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Suicide associated with COVID-19 infection: an immunological point of view

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19) is a pandemic and leading cause of death. Beyond the deaths directly caused by the virus and the suicides related to the psychological response to the dramatic changes as socioeconomic related to the pandemic, there might also be suicides related to the inflammatory responses of the infection. Infection induces inflammation as a cytokine storm, and there is an increasing number of studies that report a relationship between infection and suicide.

MATERIALS AND METHODS: We searched the World Health Organization status report and the PubMed database for keywords (COVID-19, suicide, infection, inflammation, cytokines), and reviewed five cytokine pathways between suicide and inflammation using two meta-analyses and two observational studies starting from November 31, 2020, focusing on the relationship between suicide and inflammation by infection. First, we discussed existing evidence explaining the relationship between suicidal behaviors and inflammation. Second, we summarized the inflammatory features found in COVID-19 patients. Finally, we highlight the potential for these factors to affect the risk of suicide in COVID-19 patients.

RESULTS: Patients infected with COVID-19 have high amounts of IL-1β, IFN-γ, IP10, and MCP1, which may lead to Th1 cell response activation. Also, Th2 cytokines (e.g., IL-4 and IL-10) were increased in COVID-19 infection. In COVID-19 patients, neurological conditions, like headache, dizziness, ataxia, seizures, and others have been observed.

CONCLUSIONS: COVID-19 pandemic can serve as a significant environmental factor contributing directly to increased suicide risk; the role of inflammation by an infection should not be overlooked.

Key Words:
COVID-19, Suicide, Infection, Inflammation, Cytokine.

Introduction

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in China and has become a global pandemic resulting in approximately 761,779 deaths as of August 16, 2020[1]. Many clinical symptoms regarding COVID-19 have been investigated, however, knowledge beyond these symptoms, particularly those psychologically related, remains limited. As such, the psychological perspective of suicide related to COVID-19 is an important issue to be considered. A pandemic presents a situation associated with increased suicide risk[2,3]. Indeed, some cases related to COVID-19 have been reported. Factors, such as anxiety and uncertainty, social isolation, and economic problems can explain a significant proportion of the increase in suicide risk related to the pandemic[4]. However, inflammation caused by infection is another important factor to be considered.

Inflammatory conditions, like infections, can trigger depressive symptoms and are associated with suicide. Studies[5-7] report that there is a clear difference in cytokine levels such as IL-6, IL-1β, and IL-2 between suicidal and non-suicidal patients. These inflammatory cytokines can be synthesized in the central nervous system or communicate with the brain *via* many different mechanisms, including the kynurenine pathway, monoamine metabolism, and hypothalamic-pituitary-adrenal (HPA) axis[8]. COVID-19 is also associated with a significant increase in cytokine levels, which might partly explain the suicide observed in some of the individuals who are infected[9].

Therefore, in this review, we focused on the relationship between suicide and inflammation by infection. We searched the World Health Organization status report and the PubMed database for keywords (COVID-19, suicide, infection, inflammation, cytokines), and reviewed five cytokine pathways between suicide and inflammation using two meta-analyses and two observational studies starting from November 31, 2020. First, we discussed existing evidence explaining the relationship between suicide and inflammation. Second, we summarized the inflammatory features found in COVID-19 patients. Finally, we highlight the potential for these factors to affect the risk of suicide in COVID-19 patients.

Risk Factors Associated with Suicidality

Suicide is an important issue and a significant challenge for the global public health community[10]. In the US alone, 40,000 people die due to suicide every year, and according to the World Health Organization (WHO), globally, this figure is estimated to be approximately 800,000[8,11]. In fact, WHO estimates indicate an individual will die by suicide somewhere in the world every 40 seconds[11]. As rates continually rise across countries, suicide will remain a major public health problem[12].

Inconsistency in the nomenclature has hindered the progress in suicide research and theory[13]. Suicide is defined as death caused by a self-directed injury behavior with the intent to die as a result of one's action and the suicide

attempt is the nonfatal self-directed injurious behavior with the intent to die as a result[14]. In contrast, suicidality and suicidal behavior broadly describe the overarching terminology that spans across to include suicidal ideas, plans, the process of preparation and attempts that may be fatal[15,16]. Thus, caution needs to be taken when selecting specific terms to address suicidality and associated behaviors. The following sections of this paper have maintained consistency in using the terminology as addressed above.

