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Original Article

Higher benefit-risk ratio of COVID-19 vaccination in patients with schizophrenia and major depressive disorder versus patients with bipolar disorder when compared to controls

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Abstract: Patients with major psychiatric disorders (MPD) that include schizophrenia (SCH), bipolar disorder (BP), and major depressive disorder (MDD) are at increased risk for coronavirus disease 2019 (COVID-19). However, the safety and efficacy of COVID-19 vaccines in MPD patients have not been fully evaluated. This study aimed to investigate adverse events (AEs)/side effects and efficacy of COVID-19 vaccines in MPD patients. This retrospective study included 2034 patients with SCH, BP, or MDD who voluntarily received either BBIBP-CorV or Sinovac COVID-19 vaccines, and 2034 matched healthy controls. The incidence of AEs/side effects and the efficacy of COIVD-19 vaccinations among the two groups were compared. The risk ratio (RR) of side effects in patients with MPD was 0.60 (95% confidence interval [CI]: 0.53-0.68) after the first dose and 0.80 (95% CI: 0.65-0.99) following the second dose, suggesting a significantly lower risk in the MPD group versus healthy controls. The RRs of AEs did not differ between patients and controls. Notably, fully vaccinated patients exhibited a decreased risk of influenza with or without fever compared with controls (RR=0.38, 95% CI: 0.31-0.46; RR=0.23, 95% CI: 0.17-0.30; respectively). Further subgroup comparisons revealed a significantly lower risk of influenza with fever in MDD (RR=0.13, 95% CI: 0.08-0.21) and SCH (RR=0.24, 95% CI: 0.17-0.34) than BP (RR=0.85, 95% CI: 0.69-1.06) compared to controls. We conclude that the benefit-risk ratio of COVID-19 vaccination was more favorable in SCH or MDD versus BP when compared with controls. These data indicate that COVID-19 vaccines are safe and protective in patients with MPD from COVID-19.

Keywords: COVID-19 vaccine, SARS-CoV-2, safety, effectiveness, schizophrenia, bipolar disorder, major depressive disorder

Introduction

Major psychiatric disorders (MPD) cause serious functional impairments that disrupt cognition, mood, and the performance of major life activities [1, 2]. Schizophrenia (SCH), bipolar disorder (BP), and major depressive disorder (MDD) are the most prevalent MPD [1, 2]. SCH

is characterized by hallucinations, delusions, disturbances of thoughts, speech, and behavior, social inattentiveness, and cognitive impairment [3]. BD causes characteristic extreme mood swings that include both manic/hypomanic and depressive episodes [4]. MDD presents with persistent sadness, hopelessness, loss of interest in daily activities, and psychomotor retardation [5]. Patients with MPD are highly susceptible to coronavirus disease 2019 (COVID-19) and are also at increased risk for poor clinical outcomes [6, 7], primarily due to MPD-associated disorders of immune function [8-12], kynurenine pathway activity [13], C-reactive protein levels [14], endocrine homeostasis, and host microbiosis [15]. Consequently, COVID-19 immunization is essential to protect patients with MDP [16-21]. The World Health Organization, the US National Academies of Sciences, the American Psychological Association, the World Psychiatric Association, and other psychiatric and public health authorities urge that individuals with MDP be given priority for COVID-19 vaccination [16-21].

Certain antidepressants may inhibit severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) cellular entry and propagation and may also exert anti-inflammatory effects, thereby holding promise as COVID-19 therapeutics [22]. These observations raise the hypothesis that a subset of psychotropic medications could inhibit the uptake of SARS-CoV-2 inactivated or recombinant vaccine antigens by immune effector cells and attenuate vaccine response. These findings have indeed ignited interest in elucidating the interactions between MPD, therapeutic agents, and COVID-19 vaccines. An assessment of the safety and effectiveness of COVID-19 vaccination in patients with MDP is imperative. However, studies of the safety and efficacy of COVID-19 vaccine in patients with MPD are lacking, with the exception of one pilot study that examined the interaction between a COVID-19 vaccine and three therapeutic modalities (including electroconvulsive therapy) in a Chinese psychiatrist who subjected himself to a self-study [21].

During the past twenty years, the Chinese government has made concerted efforts to destigmatize mental illness [15, 23, 24]. President-Xi Jinping has repeatedly expressed his empathy to patients with MPD. However, an ingrained stigmatization of individuals with MPD and their guardians persists [25, 26]. Consequently, many patients and their guardians are inclined to conceal their psychiatric diagnoses. Although the Chinese government has emphasized that individuals with any disease should be carefully assessed for the risk-benefit ratio of COVID-19 immunization to assure safety, many patients with MPD deny their condition when presenting for COVID-19 vaccination.

In contrast to the denial of MPD at the time of COVID-19 vaccination, patients often reported vaccine adverse events (AEs) and side effects to their psychiatrists. These symptoms suggested potential interactions between vaccines and therapeutic agents, which inspired us to study the safety and effectiveness of COVID-19 vaccines in patients with MPD.

Faced with the threat posed by pandemic COVID-19 to this group of vulnerable patients, we conducted this retrospective study of patients with SCH, BP, or MDD who denied their psychiatric diagnoses when receiving COVID-19 vaccines. We aimed to determine the incidence and severity of AEs/side effects and the efficacy of the BBIBP-CorV [27] and Sinovac COVID-19 vaccines [28] in patients with MPD.

