



The Reasons for Higher Mortality Rate in Opium Addicted Patients with COVID-19: A Narrative Review

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Abstract

The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused COVID-19 has developed into an unexampled worldwide pandemic. The most important cause of death in patients with COVID-19 is Acute Respiratory Distress Syndrome (ARDS). Opium is widely used for its analgesic features in control of acute and chronic pain related to different diseases. Opium consumption is increased over the last three decades and leads to adverse effects on the respiratory system; opium also affects the lungs' functions and respiration. The contemplative issue is the higher mortality rate due to SARS-CoV-2 infection in opium addicts' patients. Studies have shown that despite the decrease in proinflammatory cytokines production in opium addicts, there are at least 4 reasons for this increase in mortality rate: downregulation of IFNs expression, development of pulmonary edema, increase thrombotic factors, increase the expression of Angiotensin-converting enzyme 2 (ACE2). Therefore, identifying the causes of mortality and approved therapies for the treatment of COVID-19 patients who use opium for any reason is an important unmet need to reduce SARS-CoV-2 infection-related mortality. This review study demonstrated the effects of opium on immune responses and the reasons for the higher mortality rate in opium addicts' patients with COVID-19.

Keywords: Opium; Cytokine storm; COVID-19; IFNs

Introduction

Recently, a new strain of β -coronavirus (SARS-CoV-2) appeared throughout the world. WHO in Jan 2020 announced an international public health emergency (1).

Four phases have been identified for COVID-19, including 1. Early infection phase (viral replication with mild signs), 2. pulmonary phase (adaptive immune response and respiratory symptoms), 3. hyper coagulopathy Phase, and 4. hyper-inflammatory or end-organ damage phase (2).

The immune system function is an important factor in controlling the SARS-CoV-2 infection (3). ARDS is the main cause of the death in COVID-19. In SARS-CoV-2 infection, the development and progression of ARDS is due to the inflammatory cytokine storm (4). In fact, one of the significant causes of ARDS is the cytokine storm (3). The appearance and progression of SARS-CoV-2 symptoms are related to interplay of the virus and host immune responses.



Viral properties consist mutations, viral load and the survival power of the virus in vitro. In contrast, the immune system components comprise *HLA* genes, age, sex, nutritional and physical situation, and neuroendocrine-immune modulation (3). These factors all participate in COVID-19 patient state, the duration and severity of the disease, and the reinfection (3).

Opioids decreased respiratory capacity (5) and longtime use is immunosuppressive (6). Moreover, increased infection rates in individuals with opioids abuse indicate opioids suppress the immune system (7). Thus, understanding the effects of opioid on patients' prognosis with COVID-19 is critical and necessary (8). The bidirectional relation between the brain and the immune system plays an important role in COVID-19 pathogenesis. The hypothalamic-pituitary-adrenal (HPA) axis is responsible for systematic inflammation control. The hypothalamus secrete corticotrophin-releasing hormone (CRH) and arginine-vasopressin (AVP) which activate anterior pituitary (AP) to produce adrenocorticotrophic hormone (ACTH). ACTH then stimulate adrenal cortex glucocorticoids synthesis and secretion (9), and induces production of cytokine, such as IL-1, IL-6, and TNF. Upon pathogen clearance, the HPA axis activate releasing anti-inflammatory molecules, glucocorticoids, from the adrenal cortex to terminate the inflammatory responses, and negatively regulate the HPA axis. It has been shown that opioid abuse alters the HPA axis.

Exceeding generation of glucocorticoids inhibits immune responses against viruses, resulted in increased prevalence of viral infection and serious COVID-19 (10). Opioids involved in regulation of brain and immune responses (stimulate proinflammatory factors production, suppression of immunity, and damage BBB). Opioid abuse can cause irreversible BBB injury (11) and impair the HPA axis and immune responses (9). Opioid abuse induced neuroinflammation and inflammation caused by COVID-19 may reciprocally exacerbate the detrimental effects of one another, leading to severe disease. With impaired HPA axis and immune disorder, the patients are at high risk for SARS-CoV-2 infections (10). Opioids

