

# Are Individuals with Substance Use Disorders at Higher Risk of SARS-CoV-2 Infection? Population-Based Registry Study in Northern Italy

Olivera Djuric<sup>a, b</sup> Pamela Mancuso<sup>a</sup> Angela Zannini<sup>c</sup> Antonio Nicolaci<sup>c</sup>  
Marco Massari<sup>d</sup> Alessandro Zerbini<sup>e</sup> Lucia Belloni<sup>e</sup> Giorgia Collini<sup>a</sup>  
Fabio Sampaolesi<sup>f</sup> Anna Celotti<sup>d</sup> Iulica Boni<sup>c</sup> Paolo Giorgi Rossi<sup>a</sup>  
Reggio Emilia COVID-19 Working Group

<sup>a</sup>Epidemiology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy; <sup>b</sup>Center for Environmental, Nutritional and Genetic Epidemiology (CREAGEN), Section of Public Health, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; <sup>c</sup>Addiction Care Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy; <sup>d</sup>Infectious Diseases Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy; <sup>e</sup>Unit of Clinical Immunology, Allergy and Advanced Biotechnologies, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy; <sup>f</sup>SOC Malattie infettive ed epatologia, Azienda ospedaliero-universitaria di Parma, Parma, Italy

## Keywords

Coronavirus disease 2019 · Syndrome coronavirus 2 · Alcohol · Drugs · Addiction

## Abstract

**Background and Aim:** This study assesses whether individuals with substance use disorder are at greater risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than people in the general population. **Methods:** A population-based study was conducted including 3,780 individuals, diagnosed with alcohol or other drug dependence and cared for by the addiction service (AS) in the province of Reggio Emilia. Standardised incidence ratios (SIRs) and relative 95% confidence intervals (CIs) of being tested and of being SARS-CoV-2 positive in the population of interest compared with those in the general population of Reggio Emilia

were calculated. **Results:** Both individuals with alcohol and those with other drug use disorders had a lower risk of being SARS-CoV-2 positive (SIR = 0.69; 95% CI 0.32–1.30, SIR = 0.56; 95% CI 0.24–1.10, respectively), despite higher rates of being tested than the general population (SIR = 1.48; 95% CI 1.14–1.89, SIR = 1.51; 95% CI 1.20–1.86, respectively). Among HIV-negative persons, 12.5% were positive to SARS-CoV-2, while none was positive among HIV-positive persons. HCV-infected AS clients had a higher risk of both being tested for SARS-CoV-2 (SIR = 1.99; 95% CI 1.26–2.98) and of resulting positive (SIR = 1.53; 95% CI 0.50–3.58). **Conclusions:** Individuals with alcohol and/or other drug use disorders are at higher risk of being tested for SARS-CoV-2 infection but at lower risk of resulting positive than the general population. Further research is warranted in order to support our findings and to address plausible factors underpinning such associations.

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## Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly developed into a pandemic, imposing health, economic, and social burdens of unmeasurable proportions. People with substance use disorders (SUDs), including alcohol, are expected to be at higher risk of SARS-CoV-2 infection due to the presence of coexisting chronic health conditions, including chronic respiratory disease, immunosuppression due to HIV infection, or other chronic diseases, or indirectly as an effect of health-neglecting behaviours, poverty, poor-quality housing, high population densities, homelessness, imprisonment, and/or poor mental health. In addition, smoking, which is highly prevalent in the SUD population [1], may contribute to increasing risk of SARS-CoV-2 infection and may exacerbate COVID-19 severity [2].

As SUD is associated with numerous cardiorespiratory and metabolic conditions, it has been inferred that people with SUDs are also at increased risk of COVID-19 [3–5]. However, despite rapidly accumulating evidence on COVID-19, the actual risk of the disease in this population has never been directly estimated. The aim of this study was to assess whether individuals with alcohol and/or other drug use disorders are more at risk of SARS-CoV-2 infection than people in the general population and whether a diagnosis of HIV or HCV further increases this risk.

## Materials and Methods

### *Study Design and Patients*

This longitudinal registry-based cohort study was conducted on a total of 3,780 individuals, residents in the province of Reggio Emilia on December 31, 2019, who were diagnosed with alcohol or other drug use disorders and cared for by the addiction service (AS – in Italian, *SerDP*) between January 19, 1982 and February 20, 2020. This cohort was followed up to compare the COVID-19 cumulative incidence observed in SUD patients with that observed in the general population during the first phase of the epidemic, that is, from February 27, 2020 to April 12, 2020.

The International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) was used to code SUDs. Patients with a diagnosis of mental or behavioural disorders due to the use of alcohol (ICD10 F10), opioids (ICD10 F11), cannabinoids (ICD10 F12), or cocaine (ICD10 F14) were selected from the AS database.

