

## COVID-19 and Alcoholism: A Dangerous Synergy?

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**Citation:** Ojo AS, Akin-Onitolo A, Okediji P, Balogun S. COVID-19 and Alcoholism: A Dangerous Synergy?. Journal of Contemporary Studies in Epidemiology and Public Health. 2020;1(1):ep20002. <https://doi.org/10.30935/jconseph/8441>

### ABSTRACT

The 2019 novel coronavirus disease (COVID-19) has triggered the world's worst public health challenge in the last 100 years. In response, many countries have implemented disease control measures such as enforced quarantine and travel restrictions. These measures have inadvertent adverse effects on the mental health and psyche of populations. Long-term social isolation is associated with alcohol use and misuse, creating a potential public health crisis.

Alcohol and its intermediate products of metabolism have a multisystemic effect with an impact on the liver, heart, lungs as well as other organs in the body. Similarly, COVID-19 mediate a damaging effect on organ systems through cytopathic effects and cytokine storm. Alcoholism potentially increases the risk of cardiac injury, acute respiratory distress syndrome, pulmonary fibrosis, and liver damage in synergy with COVID-19; thereby worsening disease prognosis and outcome.

We conclude that the history of excessive alcohol consumption needs to be factored into the clinical management of COVID-19 patients. Similarly, epidemiologists and public health experts need to create public awareness on the need for cessation of alcohol abuse while instituting public health measures to control the spread of the infection.

**Keywords:** COVID-19, alcoholism

Received: 11 Jun. 2020 ♦ Accepted: 17 Jul. 2020

### INTRODUCTION

The 2019 novel coronavirus disease (COVID-19) has triggered the world's worst public health challenge in the last 100 years. Caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), the disease is highly contagious with primarily flu-like symptoms - fever, cough, and difficulty breathing [1]. The disease has spread to over 200 countries and territories, affecting approximately four million people, and killing over 250,000 of them. In response, countries have scrambled to implement disease control measures including rapid testing, enforced quarantine, and travel restrictions. Some of these measures have inadvertent adverse effects on the mental health and psyche of populations [2]. There is an increasing body of evidence associating medium- to long-term social isolation with alcohol use and misuse; and this has the trappings of another public health crisis [2-4].

Prior to life with COVID-19, alcohol abuse has been a challenge. About 6.0% of global mortalities are attributed to alcohol consumption [7], and alcohol-related mortality rates have gradually increased in the United States, the United Kingdom, and many other countries [5]. Recent World Health Organization (WHO) reports indicate that as much as 43% of the global population aged 16 years and above (~2.3 billion people) had consumed alcohol within the previous 12 months

[5]. It is also estimated that up to 25.5% of alcohol consumed worldwide is done illegally or without necessary supervision [6]. Although there is no clear evidence linking COVID-19 with alcohol abuse at present, stress has been identified as a major predisposing and perpetuating risk factor for alcohol abuse. There is growing evidence linking social isolation from COVID-19 control measures with psychological distress, anxiety, depression, and other mental health disorders that in turn increase the risk of alcohol abuse [2,3].

While it is easy to make a case for the effect of the COVID-19 pandemic on alcohol abuse, the direct or indirect effects of alcoholism on COVID-19 severity and outcomes are not so clear. It is crucial for the healthcare community to understand if alcoholism potentially increases the severity and risk of fatality from COVID-19. In this review, we discuss the problem of alcoholism as well as alcohol metabolism; explore the multisystemic effects of alcohol and COVID-19 with a focus on the liver, heart, and lungs; the major organs that could impact disease outcome in COVID-19. Also, we consider the evidence in support of possible synergistic interactions that might determine disease severity and outcome.

## ALCOHOLISM AND ALCOHOL ABUSE

Alcoholism, also labeled alcohol dependence in literature, describes a condition in which an individual's social role is impaired and they develop physical alcohol tolerance and withdrawal symptoms from abstinence [4]. Alcohol abuse refers to a pattern of consumption that causes adverse consequences across one or more major spheres of life (e.g. relationships, health, or work). The lifetime prevalence of alcohol dependence varies from country to country, ranging from 1.8% to 32.4%. In the United States, 8-14% of the population are alcohol dependent, and 50% of those who are alcohol dependent are likely to become alcohol abusers [8]. Across genders, men are more likely to be alcohol dependent and misuse alcohol than women, however, there has been a gradual increase in female alcohol consumption with a reduction in the gap between male and female alcohol consumption over the last few years [7,8]. Also, younger adults have the highest prevalence rates of alcohol misuse and dependence, with those between the ages of 21 and 25 years being the most affected [7].

