Psychiatric patient profiling during the COVID-19 pandemic – should schizophrenia be assigned among risk factors?

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ABSTRACT

Objective. While the identification of vulnerable groups is critical in any pandemic, scarce information has been published on COVID-19 patients with underlying psychiatric comorbidities. The present study aimed to assess whether a pre-existing diagnosis of schizophrenia represents an independent risk factor for severe COVID-19 and whether patients with schizophrenia have poorer outcomes of COVID-19 compared to patients with any other premorbid mental illness.

Methods. The present data derives from the medical records of 242 patients admitted to “Prof. Dr. Alexandru Obregia” Clinical Psychiatry Hospital (Bucharest, Romania), Department 9, with a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result between October 2020 and May 2021.

Results. 128 (52.9%) of the patients were diagnosed with a schizophrenia spectrum disorder. Psychiatric patients who developed a severe form of infection were older and more likely to have relevant somatic comorbidities for COVID-19, compared to the rest of the patients in the study sample (p<0.001). We did not identify a significant association between a particular psychiatric diagnosis and a severe form of infection (p>0.005), with only a small proportion (12.5%) of patients with a diagnosis of schizophrenia spectrum disorder having developed a severe form of infection.

Conclusion. Although a pre-existing diagnosis of schizophrenia spectrum disorder was not associated with severe forms of COVID-19, patients with schizophrenia spectrum disorders represented more than half of the population in our study, a finding that supports the higher risk of infection for this group and suggests that these patients should be considered a vulnerable population.

Keywords: COVID-19, SARS-CoV-2, coronavirus, schizophrenia, psychosis, risk factors

INTRODUCTION

Few phenomena shaped societies and cultures the way pandemics have shaped them throughout history [1]. In March 2020, the World Health Organization declared the novel Coronavirus disease 2019 (COVID-19) outbreak to be a pandemic [2]. In the weeks that followed, strict public policies (social distancing, confinement measures) have been adopted to restrict population movement, contain infection transmission, and protect vulnerable populations, such as people with chronic conditions or the elderly [3-8].

Furthermore, a critical stage as a means of managing the pandemic was the identification of high-risk groups to establish preventive strategies [9-11]. Despite a considerable variation between studies - older age, male sex, smoking status, socioeconomic deprivation, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), neoplasia, obesity, diabetes and chronic kidney disease (CKD) appeared to be consistently associated with a higher risk of severe COVID-19 and high mortality rates [8,11-15].

Most studies regarding the clinical and epidemiologic characteristics of COVID-19 have been carried
out in the general population and scarce information has been published on COVID-19 patients with underlying psychiatric comorbidities [16]. However, several cohort studies in the US reported that patients with a premorbid diagnosis of a mental disorder, especially a diagnosis of schizophrenia spectrum disorder, had a significantly higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as well as higher mortality rates in comparison with patients without a mental health diagnosis and COVID-19 [16-19]. This association may be attributable not only to the increased prevalence of comorbidities associated with COVID-19 severity (diabetes, CVD, COPD) in patients with schizophrenia, compared to the general population [20-23], but also to specific vulnerability of patients diagnosed with schizophrenia.

Taking the foregoing findings into account, we hypothesised that a premorbid diagnosis of a schizophrenia spectrum disorder represents an independent risk factor for severe COVID-19 and patients with schizophrenia spectrum disorders have poorer outcomes from SARS-CoV-2 infection compared to patients with other pre-existent mental illness. We also wanted determine whether the common risk factors for severe SARS-CoV-2 infection identified in the general population remain the same for patients with psychiatric comorbidities.

**PATIENTS AND METHODS**

This retrospective observational study was performed in "Prof. Dr. Alexandru Obregia" Clinical Psychiatric Hospital (Bucharest, Romania). The present data derives from the medical records of the 242 patients admitted to Department 9 of the hospital with a positive SARS-CoV-2 test result between 14th October 2020 and 24th May 2021. A confirmed case of COVID-19 was defined as a positive result in reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab samples. For all included patients, diagnoses were recorded according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10) classification criteria [23]. Data collected included patient demographic information, underlying comorbidities, clinical information regarding the COVID-19 infection (signs and symptoms), laboratory parameters, radiological characteristics, inpatient medication and treatment, including supplemental oxygen requirements. Furthermore, data on the duration of hospitalization were examined. Clinical outcomes were monitored until discharge.

The 242 confirmed cases of COVID-19 were further categorized by severity as asymptomatic, mild, moderate and severe. An asymptomatic case was defined by a patient with a positive RT-PCR and no signs/symptoms of COVID-19; a mild case by non-specific signs or symptoms of COVID-19, but normal chest radiograph and no dyspnoea. Signs and symptoms presence of COVID-19 pneumonia (but with oxygen saturation levels maintained above 94%) defined a moderate case. A severe case was defined as including at least one of the following criteria: respiratory rate greater than 30/min, oxygen saturation values lower than 93%, or pulmonary infiltrates in more than 50% of the pulmonary area.

