Brain, Behavior, and Immunity 114 (2023) 500–510

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

High unrecognized SARS-CoV-2 exposure of newly admitted and hospitalized psychiatric patients

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ARTICLE INFO

Keywords:
SARS-COV-2
COVID-19
Immunopsychiatry
Inflammation

ABSTRACT

Background: Patients with pre-existing mental disorders are at higher risk for SARS-CoV-2 infection and adverse outcomes, and severe mental illness, including mood and psychosis spectrum disorders, is associated with increased mortality risk. Despite their increased risk profile, patients with severe mental illness have been understudied during the pandemic, with limited estimates of exposure in inpatient settings.

Objective: The aim of this study was to describe the SARS-CoV-2 seroprevalence and antibody titers, and pro-inflammatory cytokine concentrations of newly admitted or hospitalized psychiatric inpatients without known history of COVID-19 infection, using robust quantitative multi-antigen assessments, and compare patients' exposure to that of hospital staff.

Methods: This multi-centric, cross-sectional study compared SARS-CoV-2 seroprevalence and titers of 285 patients (University Psychiatric Centre Duffel [UPCD] N = 194; Assistance-Publique-Hopitaux de Paris [AP-HP] N = 91), and 192 hospital caregivers (UPCD N = 130; AP-HP N = 62) at two large psychiatric care facilities between January 1st and the May 30th 2021. Serum levels of SARS-CoV-2 antibodies against Spike proteins (full length), spike subunit 1 (S1), spike subunit 2 (S2), spike subunit 1 receptor binding domain (S1-RBD) and Nucleocapsid proteins were quantitatively determined using an advanced capillary Western Blot technique. To assess the robustness of the between-group seroprevalence differences, we performed sensitivity analyses with stringent cut-offs for seropositivity. We also assessed peripheral concentrations of IL-6, IL-8 and TNF-a using ELLA assays. Secondary analyses included comparisons of SARS-CoV-2 seroprevalence and titers between patient

Abbreviations: AP-HP, Assistance-Publique-Hopitaux de Paris; AUC, area under the curve; BD, bipolar disorder; COVID-19, Coronavirus Disease 2019; DOH, duration of hospitalization; DOI, duration of (psychiatric) illness; HER, electronic health records; ELISA, enzyme-linked immunosorbent assay; ELLA, enzyme linked immunosorbent assay ; IgG, immunoglobulin G ; IL, interleukin; MDD, major depressive disorder; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; PSD, psychosis spectrum disorder; RT-PCR, reverse transcriptase polymerase chain reaction ; S, spike protein ; S1, spike subunit 1 ; S1-RBD, spike subunit 1 receptor binding domain ; S2, spike subunit 2 ; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 ; SMI, severe mental illness ; TNF-α, tumor necrosis factor alpha; UPCD, University Psychiatric Centre Duffel.

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https://doi.org/10.1016/j.bbi.2023.09.014
Received 27 March 2023; Received in revised form 28 August 2023; Accepted 16 September 2023
Available online 22 September 2023

diagnostic subgroups, and between newly admitted (hospitalization ≤ 7 days) and hospitalized patients (hospitalization > 7 days) and correlations between serological and cytokines.
Results: Patients had a significantly higher SARS-CoV-2 seroprevalence (67.85 % [95% CI 62.20–73.02]) than hospital caregivers (27.08% [95% CI 21.29–33.77]), and had significantly higher global SARS-CoV-2 titers ($F = 29.40$, $df = 2$, $p < 0.0001$). Moreover, patients had a 2.51-fold (95% CI 1.95–3.20) higher SARS-CoV-2 exposure risk compared to hospital caregivers (Fisher's exact test, $P < 0.0001$). No difference was found in SARS-CoV-2 seroprevalence and titers between patient subgroups. Patients could be differentiated most accurately from hospital caregivers by their higher Spike protein titers (OR 136.54 [95% CI 43.08–481.98], $P < 0.0001$), lower S1 (OR 0.06 [95% CI 0.02–0.15], $P < 0.0001$) titers and higher IL-6 (OR 3.41 [95% CI 1.73–7.24], $P < 0.0001$) and TNF-α (OR 34.29 [95% CI 5.00–258.87], $P < 0.0001$) and lower titers of IL-8 (OR 0.13 [95% CI 0.05–0.30], $P < 0.0001$). Seropositive patients had significantly higher SARS-COV-2 antibody titers compared to seropositive hospital caregivers ($F = 19.53$, $df = 2$, $P < 0.0001$), while titers were not different in seronegative individuals. Pro-inflammatory cytokine concentrations were not associated with serological status.
Conclusion: Our work demonstrated a very high unrecognized exposure to SARS-CoV-2 among newly admitted and hospitalized psychiatric inpatients, which is cause for concern in the context of highly robust evidence of adverse outcomes following COVID-19 in psychiatric patients. Attention should be directed toward monitoring and mitigating exposure to infectious agents within psychiatric hospitals.

