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Alcohol use disorder and liver injury related to COVID-19 pandemic

Giuseppe Marano, Gianandrea Traversi, Eleonora Gaetani, Roberto Pola, Angelo Emilio Claro, Marianna Mazza

Abstract

Alcohol use disorder is a complex and heterogeneous phenomenon that can be studied from several points of view by focusing on its different components. Alcohol is a hepatotoxin whose metabolism creates profound alterations within the hepatocyte. The liver is the central organ in the metabolization of alcohol, a process that also involves other organs and tissues such as the brain, heart and muscles, but which reserves the most relevant part for the liver. The anatomopathological alterations of the liver associated with the prolonged use of alcohol range from the simple accumulation of neutral fats in the hepatocytes, to cirrhosis and hepatocellular carcinoma. Alcohol abuse frequently leads to liver disease such as steatosis, steatohepatitis, fibrosis, cirrhosis, tumours. Following the spread of the COVID-19 virus, there was an increase in alcohol consumption, probably linked to the months of lockdown and smart working. It is known that social isolation leads to a considerable increase in stress, and it is also recognized that high levels of stress can result in an increase in alcohol intake. **Cirrhotic patients or subjects with liver cancer are immunocompromised, so they may be more exposed to COVID-19 infection with a worse prognosis.** This review focuses on the fact that the COVID-19 pandemic has made the emergence of alcohol-induced liver damage as a major medical and social problem.

INTRODUCTION

Excessive alcohol consumption has a dual harmful effect: it leads to the development of alcohol dependence, withdrawal symptoms and psychosocial problems, but it also elicits significantly augmented risk of developing acute and chronic dysfunction in multiple organ systems. Liver can be seriously damaged by alcohol since it is mainly metabolized by hepatocytes, but also brain, gut, pancreas, lungs and the immune system are frequently affected by this substance of abuse. Alcohol may even increase the progression of viral infections, autoimmune diseases and cancer. Augmentation of oxidative stress, aberrant posttranslational modifications of proteins, methylation impairments, alteration in lipid metabolism and signal transduction pathways, represent common mechanisms of alcohol-related organ injury affecting cell survival and function.

The considered tolerable dose of alcohol for women is up to 20 g of pure alcohol per day and for men 30 g of alcohol per day ^[1]. Alcohol consumption represents a major factor of morbidity and mortality, is in fifth place as major cause of deaths in both men and women and causes up to 139 million disability-adjusted life years ^[2]. The burden of alcohol-related liver disease (ArLD) has risen in the past two decades, particularly among the young and women. It has been observed that lockdown due to COVID-19 pandemic has led to a notable increase in alcohol abuse and misuse ^[3]. In particular, psychological symptoms such as anxiety, fear and stress result to be correlated with a general increase in alcohol consumption and, in the case of patients with alcohol use disorder (AUD), it has been outlined that social isolation can favor psychological decompensation and increased drinking or relapse ^[4]. Besides, the inaccessibility of regular clinical monitoring systems and the unavailability of professional help has caused difficulties in the treatment of patients with AUD or chronic liver disease (CLD) ^[5]. Steatosis of the liver, alcohol-related steato-hepatitis and ArLD are the most common consequences of excessive alcohol consumption^[3]. ArLD includes a broad spectrum of disease including fat accumulation, cirrhosis, hepatocellular carcinoma ^[6]. Cirrhotic

patients or subjects with liver cancer are immunocompromised, so they may be more exposed to COVID-19 infection with a worse prognosis [7].