We described the characteristics of COVID-19 patients belonging to each of the four groups. Categorical variables are presented as counts and percentage. Continuous variables are presented as mean and interval. For testing group differences, the Chi-square test was used for categorical variables and the ANOVA test for continuous variables of normal distribution. Data analysis was performed using SPSS 27 package (IBM Corp.). The level of statistical significance was established at P<0.05 (two-sided).

Approval for this study was obtained from the Ethics Committee of "Prof. Dr. Alexandru Obregia" Clinical Psychiatric Hospital (approval number 71/24.09.2021).

**RESULTS**

Of the 242 patients included in this study, 128 patients (52.9%) had a diagnosis from the schizophrenia spectrum. The psychiatric disorders diagnosed in the study population are shown in Table 1.

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia spectrum disorders</td>
<td>128 (52.9%)</td>
</tr>
<tr>
<td>Acute and transient psychotic disorders</td>
<td>32</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>79</td>
</tr>
<tr>
<td>Persistent delusional disorders</td>
<td>9</td>
</tr>
<tr>
<td>Schizoaffective disorders</td>
<td>8</td>
</tr>
<tr>
<td>Affective disorders</td>
<td>62 (25.61%)</td>
</tr>
<tr>
<td>Recurrent depressive disorder</td>
<td>37</td>
</tr>
<tr>
<td>Bipolar affective disorder</td>
<td>25</td>
</tr>
<tr>
<td>Dementia</td>
<td>28 (11.57%)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>6</td>
</tr>
<tr>
<td>Substance use disorders</td>
<td>8</td>
</tr>
<tr>
<td>Personality disorders</td>
<td>7</td>
</tr>
<tr>
<td>Acute stress reaction/ adjustment disorders</td>
<td>3</td>
</tr>
<tr>
<td>All psychiatric disorders</td>
<td>242 (100%)</td>
</tr>
</tbody>
</table>
Of the 242 patients admitted to our department, 72 (29.76%) patients were asymptomatic, 73 (30.15%) developed a mild form of COVID-19, 49 (20.24%) developed a moderate form and in 48 cases (19.9%) the infection advanced to a severe form. The sociodemographic and clinical profile of the study population is given in Table 2. Patients in the asymptomatic group were the youngest (mean age 43.8 years), while patients in the severe group were the oldest (mean age 66 years). Differences in age between groups were statistically significant (F(3,236)= 23.17, p<0.001).

Most of the patients diagnosed with schizophrenia spectrum disorders belonged to the asymptomatic and mild form group (36% and 32%, respectively). Only a small proportion (12.5%) developed a severe form of infection. We did not identify a significant association between a particular psychiatric diagnosis and a severe form of infection.

Patients in the severe form group were more likely to have relevant somatic comorbidities for COVID-19 than the other groups, and 73% of patients with severe SARS-CoV-2 infection had at least one risk factor, such as diabetes mellitus, cardiovascular disease, pulmonary disease or obesity.

Compared to patients in the asymptomatic, mild or moderate form groups, the values of lactate dehydrogenase (LDH) and CRP were significantly elevated for patients with severe symptoms (F(3,215)=14.9, p<0.001 and F(3,213)=13.2, p<0.001, respectively). Furthermore, the lymphocyte count decreased significantly in the severe symptoms group (F(3,233)=11.1, p<0.001), while the neutrophil count was significantly elevated (F(3,233)=2.87, p=0.037), compared to patients with milder forms of infection. Paraclinical characteristics of each of the 4 groups of patients are summarized in Table 3.

### TABLE 2. Demographic and clinical characteristics of the study sample

<table>
<thead>
<tr>
<th>Severity of the COVID-19 disease</th>
<th>Asymptomatic infection N=72 (29.76%)</th>
<th>Mild N=73 (30.15%)</th>
<th>Moderate N=49 (20.24%)</th>
<th>Severe N=48 (19.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 34 (47.2%) 33 (45.2%) 26 (53.1%) 13 (27.1%)</td>
<td>Female 38 (52.8%) 40 (54.8%) 23 (46.9%) 35 (72.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean (Range) 43.8 (20-85) 45.4 (21-88) 53.2 (21-93) 66 (20-93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>Schizophrenia spectrum disorders 46 (63.9%) 41 (56.2%) 25 (51%) 16 (33.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective disorders</td>
<td>15 (20.9%) 20 (27.4%) 13 (26.5%) 14 (29.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>3 (4.1%) 6 (8.2%) 6 (12.2%) 13 (27.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other mental disorders</td>
<td>8 (11.1%) 6 (8.2%) 5 (12.2%) 5 (10.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic comorbidities</td>
<td>25 (34.7%) 31 (42.4%) 21 (42.8%) 35 (73%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (8.3%) 6 (8.2%) 2 (4.1%) 7 (14.6%)</td>
<td></td>
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</tr>
<tr>
<td>Cardiovascular disease</td>
<td>13 (18%) 20 (27.4%) 15 (30.6%) 24 (50%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0 (0%) 1 (1.3%) 2 (4.1%) 2 (4.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>2 (2.8%) 4 (5.5%) 2 (4.1%) 6 (12.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2 risk factors</td>
<td>5 (6.9%) 6 (8.2%) 2 (4.1%) 13 (27.1%)</td>
<td></td>
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</tr>
</tbody>
</table>