Materials and methods

Study population

We conducted a retrospective study covering a 16-month period from August 1, 2020 to November 30, 2021 to evaluate COVID-19 vaccination and clinical outcomes of patients with MPD (SCH, BP, or MDD) receiving outpatient psychiatric treatment and who denied their psychiatric diagnoses at the time of COVID-19 vaccination. We matched healthy individuals recommended by the patients or their guardians in a control group. This retrospective cohort study population comprised 2210 patients with MPD and 2210 well-matched healthy individuals who were fully vaccinated against COVID-19.

Patients and healthy individuals came from 7 provinces/municipalities of China, representing diverse geographic regions across the nation that included the East (Wenzhou city), North

(Harbin city), Central (Tianjin, Jining, Zhengzhou, and Xinxiang cities), and West (Taiyuan, Chongqing cities). Inclusion and exclusion criteria for patients with MPD and criteria for matched healthy controls are provided in Supplementary Materials.

The Ethics Committee of Tianjin Four Center Hospital of Tianjin Medical University approved this study (Approval No. 2020-K01). Signed informed consent was provided by patients and their guardians.

COVID-19 vaccines

All subjects received either BBIBP-CorV (Sinopharm COVID-19 Vaccine, Beijing Institute of Biological Products Co., Ltd.) (Beijing, China) [27] or Sinovac COVID-19 vaccine (Sinovac Biotech Ltd., Beijing, China) [28]. BBIBP-CorV and Sinovac are inactivated SARS-CoV-2 vaccines produced in Vero cells and administered in two 0.5 ml doses injected intramuscularly into the deltoid muscle at a dosing interval of 2-4 weeks.

Outcomes

The outcome measures of COVID-19 vaccine safety were the incidence of AEs and side effects, which are defined in Supplementary Materials. The outcome measure of COVID-19 vaccine efficacy was the incidence of COVID-19 and/or influenza within the 31 days after being fully vaccinated. Case definitions of COVID-19 and influenza are provided in Supplementary Materials.

Statistical analysis

Statistical analyses were conducted by using SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA). Continuous variables were expressed as mean ± standard deviation (SD) (normally distributed data) or median ± interquartile range (non-normal data). Categorical variables were presented as numbers and percentages. Demographic and clinical characteristics and AEs of MPD patients and healthy controls were compared using the t-test (or Wilcoxon rank sum test) and chi-square test/Fisher's exact test as appropriate. A two-sided level of $P<0.05$ was considered significant.

Generalized estimating equation (GEE) with log-linked binomial model was used to assess the relative risk of AEs and side effects between patients with MPD and healthy controls. Multivariate GEE modes were used to adjust for age, sex, education level, exposure risk of working condition, economic status, and the type of vaccination [29].

Results

Study population

A total of 2034 patients and 2034 healthy controls were included. The subject qualification rate was 92.04%. Demographic, socioeconomic, and clinical characteristics of the study subjects are listed in **Table 1**. There were no significant differences in age and sex between the MPD and control groups ($P>0.05$).

Vaccine safety

The number and proportion of participants experiencing vaccine-related AEs/side effects are summarized in **Table 2**. The incidence of AEs after the first dose was 8.8% (179/2034) in patients and 7.5% (153/2034) in controls, which was similar between the two groups ($P=0.1365$). The most common AE was hypertensive crisis, accounting for 46.9% (84/179) and 39.9% (61/153) of AEs reported in patients with MPD and healthy controls experiencing AEs, respectively. Notably, the types of AEs differed significantly between patients with MPD and controls ($P<0.0001$, **Table 2**). None of the participants experiencing AEs after the first dose received a second dose.

The incidence rates of AEs following the second dose were similar between the patient and control groups (0.59%, 11/1849; and 0.37%, 7/1812; respectively; $P=0.3670$). Notably, the types of AEs after the second dose were significantly different between the patient and control groups ($P=0.0012$, **Table 2**). Specific AEs are described in Supplementary Materials.

Vaccine side effects are summarized in **Table 2**. Patients and controls experienced significantly different side effect rates after the first dose (15.1%, 308/2034; and 25.4%, 517/2034 respectively; $P<0.0001$). Influenza-like symptoms without fever were the most common side

Table 1. Demographic, socioeconomic, and clinical characteristics

Demographic, socioeconomic, and clinical characteristics		Patients with severe mental illness (n=2034)	Healthy controls (n=2034)	*p* value
Sex	Female	1117 (54.9)	1118 (55.0)	0.9749
	Male	917 (45.1)	916 (45.0)	
Education level (Years)	≤12	1257 (61.8)	1246 (61.3)	0.7230
	>12	777 (38.2)	788 (38.7)	
Job	No	197 (9.7)	196 (9.6)	0.9577
	Yes	1837 (90.3)	1838 (90.4)	
Exposure risk	1	489 (24.0)	457 (22.5)	0.0346
	2	336 (16.5)	407 (20.0)	
	3	1017 (50.0)	978 (48.1)	
	4	192 (9.4)	192 (9.4)	
High-risk occupation	1	415 (20.4)	416 (20.5)	0.9970
	2	1267 (62.3)	1261 (62.0)	
	3	350 (17.2)	355 (17.5)	
	4	2 (0.1)	2 (0.1)	
Family economic status	1	203 (10.0)	205 (10.1)	0.9469
	2	1495 (73.5)	1486 (73.1)	
	3	336 (16.5)	343 (16.9)	
Personal income	1	468 (23.0)	450 (22.1)	0.7944
	2	1186 (58.3)	1198 (58.9)	
	3	380 (18.7)	386 (19.0)	
Type of mental illness	BP	581 (28.6)	N/A	N/A
	MDD	640 (31.5)	N/A	N/A
	SCH	813 (40.0)	N/A	N/A
Therapeutic drug dose in past 16 months (mg)	Chlorpromazine equivalent	178884.2±205715.9	N/A	N/A
	Fluoxetine equivalent	18302.3±22498.4	N/A	N/A
	Valproate equivalent	265592.9±264622.3	N/A	N/A
	Diazepam equivalent	3361.6±1813.7	N/A	N/A
	Trihexyphenidyl	407.8±994.8	N/A	N/A
	Promethazine	2259.3±12372.0	N/A	N/A