To understand the complexity of suicidality, various models have been suggested, with most acknowledging the interplay between predisposing and precipitating risk factors. A seminal example includes the biopsychosocial model[17,18]. It takes a comprehensive view of suicide risk and its related factors[12]. Predisposing factors, such as genetic vulnerabilities[19], early-life adversity and trauma[20], and demographic characteristics (e.g., socioeconomic status)[21], contribute to suicidality and can lead to lasting alterations in gene expression. Moreover, certain mechanisms can affect such predisposing factors. For example, the increase in vulnerability to stresses and developmental (also called psychological) factors such as core beliefs, personality traits, and cognitive deficits, can mediate the link between predisposing factors and suicidality[16]. The other form of factors, those called precipitating or proximal, include events preceding the onset of the disorder, or in this case, suicidal behavior. That is, previous experiences, (e.g., substance use, or interpersonal, occupational, financial, or physical stressors), or conditions (e.g., those psychological, socioeconomic, and environmental, as well as pre-existing psychiatric disorders), can prompt suicidal behavior[22]. As posited in the biopsychosocial model, these forms of both predisposing and precipitating factors can interact and elicit one's vulnerability to suicide ideation, suicide attempt(s), and ultimately, suicide[14].

Pandemics and Suicidality

Previous pandemics have been found to be associated with an increase in suicide risk. In 2003, a severe acute respiratory syndrome (SARS) outbreak in Hong Kong was associated with increased suicide risk in older people[23]. Further studies[2,3] of quarantined populations amidst pandemic conditions have indicated psychological difficulties and suicide attempts among hospitalized patients. Such behavior (i.e., increased risk for suicide) may be driven by several factors, including 1) anxiety and uncertainty, 2) social isolation, and 3) economic problems[4,24]. First, it is known that individuals with underlying diseases or low resilience may exhibit suicidal ideation and attempt suicide when experiencing anxiety and uncertainty[25]. This was the case during the 2003 SARS outbreak, where these factors led to an increase in suicide among older adults[23]. Second, pandemics often isolate people from society, which may be a situation that they have not experienced before. This sense of isolation can negatively affect individuals' psychological well-being regardless of the presence of disease[4]. Third and lastly, epidemics also have a negative impact on many businesses, which leads to temporary or permanent loss of income. Such financial worries have been shown to be associated with a loss of self-esteem, despair, depression, and substance abuse amongst others[26]. Moreover, a low income may reduce accessibility to psychiatric management. As a result, individuals with underlying diseases or vulnerability (socially or economically) may be more likely to attempt or commit suicide[4].

Regarding recent circumstances, the COVID-19 pandemic, which began in December 2019, has spread precipitously worldwide. On March 11, 2020, the WHO declared COVID-19 to be a pandemic. As extant epidemics have exhibited increases in suicide risk, COVID-19 is no exception. In line with previous pandemics and epidemics, the potential effect of the current COVID-19 pandemic on mental health is profound with an expected increase in anxiety and depression as well as suicide rates[27]. Furthermore, just like the previous outbreaks, the consequence of social isolation is predicted to be associated with suicide rates[28]. However, the magnitude of the current COVID-19 pandemic far outweighs the prior epidemics with this being named as the worst pandemic in history[29]. Henceforth it is expected that social isolation, anxiety, fear of contagion, uncertainty, stress and other economic challenges may lead to greater exacerbation of stress and related disorders, including suicidality, specifically among vulnerable people[30].

According to Caballero-Dominguez et al[31], 7.6% of participants suffering COVID-19 pandemic reported a high suicide risk, which was associated with high perceived stress related to

COVID-19, risk of depressive episode, and insomnia. Also, as presented below, various cases of suicide during this pandemic have been reported[32-34].

In one case study, a 34-year-old man was hospitalized in an isolation ward because of mild COVID-19 infection. While hospitalized, he had no respiratory symptoms or fever but complained of anxiety and insomnia. Though appropriate treatment was carried out, he attempted suicide[32]. Not only in infected people but also in people with psychiatric disorders and other vulnerable individuals, suicidal behaviors have been reported during the COVID-19 pandemic. In another case study, a 60-year-old woman with undiagnosed delusional disorder attempted suicide due to increased symptoms in response to the COVID-19 pandemic[33].

Likewise, in a case study from India, a 50-year-old man associated his viral illness with COVID-19 and thought he was infected with COVID-19. He was seized with fear and panic and finally ended his life by hanging himself[34].