1. Introduction

Bidirectional associations between COVID-19 infections and mental health problems have been recorded throughout the pandemic (Taquet et al., 2021). Evidence has repeatedly shown increased SARS-CoV-2 infection (Wang et al., 2021; Ji et al., 2020; Liu et al., 2021; Bertolini et al., 2023; Karaoulanis and Christodoulou, 2021) and mortality risks in patients with pre-existing severe mental illness (SMI, i.e., major mood and psychotic disorders) (Vai et al., 2022; Vai et al., 2021; De Hert et al., 2022). Higher prevalence of other coronaviruses, such as seasonal human coronavirus (HCoV)-229E, -NL63, -OC43 and -HKU1, have been suggested in SMI, with compelling data linking HCoV to psychosis (Severance et al., 2011). Notably, increased susceptibility to infectious disease in SMI is not limited to coronaviruses, as prior studies described increased IgG antibody levels to human immunodeficiency virus, hepatitis B and C in individuals with SMI (Hughes et al., 2016; Ayano et al., 2020; Braude et al., 2021), elevated levels of Borne disease virus (Azami et al., 2018) and Epstein-Barr virus (Dickerson et al., 2019) in psychotic disorders, and a greater seroprevalence of Toxoplasma Gondii in psychotic disorders (Oncu-Oner and Can, 2022; Monroe et al., 2015) with mixed results for mood disorders (De Barros et al., 2017; Cossu et al., 2022; Snijders et al., 2019; Nayeri Chegeni et al., 2019). Conversely, and similar to other coronaviruses, such HCoV, as well as SARS-CoV-1, and Middle East Respiratory Syndrome Coronvirus (MERS-CoV) (Barthorpe and Rogers, 2022; Delanerolle et al., 2022; Rogers et al., 2020), acute and chronic neuropsychiatric complications develop in up to 30% of COVID-19 survivors (Taquet et al., 2021), and COVID-19-exposed individuals are more likely to develop *de novo* neurological and psychiatric disorders up to one year following acute SARS-CoV-2 infection (Deer et al., 2021; Meza-Torres et al., 2022). These neuropsychiatric complications are not fully preventable by vaccination, and pre-infection psychological distress or mental disorders are a risk factor for developing post-acute COVID-19 syndrome (Wang et al., 2022), as well as breakthrough infections and a poorer serological response after vaccination (Nishimi et al., 2022; Taquet et al., 2022). Somatic comorbidities and other risk factors such as obesity have been considered to contribute to the increased COVID-19 morbidity and mortality in SMI patients, as well as abnormal inflammatory responses (De Hert et al., 2022; Toubasi et al., 2021; Teixeira et al., 2021; Nemani et al., 2022). Hyper-inflammatory responses in both mild and severe cases of COVID-19 are characterized by elevated levels of interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α) (Li et al., 2022; Silva et al., 2022; Hu et al., 2022; Del Valle et al., 2020; Huang et al., 2020; Zheng et al., 2020) and associated with a higher risk of chronicity (IL-6, TNF-a) or severity (IL-8) of COVID-19 symptoms. (Low et al., 2023; Schultheiß et al., 2022; Silva et al., 2022). SMI patients exhibit peripheral changes in the levels of these and other cytokines, including increased levels of IL-6 and TNF-α during acute exacerbations in bipolar (Modabbernia et al., 2013; Rowland et al., 2018; Munkholm et al., 2013; Munkholm et al., 2013), depressive (Dowlati et al., 2010; Köhler et al., 2017; Osimo, 2020; Goldsmith et al., 2016) and psychotic disorders (Goldsmith et al., 2016; Fraguas et al., 2019; Halstead et al., 2023; Frydecka et al., 2018; De Picker et al., 2020). Structural immune dysregulation in therefore hypothesized to trigger hyper-inflammatory responses and adverse outcomes following SARS-CoV-2 infection in SMI patients (De Picker et al., 2021).

Despite their increased risks, SMI patients have been understudied during the pandemic. Reliable estimates of patients' exposure to SARS-CoV-2, in particular in inpatient contexts, and new psychiatric admissions triggered by or associated with COVID-19 are scarce. Hospitalization in itself increases the risk of infections (Jeon et al., 2012), and psychiatric hospitalization poses unique challenges that can make imposing infection control strategies difficult or undesirable (Bojdani et al., 2020; Albert et al., 2021; El Abdellati et al., 2021). The confined environment of inpatient psychiatric facilities exacerbates risk of infection as patients share common areas with limited space for social distancing (Brody et al., 2021; Brody et al., 2021), and a core part of the inpatient standard treatment involves interacting in close proximity with other patients and staff (Zhang et al., 2020). Unsurprisingly, this led to frequent severe COVID-19 outbreaks3, (Brody et al., 2021; Barnett et al., 2020; Krass et al., 2020; Shao et al., 2020). Further limiting our knowledge are methodological shortcomings related to the challenge of reliably identifying past SARS-CoV-2 exposure. Retrospective estimates from positive reverse transcriptase polymerase chain reaction (RT-PCR) or antigen tests and/or clinical COVID-19 diagnoses in electronic health records (EHR) or registries likely underestimate true exposure, in particular in populations with a risk of testing or reporting biases.

In general, most COVID-19 seroprevalence studies solely use qualitative assays for the presence/absence of antibodies against the Spike protein. Additionally, the interpretation of the test results in commercially available quantitative detection kits is hindered by a lack of reference materials, with frequent sensitivity and specificity issues. Quantitative multi-antigen assays provide the highest accuracy to identify previous SARS-CoV-2 exposure because of their enhanced specificity, ideal in low seroprevalence settings (Fotis et al., 2021). To our knowledge, such multi-antigen SARS-CoV-2 assessments have never been applied in psychiatric cohorts.

In this paper, we report the findings from a prospective and multicentric quantitative multi-antigen serological assessment of unrecognized SARS-CoV-2 exposure in patients who are currently hospitalized for acute and severe psychiatric episodes compared to hospital staff as control group, hereafter referred to as hospital caregivers. Our primary objective was to estimate and compare the SARS-CoV-2 seroprevalence and antibody titers of patients and hospital caregivers without history of

COVID-19 infection or vaccination. Secondary objectives included (1) the comparison of SARS-CoV-2 seroprevalence and titers between patients with SMI versus other mental disorders, and (2) between newly admitted (hospitalization $\leq$ 7 days) and hospitalized patients (hospitalization $>$ 7 days). We hypothesized that SARS-CoV-2 seroprevalence would be higher among I) psychiatric inpatients compared to hospital caregivers, as well as II) patients with SMI compared to other psychiatric disorders and III) patients with longer hospitalization duration. Furthermore, we measured pro-inflammatory cytokines (IL- 6, IL-8 and TNF- α) that are both stimulated during acute COVID-19 infection (Li et al., 2022; Silva et al., 2022; Ceban et al., 2021) and post-acute COVID-19 syndrome (Low et al., 2023; Schultheiß et al., 2022), and associated with major psychiatric disorders (Goldsmith et al., 2016; Boerrigter et al., 2017; Skibinska et al., 2022; Reale et al., 2021; Santoft et al., 2020); to investigate possible differences in the pro-inflammatory profile of seropositive and seronegative patients and hospital caregivers.

2. Methodology

2.1. Study design and setting

This multicentric, prospective, clinical, observational study was conducted at the University Psychiatric Centre Duffel, Belgium (UPCD) and at the psychiatric department of Mondor University hospital (DMU IMPACT), Assistance Publique–Hôpitaux de Paris, Créteil, France. The Ethical Committees of the University Hospital Antwerp and Emmaüs vzw, and of Assistance-Publique-Hopitaux de Paris (AP-HP) approved the study in Belgium and France, respectively. We enrolled newly admitted and hospitalized psychiatric patients, and a control cohort of hospital staff from both study sites.

2.1.1. Patient cohort

All newly admitted psychiatric patients and all patients hospitalized in long-stay psychiatric wards during the period between 04/01/2021 and 27/5/2021 were invited to participate in the study. Exclusion criteria were a history of COVID-19 infection, COVID-19 vaccination, and unwillingness or inability to consent.

Demographic and clinical information were collected, including patients' age of illness onset (defined as age at which the first episode of psychiatric illness occurred) and psychiatric diagnosis. None of the participants had a history of COVID-19 infections or received a COVID-19 vaccine prior to study participation. All patients tested negative for COVID-19 on RT-PCR testing within 24 h of admission, or in case of suspicion of COVID-19 infection. Blood samples of newly admitted patients were obtained within 7 days after admission, blood from patients who have been hospitalized longer (>7 days) was acquired in the same period.

