


ORIGINAL ARTICLE

Alcohol use disorder in the COVID-19 era: Position paper of the Italian Society on Alcohol (SIA)

Gianni Testino¹ | Teo Vignoli² | Valentino Patussi³ | Pierluigi Allosio⁴ |
Maria Francesca Amendola⁵ | Sarino Aricò⁶ | Aniello Baselice⁷ |
Patrizia Balbinot¹ | Vito Campanile⁸ | Tiziana Fanucchi³ | Livia Macciò⁹ |
Cristina Meneguzzi¹⁰ | Davide Mioni¹¹ | Michele Parisi¹² | Doda Renzetti¹³ |
Raffaella Rossin¹⁴ | Claudia Gandin¹⁵ | Luigi Carlo Bottaro¹⁶ | Giacomo Caio¹⁷ |
Lisa Lungaro¹⁷ | Giorgio Zoli^{17,18} | Emanuele Scafato¹⁵ | Fabio Caputo^{17,18} 

¹Unit of Addiction and Hepatology, Regional Centre on Alcohol, ASL3 San Martino Hospital, Genoa, Italy

²Unit of Addiction Treatment, Lugo (Ravenna), Italy

³Regional Centre on Alcohol, Careggi Hospital, Florence, Italy

⁴Alcohol Unit, Torino, Italy

⁵Alcohol Unit, Cosenza, Italy

⁶Gastroenterology Unit, Mauriziano Hospital, Torino, Italy

⁷Alcohol Unit, Salerno, Italy

⁸Alcohol Unit, Bari, Italy

⁹Alcohol Unit, Savona, Italy

¹⁰Alcohol Unit, Pordenone, Italy

¹¹Nursing Home Parco dei Tigli, Teolo, Italy

¹²Alcohol Unit, Nicosia, Italy

¹³Department of Internal Medicine, Mater Dei Hospital, Bari, Italy

¹⁴Alcohol Unit, Milan, Italy

¹⁵National Observatory on Alcohol, National Institute of Health, Rome, Italy

¹⁶Local Health Service, Liguria, Italy

¹⁷Centre for the Study and Treatment of Alcohol-Related Diseases, Department of Translational Medicine, University of Ferrara, Ferrara, Italy

¹⁸Department of Internal Medicine, SS Annunziata Hospital, Cento (Ferrara), University of Ferrara, Ferrara, Italy

Correspondence

Fabio Caputo, Department of Internal Medicine, SS Annunziata Hospital, University of Ferrara, Via Vicini 2, 44042 Cento, Ferrara, Italy.

Email: fabio.caputo@unife.it

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Abstract

Coronavirus disease 2019 (COVID-19) first emerged in China in November 2019. Most governments have responded to the COVID-19 pandemic by imposing a lockdown. Some evidence suggests that a period of isolation might have led to a spike in alcohol misuse, and in the case of patients with alcohol use disorder (AUD), social isolation can favour lapse and relapse. The aim of our position paper is to provide specialists in the alcohol addiction field, in psychopharmacology,

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gastroenterology and in internal medicine, with appropriate tools to better manage patients with AUD and COVID-19, considering some important topics: (a) the susceptibility of AUD patients to infection; (b) the pharmacological interaction between medications used to treat AUD and to treat COVID-19; (c) the reorganization of the Centre for Alcohol Addiction Treatment for the management of AUD patients in the COVID-19 era (group activities, telemedicine, outpatients treatment, alcohol-related liver disease and liver transplantation, collecting samples); (d) AUD and SARS-CoV-2 vaccination. Telemedicine/telehealth will undoubtedly be useful/practical tools even though it remains at an elementary level; the contribution of the family and of caregivers in the management of AUD patients will play a significant role; the multidisciplinary intervention involving experts in the treatment of AUD with specialists in the treatment of COVID-19 disease will need implementation. Thus, the COVID-19 pandemic is rapidly leading addiction specialists towards a new governance scenario of AUD, which necessarily needs an in-depth reconsideration, focusing attention on a safe approach in combination with the efficacy of treatment.

KEYWORDS

alcohol use disorder, COVID-19 infection, drug interactions, infections, telemedicine

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) first emerged in Wuhan (China) in November 2019,^{1,2} and by March 2020, the World Health Organization had declared a global pandemic. Most governments have responded to the COVID-19 pandemic by imposing a lockdown to save lives, to protect themselves and their health-care systems. Second only to China, Italy was the country worst hit by the spread of this highly infectious disease.