Relationship between Inflammation and Suicide

As mentioned above, multiple factors, including genetic, experiential, psychological, clinical, sociological, and environmental factors, can increase the risk of suicide during an epidemic. However, the role of inflammation in increasing the risk of suicide among those who are infected should also be considered. Such consideration is critical, given the complex, multiplicative nature of factors leading to suicidality, as well as the severity of outcome (i.e., an untimely loss of life).

Several conditions, including infection, can cause inflammation, which can play a critical role in the pathophysiology of suicidal behavior. Some authors[35] suggest that there may be an association between suicidal behavior and inflammatory cytokines. Studies in patients who received interferon (IFN)-based or interleukin (IL)-2 immunotherapy showed that inflammation can induce depressive symptoms which is related to suicidal behavior[36,37]. Following this seminal work, multiple studies have shown differences in cytokine levels between those who did and did not complete suicide. Isung et al[5] reported that neuroprotective cytokine IL-8 levels in cerebrospinal fluid (CSF) were lower in those who attempted suicide compared to healthy controls, and this finding demonstrates impaired control of the immune system in suicidal patients. Pandey et al[6] found that mRNA and protein levels of IL-1β, IL-6, and tumor necrosis factor (TNF)-α were increased in post-mortem brain tissue from teenage suicide victims. Another study[7] also reported that suicide attempters show increased levels of IL-6 and TNF-α, while IL-2 levels were decreased. Additionally, there were clear differences in the immune response between suicidal and non-suicidal patients. One study found increased IL-6 production, as well as an imbalance in helper T-cell type 1 (Th1) & helper T-cell type 2 (Th2) with a shift toward Th1 in non-suicidal major depression disorder (MDD) patients. Conversely, suicidal MDD patients were related to a decrease in IL-2 production[38] and an elevation of Th2 expression in the orbitofrontal cortex[39]. Another study[39] reported increased IL-4 and IL-13 expression in suicide victims, which suggested 1) heightened Th2 cytokine expression, and 2) their mRNA transcripts exist in the brains of suicided people. Exposure and sensitization to aeroallergens also explain the relationship between suicide and T cell response. This induces increased Th2 cytokine expression and increases the risk of suicide through several pathways[40].

Two meta-analyses[41,42] reviewed studies related to cytokines and suicidality. Using a sample of 18 studies, Black and Ducasse found that high plasma levels of IL-6, IL-1β, and low IL-2 were reported in patients with suicidality. IL-1β and IL-6 levels were also elevated in post-mortem brain tissue of those who completed suicide whereas a decrease in IL-8 CSF levels were reported in patients with suicidality. In addition, using 11 studies, Ducasse et al[42] analyzed the levels of 6 independent plasma cytokines [IL-2, IL-6, TNF-α, IFN-γ, IL-4, transforming growth factor (TGF)-β] among healthy controls and suicidal and non-suicidal patients. They found that suicidal patients had lower IL-2 plasma levels compared to the other two groups. Also, lower IL-4 and higher TGF-β plasma levels were reported in both suicidal and non-suicidal patients than healthy controls. However, the independent studies in their sample did not show consistent results, which may be due to differences in phenotypes of suicidal behavior, difficulty in controlling

for confounders, differences in immunoassay techniques, and genetic and epigenetic effects. Further research is needed, as these heterogeneity-inducing factors might serve as mediators or moderators between suicidality and inflammation.

Cytokines as a Mechanism Affecting Brain Function and Behavior

An increase in cytokine levels is one of the suggested mechanisms behind the association between infection and increased risks of suicide. Viral infection can activate Toll-like receptors (TLRs) that are known to play an important role in regulating immune responses[43]. Activation of TLRs induce a pro-inflammatory state and lead to the secretion of large amounts of inflammatory factors, such as IL-6, IL-12, IL-15, and TNF-α[44]. These changes in inflammatory cytokine levels can affect brain function and behavior.

They can enter the brain directly through a compromised blood-brain barrier (BBB), which is associated with increased CSF levels of glycosaminoglycan hyaluronic acid, indicative of neuro-inflammation[45]. Additionally, they communicate with the brain *via* several mechanisms, including the kynurenine pathway, monoamine metabolism, and HPA axis[8].

Kynurenine Pathway

The kynurenine pathway is active in both the peripheral and central nervous system, in which indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) catalyzes the production of kynurenine from tryptophan. Among depressed patients, blood kynurenine levels are elevated in suicide attempters compared with a depressed-only control group[46]. After production, kynurenine breaks down into neuroactive compounds like quinolinic acid (QUIN) and kynurenic acid (KYNA). Inflammatory cytokines, such as IFN-γ, IL-6, and IL-1β activate these enzymes and thereby shift tryptophan metabolism towards an increase of QUIN[47-49].

