ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2022 October 27; 14(10): 1844-1919

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJH* as 0.52. The *WJH*'s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Hepatology is 42/70.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Xiang Li*.

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5182/editorialboard.htm

PUBLICATION DATE
October 27, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

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World Journal of Hepatology

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World J Hepatol 2022 October 27; 14(10): 1875-1883

DOI: 10.4254/wjh.v14.i10.1875

ISSN 1948-5182 (online)

MINIREVIEWS

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

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

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Barve P, United States; Brennan P, United Kingdom; Freund O, Israel; Kar SK, India; Wang MK, China

Received: August 21, 2022
Peer-review started: August 21, 2022
First decision: September 8, 2022
Revised: September 26, 2022
Accepted: October 10, 2022
Article in press: October 10, 2022
Published online: October 27, 2022

Giuseppe Marano, Angelo Emilio Claro, Marianna Mazza, Department of Geriatrics, Neuroscience and Orthopedics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

Gianandrea Traversi, Dipartimento di Medicina di Laboratorio, UOSD Genetica Medica, Ospedale Generale "San Giovanni Calibita" Fatebenefratelli, Rome 00186, Italy

Eleonora Gaetani, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

Roberto Pola, Division of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome 00168, Italy

Corresponding author: Marianna Mazza, MD, PhD, Assistant Professor, Department of Geriatrics, Neuroscience and Orthopedics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, Rome 00168, Italy. mariannamazza@hotmail.com

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 metabolism of alcohol, a process that also involves other organs and tissues such as the brain, heart and muscles, but the most relevant organ is the liver. The anatomopathological alterations in 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, and tumors. Following the spread of coronavirus disease 2019 (COVID-19), 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 a major medical and social problem.

Key Words: Alcohol use disorder; Alcoholic liver disease; Liver injury; COVID-19; Alcohol abuse; Alcohol dependence

Core Tip: Alcohol use disorder is a complex phenomenon with psychological and physical consequences. Alcohol-associated liver disease is a devastating complication of alcohol use disorder. Following the spread of coronavirus disease 2019 (COVID-19) and consequent lockdown there was an increase in alcohol consumption resulting in a worrying increase in steatosis of the liver, alcohol-related steato-hepatitis and alcohol-related liver disease. In addition, patients with alcohol-associated liver disease may be more susceptible to COVID-19 and a worse prognosis. This review focuses on the emergence of alcohol-induced liver damage as a major medical and social problem during the COVID-19 pandemic.

Citation: Marano G, Traversi G, Gaetani E, Pola R, Claro AE, Mazza M. Alcohol use disorder and liver injury related to the COVID-19 pandemic. *World J Hepatol* 2022; 14(10): 1875-1883
URL: https://www.wjgnet.com/1948-5182/full/v14/i10/1875.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i10.1875

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 a significantly augmented risk of developing acute and chronic dysfunction in multiple organ systems. The liver can be seriously damaged by alcohol as it is mainly metabolized by hepatocytes, but also the brain, gut, pancreas, lungs and the immune system are frequently affected by alcohol 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 in morbidity and mortality, it ranks fifth as the major cause of death 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 the coronavirus disease 2019 (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 are 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]. In addition, 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, and hepatocellular carcinoma[6]. Cirrhotic patients or subjects with liver cancer are immunocompromised, so they may be more exposed to COVID-19 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, comorbidity 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[7]. A large longitudinal population-based study conducted in the Unites States has demonstrated a worrying rise in 60- and 90-d mortality rates in patients with ArLD who attended 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 for medical attention)[8]. Other studies reported that during the pandemic, the 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 no demonstrable adverse outcomes in patients with CLD referred to secondary care[10] or 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 were severe due to personal concerns regarding COVID-19. An interna-

tional registry study outlined that patients with cirrhosis are at increased risk of death due to COVID-19 and that mortality due to COVID-19 was higher among patients with more advanced cirrhosis and in patients with ArLD[12].

It has been shown that even an increase in alcohol consumption over short-term periods during the pandemic can worsen morbidity and mortality associated with ArLD in the long-term due to 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 found that ArLD mortality has increased among males and females in almost every age and racial/ethnic demographic, both in rate and absolute count, and 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 severe acute respiratory syndrome coronavirus-2 (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 CLD 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 of 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 will increase considerably over the next 5 years[17]. These observations are a red flag for the necessary improvement in screening for high-risk alcohol use and optimization of early treatment of abuse or misuse and its physical and psychological consequences. Research focusing on the behavioral change after the pandemic in people who already had a problem with 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 healthcare services[18]. An increase in AUD has been observed 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 CLD and ArLD still need regular follow-up examinations to prevent worsening of their clinical condition[15]. It has been demonstrated 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]. Drug-induced liver injury can potentially be 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 pools, 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. Alcohol-induced hepatic lipid metabolism involves 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 are 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. Hepatocellular carcinoma may occur as a complication of liver cirrhosis[24]. However, only a small percentage of patients with alcoholic steatosis progress to severe liver injury (Table 1).

It is known that 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. Chronic injury and death of hepatocytes lead to the recruitment of myeloid cells, secretion of inflammatory and fibrogenic cytokines, and activation of myofibroblasts. As alcoholic steatotic liver leads to high circulating levels of proinflammatory cytokines, it tends to react to COVID-19 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 dysregulation of the pulmonary inflammatory environment and CD8 T cell response. In addition, as alcohol reduces oropharyngeal tone, it can lead to an increased risk of aspiration of microbes, may modify alveolar macrophage function and very often causes malnutrition [26].