(heroin, synthetic drug fentanyl, oxycodone, hydrocodone, codeine, and morphine), are affects the endocrine system (10). Opioids have immunosuppressive properties that reduce the function of macrophages, NK cells, and T cells, and are related to higher risks of infectious diseases, like pneumonia (7). The endogenous opioid (endorphins, dynorphins, and enkephalins) and their receptors, μ (MOR), δ (DOR), and κ (KOR), are crucially linked to opioid abuse and addiction, and are linked to infection (12). Opioid receptors activation in the brain stem involved in respiratory depression and overdose mortality (13). Respiratory depression is an important cause of hypoxemia in COVID-19. Morphine desensitizes the HPA axis and suppress the anti-inflammatory glucocorticoids production through increasing proinflammatory cytokine, IL-1 β and neuroinflammation (10), therefore, significantly increase the severity and inflammatory response of opioid addicts. Peoples with opioid abuse are more susceptible to opportunistic infections (14), therefore, they are at higher risk of SARS-CoV-2 infection.

Concerning opium addiction and COVID-19, the rate of mortality in opium-addicted hospitalized patients with COVID-19 was 3.59 percent. According to the findings of this study, it seems that the rate of COVID-19 mortality in the opium-addicted patients is higher than the normal population (15). Moreover, epidemiologic studies have demonstrated an increased mortality rate in opioid addicted peoples with COVID-19 during the pandemic. Wang et al showed that opioid addict, are at higher risk for COVID-19 and worse outcomes (death: 9.6%, hospitalization: 41.0%, $P < 0.05$) (16). Therefore, opium-addicted patients are more susceptible to SARS-CoV-2 infection. However, the effects of opium consumption on the mortality rate of COVID-19 patients requires more consideration.

Despite investigations of the effects of opium on the immune responses, the mechanisms of how opium influences the host immunity in COVID-19 is still unclear. We focused on potential interactions and modulation of the immune system against SARS-CoV-2 to understand the possible

mechanisms of higher mortality rate of COVID-19 in opium addicted patients. This review study demonstrated the effects of opium on immune responses and the reasons for higher mortality rate in opium addicts' patients with COVID-19.

The Effects of Opium on Immune Responses

Opium poppy (*Papaver somniferum* L.) is a very important herbal medicine that contains more than 80 alkaloids classified in the tetrahydrobenzylisoquinoline derivatives (17). From a few thousand years ago, opium is the principle of the opioid class of drugs has been used for suppress the central nervous system (18). Pharmacologically important alkaloids of opium include analgesic morphine, codeine, thebaine, papaverine, etc. (19). Actually, morphine is the most important component of opium (20).

Opium inhibits bone marrow migration and activity of lymphocytes, indicates the immunosuppressive effect of opium (21). Furthermore, opium caused a decreased mitogenic response in lymphocyte population of peripheral blood of healthy peoples (22).

Opioids such as morphine suppress the cellular immunity and response to bacterial pathogens; this finding has been confirmed by epidemiological studies (23). Another related study demonstrated that morphine induces the immune cells apoptosis; the thymus and spleen atrophy, and inhibits the proliferation of lymphocytes (24).

Opiates such as morphine impair the innate immunity against bacteria by reducing functions of macrophages, neutrophils, nonspecific cytotoxic T cells, natural killer cells, and dendritic cells (25). The results of in vivo and in vitro experiments have shown that opioids change the immune cells function and cytokine production, consequently lead to changes in the homeostasis of the immune system. This changes results in increased susceptibility to infection (26).

Frenklakh et al reported for the first time that macrophages isolated from morphine-treated mice were more susceptible to apoptosis than macrophages from control mice. Moreover, morphine inhibits the phagocytosis ability of neutrophils and monocytes (27, 28). Long-term

treatment of animals with morphine leads to a significant reduction in phagocytic activity (29). In addition, the phagocytic activity of morphine-treated human monocytes is suppressed. (30). Furthermore, morphine stimulates the production of nitric oxide, which leads to inhibition of phagocytic activity (27). Therefore, morphine can attenuate the host's immune response (31).

