Thieme

# Prevalence of COVID-19 and Psychotropic Drug Treatment in Psychiatric In-patients in Germany in 2020: Results from a Nationwide Pilot Survey

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**ABSTRACT**

**Introduction** In patients with a pre-existing mental disorder, an increased risk for a first manifestation of a psychiatric disorder in COVID-19 patients, a more severe course of COVID-19 and an increased mortality have been described. Conversely, observations of lower COVID-19 incidences in psychiatric in-patients suggested protective effects of psychiatric treatment and/or psychotropic drugs against COVID-19.

**Methods** A retrospective multi-center study was conducted in 24 German psychiatric university hospitals. Between April and December 2020 (the first and partly second wave of COVID-19), the effects of COVID-19 were assessed on psychiatric in-patient care, the incidence and course of a SARS-CoV-2 infection, and treatment with psychotropic drugs.

**Results** Patients (n = 36,322) were admitted to the hospitals. Mandatory SARS-CoV-2 tests before/during admission were reported by 23 hospitals (95.8 %), while 18 (75 %) conducted regular testing during the hospital stay. Two hundred thirty-two (0.6 %) patients were tested SARS-CoV-2-positive. Thirty-seven (16 %) patients were receiving medical treatment for COVID-19 at the psychiatric hospital, ten (4.3 %) were transferred to an intermediate/intensive care unit, and three (1.3 %) died. The most common prescription for SARS-CoV-2-positive patients was for second-generation antipsychotics (n = 79, 28.2 %) and antidepressants (SSRIs (n = 38, 13.5 %), mirtazapine (n = 36, 12.9 %) and SNRIs (n = 29, 10.4 %)).

**Discussion** Contrary to previous studies, our results showed a low number of infections and mortality in SARS-CoV-2-positive psychiatric patients. Several preventive measures seem effective to protect this vulnerable group. Our observations are compatible with the hypothesis of a protective effect of psychotropic drugs against COVID-19 as the overall mortality and need for specific medical treatment was low.

## Introduction

COVID-19 (*coronavirus disease 2019)* was first described by the end of 2019 in Wuhan, China, as an infection caused by SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2)* [1]. By March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, which led to massive challenges for public health and for healthcare systems worldwide [2]. Additionally, COVID-19 had a significant impact on mental health, both with respect to the course of pre-existing psychiatric disorders as well as the general health of patients suffering from mental disorders [3, 4].

While a substantial number of neuropsychiatric presentations, including signs and symptoms of anxiety and depression but also psychosis-like features during the acute infection and post-acute phase were observed in previous viral pandemics like the severe acute respiratory syndrome (SARS) or the Middle East respiratory syndrome pandemic [3, 5–8], comparable findings were also reported for the COVID-19 pandemic [9]. Half of these initial findings pertained to the first cases in the Chinese province of Wuhan, were later confirmed in a consecutive review including more than 200 studies indicating a high prevalence of neuropsychiatric symptoms in SARS-CoV-2-positive patients [10]. Further studies supported the observation of an increased first incidence of a mental disorder in COVID-19 patients [11, 12]. Taquet et al. noted that patients who were hospitalized for COVID-19 were at a higher risk for receiving a first diagnosis of a psychotic disorder, especially those patients who suffered from encephalopathy [12], which, however, has been critically discussed to be a diagnostic artifact [13]. The finding of an acute COVID-19 disease to be associated with an increased risk of subsequent psychiatric illnesses, however, has been confirmed in many other studies [6, 14–18].

Vice versa, Taquet et al. [11] reported that patients suffering from a mental illness (particularly mood disorders, anxiety disorders, or psychotic disorders) showed an increased risk for COVID-19. Further, patients with mental disorders have been reported to have a more severe outcome of COVID-19, including admission to an intensive care unit and death, as evidenced by numerous studies [19, 21, 25, 26] and corroborated by a meta-analysis [20]. The same seems to hold true for a pre-existing substance abuse disorder [27]. In a study by Fond et al. [24], older patients with a diagnosis of schizophrenia had a higher risk for death than the control group, but interestingly, less admissions to an intensive care unit were observed, indicating disparities in health care between patients with and without a severe mental disorder. Regarding the more severe course of COVID-19 in patients with a mental disorder, similar results were found by Maripuu et al. [28] in a Swedish population-based register study, showing increased mortality for people with psychosis and bipolar disorder, the risk again increasing with older age. Most noteworthy, higher mortality was seen in patients with schizophrenia as compared to mood disorders [26], which did not display increased mortality.

Although the mechanisms behind the association between COVID-19 and mental disorders are not known [29], there seems to be a bidirectional relationship [11], with an increased risk for psychiatric disorders in COVID-19 patients and a more severe course and higher mortality of COVID-19 in patients with a psychiatric disorder. Several possible factors, from social to psychological up to biological factors, have to be taken into account and may play a significant part [19, 29]. In addition, an overlap between biological and genetic risk factors for COVID-19 and psychiatric disorders might play an important role [30, 31]. As enhanced inflammation represents a major pathomechanism of the SARS-CoV-2 infection affecting peripheral tissue like the respiratory system and the brain [32–34], increased inflammation also plays an important role as a common pathophysiological factor in depression, anxiety, schizophrenia, and other psychiatric disorders with elevated cytokines and other inflammatory factors in the periphery and the brain [35–40]. Thus, the scenario of an interplay between elevated inflammation in the periphery and the brain in COVID-19 and neuropsychiatric disorders seems to be a likely factor explaining the mutual interactions between both pathological conditions.

So far, most studies have indicated a generally increased risk for a SARS-CoV-2 infection and for a more severe course of COVID-19 in patients with a psychiatric diagnosis. However, a few reports suggest a lower risk for COVID-19 and a less severe course of the disease in certain groups of psychiatric patients. Plaze et al. [41] found a much lower incidence of symptomatic courses of a SARS-CoV-2 infection in psychiatric in-patients than in nurses and physicians at the same hospital wards (4 % versus 14 %). Dobre et al. [42] found a lower mortality rate for patients in special psychiatric/COVID wards when compared to the mortality rate assessed by Wang et al. [25] (2 % vs 8.5 %). The authors note that the differences may be explained by the fact that the two studies were conducted in two different countries and health care systems. A similar observation was reported by Villoutreix et al. [43], who suggested a protective effect of psychotropic drugs. In a retrospective epidemiological study in Spain, patients treated with long-acting antipsychotics had a much lower risk for SARS-CoV-2 infection and a much better outcome of COVID-19 infection than a control group [44, 45]. In a large observational study in France, Hoertel et al. [46] found a reduced risk for intubation or death in hospitalized patients with COVID-19 when using antidepressant drugs. Similar data were recently reported for selective serotonin reuptake inhibitors (SSRIs), but not for tricyclic antidepressant use [47]. This effect was mainly seen in psychiatric in-patients within the initial weeks of the COVID-19 pandemic. Subsequently, the studies above-mentioned led to the hypothesis of a beneficial effect of treatment with different psychotropic drugs on the risk of a SARS-CoV-2 infection and on the course of COVID-19 due to their proposed anti-inflammatory effects [48–51]. This hypothesis has been supported by the results of two prospective double-blind studies [52, 53] and a prospective open study [54] showing a less severe progression of COVID-19 in patients treated with fluvoxamine, which indicates a protective effect of fluvoxamine. However, real-life data that shows the positive effects of various psychotropic substance classes on COVID-19 outcomes is limited. Also, the implementation and consequences of preventive hygiene concepts in psychiatric hospitals on the number and consequence of a SARS-CoV-2 infection remain uncertain.