Note: BP, bipolar disorder; MDD, major depressive disorder; SCH, schizophrenia.

effects in controls reporting side effects (56.9%, 294/517). Myalgia and arthralgia were the most frequent symptoms in patients reporting side effects (33.8%, 104/308). After the second dose, pain, itching, or swelling were observed in 85.4% (140/164) of controls and 97.7% (132/138) of patients reporting side effects. Influenza-like symptoms without fever occurred in 11.0% (18/164) of controls reporting side effects.

Patients with MPD had a similar risk of AEs compared to controls after the first dose (adjusted risk ratio [RR]=1.19, 95% confidence interval [CI] 0.97-1.46), and second dose (adjusted RR=1.55, 95% CI 0.60-3.99) in multivariate analysis. Interestingly, the adjusted RR of side effects after the first dose (RR=0.60, 95% CI 0.53-0.68) and the second dose (RR=0.80, 95% CI 0.65-0.99) suggested a lower risk of side effects in the MPD group compared to controls (**Table 3**).

Vaccine efficacy

No cases of COVID-19 occurred in patients with MPD or in controls. None of the fully vaccinated participants developed persistent high fever (≥ 39.5°C, ≥ 72 h) and severe pneumonia. In contrast to fully vaccinated controls, fully vaccinated patients with MPD exhibited decreased risks of influenza with or without fever (adjusted

Table 2. COVID-19 vaccine adverse events/side effects and efficacy

		Patients with severe mental illness (n=2034)	Healthy controls (n=2034)	*p* value
COVID-19 vaccine	BBIBP-CorV	1540 (75.7)	1530 (75.2)	0.7156
	Sinovac	494 (24.3)	504 (24.8)	
AEs after 1st dose	No	1855 (91.2)	1881 (92.5)	0.1365
	Yes	179 (8.8)	153 (7.5)	
Types of AEs after 1st dose	Acute myocardial infarction	0 (0.0)	1 (0.7)	<0.0001
	Allergic purpura	0 (0.0)	1 (0.7)	
	Anaphylactic shock	27 (15.1)	11 (7.2)	
	Encephalitis	0 (0.0)	1 (0.7)	
	Hypertensive crisis	84 (46.9)	61 (39.9)	
	Hypochondriasis	0 (0.0)	14 (9.2)	
	Hypotension shock	29 (16.2)	7 (4.6)	
	Leukemia	1 (0.6)	0 (0.0)	
	Persistent high fever	16 (9.0)	48 (31.4)	
	Seizure	4 (2.2)	1 (0.7)	
	Unexplained severe malaise	18 (10.1)	3 (2.0)	
	Severe panic episode	0 (0.0)	5 (3.3)	
AE onset after 1st dose (hours)		0.5±0.0	0.5±11.5	<0.0001
AE resolution (hours)		12.0±21.0	24.0±376.0	<0.0001
Side effects after 1st dose	No	1726 (84.9)	1517 (74.6)	<0.0001
	Yes	308 (15.1)	517 (25.4)	
Types of side effects after 1st dose	Fatigue	11 (3.6)	10 (1.9)	<.00001
	Influenza-like symptoms without fever	73 (23.7)	294 (56.9)	
	Muscle and joint pain	104 (33.8)	73 (14.1)	
	Nausea and vomiting	71 (23.1)	39 (7.5)	
	Pain, itch, or swelling	49 (15.9)	101 (19.5)	
Side effect onset after 1st dose (hours)		12.0±21.5	24.0±21.0	<0.0001
Side effect resolution (hours)		72.0±60.0	72.0±72.0	0.0001
Vaccinated 2nd dose	Yes	1849 (90.9)	1812 (89.1)	0.0532
	No	185 (9.1)	222 (10.9)	
AEs after 2nd dose	No	1844 (99.41)	1874 (99.63)	0.3670
	Yes	11 (0.59)	7 (0.37)	
Types of AEs after 2nd dose	Severe panic attack	0 (0.0)	5 (71.4)	0.0012
	Anaphylactic shock	1 (9.1)	0 (0.0)	
	Hypertensive crisis	8 (72.7)	0 (0.0)	
	Hypochondriasis	0 (0.0)	2 (28.6)	
	Hypotensive shock	2 (18.2)	0 (0.0)	
AE management	Antidepressant therapy	0 (0.0)	5 (71.4)	0.0001
	Symptomatic treatment	11 (100.0)	0 (0.0)	
	Antipsychotic agent treatment	0 (0.0)	2 (28.6)	
AE onset after 2nd dose (hours)		0.5±0.0	480.0±240.0	<0.0001
AE resolution (hours)		9.0±4.0	2160.0±696.0	0.0005
Side effects after 2nd dose	No	1717 (92.6)	1717 (91.3)	0.0809
	Yes	138 (7.4)	164 (8.7)	
Type of side effects after 2nd dose	Fatigue	6 (4.3)	6 (3.7)	0.0003
	Influenza-like symptoms without fever	0 (0.0)	18 (11.0)	
	Pain, itch, or swelling	132 (95.7)	140 (85.4)	
Side effect onset after 2nd dose (hours)		7.0±2.5	12.5±5.0	0.0071
Side effects resolution (hours)		5.0±6.0	6.0±1.0	0.0025
SARS-CoV-2 infection		0	0	n/a

