support such a role of melatonin in adult insomnia (62–65).

In normal aged subjects and in demented patients with disturbed synchronization of the sleep/wake cycle (66, 67) melatonin administration is helpful to reduce the variation of onset time of sleep. In demented patients, melatonin improved the circadian rhythm, cognition and mood, and diminishes nocturnal restlessness (68). In the long term, melatonin administration halted evolution of minimal cognitive decline to Alzheimer´s disease. This effect may be relevant in the control of residual effects of COVID 19 disease. Indeed, in a recent study including 84,285 Great British Intelligence Test with biologically confirmed COVID-19 infection, people who had recovered, including those no longer reporting symptoms, exhibited significant cognitive deficits (69). The scale of the observed deficits was equivalent to the average 10-year decline in global performance between the ages of 20 to 70 within the same dataset. “Brain fog”, i.e., confusion, forgetfulness, inability to focus, fatigue, and low mental energy (70, 71) is thus an emerging major sequel of COVID-19 infection. In this context the neuroprotective properties of melatonin deserve consideration (72).

4. MELATONIN USE IN COVID-19 PANDEMIC

In severely infected patients with COVID-19, an excessive inflammation, a depressed immune system, and activated cytokine storm contribute substantially to pathogenesis. In light of the public health problem triggered by the spread of COVID-19 and in the face of essentially null options for prevention or treatment presently available, a number of recent reports have put forth the use of melatonin to treat COVID-19 disease (73–81).

In diseases showing a high level of inflammation, the application of melatonin showed promising results with strong attenuation of circulating cytokine levels. This was documented in patients with diabetes mellitus and periodontitis (82) and severe multiple sclerosis (83). In the acute phase of inflammation, during surgical stress (84), cerebral reperfusion (85) or reperfusion of the coronary artery (86), treatment with melatonin reduced the level of proinflammatory cytokines.

According to the COVID-19 clinical reports, patients with severe infection have an increased risk of sepsis and cardiac arrest (87, 88). The available information indicates that the application of melatonin can improve septic shock through inhibition of the NLRP3 inflammasome pathway (89). Interestingly, the upregulation of matrix metalloprotease 9 MMP9 (activated during NLRP3 inflammasome) was found to be correlated with COVID-19 related cytokine storm (79), and a recent meta-analysis indicates that melatonin may interact with MMP9 in the extracellular matrix of the respiratory tract from the SARS-CoV-2 patients to reduce inflammation during COVID-19 infection (80).

Melatonin has a preventive effect against sepsis-induced kidney damage, septic cardiomyopathy, and liver damage (90–92). Melatonin has also been reported as beneficial in patients with myocardial infarction, cardiomyopathy, hypertensive heart disease, and pulmonary hypertension. In the ICU, deep sedation is associated with increased long-term mortality, and the application of melatonin reduces the use of sedation and the frequency of pain, agitation and anxiety and improves the quality of sleep (93). Therefore, the rationale for the use of appropriate doses of melatonin in COVID-19 focuses not only on attenuation of infection-induced respiratory disorders, but also on general improvement and prevention of possible complications, like the cardiac and neurologic ones.

A recent study determined the efficacy and tolerability of a high dose of melatonin (36 mg/day to 72 mg/day p.o. in 4 divided doses) as an adjuvant therapy, in addition to standard and/or empirical therapy in COVID-19 pneumonia (94). The 10 patients given melatonin had high-risk features determined for age (> 60 years) or/and established comorbidities. No significant side effects were noted except for drowsiness. Benefits of time were observed for clinical improvement (reduction of symptoms, stabilization and/or regression of lung infiltrates, decrease in proinflammatory markers), as well as the need for mechanical ventilation, duration of hospital stay and outcome (death, or recovery and discharge) (94).

Another recent report was a retrospective analysis based on the clinical experience at the Columbia University Irving Medical Center related to drugs used to treat respiratory distress in COVID-19-infected patients who required endotracheal intubation (95). After a comprehensive evaluation of 791 patients diagnosed with COVID-19 who required intubation, the application of melatonin is the only drug that was statistically associated with higher positive clinical outcome including survival of patients intubated and in those requiring mechanical ventilation. Presently 8 clinical trials looking for melatonin therapeutic effects in COVID pandemic are in different phases of development (https://clinicaltrials.gov/).

5. PRELIMINARY OBSERVATION ON MELATONIN EFFICACY IN PNEUMONIA ASSOCIATED WITH COVID-19 PATIENTS PNEUMONIA ADMITTED TO NICU

Sleep deficiency is one of the most common complains in patients with respiratory diseases, and insomnia results in a significant deterioration in respiratory performance, even in a healthy person (96). Indeed, sleep disruption has been reported as extremely common in the pulmonary ICU (97).