Alcohol consumption worldwide is responsible for approximately 5.9% of all deaths (3.3 million deaths) and accounts for 5.1% of the global disease burden.^{3,4} In addition, alcohol consumption can lead to approximately 200 different diseases, including fourteen different types of cancer, a greater susceptibility to infections,^{3,4} and can also have an addictive element.⁵ Moreover, the worldwide prevalence of alcohol use disorder (AUD) ranges between 3% and 15%.^{6,7}

Some evidence suggests that the period of isolation might have led to a spike in alcohol abuse.⁸ Indeed, a recent study performed in China during the period of lockdown for COVID-19 showed that hazardous and harmful drinking both increased greatly from 4.4% to 11.1%.⁹

Thus, a better awareness in the management of AUD in patients affected by COVID-19 and availability of a model of reorganization of Centres for Alcohol Addiction Treatment (CAAT) will be an essential part of the clinical skills of specialists in addictive disorders who will encounter patients with this complex condition in their daily clinical practice.

2 | METHODS

A panel of clinicians, psychologists, and social-health professionals consisting of specialists in gastroenterology, clinical pharmacology, psychiatry, internal medicine, gerontology, toxicology experts in the treatment of AUD, and psychotherapists was identified as appropriate by the board of the Italian Society of Alcoholology (ISA) and met via 'call conferences' and other technological forms of meeting during the lockdown period (from 2 March to 18 May 2020) to draft the ISA's criteria for the management of AUD in patients with COVID-19. On the grounds of their competence, role, expertise and publications in the field of AUD, 20 of them were chosen to collect and finalize the draft and its recommendations. The final paper then underwent revision and approval by the ISA board. This discussion lasted until 18 May 2020.

The aim of our position paper was to consider some critical issues regarding the management of AUD in the era of COVID-19 infection. In our opinion, the most significant topics to be discussed are (a) the susceptibility of AUD patients to infection; (b) the pharmacological interaction between medications used to treat AUD and to treat COVID-19; (c) the reorganization of CAATs in the COVID-19 era. The data used to prepare the position paper are based on the analysis of the scientific literature published between 1 March 2020 and 31 October 2020. In particular, in the development process of this position paper we consulted the indications of the European Centre for Disease Prevention and Control (ECDC), of the World Health Organization (WHO) with their continuous updates on COVID-19,^{10,11} and of the European Association for the Study of the

Liver (EASL) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).^{12,13}

Thus, the position paper was produced with the intent of providing specialists in the alcohol addiction field, in psychopharmacology, gastroenterology and in internal medicine with appropriate tools to better manage patients with AUD and COVID-19. However, it was not possible to identify any degrees and levels of evidence for the final recommendations due to the lack of scientific papers published regarding AUD and COVID-19.

3 | THE CORONAVIRUS DISEASE 2019

Several cases of pneumonia inducing a severe acute respiratory syndrome (SARS) were identified in December 2019 in Wuhan (Hubei province, China).^{1,2} Subsequently, the Chinese Centre for Disease Control of Prevention attributed the pneumonia to COVID-19.¹⁴ Six coronavirus species causing human infection had already been identified. In particular, the Middle East Respiratory Syndrome Coronavirus (MERS) and SARS.^{14,15} COVID-19 is the seventh species with amino acid sequences shared with SARS by about 90%.^{1,16} COVID-19 receptor sites present a strong interaction with angiotensin 2 converting enzyme (ACE2) receptors mainly present in the lung, gut, kidney and liver sites, even though other localizations have been identified.¹⁷ This results in easier penetration and diffusion, especially in the lower respiratory tract; indeed, ACE2 is mainly expressed in type 2 alveolar cells. Human-to-human transmission is possible not only via the respiratory route but also via the faecal-oral route.^{17,18} Faecal positivity with negative serum test has been reported; indeed, a gastrointestinal tropism has also been identified for SARS in intestinal biopsies and stools.^{18,19} Moreover, viral infections are responsible for the so called 'hyper-inflammatory syndrome' characterized by a pro-inflammatory molecule (cytokine) storm with multi-organ failure and increased mortality rates.²⁰

The most frequent symptoms of COVID-19 are: fever (90%), dry cough (82.6%), asthenia with headache and myalgias (70%) and dyspnoea (50%). Even less frequent, gastroenterological signs and symptoms have been described too.^{2,18,19} Progression is characterized by bilateral interstitial pneumonia complicated by acute respiratory distress syndrome, and acute heart and kidney complications.¹⁷

The WHO recommends that all patients with suspected COVID-19 infection should undergo a nasopharyngeal/pharyngeal swab in laboratories authorized to perform nucleic acid amplification diagnostic tests: real-time polymerase chain reaction (RT-PCR). This test has proven to be the most sensitive and specific tool for identifying COVID-19.²¹

