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Clinical vulnerability for severity and mortality by COVID-19 among users of alcohol and other substances

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ABSTRACT

The COVID-19 pandemic is a public health emergency. Individuals with substance use disorder have a higher risk of infection and may suffer from more severe forms of the disease. Our goal is to investigate the prevalence of risk factors for COVID-19 severity in individuals with different substance use and explore whether specific types of substance are potentially associated with more clinical risk factors which could increase morbimortality in this population. The sample included 821 men hospitalized at an inpatient Addiction unit (305 alcohol users, 233 cocaine/crack users, and 283 multusers). Data were collected using the Addiction Severity Index version 6. The most prevalent risk factors for COVID-19 severity observed in our sample were: smoking (82.5%), arterial hypertension (26.6%), respiratory problems (23.4%), and history of homelessness (25.1%). Arterial hypertension and cirrhosis occurred more frequently among alcohol users. Multusers lived in the streets longer and had a higher prevalence of HIV than alcohol users. Overall, 28% of the sample had three or more risk factors. The frequency of risk factors was high and this scenario suggests that these individuals could be more susceptible to worse COVID-19 prognosis. Therefore, prevention strategies directed at specific characteristics of substance users merit attention during the pandemic.

1. Introduction

The identification of vulnerable individuals and those who are more susceptible to the infection for COVID-19 – with more severe clinical conditions and higher mortality rates – is essential to implement specific and efficient strategies (CDC, 2020). Individuals with substance use disorder (SUD) have a complex clinical profile, presenting many psychiatric and clinical comorbidities, besides social vulnerabilities (Lagisetty et al., 2017; Peacock et al., 2018). This population often has an unhealthy lifestyle, represented by poor nutritional status (Jeynes and Gibson, 2017) and body mass index, lack of exercise (Blackstone and Herrmann, 2016; Sayon-Orea et al., 2011; Traversy and Chaput, 2015), with compromised employment and academic performance (WHO, 2020). Moreover, vulnerable populations are less likely to adopt protective measures (for example, wearing masks, hand sanitizers, and social distancing), hampering the implementation of public health policies (Mesa Vieira et al., 2020). In this population, the countless difficulties related to accessing the health system and the monitoring of treatment end up aggravating this challenging scenario.

In addition, immunological alterations have been observed in individuals with SUD (Cohen et al., 1993; Schuch-Goi et al., 2017; Sureshchandra et al., 2019; Zaparte et al., 2019). Studies showed that alcohol and cocaine/crack abuse increase the risk for infectious diseases (Butler et al., 2017; GBD 2016 Alcohol and Drug Use Collaborators., 2018; Halpern et al., 2017; Peacock et al., 2018; WHO, 2018). For instance, the use of substances facilitates influenza infection and leads to a worse prognosis (Godoy et al., 2018; Meyerholz et al., 2008).

In this sense, individuals diagnosed with SUD might have an increased risk of COVID-19 and a worse prognosis. Indeed, higher rates of hospitalizations and deaths were observed in individuals with SUD and COVID-19 compared to individuals with COVID-19 but without SUD (Wang et al., 2021). Nonetheless, these individuals still have received little attention during the COVID-19 pandemic (Harris, 2020; Ornell et al., 2020), mainly in developing countries.

All of these aspects represent major challenges for the health system. Public policies for individuals who use substances should be developed
based on the particularities of this population, including prevention and treatment strategies that address both medical and psychosocial care. Since few data is available, the first step to implement these policies is to identify epidemiological characteristics and vulnerabilities previously associated with COVID-19 severity in this group of individuals. In this sense, our goal is to investigate the prevalence of risk factors for COVID-19 severity in a sample of individuals who use illicit and licit substances and explore whether specific types of substance are potentially associated with more clinical risk factors which could lead to morbimortality in this population.