Table 1. NICU, laboratory-confirmed, pneumonia associated with COVID-19 patients treated (Buenos Aires) or non-treated (New York) with melatonin.

	Centro Gallego of Buenos Aires n=37 n (%) or mean (SD)	**New York metropolitan region (**98) **n=60** n (%) or mean (SD)	**p**
Female	17 (45.9%)	8 (13.3%)	< 0.001 [a]
Age (years)	60.2 (19.4)	58.7 (13.4)	ns [c]
Length of stay (days)	4.9 (2.6)	10.7 (8.4) [b]	< 0.001 [c]
Death	1 (2.7%)	8(14.6%)	ns [a]

a. chi square test; b. Length of stay Mean and SD were estimated from median and interquartile range values reported in (98). Calculations were conducted as described elsewhere (99). c. Student' t-test; ns: non-significant.

In a recent therapeutic algorithm for the use of melatonin in patients with COVID-19 a dose of 3 to 10 mg/day dose of melatonin was proposed for elderly patients with co-morbidities like sleep disruption (100). We employed a 9-mg melatonin dose to improve clinical conditions and hastened recovery in a group of 37 hospitalized patients with COVID-19 pneumonia (Table 1). This was a retrospective cohort study of a limited clinical database of confirmed pneumonia associated with COVID-19 patients hospitalized at Centro Gallego of Buenos Aires. All patients were diagnosed as per the World Health Organization's interim guidance document. Collected information on consecutive patients admitted to the general ward from August 31, 2020, to September 11, 2020, as per our inclusion and exclusion criteria, was obtained. The ethics committee of Centro Gallego of Buenos Aires approved this study and permitted a waiver of informed consent from the study participants.

Patients were eligible for the study if they met the following inclusion criteria 1) Age > 18 years old, 2) Confirmed cases of SARS-CoV-2 by PCR method, 3) Admitted in general ward, 4) Bilateral infiltrate on chest imaging validated by radiology staff. Nasopharyngeal swab samples were obtained from all patients at admission and tested using real-time reverse transcriptase-polymerase chain reaction assays to identify SARS-CoV-2 infected patients. Limited available information included sex, age, length of stay and outcome (discharge or ICU transfer). All patients were on corticosteroid treatment and received 9 mg of melatonin p.o. at 2200 h daily. The primary outcomes were the composite outcome of intensive care unit (ICU) transfer, intubation, or death and length of stay. No relevant side effect of melatonin was recorded in the sample of patients examined.

Results are summarized in Table 1. As a comparison, data from a NICU, laboratory-confirmed, COVID-19 pneumonia study performed in the New York metropolitan region were employed, considering only the subgroup of patients under corticosteroid treatment (98). Although we cannot discard that patients from our study were less severely affected than those from the New York series, melatonin administration reduced by half the length of stay of pneumonia associated with COVID-19 patients. It must be stressed that this is a retrospective cohort study of a limited clinical database from which, unfortunately, no more information was available, like for example, that derived from non COVID-19 patients hospitalized in the same

NICU. Clearly, the samples in Table 1 might not be comparable, and the possible effect of melatonin in reducing length of stay needs further examination.

6. CONCLUSIONS

The current COVID-19 pandemic is the most devastating event in recent history. As above discussed, in the ICU, deep sedation is associated with increased long-term mortality, and the application of melatonin reduces the use of sedation and the frequency of pain, agitation and anxiety and improves the quality of sleep. Properly administered, the chronobiotic/cytoprotective agent melatonin may restore the optimal circadian pattern of the sleep-wake cycle and improve clinical condition in individuals with COVID-19 pneumonia.

A recent study endorses the efficacy and tolerability of a high dose of melatonin as an adjuvant therapy in ICU patients, in addition to standard and/or empirical therapy for COVID-19 pneumonia (94) and preliminary data of Table 1 suggesting the efficacy of a relatively low dose of melatonin to reduce NICU length of stay in pneumonia associated with COVID-19 patients support such a view.

Melatonin has been used as a sleep aid for decades without any serious adverse effects being reported (101, 102). Moreover, it has often been used in critically ill patients to improve sleep and wellbeing, both of which would also be beneficial to SARS-CoV-2 infected patients. It is a molecule with an uncommonly high safety profile and can be administered via numerous routes including orally. It is inexpensive, stable without refrigeration and would be particularly useful in underdeveloped countries where access to high quality health care may be lacking.

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AUTHORSHIP

Conceptualization: D.P.C., L.I.B., D.E.V. Writing, Original draft: D.P.C. Writing, Review & Editing: D.P.C., L.I.B., D.E.V., P.C., A.V.C., C.G.R. Data curation: L.I.B, P.C., A.V.C., C.G.R.

CONFLICT OF INTEREST

All authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

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