Therefore, we initiated the present pilot survey evaluating preventive measures in psychiatric hospitals in Germany, the number of COVID-19 cases in psychiatric hospitals, and the course and outcome of COVID-19 in patients admitted to academic psychiatric hospitals in relation to subsequent treatment with psychotropic drugs during the first and partly second pandemic wave.

## Methods

### Survey in psychiatric hospitals

In the present pilot survey, we evaluated the impact of the COVID-19 pandemic on psychiatric university hospitals in Germany focusing on preventive measures for COVID-19. Besides general information about preventive measures, we specifically asked for the number of SARS-CoV-2-positive patients and the course and outcome of the COVID-19 illness, somatic comorbidities, and the treatment with psychotropic drugs.

We contacted all German Psychiatric University Hospitals for participation via personal email contact using the mailing list of the Association of Heads of Department of Psychiatry in Germany (LIPPs e.V.; www.uni-lipps.de). Out of 38 university departments, 24 responded and completed the retrospective anonymous survey, including the time from April until December 2020. This study can, therefore, be considered a representative of academic psychiatric settings in Germany. A standardized questionnaire was sent to the hospitals for data acquisition. In this retrospective survey, no individual patient data was obtained, and all the information was anonymized so that no ethical vote was required according to German law.

We asked the participating institutions for information about restrictions on the number of admissions in general, limitations on the therapeutic portfolio**,** assumed financial losses due to COVID-19, as well as loss of clinical staff due to the COVID-19 pandemic. We also asked for information about the management of COVID-19 restrictions regarding SARS-CoV-2 testing, especially the frequency of SARS-CoV-2 tests, implementation of an isolation ward for SARS-CoV-2-positive patients within the psychiatric clinic and an obligatory transfer to non-psychiatric isolation wards if a SARS-CoV-2 test was positive.

The participating hospitals reported the total number of admissions between April 2nd and December 31st 2020, the number of SARS-CoV-2-positive cases, and the number of patients requiring specific somatic or even ICU care due to COVID-19 at this time. Additionally, we asked the participating hospitals to report further information about the SARS-CoV-2-positive cases, including age, main psychiatric diagnosis (specified by the International Statistical Classification of Diseases and Related Health Problems (ICD-10)), medication, occurrence and severity of COVID-19 symptoms, required somatic care as well as information about a lethal outcome.

### SARS-CoV-2-positive cases in the city of Frankfurt in the time from April until December 2020: a non-psychiatric cohort

The Frankfurt Health Protection Authority reported the number of all SARS-CoV-2-positive cases for the city of Frankfurt am Main

(total population about 758 847 [55]) in the time from April until December 2020. In addition, information about age, required medical care, or hospital admission, as well as information about a lethal outcome, were followed up and reported. Importantly, it is mandatory in Germany to report positive SARS-CoV-2 tests, while testing was only required for specific purposes so that the actual number of infections may be up to five times higher than reported cases [56].

### Statistical analysis

The obtained data was assessed by the Statistical Package for Social Sciences (IBM SPSS Statistics Version 28.0.0.0) and Microsoft Excel (Version 16.74). For descriptive analyses, frequencies, percentages, means, standard deviation, and minimum and maximum values, were assessed. For correlation analysis, Spearman-Rho and Kendall-Tau-b were performed, with significance was established at $p < 0.05$.

## Results

### Preventive and organizational measures in psychiatric hospitals and their consequences

All 24 participating psychiatric hospitals provided information about organizational adjustments, including preventive measures, due to the COVID-19 pandemic (▶ **Table 1**). Mandatory care service for psychiatric patients in their region was provided by 18 hospitals (75 %). Out of the 24 hospitals, 21 (88 %) reported a fewer number of admissions between April and December 2020 due to restrictions imposed by COVID-19-related organizational measures. Twenty-two hospitals (92 %) had to restrict therapies for in-patients (e. g., group therapies or a number of available therapies). Economic losses due to the COVID-19 pandemic were reported by 19 hospitals (79 %). One hospital had to reduce staff due to economic losses, while 13 hospitals (54 %) reported a staff shortage due to COVID-19 itself.

Twenty-three hospitals (95.8 %) screened for SARS-CoV-2 before or during admission to the hospital and 18 hospitals (75 %) reported regular SARS-CoV-2 tests during the hospital stay. Twenty-one hospitals (88 %) reported that patients had to be isolated at special areas within the psychiatric hospital until the SARS-CoV-2 test results were available. A special isolation ward for SARS-CoV-2-positive patients was implemented in 21 hospitals (88 %), while six hospitals (25 %) reported an obligatory transfer to non-psychiatric isolation wards if the SARS-CoV-2 test was positive. Thus, most SARS-CoV-2-positive patients continued to be cared for at the psychiatric hospital.

▶ **Table 1** Impact of the COVID-19 pandemic on the organization of the participating 24 psychiatric hospitals and patient care. SARS-CoV-2: *severe acute respiratory syndrome coronavirus 2*; COVID-19: coronavirus disease 19

| | Yes | No | Not specified |
|---|---|---|---|
| | N (%) | N (%) | N (%) |
| SARS-CoV-2 screening | | | |
| before admission | 23 (95.8) | 0 (0) | 1 (4) |
| regularly during the hospital stay | 18 (75) | 5 (21) | 1 (4) |
| Isolation until SARS-CoV-2 test result | 21 (88) | 1 (4) | 2 (8) |
| Isolation ward within the psychiatric hospital for COVID-19 cases | 21 (88) | 2 (8) | 1 (4) |
| Obligatory transfer to a non-psychiatric isolation ward if the SARS-CoV-2 test is positive | 6 (25) | 17 (71) | 1 (4) |
| Mandatory psychiatric service | 18 (75) | 4 (17) | 2 (8) |
| Restrictions | | | |
| on the number of admissions | 21 (88) | 1 (4) | 2 (8) |
| on available in-patient therapies | 22 (92) | 0 (0) | 2 (8) |
| Losses due to COVID-19 pandemic | | | |
| economic losses | 19 (79) | 3 (13) | 2 (8) |
| staff reduction due to economic loss | 1 (4) | 21 (88) | 2 (8) |
| staff shortage due to COVID-19 | 13 (54) | 9 (38) | 2 (8) |

### Prevalence and severity of SARS-CoV-2 infection in in-patients of psychiatric hospitals

During April and December 2020, 36,322 hospital admissions were reported by the 24 participating psychiatric hospitals (mean = 1,513, SD = 1,154, min = 300, max = 4,724). During this period, 232 patients (0.6 %) tested positive for SARS-CoV-2 (per institution: mean = 10, SD = 15, min. = 0, max. = 60). The mean age was 51 years (SD = 21; min = 9, max = 94). Out of these 232 patients, 37 (16 %) patients required specific medical treatment, 10 (4.3 %) were transferred to an ICU, and three (1.3 %, which represent the overall infection fatality ratio) patients died of COVID-19 (▶ **Table 2**).