There are many factors that contribute to the increased risk of mortality from COVID-19 in patients with ArLD. For example, comorbid clinical pictures such as malnutrition and metabolic syndrome are frequently observed in patients with ArLD and have been associated with poor clinical outcomes in patients with COVID-19 infection [7]. A large longitudinal population-based study conducted in the United States has outlined a worrying rise in 60-and 90-day mortality rates in patients with ArLD who turned to emergency departments or were inpatients during the pandemic, due to the increase in alcohol use and stress, to the direct impact of COVID-19 but also to its indirect effect on the healthcare system (inadequate medical resources, delays in follow-up visits or presenting to medical attention) [8]. Other studies reported that during pandemic rates of hospitalization, severity at admission and mortality during hospitalization for cirrhosis were not different compared to previous years [9], that in immediate and medium-term lockdown there were not demonstrable adverse outcomes in patients with chronic liver disease referring to secondary care [10] or even demonstrated a substantial decline in cirrhosis hospitalizations [11]. These observations could depend on initiatives projected to preserve inpatient resources, and guidance encouraging patients to remain home, and can reflect in part the fact that patients avoided hospital presentation until symptoms are severe because of personal concerns about COVID-19. An international registry study has outlined that patients with cirrhosis are at increased risk of death due to COVID-19 and has outlined that mortality due to COVID-19 infection was higher among patients with more advanced cirrhosis and patients with alcohol-related liver disease [12].

It has been outlined that even an increase in alcohol consumption in short-term periods during the pandemic can worsen morbidity and mortality associated with ArLD in the long term because of several behavioral changes (coping mechanisms to deal with emotional stress and chronic uncertainty) [13]. On the other hand, an epidemiological study conducted on United States mortality data has found that ArLD mortality has

increased among males and females in almost every age and racial/ethnic demographic, both in rate and absolute count, also before the pandemic (from 2017 to 2020) and this rise has been amplified due to COVID-19^[14]. All these data demonstrate that it is pivotal to administer vaccination as a preventive measure in patients with liver disease as soon as possible in order to reduce the risk of SARS-CoV-2 infection and severe disease^[15]. It should be noted that despite the strong and repeated recommendations, overall vaccination coverage in patients with chronic liver disease remains poor and low immunization rates are frequently due to lack of information on vaccine safety, inadequate access to healthcare and poor financial reimbursement for healthcare providers^[16].

A simulation model of the long-term drinking patterns for people with lifetime AUD has revealed that if the increase in alcohol consumption registered in the United States in the first year of the pandemic continues with similar characteristics, alcohol-related mortality, morbidity and associated costs risk to considerably increase over the next 5 years^[17]. These observations impose a red flag on the necessity of improvement of screening for high-risk alcohol use and optimization of early treatment of abuse or misuse and its physical and psychological consequences. A research focusing on the behavioral change after pandemic in people who already had a problem of excessive alcohol drinking showed how subjects with risky or hazardous consumption increased both quantity and frequency of alcohol assumption in most European countries, underlining the urge to establish regulations to define online and home delivered alcoholic beverages availability and the need to carefully restructure health care services^[18]. It has been observed an increase in alcohol use disorder in women, racial and ethnic minorities, and in those experiencing poverty in the context of poor access to alcohol treatment, leading to increasing rates of alcohol-associated liver diseases. The diffusion of telemedicine use contributes to provide effective protection to reduce cross-infection between clinicians and patients, but subjects with chronic liver disease and ArLD still need regular follow-up examinations to prevent worsening of their clinical condition^[15]. It has been noticed that ArLD patients with recent hospital admission

were more motivated to cut down alcohol consumption, and motivation predicted engagement in alcohol misuse treatment^[19].

ALCOHOL AND LIVER INJURY

The most frequent cause of acute liver injury is alcohol (in particular in the form of alcohol binge drinking) followed by hepatitis (A, B, E, autoimmune) and some drugs^[20].

¹ Drug-induced liver injury (DILI) can be potentially caused by several agents, including both prescribed and non-prescribed compounds, herbal and dietary supplements, over-the-counter products and illicit substances^[21].

Alcohol has broad effects on hepatic lipid metabolism leading to an increase in hepatic fatty acids pool, which can be esterified and stored in lipids droplets as triglycerides. Chronic alcohol consumption provokes the lipolysis of triglycerides stored in white adipose tissue, which enter the circulation and can be taken up by the liver. ⁶ Alcohol-induced hepatic lipid metabolism comprehends altered hepatic lipid uptake, de novo lipid synthesis, fatty acid oxidation, hepatic lipid export, and lipid droplet formation and catabolism^[22]. These mechanisms together with other complex effects, some of which not yet fully understood, contribute to the development of hepatic steatosis^[23]. Alcoholic liver injury has a progression from steatosis up to scarring, inflammation and architectural distortion leading to cirrhosis. ¹⁷ Hepatocellular carcinoma may occur as a complication of cirrhotic liver^[24]. However, only a small percentage of patients with alcoholic steatosis progress to severe liver injury (Table 1).