2. Methods

2.1. Sample

The total sample included 821 males with diagnosis of SUD (following DSM-5 criteria) hospitalized at an inpatient unit specialized in drug addiction at a public hospital in Porto Alegre, Brazil. Only individuals with 18 years of age or older who reported alcohol and/or cocaine/crack as the preferred substances were included in the study. Individuals with presence of psychotic disorders, and/or severe cognitive deficits that could impair the reliability of the answers were excluded.

2.2. Procedures

The research protocol was applied by trained junior researchers under the supervision of a senior with broad experience in SUD. This assessment was performed after stabilization of initial withdrawal symptoms (usually between the 5th and the 15th day of hospitalization). Sociodemographic and clinical data, as well as data concerning the patient’s substance use profile, were collected using the Addiction Severity Index version 6 (ASI-6) (Kessler et al., 2012). Clinical comorbidities were assessed through self-report. This data was also extracted from ASI-6, and individuals were asked to only report health complications diagnosed by medical or other health professionals, ensuring greater reliability. Additionally, data on the presence of HIV infection was obtained from hospital records, through laboratory tests.

2.3. Ethics

The study was approved by the Ethics committee of Hospital de Clínicas de Porto Alegre (protocol number 2014-0249). All participants provided written informed consent prior to the inclusion.

2.4. Statistical analysis

Data were entered into the online platform REDCap and exported to the IBM SPSS statistics for analysis. Based on recent studies, the following risk factors for COVID-19 severity were evaluated: age, smoking history, positive diagnosis for HIV, clinical comorbidities (hypertension, diabetes, heart, respiratory, kidney, or liver disease), and recent history of homelessness (living on the streets or in shelters) (Cook et al., 2020; Grasselli et al., 2020; Onder et al., 2020; Shi et al., 2020; Williamson et al., 2020). The age of de patients was described by the mean and standard deviation. Prevalence of factors are presented using percentages and 95% confidence intervals. Association analyses between each risk factor and substance type were performed using Pearson chi-square. All p-values reported were adjusted by Bonferroni correction. In all analyses, a significance level of 5% was adopted.

3. Results

Our sample included 305 alcohol users, 233 cocaine/crack users, and 283 men who used multiple substances (including alcohol and cocaine/crack). Mean age was 41 years; SD:12 years. Regarding the risk factors listed above, we found a high prevalence of smoking history (82.5%), with similar estimates across groups. Other risk factors were frequently detected among individuals with SUD, including arterial hypertension, respiratory problems, and recent history of homelessness (Table 1).

The prevalence of arterial hypertension differed between the three groups of substance users. This risk factor was more frequent among alcohol users, followed by users of multiple substances and cocaine/crack users (p-value ranging between .003 and <.001). History of heart disease was also more prevalent in the alcohol group than in the other two groups ($\chi^2$=11.0; $p = .003$ for cocaine/crack and $\chi^2$=12.3; $p = .001$ for users of multiple substances), as well as the number of individuals over 60 years of age ($\chi^2$=58.1; $p < .001$ for cocaine/crack group and $\chi^2$=44.0; $p < .001$ for users of multiple substances). Moreover, alcohol users present more cirrhosis than cocaine/crack users ($\chi^2$=17.2; $p < .001$). On the other hand, users of multiple substances and cocaine/crack users showed a higher prevalence of recent history of homelessness compared to alcohol users ($\chi^2$=24.5; $p < .001$ and $\chi^2$=13.1; $p = .001$). Users of multiple substances showed a higher frequency of HIV than alcohol users ($\chi^2$=12.7; $p = .001$).

The frequencies of number of risk factors associated with higher COVID-19 severity (from the 10 listed above) in our sample are showed in Fig. 1. Three or more clinical risk factors were more frequent among alcohol users compared to cocaine/crack users ($\chi^2$=9.8; $p = 0.005$), whom, on the other hand, had a higher frequency of only 1 or 2 factors ($\chi^2$=6.4; $p = 0.035$). Considering our data, approximately 8% of the sample had no risk factors for COVID-19, around 65% had 1 or 2 risk factors, and approximately 28% had 3 or more risk factors.