QUIN is an N-methyl-D-aspartic acid (NMDA) receptor agonist predominantly produced by microglia and macrophages[50]. It has agonistic effects on the NMDA receptor by acting through the NR1 + NR2A and the NR1 + NR2B subunits[51,52]. QUIN was found to increase reactive oxygen species (ROS) and neuronal glutamate release, and decrease glutamate uptake and recycling by astrocytes, and increase astrocytic production of pro-inflammatory cytokines[53-55]. KYNA, on the other hand, antagonizes the glycine co-agonist site of the NMDA receptor and is predominantly produced by astrocytes[51]. Besides the NMDA receptor, KYNA has also antagonistic effects on the AMPA receptor and α7 nicotinic acetylcholine receptor (α7nAChR)[56], it is known to have neuroprotective and anticonvulsive properties[57,58].

QUIN levels were found to be associated with increased suicide risk and levels of inflammatory cytokines, and the QUIN levels were increased in the CSF of suicidal patients[59]. In fact, QUIN levels were found higher in CSF of suicide attempters than in healthy controls. It was also positively correlated with IL-6 in CSF, suggesting the relationship between the activation of kynurenine pathway and active inflammation[60]. Furthermore, after a 2-year follow-up period, QUIN levels were elevated among suicide attempters with high IL-6 and lower KYNA levels also found to be associated with the severity of suicidal ideation and depressive symptoms[61].

Monoamine Metabolism

Besides increasing kynurenine production by making IDO steal tryptophan from the serotonin synthesis pathway, cytokines can decrease the production of serotonin[40]. Studies[62] relating to suicidal behavior have shown that there is an abnormality of the serotonin system (e.g., decreased serotonin metabolites and increased serotonin receptors). Inflammatory cytokines can affect these serotonin systems in many ways, and this might be one of the mechanisms that link inflammation with suicidal behavior[63]. It has also been demonstrated[62] that serotonin in patients with suicidal behavior have a relationship between lower serotonin levels in the blood and suicidal behavior. This may result from the activation of cytokines, such as IL-1β and TNF-α, which have been shown to increase the expression of serotonin transporter, consequently reducing the levels of serotonin[64]. Taken together, the above studies suggest potential mediating mechanisms between inflammatory responses and suicidal behavior may in fact stem from

the effects on serotonin levels. Further studies are needed to distinguish the strength of such effects as well as additional mechanisms in which the inflammation-suicide relationship is influenced.

HPA Axis

IFN-α treatments have been demonstrated to activate the HPA axis by increasing the level of cortisol and adrenocorticotropic hormone levels. Such forms of HPA axis activation are associated with the onset of depressive symptoms compared to those who did not receive treatment[65]. In addition, a systematic review of HPA axis dysregulation in association with various pathophysiological processes including mood disorders and suicidal behaviors, has reported HPA axis activity to be involved in suicide risk regardless of the presence or absence of other psychiatric conditions[66].

By contrast, cytokines have been shown to activate the HPA axis, which induces a change in the levels of corticotropin-releasing hormone and cortisol that leads to detrimental effects on neurons[40]. In one study[67], administration of cytokines such as IL-1, IL-6, and TNF-α activated the HPA axis in both animals and humans. Likewise, previous literature has described cytokines to affect the neuroendocrine function through the increase of HPA axis activity, specifically with acute cytokine administration associated with the increase in corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol release. All these increases have been presented in patients with depressive disorders[68]. This demonstrates cytokines activating HPA axis and its relevance to one's suicidality.

Infection and Suicide

Infection induced inflammations may also indirectly lead to suicidality. These infections can affect the brain directly or reach the brain through peripheral inflammation that generates molecular mediators like cytokines.

Compared to the general population, patients with chronic hepatitis C virus infection showed a higher prevalence of depression and suicide risk[69]. Okusaga et al[70] showed that seropositivity for influenza A, B, and coronaviruses were related to a history of mood disorders. Also, seropositivity for influenza B was higher in patients with a history of attempted suicide.

Lyme and associated diseases (LAD) are another infections that are linked to suicidality and combined suicidal and homicidal tendencies in individuals after being infected[71]. It was found that chronic infections of *Borrelia burgdorferi* showed increased quinolinic acid in cerebrospinal fluid[72].