4 | INFECTIONS, AUD AND COVID-19

It is well known that alcohol consumption increases the risk of infections.^{22,23} Chronic alcohol consumption compromises the entire immunological system,^{22,23} increasing the risk of severe virus

infections by strengthening the inflammatory reaction. Ethanol is able to interact at different levels, acting both on natural or innate immunity (phagocytosis, natural killer cells and complement) and on specific or acquired immunity.²²⁻²⁴ Experiences in both animals and humans have shown a reduction in the number and function of peripheral T cells, and inhibition of the activation of T cells, and an increase in apoptosis. In addition, a reduction of peripheral B cells with alteration of the production of immunoglobulins has been documented.²²⁻²⁴

AUD patients may frequently be affected by infections in the urinary and respiratory tracts.²³ Some viral infections (i.e., influenza or para-influenza viruses) favour bacterial overlap and growth (i.e., *Klebsiella* and *Streptococcus pneumoniae*),^{25,26} and community acquired pneumonia.²⁷ Indeed, alcohol disrupts ciliary function in the upper airways and weakens the barrier function of the epithelia in the lower airways. In addition to pneumonia, alcohol consumption has been linked to pulmonary diseases, including tuberculosis, respiratory syncytial virus, and adult respiratory distress syndrome (ARDS). It has been demonstrated, in fact, that almost 50% of ARDS are due to the toxic effect in the lung by alcohol misuse,²⁸ and it is important to underline that ARDS represents one of the major complications inducing death in COVID-19 infection.^{1,2} Therefore, it should be hypothesized that patients with AUD may be more at risk of this complication when infected by COVID-19.

Moreover, in patients with AUD, it is well known that the reduction of the pharyngeal tone, the increased risk of aspiration of micro-organisms, the worsening of alveolar macrophage function and malnutrition increase the risk of infections.^{22,23} Also, some studies performed among the general population with no AUD, showed that risk of infections does not correlate with the amount of alcohol intake,²⁹ and a recent meta-analysis identified an 83% increase in risk of pneumonia in drinkers consuming higher amounts of alcohol compared with abstainers or lower consumers.²³ Conversely, an epidemiological experience investigating lifestyle risk factors in the general population did not find associations between alcohol consumption and risk of infectious diseases,³⁰ and a more recent study has shown a weak evidence for a link between excessive alcohol intake and the risk for COVID-19 hospitalization.³¹ Thus, while for patients with an AUD diagnosis, the correlation between alcohol consumption and the risk of infections is widely ascertained, about the general population without a diagnosis of AUD, this correlation risk remains still controversial. In addition, we should take into account that no safe level of alcohol consumption exists,⁴ and that the World Health Organization have clearly stated the presence of four levels of risk (light, moderate, high and very high) due to alcoholic beverages with no category of safe level.³

5 | DRUG-DRUG INTERACTIONS, AUD AND COVID-19

COVID-19 does not have a validated pharmacological approach. Several experimental studies have been implemented to test the efficacy mainly of anti-viral therapy, hydroxychloroquine, and corticosteroid with an overall high prevalence of adverse drug

reactions using lopinavir/ritonavir and umifenovir for the treatment of COVID-19.^{21,32–34} A recent finding shows that remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.³⁵ However, remdesivir is currently the only drug approved in Italy for the treatment of COVID-19.³⁶ Moreover, corticosteroids (dexamethasone) are currently considered the only drug efficient in reducing the mortality in patients with severe COVID-19 disease needing oxygen support,³⁷ and the use of low molecular weight heparin seems promising in hospitalized COVID-19 patients even though the measurement of the real efficacy is still ongoing.³⁸

All these pharmacological therapies may negatively interfere with drugs currently used to treat patients with AUD. Hydroxychloroquine may potentially induce an increase in liver toxicity and neuropathy when used with disulfiram, and may increase the risk for the onset of diarrhoea with acamprosate.^{39,40} Besides, because deterioration of liver and kidney function are frequently shown during remdesivir treatment and alcohol-related liver disease is frequently found in AUD, patients should be monitored for the onset of these adverse events.^{41,42} Thus, in the case of COVID-19 therapy with experimental drugs, due to the severity of symptoms, the discontinuation of adversative or anti-craving drugs needs to be carefully evaluated.