4. Discussion

This study shows a high prevalence of risk factors related to the severity and mortality by COVID-19 among users of alcohol and other substances. Alcohol users exhibit a larger number of risk factors for more severe forms of COVID-19 compared to cocaine/crack and multisubstances groups. In fact, chronic alcohol use was previously related to metabolic, and hepatic diseases (Li et al., 2019; Stubbs and Morgan, 2011), and cardiac hypertrophy, which may increase the severity of heart disease (Varga et al., 2015). This is alarming since COVID-19 infection could affect multiple organs, such as heart, liver, and hematopoietic tissue, resulting in the worsening of the disease.

Among the risk factors analyzed, the prevalence of tobacco consumption stands out since it is very common in our sample (82%), compared to the estimates for the Brazilian population (15%; Malta et al., 2015b). The use of alcohol and tobacco are risk factors not only for COVID-19, but for other respiratory infections, such as influenza, worsening the prognosis (Godoy et al., 2018; Meyerholz et al., 2008). The effects of tobacco on lung health and on the immune system make this population especially vulnerable to COVID-19 (Vardavas and Niki-tara, 2020). Accordingly, a recent Chinese study found that patients with smoking history are 14 times more likely to progress from COVID-19 to pneumonia (Liu et al., 2020).

In addition, the prevalence of chronic diseases in our sample is higher than in the general Brazilian population (Sousa et al., 2012), especially in alcohol users. These individuals are typically older when seeking treatment for addiction, which contributes to their vulnerability and presence of more chronic conditions. Overall, our sample presents a higher prevalence of hypertension (26.6%, up to 38% in alcohol users) (Malta et al., 2015a), heart disease (6.7%, up to 11.5% in alcohol users), respiratory disease (23.4%) (Leal et al., 2018), kidney disease (3.6%, up to 4.6% in multisubusers) (Moura et al., 2015), and cirrhosis (4.4%, up to 7.9% in alcohol users) (de Carvalho et al., 2020) compared to the Brazilian general population (21.4%, 3.9%, 3% 1.4%, and <1% respectively). On the other hand, the rate of diabetes was slightly lower (5.7%) if compared to the data from the National Study on Health (6.2%) (Malta et al., 2015a).

The high prevalence of HIV, of about 7% (in multisubusers, this estimate...
isolation and go in search of substances, increasing the risk of contamination. For example, there has been an increase in marijuana sales after the onset of the pandemic, particularly among young people. This increase is likely due to the restriction of personal mobility, which is a common feature of this time. Other studies, such as those by Halpern et al., Serafini et al., and Sinha et al., have reported similar findings, suggesting that the pandemic has led to an increase in the use of substances. In the United States, these trends have been particularly pronounced in communities with high rates of mental and physical health problems, such as those affected by the ongoing opioid crisis.

individuals with addiction. The occurrence of HIV is associated with a substantial imbalance in the immune system, especially CD4+ T cells. Furthermore, the interruption of retroviral treatment was previously described among individuals with SUD (McNeil et al., 2017). Altogether, this scenario illustrates important clinical vulnerabilities and higher susceptibility to infections among individuals with addiction.

Individuals with SUD, especially cocaine/crack users, show higher rates of mental and physical health problems (Santos Cruz et al., 2013). Emotional symptoms, such as fear, loneliness, anxiety, stress, and sadness, might be intensified during the quarantine (Brooks et al., 2020), leading to negative impacts in the lifestyle routine. Especially in the surrounding environment, and possibly substance use and substance use disorders related to the use of multiple substances – cocaine/crack and alcohol. Respiratory: respiratory problems or tuberculosis; Homelessness: having spent nights on the streets or in shelters within the last 5 months; Cardiac and chronic kidney disease: presence of any cardiac or kidney problem. A-B-C-D distinct letters indicate statistically significant differences.

