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Psychiatric symptoms before and after COVID-19 vaccination: A cohort study of hospitalized schizophrenia patients

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ABSTRACT
This study aimed to examine the impact of COVID-19 vaccination on the psychiatric symptoms of hospitalized schizophrenia patients and to evaluate the association between the severity of psychiatric symptoms and the COVID-19 vaccination decision. We assessed the psychiatric symptoms of 330 hospitalized schizophrenia patients who accepted the vaccine and 114 patients who declined the vaccine option with PANSS before and after vaccination. We showed that the unwillingness to receive the vaccine is correlated with a higher level of psychiatric symptoms. COVID-19 vaccination is associated with slight deterioration of the schizophrenia symptoms of elderly hospitalized patients.

1. Introduction
The COVID-19 pandemic has become a serious problem worldwide. Undoubtedly, bringing vaccines to the COVID-19 vulnerable people is important to increase population immunity. Schizophrenia is associated with higher chance of infection (Mohan et al., 2021; Tzur Bitan et al., 2021; Vai et al., 2021), and has been identified as the second greatest risk factor for COVID-19 death (Nemani et al., 2021). In particular, hospitalized schizophrenia patients are at high risk for acquiring and transmitting COVID-19 (Benson et al., 2020; Li, 2020; Zhu et al., 2020). A consensus view is that people with schizophrenia should be prioritized for the COVID-19 vaccine (De Hert et al., 2021; Mazereel et al., 2021; Siva, 2021). Nevertheless, schizophrenia patients are known to be less likely to make a vaccination decision (Arumuham et al., 2022; Raffard et al., 2022; Samaali et al., 2022; Tzur Bitan, 2021). Conceivably, the unwillingness to receive vaccination should exaggerate the risk of COVID-19 among the schizophrenia.

Although it has been established that schizophrenia patients have a higher risk for severe COVID-19, little is known about the effect of COVID-19 vaccination on psychiatric symptoms. Additionally, there is limited information on how psychiatric symptoms are associated with the COVID-19 vaccine decision within the schizophrenia population. This study aims to investigate the impact of COVID-19 vaccination on the psychiatric symptoms of hospitalized patients with schizophrenia and the relationship between the severity of psychiatric symptoms and willingness to take the vaccine.

2. Methods
Sampling of the research consisted of 475 hospitalized patients from Tianjin Jianhua Hospital. All the participants were diagnosed with schizophrenia according to ICD-10. Patients with intellectual disability and comorbidity of personality disorder or drug/alcohol dependence were excluded. Among the hospitalized patients, 353 accepted the vaccine offers, and 122 declined the offers. A total of 23 patients in the vaccinated group and 8 in the unvaccinated group were discharged from the hospital during the study. These patients were excluded from the analyses. Psychiatric symptoms of the hospitalized patients were assessed by trained psychiatrists using the Positive and Negative Syndrome Scale (PANSS) twice: once at baseline and once one-month post-vaccination.

All the patients and their guardians were informed about the possible side effects of the COVID-19 vaccine. SARS-CoV-2 Vaccine (Wang et al., 2020) manufactured by Sinopharm was administrated by intra-muscle injection. The vaccine is free of charge.

All the statistical analyses were performed using IBM SPSS v20.0. To
compare the demographic and clinical characteristics, we used unpaired t-test and Chi-square test. We used the Wilcoxon Signed-Rank test to compare the PANSS scores before and after the vaccination because the difference between the paired PANSS score is non-normally distributed.

3. Results

Demographic and clinical information is presented in Table 1. No participants developed an immediate allergic reaction within 2-hr post-vaccination. None of the patients in either group was infected with the COVID-19 virus during this study.

Group comparisons indicated that vaccination refusal was related to the higher baseline level of psychotic symptoms (p = 0.01, Cohen’s d = 0.34). Further analysis suggests that both the negative and general psychopathology subscale scores significantly correlate with the likelihood of rejecting the vaccine offer among hospitalized schizophrenia patients (positive: Cohen’s d = 0.22, p = 0.035; general: Cohen’s d = 0.32, p = 0.002).

Next, we investigated if COVID-19 vaccination would have an impact on the psychiatric symptoms of the hospitalized patients. As shown in Table 2, the PANSS total, negative subscale, and general psychopathology subscale scores significantly increased after vaccination (total: p = 0.002; negative: p = 0.001; general: p = 0.004). However, the effect magnitude for the change is very small (total: Cohen’s d = 0.17; negative: Cohen’s d = 0.18; general: Cohen’s d = 0.17). Nevertheless, in the unvaccinated group, no significant difference was observed.

