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Dysregulated inflammation may predispose patients with serious mental illnesses to severe COVID-19 (Review)

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Abstract. Genetic and nongenetic factors associated with an increased inflammatory response may mediate a link between severe coronavirus disease 2019 (COVID-19) and serious mental illness (SMI). However, systematic assessment of inflammatory response-related factors associated with SMI that could influence COVID-19 outcomes is lacking. In the present review, dietary patterns, smoking and the use of psychotropic medications are discussed as potential extrinsic risk factors and angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphisms are considered as potential intrinsic risk factors. A genetics-based prediction model for SMI using ACE-I/D genotyping is also proposed for use in patients experiencing severe COVID-19. Furthermore, the literature suggests that ACE inhibitors may have protective effects against SMI or severe COVID-19, which is often linked to hypertension and other cardiovascular comorbidities. For this reason, we hypothesize that using these medications to treat patients with severe COVID-19 might yield improved outcomes, including in the context of SMI associated with COVID-19.

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), was initially viewed as a primarily respiratory disease, leading to viral pneumonia in some cases. However, it is now recognized as a complex disease affecting various body systems (1). Among these effects, an accumulating body of research links severe COVID-19 to new-onset mental illness (2-5).

The data on whether mental illness affects the severity of COVID-19 are mixed. Studies indicate that the prevalence of COVID-19 among patients with serious mental illness (SMI) is either lower than (6) or similar to that among patients without a history of mental illness (7). However, patients with SMI are reported to have a slightly higher risk for severe clinical outcomes following infection with COVID-19 compared with those who do not have a history of mental illness (7). These findings suggest that COVID-19 and SMI might be reciprocal risk factors, raising the question of which pathways might link these two factors. A disadvantageous effect of SMIs on COVID-19 outcomes has been attributed primarily to medication non-adherence (7,8) and cardiovascular comorbidities (7,9). Another potential explanation is that the shared attribute of increased inflammation may constitute the link between SMI and severe COVID-19 (10). Sedentary habits and low physical activity during COVID-19 quarantine have been associated with an inflammatory state and a negative impact on mental health (11-13).

Severe COVID-19 comprises the presence of pneumonia, severe acute respiratory distress syndrome, microvascular thrombosis and/or cytokine storms, all of which involve underlying inflammation (14). Numerous proinflammatory cytokines reportedly associated with severe COVID-19 (15)

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are also linked with SMIs, including schizophrenia, depression and bipolar affective disorder (16-19). Several recent reports have described new-onset depression in patients with COVID-19, accompanied by increased levels of interleukin-6, a key molecule in the cytokine storm (4,10,20). These findings suggest that SMI-associated factors that could affect COVID-19 outcomes and vice versa should be investigated for their association with the inflammatory response. Thus far, the systematic evaluation of candidate factors is lacking (7).

In the present review, some of these candidate factors are critically discussed (Fig. 1). The initial focus is on psychotropic medication use, unhealthy dietary patterns and excessive smoking as potential extrinsic factors in existing mental illness that might heighten the risk of severe COVID-19. Next, the role of angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphisms as possible intrinsic factors in the development of both SMIs and COVID-19 is addressed. In addition, the possibility of using genetics-based methods to predict the new-onset SMI risk among patients experiencing severe COVID-19 is examined. Finally, some therapeutic options that might be relevant to the prevention of SMI onset following severe COVID-19 are proposed.

2. Psychotropic medications as possible modulators of COVID-19 severity with existing SMI

Previous studies have suggested that psychotropic medications could affect inflammatory processes. Various antipsychotics, antidepressants and antiepileptics have been shown to favor the anti-inflammatory state by increasing levels of anti-inflammatory cytokines and decreasing those of proinflammatory cytokines (21-24).