In summary, there are three main points in this study: a) people who use substances have more risk factors for COVID-19 than the general population; b) they are more prone to complex clinical conditions, associated with worse prognoses and possibly higher morbimortality by the virus; c) since the literature shows that the emotional effects of the pandemic and the quarantine (or lockdown) may intensify the use of alcohol or other substances, as well as relapse, this study suggests that the surrounding environment, and possibly substance use and substance use seeking might increase the risk for infection by physical contact. To this, we add the increased risk due to sharing drug paraphernalia between users of substances such as crack. Neglecting specific characteristics and risks of this population may contribute to the collapse of the health system and impact other areas such as public safety. Therefore, prevention strategies directed at specific characteristics of substance users merit particular attention during the pandemic.

Table 1
Prevalence (95% CI) of risk factors for COVID-19 in individuals with substance use disorder.

|                          | Total n=821 | Alcohol n=305 | Cocaine/Crack n=233 | Multiusers n=283 |
|--------------------------|-------------|---------------|----------------------|-----------------|
| Nicotine dependence      | 82.5 (79.7-85.0) | 80.7 (75.8-84.9) | 83.7 (78.3-88.2) | 83.4 (78.5-87.5) |
| High blood pressure      | 26.6 (23.6-29.7) | 38.0 (32.6-43.7) | 12.9 (8.9-17.9) | 25.4 (20.5-30.9) |
| Homelessness*            | 25.1 (22.8-28.2) | 15.4 (11.5-20.0) | 28.4 (22.6-34.7) | 25.8 (24.7-38.7) |
| Respiratory*             | 23.4 (20.3-26.4) | 23.3 (18.7-28.4) | 21.2 (16.1-27.1) | 25.2 (20.3-30.7) |
| HIV                      | 7.3 (5.6-9.3) | 3.7 (1.9-6.5) | 7.1 (4.1-11.8) | 11.4 (7.9-15.7) |
| Cardiac disease*         | 6.7 (5.1-8.6) | 11.5 (8.1-15.0) | 3.9 (1.8-7.2) | 3.9 (2.0-6.9) |
| Age > 60 years           | 6.3 (4.8-8.2) | 15.7 (11.8-20.3) | 0 (0-1.6) | 1.4 (0.4-3.6) |
| Diabetes                 | 5.7 (4.2-7.6) | 7.9 (5.1-11.5) | 3.9 (1.8-7.2) | 4.9 (2.7-8.1) |
| Cirrhosis                | 4.4 (3.1-6.1) | 7.9 (5.1-11.6) | 0.9 (0-1.3) | 3.5 (1.7-6.4) |
| Chronic kidney disease*  | 3.6 (2.4-5.1) | 3.6 (1.8-6.4) | 2.1 (0.7-4.9) | 4.6 (2.5-7.7) |

Data shown as % (95% confidence interval). *Includes individuals with disorders related to the use of multiple substances – cocaine/crack and alcohol. Respiratory: respiratory problems or tuberculosis; Homelessness: having spent nights on the streets or in shelters within the last 5 months; Cardiac and chronic kidney disease: presence of any cardiac or kidney problem. A-B-C-D distinct letters indicate statistically significant differences.

reached 11.4%) found in our study is another important point to be discussed. In Brazil, the estimated prevalence of HIV is 0.4% (Pereira et al., 2019; Swarczwalder et al., 2016). The occurrence of HIV is associated with a substantial imbalance in the immune system, especially regarding CD4+ T cells. Furthermore, the interruption of retroviral treatment was previously described among individuals with SUD (McNeil et al., 2017). Altogether, this scenario illustrates important clinical vulnerabilities and higher susceptibility to infections among individuals with addiction.