Given that the total PANSS score increased significantly after vaccination, we wondered if the change could be more prominent in a sub-population of the hospitalized patients. Interestingly, univariate regression analysis suggests that age is significantly associated with the change in PANSS scores in the vaccinated group but not the unvaccinated group. (Vaccinated: p = 0.02, r = 0.17; Unvaccinated: p = 0.72, r = 0.03) Thus, we divided the participants into two age groups. (Table 3).

Wilcoxon Signed-Rank test revealed that the PANSS scores were not significantly different after vaccination for the young sub-group within vaccinated patients. In contrast, the PANSS total, negative subscale and general psychopathology subscale scores for post-vaccination are significantly different from the baseline in the elder vaccinated subgroup (total: p < 0.001, Cohen’s d = 0.24; negative: p = 0.002, Cohen’s d = 0.24; general: p = 0.001, Cohen’s d = 0.28). The effect size became greater when we only considered elderly patients. These results indicate that elderly schizophrenia patients are more likely to be adversely affected by the vaccination. By comparison, there is no significant change in PANSS total and subscale scores for the unvaccinated patients in either of the two age groups.

4. Discussion

The COVID-19 pandemic has brought about severe social devastation and is associated with adverse mental health consequences (Tandon, 2021, 2022). Vaccines effectively curbed the spread of the virus and helped us move beyond the pandemic (Tandon, 2022), yet some populations may experience anxiety or fear related to receiving the vaccine (Chou and Budenz, 2020). Here, we examined the interrelation between COVID-19 vaccination and the psychiatric symptoms of hospitalized schizophrenia patients. Our results showed that the severity of psychiatric symptoms is correlated with the unwillingness to take the vaccine among hospitalized schizophrenia patients. We also found that the COVID-19 vaccination may slightly but significantly increase the PANSS scores of elderly schizophrenia patients.

Previous studies have shown that people with mental illness are under-vaccinated (Arunumham et al., 2022; Raffard et al., 2022; Samaali et al., 2022; Tzur Bitan, 2021). Herein, we conducted research specifically with hospitalized patients and reached a similar conclusion. Possible contributing factors to the under-vaccination of hospitalized patients may include impaired judgment, decreased foresight, low educational level, and fear or anxiety. All these factors are correlated with the severity of psychiatric symptoms.

Another interesting finding here is that the vaccination may trigger a slight deterioration of psychotic symptoms of hospitalized schizophrenia, especially for elderly patients. It is likely that the act of vaccine administration rather than the vaccine itself contributes to the increase in PANSS scores. Two possible explanations may account for this observation.

First, all the participants had been informed about the possible side effect prior to vaccination. The anticipation of the side-effect may result in a nocebo-like response that worsens the pre-existing psychiatric symptoms. Second, many of the participants in this study are long-term hospitalized psychiatric patients. Many of them simply took this hospital as an alternative to a mental health residential facility. Their social network was isolated, and their lives were not severely affected by the pandemic. The act of vaccination could be an external stressor reminding them about the pandemic and bringing anxiety or depression to them.

There are several limitations of this study. First, we did not include a placebo group who agreed to receive the vaccine but were given a placebo. Due to ethical considerations, the COVID-19 vaccine was administered to all who agreed to receive the vaccine. Second, we could not rule out the possibility that the vaccine may affect the medications. Third, the participants were recruited from a psychiatric hospital offering long-term inpatient care for elderly patients. The findings might be less applicable for participants from other hospitals.

This study has two implications. First, psychiatrists should fully understand the pros and cons of the COVID-19 vaccination and provide optimal guidance for schizophrenia patients. Second, psychiatrists should keep an eye on the psychotic status of elderly patients following

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Table 1

| Demographic and clinical information | Vaccinated patient (n = 330) Mean (SD) | Unvaccinated patient (n = 114) Mean (SD) | t / χ² (p value) |
|------------------------------------|---------------------------------------|----------------------------------------|-----------------|
| Age                               | 57.2 (10.0)                           | 59.1 (10.5)                            | -1.714 (0.087)  |
| Gender (%female)                  | 46.7 %                                | 51.8 %                                 | 0.879 (0.349)   |
| Duration of illness (years)       | 29.7 (10.6)                           | 31.4 (11.0)                            | -1.416 (0.158)  |
| Age of illness onset              | 27.4 (9.5)                            | 27.7 (9.7)                             | -0.227 (0.820)  |
| Medications                       |                                       |                                        |                 |
| Antipsychotics (%)                | 95.5 %                                | 93.9 %                                 | 0.458 (0.499)   |
| Antidepressants (%)               | 3.6 %                                 | 3.5 %                                  | 0.004 (0.950)   |
| Sedatives/Hypnotics (%)           | 46.7 %                                | 61.4 %                                 | 7.361 (0.007)   |
| Mood stabilizers (%)              | 14.8 %                                | 17.5 %                                 | 0.469 (0.495)   |
| Symptoms post vaccination         |                                       |                                        |                 |
| Cough or Sore throat              | 5.5 % (18 cases)                      | 3.5 % (4 cases)                        | 0.681 (0.409)   |
| Fever                             | 0.3 % (1 case)                        | 0 %                                    |                |
| Headache or Dizziness             | 0 %                                   | 0 %                                    |                |
| Baseline PANSS score              |                                       |                                        |                 |
| Total PANSS score                 | 63.8 (13.9)                           | 69.0 (16.2)                            | -3.304 (0.01)   |
| Positive subscale score           | 15.0 (5.2)                            | 16.2 (5.7)                             | -1.939 (0.053)  |
| Negative subscale score           | 18.6 (7.4)                            | 20.3 (7.4)                             | -2.117 (0.035)  |
| General psychopathology subscale  | 30.1 (6.3)                            | 32.51 (8.5)                            | -3.152 (0.002)  |