Because patients with severe mental illness (SMI) have been identified as an at-risk group for adverse COVID-19 outcomes (for meta-analysis, see (Vai et al., 2021)), including higher mortality estimates than patients with other psychiatric disorders, we categorized patients into SMI and NON-SMI clinical subgroups based on the DSM-5 diagnosis in their clinical records. SMI was defined as psychosis spectrum disorders (PSD; such as [incl. DSM-5 code] schizophrenia [295.90], schizoaffective disorder [295.70], psychotic disorder not otherwise specified [298.9], and delusional disorder [297.1]), unipolar major depressive disorder (MDD, [DSM-5 code: 296.20-29626, 296.30-296.36]) and bipolar disorder (BD, both type I and type II). NON-SMI included other psychiatric conditions, such as anxiety disorders [DSM-5 code: 309.21, 300.29, 300.23, 300.01, 300.22, 300.02], substance use disorders (alcohol and drug related disorders), personality disorders (Cluster A, B, C), and adjustment disorders [DSM-5 code: 309.0, 309.24, 309.28, 309.3, 309.4, 309.9].

2.1.2. Control cohort

Both clinical and non-clinical psychiatric hospital staff of AP-HP and UPCD, referred to as hospital caregivers, were recruited as control group for this study and sampled within the same time period. The same exclusion criteria as for the patient population applied. Hospital caregivers were not systematically screened with RT-PCR tests, but underwent RT-PCR testing in case of suspected COVID-19 infection or following a risk contact.

2.2. Laboratory assays

Blood samples of non-fasting individuals were collected by venipuncture and processed for serum extraction according to standardized protocol, aliquoted and subsequently stored at −80 °C until analysis. Never-thawed aliquots stored less than 6 months before experiments were analyzed using an advanced capillary Western Blot technique and carried out according to the manufacturer's recommendations (Simple Western method Proteinsimple/Bio-techne, San Jose, CA, USA) for SARS-CoV-2 immunoglobulin G (IgG), as has been previously described (Albecka et al., 2021).

A panel of human IgG antibodies reactive against recombinant viral antigens nucleocapsid (NC), Spike (S; full length, consisting of subunits 1 and 2), Spike subunit 1 (S1), Spike subunit 2 (S2) and Spike subunit 1 receptor binding domain (S1-RBD) proteins were quantitatively characterized, and presented as AUC (area under the curve) values on the electropherogram analyzed by the Compass® software provided with the Jess device. An overview of the human SARS-CoV-2 virus protein structures is presented in Fig. 1.

A second panel of pro-inflammatory cytokines associated with both SARS-CoV-2 disease severity (Del Valle et al., 2020) and major psychiatric disorders was assessed. Circulating serum levels of IL-6, IL-8 and TNF-α (COVID-19 Cytokine Storm Panel, Proteinsimple/Bio-techne, San Jose, CA, USA) were measured using immunoassay technique based on microfluidics ELLA assays (enzyme linked immunosorbent assay) with quantitative output (pg/mL). Results were analyzed with Simple Plex Explorer (Proteinsimple/Bio-techne, USA). Analysts were blinded for subjects' clinical status.

2.3. Cut-offs for SARS-CoV-2 seropositivity

We used a cut-off of $1.2\ 10^6$ for the cumulated AUC of chromatogram peaks for all antigens, thus combined to determine the serological status of a sample (conform manufacturer recommendations) (ProteinSimple, 2021). Test results are categorized as SARS-CoV-2 positive above this cut-off of $1.2\ 10^6$, and as negative below the cut-off. This is referred to as the primary cut-off for serological status, or CO1. To further evaluate the robustness of the between-group seroprevalence differences, we performed sensitivity analyses based on auxiliary predetermined criteria for alternative cut-offs (CO2-CO9, summarized in Supplementary Table 1). For these sensitivity analyses, we defined a method to set the detection cut-off specific for SARS-CoV-2 seropositivity determination, including the signal to noise ratio (S/N) specific for the SARS-CoV-2 nucleocapsid (NC), considering that it is the most common antigen against various coronaviruses, as well as for the spike (S) antigen to take into account potential cross-reactivity with other coronaviruses and immunization. To increase reactivity specificity, the S/N ratio for nucleocapsid and spike were set at 10 (according to standard best practice) and 20 (stringent). This way, we can assess the robustness of the between-group seroprevalence differences. For details, see Supplementary Table 1.

2.4. Data processing and statistical analysis

All analyses were performed in JMP® Pro (version 16; SAS Institute Inc., Cary, NC, USA). Non-normally distributed immune parameters (SARS-CoV-2 IgG antibody and cytokine concentration) were log-transformed prior to use of parametric statistics. Statistical significance was set at a P-value < 0.05, and for primary analyses correction for multiple testing was performed using False Discovery Rate (FDR).

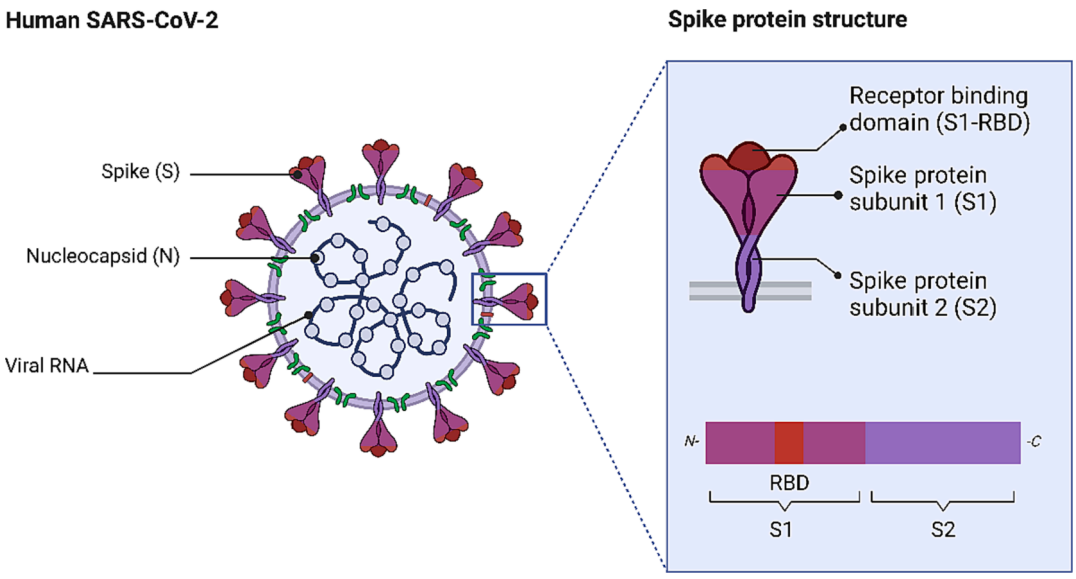

Fig. 1. Schematic representation of human SARS-CoV-2 and its protein structures. Created with BioRender.com.