The production of cytokines is one of the main mechanisms for regulating immune responses. Cytokines like IL-1, IL-2, IL-6, and tumor necrosis factor alpha (TNF- α) play significant roles in the pathogenesis of various immune-mediated disorders (32). Morphine changes the production of the innate immune system's cytokines, including IL-1 β , and TNF- α (32). Morphine also decreases the production of TNF- α by mast cells, thereby reducing the primary innate peritoneal immune responses (33).

Moreover, chronic morphine treatment can reduce IL-1 and IL-6 production. The absence of TNF- α , IL-1, and IL-6 cytokines results in postpone the recruitment of neutrophils, which increases the susceptibility for bacterial infection. Then, TNF- α expression causes more nitric oxide production and increases macrophage apoptosis (34). Therefore, according to the above studies, it can be concluded that morphine acts as a suppressor of cytokine production (32). Furthermore, the function of NK cells in morphine-treated mice is significantly reduced (35).

Integrin family molecules including lymphocyte function-associated antigen-1 (LFA-1) and Macrophage-1 antigen (MAC-1) (36, 37) are involved in adhesion of leukocytes to the endothelium and immune cells migration (31). Integrins bind to the immunoglobulin-family adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and ICAM-2 on endothelium (38). Morphine has anti-inflammatory effects (39, 40) and suppress the recruitment of neutrophils by reducing the adhesion of leukocytes to the extracellular matrix proteins (41, 42). Besides, administration of exogenous opioid can inhibit the IL-8-induced chemotaxis of human peripheral blood neutrophils (41, 42).

Inflammatory cytokines, TNF α and IL-1 can induce the expression of ICAM-1. Morphine could reduce the production of ICAM-1 and the adhesion of neutrophils (38). Moreover, morphine significantly inhibits the expression of monocyte chemoattractant protein-1 (MCP-1) in response to lipopolysaccharide (LPS) (43). Morphine could inhibit chemokine-mediated immune cells migration in response to pathogen infection (44). Interestingly, morphine alters the CD4⁺ and CD8⁺ of T cell subsets (45, 46). CD4⁺ T cells of patients taking morphine after operation for pain control are decreased (47). Morphine could suppress the proliferation of T cells in vitro (46, 48). Inhibition of T cell receptor (TCR) and co-receptor CD28 signaling or blocking co-stimulatory molecules (like B7 family) on the activated antigen presenting cells (APCs) are the

most important pathways to suppress the T cell division. Nevertheless, morphine could prevent T cell-mediated immunity through inhibiting of TCR signaling (49). The production of IFN- γ in anti-CD3/CD28-stimulated T cells is decreased by means of morphine (50).

IL-10 also suppress Th1 cells development and activation (51); mice receiving long-term morphine could significantly enhance the IL-10 synthesis by splenocytes (52). Moreover, in opium addicts the serum level of IL-10 and TGF- β are higher than controls (24, 53). In addition, morphine can increase secretion of IL-4 and IL-5 (54, 55) and reduce IFN- γ production in peripheral blood mononuclear cells in HIV-1 infection (43). As a result, opioids suppress the immune responses and ease the entry of viruses into the body, therefore increase comorbidity (Table1).

Table 1: Cells of the immune system, including B cells, T cells, macrophages, neutrophils, DCs and, NK Cells which may be regulated by opioids specially morphine abuse

<i>The Effects of Opioids on Immune Cells Functions</i>	
B cells	↓ Ab ↓ Proliferation, MHC Expression
Th cells	↓ IFN γ , IL-12, IL-12 β 2, Th1 Death ↑ IL-4, IL-10, Th2 Differentiation
Macrophages	↓ Phagocytosis, Bactericide, Migration ↓ TNF α , GM-CSF, IL-6
Neutrophil	↓ Chemotaxis, Bactericide, Migration ↓ Cytokine and chemokine production
DCs	↓ Antigen Presentation
NK Cells	↓ Cytotoxicity
Mast Cells	↓ TNF- α

The Reasons for the Higher Mortality Rate in Opium Addicts Patients with COVID-19

The above reasons indicate decrease in immune response and cytokine production in opium addicts and it seems that cytokine storm and recruitment of immune cells to the lungs are low in these COVID-19 patients.