Drugs other than alcohol were classified as opioids, cocaine-related, cannabinoids, or other. If a patient was concurrently diagnosed with two or more SUDs, the diagnosis made first was considered as the exposure. Alcohol and other drug dependences were

classified as follows: if both alcohol and illicit drug abuse were present, the latter was considered, based on the fact that people who are dependent on illicit drugs are more likely to have an alcohol use disorder than people with alcoholism to have a drug use disorder (National Institute on Alcohol Abuse and Alcoholism – NIAAA, 2006).

### *Setting*

The AS carries out prevention, treatment, and rehabilitation of use disorders, addiction to legal and illegal psychoactive substances, and gambling. It provides care to people with addiction either directly through the local health authority clinics or through private clinics that have entered into an agreement with the National Health Service. Referral to the AS can be voluntary or mandatory, as a complementary penalty by order of the police and judicial authorities.

The first COVID-19 case in Reggio Emilia has been diagnosed on February 27, 2020. Up to April 12, 2020, 5,032 cases were diagnosed, corresponding to a cumulative incidence in the general population of 9.5/1000 inhabitants.

### *Data Sources*

In the province of Reggio Emilia, a surveillance system with dedicated software that collects data on patients tested for SARS-CoV-2 and, if they tested positive, on the outcome of their disease. The surveillance is fed by several sources: the local health authority public health service epidemiological investigations, contact tracing, and symptom surveillance of contacts isolated at home, laboratory reports, emergency room and hospital electronic records, and death certificates. The system was developed for the purpose of managing each individual case. During the first phase of the epidemic, only symptomatic patients had been tested, with very few exceptions.

The SARS-CoV-2 database, including all diagnoses from the beginning of the epidemic up to April 12, 2020, was linked with the registry of SUDs extracted from the AS database. The database reports the substance use-related diagnoses, the type of care received, the most recent HIV and HCV tests done, and their results. Both the registries are linked with the resident population register to determine whether patients are residents of the province of Reggio Emilia.

### *Statistical Analysis*

Age, sex, district of residence standardised incidence ratios (SIRs), and relative 95% confidence intervals (CIs) of being tested and of being SARS-CoV-2 positive in the population of interest compared with the general population of the province of Reggio Emilia were computed by dividing the number of observed cases in the population of interest by the expected number of cases. The expected number of cases was computed applying age-, sex-, and district-specific rates from the general population of province of Reggio Emilia and to the SUD cohort age- and sex groups. SIRs were also calculated for the following subcohorts: according to the first diagnosis (alcohol use disorder and drug use disorder), having at least a diagnosis of alcohol use disorder and use of opioids, having a HCV-positive test in one's lifetime, having a negative HCV test, and never tested for HCV. Due to the different distribution of both the prevalence of AS clients and the spread of COVID-19 within the province, SIRs were also adjusted for the district of residence. All analyses were performed by using Stata version 13.0 (College Station, TX, USA).

**Table 1.** Number of AS patients tested and positive for SARS-CoV-2, by type of addiction and by presence of HIV or HCV infection

|                             | AS clients |        |       | Tested for SARS-CoV-2 |        |       | Positive for SARS-CoV-2 |        |       |
|-----------------------------|------------|--------|-------|-----------------------|--------|-------|-------------------------|--------|-------|
|                             | male       | female | total | male                  | female | total | male                    | female | total |
| Overall                     | 3,059      | 721    | 3,780 | 117                   | 32     | 149   | 14                      | 3      | 17    |
| First diagnosis             |            |        |       |                       |        |       |                         |        |       |
| Alcohol use disorder        | 1,057      | 393    | 1,450 | 50                    | 14     | 64    | 9                       | 0      | 9     |
| Drug use disorder           | 2,002      | 328    | 2,330 | 67                    | 18     | 85    | 5                       | 3      | 8     |
| Opioids                     | 977        | 196    | 1,173 | 38                    | 10     | 48    | 2                       | 3      | 5     |
| Cocaine                     | 495        | 50     | 545   | 8                     | 3      | 11    | 1                       | 0      | 1     |
| Cannabis                    | 530        | 82     | 612   | 21                    | 5      | 26    | 2                       | 0      | 2     |
| Single dependence diagnosis |            |        |       |                       |        |       |                         |        |       |
| Alcohol use disorder        | 1,174      | 422    | 1,596 | 57                    | 16     | 73    | 9                       | 1      | 10    |
| Drug use disorder           | 2,263      | 374    | 2,637 | 84                    | 20     | 104   | 5                       | 3      | 8     |
| Opioids                     | 1,060      | 213    | 1,273 | 44                    | 11     | 55    | 2                       | 3      | 5     |
| Cocaine                     | 558        | 53     | 611   | 11                    | 3      | 14    | 1                       | 0      | 1     |
| Cannabis                    | 645        | 108    | 753   | 29                    | 6      | 35    | 2                       | 0      | 2     |
| HIV tested                  |            |        |       |                       |        |       |                         |        |       |
| HIV–                        | 1,760      | 399    | 2,159 | 71                    | 17     | 88    | 9                       | 2      | 11    |
| HIV+                        | 62         | 26     | 88    | 3                     | 3      | 6     | 0                       | 0      | 0     |
| Not tested                  | 1,237      | 296    | 1,533 | 43                    | 12     | 55    | 5                       | 1      | 6     |
| HCV tested                  |            |        |       |                       |        |       |                         |        |       |
| HCV–                        | 1,857      | 489    | 2,346 | 79                    | 24     | 103   | 10                      | 0      | 10    |
| HCV+                        | 334        | 86     | 420   | 17                    | 6      | 23    | 2                       | 3      | 5     |
| Not tested                  | 868        | 146    | 1,014 | 21                    | 2      | 23    | 2                       | 0      | 2     |