Differences in clinical and demographic parameters between study sites were examined by two-tailed independent t-tests (followed by Welch's correction) for continuous variables and Pearson chi-square tests in case of categorical variables. Outcomes are presented descriptively, e.g. mean ± standard deviation (SD) and percentages unless otherwise specified.

2.4.1. SARS-CoV-2 seroprevalence rates and antibody titers

We compared SARS-CoV-2 antibody titers and seroprevalence rates between patients and hospital caregivers in both sites. We performed nominal logistic regression to test between-group differences in SARS-CoV-2 seropositivity rates, based on CO1 in main analysis and CO2-CO9 in sensitivity analyses. To account for site effects, we included group (2 levels, patients and hospital caregivers) nested in site (2 levels, UPCD and AP-HP) as fixed effect in the model (serological status = group[site] + site). Quantitative between-group differences in global and multiple antigen-specific SARS-CoV-2 antibody titers were examined using a series of linear regression models (AUC IgG = group[site] + site) in the whole study population and in a subgroup of SARS-CoV-2 positive individuals only. Possible confounding effects of age, sex, duration of psychiatric illness and first psychiatric episodes were investigated.

2.4.1.1. Secondary objectives. To compare SARS-CoV-2 seroprevalence rates and antibody titers between patients of different diagnostic categories and hospitalization durations, we repeated the nominal logistic and linear regression models to compare subgroups: 1) between SMI and NON-SMI, 2) between the largest underlying diagnostic groups (PSD, BD, MDD and other psychiatric diagnoses), and 3) between newly admitted (hospitalization ≤ 7 days) and hospitalized groups (hospitalization > 7 days).

2.4.2. Pro-inflammatory profile

We assessed immune aberrations related to SARS-CoV-2 exposure with linear regression models to determine significant between-group differences (patient v. hospital caregiver; SMI v. NON-SMI; PSD v. BD v. MDD v. NON-SMI) in seropositive and seronegative individuals, also accounting for site effects (pro-inflammatory cytokine = serological status + group[site] + site), and determined if pro-inflammatory cytokine concentration could predict serological status in patients and hospital caregivers (serological status = pro-inflammatory cytokine + group[site] + site). We also tested the discriminatory capacity of the combined serological and immunological markers to accurately differentiate patients from controls in nominal logistic regression (subject = pro-inflammatory cytokines + SARS-CoV-2 antigen-specific antibodies).

2.4.3. Exploratory analyses among SARS-CoV-2 positive individuals

We performed post-hoc exploratory analyses in seropositive individuals to understand underlying differences in the serological and pro-inflammatory signatures between patients and hospital caregivers by repeating the nominal logistic and linear regression models comparing subgroups. Additionally, Pearson correlations were performed to test associations between different serological and pro-inflammatory markers in seropositive subjects.

3. Results

3.1. Characteristics of study population

A total of 285 patients (UPCD N = 194; AP-HP N = 91), and 192 healthy volunteers (UPCD N = 130; AP-HP N = 62) were included in this study. None of the patients had a history of SARS-CoV-2 infection or vaccination. Demographic characteristics of the study population are presented in Table 1A-Table 1B. Of the 194 UPCD patients, 82% were newly admitted (hospitalization ≤ 7 days), and 35 patients had been hospitalized longer. In contrast, the AP-HP patient group consisted of 24.4% (22/90) newly admitted patients, and the other 75.6% (68/90) had a longer hospitalization duration. The majority of both UPCD and AP-HP patients had an SMI diagnosis (67.6%), but the distribution of diagnoses differed between the study cohorts. These contrasts likely reflected differences in the clinical policies for psychiatric hospitalization between the two sites.

3.2. SARS-CoV-2 seroprevalence rates and antibody titers

3.2.1. Patient v. hospital caregiver

A total of 192 out of 283 patients were seropositive to SARS-CoV-2 based on the primary seropositivity cut-off (CO1), corresponding to a seroprevalence of 67.85 % (95% CI 62.20–73.02). Moreover, 52 of 192 healthy hospital caregivers of the UPCD and AP-HP tested in the same period were seropositive, corresponding to a seroprevalence of 27.08% (95% CI 21.29–33.77). This finding remained robust in 8 out of 8 of the sensitivity analyses using more stringent criteria for seropositivity in the total cohort as demonstrated in Supplementary Table 2. Psychiatric

Table 1.A
Characteristics of study population per study cohort.

	UPCD		AP-HP			
	Patients (N = 194)	Hospital Caregivers (N = 130)	Patients (N = 91)	Hospital Caregivers (N = 62)	T-test or χ^2-test	P-value
Age[a,*]	46.5 ± 17.5	46.5 ± 11.0	42.3 ± 15.4	43.6 ± 10.7	3.76	ns
Sex (%F)*	48.5	83.9	41.8	66.1	1.12	ns
SMI-status (%SMI)	60.8	–	82.8	–	13.20	0.0003

a Mean ± SD.
*Missing data AP-HP caregivers.

Table 1.B
Characteristics of study population per study cohort.

	UPCD		AP-HP			
Patients (N, %)	**Newly admitted (159, 82.0)**	**Hospitalized (35, 18.0)**	**Newly admitted (22, 24.4)**	**Hospitalized (68, 75.6)**	**T-test or χ^2-test**	**P-value**
Diagnosis	BD N = 15 MDD N = 51 PSD N = 17NON-SMI N = 76	BD N = 5 MDD N = 3 PSD N = 27NON-SMI N = 0	BD N = 1 MDD N = 6 PSD N = 10NON-SMI N = 3	BD N = 8 MDD N = 12 PSD N = 35NON-SMI N = 11	26.12	<0.0001
DOI < 12 m (%)	31.4	2.9	18.8	12.5	16.83	<0.0001
Age of illness onset[a]	37.9 ± 19.8	32.3 ± 12.6	28.2 ± 14.5	32.3 ± 14.8	2.86	0.046
First psychiatric episode (%)	31.4	2.9	19.1	5.9	24.66	<0.0001
DOH blood draw[a]	2.6 ± 1.6	372.4 ± 442.8	2.8 ± 2.8	187.5 ± 353.5	−6.97	<0.0001

a Mean ± SD.
*Missing data AP-HP caregivers..
DOI: duration of (psychiatric) illness; BD: bipolar disorder; MDD: major depressive disorder; PSD: psychosis spectrum disorder; DOH: duration of hospitalization.

patients had a 2.51 (95% CI 1.95–3.20) fold higher risk of being SARS-CoV-2 positive (Fisher's exact test, $P < 0.0001$) compared to hospital caregivers, and the highest patient-caregiver global seroprevalence difference was observed in UPCD (UPCD OR 8.77 [95% CI 5.00–15.32], $P < 0.0001$; AP-HP OR 4.08 [95% CI 1.98–8.42], $P < 0.0001$).