Therefore, what is the reason for the increase in the mortality rate of these patients?

Altogether, it can be predicted that opioid abuse would suppress the immune system function that could deteriorate the prognosis for the end-organ damage phase of COVID-19, which results in

endothelium injury of lung's alveolar and co-infection with bacterial pneumonia (Fig. 1).

1- Down regulation of IFNs Expression

The most important cytokines in antiviral immune responses and clearance of viruses are Type I/III IFNs. If IFNs are produced at the beginning of the infection and localized in the lungs, they effectively inhibit the corona virus infection (56, 57). Expression of Type I IFNs stimulate antiviral state in uninfected cells by binding the IFNAR, afterwards inducing infection control and viral clearance (58). SARS-CoV-

2 is more sensitive than SARS-CoV-1 to IFN-I/III pretreatment in vitro (4, 59-61).

Moreover, SARS-CoV-1 and SARS-CoV-2 have similar tropism for types I and II pneumocytes, as well as alveolar macrophages. Besides, the ability of infection and replication of SARS-CoV-2 is more than SARS-CoV-1. The higher viral loads of SARS-CoV-2 infection resulted in defect of IFNs (type I, II or III) production in the infected human lung tissues (62). Cytopathic viruses kill the target cells. Therefore, the greater replication of cytopathic viruses associated with the more cells die (63).

Cytopathic viruses, including SARS-CoV-2 (64) involved in death and damage of virus-infected

airway epithelial cells and tissues as a part of the virus life cycle (65), and associated with high levels of virus and vascular leakage, as observed in COVID-19 patients (66). Given that COVID-19 is a cytopathic virus, further replication will have more cytopathic effects.

Morphine suppressed the production of antiviral cytokines, such as IFN- α and IFN- γ by immune cells (35, 50, 67). As a result, the replication and severity of viral infections in opium addicts is higher than normal people are, and has a more lethal effect on lung cells. Collectively, the more replication of virus causes the more death of lung cells.

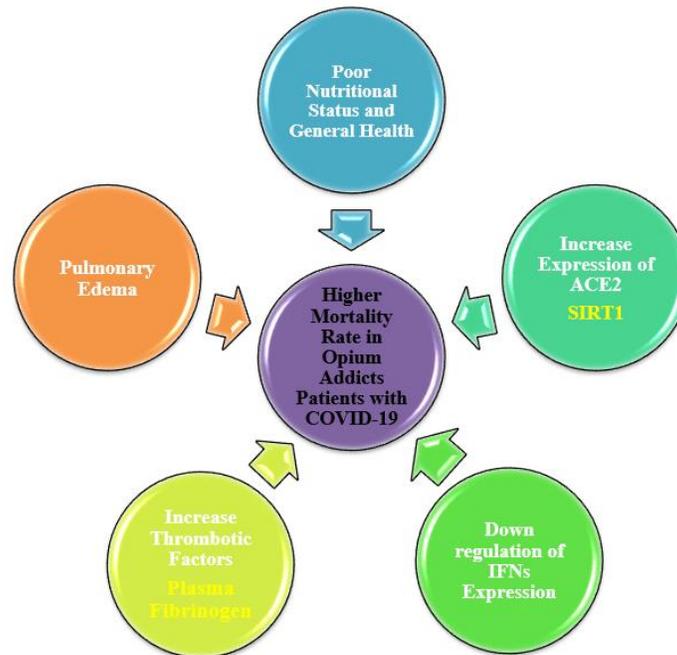


Fig. 1: The reasons for the higher mortality rate in opium addicts patients with COVID-19

2- Development of Pulmonary Edema

For different reasons opioid abuse may lead to COVID-19 complexity and seriousness. Opioids could directly damage to the respiratory system and cause chronic obstructive pulmonary disease (COPD), ARDS and lung injury, probably increased COVID-19 severity and mortality (13, 68, 69).

Opioids may involve directly in pulmonary pathology, changes of hemodynamics and devel-

opment of lung edema (70). The possible mechanism opioids-associated pulmonary edema is related to endothelial dysfunction (71). The pathologic features of the lung in ARDS is happened due to the severe injury to the alveolar capillary. Extravasation of intravascular fluid results in the onset of the permeability pulmonary edema and ARDS (72).