AS, addiction service; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

## Results

Overall, 149 (3.9%) AS patients were tested for SARS-CoV-2 virus, of whom 17 (11.4%) resulted positive (Table 1). In the group of individuals with alcohol dependence as first diagnosis, 64 (4.4%) were tested, of whom 9 (14.1%) were positive, while among those with a drug dependency as first diagnosis, 3.6% were tested, of whom 9.4% were positive.

Among those tested for HCV, there were twice as many individuals who were positive for SARS-CoV-2 among HCV-positive persons than among HCV-negative persons [21.7% (5/23) versus 9.7% (10/103)] (Table 2). In the group of HIV-negative persons, 12.5% (11/88) were positive for SARS-CoV-2 virus, while none of the HIV-positive persons tested positive (0/6).

Both individuals with alcohol and those with drug dependence as first diagnosis had a lower risk of being SARS-CoV-2 positive (SIR = 0.69; 95% CI 0.32–1.30, SIR = 0.56; 95% CI 0.24–1.10, respectively), despite the higher rate of testing in these populations than the general population (SIR = 1.48; 95% CI 1.14–1.89, SIR = 1.51; 95% CI 1.20–1.86, respectively). Only HCV-infected AS

patients had a higher risk of both being tested for SARS-CoV-2 (SIR = 1.99; 95% CI 1.26–2.98) and of testing positive (SIR = 1.53; 95% CI 0.50–3.58).

## Discussion

Although compatible with a random fluctuation, we observed lower risk of contracting SARS-CoV-2 virus for both alcohol- and for drug-dependent individuals, overall as well as for those who were HIV-positive, despite a higher probability of being tested for SARS-CoV-2. To our knowledge, this is the first study to directly assess the risk of infection in this population, which makes a comparison with previous literature impossible. Some indirect evidence, based on the distribution of co-occurring conditions in SUD patients (which represent a risk factor for infectious diseases in general), suggests that people who smoke crack cocaine may be more likely to have more severe COVID-19 disease [4]. With the limitation of low precision and high risk of bias, the study by Saeedi et al. [6] reported a high rate (10.8%) of opium addiction in 93 patients admitted to a COVID-19 referral hos-

**Table 2.** SIRs\* of being tested and of being SARS-CoV-2 positive among AS patients, by type of addiction and by presence of HIV or HCV infection

|                             | Risk of testing SARS-CoV-2 |      |      |        |      | Risk of being SARS-CoV-2 positive |       |      |        |      |
|-----------------------------|----------------------------|------|------|--------|------|-----------------------------------|-------|------|--------|------|
|                             | Obs                        | Exp  | SIR  | 95% CI |      | Obs                               | Exp   | SIR  | 95% CI |      |
| Overall                     | 149                        | 99.7 | 1.49 | 1.26   | 1.75 | 17                                | 27.4  | 0.62 | 0.36   | 0.99 |
| First diagnosis             |                            |      |      |        |      |                                   |       |      |        |      |
| Alcohol use disorder        | 64                         | 43.3 | 1.48 | 1.14   | 1.89 | 9                                 | 13.0  | 0.69 | 0.32   | 1.30 |
| Drug use disorder           | 85                         | 56.5 | 1.51 | 1.2    | 1.86 | 8                                 | 14.4  | 0.56 | 0.24   | 1.10 |
| Single dependence diagnosis |                            |      |      |        |      |                                   |       |      |        |      |
| Alcohol use disorder        | 73                         | 47.0 | 1.55 | 1.22   | 1.95 | 10                                | 14.00 | 0.71 | 0.34   | 1.31 |
| Opioids                     | 55                         | 32.2 | 1.71 | 1.29   | 2.23 | 5                                 | 8.4   | 0.59 | 0.19   | 1.39 |
| HCV positivity              |                            |      |      |        |      |                                   |       |      |        |      |
| HCV-                        | 103                        | 62.2 | 1.66 | 1.35   | 2.01 | 10                                | 17.0  | 0.59 | 0.28   | 1.08 |
| HCV+                        | 23                         | 11.6 | 1.99 | 1.26   | 2.98 | 5                                 | 3.3   | 1.53 | 0.59   | 3.58 |

Obs, observed number of cases; Exp, expected number of cases; SIR, standardised incidence rate; CI, confidence interval; AS, addiction service; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. \* Adjusted for age, sex, and district of residence.

pital and 4 times higher the mortality associated with a diagnosis of opium addiction.