Antipsychotics. Clinical trials have shown that aspirin, estrogens, N-acetylcysteine, minocycline, pregnenolone, celecoxib and n-3 polyunsaturated fatty acids (PUFAs) have antipsychotic effects (25). Other studies have indicated that by promoting an enhanced anti-inflammatory state, specific atypical antipsychotic medications may dysregulate innate and adaptive immune responses (Fig. 1), thereby increasing susceptibility to respiratory infections, including COVID-19 (26,27). In a preclinical study, the treatment of healthy mice with low-dose risperidone diminished the secretion of several important proinflammatory cytokines. In addition, risperidone inhibited an antibody response in the animals following vaccination with Pneumovax23® (26). The latter observation is alarming, given increasing concerns about secondary bacterial pneumonia, including pneumococcal pneumonia, during COVID-19 (22). Furthermore, in a large group of individuals with schizophrenia-spectrum disorders (n=6,309), among whom 102 tested positive for COVID-19, those treated with clozapine had a ~3-fold increased risk for COVID-19 infection compared with those taking other antipsychotic medications (27). Several adverse effects of clozapine, including diabetes, obesity and hypersalivation (leading to aspiration pneumonia), have been proposed to contribute to the mechanism by which clozapine treatment affects COVID-19 risk (28). Moreover, clozapine treatment affects the innate immune system, leading to transient eosinophilia, cytokine release and fever during early treatment, and to neutropenia and agranulocytosis in a small

minority of patients. Recent data also imply a link between clozapine treatment and adaptive immunity. Specifically, patients treated with clozapine experienced a significant reduction in all three classes of circulating immunoglobulins (M, A and G) compared with those treated with alternative antipsychotics (29).

The use of antipsychotics has also been reported to be associated with reduced physical activity, possibly because of the side effects of antipsychotics, which include extrapyramidal symptoms and fatigue (30,31). However, physical activity supports immune function in viral respiratory infections by triggering the release of stress hormones, namely catecholamines and glucocorticoids, which are responsible for dampening local inflammation, and by promoting the secretion of anti-inflammatory cytokines (11,12). Studies have demonstrated that physical activity also offers benefits for mental well-being and may prevent symptoms associated with depression and anxiety during COVID-19 quarantine (11,32). One large study of people from the general population in Italy (n=2,524) revealed that reduced total physical activity during quarantine had a negative effect on Psychological General Well-Being Index scores (11). Furthermore, a cross-national study involving people living in Germany, Italy, Russia and Spain indicated that individuals with symptoms of depression were at risk of a worsening psychological state during the COVID-19 pandemic and that physical activity counteracted this negative effect (32). The favorable effects of physical activity on psychological health have been attributed to stimulation of the cholinergic, dopaminergic and serotonergic neurotransmitter systems, endogenous opioid release and the expression of several trophic factors, including brain-derived neurotrophic factor (13,33).

Antidepressants. Nonsteroidal anti-inflammatory medications, various pro-inflammatory cytokine inhibitors, statins, n-3 PUFAs, pioglitazone, minocyclin and modafinil have been indicated to exert antidepressant effects (34). Certain antidepressant medications from the selective serotonin reuptake inhibitor class, such as fluvoxamine, may exert favorable effects on patients with COVID-19 because of their immunomodulatory action. A preliminary clinical trial of fluvoxamine compared with placebo showed that adult patients with symptomatic COVID-19 treated with fluvoxamine had a lower likelihood of clinical deterioration and serious adverse events over 15 days (35). A protective effect of fluvoxamine in COVID-19 might arise from the ability of the drug to stimulate σ -1 receptor activity. The σ -1 receptor is an important endoplasmic reticulum chaperone protein with various cellular functions, including regulation of cytokine production (36). In addition, fluvoxamine accumulates in lysosomes, endosomes and biological membranes, where it interferes with the endosomal pathway and intracellular membrane trafficking crucial for viral infection (37).