All psychiatric patients also had significantly higher global SARS-CoV-2 antibody titers compared to their hospital caregivers (see Table 2), both in the entire study population ($F = 29.40$, $df = 2$, $p < 0.0001$) and even among SARS-CoV-2 positive individuals ($F = 19.53$, $df = 2$, $P < 0.0001$).

Overall, patients had elevated titers of spike antibody concentration (S1, S2, S1-RBD and Spike full length), but not nucleocapsid antibody. No difference in mean global SARS-CoV-2 serology was observed among the seronegative samples (Fig. 2).

Furthermore, we did not find any significant effect of age, sex, duration of psychiatric illness or the presence of a first psychiatric episode on SARS-CoV-2 serology.

Table 2
Linear regression model cohort differences in SARS-CoV-2 antigen-specific and global serology in patients and hospital caregivers.

Marker	Term	F-ratio	FDR P-value
Serology			
S1-RBD (AUC)	Group[Site]	10.62	<0.0001
	Site	13.87	0.0002
S1 (AUC)	Group[Site]	3.57	0.0290
	Site	11.73	0.0013
S2 (AUC)	Group[Site]	14.67	<0.0001
	Site	27.84	<0.0001
S (AUC)	Group[Site]	32.48	<0.0001
	Site	11.16	0.0001
NC (AUC)	Group[Site]	3.13	ns
	Site	0.53	ns
Global SARS-CoV2 titer (AUC)	Group[Site]	29.40	<0.0001
	Site	19.19	<0.0001

Based on log-transformed values. AUC: area under the curve; S: spike; NC: nucleocapsid.

3.2.2. *Diagnostic groups and hospitalization duration*

Previous findings suggest patients with SMI to be more susceptible to COVID-19 than patients without SMI (Vai et al., 2021). We therefore reciprocally compared underlying diagnostic groups with (SMI versus other diagnoses) in our study. Global SARS-CoV-2 serology was significantly higher both in the SMI and NON-SMI group as compared to their hospital caregivers, but we did not find significant differences between patients with SMI and other psychiatric disorders in global and antigen-specific SARS-CoV-2 serology (see Table 3), nor in seroprevalence a finding which remained robust in sensitivity analyses with 8/8 more stringent positivity cut-offs (Supplementary Table 3).

We also did not find significant differences in SARS-CoV-2 serology (Supplementary Table 4) between any of the four most prevalent diagnostic groups (BD, MDD, PSD and other psychiatric disorders), nor in seroprevalence (overall seroprevalence BD: 71.42% [95% CI 52.94–84.75], MDD: 73.24% [95% CI 61.95–82.15], PSD: 67.42% [95% CI 57.13–76.26] and NON-SMI: 62.64% [95% CI 52.38–71.88]). The robustness of this finding was confirmed in 8/8 sensitivity analyses (Supplementary Table 5). Similarly, we found no difference between newly admitted and longer hospitalized patients in terms of SARS-CoV-2 seroprevalence rates and antibody titers (see Supplementary Tables 6-7), which we could establish in sensitivity analyses.

3.3. *Pro-inflammatory markers and serological status*

We observed significant differences in serum cytokine concentrations between patients and hospital caregivers, after accounting for site effect (see Supplementary Table 8): mean concentrations of IL-6 and TNF-α levels were significantly higher, while IL-8 was significantly lower among psychiatric patients. However, pro-inflammatory cytokine levels did not differ between seropositive and seronegative individuals. Additionally, we found that pro-inflammatory cytokine concentration could not predict SARS-COV-2 serological status in patients nor in their

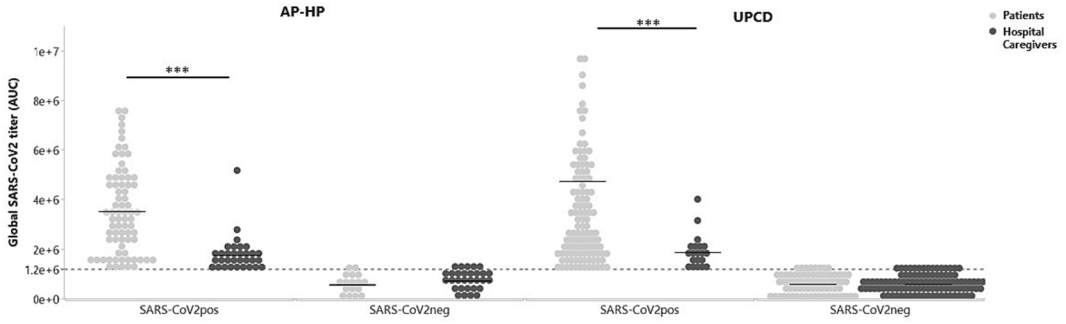

Fig. 2. Global SARS-CoV-2 titer per serological status for patients and hospital caregivers in the AP-HP and UPCD cohorts. AUC: area under the curve.

Table 3
Linear regression model cohort differences in SARS-CoV-2 antigen-specific and global serology in SMI and NON-SMI subgroups.

Marker	Term	F-ratio	FDR P-value
Serology			
S1-RBD (AUC)	Group[Site]	0.94	ns
	Site	1.20	ns
S1 (AUC)	Group[Site]	1.37	ns
	Site	1.01	ns
S2 (AUC)	Group[Site]	0.23	ns
	Site	3.69	ns
S (AUC)	Group[Site]	1.56	ns
	Site	1.80	ns
NC (AUC)	Group[Site]	2.36	ns
	Site	0.03	ns
Global SARS-CoV2 titer (AUC)	Group[Site]	0.99	ns
	Site	1.30	ns

Based on log-transformed values. AUC: area under the curve; S: spike; NC: nucleocapsid.

hospital caregivers (data not shown).

We also found no difference in pro-inflammatory cytokines between seropositive and seronegative SMI and other psychiatric patients (Supplementary Table 8). Similarly, no significant difference in pro-inflammatory cytokine concentration was observed when comparing the underlying diagnoses (PSD, MDD, BD and other psychiatric diagnoses; see Supplementary Table 8) and when comparing newly admitted and hospitalized patient groups (Supplementary Table 7).