Table 1 Progression of alcoholic liver injury[24]

Patients with AUD (alcohol use disorder)
90%-100% present with steatosis
10%-35% have alcoholic hepatitis
8%-20% develop cirrhosis
1%-2% develop hepatocellular carcinoma as a complication of cirrhosis

AUD: Alcohol use disorder.

As already mentioned, many studies have confirmed 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. SARS-CoV-2 is responsible for a direct cytopathic effect on hepatocytes. 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 the presence of SARS-CoV-2 infection is largely unknown[30]. It has been described that this virus enters the cell through angiotensin converting enzyme 2 (ACE2) receptors, which are abundant in many areas of the body, including cholangiocytes and hepatocytes. The consumption of alcohol reduces both innate and acquired immune activity with a probable liver increase in ACE2 receptors. It has been observed 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 the treatment of COVID-19[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 drug-drug or alcohol-drug combinations, cause cellular stress responses and injury to liver cells[32]. In addition, a direct relationship between the grade of liver injury and severity of the disease has been established[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, 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 hypothesized as one of the possible explanations for 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 dysfunction 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 is 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; therefore, it is predictable that patients with CLD may be susceptible to more severe respiratory infections or be at increased risk of death. Many studies have shown that hospitalized COVID-19 patients with CLD have 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 in patients with cirrhosis who have a worse disease course and even death following COVID-19, such as excess systemic inflammation, intestinal dysbiosis, cirrhosis-induced immune dysfunction, and coagulopathies[36].

As expected, the presence of AUDs, especially with active alcohol consumption, may worsen the disease course and prognosis[20]. COVID-19 can overlap with pre-existing CLD or induce liver damage directly or indirectly. ACLF patients show a significant increase in 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, admission to the intensive care unit and higher mortality[37,38], while others have shown 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 charac-

terized 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 a 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 results in the liver losing its homeostatic role in controlling bleeding and thrombosis; in parallel one of the features of COVID-19 is hypercoagulability with consequent venous and arterial thrombosis.

Increased alcohol consumption is a consequence that often occurs following a crisis or a traumatic event[43]. An increasingly large number of studies have shown that there has been a substantial increase in the use and abuse of psychoactive substances, alcohol, and tobacco during the COVID-19 pandemic, in particular alcohol intake has risen substantially 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, and suggests 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 an exponential increase also in the younger population[47], the multiple opportunities for consumption by anyone who wants to do so and, therefore, the exposure of a considerable number of people to alcohol-related problems of various types[48] requires the adoption of measures to limit the 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 the 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 lesions in 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 becoming infected with it. Conversely, however, those who consume harmful levels 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 increased production of immunoglobulins, alters the balance between different T lymphocytes, impairs the number of T lymphocytes and their functioning, and promotes cell apoptosis. Furthermore, alcohol is a potential risk factor for pneumonia *via* 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 increases the risk of infections[26,51,52].

Finally, it should be noted that the elevated risk of infections in addition to the effects of alcohol on the immune system, can also be associated with the presence of ArLD.

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 by alcohol, but there is then 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 emotions. 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]

believes that alcohol is one of the ways used to escape deep and intolerable anxieties, even of a psychotic nature, caused by the increase in both pleasant and unpleasant affects. The psychic apparatus in particular situations is unable to adequately cope with emotions and affects. Humans are complex and are continuously between different conscious and unconscious states. 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 a perspective, alcohol can become a "transitional object"[55] that seems to offer security and comfort, but conversely tends to be an obstacle to development and integration of self.

While the majority of patients with COVID-19 have no or mild liver function abnormalities during their illness, it is important to closely monitor patients with preexisting liver disease, the elderly, obese subjects or individuals who daily consume high amounts of alcohol[29]. As the COVID-19 pandemic and subsequent lockdown have led to a significant increase in AUD and liver injury worldwide, 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) should interact and strictly collaborate through a multidisciplinary intervention aimed at better management of patients in terms of both prevention and prognosis. Psychological support involving patients and their families/caregivers (locally or *via* telemedicine/telehealth) are 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 interventions in this field, could result in obtaining an important level of care and allow specialists to concentrate on particularly complex situations of discomfort. Furthermore, it is essential to undertake actions aimed at raising awareness in consumers of the risks and harm that the use of alcohol entails, and to provide interventions in relation to personal well-being and quality of life[56-58]. Research has shown that the most effective way to help someone with an alcohol use problem who may be at risk of developing an AUD is to intervene early, before the condition progresses. Seeking help for alcohol abuse is still low, mainly due to stigmatization. It is pivotal to provide policy development, to increase healthcare stakeholders' awareness and skills, and to build 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.

FOOTNOTES

Author contributions: Mazza M and Marano G designed the study and wrote the first draft of the manuscript; Traversi G, Gaetani E, Pola R, and Claro AE supervised and added important contributions to the paper; All authors have read and agreed to the published version of the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Country/Territory of origin: Italy

ORCID number: Giuseppe Marano 0000-0001-7058-4927; Angelo Emilio Claro 0000-0003-1826-404X; Marianna Mazza 0000-0002-3007-8162.

S-Editor: Liu JH
L-Editor: Webster JR
P-Editor: Liu JH

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