Antiepileptics. Antiepileptics are regularly used to treat bipolar affective disorder, and are also prescribed to patients with schizophrenia at a lower rate, estimated at 20% (38,39). To the best of our knowledge, no studies have indicated a possible link between antiepileptic use and COVID-19 among patients with SMI. However, the use of antiepileptics has been reported to

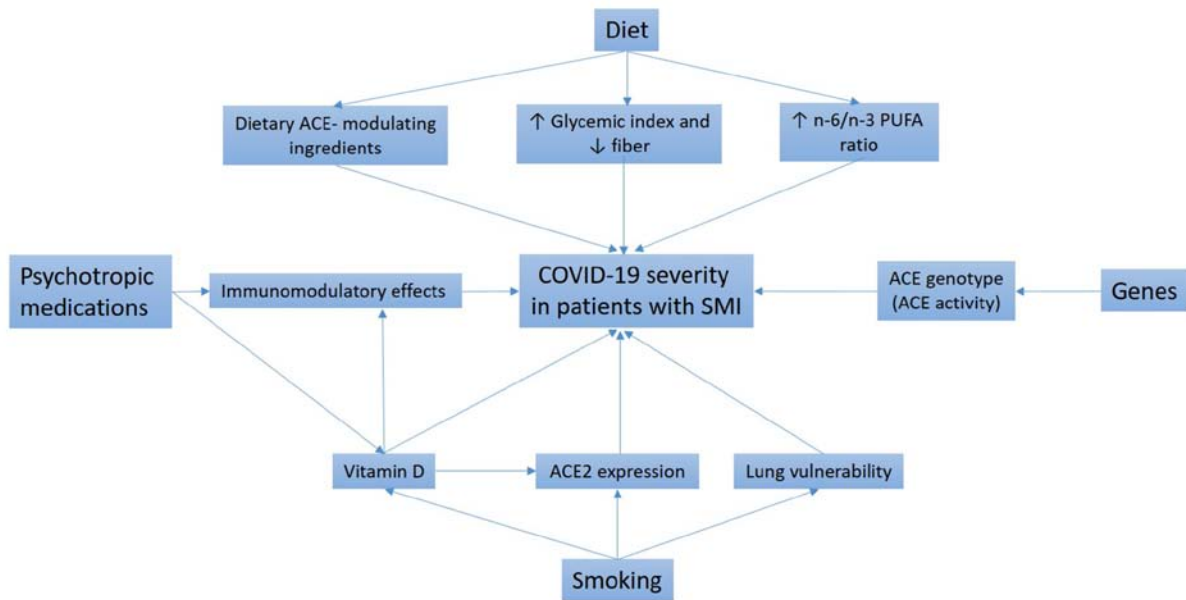


Figure 1. Proposed factors leading to more severe COVID-19 in patients with SMI. COVID-19, coronavirus disease 2019; SMI, serious mental illness; ACE, angiotensin-converting enzyme; PUFA, polyunsaturated fatty acids.

have an association with vitamin D deficiency (Fig. 1), which has been recognized as an important modulator of innate and adaptive immune responses (40). Several mechanisms have been proposed to explain the link between antiepileptic use and vitamin D deficiency (41-43). Certain antiepileptic drugs, for example, carbamazepine, phenobarbital, phenytoin, primidone and topiramate, induce the hepatic cytochrome system, leading to increased catabolism of the active form of vitamin D (1,25-dihydroxyvitamin D) (43). Furthermore, antiepileptic drugs may bind to the steroid and xenobiotic receptor transcription factor, potentially interacting with the vitamin D-responsive element for vitamin D-24-hydroxylase and thereby activating the enzyme (41,43).

Vitamin D supplementation. Several studies have convincingly shown an association between vitamin D deficiency and COVID-19 severity (44,45). Recently conducted interventional clinical studies have further emphasized the importance of vitamin D in the prevention of severe COVID-19 outcomes (46,47). Several mechanisms have been proposed for the protective effects of vitamin D in COVID-19 (Fig. 1), including immunomodulatory activity, the enhancement of defensin and interferon α expression, and initiation of local pro-regenerative processes (48,49). The vitamin D-mediated reduction of proinflammatory cytokine hypersecretion is an important protective effect because of its role in preventing the development of a cytokine storm (50,51). In addition, vitamin D deficiency is associated with accelerated thrombogenesis and a consequent increase in thrombotic episodes, which are frequently observed in patients with severe COVID-19 (52,53).