In vitro, morphine alters the viability of vascular endothelial cells in a dose and time-dependent manner. Nitric oxide concentration and the production of reactive oxygen species were increased with morphine compared to control solution.

"In vitro, morphine alters the viability of vascular endothelial cells in a dose and time dependent manner" (70). Production of Nitric Oxide and reactive oxygen intermediates were augmented in response to morphine compared to control (70). Furthermore, addition of a nitric oxide synthase inhibitor prevented morphine-induced apoptosis of endothelial cells. This study demonstrated that morphine not only could affect cell death in vascular endothelium but also suggested a possible mechanism for morphine-induced endothelial dysfunction by production of reactive oxide species (73).

Liu et al investigated the influence of morphine and LPS on endothelial permeability and realized a considerable increase in vascular permeability and cellular apoptosis (74). Altogether, the above data support that the increased vascular permeability and endothelial dysfunction have important role in opiate induced pulmonary edema (70).

Opioids also play an important role in bronchoconstriction and exacerbating of pre-existing airways sickness. Opioid receptors are expressed in bronchial epithelium, nerve fibers and glands of bronchial walls (75). Many opioids are strongly induced production of histamine and consequently causes to incidence of anaphylactoid symptoms. Moreover, retrospective data suggested the association between asthma exacerbations with use of opioids (47).

However, opioid addicted people are at higher risk of infections, especially respiratory diseases because of the long-term abuse (76). Opioids damage the respiratory system, many addicts who use the opioids through an inhalation way are more susceptible to SARS-CoV2 infection (5). Opioids can decrease the sensitivity of medullary respiratory centers and response to hypoxia and hypercapnia that resulted in reduced ventilation, exacerbating the respiratory symptoms of COVID-19 (8).

3- Increase Thrombotic Factors

Increased plasma fibrinogen is also considered as an independent risk factor for Coronary Artery Disease (CAD). It can increase the risk of thrombosis. Plasma fibrinogen is significantly higher in opium-addicted patients. "Increased plasminogen activator Inhibitor-1 (PAI-1) PAI-1 inhibits the formation of plasmin through inhibitory effects on plasminogen activator and consequently prevents the clotting cascade in the arteries" (77). Study of 160 patients with CADs showed that the serum level of PAI-1 was higher in addicted patients with congestive heart disease (CHD) compared to non-addicted patients (77).

4- Increase Expression of ACE2

SIRT1 (Sirtuin 1) coordinates various biological functions, including cell differentiation, apoptosis, autophagy, development, cancer, metabolism, and circadian rhythms by deacetylating various substrates, including histones, enzymes, and transcription factors (78).

SIRT1 regulates the expression of ACE2 mRNA by binding to the promoter region of ACE2 (79). Chronic cocaine consumption enhances SIRT1 and SIRT2 expression, whereas chronic use of morphine stimulates SIRT1 expression (80).

Therefore, it can be concluded that opium consumption enhances the expression of SIRT1 and then increases ACE2 (receptor for SARS-CoV-2). Studies on the viral pathogenesis have indicated that differences in COVID-19 disease prevalence and severity are associated with sex, and smoking is related to higher expression of ACE2, so that might also be a factor (81).

Conclusion

There are several reasons for the increase in mortality in people with COVID-19 who are addicted to opium. A part from personal hygiene and lifestyle issues, the effects of opium on the immune system, respiratory cells and other markers have been identified. Therefore, treatments such as interferon therapy at the beginning of infection with SARS-CoV-2, can be very effective in re-

covery of these patients and reduce mortality in them. Furthermore, opioid-addicted patients due to various socio-economic factors for example loss of accessibility to health care and supportive services, housing instability, poor health situation, and congregate opioid use may not abide by social distancing and other preventive measures. Regarding the above reasons, susceptibility to SARS-COV2 infection peoples will increase (82). Finally, an important issue should be considered is that opium addicts are likely to have poorer nutritional status and general health than non-addicts. Therefore, further study is needed on socioeconomic conditions that increase infection risk and potential immune regulation due to opioids use in these people.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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