Psychiatric comorbidity is frequent in patients with AUD. Alcohol is the psychoactive substance most frequently used by patients with psychiatric disease. Some 40%–70% of patients with AUD have a psychiatric comorbidity, and conversely, AUDs are three times more frequent in patients with schizophrenia or bipolar disorder.^{7,43} Hydroxychloroquine may cause the lengthening of the QT interval,^{44,45} and on the other hand, alterations in the QT interval are also caused by psychotropic drugs (tricyclic antidepressants, antipsychotics, mono amino oxidase inhibitors, antiepileptics, bupropion and others).⁴⁶ Specifically, a meta-analysis of 16 prospective controlled studies⁴⁷ showed that serotonin-specific reuptake inhibitors (especially citalopram) cause significant prolongation of the QT interval and tricyclic antidepressants can also cause this side effect. However, the risk of side effects was lower than duloxetine or paroxetine.⁴⁷

Monitoring of drug–drug interactions in patients with AUD under multidrug treatment needs to be planned.⁴² Further precautions are, thus, warranted in patients with AUD who need anti-viral or anti-inflammatory treatment for COVID-19, with the aim of discontinuing anti-craving or adversative drugs in the case of severe side-effects. Specifically, some authors recommend the following cut-offs for immediate suspension: alanine aminotransferase (ALT) values greater than three or five times the normal level and/or bilirubin levels beyond the normal limits.^{35–38,41}

6 | REORGANIZATION OF THE MANAGEMENT OF AUD

All healthcare systems need to be reorganized during and after the COVID-19 pandemic, and also the CAATs in order to combine

operator safety with patient safety and care. The CAATs need essential equipment to carry out their clinical activities.

Some general rules are also warranted. Regarding the operators, working meetings in a CAAT could be carried out guaranteeing a safe distance between the participants, even though it would be better to hold meetings using the digital platforms easily downloaded electronically. In addition, some general rules need to be followed during the daily activities in CAATs.

6.1 | Group activities

Suspension of all group activities such as Alcoholic Anonymous or groups with operators and patients are warranted. AUD is a disease with frequent relapses with worsening of the psycho-physical clinical conditions; in addition, patients with AUD are at greater risk for an irregular lifestyle, sometimes a lack of access to common hygiene rules (imprisonment and homelessness) with a consequent greater difficulty to access the healthcare system. Thus, continuous psychosocial support is crucial. In the context of COVID-19 lockdown, the absence of self-help groups may be a serious problem, also in consideration of the fact that only a small number of self-help groups are active via web.⁴⁸ However, only where the majority of the participants had access to technology provided, groups have been converted to e-group treatment. For the others with low socio-economic status and living in poor conditions where the access to online services or telemedicine may be difficult, weekly telephone calls may be done.⁴⁹ Indeed, in order to share experiences of the self-help participants, the support by professional facilitators (physicians and psychologists) through telephone calls during the Phase 1 (during the 2 months of lockdown) of pandemic played a relevant role. In addition, it is widely demonstrated that social isolation increases the risk for relapse and patients frequently turn to alcohol use to alleviate their negative feelings.⁵⁰ Thus, peers, family members and addiction treatment providers should be alert to this possibility.⁵¹

In Italy, very few experiences with telemedicine for group treatment have been studied. Namely, a recent clinical experience during the Phase 1 of a group treatment of patients affected by AUD and alcohol-related liver disease, showed that the simultaneous connection by participants from their homes via a web-based program (Skype: Microsoft) provided encouraging results in limiting the risk of recurrent harmful alcohol consumption.⁵²

6.2 | Telemedicine/telehealth

Telemedicine is the remote delivery of healthcare services using the internet. Some people refer to it as ‘telehealth’ or ‘mhealth’ (short for ‘mobile health’). Video technology (like Skype) also enables people to report their problems to a doctor. Telemedicine has a wide range of applications. It can be used for counselling, chronic disease monitoring and management, professional education, and more. With modern telecommunications, a patient can call a doctor, describe his or her

symptoms and receive a diagnosis and a prescription in a few minutes. Telemedicine enhances convenience, reduces travel time and costs and offers additional benefits for patients, physicians and the greater healthcare system.