There are other predisposing factors accounting for inter- and intra-group differences in the prevalence rates of alcoholism and alcohol abuse. These include marital status, with those who are not married having the highest rates; burnout, with those under high levels of physical stress having higher consumption rates; family history of alcohol dependence; and poor mental health states [6,7]. Apart from the identifiable environmental factors associated with alcoholism, studies have pointed at a potential genetic predisposition in alcohol abusers. Advances in neurobiological research have linked addiction with neural pathways through which genetic vulnerabilities to alcohol consumption can be explained [8]. Research has shown that 18-27% of male children born to alcoholic parents develop problems with alcohol misuse problems even when raised by foster parents, as compared to 6% of male children from non-alcoholic parents [9]. Also, studies on identical twins show that there were a lot of similarities in the drinking frequency of identical twins than non-identical twins [9]. While not much can be done to alter the genetic predisposition to alcoholism, environmental influences can be manipulated to reduce the risk of alcohol abuse.

Contrary to popular opinion that consumption of alcohol in minimal amounts from time to time helps to prevent conditions such as heart disease, dementia, cognitive decline, and diabetes; many studies have shown that even modest alcohol use contributes to more than 60 acute and chronic health conditions [5,6,10]. Most of the health implications of alcohol occur through mechanisms arising from other disease states such as liver diseases, cancers, hypertension, heart disease, road accidents, interpersonal conflicts, and violence [6]. It would be expected that the negative effects of alcohol on the human body become magnified when combined with COVID-19 which similarly has multisystemic effects; and yet is in itself associated with a public health response that induces a great deal of psychological distress and an increased likelihood of alcohol misuse, triggering a vicious cycle.

## ALCOHOL METABOLISM

The liver is the primary organ of alcohol metabolism. According to Leibing and Meyer, the detoxification of alcohol (ethanol) occur through major and minor pathways [40]. The major pathway described involves the conversion of ethanol to acetaldehyde by hepatic cytosolic

alcohol dehydrogenase, followed by further oxidation of acetaldehyde to acetate in the mitochondria by acetaldehyde dehydrogenase. Both enzymes require nicotinamide adenine dinucleotide (NAD<sup>+</sup>) as a cofactor. Cytosolic acetaldehyde dehydrogenase plays a minor role in acetaldehyde oxidation [40]. Acetate is further metabolized in non-hepatic tissues to carbon-dioxide and water. The intermediate product of this pathway; acetaldehyde, though short-lived, is toxic and is believed to be responsible for some of the toxic effects and contributes to organ damage in alcoholism [42]. Three minor pathways of ethanol metabolism have been described: the microsomal ethanol-oxidizing system (MEOS), active at high ethanol concentration and uses cytochrome P450 enzyme (CYP2E1) and nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor to oxidize ethanol to acetaldehyde; formation of fatty acid ethyl esters (FAEEs) in a series of non-oxidative enzymatic esterification reactions; and oxidation to acetaldehyde in peroxisomes through the action of catalase [40]. These compounds contribute to organ injury in alcoholism [42,43].

## COVID-19: A SYSTEMIC DISEASE

The entry of SARS-CoV-2 into human cells is facilitated by the angiotensin-converting enzyme 2 (ACE2) receptor on cellular surfaces, thereby triggering a series of immunological responses that play a role in disease pathogenesis and manifestations. These ACE2 receptors are commonly found on cells in the lungs, intestine, heart, kidney, blood vessels, testes, and brain; which partly explain the involvement of these organs in COVID-19 [11]. Current evidence suggests organ involvement results from direct viral-induced and cytokine-mediated dysfunction [12]. In the bid to trigger a response to the entry of SARS-CoV-2, there is a release of proinflammatory cytokines and immune cells which often becomes exaggerated and causes varying degrees of tissue damage. Elevated proinflammatory cytokines such as IL-1, IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interferon- $\gamma$  have been correlated with higher disease severity in COVID-19 [13].

The respiratory system is the primary system involved in COVID-19. Aside from common symptoms such as cough, sore throat, and runny nose; pulmonary manifestation of acute lung injury leading to acute respiratory distress syndrome (ARDS) is the leading cause of death in COVID-19 [14]. In addition, there is evidence that survivors of COVID-19 could develop pulmonary fibrosis post-recovery [15]. The liver is equally affected by COVID-19. Markers of liver injury such as elevated bilirubin, aminotransferases, and gamma-glutamyl transferase (GGT) have been found to correlate with disease severity [16]. Although the exact mechanism of liver damage is not known, there are hypotheses that this is due to viral-mediated cell injury as a result of the presence of ACE2 in cholangiocytes and cytokine-induced liver injury [17,18]. In addition, liver damage could complicate the use of antiviral medications used in the treatment of COVID-19 [18].