3. Dietary factors as possible modulators of COVID-19 severity among patients with SMI

PUFAs. Dietary intake represents another important modulator of the inflammatory response (Fig. 1). Numerous studies have

indicated that the dietary patterns of patients with SMI are characterized by a high intake of saturated fat and calories and a high n-6/n-3 PUFA ratio (54-59). These increases in saturated fat and the n-6/n-3 PUFA ratio are associated with an overall increase in the production of pro-inflammatory cytokines and an overreactive inflammatory response (60,61). Furthermore, the consumption of monounsaturated fatty acids, fiber, fruit and vegetables, which exert potent anti-inflammatory effects, is often low among patients with SMI (54-59).

A number of PUFAs act as natural ligands of peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding protein (SREBP) transcription factors, which regulate lipid and glucose metabolism, and overall energy homeostasis (62-64). Thus, an unbalanced n-6/n-3 PUFA ratio in patients with SMI could indirectly contribute to diabetes, dyslipidemia and obesity risk via PPAR and SREBP transcriptional activation. This speculation may be relevant to COVID-19 because a greater risk of severe outcomes has been reported among individuals with diabetes, dyslipidemia and/or obesity (65,66).

A dietary deficiency of n-3 PUFAs can lead to changes in the phospholipid fatty acid composition of membranes, and thereby induce changes in the collective physicochemical properties of the bilayer, such as flexibility and fluidity (67). These modifications can affect the function of membrane proteins that mediate the action of insulin, such as glucose transporter type 4, and lead to insulin resistance, diabetes and dyslipidemia (67-69). In addition, *in vitro* studies have indicated that membrane n-3 PUFA levels influence the therapeutic efficiency of psychotropic drugs, as n-3 PUFAs facilitate the intercalation of the drugs between acidic glycerophospholipids (68).

Fermented foods. Notably, an article by Bousquet *et al* (70) published during the first pandemic wave in the spring of 2020 indicated that diet may play a role in the immune defense

against COVID-19 and could explain some differences in COVID-19 mortality risk. Specifically, the authors proposed an association between the consumption of foods with potent anti-ACE activity and a low prevalence of COVID-19 mortalities. These foods include uncooked or fermented cabbage, which is widely consumed in a number of European countries with low mortality rates, as well as in Korea and Taiwan. Furthermore, fermented milk, another natural ACE inhibitor, is widely consumed in Bulgaria, Greece and Turkey, all of which also have had relatively low mortality rates. These findings may be mechanistically explained by a reduced production of angiotensin II (Ang II), which can act as a proinflammatory molecule, contributing to acute lung injury and favoring more severe COVID-19 manifestations (71,72). In addition, the microbiota present in fermented dairy products is linked to the induction of gut-mediated pulmonary immunity, providing protection against respiratory infections and inflammation (73-75).

Fruit, vegetable, and fiber intake. Recently, Abdulah and Hassan (76) explored COVID-19 infection and mortality rates in the context of dietary factors among 158 countries worldwide and identified a clear association of dietary patterns with epidemiological variables. Their data demonstrated strong positive correlations between a higher intake of fruits and SARS-CoV-2 infection, and between sugar-sweetened beverages and COVID-19 mortality. By contrast, they found that a higher intake of beans and legumes was associated with a negative effect on infection and mortality rates, suggesting that foods with a high glycemic index may be a risk factor for infection or mortality. Such findings could be explained by an excess caloric intake leading to weight gain, obesity and insulin resistance, which have been strongly linked to a hyperinflammatory response during viral infections, as well as to a generally higher respiratory infection rate (77,78). By contrast, beans and legumes are known for their low glycemic index, and contain the essential amino acids and micronutrients required for an appropriate and precisely targeted immune response (79,80). Furthermore, dietary fiber, abundantly present in a legume-rich diet, creates a suitable milieu for the survival and growth of gut microbiota and provides metabolic precursors for secondary bacterial metabolites that affect immunity and neurotransmission (81,82).