Treating alcohol problems can be a sensitive matter. In fact, people with AUD often suffer from stigma when they seek treatment and may prefer to address their problems privately. In these subjects, telemedicine is a revelation: it enables the entire process to be done discreetly at home. In addition, telemedicine may allow patients with AUD to stay in treatment and to receive counselling, reinforcing complete abstinence from alcohol or avoiding relapse. It has been demonstrated that telemedicine or telehealth can be a useful tool for patients with addiction.⁵³ Results from a systematic review conducted in three locations (the United States, the European Union and Australia) indicate that telemedicine (interventions including mobile health, electronic health, telephone and two-way video) reduced alcohol consumption, increased quality of life and decreased costs.⁵⁴ In addition, a systematic review on interventions delivering treatments for substance use disorders, including those involving alcohol, showed that telemedicine-delivered treatments were a promising alternative, especially when evidence-based treatments are not readily available.⁵⁵ For specific treatment and substance use categories, particularly when treatment retention is the key outcome, it is also possible that telemedicine could result in greater treatment retention due to increased accessibility for patients. Therefore, this form of support for patients with AUD, in a period of social distancing, needs to be implemented. This is also true when the clinical and social disaster induced by COVID-19 is attenuated. In fact, a study performed in China among health professionals demonstrated that exposure to an outbreak such as the SARS epidemic in 2003 led, 3 years later, to an increase in alcohol addiction as a consequence of the post-traumatic stress disorder induced by this severe infection disease.⁵⁶ Sporadic data of some Italian regions not further confirmed showed that telemedicine/telehealth accomplished up to 15% of the total interventions of the CAAT during Phases 1 and 2 (post-lockdown period). It is worth to note that, in Italy, in health services and hospital telemedicine is at the beginning of its use, and it now remains a clinical intervention strictly related to a telephone call, e-mail and video calls. However, on 27 October 2020, the Italian Minister of Health has approved the Italian guidelines for the implementation of telemedicine which will be progressively adopted by all Italian regions becoming an integrated part of their clinical intervention.⁵⁷

6.3 | Outpatient treatment (urgent intervention)

If patient requires an urgent intervention due to a rapid worsening of the clinical condition, or the administration of a pharmacological therapy, some simple rules need to be established. Access to the CAAT needs to be regulated to only one patient at a time in order to avoid gatherings in the waiting room. This could be achieved by setting up a filter area with a sorting officer. Signs must be posted on the access pathways to the CAAT and in the waiting room that illustrate the

procedures adopted and reiterate the need to comply with the rules of conduct suggested by the Ministry of Health. The waiting rooms need to be reorganized with a limited number of seats, which must be at a safe distance from each other as required by law (at least 1 m apart in Italy). In the case of aligned and non-separable seats, signs must be placed on the seats that cannot be used. However, extended stay in the CAAT must be avoided. Accompanying persons cannot enter: only those who accompany non-self-sufficient people are admitted. Patients must leave any items of clothing and bags on a dedicated chair; if patients are wearing gloves, they are invited to take them off and disinfect their hands, and patients are then provided with a surgical mask. Patients are asked if they have symptoms (i.e., fever and cough), and their temperature is detected with the thermo-scanner. If a patient has a body temperature $\geq 37.5^{\circ}\text{C}$, he/she is invited to go home and call his/her doctor and/or the dedicated facilities indicated by the health authorities. The patient will then be followed up by telephone. Moreover, during the examination, health workers need to wear personal protective equipment (PPE) and take care of hand hygiene before and after each operation is performed. PPE must be replaced if it gets wet; gloves must always be removed (properly) at the end of each operation and replaced after hand hygiene. Goggles/visors are reusable after sanitization with a chlorine-based product. The premises should be sanitized after each operation.

In Italy, during Phase 1, due to lockdown measures and fears of patients, CAAT healthcare reduced their clinical interventions by 20%–50%. The reduction of clinical activity allowed the operators the opportunity to reorganize their modality of clinical settings with preventive measures to guarantee safety for operators and patients. Indeed, during Phase 2, outpatient visits began to be safety done and planned every half an hour. In addition, for in-patients where the access for the visit of a family member has been forbidden during the period of lockdown (Phase 1), video calls with family members have been implemented, a controlled opening visits in a safe way during Phase 2 (post-lockdown) was planned, and a return to a forbidden access during the current second wave of pandemic began in early October 2020 was further introduced.

6.4 | Alcohol related liver cirrhosis and liver transplantation

Even though patients with alcohol-related liver cirrhosis are more at risk for bacterial infection, data on the impact of viral infections have been less well studied.^{50,58} However, a recent multicentre retrospective study showed that patients with cirrhosis and SARS-CoV-2 infection presented an overall 30-day mortality rate of 34%, concluding that COVID-19 was associated with liver function deterioration and elevated mortality in patients with cirrhosis.⁵⁹ Likewise, a further US study showed a high mortality rate (30%) among patients with pre-existent chronic liver disease infected by SARS-CoV-2.⁶⁰