As known, the liver plays a homeostatic role in the systemic immune response. Alcoholic steatotic liver is a fragile medium and is more sensitive to drug damage, vascular changes and hypoxia. In fact, alcoholism is considered a proinflammatory condition. ¹⁴ Chronic injury and death of hepatocytes lead to the recruitment of myeloid cells, secretion of inflammatory and fibrogenic cytokines, and activation of myofibroblasts. Since alcoholic steatotic liver leads to high circulating levels of proinflammatory cytokines, it tends to react to COVID-19 infection with a massive inflammatory response (the so-called inflammatory “tsunami”, induced by both

infection and previous alcohol consumption) and to cause excessive expression of apoptotic factors and consequent multi-organ failure^[25].

It has been demonstrated that chronic alcohol consumption may augment the risk for severe influenza virus infections through the dysregulation of the pulmonary inflammatory environment and CD8 T cell response. Besides, since alcohol reduces oropharyngeal tone it can lead to increased risk of aspiration of microbes, may modify alveolar macrophage function and very often it causes malnutrition^[26].

As already mentioned, many studies agree in affirming that an increase in alcohol consumption in a short-term period during the COVID-19 pandemic can cause long-term ArLD-related morbidity, hospitalizations and mortality^[13-15, 17, 27] and that abnormal liver biochemical tests are often closely related to the severity and prognosis of patients with COVID-19^[28].

SARS-COV-2 EFFECTS ON THE LIVER

Patients with COVID-19 often show liver involvement that may influence disease prognosis and outcome.²¹ Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) virus is responsible of direct cytopathic effect on hepatocytes.³ The COVID-19 associated liver injury is defined as liver injury directly due to the virus or its treatment in patients with or without preexisting liver damage^[29]. The exact mechanism of liver injury in SARS-CoV-2 infection remains largely unknown^[30]. It has been described that this virus enters the cell through angiotensin converting enzyme 2 (ACE2) receptors,²² which are abundant in many districts of the body, included cholangiocytes and hepatocytes. The consumption of alcohol reduces both innate and acquired immune activity with a probable liver increase of ACE2 receptors. It has been noticed that liver dysfunction in COVID-19 is not only due to cholangiocyte dysfunction, but also to the cytokine storm generated by lung damage and to hepatotoxicity related to several drugs used during treatment of the COVID-19 disease^[31]. In particular, liver biopsies in COVID-19 patients showed that liver injury is multifactorial: direct cytotoxicity by the virus, hyper-inflammatory reaction to infection, systemic hypoxia and hepatic

congestion related to cardiomyopathy and drug-induced liver injury. In fact, the anti-COVID-19 drugs, especially with drug-drug or alcohol-drug combinations, cause cellular stress responses and injuries in the liver cells [32]. In addition, it has been established a direct relationship between grade of liver injury and severity of the disease [33]. Elevated liver enzymes appear to be a risk factor for disease progression, even in the absence of underlying liver disease [30]. Mild aspartate transaminase (AST) elevation is considered an early sign of severe COVID-19 disease, while high alanine transaminase (ALT) levels are considered an independent predictor of prolonged SARS-CoV-2 RNA shedding. AST and ALT levels greater than three times the upper limit of normal have been associated with increased mortality [34].

Acute-on-chronic liver failure (ACLF) has been hypotized as one of the possible explanations of higher mortality in liver disease patients with COVID-19: it is characterized by two types of liver injury in combination, one acute (liver-specific or systemic) and one chronic (often misunderstood). It has also been observed that the addition of liver and kidney dysfunctions in critically ill patients can increase mortality. The MELD (End-Stage Liver Disease) score has been developed to assess risk in patients with liver cirrhosis: it can be considered a useful score to deduce both liver and kidney function (based on total bilirubin, creatinine, and International Normalized Ratio-INR) and a possible practical predictor of short- and long-term mortality and morbidity in patients with COVID-19 [35]. SARS-CoV-2 infection highlights the pre-existing weaknesses of the individual organ systems, so it is predictable that patients with chronic liver disease may be susceptible to more severe respiratory infections or be at increased risk of death. Many studies have outlined that hospitalized COVID-19 patients with chronic liver disease presented an acute rise in liver enzymes, which results in a severe condition requiring mechanical ventilation and even leading to death. There are other plausible pathogeneses behind the patients with cirrhosis who have a worst course of disease and even death following COVID-19 infection, such as the excess systemic inflammation, intestinal dysbiosis, cirrhosis-induced immune dysfunction, and coagulopathies [36].