▶ **Table 2** Characteristics of all SARS-CoV-2-positive patients admitted to the 24 psychiatric university hospitals between April and December 2020. The table presents the number of all patients admitted to the clinics for in-patient treatment, the number of SARS-CoV-2-positive cases, the number of patients requiring specific COVID-19 treatment, the number of COVID-19 patients requiring intensive care treatment, and the number of COVID-19 patients who died due to Sars-CoV-2; *means ± SD. SARS-CoV-2: *severe acute respiratory syndrome coronavirus 2*; COVID-19: coronavirus disease 19

| | Total number (%) | Number per hospital*(min-max) |
|---|---|---|
| All admissions to psychiatric hospitals | 36 322 (100) | 1513 ± 1154*(300–4724) |
| SARS-CoV-2 positive psychiatric in-patients | 232 (0.6) | 10 ± 15*(0–60) |
| Patients needing specific medical treatment due to COVID-19 | 37 (0.1)/(16) | 1.5 ± 2.7*(0–10) |
| Patients needing ICU treatment due to COVID-19 | 10 (0.03)/(4.3) | 0.4 ± 1.1*(0–2) |
| COVID-19 associated deaths | 3 (0.008)/(1.3) | 0.1 ± 0.4*(0–2) |

Most psychiatric hospitals (n = 18; 75 %) reported none to ten SARS-CoV-2-positive psychiatric patients during the assessed time. Four hospitals (17 %) reported 11 to 15 SARS-CoV-2-positive patients and only two hospitals (8 %) reported 49 and 60 SARS-CoV-2-positive patients, respectively. Notably, both hospitals had high overall admission rates (n = 2761 and n = 4724). More than half of the psychiatric hospitals (n = 14; 58 %) reported no need for specific medical treatment for any of the SARS-CoV-2-positive patients (58 %). Seven hospitals (29 %) reported one to four SARS-CoV-2-positive psychiatric patients who needed COVID-19-specific medical treatment. One psychiatric hospital reported the need for COVID-19-specific medical treatment in six SARS-CoV-2-positive patients, while only two hospitals (8 %) reported seven respectively ten cases of specific medical treatment needed for the SARS-CoV-2-positive patients. Again, those hospitals had high overall admission rates (n = 2761 and n = 4724) as well as a high number of SARS-CoV-2-positive patients (n = 49 and n = 60). Notably, 18 psychiatric (75 %) hospitals reported no need for intensive care treatment for the SARS-CoV-2-positive patients. Four hospitals (17 %) reported one patient needing intensive care treatment. Only one hospital each reported two (4 %) respectively five (4 %) cases of needed intensive care treatment for SARS-CoV-2-positive psychiatric patients (▶ **Table 3**). Concerning COVID-19-associated mortality, 22 (92 %) psychiatric hospitals reported no death due to COVID-19. One psychiatric hospital reported one death, and another reported two deaths due to COVID-19.

## Diagnoses and treatments of SARS-CoV-2-positive patients

More detailed information about the SARS-CoV-2-positive patients could be obtained for 165 cases (71 % of all cases) (▶ **Table 4**). Mood disorders (F3x) were the most common diagnosis (n = 70), followed by neurotic, stress-related, anxious, or somatoform disorders (n = 25). The mean age of SARS-CoV-2-positive patients was 51 years (SD 21; min 19, max 94). There was a significant correlation between the severity of symptoms and COVID-19-specific medical treatment ($p < 0.001$), and between age and severity of symptoms ($p = 0.009$).

Regarding COVID-19 symptoms, 55 (33 %) SARS-CoV-2-positive patients reported no COVID-19 symptoms. Fifty-seven (35 %) SARS-CoV-2-positive patients reported only mild symptoms, 12 (7 %) reported moderate and 7 (4 %) severe symptoms due to COVID-19 (▶ **Table 3**).

Ninety-two (56 %) SARS-CoV-2-positive psychiatric patients required no specific treatment against COVID-19. A close monitoring of COVID-19 symptoms was necessary in 34 patients (21 %). Seven patients (4 %) required oxygen supply, five patients (3 %) were transferred to an intermediate care unit, and two patients (1 %) to an intensive care unit (▶ **Table 3**).

Information about psychotropic drug treatment was available for 165 (71 %) of the SARS-CoV-2-positive patients. In total, 280 prescriptions for psychotropic drugs were assessed (▶ **Table 6** online). The most common prescription was for second-generation antipsychotics (n = 79, 28.2 %). The next most common prescription was for SSRIs (n = 38, 13.5 %), mirtazapine (n = 36; 12.9 %), and

▶ **Table 3** Specific information about SARS-CoV-2-positive psychiatric patients regarding age, COVID-19 symptoms, and required COVID-19 treatment. SARS-CoV-2: *severe acute respiratory syndrome coronavirus 2*; COVID-19: coronavirus disease 19

| | **Mean ± SD (min-max)** |
|---|---|
| **Age (years)** | **51 ± 21 (19–94)** |
| | **N (%)** |
| COVID-19 symptoms | |
| no symptoms | 55 (33) |
| mild symptoms | 57 (35) |
| moderate symptoms | 12 (7) |
| severe symptoms | 7 (4) |
| COVID-19 associated treatment | |
| no specific treatment | 92 (56) |
| close monitoring | 34 (21) |
| oxygen requirement | 7 (4) |
| intermediate care unit | 5 (3) |
| intensive care unit | 2 (1) |

▶ **Table 4** Main diagnosis (according to ICD-10) of the 165 SARS-CoV-2 positive psychiatric patients admitted to the psychiatric departments. SARS-CoV-2: *severe acute respiratory syndrome coronavirus 2*

| **Diagnoses** | **Number of admitted patients (%)** |
|---|---|
| F0x (organic, including symptomatic mental disorders) | 22 (13.3) |
| F1x (mental and behavioral disorders due to psychoactive substance use) | 24 (14.5) |
| F2x (schizophrenia, schizotypal, and delusional disorders) | 18 (10.9) |
| F3x (mood (affective) disorders) | 70 (42.4) |
| F4x (neurotic, stress-related, and somatoform disorders) | 25 (15.2) |
| F6x (disorders of adult personality and behavior) | 3 (1.8) |
| F7x (mental retardation) | 2 (1.2) |
| F9x (behavioral and emotional disorders with onset usually occurring in childhood and adolescence) | 1 (0.6) |

▶ **Table 5** Characteristics of all SARS-CoV-2 positive cases registered in the city of Frankfurt between April and December 2020 (data obtained by the Frankfurt Public Health Office; data as of 01.06.2021). SARS-CoV-2: *severe acute respiratory syndrome coronavirus 2*

| | **Age (years) (means ± SD) (min-max)** |
|---|---|
| **Age (years)** | **44 ± 18 (18–106)** |
| | **Number of patients (%)** |
| all SARS-CoV-2 positive cases | 18453 (100) |
| hospital admissions | 2096 (11.4) |
| due to COVID-19 | 1112 (6) |
| due to other disease | 423 (2.3) |
| for isolation purpose | 12 (0.1) |
| unknown reason | 36 ( 0.2) |
| Deaths | 472 (2.6) |

serotonin and norepinephrine reuptake inhibitors (SNRI; n = 29, 10.4 %). First-generation antipsychotics were prescribed 24 times (8.6 %), mostly phenothiazines (n = 9) and butyrophenones (n = 15). Benzodiazepines were prescribed in 21 cases (7.5 %) and pregabalin in 6 cases (2.1 %). Less common prescriptions were for mood stabilizers (n = 17; 6.4 %), other antidepressants (n = 11, 3.9 %), tricyclic antidepressants (n = 8, 2.9 %), and antidementia drugs (n = 2, 0.7 %). Fifty-seven patients (34.3 %) received two different psychotropic drugs. Fifty-six patients (33.7 %) were treated with one psychotropic drug. Twenty-six patients (15.7 %) received three different psychotropic drugs, and nine patients (5.4 %) received four different drugs. In 18 cases (10.8 %), no medication was reported, although it is unclear if patients did not receive any psychotropic drugs or if data was missing.