Moreover, the emergence of COVID-19 has a substantial impact on the transplants' community worldwide. International position papers on the transplants' management during pandemic recommend

screening for SARS-CoV-2 infection of donors and recipients, while transplant policies differed from country to country based on population infection rates and available diagnostic resources.^{61,62} A recent Italian study showed that LT activity was not reduced compared with the corresponding period in 2019, and no transplanted patients contracted COVID-19.⁶³ The main measures introduced in standard of care were the exclusion of COVID-19-positive donors and recipients, staff training, and the application of infection control measures to minimize the risk of spread. In particular, considering that during pandemic beds in intensive care units (ICUs) are reallocated to patients with respiratory failure due to the infection, in order to improve the safety of both patients and staff, physical separation of the two sectors (the so-called 'clean' and 'dirty' areas) of the ICUs with strict monitoring of no cross-traffic was adopted. In a recent Italian experience, beds devoted to LT-ICU area have been obtained inside the spaces usually used in the operating room to guarantee complete isolation from the remaining 'clean' beds of ICU.⁶³

Furthermore, modification of the protocol regarding months of alcohol abstinence before liver transplantation (LT) has been not introduced; however, for those patients with a rapid worsening of MELD, a well-established psychosocial and family support, a high motivation to abstain, and a deep consciousness in their alcohol problems, 3 months of abstinence are considered suitable period.^{64,65} In addition, in selected patients with severe acute alcoholic hepatitis not responder to corticosteroid therapy, acute LT is considered appropriate.^{64,65}

6.5 | Collecting samples

If medications are administered in the CAAT, protective goggles and surgical masks need to be worn by the nurses treating asymptomatic patients, plus disposable gowns and goggles/visors in the case of symptomatic patients. When blood, urine and hair samples are taken for the detection of acute or chronic alcohol misuse,⁵ nurses need to be provided with PPE: surgical masks, gloves, disposable gowns and hair caps. PPE must then be removed according to the prescribed safety methods. At the end of the activities, sanitization of surfaces, instruments and the environment plus ventilation are required.

7 | AUD AND SARS-COV-2 VACCINATION

European Union's vaccination policy leaves the states members free to choose their own vaccination strategy. In the majority of worldwide countries, four vaccines have been approved: (a) the Pfizer-BioNTech's BNT162b2 vaccine; a two-dose regimen of vaccine offer 95% protection against COVID-19 in persons 16 years of age or older⁶⁶; (b) the Moderna mRNA 1273 vaccine Moderna; vaccine's efficacy against COVID-19 was 94.1%⁶⁷; (c) Vaxzevria ChAdOx1 nCov-19 Vector vaccine from AstraZeneca; the vaccine has shown acceptable safety and efficacy against symptomatic COVID-19⁶⁸; (d) Ad26.COVS Vaccine Janssen-Johnson & Johnson; the vaccine,

administered in a single dose, confers protection against symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection, being effective against severe-critical disease, hospitalization and death.⁶⁹

Accordingly with European Union's vaccination guidelines, priority groups defined for vaccination included elderly people, residents and personnel of long-term care facilities, healthcare workers, social care personnel and people with certain comorbidities (i.e., diabetes, cancer, chronic kidney or liver conditions, HIV or other immune-deficiency conditions, heart conditions, asthma, and clinical obesity), while AUD patients or patients with drugs addiction are not included in the priority groups.^{70,71} Conversely, in the United States, the Centers for Disease Control prioritizes the tobacco use disorder in the vaccination line, although other substance use disorders have not been included in high-risk classes.^{72,73}

Italy will be able to count on the availability of over 255 million doses and has recently updated the recommendations on target populations for the vaccination campaign, granting the highest priority to the new macro-category of high fragility, which includes the extremely vulnerable, that is, people suffering from specific conditions who, due to pre-existing organ damage or who due to an impaired immune response to SARS-CoV-2, present a particularly high risk of developing serious or lethal forms of COVID-19 and the category of severely disabled people, their cohabiting family members and

TABLE 1 Recommendations for the reorganization of the Centres for Alcohol Addiction Treatment (CAAT) area during and post-COVID-19 pandemic

- Physicians, nurses, and psycho-social workers in the CAAT, for a safe performance of their daily clinical activity need of liquid soap/ alcohol-based solution for hand hygiene, personal protective equipment (PPE), surgical mask, gloves,
- Disposable long-sleeved raincoat gown/trinitrotoluene (TNT) gown, filtering face piece particles (FFP) 2 or 3 masks, full-body suits and shoes: when they perform outdoor visits for patients at home or in prison
- Professional staff need to use telemedicine/telehealth (e-mail, telephone or video call) to manage therapeutic alliance, to maintain clinical activity, and psychological intervention, and to support caregivers
- It is preferable to make outpatient visits in the CAAT only for urgent and severe clinical cases using chlorine-based sanitizing product to clean the room at the end of every outpatient visit-requesting a swab check in the case of suspected SARS-CoV-2 infection
- The access in the CAAT is maximum every half an hour, patient needs to wear surgical mask, at the entrance his/her temperature has to be checked with a thermo-scanner, and some box with alcohol-based solution for hand hygiene need to be placed at the entrance of physicians or nurses' rooms
- If a patient needs hospitalization for detoxification from alcohol, or for the treatment of a severe alcohol withdrawal syndrome, plan two swabs which need to be negative to favour hospitalization in the COVID free area
- If a patient needs to enter a residential programme (i.e., community), plan two swabs which need to be negative, and, in any case, before entrance foresee 14 days of quarantine for the patient