3.3.1. Pro-inflammatory profile of patients and hospital caregivers

Based on nominal regression, psychiatric patients could be differentiated most accurately from hospital caregivers by their higher spike protein titers (OR 136.54 [95% CI 43.08–481.98, P < 0.0001), lower S1 (OR 0.06 [95% CI 0.02–0.15], P < 0.0001) titers, and higher levels of IL-6 (OR 3.41 [95% CI 1.73–7.24], P < 0.0001) and TNF-α (OR 34.29 [95% CI 5.00–258.87], P < 0.0001), but lower levels of IL-8 (OR 0.13 [95% CI 0.05–0.30], P < 0.0001), with a combined AUC = 0.89 on the ROC-curve (Fig. 3).

3.4. Exploratory analyses among seropositive individuals

3.4.1. Between-group differences in SARS-CoV-2 antibody titer and pro-inflammatory components in seropositive individuals

All spike antibody concentrations (S, S1, S1-RBD and S2), but not nucleocapsid were significantly higher in seropositive patients compared to hospital caregivers, with a site effect in S2 antibody titers (Table 4). Seropositive newly admitted patients had higher Spike (full length), S2 and global SARS-CoV-2 titers, an effect carried by the UPCD cohort as seen in Supplementary Table 9. In addition, higher duration of psychiatric illness from onset was associated with higher titers for Spike (full length) protein (F = 7.79, df = 2, P = 0.0058). We found no

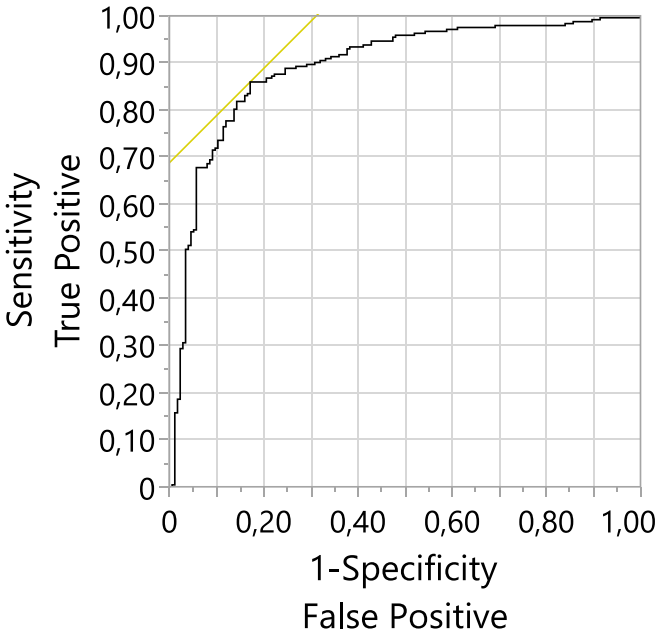

Fig. 3. Receiver operating characteristic (ROC) curve for nominal regression model. ROC curve showing sensitivity versus specificity for discrimination of psychiatric patients and hospital caregivers.

Table 4
Linear regression model cohort differences in global and SARS-CoV-2 antigen-specific serology in seropositive patients and hospital caregivers.

Marker	Term	F-ratio	FDR P-value
Serology			
S1-RBD (AUC)	Group[Site]	5.41	0.0101
	Site	2.89	ns
S1 (AUC)	Group[Site]	5.44	0.0098
	Site	0.37	ns
S2 (AUC)	Group[Site]	13.79	<0.0001
	Site	9.39	0.0024
S (AUC)	Group[Site]	28.79	<0.0001
	Site	3.16	ns
NC (AUC)	Group[Site]	0.85	ns
	Site	0.25	ns
Global SARS-CoV2 titer (AUC)	Group[Site]	19.53	<0.0001
	Site	0.22	ns

Based on log-transformed values. AUC: area under the curve; S: spike; NC: nucleocapsid.

significant differences within diagnostic groups (Table 5-6) in terms of SARS-CoV-2 titers.

Seropositive patients and hospital caregivers were not different in their circulating pro-inflammatory cytokine levels, as seen in

Table 5
Linear regression model cohort differences in global and SARS-CoV-2 antigen-specific serology in seropositive SMI and NON-SMI subgroups.

Marker	Term	F-ratio	FDR P-value
Serology			
S1-RBD (AUC)	Group[Site]	0.02	ns
	Site	0.08	ns
S1 (AUC)	Group[Site]	0.56	ns
	Site	2.20	ns
S2 (AUC)	Group[Site]	0.63	ns
	Site	0.67	ns
S (AUC)	Group[Site]	3.91	ns
	Site	1.58	ns
NC (AUC)	Group[Site]	2.40	ns
	Site	1.64	ns
Global SARS-CoV2 titer (AUC)	Group[Site]	0.71	ns
	Site	0.47	ns

Based on log-transformed values. AUC: area under the curve; S: spike; NC: nucleocapsid.

Table 6
Linear regression model cohort differences in global and SARS-CoV-2 antigen-specific serology in seropositive underlying diagnostic groups.

Marker	Term	F-ratio	FDR P-value
Serology			
S1-RBD (AUC)	Group[Site]	0.34	ns
	Site	0.17	ns
S1 (AUC)	Group[Site]	0.40	ns
	Site	1.53	ns
S2 (AUC)	Group[Site]	0.94	ns
	Site	0.88	ns
S (AUC)	Group[Site]	1.54	ns
	Site	3.34	ns
NC (AUC)	Group[Site]	2.10	ns
	Site	0.89	ns
Global SARS-CoV2 titer (AUC)	Group[Site]	1.97	ns
	Site	0.18	ns

Based on log-transformed values. AUC: area under the curve; S: spike; NC: nucleocapsid.

Supplementary Table 10. However, among seropositive patients, pro-inflammatory cytokines were increased in patients with SMI compared to other psychiatric diagnoses, which was mostly carried by AP-HP.

3.4.2. Correlation analyses

We performed multivariate correlation analysis of all seropositive samples. The correlogram only revealed significant correlations > 0.3 between titers of the spike protein and its subunits in patients, but not in hospital caregivers (Supplementary Fig. 1, for detailed overview see Supplementary Table 11).

4. Discussion

4.1. High unrecognized SARS-CoV-2 exposure of psychiatric patients

This is the first study to perform a multiantigen assessment of SARS-CoV-2 seroprevalence among hospitalized psychiatric patients. Our results reveal a very high unrecognized SARS-CoV-2 exposure of newly admitted and hospitalized psychiatric patients without reported history of infection and no prior vaccination. Patients had an increased seroprevalence and higher antibody titers compared to hospital caregivers, and these findings remained robust across a range of sensitivity analyses using more stringent serological cut-offs.