Individuals with SUD, especially cocaine/crack users, show higher rates of mental and physical health problems (Santos Cruz et al., 2013). Emotional symptoms, such as fear, loneliness, anxiety, stress, and sadness, might be intensified during the quarantine (Brooks et al., 2020), leading to negative impacts in the lifestyle routine. Especially in individuals with SUD, the management of negative emotions and feelings may be impaired, followed by substance use and relapse (Kelly et al., 2016; Serafini et al., 2016; Sinha et al., 2009). In the United States, for example, there has been an increase in marijuana sales after the onset of the quarantine (Levin, 2020). Individuals can also break through the isolation and go in search of substances, increasing the risk of contamination or even becoming potential vectors of transmission. Despite their numerous vulnerabilities (Halpern et al., 2017), this population faces barriers to access the health system, even in primary care (McNeil et al., 2017). Moreover, around 25% of our sample was homeless recently, being exposed to greater risk situations for infectious diseases, and having less support and access to preventive health measures.

According to substance use. *Frequency of 1 or 2 factors differs between alcohol and cocaine/crack users (p = 0.035) **Three or more risk factors differs between alcohol and cocaine/crack users (p = 0.005)
CRediT authorship contribution statement

D. Benzano: Conceptualization, Writing – original draft, Methodology, Formal analysis. Felipe Ornell: Conceptualization, Writing – original draft. Jaqueline Bohrer Schuch: Conceptualization, Data curation, Writing – review & editing. Flavio Pechansky: Writing – review & editing, Resources. Anne Orgler Sordi: Writing – review & editing. Lisia von Diemen: Writing – review & editing, Resources. Felix Henrique Paim Kessler: Conceptualization, Writing – review & editing, Resources. Supervision.

Declaration of Competing Interest

None

References

Arcadepani, F.B., Tardelli, V.S., Fidalgo, T.M., 2020. The SARS-CoV-2 threat in Cracovia, an open-air drug use scene in Brazil. Int. J. Drug Policy. https://doi.org/10.1016/j.drugpo.2020.102835.

Blackstone, S.R., Herrmann, L.K., 2016. Relationships between illicit drug use and body mass index among adolescents. Health Educ. Behav. 43 (1), 21–24. https://doi.org/10.1177/1090198115597941.

Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., GBD 2016 Alcohol and Drug Use Collaborators., 2018. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry 5 (12), 987–1012. https://doi.org/10.1016/S2215-6701(16)30337-7.

Cook, D.J., Marshall, J.C., Fowler, R.A., 2020. Critical illness in patients with COVID-19: mounting an effective clinical and research response. JAMA. https://doi.org/10.1001/jama.2020.5775.

de Carvalho, J.R., Portugal, F.B., Flor, S.L., Campos, R.M., Schramm, J.M.A., 2020. Method for estimating the prevalence of chronic hepatitis B and C and cirrhosis of the liver in Brazil, 2008. Epidemiol. e Saude Serv. 23, 9. https://doi.org/10.5123/S1679-47942014000400011.

GDB 2016 Alcohol and Drug Use Collaborators., 2018. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry 5 (12), 987–1012. https://doi.org/10.1016/S2215-6701(16)30337-7.

Godoy, P., Castillo, J., Soldevila, N., Mayoral, J.M., Toledo, D., Martin, V., Astray, J., Arcadepani, F.B., Tardelli, V.S., Fidalgo, T.M., 2020. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Med. J. Hosp. Infect. 103 (3), 319–326. https://doi.org/10.1016/j.infect.2020.01.003.

Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., Cereda, D., Grassi, G., Fumagalli, R., Keim, R., Rona, R., Valsecchi, R., Cattaneo, S., Colombo, S., Cirri, S., Filippi, G., Castelli, G., Aldegheri, G., Gallioli, G., Lotti, G., Albano, G., Landoni, G., Barbara, E., Beretta, E., Boselli, E., Storti, E., Harizay, F., Della, M.F., Lorini, F.L., Antonini, B., Capra, C., Troiano, C., Roscitano, C., Radrizzani, D., Chiumello, D., Yu, H., Hui, D., Liu, H., Jin, X., Zhang, J., Liu, F., Yang, R., Wang, L., Huang, H., Yang, B., Huang, C., 2020. Association with substance use disorders in Brazil: results from the National Survey on Access, Utilization, and Promotion of Rational Use of Medicines in Brazil (PRAMUS). 2014. Cad. SaúdePublica 34 (10), https://doi.org/10.1590/1980-5497201400208217.