Acute myopericarditis, arrhythmias, shock, and heart failure have also been reported as cardiac manifestations of COVID-19 [19,20]. Due to the presence of ACE2 in the heart, it is thought that both viral-mediated and cytokine-induced injury are responsible for cardiac damage [21]. Cardiac involvement with or without respiratory failure has been implicated in as much as 40% of COVID-19 mortalities [22]. Elevated cardiac enzymes such as troponin I, troponin T, creatinine kinase MB, and pro-B-type natriuretic peptide (proBNP) which are also markers of cardiac injury have been found to correlate with the risk of

admissions to the intensive care unit (ICU) and death [23]. Hematuria, proteinuria, and elevated blood urea nitrogen and creatinine have been reported in COVID-19 patients; with as much as 5% of them presenting with acute kidney injury [24,25].

Other organs are also affected by COVID-19. Nausea, vomiting, and diarrhea are gastrointestinal manifestations reported in up to 29% of patients [26]. In the brain, the presence of ACE2 in vascular endothelium is thought to be responsible for viral meningitis and encephalitis reported in some patients [27,28]. Similarly, anemia, lymphopenia, leukocytosis, and coagulation disorders have been reported in COVID-19, and the presence of these hematologic conditions correlate with negative disease outcome [22,29]. Studies have also reported ocular involvement with conjunctivitis, and skin lesions, such as erythematous and vesicular rashes in patients with COVID-19 [30,31]. This evidence clearly indicates that the disease is much more than just a respiratory disease, as it has the capacity to inflict damage on several other organ systems in the body.

## ALCOHOLISM, COVID-19, AND LUNG

The deleterious effects of alcohol on the lung have been described in many studies. Although it has not been implicated as a direct cause of any lung disease, various mechanisms of alcohol-induced lung damage have been documented. One mechanism is the impaired mucociliary escalator mechanism due to desensitized cilia which is an important adaptation for the clearance of particulate matter, pathogens, and mucus from the airways has been reported [32]. This is linked with an increased risk of lung infections. An impaired ciliary function has also been linked to other respiratory diseases such as chronic obstructive pulmonary disease, asthma, bronchiectasis, and lung abscess [35]. In chronic alcoholics, host defenses against infections are compromised. Bronchoalveolar epithelial tight junctions, an important component of the innate defense against pathogens, are disrupted [33]. In addition, alcoholism has been shown to cause alveolar macrophage dysfunction [34]. These first-line defenses against pathogens are compromised which increases the risk of lung infections.

The risk of acute respiratory distress syndrome (ARDS) has been found to be 3 to 4 times higher in alcoholics when compared to the general population [35]. Glutathione, an important antioxidant, has been shown to be depleted in the alveolar epithelial fluid of alcoholics [36]. Alveolar glutathione depletion is also a characteristic finding in ARDS which is the leading cause of death in COVID-19 [18,36]. Excessive alcohol consumption has been linked with impaired repair mechanisms after lung injury. When the repair mechanisms become faulty, there is a risk of overexpression of pro-fibrotic cytokines such as transforming growth factor- $\beta$  which becomes a potent force in the development of pulmonary fibrosis [37]. Considering the above evidence, alcoholism has the potential to increase the risk of lung infections, ARDS, death, and long-term possibility of developing pulmonary fibrosis in COVID-19 survivors.

## THE ALCOHOLIC'S HEART AND COVID-19

The effect of alcohol on the cardiovascular system has long been recognized. Cardiac effects of alcohol depend on the dosage, duration of use, and individual peculiarities [38]. At low to moderate alcohol usage,

beneficial effects on the heart have been described as increased coronary blood flow, increased high-density lipoprotein, and reduced thrombogenesis [39]. This has an overall cardioprotective function. However, higher dosage and chronic use of alcohol have been linked with detrimental effects on the heart [38]. Cardiac involvement appears to be mediated by direct alcohol toxicity as well as damage caused by the reactive intermediate product of metabolism: acetaldehyde [40]. This results in disrupted myocardial architecture, leading to reduced contractility and ejection fraction [41]. Alcoholic cardiomyopathy is characterized by cardiomegaly due to cardiac wall hypertrophy, dilated chambers, and interstitial fibrosis; all of which contribute to reduced contractility, heart failure, and sudden cardiac death [40]. The proposed mechanisms for alcohol-induced cardiomyopathy include apoptosis, lipid peroxidation, mitochondrial dysfunction, oxidative stress, and acetaldehyde-mediated protein adduct formation [40]. Other adverse effects of chronic alcoholism on the heart include hypertension, dyslipidemia, and arrhythmias [39]. In patients with COVID-19, an acute myocardial injury could result from direct viral cytopathic effects and repercussions of cytokine storm leading to arrhythmia, shock, and heart failure [19,20]. It is clear that alcoholism creates a potential synergy between alcohol-mediated cardiac injury and COVID-19-induced heart damage, thereby worsening the prognosis of patients with COVID-19. With cardiac dysfunction contributing to 40% of deaths in COVID-19 [22], alcoholism could potentially raise the mortality rate from cardiac causes.