Influenza without fever after 2nd dose	No	1794 (96.7)	1622 (86.2)	<0.0001
	Yes	61 (3.3)	259 (13.8)	
Influenza with fever after 2nd dose	No	1719 (92.8)	1536 (81.7)	<0.0001
	Yes	136 (7.3)	345 (18.3)	
COVID-19 antibody status	Negative	123 (90.4)	195 (56.5)	<.00001
	Positive	13 (9.6)	150 (43.5)	
Time between 2nd vaccine dose and antibody test (days)		35.0±6.0	34.0±14.0	0.8829

COVID-19, coronavirus disease 2019; AE, adverse event.

Table 3. COVID-19 vaccine adverse event/side effect incidence and efficacy in MPD and control groups

	Univariate analysis RR (95% CI) (Patients vs. controls)	*p* value	Multivariate analysis RR (95% CI) (Patients vs. controls)	*p* value
AEs after 1st dose	1.17 (0.95-1.44)	0.6890	1.19 (0.97-1.46)	0.5894
Side effects after 1st dose	0.60 (0.52-0.68)	0.0357	0.60 (0.53-0.68)	0.0023
AEs after 2nd dose	1.54 (0.60-3.96)	0.3182	1.55 (0.60-3.99)	0.2157
Side effects after 2nd dose	0.82 (0.66-1.02)	0.0493	0.80 (0.65-0.99)	0.0120
Influenza without fever after 2nd dose	0.23 (0.18-0.30)	0.0001	0.23 (0.17-0.30)	<0.0001
Influenza with fever after 2nd dose	0.38 (0.32-0.46)	<0.0001	0.38 (0.31-0.46)	<0.0001

COVID-19, coronavirus disease 2019; AE, adverse event. Results of multivariate analysis were adjusted for age, sex, education level, workplace exposures, economic status, and type of vaccine.

RR=0.38, 95% CI 0.31-0.46; adjusted RR= 0.23, 95% CI 0.17-0.30, respectively) (**Table 3**). Post-vaccination SARS-CoV-2 seroprevalence in controls who developed febrile influenza was 43.5% (150/345), higher than that in patients with MPD (9.6%, 13/136) (P<0.0001) (**Table 2**).

Differences in COVID-19 vaccine safety and efficacy between MPD subgroups

Patients with MPD were stratified into BP, MDD, and SCH subgroups. The number and proportion of patients experiencing AEs/side effects in each subgroup are summarized in **Table 4**. There were no significant differences in AE incidence among the three subgroups, whereas rates of side effects from the first and second doses were significantly different (P=0.0054, P<0.0001). Information regarding AEs/side effects in the subgroups is provided in Supplementary Materials.

The adjusted RR of AEs after the first dose in MDD (RR=1.15, 95% CI 0.85-1.57), SCH (RR= 1.35, 95% CI 1.05-1.75), and BP (RR=1.00, 95% CI 0.72-1.38) suggested that the risk of AEs was not significantly increased in either subgroup compared to controls (**Table 5**). Notably, the risk of side effects after the first dose was significantly decreased in MDD (RR=0.65, 95% CI 0.54-0.79), BP (RR=0.66, 95% CI 0.54-0.80), and SCH (RR=0.50, 95% CI 0.41-0.61) compared to controls. The adjusted RR of AEs after the second dose was 2.63 (95% CI 0.88-7.82) in MDD, 1.42 (95% CI 0.42-4.84) in SCH, and 0.49 (95% CI 0.06-3.94) in BP patients, suggesting a lower risk of AEs compared to controls (**Table 5**).

Compared to controls, patients with MDD or SCH demonstrated a decreased risk of influenza with or without fever (adjusted RR of influenza with fever in MDD=0.13, 95% CI 0.08-0.21; adjusted RR of influenza without fever in MDD=0.18, 95% CI 0.11-0.30; adjusted RR of influenza with fever in SCH=0.24, 95% CI 0.17-0.34; adjusted RR of influenza without fever in SCH=0.37, 95% CI 0.26-0.51) (**Table 5**). However, the risk of influenza with fever was similar in patients with BP and controls (adjusted RR=0.85, 95% CI 0.69-1.06), whereas the risk of influenza without fever was significantly lower in BP compared with healthy controls (adjusted RR=0.10, 95% CI 0.05-0.21) (**Table 5**). Moreover, the risk of influenza with fever in patients with SCH or MDD was decreased in

Table 4. COVID-19 vaccine adverse events/side effects and efficacy in MPD subgroups