4. Cigarette smoking as a possible modulator of COVID-19 severity among patients with SMI

The estimated prevalence of smoking among people with SMI is 50-80% worldwide, which is significantly higher than that in the general population, and people with SMI are also more likely to smoke heavily, considered as ≥ 30 cigarettes or 1.5 packs daily (83-85). The reported prevalence of smoking among patients with schizophrenia is higher than that in patients with bipolar disorder or depression (86,87). Several mechanisms have been proposed to explain the link between cigarette smoke and inflammation, such as an imbalanced ratio of pro-inflammatory and anti-inflammatory cytokines, impairment of the innate immune response and increased oxidative stress (88,89).

Smoking and COVID-19. Studies of patients with COVID-19 have identified cigarette smoking as an important risk factor for severe outcomes (90-92) (Fig. 1). The elevated rates of severe COVID-19 in individuals who smoke may be attributable to diseases associated with smoking, for example, chronic obstructive pulmonary disease, diabetes and cardiovascular disease (90,92). Furthermore, cigarette smoke has been proposed to increase expression of the ACE2 receptor in the bronchial epithelium (Fig. 1). This receptor is the mediator of SARS-CoV-2 entry into host cells (90,91). However, considering the anti-inflammatory properties of ACE2, certain studies have claimed that the upregulation of ACE2 by smoking may exert a protective effect against COVID-19 rather than a harmful one (93,94). One possible explanation for this is that the ACE2-mediated cleavage of detrimental Ang II becomes more efficient and subsequently increases the production of angiotensins 1-7 (Ang 1-7), which show anti-inflammatory and proregenerative activity (71,95). Moreover, the nitric oxide produced during smoking promotes the maintenance of airway dilation and filtration prior to its entry into the lungs (94,96) and also inhibits the replication of SARS-CoV-2 *in vitro* (94,97).

Smoking, SMI medications and COVID-19. Among people with SMI, smoking is likely to interact with factors modulating vulnerability to COVID-19, such as the use of psychotropic medications and maintenance of an unhealthy dietary pattern (98-101). For instance, smoking has been shown to increase the clearance of specific antipsychotics, namely clozapine and olanzapine, and antidepressants, namely fluvoxamine, duloxetine, mirtazapine and trazodone, by inducing their metabolism in the liver, suggesting that smokers may be at risk of undertreatment (98,101). In addition, nicotine has been reported to have inhibitory effects on the activity and concentration of various antiepileptic medications, including lamotrigine, carbamazepine, diphenylhydantoin, phenobarbital and topiramate in animals (98), while cigarette smoking was shown to reduce serum levels of lamotrigine in a clinical study (99).

Smoking, diet and COVID-19. Certain studies have indicated a link between smoking and an unhealthy or proinflammatory dietary pattern among patients with SMI (57,102,103). For instance, smokers with schizophrenia are reported to be more likely to consume salt and saturated fat, and less likely to follow a high-fiber and low-calorie diet compared with nonsmokers (102). In addition, among individuals with depression, current smokers reported consuming more high-fat foods compared with never smokers and more fast-food fats compared with former and never smokers (103). Furthermore, several reports suggest a poorer diet accompanied by lower levels of physical activity among smokers with bipolar disorder compared with healthy individuals (104-106).

Smoking, vitamin D deficiency and COVID-19. Smoking has been identified as an important factor contributing to vitamin D deficiency (Fig. 1) among patients with SMI (107,108). A suggested mechanism for the link between smoking and vitamin D deficiency is that cigarette smoke decreases the production of 1,25-dihydroxyvitamin D in lung

epithelial cells (109,110). In addition, various cigarette smoke extracts have been demonstrated to inhibit translocation of the vitamin D receptor from the nucleus to microsome in human alveolar basal epithelial cell line (111).