Information on comorbid somatic diagnosis was available in 82 cases, with a diagnosis of hypertension being the most common (n = 28). Twenty patients had no reported comorbid diagnosis. Seventeen patients had a neurological diagnosis in their medical history, with known epilepsy being the most common (n = 5). Diabetes was present in 12 patients; 9 patients had an additional cardiovascular disease (▶ **Table 7** online).

### Results for the control group provided by the Frankfurt Health Protection Authority

Between April and December 2020, 18,453 SARS-CoV-2-positive cases (2.5 % of the total city population) were registered at the Frankfurt Health Protection Authority (▶ **Table 5**). The mean age was 44 years (SD 18; min 18, max 106). Two-thousand ninety-six patients (11.3 %) positive for SARS-COV-2 were admitted to a hospital during that time, in 6 % (n = 1,112) due to COVID-19, in 0.1 % (n = 12) for isolation, in 2.3 % for other reasons (n = 423). Four hundred seventy-two of the SARS-CoV-2-positive patients died (2.6 %). There was a significant correlation between age and mortality ($p < 0.001$), age and hospitalization ($p < 0.001$) and between hospitalization and mortality ($p < 0.001$).

## Discussion

Many studies indicate that COVID-19 is associated with an increased risk for psychiatric disorders, including depression, anxiety, and psychotic disorders. Similar findings have been reported during other Coronavirus infections [3]. Importantly, further studies showed an increased risk for a SARS-CoV-2 infection and a more severe course of COVID-19 in psychiatric patients [11, 21, 22, 25], although comorbidity may have an important role therein. Comorbid medical conditions are frequent, especially in severe mental disorders, leading to reduced life expectancy; if they are accounted for, increased COVID-19 mortality rates in mental disorders were no longer observed [57]. Our study showed that during the first and partly during the second pandemic wave, there were low rates of infections and mortality due to COVID-19 and the efficacy of measures taken to protect the vulnerable population of people suffering from mental disorders. This timeframe poses a suitable period for our research questions as, at this time-point, the menace of the unknown consequences of the pandemic and the lack of options for vaccination were two major aspects impacting care in hospitals.

### Effects of the COVID-19 pandemic on psychiatric in-patient care in University Hospitals

In contrast to the above-mentioned higher risk for COVID-19 in psychiatric patients, the availability of psychiatric care was widely reduced during the COVID-19 pandemic, with contradicting data about the actual utilization of mental health care systems by psychiatric patients [58, 59]. Simpson et al. [58] found that the impact of the pandemic on volumes and hospitalizations varied by site among three psychiatric emergency services across the United States. Aly et al. [59] found a stable number of psychiatric consultations in their study, while the share of psychiatric emergency visits was increased. Hoyer et al. [60] reported a decreased number of psychiatric emergency contacts in Germany during the COVID-19 pandemic. In a retrospective study conducted in Germany between March and May 2020, the authors showed that emergency hospital admissions as well as the length of the hospital stay, significantly decreased [61]. These findings are in line with further studies showing decreased emergency service visits due to mental illnesses [62–65]. Adorjan et al. [66] showed in a study conducted in Germany that although psychiatric hospitals were responding effectively to the COVID-19 pandemic concerning preventive measures, the reduction of treatment capacity led to a worsened care situation for psychiatric patients.

Similar to the previous reports, most of the 24 participating hospitals reported a reduced number of admissions (n = 36.322) during the time of the survey and economic losses, reduced availability of nursing and medical staff, and restrictions on therapeutic options. However, contrary to many other studies indicating an increased risk for COVID-19 in patients with a psychiatric diagnosis, the number of SARS-CoV-2-positive patients at the time of admission or during the hospital stay in our survey was rather small (n = 232) and made up only 0.6 %. As indicated by the data provided by the Frankfurt Health Protection Authority, even for the general population of the city of Frankfurt, the infection rate was about 2.5 % during the same period. This is substantially higher than the infection rate in our cohort of admitted psychiatric patients, which have been described as a high-risk population in other studies.

### COVID-19 morbidity and mortality in psychiatric in-patients

Most SARS-CoV-2-positive psychiatric in-patients reported only mild symptoms (35 %) while 7 % reported moderate and 4 % severe symptoms. Noticeably, 33 % reported no COVID-19-associated symptoms at all. Overall, we could not confirm a more severe course in COVID-19 psychiatric patients, as reported by several previous mentioned studies. Moreover, the results seem more in line with early data from China characterizing COVID-19 patients in general [67]. The mean age of SARS-CoV-2-positive patients (51 ± 21.0 years) in our survey was slightly higher as compared to data from Fasshauer et al. [61, 68] assessing the mean age of all psychiatric admissions during the same time span to different psychiatric hospitals in Germany. Also, the mean age of SARS-CoV-2-positive psychiatric patients was higher than the mean age of SARS-CoV-2-positive patients in the population of Frankfurt during the same time span (assessed by the Frankfurt Health Protection Authority) (44.2 ± 18.4 years).

When comparing COVID-19-related mortality rates, case fatality ratios (CFR) have to be distinguished from infection fatality ratios (IFR). The latter relate deaths to the number of overall infections, whereas the former relate deaths to the number of cases. As screening for SARS-CoV-2 on admission and during in-patient stay was mandatory in all but one hospital in our study, our data can be interpreted as IFR numbers. Our sample had an overall size of n = 36,322; thereof, 232 patients tested positive (0.6 %), of which three died, which corresponds to an IFR of 1.3 %. Due to the low absolute number, this must be interpreted with caution. It is well known that comorbid conditions and especially age, have a large effect on the IFR; in the age group up to 59 years of age < 0.5 %, ca. 1 % for those aged 60 to 69 years, and > 10 % for those > 75 years [56]. Given the low numbers, solid statistical comparison with published IFR is hard; however, our data do not argue that the IFR is dramatically different in psychiatric in-patients as compared to the general population.

SARS-CoV-2-related fatalities from the Frankfurt general population, provided by the Frankfurt Health Protection Authority, can be considered as CFR as mainly symptomatic individuals were tested (although this also extended also to non-symptomatic individuals and patients symptomatic for other reasons). The CFR in Frankfurt in 2020 was 2.6 %, and hence twice the number of the IFR found in our sample. Assuming a factor of three to five regarding underreporting again puts our IFR in the same range as expected for the general population. Regarding population-based mortality, 112,826 patients died of COVID-19 in Germany in 2020, corresponding to 0.13 % of the German population [69]. In our sample, 0.008 % of psychiatric in-patients died of COVID-19. Again, due to the small number of deceased cases, we abstained from statistical comparison. However, we cautiously conclude from this data that mental disorders, at least in an in-patient setting, do not lead to increased mortality rates due to COVID-19, probably due to early intervention and also due to the preventive interventions implemented at the hospitals, which prove to be efficacious.

Still, even though there was a significant correlation between age and severity of symptoms in our survey and higher age has been discussed to be a risk factor for a more severe course of COVID-19 as well as higher mortality [25], mortality was lower in our cohort of psychiatric patients also when compared to the general population of Frankfurt (1.3 % vs. 2.6 %) despite the higher mean age in our patients.