		BP (n=581)	MDD (n=640)	SCH (n=813)	*p* value
COVID-19 Vaccine	BBIBP-CorV	421 (72.5)	638 (99.7)	481 (59.2)	<0.0001
	Sinovac	160 (27.5)	2 (0.3)	332 (40.8)	
AE after 1st dose	No	538 (92.6)	588 (91.9)	729 (89.7)	0.1251
	Yes	43 (7.4)	52 (8.1)	84 (10.3)	
Side effects after 1st dose	No	485 (83.5)	526 (82.2)	715 (87.9)	0.0054
	Yes	96 (16.5)	114 (17.8)	98 (12.1)	
Vaccinated 2nd dose	Yes	540 (92.9)	588 (91.9)	727 (89.4)	0.1652
	No	41 (7.1)	52 (8.1)	86 (10.6)	
AE after 2nd dose	No	539 (99.8)	582 (99.0)	723 (99.4)	0.1881
	Yes	1 (0.2)	6 (1.0)	4 (0.6)	
Side effects after 2nd dose	No	539 (99.8)	582 (99)	723 (99.4)	<0.0001
	Yes	1 (0.2)	6 (1.0)	4 (0.6)	
Influenza without fever after 2nd dose	No	532 (98.5)	573 (97.4)	689 (94.8)	0.0006
	Yes	8 (1.5)	15 (2.6)	38 (5.2)	
Influenza with fever after 2nd dose	No	453 (83.9)	572 (97.3)	696 (95.7)	<0.0001
	Yes	87 (16.1)	16 (2.7)	31 (4.3)	
COVID-19 antibody status	Negative	79 (90.8)	14 (87.5)	28 (90.3)	0.9464
	Positive	8 (9.2)	2 (12.5)	3 (9.7)	

COVID-19, coronavirus disease 2019; MPD, major psychiatric disorders; BP, bipolar disorder; MDD, major depressive disorder; SCH, schizophrenia; AE, adverse event.

comparison with the BP subgroup (adjusted RR=0.30, 95% CI 0.20-0.44 in SCH versus BP; adjusted RR=0.14, 95% CI 0.08-0.24 in MDD versus BP) (**Table 5**). However, compared to patients with BP, patients with SCH demonstrated an increased risk of influenza without fever (adjusted RR=3.42, 95% CI 1.61-7.26), whereas compared to patients with BP, the risk of influenza without fever was similar in patients with MDD (adjusted RR=1.62, 95% CI 0.69-3.80) (**Table 5**).

Discussion

This study of the safety and efficacy of COVID-19 vaccines provides vital information to assist psychiatrists and other physicians in the care of patients with MPD. First, the incidence of COVID-19 vaccine-related AEs in patients with MPD was not significantly increased, while the risk of side effects was significantly reduced compared to controls; this evidence affirms the practice of providing COVID-19 vaccinations to patients with MDP. Second, COVID-19 vaccination was associated with a significantly lower incidence of influenza with and without fever in MDD or SCH patients compared to BP patients. Third, compared to controls, patients with BP did not show decreased risk of influenza with fever although the risk of influenza without fever was significantly reduced. Fourth, the risk of influenza without fever was increased in SCH compared to BP patients, whereas the risk of influenza with fever was significantly decreased in SCH or MDD.

Our findings affirm the prioritization of patients with MPD for COVID-19 vaccination [16]. Our data may also suggest that fully vaccinated BP patients, especially those in the hypo-manic phase, should receive specific measures to prevent influenza, as patients often neglect influenza-like illnesses, thus facilitating disease progression and pneumonia [30, 31].

Because none of the participants contracted COVID-19, we conclude that all fully-vaccinated patients and controls acquired protective immunity. This outcome is attributed to the implementation of strict infection prevention and control strategies introduced by our government that include free COVID-19 vaccination, social distancing, mask-wearing, and timely disinfection of public transport. Our data also demonstrated a higher post-vaccination SARS-CoV-2 seroprevalence among controls

Table 5. Comparison of AEs/side effects and efficacy of COVID-19 vaccine among MPD subgroups and controls