* Unpaired Student’s t-test for quantitative variables and Chi-square test for categorical variables. Significant p-values were highlighted in bold.
Table 2
Comparison of the Positive and Negative Symptoms subscale scores (PANSS) before and after vaccination.

|                     | Vaccinated          | Unvaccinated         |
|---------------------|---------------------|----------------------|
|                     | Baseline Mean (SD)  | Post-vaccination Mean (SD) | z-score | p-value | Baseline Mean (SD)  | Post-vaccination Mean (SD) | z-score | p-value |
| Total PANSS score   | 63.8 (13.8)         | 65.1 (15.5)          | -3.103   | 0.002   | 68.9 (16.2)         | 70.0 (17.0)          | -0.516   | 0.610   |
| Positive subscale   | 15.0 (5.2)          | 15.0 (5.2)           | -0.711   | 0.477   | 16.2 (5.7)          | 16.9 (5.9)           | -1.591   | 0.112   |
| Negative subscale   | 18.6 (7.4)          | 19.3 (8.0)           | -3.245   | 0.001   | 20.3 (7.4)          | 20.4 (8.0)           | -0.005   | 0.996   |
| General psychopathology subscale score | 30.1 (6.3) | 30.8 (6.6) | -2.889   | 0.004   | 32.5 (8.5)          | 32.6 (8.0)           | -1.537   | 0.124   |

* Paired Wilcoxon Signed-Rank test. Significant p-values were highlighted in bold.

Table 3
Difference in PANSS scores among young and old patients.

|                     | Young group (aged from 26 to 57, n = 166 for the vaccinated; n = 41 for the unvaccinated) | Old group (aged 58 or above, n = 164 for the vaccinated; n = 73 for the unvaccinated) | Young vs. Old (baseline) |
|---------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------|
|                     | Baseline Mean (SD)  | Post-vaccination Mean (SD) | z-score (p-value) | Baseline Mean (SD)  | Post-vaccination Mean (SD) | z-score (p-value) | t-value (p-value) |
| Total PANSS score   | 63.6 (13.5)         | 65.5 (15.4)          | -3.233 (0.001)  | 0.240 (0.810) | 0.240 (0.810) |
| Positive subscale   | 15.0 (5.3)          | 14.9 (5.1)           | -0.872 (0.383)  | 0.148 (0.883) | 0.148 (0.883) |
| Negative subscale   | 18.7 (7.1)          | 19.6 (7.7)           | -2.962 (0.003)  | -0.308 (0.758) | -0.308 (0.758) |
| General psychopathology subscale score | 30.9 (6.0) | 31.0 (6.6) | -3.225 (0.001) | 0.761 (0.447) | 0.761 (0.447) |

* Paired Wilcoxon Signed-Rank test.
* Unpaired Student’s t-test.

the administration of a COVID-19 vaccine and, when necessary, take means to relieve the psychological pressure.

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Data sharing
The raw data for the tables presented in this study are included in the supplementary materials. Further inquiries can be directed to Y. F. (fuyuan@tmu.edu.cn).

Ethics Statement
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving patients were approved by the ethics committees of Tianjin Jinhua Hospital, approval number: JHLSK2021-01.

CRediT authorship contribution statement
F. J. and Y. F. conceived the project. F. J., H. G., X. L. and X. Z. collected the data. H.G. supervised the data collection. F. J., C. D. and Y. F. analyzed the data and discussed the results and implications. Y. F. wrote the manuscript. L. W. edited the manuscript. F. J., C. D. and H. G. contributed equally to this work.

Conflict of Interest Statement
The authors declare no competing interests.

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Appendix A. Supporting information
Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2022.103319.

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