## Effect of a psychiatric diagnosis on the incidence and course of COVID-19

The rather low infection rate of 0.6 % is remarkable since several reports have pointed to an enhanced risk for a SARS-CoV-2 infection for patients with a psychiatric diagnosis [20, 25]. Previous studies suggested that patients with a psychotic disorder or addictive disorder might be at higher risk for COVID-19 [70, 71]. Interestingly, we saw fewer SARS-CoV-2-positive patients with a substance-related disorder and a high percentage of patients with a mood disorder and anxiety disorder. Mood disorders were the most common main diagnosis (about 42.4. %), this being in line with previous data from Adorjan et al. [66]. As we only assessed the diagnosis from SARS-CoV-2-positive patients, it remains unclear if patients with a mood disorder had a higher risk for a SARS-CoV-2 infection or if the total number of admissions due to a mood disorder was higher. Notably, previous studies showed a significant reduction in emergency hospital admissions due to affective disorders during the pandemic [61, 62]. Fasshauer et al. [61, 68] assessed all psychiatric diagnoses leading to hospital admission in the same period as our survey in several psychiatric hospitals in Germany. The total number of admissions was significantly lower when compared to a pre-pandemic control period, with substance-related disorders being the most common diagnosis before and during the pandemic, the overall reduction in admissions affecting all psychiatric diagnosis groups, with a significant reduction of admissions for affective disorders [61, 68].

Regarding the increased risk for COVID-19 in patients with depression, ADHD, bipolar disorder, or schizophrenia, several risk factors were discussed [25]. Apart from difficulties in appraising health information and complying with preventive measures, life circumstances, including housing (e. g., hospitals, residences, unstable housing, or homelessness) and a more unsafe environment due to socioeconomic disadvantages might put psychiatric patients at higher risk. Furthermore, the authors of the above-mentioned study discuss a disorder related elevated risk e. g., inattention in ADHD or delusional symptoms in schizophrenia leading to limited mask-wearing or the high risk for comorbid medical conditions in psychiatric patients causing severe COVID-19 illness [25]. Yao et al. [72] hypothesized that a general vulnerability to infections, a greater risk-taking behavior, as well as lower availability of psychiatric care and treatments are responsible for the higher risk for COVID-19 and, in particular, a higher risk for a more severe course of COVID-19 and higher mortality in psychiatric patients. Lee et al. [73] noted that even though people with a previous diagnosis of a mental disorder had no increased risk for a SARS-CoV-2 infection in a cohort study from Korea, they had a slightly higher risk for a more severe clinical outcome of COVID-19. The authors suggested that a reduction in self-care and risk avoidance, isolation from society, and physical health conditions might be responsible for the effect of the severity of mental illnesses on the outcome of COVID-19. They conclude that a severe mental illness is a relevant risk factor for a severe COVID-19 illness, and psychiatric care should be included when those patients are treated for COVID-19. Moreover, the reduction of psychological distress might have a relevant impact [74].

Addressing the higher risk for a SARS-CoV-2 infection and more severe course of COVID-19 in psychiatric patients due to several risk factors as mentioned above, preventive measures, e. g., special isolation wards for psychiatric COVID-19 patients, were established in several countries [75–78]. In line with this approach, the participating hospitals in our survey reported preventive measures, e. g., special isolation wards within the psychiatric clinics or regular SARS-CoV-2 screenings before and during the hospital stay. Therefore, as the infection rate in our survey was low, we argue that many preventive measures taken by psychiatric hospitals seem to have been effective in reducing the enhanced risk for psychiatric patients. Factors related to the hospital admission and stay (general hygiene, isolation, further restrictions) could be connected with the relatively low risk of a SARS-CoV-2 infection in our patients.

Additional risk factors for a more severe course of COVID-19 are somatic comorbidities like cardiovascular, respiratory, metabolic,

and infectious diseases [42, 57, 73]. This seems notable as psychiatric patients are also at risk for the above-mentioned somatic comorbidities. In line with these observations, we found a substantial number of somatic comorbidities in the 232 COVID-19 patients admitted to one of the participating hospitals, including hypertension, metabolic, pulmonary, and neurological diseases. Still, while psychiatric patients are already at risk for the above-mentioned somatic comorbidities and somatic comorbidity, e. g., hypertension, seems to be a substantial risk factor for the outcome of psychiatric COVID-19 patients [42, 57, 79], the results of low infection rates in our cohort, as well as a mild course of COVID-19 and a low death rate, seems even more notable. Regarding the higher risk for a more severe course of COVID-19 in psychiatric patients with somatic comorbidities [57], the available medical treatment during the stay at the hospitals may have played a role in the course of COVID-19.

However, while it is quite feasible that these factors are partially relevant for the low infection rate, they are less likely to have a major impact on the benign course of COVID-19, including the comparably low death rates. Besides social (e. g., reduced self-care) and psychological factors (e. g., enhanced stress), biological factors therefore seem to play a major role [19, 29]. It appears that within the biological factors, inflammation is the best candidate as many findings indicate elevated mechanisms of inflammation in COVID-19 as the most likely common pathophysiological risk factor [25, 48, 80], affecting peripheral tissues like the respiratory system but also the brain [32]. In fact, neuroinflammation seems to be specifically relevant for psychiatric symptoms in the first weeks after the index infection with SARS-CoV-2 [80]. On the contrary, increased inflammation plays an important role as a common pathophysiological factor for depression and anxiety, as well as other psychiatric disorders with elevated measures of cytokines and other inflammatory markers in the periphery and the brain [35–40, 81, 82]. Thus, the scenario of an interplay between elevated inflammation in the periphery and the brain during COVID-19 and neuropsychiatric disorders, like depression [81], schizophrenia [40], and bipolar disorder [82] seem to be the most likely factor explaining the mutual interactions between both pathological conditions [25, 33].

## Effect of psychotropic drug treatment on incidence and course of COVID-19

Contrary to this interplay and the well-documented higher infection rate for COVID-19 and a higher rate of mortality in psychiatric patients [21, 25], a few other reports suggested rather low SARS-CoV-2 infection rates or less severe course of COVID-19 in psychiatric in-patients [41–43]. However, most of these findings were made at specific psychiatric wards and in patients who required treatment with psychotropic drugs [41–43]. This finally led to the concept of a beneficial effect of psychotropic drug treatment on the risk of getting COVID-19 and on the course of COVID-19 due to the intrinsic anti-inflammatory properties of psychotropic drugs [48, 83–86]. Plaze et al. [41] found fewer cases of symptomatic COVID-19 in psychiatric patients than among healthcare staff at the same hospital wards in French hospitals (4 % versus 14 %). A similar observation was reported by Villoutreix et al. [43], who suggested a protective effect of psychotropic drugs. Plaze et al. [41] speculated about a protective effect of the therapy with psychotropic drugs, especially with antipsychotics of the phenothiazine type. Further clinical data for chlorpromazine or other phenothiazine antipsychotics have not yet been reported [48]. In a retrospective epidemiological study in Spain, patients treated with long-acting antipsychotics (aripiprazole, risperidone, paliperidone) had a much lower risk for a SARS-CoV-2 infection and a much better outcome in the case of COVID-19 than a control group [44]. Similar results were shown by Canal-Rivero et al. [44], who showed lower COVID-19 incidences in psychiatric in-patients compared to the general populations of Sevilla. Still, only psychiatric patients treated with long-acting antipsychotics were included in this study. Rather low SARS-CoV-2 infection rates have also been reported for schizophrenic in-patients in Mexico [87] and Romania [88]. In both studies, the authors speculated about the protecting role of the treatment with antipsychotics.