	Comparison subgroups	Univariate analysis RR (95% CI)	*p* value	Multivariate analysis RR (95% CI)	*p* value
AE after 1st dose	BP vs. Control	0.98 (0.71-1.36)	0.2541	1.00 (0.72-1.38)	0.1890
	MDD vs. Control	1.08 (0.80-1.46)	0.1369	1.15 (0.85-1.57)	0.1483
	SCH vs. Control	1.37 (1.07-1.77)	0.0007	1.35 (1.05-1.75)	0.0179
Side effects after 1st dose	BP vs. Control	0.65 (0.53-0.79)	<0.0001	0.66 (0.54-0.80)	0.0010
	MDD vs. Control	0.70 (0.58-0.84)	<0.0001	0.65 (0.54-0.79)	<0.0001
	SCH vs. Control	0.47 (0.39-0.58)	<0.0001	0.50 (0.41-0.61)	<0.0001
AEs after 2nd dose	BP vs. Control	0.48 (0.06-3.93)	0.0563	0.49 (0.06-3.94)	0.8571
	MDD vs. Control	2.64 (0.89-7.83)	0.9833	2.63 (0.88-7.82)	0.7469
	SCH vs. Control	1.42 (0.42-4.85)	0.5630	1.42 (0.42-4.84)	0.4260
Side effects after 2nd dose	BP vs. Control	1.57 (1.22-2.03)	<0.0001	1.57 (1.22-2.02)	0.0001
	MDD vs. Control	0.32 (0.20-0.52)	<0.0001	0.26 (0.16-0.43)	<0.0001
	SCH vs. Control	0.68 (0.50-0.94)	<0.0001	0.77 (0.56-1.05)	0.0500
Influenza without fever after 2nd dose	BP vs. Control	0.10 (0.05-0.21)	<0.0001	0.10 (0.05-0.21)	<0.0001
	MDD vs. Control	0.18 (0.11-0.3)	<0.0001	0.18 (0.11-0.30)	<0.0001
	SCH vs. Control	0.37 (0.26-0.51)	<0.0001	0.37 (0.26-0.51)	<0.0001
Influenza with fever after 2nd dose	BP vs. Control	0.86 (0.69-1.06)	0.3690	0.85 (0.69-1.06)	0.4579
	MDD vs. Control	0.14 (0.09-0.23)	0.0023	0.13 (0.08-0.21)	<0.0001
	SCH vs. Control	0.22 (0.16-0.32)	0.0001	0.24 (0.17-0.34)	0.0177
AEs after 1st dose	MDD vs. BP	1.10 (0.74-1.62)	0.6974	1.27 (0.88-1.83)	0.6582
	SCH vs. BP	1.40 (0.98-1.98)	0.5821	1.26 (0.92-1.73)	0.6030
Side effects after 1st dose	MDD vs. BP	1.08 (0.84-1.38)	0.6317	0.88 (0.69-1.13)	0.7000
	SCH vs. BP	0.73 (0.56-0.95)	0.0211	0.82 (0.63-1.06)	0.0290
AEs after 2nd dose	MDD vs. BP	5.45 (0.66-45.11)	0.9851	5.38 (0.65-44.63)	0.8090
	SCH vs. BP	2.94 (0.33-26.21)	0.6938	2.95 (0.33-26.28)	0.9600
Side effects after 2nd dose	MDD vs. BP	0.20 (0.12-0.34)	0.0004	0.16 (0.10-0.28)	<0.0001
	SCH vs. BP	0.43 (0.31-0.62)	0.0026	0.50 (0.35-0.70)	0.0039
Influenza without fever after 2nd dose	MDD vs. BP	1.70 (0.73-3.98)	0.4820	1.62 (0.69-3.80)	0.6044
	SCH vs. BP	3.49 (1.64-7.42)	0.0495	3.42 (1.61-7.26)	0.0288
Influenza with fever after 2nd dose	MDD vs. BP	0.17 (0.10-0.28)	0.0001	0.14 (0.08-0.24)	<0.0001
	SCH vs. BP	0.26 (0.18-0.39)	<0.0001	0.30 (0.20-0.44)	<0.0001

COVID-19, coronavirus disease 2019; AE, adverse event; BP, bipolar disorder; MDD, major depressive disorder; SCH, schizophrenia; RR, risk ratio; CI, confidence interval. Results of multivariate analysis were adjusted for age, sex, education level, exposure to working environment, economic status, and type of vaccine.

compared to MPD patients tested in the context of febrile influenza. Due to the absence of previous information regarding COVID-19 vaccine-induced seroconversion in patients with MPD, we cannot make further comparisons to explain this difference. Certain antidepressants that include selective serotonin reuptake inhibitors may reduce SARS-CoV2 cellular entry and exert immunomodulatory effects [22], and have shown promise as COVID-19 therapies in three clinical trials [32, 33]. Based on these findings, we hypothesize that antipsychotics that exert serotonin re-uptake inhibition similar to antidepressants (e.g. olanzapine, clozapine, ziprasidone, risperidone, aripiprazole) [34-36], may inhibit the cellular entry and propagation of SARS-CoV-2 virus and attenuate pro-inflammatory cytokine cascades, potentially offering novel therapeutic options for COVID-19. Furthermore, we hypothesize that drugs that inhibit SARS-CoV-2 entry may inhibit uptake and processing of inactivated or recombinant vaccine antigens by immune effector cells, thereby reducing post-vaccine seroconversion. This hypothesis is supported by the lower post-vaccination SARS-CoV-2 seroprevalence in MPD patients vs. controls tested in the context of febrile influenza-like illness and by the

lower rate of side effects in MPD patients vs. controls. However, the clinical relevance of postvaccination seronegativity is unclear, because laboratory correlates of clinical protection are undefined [37-40] and because no cases of COVID-19 were observed in either group. This hypothesis may be worthy of future research.

Several limitations of our study should be mentioned. The first is its retrospective observational design. Outcome data were retrieved from outpatients. The strength of evidence of retrospective studies may be inferior to that of prospective studies, although we made every effort to ensure the accuracy of information regarding AEs and efficacy. Second, the potential effect of psychotropic agents on COVID-19 vaccine efficacy are difficult to determine. This potential interaction should be studied further. Third, patients with MPD were not stratified into subsets of first-episode or relapsed cases. There might be a link between initial or recurrent disease and the safety and efficacy of COVID-19 vaccines. Fourth, although we used a detailed questionnaire, our study may have been confounded by recall bias. Fifth, post-vaccination seroconversion was evaluated only in participants presenting with influenza, which may have introduced selection bias. The lower SARS-CoV-2 seroprevalence in patients of MPD with influenza and fever versus controls cannot be used as an index to evaluate the clinical efficacy of COVID-19 vaccines. Sixth, although study participants had normal memory function to assure accuracy in recalling their medical regimens and COVID-19 vaccine-related information, sample bias could not be avoided. Hence, prospective studies should be conducted to fully clarify the safety and efficacy of COVID-19 vaccines.