LDH = lactate dehydrogenase normal range = 125-220 U/L; CRP = C-reactive protein normal range=0-5 mg/L; lymphocyte count normal range = 1.5-4.5 x10⁹ /L; neutrophil count normal range = 2.0-8.0 x10⁹ /L

### TABLE 3. Paraclinical characteristics of the study sample

<table>
<thead>
<tr>
<th>Severity of the COVID-19 disease</th>
<th>Asymptomatic infection N=72 (29.76%)</th>
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<th>Severe N=48 (19.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory parameters</td>
<td>Mean LDH value (LDH range)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean LDH value (LDH range)</td>
<td>218.3 (95-690) U/L</td>
<td>204.4 (114-444) U/L</td>
<td>270.4 (130-700) U/L</td>
<td>327 (154-606) U/L</td>
</tr>
<tr>
<td>Mean CRP value (CRP range)</td>
<td>12 (18-115) mg/L</td>
<td>16 (13-217) mg/L</td>
<td>29.2 (22-194) mg/L</td>
<td>53.3 (30-294) mg/L</td>
</tr>
<tr>
<td>Lymphocyte count mean value</td>
<td>2.16 (0.45-4.7) x10^9/L</td>
<td>1.85 (0.32-3.8) x10^9/L</td>
<td>1.57 (0.27-5.9) x10^9/L</td>
<td>1.21 (0.27-3.2) x10^9/L</td>
</tr>
<tr>
<td>Neutrophil count mean value</td>
<td>4.0 (0.78-14.35) x10^9/L</td>
<td>3.75 (0.68-13.36) x10^9/L</td>
<td>4.9 (0.5-14.7) x10^9/L</td>
<td>4.96 (0.95-17.1) x10^9/L</td>
</tr>
</tbody>
</table>
DISCUSSION

In our study, about half (52.9%) of the patients with a previous psychiatric disorder that were included had a schizophrenia spectrum disorder. This result supports the hypothesis that patients with a schizophrenia spectrum disorder have an increased susceptibility to SARS-CoV-2 infection compared to other mental disorders. Evidence from a meta-analysis conducted by Vai et al. [24], which included 23 studies, showed that patients with any premorbid mental disorder had a higher risk of SARS-CoV-2 infection than the general population. However, other studies indicated that among patients diagnosed with mental illness, those with a schizophrenia spectrum disorder have the highest risk of COVID-19: Ji et al. [25] found an increased risk of COVID-19 in patients with schizophrenia (odds ratio range (ORR), 1.614–1.721) and Wang et al. [26] reported that patients with a diagnosis of schizophrenia have significantly higher odds of COVID-19 infection after adjusting for possible confounders (adjusted odds ratio (AOR), 7.34, 95% CI: 6.65–8.10, p < 0.001). A large retrospective cohort study found that schizophrenia spectrum disorders might be an independent risk factor for SARS-CoV-2 infection (risk ratio (RR), 1.17, 95% CI: 1.02–1.33, p = 0.022) [17].

Many studies support the hypothesis that schizophrenia patients have a high vulnerability to COVID-19 and that a pre-existing diagnosis of schizophrenia spectrum disorder is associated with poor outcomes of COVID-19 [24,27,28]. Schizophrenia spectrum disorders appear to be significantly associated with mortality (OR, 2.67, 95% CI: 1.48-4.80) after adjusting for confounding factors, while no association was found between diagnoses of mood disorders or anxiety disorder and COVID-19 related mortality [16]. A case-control study found that patients with schizophrenia spectrum disorders are 1.3 times more likely to develop a severe form of SARS-CoV-2 infection and to have poor outcomes, such as invasive ventilation, admission to intensive care unit or death (AOR, 1.3, 95% CI: 1.0–1.7) [26], findings that were supported by other cohort studies [18,19]. Another case-control study showed that schizophrenia was associated with severe forms of COVID-19 after adjusting for other prognostic factors (ORR, 1.206–1.645) [25].