TABLE 2 Recommendations for the management of AUD patient during and post COVID-19 pandemic

1. Asymptomatic patients:

- The patient must stay at home
- A telephone call evaluation may be carried out at least once a week for a rapid check of the clinical condition regarding alcohol use
- Do not discontinue adversative, anti-craving or psychotropic drugs
- Alert peers and family members of AUD patients that their social isolation may increase the risk for relapse to alcohol use
- Employ e-group treatment where the majority of the participants had access to technology, while for those living in poor conditions maintain monitoring of clinical conditions through telephone calls

2. Symptomatic patients:

- Do not visit patients, and in accordance with specialists (experts in infection diseases, internal medicine or pneumologists), hospitalization in a COVID-19 area may be necessary
- Telemedicine (phone calls, e-mail or video calls) should be encouraged
- If the patient enters in a COVID-19 clinical pharmacological trial with hydroxychloroquine, anti-virals, corticosteroids and low molecular weight heparin, a careful evaluation of the discontinuation of adversative/anti-craving drugs or re-modulation of the dosage or substitution of the psychotropic drugs due to the drug interactions and/or worsening of symptoms may be planned
- In patients treated with psychotropic drugs and hydroxychloroquine or anti-virals, frequent blood samples of ALT and bilirubin levels need to be taken: if ALT is >3–5 times higher than normal and bilirubin levels are beyond the limits, psychotropic drugs (i.e., anti-depressants) need to be discontinued
- Consider that, due to more susceptibility in AUD patients to infections in general, use of corticosteroid may be used only in case of severe form of SARS-CoV-2 infections needing an oxygen support preferably in hospitalized patients

3. Patients with alcoholic liver disease (ALD):

- Patients with compensated ALD should postpone medical visits and routine laboratory controls, and telemedicine (phone calls, e-mail or video calls) should be encouraged limiting outpatient visits to those with high MELD (score >20);
- Patients should be encouraged to receive pneumococcus and influenza vaccinations
- Treatment for alcoholic liver cirrhosis-associated complications (portal hypertension, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis and gastrointestinal bleeding) should be continued (when it is possible such as for paracentesis, in a day hospital setting), and when patients need hospitalization, this may be done in a non-COVID ward after the performance of the SARS-CoV-2 testing
- ALD with cirrhosis are a priority category for SARS-CoV-2 vaccination
- In hospitalized patients, video-calls with family members may be planned

4. Patients awaiting liver transplantation (LT):

- In LT-ICU the main measures of standard of care may be (a) the exclusion of SARS-CoV-2 positive donors and recipients; (b) positive professional staff may stay at home; (c) apply infection control measures in order to minimize the risk of spread; (d) a physical separation in two sectors (the so called 'clean' and 'dirty' areas) in the LT-ICU with a strict monitoring of no cross-traffic
- LT in patients resulted positive for SARS-CoV-2 infection may be postponed after resolution of the infection
- Even though the 6 months rule remains a valid criterion for LT for AUD patients, in selected patients (poor short-term prognosis with MELD score >20, high motivation to abstain, deep consciousness of his/her drinking status of the disease, the presence of a solid psycho-social and family supports) 3 months of abstinence may be adequate
- In selected patients affected by a severe acute alcoholic hepatitis not responder to corticosteroid therapy, acute LT may be considered appropriate after an accurate evaluation of a multidisciplinary professional group
- Post-LT immune-suppression regimens should not be changed; however, in patients diagnosed with COVID-19, reduction of doses should be considered
- Patients undergone LT are a priority category for SARS-CoV-2 vaccination

Abbreviations: ALT, alanine transaminase; AUD, alcohol use disorder; ICU, intensive care unit.

caregivers who provide ongoing assistance.⁷⁴ Even though AUD patients show a higher vulnerability to COVID-19, in Italy, they have not been currently included in high-risk classes.⁷⁵