In conclusion, patients with MPD did not experience an increased risk of AEs after COVID-19 vaccination compared to well-matched healthy controls. Vaccination protected all participants from COVID-19. Furthermore, fully vaccinated patients with SCH or MDD showed lower risks of influenza with and without fever than those with BP. These findings suggest that COVID-19 vaccines are safe and protective in patients with severe MPD, especially those with SCH or MDD.

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Disclosure of conflict of interest

None.

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Supplementary Materials

Supplementary materials and methods

Inclusion and exclusion criteria for patients with MPD and matching controls

Inclusion criteria were: (1) voluntary participation; (2) age 18-59 years; (3) SCH, BP, or MD treated continuously with pharmacologic agents. Qualitative diagnoses of SCH, BP, and MDD were based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria [1] through the Structural Clinical Interview for DSM-IV (SCI-D) [2]; (4) patients with MPD have appointed guardians; (5) full insight, defined by the Birchwood Insight Scale (BIS) [3] and Beck Cognitive Insight Scale [4]; (6) normal memory function, defined by the Wechsler Memory Scale (Fourth edition) [5]; (7) stable symptoms and comprehension of the questionnaire and ability to answer accurately, and verification of answers by their guardians; (8) verifiable documentation of COVID-19 vaccination; (9) verifiable documentation of pharmacologic therapies; (10) ability to recall positive or negative histories of COVID-19 and influenza with/without fever, and verifiable paper-based records provided by a local health department.

Exclusion criteria were: (1) other mental disorders (e.g., personality disorder, stress psychosis, menstrual psychosis, dementia, post-stroke depression, postpartum depression); (2) psychosis, bipolar-like symptoms, depressive symptoms caused by encephalopathy and/or other organ system diseases; (3) mental retardation; (4) inability to complete the survey.

During enrollment of well-matched healthy individuals, SCI-D (NP version) was used to exclude candidates with any mental disorder [2]. A documented psychiatric history was also an exclusion criterion for controls.

We matched healthy controls according to the ranked order of the following major corresponding factors [6]: (1) sex, (2) age, (3) occupational exposure to risk factors, (4) economic circumstances, (5) employment and unemployment, and (6) education level. We also reviewed the National COVID-19 Vaccination Record provided by the Chinese Ministry of Health to ensure the accuracy of COVID-19 vaccination status, including full and partial vaccination/reasons for deferral for both the healthy controls and patients with MPD. In addition, we acquired data on SARS-CoV-2 infection and influenza/fever that could be verified by the National COVID-19 Vaccination Record (Chinese Ministry of Health) and paper-based medical records provided by each local health department.

Tools

For patients with MPD, we designed a questionnaire that queried sociodemographic data, psychiatric diagnosis, mental illness duration, cumulative therapeutic agent dosage, occupational exposure to risk factors, COVID-19 vaccination record, histories of COVID-19 and influenza, outpatient documentation of fever, SARS-CoV-2 nucleic acid test results, and SARS-CoV-2 antibody test results. All information was validated by their guardians.

For matched controls, we designed a questionnaire that queried sociodemographic data, occupational risk factors, COVID-19 vaccination record, histories of COVID-19 or influenza, outpatient documentation of fever, SARS-Co-V-2 nucleic acid test results, and SARS-Co-V-2 antibody test results.

Investigative procedure

First, all participating psychiatrists were trained to use the questionnaires. Second, participating psychiatrists recruited suitable patients for participation. After completion of the patient survey, the psychiatrist invited patient guardians to recommend a healthy individual to participate as a control. When the recommended healthy individuals volunteered to participate, they were screened by using the SCI-D

(NP version) and assessed according to the abovementioned rank order to assure matching according to the healthy control criteria. After the assessment, controls completed the questionnaire. All information (such as vaccination dates, outpatient febrile illnesses, and outpatient treatment) was validated by examining paper-based medical records provided by a local health department.

Adverse events

Adverse events (AEs) were defined as serious reactions following COVID-19 vaccination that can threaten life and require urgent medical intervention, such as anaphylactic shock, allergic asthma, or persistent high fever (body temperature ≥ 39.5°C, that persists for ≥ 72 hours despite antipyretic therapy), and psychological reactions requiring psychiatric intervention (e.g., persistent panic attack, stress reaction with psychotic symptoms).

Side effects

Side effects were defined as physical or psychological discomfort after COVID-19 vaccination that did not substantially influence the ability of the individual to function and did not require medical intervention. Examples include local inflammatory reactions at injection sites and fatigue.

Influenza with fever and without fever

Influenza was defined as "an acute respiratory disease caused by influenza virus. Clinical manifestations of influenza are primarily a cluster of systemic symptoms, such as fatigue, headache, cough, muscle pain, and fever, while respiratory symptoms are mild". According to the clinical characteristics and severity of influenza provided by Call et al. [6] and Ryu et al. [7], influenza virus infections are common in people of any age, and approximately 50% of cases present with fever. Consequently, in this study, we re-defined influenza to two clinical subtypes, influenza without and with fever (body temperature ≥ 37.5°C).