5. ACE polymorphisms

ACE polymorphism overview. Genetic variations have been proposed to play a role in vulnerability to SMIs (112-114) as well as to COVID-19 (115-117). To the best of our knowledge, no studies have established a direct genetic link between COVID-19 and SMI. However, several findings suggest the possibility that the ACE gene might be relevant to both SMI and COVID-19 (Fig. 1). Within the renin-angiotensin system (RAS), ACE produces pro-inflammatory Ang II, which is in turn cleaved by ACE2, resulting in the formation of anti-inflammatory Ang1-7. Given this association, ACE activity can be considered proinflammatory, whereas ACE2 exerts anti-inflammatory effects by opposing ACE (71,72). A functional insertion/deletion (I/D) polymorphism (rs1799752) in intron 16 of the ACE gene is the most studied RAS-associated polymorphic variant and (118) has been investigated among patients with SMI (119-128). This ACE-I/D polymorphism accounts for ~50% of the variance in serum ACE levels; individuals homozygous for the D allele have the highest ACE levels, individuals homozygous for the I allele have the lowest ACE levels, and those who are heterozygous for the I and D alleles exhibit intermediate levels (118).

ACE polymorphisms in SMI. Results of a meta-analysis that included a large number of participants (n=10,223) in case-control studies indicated that the ACE-DD homozygous genotype was associated with an elevated risk of depression in a Caucasian and mixed ethnic group consisting of several European populations (German, British, Belgian, Finish and Israeli) and Asian populations (Japanese and Chinese) (119). Several studies have indicated that the ACE-I/D polymorphism might be associated with an elevated risk of schizophrenia, although the results were conflicting (120-122) and not confirmed in a meta-analysis (123). A greater risk for schizophrenia was observed among individuals carrying the ACE-D allele (ACE-DD homozygous and ACE-ID heterozygous) in the Turkish and Iranian populations (120,121), and among those carrying the ACE-I allele (ACE-II homozygous and ACE-ID heterozygous) in the Spanish population (122). Furthermore, a greater severity of schizophrenia, based on Positive and Negative Syndrome Scale psychopathology evaluations (124-126) and improved response to specific antidepressants, was detected among individuals who were ACE-DD homozygous and ACE-D carriers (127,128).

ACE polymorphisms in COVID-19. A number of studies have assessed the relevance of the ACE-I/D polymorphism in COVID-19-associated deaths. During the first wave of the pandemic, Delanghe *et al* (129) compared the D-allele frequency of the ACE gene in 25 European countries with the prevalence and mortality rates of COVID-19. The authors concluded that the prevalence of COVID-19 and mortality were negatively correlated with frequency of the ACE-D allele, indicating that this allele might be protective. The

protective effects of this allele against COVID-19 prevalence and mortality were supported by a further study from the same research team, in which COVID-19 risk and ACE-I/D polymorphism were assessed in 33 countries from Europe, North Africa and the Middle East (130). In that study, the authors also assessed whether COVID-19 infection was correlated with additional immune system-associated human plasma protein polymorphisms, including the F and S alleles of complement C3, the C282Y mutation of homeostatic iron regulator (HFE), the Hp1 and Hp2 alleles of haptoglobin, and the DBP1 and DBP2 alleles of vitamin D-binding protein; however, no significant associations were detected. The ACE-D allele results in higher ACE activity, favoring a more intense inflammatory response through increased production of Ang II. According to the principle of classical competitive inhibition, such findings may be explained in part by the competition between large amounts of Ang II, which is the ACE2 substrate, and SARS-CoV-2 in binding to the ACE2 receptor. However, a meta-analysis of ACE-D allele distribution in various European countries revealed high frequencies in Spain, Italy and the United Kingdom (131), which are among those most severely affected by COVID-19. Thus, the ACE-D allele may be a harmful rather than a protective factor in COVID-19.