Levin, D. 2020. Is Marijuana an ‘Essential’ Like Milk or Bread? Some States Say Yes. https://www.nytimes.com/article/coronavirus-weed-marijuana.html. The New York Times.

Li, X., Jiao, X., Yang, X., Gao, P., 2019. Diabetes mellitus and risk of hepatic fibrosis/ cirrhosis. BioMed Res. Int. https://doi.org/10.1155/2019/5308308, 2019.

Liu, W., Tao, Z.W., Wang, L., Yuan, M.L., Liu, K., Zhou, L., Wei, S., Deng, Y., Liu, J., Liu, H.G., Ming, Y., Yi, H., 2021. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Clin. Med. J. https://doi.org/10.1016/j.clinmed.2020.03.013.

Malta, D.C., Shibuya, S., Sabariego, C., Adachi, J., 2018. Health care in adults with self-reported hypertension in Brazil according to the National Health Survey, 2013. Rev. Bras. Epidemiol. 18 (Suppl 2) https://doi.org/10.2427/1518.00280315.

Malta, D.C., Vieira, M.L., Sabariego, C., Caiet, R., Brito, S.M., Dos-Reis, A.A., 2015b. Smoking trends among Brazilian population - National Household Survey, 2008 and the National Health Survey, 2013. Rev. Bras. Epidemiol. 18 (Suppl 2) https://doi.org/10.2427/1518.00280315.

McNeil, R., Kerr, T., Coleman, B., Maher, L., Milloy, M.J., Small, W., 2017. Antiretroviral therapy interruption among HIV positive people who use drugs in a setting with a community-wide HIV treatment-as-prevention initiative. AIDS Behav. 21 (2), 402–409. https://doi.org/10.1007/s10461-016-1470-2.

Mesa Vieira, C., Franco, O.H., Gómez Restrepo, C., Abel, T., 2020. COVID-19: the forgotten priorities of the pandemic. Maturitas 136, 38-41. https://doi.org/10.1016/j.maturitas.2020.04.004.

Meyerholz, D.K., Edsen-Moore, M., McGill, J., Coleman, R.A., Cook, R.T., Legge, K.L., 2010. Negative affect, depressive symptoms, and susceptibility to the common cold. Am. J. Public Health 83 (9), 1282–1288. https://doi.org/10.2105/AJPH.2010.195617.

Serafini, K., Toohey, M.J., Kiluk, B.D., Carroll, K.M., 2016. Anger and its association with HIV risk behaviors among African American and HIV-negative young adults: an online assessment study. Publica 34 (10), https://doi.org/10.3848/P.2237-6089-2016-0076.

Leal, L.F., Bertoldi, A.D., Menezes, A.M.B., Borges, R.B., Mengue, S.S., Gazzana, M.B., Pizzol, T.D.S.D.O.S., 2018. Indications, access, and use of medicines for chronic respiratory diseases in Brazil: results from the National Survey on Access, Utilization, and Promotion of Rational Use of Medicines in Brazil (PRAMUS). 2014. Cad. Saúde Publica 34 (10), https://doi.org/10.1590/1980-5497201400208217.

Leal, F., Bertoldi, A.D., Menezes, A.M.B., Borges, R.B., Mengue, S.S., Gazzana, M.B., Pizzol, T.D.S.D.O.S., 2018. Indications, access, and use of medicines for chronic respiratory diseases in Brazil: results from the National Survey on Access, Utilization, and Promotion of Rational Use of Medicines in Brazil (PRAMUS). 2014. Cad. Saúde Publica 34 (10), https://doi.org/10.1590/1980-5497201400208217.