Several studies reported possible protective effects of antidepressant drugs in COVID-19 patients [46, 47, 50, 83, 89–91]. Notably, most of the patients in our survey were prescribed more than one psychotropic drug. Further, only 21 patients received medication with benzodiazepines, a drug group associated with an increased incidence of infections, by activating GABA-ergic receptors in immune cells [92]. This appears interesting as benzodiazepines have been associated with a rather poor outcome in COVID-19 patients [93]. Therefore, the rather low number of benzodiazepine prescriptions might be an additional factor responsible for the rather less severe course of COVID-19 in our survey.

As the protective effects of psychotropics drugs were mainly seen in psychiatric patients under drug treatment within the first weeks of SARS-CoV-2 infection, the observation would agree with a complex interaction of the neuroinflammation during the acute phase of the COVID-19 and the intrinsic anti-inflammatory effects of many antidepressants and antipsychotics [48]. Still, it seems that the underlying pharmacological properties for these protecting effects are not specific for individual classes of psychotropic drugs but are rather individual properties of single members of different psychotropic drug classes independent of their primary mechanism of action [48]. Anti-inflammatory properties, including binding to sigma-receptors, lysosomotropic effects, and inhibition of sphingomyelinase, seem to play a major role [48, 49, 51, 84, 89, 94, 95]. Many of the prescribed drugs in our study can be assigned to one of the categories given above with a possible anti-COVID activity [43, 48, 49, 51, 84, 94, 95]. Thus, the broad treatment of our patients with various psychotropic drugs might be an additional factor explaining the rather moderate course of COVID-19 and low death rate as well as low infection rate in our patients.

Our findings are in contrast to other reports indicating a higher risk for a worse outcome, including higher mortality, of COVID-19 in psychiatric patients [11, 21, 28].

Besides somatic comorbidities, as suggested by Hoertel et al. [79], side effects of the psychotropic drugs given to patients during their stay at the hospital may also play a role [96, 97]. This was also seen in a most recent study by D'Andrea et al. [98] who found a substantially higher death rate in patients treated with psychotropic drugs, especially first and second-generation antipsychotics, during a stay at the university clinic of Bologna. Notably, the most common diagnosis was an organic disorder (ICD-10 F00-F09), a patient population that is generally more at risk regarding the

treatment with antipsychotics. Thus, concerning the outcome of COVID-19 in psychiatric patients, not only the use of psychotropic drugs, comorbidities, and specific care in a psychiatric ward must be taken into account, but also the main psychiatric diagnosis leading to the prescription of the psychiatric medication.

### Limitations

Although collecting data from 24 psychiatric university hospitals, 18 of them with mandatory care for psychiatric patients, is a major strength of this study, collecting data from different hospitals might cause diverse reporting due to heterogeneous clinical settings. The data was obtained between April and December 2020, a timeframe including a lockdown from the end of March till the end of April, as well as a time with loosened restrictions until November 2020. No information was obtained during which of the above-mentioned periods the patients tested SARS-CoV-2-positive, but restrictions for the healthcare system were mostly homogenous throughout the pandemic.

While psychiatric patients are at risk for comorbid somatic disorders as assessed in our survey, several other risk factors for a severe course of COVID-19 and higher mortality have been identified, predominantly older age, smoking, obesity, male sex, and cardiovascular and respiratory disease [99–101]. This survey used a pragmatic retrospective design to collect data as resources by clinicians during the COVID-19 pandemic were limited. As no data on sex, race, BMI, smoking, and further risk factors for mortality were assessed, we can`t exclude that possibly lower incidence of risk factors contributed to the milder course of COVID-19 and lower mortality in our study cohort.

## Conclusion

While the COVID-19 pandemic led to massive challenges for people`s mental health, psychiatric care was widely reduced during the COVID-19 pandemic, even though studies proposed a higher risk for COVID-19 in patients suffering from mental disorders. Interestingly, several studies showed a lower risk for patients treated in psychiatric wards and patients receiving different psychotropic drugs. In line with these results, we found no elevated risk for COVID-19 infection, for a more severe course or a higher mortality of COVID-19 in a cohort of in-patients from 24 psychiatric university hospitals in Germany. Two points seem most noteworthy. First, preventive measures, as taken by the German psychiatric hospitals, seem to have been highly effective in lowering the risk of a SARS-CoV-2 infection; given the low number of overall infections, apparently, no significant number of nosocomial infections occurred. Second, for most of the antipsychotics and antidepressants prescribed to the patients, intrinsic anti-inflammatory effects are well documented [35, 102, 103]. Our findings about a rather low rate of COVID-19 in psychiatric patients admitted to psychiatric university hospitals in Germany could support the hypothesis of a protective effect of many antidepressants and antipsychotics against COVID-19. As the overall prescriptions were heterogeneous, the results point to a rather unspecific protective effect of the psychotropic drugs. Still, further studies with larger cohorts of patients and more detailed information are needed to address this question.


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## Conflict of interest

Johannes Kornhuber is a co-inventor on the following patent application: INHIBITORS OF ACID SPHINGOMYELINASE FOR PREVENTING AND TREATING THE COVID-19 DISEASE International Application No. PCT/EP2021/067427; United States national stage of the PCT application (Application No. 18/002,814). Jürgen Deckert: Studies funded in the context of the COVID Network University Medicine (NapKon, EgePan, CollPan). Alkomiet Hasan has received paid speakerships from Recordati, Janssen, Otsuka, and Lundbeck. He was a member of Recordati, Otsuka, Lundbeck, and Janssen advisory boards.

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## References


[1] Zhu N, Zhang D, Wang W et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727–733. DOI: 10.1056/NEJMoa2001017

[2] WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. In https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

[3] Rogers JP, Chesney E, Oliver D et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: A systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 2020; 7: 611–627. DOI: 10.1016/S2215-0366(20)30203-0

[4] WHO. The impact of COVID-19 on mental, neurological and substance use services. In: 2020 https://www.who.int/publications/i/item/978924012455

[5] Dyall J, Gross R, Kindrachuk J et al. Middle East respiratory syndrome and severe acute respiratory syndrome: Current therapeutic options and potential targets for novel therapies. Drugs 2017; 77: 1935–1966. DOI: 10.1007/s40265-017-0830-1

[6] Zhao YJ, Jin Y, Rao WW et al. The prevalence of psychiatric comorbidities during the SARS and COVID-19 epidemics: A systematic review and meta-analysis of observational studies. J Affect Disord 2021; 287: 145–157. DOI: 10.1016/j.jad.2021.03.016

[7] Wade D, Howell D, Beadman M et al. Characterising neuropsychiatric disorders in patients with COVID-19. Lancet Psychiatry 2020; 7: 933–934. DOI: 10.1016/S2215-0366(20)30380-1

[8] Gholami M, Safari S, Ulloa L et al. Neuropathies and neurological dysfunction induced by coronaviruses. J Neurovirol 2021; 27: 380–396. DOI: 10.1007/s13365-021-00977-x

[9] Rogers JP, Chesney E, Oliver D et al. Psychiatric and neuropsychiatric syndromes and COVID-19 - Authors' reply. Lancet Psychiatry 2020; 7: 664–665. DOI: 10.1016/S2215-0366(20)30304-7

[10] Rogers JP, Watson CJ, Badenoch J et al. Neurology and neuropsychiatry of COVID-19: A systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives. J Neurol Neurosurg Psychiatry 2021; 92: 932–941. DOI: 10.1136/jnnp-2021-326405