Patients with schizophrenia spectrum disorder have a low socioeconomic status, defined by homelessness or living in congregate housing or long-term care facilities, lack of a social support network and financial difficulties, making them more vulnerable to viral or bacterial infections due to inadequate infection control [29–31]. Other factors that can increase the vulnerability of these patients to infection are represented by cognitive impairment, leading to scarce adaptive social interactions, low risk assessment capacity, non-compliance with protective measures and the presence of delusions, which can interfere with acceptance of the SARS-CoV-2 existence [30,32].

Once infected with SARS-CoV-2, patients with schizophrenia spectrum disorders are believed to be at risk of a poor outcome of COVID-19. Firstly, they have limited access to healthcare services and face communication difficulties with health care providers due to prejudice, stigma and structural discrimination of this psychiatric population, therefore these patients are inclined to have more undiagnosed or untreated disorders and their COVID-19 symptoms tend to be identified later than in the general population [33,34].

Secondly, smoking status, present in 60 to 90% of patients with schizophrenia spectrum disorders, increases the risk of severe respiratory complications from COVID-19 [35-37].

Thirdly, patients with schizophrenia spectrum disorders have poorer physical health, with two to three times higher mortality rate than the general population due to frequent physical comorbidities (obesity, diabetes, CVD, COPD) and a life expectancy 10-20 years lower than the general population [38,39]. Furthermore, adverse effects of medication, such as metabolic syndrome, weight gain, and increased activity in the coagulation system, are associated with chronic treatment with second-generation antipsychotics. These side effects are cited as a risk factor for severe COVID-19 [40-42]. Clozapine-treated patients appear to have higher rates of COVID-19 infection and pneumonia than those treated with other antipsychotics [43,44]. This might be explained by alterations in both the innate and adaptive immune system associated with chronic treatment with clozapine and by hypersalivation, a side effect of clozapine that increases the risk of aspiration pneumonia [43-45].

Patients with schizophrenia spectrum disorders have high susceptibility to stress and anxiety due to social isolation during the pandemic [46,47] and studies have reported that stress upregulates proinflammatory cytokines [48-50]. Moreover, patients with schizophrenia have an imbalanced immune system with an already existing upregulation of pro-inflammatory cytokines, particularly high levels of interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), growth differentiation factor 15 (GDF-15) and C-reactive protein (CRP) [32,49-51]. The dysregulation of the immune system pre-existent in these patients may lead to a more severe SARS-CoV-2 infection in this population [32].

However, we found no robust evidence to demonstrate the association of a diagnosis of schizophrenia spectrum disorder with a severe outcome of COVID-19 in our sample. This may be explained by the fact that the population sample consisted of psychiat-
ric inpatients, but also by the fact that in our study the patients with a schizophrenia spectrum disorder were younger and had low rates of somatic comorbidities. Furthermore, no association was found between any psychiatric diagnosis and the severity of the SARS-CoV-2 infection.

Most of the patients in our sample were represented by women, a finding consistent with another study that found that female patients with mental illness have higher odds of COVID-19, compared to male patients [26]. Surprisingly, most of the patients in the severe group were also women, although all studies support the male sex as a risk factor for severe infection [8,11-14]. This result may be due to the small sample size studied. Compared to patients with milder forms of SARS-CoV-2 infection, patients in the severe form group were significantly older and had a higher proportion of somatic comorbidities, particularly obesity, diabetes and CVD, which was consistent with the findings of other studies [8,11-15,52].

Regarding laboratory data, patients with a severe form of COVID-19 had significantly higher LDH and CPR values than the other patients, significantly elevated neutrophil count and significantly decreased lymphocyte count, compared to patients with a milder symptom profile. These findings were consistent with previous studies [52-55].

Based on the clinical and paraclinical characteristics of the severe form group, our study showed that important negative prognostic factors of the outcome in patients with COVID-19 remain older age, the presence of somatic comorbidities and laboratory values - high blood levels of CRP, LDH, elevated neutrophil count and decreased lymphocyte count.

LIMITATIONS

The statistical power of the study may be reduced by the small size of the population sample. Another limitation of the study may be caused by the fact that the population studied was restricted to psychiatric inpatients. Patients with a prior psychiatric diagnosis and a stable illness course who acquired SARS-CoV-2 infection may have been hospitalized in a coronavirus specialized clinic from our area.

CONCLUSIONS

In our study, a pre-existing diagnosis of schizophrenia spectrum disorder was not associated with severe forms of COVID-19. However, patients with schizophrenia spectrum disorders represented more than half of the population in our study, a finding that supports the higher risk of infection for this group. In conclusion, psychiatric patients, especially those diagnosed with a severe mental disorder, such as schizophrenia spectrum disorder, should be considered a vulnerable population. Designing and implementing preventive quality strategies, such as including this population in the vaccination priority group, should be crucial for the authorities. Furthermore, limited access to healthcare for this population should be prevented by close monitoring, from family to primary care physician and psychiatrist and by social integration strategies.

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