Moreover, there are no specific data regarding the immune response to the vaccines against SARS-CoV-2 in patients with liver disease. According to the European Association for the Study of the Liver (EASL)⁷⁶ and the Italian Association for the Liver Study (AISF),⁷⁷ in patients with chronic liver disease without cirrhosis, the immune response is not attenuated. EASL and AISF state that patients with

chronic liver disease without cirrhosis do not have an increased risk of incidence and severity of COVID-19, and therefore, vaccination against SARS-CoV-2 should follow the priority criteria established for the general population, taking into account age and comorbidities, while the priority for the vaccination against SARS-CoV-2 comprises patients with advanced liver diseases independently by the aetiology, patients undergone to LT, and patients affected by hepatobiliary cancers.^{76,77} Because ALD without liver cirrhosis may have a higher risk of developing severe COVID-19 disease, more evidence needs to be

gained to determine whether this category should be prioritized for vaccination.⁷⁷

In addition, the relation between alcohol consumption and vaccine efficacy should still be clarified. Although there is no evidence to indicate that alcohol consumption within the recommended limits will affect the vaccine's effectiveness, there is some evidence that regular heavy drinking might impair the body's ability to build immunity in response to some vaccines.^{78,79} In fact, a study found that a single episode of binge drinking with mean peak blood alcohol levels above 130 mg/dL is sufficient to affect the immune system causing an early and transient pro-inflammatory state followed by an anti-inflammatory state.⁸⁰ Thus, as precautionary advice, we recommend avoiding binge drinking and heavy alcohol use around the time of vaccination.⁸¹

8 | CONCLUSION

AUD complicated or not by the alcohol-related liver disease is a clinical condition in which medical and psycho-social problems are combined. The isolation induced by the COVID-19 pandemic has significantly worsened the suffering of patients with AUD and of their family as well. In the near future, social distancing and the vaccination campaigns will remain the only weapon available to contain this pandemic; CAATs will therefore need to improve and review the clinical activities practiced up until now, starting from the solid relationship between operators and patients, which plays an important role in the management of AUD and in the prevention of relapses. Therapeutic alliance and early identification of relapses thus remain two decisive elements in order not to impair complete abstinence from alcohol as the result of many months or years of work with patients. In this regard, the improvement of the relationship between operators in the CAAT and caregivers will also play a relevant role. Indeed, we may not be able to predict the timing of infectious pandemics accurately, we can be sure that they will present again in the future. The COVID-19 experience is not a first, and nor will it be the last. Telehealth does have a critical role in emergency responses. Thus, we must ensure appropriate integration of telemedicine/telehealth into our addiction service,^{57,82} and the engagement of clinicians, nurses, patients and caregivers will become of paramount importance.^{55-57,83} Traditional access to healthcare services (outpatient visit) and telehealth may be offered together from one hand to allow to professional staff and patients to overcome logistic limitations of the access to care, and on the other hand to better rationalize the healthcare resources.

Moreover, as happened when dealing with HIV and hepatitis C virus (HCV) infections when shared interventions between clinicians and researchers working in the fields of addiction diseases, infection diseases, and hepato-gastroenterology combined their forces and achieved excellent results which brought HIV towards a treatable and chronic disease and HCV towards its complete resolution, multi-disciplinary and shared clinical intervention needs to be actively renewed in dealing with the current health crisis.^{84,85} Namely, the clinical approach in the management of AUD patients with alcohol-related liver disease and ALC needs a profound rearrangement with a strict

collaboration of several professional figures experts in alcohol addiction treatment (physicians and psychologists), gastroenterologists, hepatologists and surgeons to guarantee safety to professional staff and patients together with helping patients in achieving and maintain alcohol abstinence in a condition of isolation.⁵⁰ Lastly, peers and caregiver such as family member play a crucial role.

The COVID-19 pandemic has thus rapidly carried us towards a new governance scenario of alcohol addiction, which necessarily requires an in-depth review of the management of AUD with a new safe approach without losing the therapeutic efficacy of multi-disciplinary treatment.^{84,85} In light of this situation, we have formulated some recommendations (Tables 1 and 2).

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AUTHORS' CONTRIBUTION

G. T. and F. C. were responsible for the study concept and design. T. V., P. A., M. F. A., S. A., A. B., P. B., V. C., T. F., L. L., L. M., C. M., D. M., M. P., D. R., R. R. and C. G. contributed to the acquisition of the literature findings. G. T. performed the first draft of the manuscript, and F. C. completed the final draft. V. P., L. C. B., G. C., G. Z. and E. S. provided critical review of the manuscript for important intellectual content. All authors critically reviewed the content and approved the final version for publication.

DATA AVAILABILITY STATEMENT

n/a

ORCID

Fabio Caputo  <https://orcid.org/0000-0002-8953-8338>

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