Previous literature on the prevalence of SARS-CoV-2 infection in psychiatric populations has mostly focused on RT-PCR-based EHR, which reported an increased susceptibility of COVID-19 infection in psychiatric patients (Taquet et al., 2021; Wang et al., 2021; Jeon et al., 2021; Orlando et al., 2021; Yang et al., 2020). Other studies found no, or lower exposure risk in psychiatric patients as compared to non-psychiatric controls (Sass et al., 2022; van der Meer et al., 2020; Tzur Bitan et al., 2021). Notably, these studies also reported disproportionately higher testing rates in the patient groups (van der Meer et al., 2020; Tzur Bitan et al., 2021), which may lead to an underestimation of the risk in people with psychiatric disorders. To date, we found only one cross-sectional study (Sass et al., 2022) performed in Denmark that assessed global IgG-based SARS-CoV-2 seroprevalence in SMI patients receiving inpatient or outpatient care, using a qualitative enzyme-linked immunosorbent assay (ELISA) of S1-RBD SARS-CoV-2 antibodies. This study was performed in a similar time window as our study. The authors found significantly lower SARS-CoV-2 seropositivity among patients with SMI (4.96% [95% CI 3.87–6.35]) than among blood donors (12.24% [95% CI 11.41–13.11]; RR = 0.41 [95% CI 0.31–0.52]; $p < 0.001$). The low patient SARS-CoV-2 seroprevalence rate was attributed to great social assistance and housing, and close interaction between patient and health care provider that might have increased understanding of the pandemic in patients and thereby decreased their risk of infection. Considering our study was performed in the metropole of Paris, France and suburban Duffel, Belgium; with similar health care and social systems as Denmark, and both our patient and control group have no history of SARS-CoV-2 infection; we believe this contrasting outcome can mainly be explained by the limitations of qualitative ELISA solely detecting anti-RBD antibodies as detection method for past SARS-CoV-2 exposure (Brouwer et al., 2021; Ong et al., 2020).

We also found some degree of unrecognized exposure among hospital caregivers. Estimates of unrecognized SARS-CoV-2 infection based on antibody testing among the general population ranged from 20% to 85% (BuitragoBuitrago-Garcia et al., 2020; Oran and Topol, 2021). According to a recent meta-analysis, 35.1% of infections with SARS-CoV-2 are truly asymptomatic (i.e. > 7 days symptom free after test) (Sah et al., 2021), which seems to correspond to the 27.08% seroprevalence found among our hospital caregivers, but does not fully explain the much higher seroprevalence in our patient group.

Psychiatric patients in general are at higher risk of contracting viral infections due to a myriad of factors including immune dysregulation, somatic comorbidities, or symptoms of the mental disorders such as impaired executive functioning. Moreover, hospitalized patients residing in psychiatric inpatient facilities may be at higher risk of viral exposure (Bojdani et al., 2020; Albert et al., 2021), but we found no influence of the duration of hospitalization on the risk of SARS-CoV-2 exposure. Furthermore, it is also possible that our findings reflect a reduced access to RT-PCR testing with mild symptoms, or an altered serological response after COVID-19 infection in patients with mental disorders, with higher antibody titers persisting for a longer period of time after infection compared to controls.

4.1.1. Metropoles v. suburbs

In our study, the seroprevalence was significantly higher for both patients and hospital caregivers in the metropolitan site of Paris (AP-HP) as compared to the Belgian suburbs (UPCD). The dense metropolitan site of Paris was a COVID-19 hotbed in Europe most of the duration of the COVID-19 pandemic. COVID-19 source control and transmission prevention, with strict follow up of measures against COVID-19, and daily nasopharyngeal swab RT-PCR for all new admissions and symptomatic patients and staff have been implemented early and consistently during the pandemic (El Abdellati et al., 2021) in both sites. A higher exposure rate in the metropolitan area is possibly due to the higher use of public transportation, which has previously been associated with SARS-CoV-2 (Ellingjord-Dale et al., 2022). Additionally, differences in COVID-19 policy measures between both countries might have impacted the viral exposure of the population, but this has not been comprehensively investigated.

4.1.2. No difference in SARS-CoV-2 exposure and titers between patient subgroups

Previous studies have provided limited evidence for an increased risk of SARS-CoV-2 infection among patients with SMI (Ji et al., 2020; Liu et al., 2021; Ceban et al., 2021; Seon et al., 2021), in particular depression and psychotic disorders, and in patients with substance use disorders [3; Wang et al., 2021]. In our study, we could not find differences in SARS-CoV-2 global and antigen-specific titers in severe mental illness compared to other psychiatric disorders, or between the diagnostic groups. The interpretation of this finding is however impacted by the limited and unevenly distributed sample sizes of the different diagnostic groups, and the possible confounding effect of the psychotropic (poly)pharmacy (McQueenie et al., 2020). Whether psychopharmaceuticals are associated with higher or lower risk of COVID-19, is still a matter of debate (Vai et al., 2022). Immune-modulatory properties of some psychopharmaceutical drugs have previously been described. Antidepressants were more consistently associated with lower risks of COVID-19 (Vai et al., 2022; De Hert et al., 2022), while both high and low risk of exposure and illness severity were observed for antipsychotics and mood stabilizers (Vai et al., 2022; De Hert et al., 2022; Nemani et al., 2022; De Picker et al., 2022).

4.2. Post-SARS-CoV-2 immune profile in patients

A broad and sustained poly-antigenic immunoreactivity like the one found among patients in our study is usually associated with COVID-19 severity and worse clinical prognosis (Dispinseri et al., 2021; Whitcombe et al., 2021; Moradi et al., 2021; Tea et al., 2021). Notably, a higher IgG response profile is more often observed in patients with persistent post-acute symptoms than in those with acute COVID-19 (Soares et al., 2023). The latter is in line with our own findings, as we found that patients could be differentiated from hospital caregivers by the combination of higher overall spike IgG levels, IL-6 levels and TNF-α levels, and lower levels of IL-8 and anti-S1 antibody titers, which is similar to the immune profile observed in patients presenting with post-SARS-CoV-2 immune profile (Schultheiß et al., 2022; Schultheiß et al., 2023). While the clinical picture of post-acute COVID-19 syndrome commonly includes neuropsychiatric complications (Davis et al., 2023), we should emphasize that none of our participants had received an official diagnosis for post-acute COVID-19 syndrome at the time of inclusion.