Given the association of ACE-DD with the highest ACE activity and consequently high production levels of proinflammatory and profibrotic Ang II, Bellone and Calvisi (132) examined the correlation of COVID-19-associated deaths with ACE-DD and ACE-II genotypes in 25 European countries. The authors detected a significant positive correlation between ACE-DD frequency and COVID-19-associated deaths. By contrast, the ACE-II genotype frequency was inversely correlated with COVID-19-associated deaths, and no correlation was found between ACE-ID and COVID-19-associated mortality. The relevance of ACE-I/D polymorphism to COVID-19 severity was evaluated in a global meta-analysis including a high number of participants (n=48,758) from 30 countries. The authors investigated COVID-19 recovery and mortality rates according to the ACE-I/D allele frequency ratio (133). They found that an increased ACE-I/D allele ratio was associated with an increased rate of recovery, but identified no significant association between mortality rate and the ACE-I/D ratio.

Role of ACE inhibitors. The disadvantageous effects in COVID-19 of the ACE-DD homozygous genotype and, by implication, high ACE activity (118), is supported by recent clinical studies showing a lower rate of severe disease and lower all-cause mortality among patients with COVID-19 whose hypertension was being treated with ACE inhibitors (134-137). In addition, evidence suggests that an abrupt suspension of ACE inhibitors in patients with COVID-19 and cardiovascular disease may result in clinical deterioration and worse outcomes (136,138,139). In addition, the results of some preclinical studies suggested that ACE inhibition shows promise in the mitigation of psychotic symptomatology and cognitive deficits (140-142). Furthermore, human studies have indicated that ACE inhibitors may have favorable effects on cognitive deficits in schizophrenia, possibly by modulating the cleavage of specific neuropeptides, such as substance P and neurotensin (141,142).

ACE polymorphisms and risk for SMI after COVID-19. As aforementioned, ACE-I/D polymorphisms have potential relevance in SMI (119,120-123) and severe COVID-19 (129,130,132,133). In addition, severe COVID-19 has been associated with increased post-infection occurrence of SMI (2-5), probably in predisposed individuals (115-117). For these reasons, the genotyping of individuals with severe COVID-19 might be useful for predicting COVID-19 outcomes and new-onset SMI associated with COVID-19. Moreover, using ACE inhibitors to treat patients with severe COVID-19 might yield more favorable outcomes, not only for mitigating the disease but also for preventing the development of SMI as a secondary effect of COVID-19.

6. Conclusion

SMI and severe COVID-19 appear to have an increased inflammatory response in common. Numerous extrinsic and intrinsic factors may act as modulators of inflammatory processes among patients with SMI. Extrinsic factors, such as an unhealthy dietary pattern and excessive smoking, could contribute to the etiology of severe COVID-19 in people with SMI, as in the general population, but are potentially modifiable through lifestyle changes. In addition, physical activity, which has been reduced during COVID-19 quarantine, is relevant to the ability of the immune system to defend against viral infection, as well as to psychological health and well-being. However, the etiopathogenesis of severe COVID-19 may be heterogeneous among patients with SMI because of interactions among these factors, antipsychotic medications and genetic polymorphisms, such as ACE-I/D. Within the RAS, ACE simultaneously promotes the inflammatory response and counteracts the activity of ACE2, the host receptor that mediates SARS-CoV-2 cell entry. Several studies support the relevance of the functional ACE-I/D polymorphism in both SMI and severe COVID-19. For this reason, genotyping individuals with severe COVID-19 for the ACE-I/D polymorphism might offer predictive utility for COVID-19 outcomes and the risk of new-onset, COVID-19-associated SMI. Furthermore, ACE inhibitors exhibit promise for the mitigation of psychotic symptomatology and cognitive deficits, and their positive effects in severe COVID-19 accompanied by hypertension and other cardiovascular comorbidities have been reported. Thus, the administration of ACE inhibitors to patients with severe COVID-19 might be of benefit in the mitigation of severe disease and prevention of new-onset SMI secondary to COVID-19 disease.

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Availability of data and materials

Not applicable.

Authors' contributions

SN and HJ designed the study and wrote the manuscript. VP, DK and ABT wrote and drafted the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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