A reliable interpretation of these results is even more challenging when considering the association between smoking and the risk of severe COVID-19. Although peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection among smokers are lacking, meta-analyses suggest that smokers have a higher risk of severe COVID-19 disease and death [7]. In a prospective study of 500,000 adults, analysis adjusted for important baseline characteristics showed that current smokers were slightly more likely than never smokers to test positive for COVID-19 [8].

Our results suggest that the risk of contracting the SARS-CoV-2 virus is not higher in HIV-positive AS patients than it is in the general population, consistently with what Del Amo and colleagues [9] reported in a cohort study including 60 Spanish HIV hospitals, Guo et al. [10] observed in HIV/AIDS patients in two districts in Wuhan, China, and Vizcarra observed in a large cohort study conducted in Madrid after inclusion of suspected COVID-19 cases [11]. However, all this should be interpreted with caution since most of these authors did not control their analyses for comorbidities and other confounders.

The strength of our study is that, to our knowledge, it is the first observational study to directly assess the risk of SARS-CoV-2 infection in a marginalized population of individuals with an SUD. Our results contradict current beliefs and provide a new perspective on the risk factors for SARS-CoV-2 infection.

The main limitation of this study is the limited generalisability of the results. While the increased testing in this population could be the result of more intensive medical follow-ups, the protective effect we noted was the result of a mix of behavioural, human, social (social isolation), environmental, and biological factors that reduced exposure to the virus and the probability of infection and/or of having symptoms. Behaviours and the social environment vary between countries and communities. Up to 90% of alcohol-dependent people and more than 60% of high-risk opioid clients in Italy belong to the hard-to-reach population as they do not seek or have not been referred to rehabilitation or drug replacement treatment [12].

## Conclusion

Individuals with alcohol and/or other drug use disorders are at higher risk of being tested for SARS-CoV-2 infection but at lower risk of resulting positive than the general population. Further research is warranted in order to support our findings and to address plausible factors underpinning such associations.

## Appendix

The following are members of the Reggio Emilia COVID-19 Working Group:

Massimo Costantini, Roberto Grilli, Massimiliano Marino, Giulio Formoso, Debora Formisano, Ivano Venturi, Cinzia Campari, Francesco Gioia, Serena Broccoli, Marta Ottone, Pierpaolo Pattacini, Giulia Besutti, Valentina Iotti, Lucia Spaggiari, Chiara Seidenari, Licia Veronesi, Paola Affanni, Maria Eugenia Colucci, Andrea Nitrosi, Marco Foracchia, Rossana Colla, Marco Massari, Anna Maria Ferrari, Mirco Pinotti, Nicola Facciolongo, Ivana Latuada, Laura Trabucco, Stefano De Pietri, Giorgio Francesco Danelli, Laura Albertazzi, Enrica Bellesia, Simone Canovi, Mattia Corradini, Tommaso Fasano, Elena Magnani, Annalisa Pilia, Alessandra Polese, Silvia Storch Incerti, Piera Zaldini, Efre Bonelli, Bonanno Orsola, Matteo Revelli, Carlo Salvarani, Carmine Pinto, Pamela Mancuso, Francesco Venturelli, Massimo Vicentini, Cinzia Perilli, Elisabetta Larosa, Eufemia Bisaccia, Emanuela Bedeschi, Alessandro Zerbini, and Paolo Giorgi Rossi.

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## Statement of Ethics

The study was approved by the Area Vasta Emilia Nord Ethics Committee on 04/07/2020 (protocol number 2020/0045199). Patients' informed consent to participate in the study was obtained whenever possible, given the retrospective nature of the study.

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## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

P.G.R., A.N., and A.Z. conceptualized the work and designed the study; O.D. performed the literature search and wrote the article; M.M., A.Z., I.B., F.S., A.C., and G.C collected and curated the data; P.M. performed statistical analysis; A.Z., A.N., and M.M. critically reviewed and edited the manuscript; and the Reggio Emilia COVID-19 Working Group contributes to data collection and quality assurance. All authors provided critical revisions of the draft and approved the submitted draft.