## COVID-19 AND ALCOHOLIC LIVER DISEASE

Very few studies have examined the relationship between COVID-19 and pre-existing liver disease, and studies that investigate the relationship between alcoholic liver disease and COVID-19 are lacking. Studies suggest that only 2-11% of COVID-19 patients had underlying liver disease. However, the studies do not provide information on the type of disease or explore the interaction with COVID-19 [47,50]. Another study suggests a higher prevalence of about 30% [50]. Liver disease is an important cause of alcohol-related morbidity and mortality, and this is because alcohol is largely metabolized by hepatocytes [42]. On the other hand, the incidence of liver injury among COVID-19 cases ranges from 14.8% to 53%, characterized by deranged liver function tests [17]. Broadly, alcohol causes liver injury through the generation of reactive oxygen species (ROS) that cause oxidative stress, decreased antioxidant capacity, altered cellular redox state, increased lipid peroxidation, and formation of antigenic acetaldehyde and protein adducts [42,43]. Chronic or significant exposure of hepatic cells to alcohol triggers inflammation by causing continued activation of immune cells [42,43]. Even though the mechanism of liver injury in COVID-19 is not fully understood, the proposed mechanisms include hypoxia, viral cytopathic effects, immune-mediated and drug-induced injury. Scientists have suggested that hypoxia from raised right atrial pressure arising from high positive end-expiratory pressure in ventilated patients and slow venous return cause damage to the liver [44]. There is, however, insufficient evidence to support this as patients without ventilation support also have abnormal liver function tests [45].

It is also suggested that SARS-CoV-2 causes direct damage to hepatocytes as the presence of its RNA in stool samples portends possible liver infiltration via the portal circulation [46,47]. ACE2

receptors are expressed in liver cells but more so in cholangiocytes. As such, cholangiocyte damage is thought to cause liver injury [17,47], however, the evidence is inconclusive. A study of 202 COVID-19 cases showed a predominant hepatocellular pattern of liver injury [46,48], while another study showed a mix of hepatocellular and cholestatic injury [49]. Postmortem findings suggest immune-mediated injury [46], with the presence of T-cell overactivation and microvesicular steatosis, and drug-induced damage [49]. The widespread inflammatory response, or cytokine storm, initiated by SARS-CoV-2 can cause liver damage from T-cell infiltration and dysregulation of the innate immune system [45]. Drug-induced injury is also considered a significant contributor in COVID-19 as studies show that frequently used drugs including antibiotics [45,47] and antiviral agents like lopinavir/ritonavir [17,49] and remdesivir [44] might play a role. The alcohol-induced expression of CYP2E1 can also interfere with COVID-19 management by increasing drug hepatotoxicity. Similarly, alcoholism may hasten drug-induced liver damage in COVID-19 patients. There is a need for caution with COVID-19 medications and clinicians need to actively monitor drug levels particularly for those metabolized by the liver. Although available evidence suggests that COVID-19 liver injury does not significantly contribute to disease burden, the liver function needs to be closely monitored.

## FUTURE DIRECTION

The ability of alcohol to induce hepatic enzymes has been described, as well as its role in causing cardiac injury, impaired lung repair mechanisms, increased risk of lung infections, and ARDS. However, there is still a need for further research to better understand the interaction between COVID-19 and the spectrum of alcoholic liver disease, determine the mechanisms of COVID-19-associated liver injury, and assess the direct impact of alcoholism on disease outcomes in COVID-19. As the risk of pulmonary fibrosis is increased in COVID-19 survivors, there might be a need for extended follow up for survivors, especially those with a history of alcoholism and any additional predisposition to pulmonary fibrosis with pulmonary function tests and high-resolution computed tomography scan. Furthermore, the scientific community needs to explore the effect of alcoholism on viral transmission, disease severity, survival, and so on. Finally, there is a need for more primary data on the alcohol use status of COVID-19 patients; and the immediate and short-term benefits of stopping alcohol abuse among COVID-19 patients.

## CONCLUSION

COVID-19 has continued to pose serious public health challenges to the entire world. Current measures aimed at stemming the tide are associated with increased physical and mental stress, potentially increasing the risk of alcoholism. Considering the multisystemic effects of both excessive alcohol consumption and COVID-19, alcohol abuse synergistically increases the risk of cardiac injury, acute respiratory distress syndrome, pulmonary fibrosis, and liver damage in COVID-19; thereby worsening disease prognosis and outcome. History of excessive alcohol consumption needs to be factored into the clinical management of COVID-19 patients. Similarly, epidemiologists and public health experts need to create public awareness on the need for cessation of

alcohol abuse while instituting public health measures to control the spread of the infection.

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