Leal, F., Bertoldi, A.D., Menezes, A.M.B., Borges, R.B., Mengue, S.S., Gazzana, M.B., Pizzol, T.D.S.D.O.S., 2018. Indications, access, and use of medicines for chronic respiratory diseases in Brazil: results from the National Survey on Access, Utilization, and Promotion of Rational Use of Medicines in Brazil (PRAMUS). 2014. Cad. Saúde Publica 34 (10), https://doi.org/10.1590/1980-5497201400208217.
hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 5 (7) https://doi.org/10.1001/jamacardio.2020.0950.

Sinha, R., Fox, H.C., Hong, K.A., Bergquist, K., Bhagwagar, Z., Siedlarz, K.M., 2009. Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. Neuropsychopharmacology 34 (5), 1198–1208. https://doi.org/10.1038/npp.2009.78.

Souza, S.P.O., Mascarenhas, M.D.M., Silva, M.C.B., Almeida, R.A.M., 2012. Knowledge about mandatory notifiable diseases among professionals of Family Health Strategy in the municipality of Teresina, state of Piauí, Brazil - 2010. Epidemiol. Serv. Saude 21, 9. https://doi.org/10.5123/S1679-49742012000300012.

Stubbs, M.A., Morgan, M.Y., 2011. Managing alcohol dependence and alcohol-related liver disease: a problem for the hepatologist, psychiatrist or economist? Clin. Med. 11 (2) https://doi.org/10.7861/clinmedicine.11-2-189.

Sureshchandra, S., Raus, A., Jankeel, A., Ligh, B.J.K., Walter, N.A.R., Newman, N., Grant, K.A., Messaoudi, I., 2019. Dose-dependent effects of chronic alcohol drinking on peripheral immune responses. Sci. Rep. 9 (1) https://doi.org/10.1038/s41598-019-44302-3, 7847–7847.

Varga, Z.V., Ferdinandy, P., Lianudet, L., Pscher, P., 2015. Drug-induced mitochondrial dysfunction and cardiotoxicity. American journal of physiology. Heart and circulatory physiology 309 (9). https://doi.org/10.1152/ajpheart.00564.2015.

Volkow, N, 2020. COVID-19: Potential Implications for Individuals with Substance Use Disorders. NIDA.

Volkow, N.D., Kaelber, D.C., Xu, R., Volkow, N.D., 2021. Correction: COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. Mol. Psychiatry 26 (1), 40. https://doi.org/10.1038/s41380-020-00895-0.

WHO, 2018. Global Status report on Alcohol and Health 2018. World Health Organization. WHO, 2020. World Drug Report 2020. W. H. Organization. //wdr.unodc.org/wdr2020/en/press.html.

Williamson, E.J., Walker, A.J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C.E., Curtis, H.J., Mehrkar, A., Evans, D., Inglesby, P., Cockburn, J., McDonald, H.I., Mackenna, B., Tomlinson, L., Douglas, I.J., Rentch, C.T., Mathur, R., Wong, A.Y.S., Grieve, R., Harrison, D., Forbes, H., Schultz, A., Croker, R., Parry, J., Hester, F., Harper, S., Perera, R., Evans, S.J.W., Smeeth, L., Goldacre, B., 2020. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature. https://doi.org/10.1038/s41586-020-2521-4.

Zaparte, A., Schuch, J.B., Viola, T.W., Baptista, T.A., Beidacki, A.S., do Prado, C.H., Sanvicente-Vieira, B., Bauer, M.E., Grani-Oliveira, R., 2019. Cocaine use disorder is associated with changes in Th1/Th2/Th17 cytokines and lymphocytes subsets. Front. Immunol. 10 https://doi.org/10.3389/fimmu.2019.02435.