[11] Taquet M, Luciano S, Geddes JR et al. Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021; 8: 130–140. DOI: 10.1016/S2215-0366(20)30462-4

[12] Taquet M, Geddes JR, Husain M et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: A retrospective cohort study using electronic health records. Lancet Psychiatry 2021; 8: 416–427. DOI: 10.1016/S2215-0366(21)00084-5

[13] Rogers JP, David AS. A longer look at COVID-19 and neuropsychiatric outcomes. Lancet Psychiatry 2021; 8: 351–352. DOI: 10.1016/S2215-0366(21)00120-6

[14] Klaser K, Thompson EJ, Nguyen LH et al. Anxiety and depression symptoms after COVID-19 infection: Results from the COVID Symptom Study app. J Neurol Neurosurg Psychiatry 2021; 92: 1254–1258. DOI: 10.1136/jnnp-2021-327565

[15] Nalleballe K, Reddy Onteddu S, Sharma R et al. Spectrum of neuropsychiatric manifestations in COVID-19. Brain Behav Immun 2020; 88: 71–74. DOI: 10.1016/j.bbi.2020.06.020

[16] Parra A, Juanes A, Losada CP et al. Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. Psychiatry Res 2020; 291: 113254. DOI: 10.1016/j.psychres.2020.113254

[17] Rentero D, Juanes A, Losada CP et al. New-onset psychosis in COVID-19 pandemic: A case series in Madrid. Psychiatry Res 2020; 290: 113097. DOI: 10.1016/j.psychres.2020.113097

[18] Varatharaj A, Thomas N, Ellul MA et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. Lancet Psychiatry 2020; 7: 875–882. DOI: 10.1016/S2215-0366(20)30287-X

[19] Vai B, Mazza MG, Delli Colli C et al. Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: A systematic review and meta-analysis. Lancet Psychiatry 2021; 8: 797–812. DOI: 10.1016/S2215-0366(21)00232-7

[20] Toubasi AA, AbuAnzeh RB, Tawileh HBA et al. A meta-analysis: The mortality and severity of COVID-19 among patients with mental disorders. Psychiatry Res 2021; 299: 113856. DOI: 10.1016/j.psychres.2021.113856

[21] Li L, Li F, Fortunati F et al. Association of a prior psychiatric diagnosis with mortality among hospitalized patients with coronavirus disease 2019 (COVID-19) infection. JAMA Netw Open 2020; 3: e2023282. DOI: 10.1001/jamanetworkopen.2020.23282

[22] Li L, Roberts SC, Kulp W et al. Epidemiology, infection prevention, testing data, and clinical outcomes of COVID-19 on five inpatient psychiatric units in a large academic medical center. Psychiatry Res 2021; 298: 113776. DOI: 10.1016/j.psychres.2021.113776

[23] Fond G, Nemani K, Etchecopar-Etchart D et al. Association between mental health disorders and mortality among patients with COVID-19 in 7 countries: A systematic review and meta-analysis. JAMA Psychiatry 2021; 78: 1208–1217. DOI: 10.1001/jamapsychiatry.2021.2274

[24] Fond G, Pauly V, Leone M et al. Disparities in intensive care unit admission and mortality among patients with schizophrenia and COVID-19: A national cohort study. Schizophr Bull 2021; 47: 624–634. DOI: 10.1093/schbul/sbaa158

[25] Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: Analysis from electronic health records in the United States. World Psychiatry 2021; 20: 124–130. DOI: 10.1002/wps.20806

[26] Nemani K, Li C, Olfson M et al. Association of psychiatric disorders with mortality among patients with COVID-19. JAMA Psychiatry 2021; 78: 380–386. DOI: 10.1001/jamapsychiatry.2020.4442

[27] Balaram K, Marwaha R, Kaelber DC. The effects of substance use on severe acute respiratory syndrome coronavirus infection risks and outcomes. Curr Opin Psychiatry 2021; 34: 386–392. DOI: 10.1097/YCO.0000000000000711

[28] Maripuu M, Bendix M, Ohlund L et al. Death associated with coronavirus (COVID-19) infection in individuals with severe mental disorders in Sweden during the early months of the outbreak-an exploratory cross-sectional analysis of a population-based register study. Front Psychiatry 2020; 11: 609579. DOI: 10.3389/fpsyt.2020.609579

[29] Taquet M, Harrison PJ. Why is COVID-19 associated with mental illness. Med (N Y) 2021; 2: 899–902. DOI: 10.1016/j.medj.2021.06.009

[30] Moni MA, Lin PI, Quinn JMW et al. COVID-19 patient transcriptomic and genomic profiling reveals comorbidity interactions with psychiatric disorders. Transl Psychiatry 2021; 11: 160. DOI: 10.1038/s41398-020-01151-3

[31] Quincozes-Santos A, Rosa RL, Tureta EF et al. COVID-19 impacts the expression of molecular markers associated with neuropsychiatric disorders. Brain Behav Immun Health 2021; 11: 100196. DOI: 10.1016/j.bbih.2020.100196

[32] Song E, Zhang C, Israelow B et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain. J Exp Med 2021; 218. DOI: 10.1084/jem.20202135

[33] Raony I, de Figueiredo CS, Pandolfo P et al. Psycho-neuroendocrine-immune interactions in COVID-19: Potential impacts on mental health. Front Immunol 2020; 11: 1170. DOI: 10.3389/fimmu.2020.01170

[34] Tang SW, Helmeste D, Leonard B. Inflammatory neuropsychiatric disorders and COVID-19 neuroinflammation. Acta Neuropsychiatr 2021; 33: 165–177. DOI: 10.1017/neu.2021.13

[35] Baumeister D, Ciufolini S, Mondelli V. Effects of psychotropic drugs on inflammation: Consequence or mediator of therapeutic effects in psychiatric treatment. Psychopharmacology (Berl) 2016; 233: 1575–1589. DOI: 10.1007/s00213-015-4044-5

[36] Meyer JH, Cervenka S, Kim MJ et al. Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. Lancet Psychiatry 2020; 7: 1064–1074. DOI: 10.1016/S2215-0366(20)30255-8

[37] Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: Depression fans the flames and feasts on the heat. Am J Psychiatry 2015; 172: 1075–1091. DOI: 10.1176/appi.ajp.2015.15020152

[38] Kohler CA, Freitas TH, Stubbs B et al. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: Systematic review and meta-analysis. Mol Neurobiol 2018; 55: 4195–4206. DOI: 10.1007/s12035-017-0632-1

[39] Troubat R, Barone P, Leman S et al. Neuroinflammation and depression: A review. Eur J Neurosci 2021; 53: 151–171. DOI: 10.1111/ejn.14720

[40] Muller N. Inflammation in Schizophrenia: Pathogenetic aspects and therapeutic considerations. Schizophr Bull 2018; 44: 973–982. DOI: 10.1093/schbul/sby024

[41] Plaze M, Attali D, Petit AC et al. Repurposing chlorpromazine to treat COVID-19: The reCoVery study. Encephale 2020; 46: 169–172. DOI: 10.1016/j.encep.2020.05.006

[42] Dobre D, Schwan R, Jansen C et al. Clinical features and outcomes of COVID-19 patients hospitalized for psychiatric disorders: A French multi-centered prospective observational study. Psychol Med 2021; 1–9. DOI: 10.1017/S0033291721001537

