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CORRESPONDENCE

Mechanisms for substance use disorders in COVID-19

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To the Editor:

I read with interest Wang and colleagues' epidemiological findings that substance use disorders (SUDs), such as opioid (OUD), tobacco (TUD), alcohol (AUD) and cocaine (CUD) use disorders, are correlated with COVID-19 [1]. They found that OUD conferred the greatest risk for COVID-19, followed by TUD and AUD, all in large effect sizes (adjusted odds ratio (AOR) = 10.2 for OUD, 8.2 for TUD and 7.8 for AUD). They also found the risk was greater in African Americans than in European Americans. I was assuming that the authors were focused on symptomatic COVID-19 which represents developed forms of this disease. We might interpret these impressive findings with vulnerability for the disease development (from infection to symptom appearing) as well as progression (from symptom appearing to severe forms such as Intensive Care Unit (ICU) necessity and death). By searching the literature for SUDs effects on immune system and organ injury, and genetics, the vulnerability can be understood mechanistically.

SUDs may damage the immune system [2–4]. COVID-19 is an infectious disease so that its development and progression are regulated largely by the immune system. This infectious disease may progress to severe forms in patients with SUDs likely attributable to weakened immunity as a result of SUDs.

On the other hand, clinical investigations observed that SUDs may upregulate expression of the receptor ACE2 for SARS-CoV-2, which is the coronavirus causing COVID-19. For example, patients with TUD carried elevated ACE2 expressions in their airway [5, 6]. This line of evidence suggests that patients with SUDs are vulnerable to the infection. ACE2 happens to be a receptor for morphine and dynorphin too but it remains yet unclear whether this function involves COVID-19.

Hence, the disease development may target those with SUDs. If this is true, patients with COVID-19, especially those with severe forms, may carry known genetic risks for SUDs. To test this molecular hypothesis, literature was searched and obtained genetic evidence is summarized as a SUDs-related 60-gene network in Supplementary Table (see Ref. 7 for genetic databases used).

A recent genome-wide association study (GWAS) identified the ubiquitously expressed transcription factor *LZTFL1* as the most significant genetic risk for severe COVID-19 in Europeans [7]. Interestingly, *LZTFL1* has been found by Gelernter and colleagues as a genetic risk also for modulating methadone dosing in European American, not in African American, patients with OUD, based on six markers across the gene ($\beta = -0.23 \sim -0.35$, $P = 4.1 \sim 1.6 \times 10^{-5}$) [8], implying its population-dependent genetic role in opioid signaling. Furthermore, *LZTFL1* displayed a protective effect against COVID-19 severity ($AOR_{meta} = 0.56 \sim 0.47$) in the European patients, consistent with the epidemiological observation of less exacerbating effect of SUDs in European Americans than African Americans. Of the note, the six methadone-dosing markers were not associated with COVID-19 severity, suggesting that two different functional haplotypes be involved. The regulatory mechanisms of *LZTFL1* thus warrant future investigation.

As more consistency, seven others of the sixty genes are also associated with severe COVID-19 in the GWAS, including *PDYN*, *BDNF*, *ENTPD6*, *ADH1C*, *HEY1*, *PLAGL1*, and *HIVEP2* (Supplementary Table). A half of the eight significant associations are in genes encoding neuronal transcription factors (TFs), which was a 4-fold enrichment comparing to non-TF associations. *HEY1* showed the next most significant association. This gene is a TF known for AUD/TUD-related *SLC6A3*, another gene with nominal significant P_{meta} values here. Comparing to *ADH1B*, *ADH1C*

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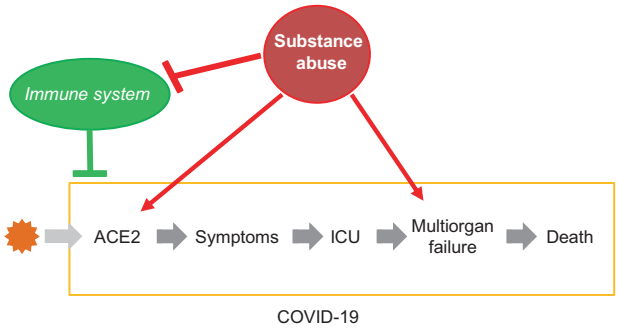

Fig. 1 Triple action of substance abuse in COVID-19. Brown, the coronavirus SARS-CoV-2. In addition, AUD might cause behavioral disinhibition for increased exposure to infection.

($AOR_{meta} = 0.4$) showed greater associations in terms of both significance and effect size. AUD has been implicated in multiple organ damage [9] and is well positioned to contribute to multiorgan failure which is a common cause of COVID-19-related mortality [10]. Based on an approximate estimation, this network has >85% of P_{meta} values as <0.05, which is a 17-fold enrichment comparing to the whole GWAS data (~5.2%). These data suggest that this SUDs-related genetics is well implicated in patients with severe COVID-19, supporting the hypothesis that patients with COVID-19, especially those with severe forms, may carry known genetic risks for SUDs; that is, COVID-19 development and progression target those with SUDs. Clinically, these shared genetic risks may help to identify individuals at high risk for the comorbidity development.

To sum up (Fig. 1), SUDs can exacerbate SARS-CoV-2 infection in three ways, that is, facilitating the viral entry, impairing the immune system, and injuring other organs such as heart, lung, liver and kidney, which also highlights the systemic toxicity of abused substances. For the moment, this may help explain how COVID-19 targets patients with SUDs in a large effect size manner.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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