As expected, the presence of alcohol use disorders (AUDs), especially with active alcohol consumption, may worsen course of disease and prognosis [20]. COVID-19 infection can overlap with pre-existing chronic liver disease or induce liver damage directly or indirectly. ACLF patients show a great increase of inflammatory markers and proinflammatory cytokines, features that are frequently observed in severe SARS-CoV-2 infection. Some studies have claimed that patients with ACLF of alcoholic etiology have significantly prolonged hospital stay, severe COVID-19 illness, admission in intensive care unit and higher mortality^[37, 38], while others have outlined that ACLF is often triggered not only by ongoing alcohol consumption, but also gastrointestinal bleeding and/or infections, and from a pathophysiological point of view it is characterized by uncontrolled systemic inflammation coupled with paradoxical immunoparesis. ACLF has a clear pathogenesis and epidemiological burden and is different from decompensated cirrhosis; it represents a challenging condition with rapid clinical course, high short-term mortality and varying clinical phenotypes^[39, 40].

There is a positive correlation between the stage of cirrhosis and the augmented risk of COVID-19-related liver injury and mortality^[41, 42]. Cirrhosis makes the liver lose the homeostatic role in controlling bleeding and thrombosis; in parallel one of the features of COVID-19 disease is hypercoagulability with consequent venous and arterial thrombosis.

The increase in alcohol consumption is a consequence that often occurs following a crisis or a traumatic event^[43]. An increasingly large number of research is showing that there has been a substantial increase in the use and abuse of psychoactive substances, alcohol, tobacco during the COVID-19 pandemic, in particular alcohol intake would have had a substantial rise by 10-23%^[44].

Consumers describe substance use/abuse as a way, albeit problematic and potentially pathogenic, to cope with anxiety regarding COVID-19^[44].

Anxiety about COVID-19 is more than just a worry about infection. Scientific research seems to provide evidence that this is a stress syndrome, a disturbing condition with a possible physiognomy. This condition can provoke an anxious and traumatic reaction

or a response that appeals to mechanisms of denial and repression, suggest that the behaviors of addiction have a dissociative nature linked to the management of negative emotions and feelings^[45].

Alcohol can be used to alleviate stress related to social isolation, negative emotions, boredom, changes in one's routine, high levels of anxiety and worries, in particular fears of the danger of COVID-19. Furthermore, alcohol can exert an inhibitory effect on the nervous system, generating temporary relief from anxiety, depression, anger, sleep disorders and post-traumatic stress disorder^[46].

Those who tend to put in place mechanisms of denial and repression have difficulty in making contact with their emotions and may have an externally oriented cognitive style. These individuals can get used to expressing their sensations, favoring the non-verbal channel, through the development of compensation mechanisms such as compulsive drinking, performing a function of management and avoidance of seemingly uncontrollable emotions.

This reaction to interpersonal trauma, through abuse, can become a dysfunctional coping mechanism that modulates the sensations between the body and emotions, with the risk of dissociative interference in the connections among affects, cognition and voluntary control of behavior.

CONCLUSION

The pressing situation in which the current society finds itself in terms of alcohol consumption, with the exponential increase also in the young population^[47], the very wide opportunities of consumption for anyone who wants to do so and, therefore, the exposure of a considerable number of people to alcohol-related problems of various kind^[48] requires the adoption of measures to limit the new COVID-19 pandemic and the severity of the effects of the disease.

Alcohol consumption is associated with many diseases and is often the cause of injuries and trauma related to road accidents, assaults and episodes of domestic violence. **In addition, as a consequence of new consumption patterns of alcohol during lockdown**

due to COVID-19 pandemic, many social and psychological issues such as domestic violence, mental diseases, and impairment of family quality have been aggravated [49, 50].