The risk for suicidality was increased in human immunodeficiency virus (HIV) infection and, according to the study by Serafini et al[73], HIV patients' prevalence of MDD, suicidal ideation, and suicide attempts ranged from 14.0% to 27.2%, 13.6% to 31%, and 3.9% to 33% respectively. In addition, individuals with HIV have reported a consistent association between MDD, suicidal ideation, and poor quality of life[73]. *Toxoplasma gondii* is another pathogen studied in this field, and its latent infection was identified to be a risk factor of suicides and suicide attempts[74]. It is known that *T. gondii* alters the glutamatergic and dopaminergic neurotransmission by increasing the levels of cytokines, QUIN, and dopamine, which may lead to suicidal behavior[8]. These kinds of neurotropic pathogens may induce severe psychiatric symptoms, as they can directly invade the brain and induce neuroinflammation.

According to Lund-Sørensen et al[75], people who have had hospital contact due to infections had a more than 40% increased risk of death by suicide, even after controlling for the psychological effect of being hospitalized. Also, both peripheral and central nervous system infections were found to be related to increased suicide risk. Among those infections, the highest risk was found in patients with hepatitis infection and HIV infection or acquired immune deficiency syndrome.

COVID-19 Infection Associated with Suicide

Our attention now turns to COVID-19 infection and suicide. We posit here the COVID-19 pandemic could induce suicidal behavior through the interaction of many different factors (Figure 1).

Considering infection factors, immune cell infection and the recruitment of uninfected cells can induce massive inflammatory responses. In viral infections, host response and clearance generally depend on type I interferon (T1IFN) expression. Once the viral infection is sensed by pattern associated molecular patterns (PAMPs), expression of T1IFN, and pro-inflammatory cytokines (IL-1, IL-6, TNF-α through NFκB) increases[76]. Indeed, patients infected with COVID-19 have high amounts of IL-1β, IFN-γ, IP10, and MCP1, which may lead to Th1 cell response activation[9].

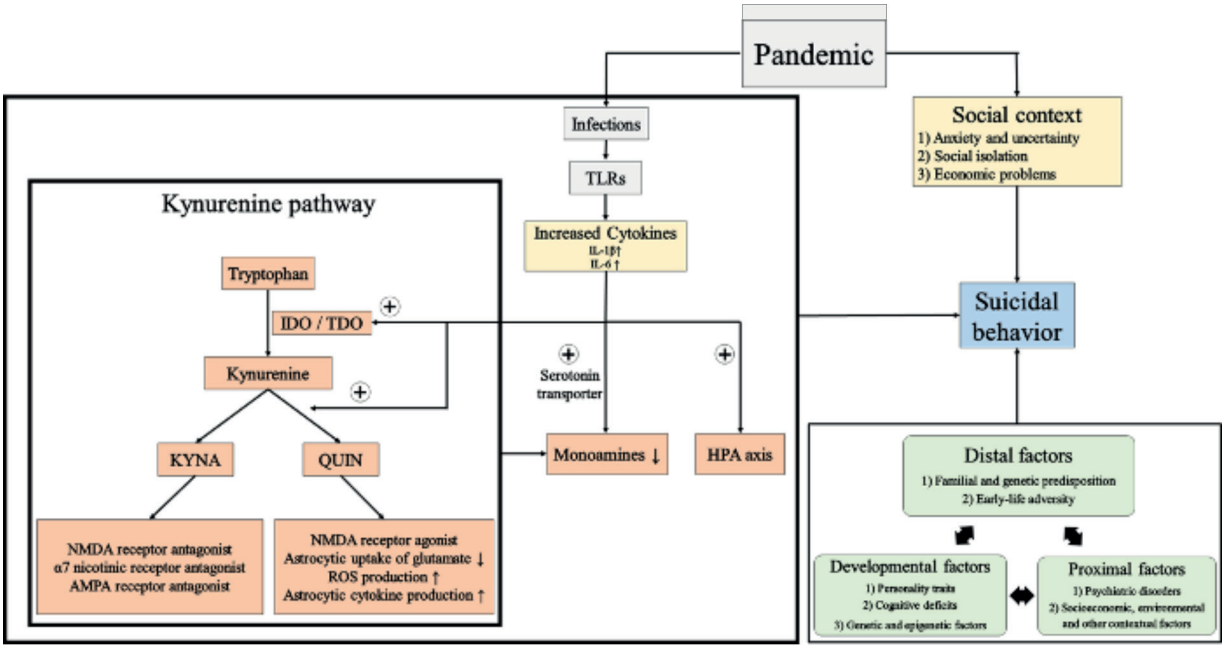

Figure 1. Hypothesized mechanisms underpinning suicidal behavior during pandemics essential inflammation-related clues. TLR, Toll-like receptors; IL-1β, interleukin-1β; IL-6, interleukin-6; IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; KYNA, kynurenic acid; QUIN, quinolinic acid; NMDA, N-methyl-D aspartic acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ROS, reactive oxygen species; HPA, hypothalamic-pituitary-adrena.