SARS-Cov-2 infection

COVID-19 was defined by specific symptoms related to COVID-19, chest computed tomography scan demonstrating radiographic features of COVID-19, and positive nucleic acid testing for SARS-CoV-2 [8-10].

SARS-CoV-2 nucleic acid and antibody testing

In accordance with our government policy for COVID-19 pandemic response, the first recommendation for febrile individuals is to present for outpatient screening to determine whether their fever is caused by SARS-CoV-2, influenza, or other etiologies. A SARS-CoV-2 nucleic acid test [9] should be performed, and patients undergo inpatient evaluation if COVID-19 is confirmed. Patients with influenza and fever receive outpatient therapy. Patients may request SARS-CoV-2 antibody testing to determine post-vaccination serostatus. Hence, we also acquired data regarding vaccine-induced-seropositivity in patients who requested antibody testing.

Supplementary results

Subjects

A total of 2210 patients with MPD and 2210 healthy controls were retrospectively recruited in this study; 2034 patients and 2034 controls were included for analysis after the exclusion of 176 patients and 176 control candidates.

Adverse events (AEs) in patients with MPD and controls

After the first COVID-19 vaccine dose, AEs in patients and controls were hypotensive shock (16.8% vs. 4.6%), anaphylactic shock (15.1% vs. 7.2%), persistent high fever (9.0% vs. 31.4%), medically unexplain-

able severe malaise (10.1% vs. 2.0%), seizure (2.2% vs. 0.7%), leukemia (0.6% vs. 0), severe panic episode (0 vs. 3.3%), acute myocardial infarction (0 vs. 0.7%), allergic purpura (0 vs. 0.7%), and encephalitis (0 vs. 0.7%). Following the second dose, AEs in patients vs. controls were hypertensive crisis (72.7% vs. 18.2%), anaphylactic shock (9.1% VS. 0), severe panic attack (0 VS. 71.4%), and hypochondriasis (0 VS. 28.6%).

AEs/side effects in MPD subgroups

After the first dose, AEs occurred in 84 SCH (10.30%, 84/813), 52 MDD (8.10%, 52/640), and 43 BP (7.40%, 43/581) patients. AEs after the second dose were observed in 6 MDD (1.0%, 6/588), 4 SCH (0.6%, 4/727), and 1 BP patient (0.2%, 1/540). There were no significant differences of AE incidence rates among the three subgroups, whereas the percentages of side effects from the first and second doses were significantly different among the subgroups ($p=0.0054$, $p<0.0001$). After the first dose, side effects were observed in 114 MDD (17.80%, 114/640), 98 SCH (12.10%, 98/813), and 96 BP patients (16.50%, 96/581). Following the second dose, side effects occurred in 6 MDD (1.00%, 6/588), 4 SCH (0.60%, 4/727), and 1 BP patient (0.20%, 1/540).

AE/side effect rankings according to incidence and severity

The ranking of AE incidence rates in patients with MPD after the first dose was hypertensive crisis, hypotensive shock, anaphylactic shock, unexplained severe malaise, persistent high fever, seizure, and leukemia. By contrast, rankings of AE incidence in controls were hypertensive crisis, persistent high fever, hypochondriasis, anaphylactic shock, hypotensive shock, severe panic episode, unexplained severe malaise, seizure, encephalitis, and acute myocardial infarction. The rankings of AEs according to severity were anaphylactic shock, hypotensive shock, encephalitis, acute myocardial infarction, seizure, and leukemia.

The rankings of side effect incidence in patients with MPD were myalgia and arthralgia, influenza-like symptoms, nausea and vomiting, pain, pruritis, or swelling, and fatigue. In contrast, ranking of side effect incidence of controls was influenza-like symptoms without fever, pain, itch, or swelling, myalgia and arthralgia, nausea and vomiting, and fatigue. Both the AE and side effect rankings were significantly different between patients and controls.

Fortunately, all patients and controls recovered from side effects after symptomatic treatment. As of November 30th, 2021, the end of this study, no chronic sequelae of COVID-19 vaccine side-effects have been reported. These findings have important clinical implications, suggesting that patients should be carefully monitored for the onset of encephalitis, acute myocardial infarction, seizure, leukemia, hypertensive crisis, hypotensive shock, anaphylactic shock, persistent high fever during and after COVID-19 vaccination.

Effects of COVID-19 vaccination on influenza and COVID-19 seropositivity

In 1855 patients with MPD who were fully vaccinated, 136 (7.3%) received outpatient treatment for influenza with fever, of whom 13 (9.6%, 13/136) tested positive for SARS-CoV-2 antibodies, but negative in nucleic acid testing. In addition, 61 patients (3.29%) presented with influenza without fever. After symptomatic treatment, all recovered within 7 days. Among 1881 fully vaccinated controls, 345 (18.3%) received outpatient treatment for influenza with fever, of whom 150 (43.5%) tested positive for SARS-CoV-2 antibodies, but negative in nucleic acid testing. Furthermore, 259 (13.8%) developed influenza without fever. After symptomatic treatment, all patients recovered within 7 days. The time interval between second vaccination and antibody assay was 35.0±6.0 days in controls and 34.0±14.0 days in the 13 patients with MPD.

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