A significant problem is acute alcohol intoxication and chronic toxicity, that is, the silent and progressive lesion of vital organs due to prolonged consumption of alcohol even if in moderate doses. The most important point to remember is that alcohol consumption does not protect against COVID-19 in any way, does not destroy the virus and does not prevent from becoming infected with it. Conversely, however, those who make a harmful consumption of alcohol are at an increased risk of infection. The harmful consumption of alcohol, in fact, affects all components of the immune system; alcohol causes a reduction in the number and functions of B lymphocytes and an increased production of immunoglobulins, alters the balance between different T lymphocytes, impairs the number of T lymphocytes and their functioning, promotes cell apoptosis. Furthermore, alcohol is a potential risk factor for pneumonia through other mechanisms: it reduces oropharyngeal tone, increasing the risk of microbial aspiration, and modifies the function of alveolar macrophages, alcohol often causes malnutrition, a condition that rises the risk of infections [26, 51, 52].

Finally, it should be noted that the enlarged risk of infections in addition to the effects of alcohol on the immune system, can also be associated with the presence of an alcohol-related liver disease.

Alcohol can perform various “therapeutic effects” from a psychological point of view. Individuals develop the “magical” expectation that psychological difficulties and suffering can be diluted in alcohol, but then there is disillusionment and an even more painful state of helplessness and frustration. People who abuse alcohol try to alleviate intolerable feelings of helplessness and weakness caused by overwhelming affections. Unconsciously, there is the fantasy that alcohol can substantially change one’s psychic state and repair or replace damaged or missing psychological functions [53]. Mc Dougall [54] conceives alcohol as one of the ways to escape from deep and intolerable anxieties, even of a psychotic nature, caused by the arising of both pleasant and unpleasant affects. The psychic apparatus in particular situations is unable to adequately cope with

emotions and affects. The human person is conceivable as a complex and continuous game between different conscious and unconscious masks. A balance between the internal world and the external world, and among parts of the internal world itself, is achieved by means of objects that are “transitional” and transformative. In such perspective alcohol can become as a “transitional object” [55] that illusory seems to offer security and comfort, but conversely tends to become a petrifying mask and an obstacle to development and integration of self.

While the majority of patients with COVID-19 have no or mild liver function abnormalities during the illness, it results important to closely monitor patients with preexisting liver disease, the elderly, obese subjects or individuals who daily consume high amount of alcohol [29]. Since the COVID-19 pandemic and subsequent lockdown have led to a significant increase of AUD and liver injury all over the world, it seems important to stress that all specialists involved in the field of alcohol addiction and liver disease (specialists in virology, immunology, psychiatry, internal medicine, hepatology, gastroenterology and pharmacology) interact and strictly collaborate through a multidisciplinary intervention aimed to better manage patients in terms of both prevention and prognosis. A psychological support involving patients and their families/caregivers (locally or *via* telemedicine/telehealth) results of pivotal importance to guarantee the efficacy of treatments [3]. In particular, mental health services should continue to guarantee access to care as usual and alcohol treatment programs should remain available for patients even during a pandemic.

There is a need to accelerate strategies to combat the risks and damage caused by alcohol and therefore it is important to promote measures on the issue of health education.

Reaching general practitioners, stimulating them and training them for short-term intervention in this field, means to obtain an important level of care and allows concentrating the activity of specialist structures on particularly complex situations of discomfort. Furthermore, it is essential to undertake an action aimed at raising awareness in consumers of the risks and harm that the use of alcohol entails is essential,

trying to stimulate interventions in defense of personal well-being and quality of life [56-
11⁵⁸]. Research shows that the most effective way to help someone with an alcohol use
problem who may be at risk for developing an alcohol use disorder is to intervene early,
before the condition progresses. Help seeking for alcohol is still low, mainly due to
stigmatization. It remains pivotal to provide policy development, to increase healthcare
stakeholders' awareness and skills, and building relationships with specialist services.
Screening on a large scale, including men, women and particularly young people,
tailored interventions, appropriate training and support for nursing staff, can guarantee
timely and effective care and improve patient satisfaction and health outcomes.

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