Antibody titers reflect the complex interplay between emerging infection and underlying host immunity. Different processes may impact an individual's immunogenicity to SARS-COV-2, including past exposures and pre-existing immunity to other similar viruses, such as seasonal human coronavirus (HCoV). Indeed, increased seroprevalence of seasonal human coronavirus (HCoV) in psychiatric patients as compared to non-psychiatric controls has previously been described (Severance et al., 2011), and a pre-existing immune response elicited by HCoV to SARS-CoV-2 has been proposed to influence the clinical course of COVID-19 (Tornesello et al., 2023; Ng et al., 2020; Bonifacius et al., 2021). Regions of high homology between HCoV and SARS-CoV-2 have been identified as a possible source of this cross-reactivity (Murray et al., 2023). However, the role of cross-reactive antibodies elicited by prior HCoV infections on the clinical outcomes of SARS-CoV-2 infection is currently unclear. While elevated SARS-CoV-2 antibody levels may be induced by pre-existing HCoV exposure, the evoked transient humoral immune response is non-neutralizing and does not protect from SARS-CoV-2 infection (Tornesello et al., 2023; Anderson et al., 2021). Numerous factors contribute to the capacity of an individual to generate cross-reactivity. For example, the nature and extent of immune responses are likely impacted by temporal alignment of distinct viral infections, and both increasing immunological and biological age (Selva et al., 2021).

Overall, patients in our study presented with high titers of spike antibody concentration (S1, S2, S1-RBD and Spike full length), but not nucleocapsid (N) antibody. Higher levels of IgG antibodies against N have been demonstrated both in patients with severe acute disease and those with post-SARS-CoV-2 immune profile as compared to asymptomatic individuals (Tornesello et al., 2023). However, a disparity in longevity of SARS-CoV-2 antibodies has been described, with antibodies targeting the spike domain (RBD, S1 and S2) persisting longer than anti-N protein (Herrington et al., 2021) antibodies. Given that our study participants might not have been recently exposed to COVID-19, low anti-N antibodies are to be expected. Increased Spike antibody titers are positively correlated with severe COVID-19 outcome in general (Ryan et al., 2022; Dan et al., 2021; Piccoli et al., 2020; Robbiani et al., 2020), and have been suggested as the facilitating antibody in individuals with post-SARS-CoV-2 immune profile (Theoharides, 2022). HCoV cross-reactivity primarily boosts antibodies targeting the S2 domain, which is considerably more conserved between HCoV and SARS-CoV-2 than the S1 domain (Anderson et al., 2021; Ng et al., 2021).

Finally, persistently elevated Il-6 and TNF-α levels have previously been associated with post-SARS-CoV-2 immune profiles (Silva et al., 2022). However, the higher concentrations of pro-inflammatory cytokine levels we found in patients are more likely related to patients' underlying psychiatric disorder, considering they were not associated with the serological status, and highest in patients with severe mental illness.

4.3. Limitations and future perspectives

To the best of our knowledge, this is the first study to prospectively screen newly admitted and hospitalized psychiatric patients with severe and acute clinical states for SARS-CoV-2 seroprevalence and antibody titers. Our study has several strengths, including the range of sensitivity analyses for SARS-CoV-2 seropositivity, and the multiantigen assessment which improves diagnostic performance and increases serological specificity (Fotis et al., 2021). We also acknowledge several limitations in our study. Firstly, due to the observational and cross-sectional study design, no conclusions of causality can be drawn. Because we only included individuals who never tested positive for COVID-19, we do not know the timing or the clinical presentation of the acute SARS-CoV-2 exposure, nor how this relates to the current psychiatric symptoms or immune profile. Our current findings only apply to patients without known SARS-CoV-2 exposure, and can therefore not be generalized to patients with clinical COVID-19 infections. Future work should explore how the clinical presentation of the COVD-19 infection, and in particular the severity and chronicity of symptoms, corresponds with IgG titers among psychiatric patients. Secondly, our study samples were collected at two clinical sites with different background exposure to the virus, as well as different demographical characteristics of the sample. The replication of our main findings across the two study sites however reinforces the validity of these results. Thirdly, possible confounders such as comorbid somatic risk factors were not reported or recorded, and individual demographic information (age and sex) for AP-HP caregivers was missing. Finally, both selection and testing bias could have influenced our results. Compared to the general population, hospital employees are both more exposed to infection, but also better informed and equipped to protect themselves against infections which may respectively under- or overestimate the effect sizes in our seroprevalence comparisons. While newly admitted patients were routinely screened with RT-PCR testing, hospital caregivers and hospitalized patients only underwent RT-PCR testing in case of suspected COVID-19 infection or following a risk contact. RT-PCR also has a lower sensitivity in pre- or asymptomatic infection. Because individuals with a history of a positive RT-PCR were excluded from the study, this testing bias could have resulted in a lower seroprevalence among newly admitted patients and a higher seroprevalence among hospital caregivers and hospitalized patients.

Given their susceptibility to severe infection, the identification of factors associated with the risk and outcomes of SARS-CoV-2 infection

among psychiatric inpatients is of critical importance. Previous studies suggested increased vulnerability in psychiatric patients due to 1) underlying immune aberrations related to their psychiatric symptomatology or psychopharmacological drugs, 2) increased vulnerability caused by lifestyle risk factors and comorbidities (Vai et al., 2021), and 3) the fact that understanding healthcare information (De Hert et al., 2022) or gaining access to appropriate healthcare can be challenging for patients. In light of the robust evidence of increased mortality risks following COVID-19 in psychiatric patients, attention should be directed toward monitoring and decreasing SARS-CoV-2 exposure and, for that matter, of any infectious agent within psychiatric hospitals. In this context, the very high unrecognized exposure to SARS-CoV-2 demonstrated in our work is cause for concern and further study.

5. Conclusion

We found high unrecognized exposure to SARS-CoV-2 and robust differences in seroprevalence rates and antibody titers between psychiatric patients and hospital staff among both newly admitted and hospitalized patients. Our study addresses different missing gaps in this topic, and our findings offer opportunities for further research involving other neuro-inflammatory pathways that are triggered by viral infection which will help us further understand these observations.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Unrelated to the submitted work, LDP reports grants from Boehringer-Ingelheim and Janssen R&D, MM reports grants from Janssen R&D, Boehringer Ingelheim Pharma GmbH & Co. and Takeda Pharmaceutical Company, VC reports grants from Janssen R&D and Takeda Pharmaceutical Company, and UM has received financial support from Boehringer Ingelheim Pharma GmbH & Co. and Takeda Pharmaceutical Company. HP receives compensation for his work at Geneuro-Innovation SAS, France, RT, UM, LDP and ML are members of the ECNP Immuno-NeuroPsychiatry Network.

Data availability

Data will be made available on request.

Acknowledgments

This study was completed with the support of the ECNP Immuno-NeuroPsychiatry Network, AP-HP, Université Paris-Est-Créteil (UPEC), Fondation Fondamental, UPCD and the University of Antwerp. We thank all patients and hospital staff who have participated in this study, and express our gratitude to the clinical teams of AP-HP and UPCD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.09.014.

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