Also, Th2 cytokines (e.g., IL-4 and IL-10) were increased in COVID-19 infection[9]. Like other infections, an increase in these molecular mediators can affect the brain via the mechanisms mentioned above.

In addition, the neurotropic potential of COVID-19 has been proposed. A recent review reported that 25% of COVID-19 patients show neurological manifestations[77]. In COVID-19 patients, neurological conditions like headache, dizziness, ataxia, seizures, and others have been observed[78]. These neurological symptoms seem to develop in more severe patients than in mild or moderate patients[79]. Also, brain tissue edema and partial neuronal degeneration were reported based on autopsy[80].

For these reasons, COVID-19 has the possibility of inducing suicidal behavior through inflammatory mechanisms. Indeed, a case of suicide in COVID-19 patients without any respiratory symptoms or fever has been reported[32]. However, whether COVID-19 can directly invade the brain is still unclear, as COVID-19 patients with neurological symptoms showed low or undetectable COVID-19 RNA levels in CSF[81]. Moreover, the meta-analysis data about cytokines and COVID-19 infection study does not always exhibit the same tendency (Table I). Whilst it has indicated the relationships between lower IL-2 and suicidal behavior, most infections including COVID-19 showed increased IL-2 plasma levels. Importantly, while lower IL-4 was reported in both suicidal and non-suicidal patients compared to healthy controls, COVID-19 patients exhibited increased IL-4. Although IL-1β and IL-6 displayed a similar tendency, further studies concerning inflammatory responses of suicide itself and relationship in COVID-19 patients are now required. The neurotropic potential of COVID-19 should also be studied. Currently, there are very few studies on COVID-19 and related cytokine aberration, and it is difficult to generalize aforementioned cytokine alteration in COVID-19 infection.

Conclusions

COVID-19 pandemic is a worldwide problem with a rising death count and outcomes related to it merit consideration, such as suicide. It can be postulated that the kynurenine pathway, monoamine metabolism, and HPA-axis affect brain functions and induce suicidal behaviors *via* cytokines produced by

Table I. Cytokine alterations found among people with suicidal behavior and COVID-19 infection.

Cytokines	Meta-analysis about cytokines and suicidal behavior						Studies of cytokines and COVID-19 infection					
	Studies	Study design	Tendency	Country	Sample size	Sample	Studies	Study design	Tendency	Country	Sample size	Sample
IL-1β	Black et al[41], 2015	Meta-analysis	Increase	U.S.	583 patients with suicidality, 315 patients without suicidality, and 845 healthy controls	Plasma	Huang et al[9], 2020	Observation study	Increase	China	41 patients diagnosed with COVID-19	Plasma
IL-6	Black et al[41], 2015	Meta-analysis	Increase	U.S.	583 patients with suicidality, 315 patients without suicidality, and 845 healthy control	Plasma	Huang et al[9], 2020	Observation study	Increase	China	41 patients diagnosed with COVID-19	Plasma
							Yanlei et al[82], 2020				54 patients diagnosed with COVID-19	
IL-2	Ducasse et al[83], 2015	Meta-analysis	Decrease	France	494 suicidal patients, 497 non-suicidal patients and 398 healthy controls.	Plasma	Huang et al[9], 2020	Observation study	Increase	China	41 patients diagnosed with COVID-19	Plasma
IL-4	Ducasse et al[83], 2015	Meta-analysis	Decrease	France	494 suicidal patients, 497 non-suicidal patients and 398 healthy controls.	Plasma	Huang et al[9], 2020	Observation study	Increase	China	41 patients diagnosed with COVID-19	Plasma
TGF- β	Ducasse et al[83], 2015	Meta-analysis	Decrease	France	494 suicidal patients, 497 non-suicidal patients and 398 healthy controls.	Plasma	N/A	N/A	N/A	N/A	N/A	N/A

COVID-19, coronavirus disease 2019. IL-1β, interleukin-1β. IL-4, interleukin-4. IL-6, interleukin-6. TGF- β, transforming growth factor-β.

COVID-19 infection. Though pandemics can serve as a significant environmental factor contributing directly to increased suicide risk, the role of inflammation by an infection should not be overlooked.

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