[43] Villoutreix BO, Beaune PH, Tamouza R et al. Prevention of COVID-19 by drug repurposing: Rationale from drugs prescribed for mental disorders. Drug Discov Today 2020; 25: 1287–1290. DOI: 10.1016/j.drudis.2020.06.022

[44] Canal-Rivero M, Catalan-Barragan R, Rubio-Garcia A et al. Lower risk of SARS-CoV2 infection in individuals with severe mental disorders on antipsychotic treatment: A retrospective epidemiological study in a representative Spanish population. Schizophr Res 2021; 229: 53–54. DOI: 10.1016/j.schres.2021.02.002

[45] Canal-Rivero M, Catalan-Barragan R, Rubio-Garcia A et al. The role of antipsychotics against COVID-19: A topic for debate. Schizophr Res 2021; 235: 5–6. DOI: 10.1016/j.schres.2021.07.003

[46] Hoertel N, Sanchez-Rico M, Vernet R et al. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: Results from an observational study. Mol Psychiatry 2021; 26: 5199–5212. DOI: 10.1038/s41380-021-01021-4

[47] Min KH, Kim TH, Oh SJ et al. COVID-19 prognosis in association with antidepressant use. Pharmacopsychiatry 2022; 55: 220–227. DOI: 10.1055/a-1842-7859

[48] Mueller JK, Riederer P, Muller WE. Neuropsychiatric drugs against COVID-19: What is the clinical evidence? Pharmacopsychiatry 2022; 55: 7–15. DOI: 10.1055/a-1717-2381

[49] Creeden JF, Imami AS, Eby HM et al. Fluoxetine as an anti-inflammatory therapy in SARS-CoV-2 infection. Biomed Pharmacother 2021; 138: 111437. DOI: 10.1016/j.biopha.2021.111437

[50] Hoertel N. Do the selective serotonin reuptake inhibitor antidepressants fluoxetine and fluvoxamine reduce mortality among patients with COVID-19. JAMA Netw Open 2021; 4: e2136510. DOI: 10.1001/jamanetworkopen.2021.36510

[51] Hashimoto Y, Suzuki T, Hashimoto K. Old drug fluvoxamine, new hope for COVID-19. Eur Arch Psychiatry Clin Neurosci 2022; 272: 161–163. DOI: 10.1007/s00406-021-01326-z

[52] Lenze EJ, Mattar C, Zorumski CF et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: A randomized clinical trial. JAMA 2020; 324: 2292–2300. DOI: 10.1001/jama.2020.22760

[53] Reis G, Dos Santos Moreira-Silva EA, Silva DCM et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: The TOGETHER randomised, platform clinical trial. Lancet Glob Health 2022; 10: e42–e51. DOI: 10.1016/S2214-109X(21)00448-4

[54] Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. Open Forum Infect Dis 2021; 8: ofab050. DOI: 10.1093/ofid/ofab050

[55] Main Fa https://frankfurt.de/-/media/frankfurtde/service-und-rathaus/zahlen-daten-fakten/pdf/pdf-fsa/2021/fsa_2021_07_bevoelkerung_ende2020.ashx In: Frankfurt Statistik.aktuell: 2021

[56] Wagner R, Peterhoff D, Beileke S et al. Estimates and determinants of SARS-Cov-2 seroprevalence and infection fatality ratio using latent class analysis: The population-based Tirschenreuth Study in the Hardest-Hit German County in spring 2020. Viruses 2021; 13. DOI: 10.3390/v13061118

[57] Hoertel N, Sanchez-Rico M, Herrera-Morueco JJ et al. Comorbid medical conditions are a key factor to understand the relationship between psychiatric disorders and COVID-19-related mortality: Results from 49,089 COVID-19 inpatients. Mol Psychiatry 2022; 27: 1278–1280. DOI: 10.1038/s41380-021-01393-7

[58] Simpson SA, Loh RM, Cabrera M et al. The impact of the COVID-19 pandemic on psychiatric emergency service volume and hospital admissions. J Acad Consult Liaison Psychiatry 2021; 62: 588–594. DOI: 10.1016/j.jaclp.2021.05.005

[59] Aly L, Sondergeld R, Holzle P et al. The COVID-19 pandemic has not changed the number but the type of psychiatric emergencies: A comparison of care data between 2019 and 2020. Nervenarzt 2020; 91: 1047–1049. DOI: 10.1007/s00115-020-00973-2

[60] Hoyer C, Ebert A, Szabo K et al. Decreased utilization of mental health emergency service during the COVID-19 pandemic. Eur Arch Psychiatry Clin Neurosci 2021; 271: 377–379. DOI: 10.1007/s00406-020-01151-w

[61] Fasshauer JM, Bollmann A, Hohenstein S et al. Emergency hospital admissions for psychiatric disorders in a German-wide hospital network during the COVID-19 outbreak. Soc Psychiatry Psychiatr Epidemiol 2021; 56: 1469–1475. DOI: 10.1007/s00127-021-02091-z

[62] Clerici M, Durbano F, Spinogatti F et al. Psychiatric hospitalization rates in Italy before and during COVID-19: did they change? An analysis of register data. Ir J Psychol Med 2020; 37: 283–290. DOI: 10.1017/ipm.2020.29

[63] Goldenberg MN, Parwani V. Psychiatric emergency department volume during Covid-19 pandemic. Am J Emerg Med 2021; 41: 233–234. DOI: 10.1016/j.ajem.2020.05.088

[64] Pignon B, Gourevitch R, Tebeka S et al. Dramatic reduction of psychiatric emergency consultations during lockdown linked to COVID-19 in Paris and suburbs. Psychiatry Clin Neurosci 2020; 74: 557–559. DOI: 10.1111/pcn.13104

[65] Montes JM, Hernandez-Huerta D. Impact of the COVID-19 pandemic on acute inpatient psychiatric units in Spain. Psychiatry Res 2021; 304: 114136. DOI: 10.1016/j.psychres.2021.114136

[66] Adorjan K, Pogarell O, Probstl L et al. Impact of the COVID-19 pandemic on the care situation in psychiatric hospitals in Germany. Nervenarzt 2021; 92: 562–570. DOI: 10.1007/s00115-021-01129-6

[67] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239–1242. DOI: 10.1001/jama.2020.2648

[68] Fasshauer JM, Bollmann A, Hohenstein S et al. Psychiatric emergency admissions and inpatient length of stay before and during the COVID-19 pandemic in Germany. Psychiatr Prax 2022; 49: 271–275. DOI: 10.1055/a-1726-8654

[69] [Anonymous] https://de.statista.com/statistik/daten/studie/1102667/umfrage/erkrankungs-und-todesfaelle-aufgrund-des-coronavirus-in-deutschland/ 2022;

[70] Ji W, Huh K, Kang M et al. Effect of underlying comorbidities on the infection and severity of COVID-19 in Korea: a nationwide case-control study. J Korean Med Sci 2020; 35: e237. DOI: 10.3346/jkms.2020.35.e237

[71] Wang QQ, Kaelber DC, Xu R et al. COVID-19 risk and outcomes in patients with substance use disorders: Analyses from electronic health records in the United States. Mol Psychiatry 2021; 26: 30–39. DOI: 10.1038/s41380-020-00880-7

[72] Yao H, Chen JH, Xu YF. Patients with mental health disorders in the COVID-19 epidemic. Lancet Psychiatry 2020; 7: e21. DOI: 10.1016/S2215-0366(20)30090-0

[73] Lee SW, Yang JM, Moon SY et al. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: A nationwide cohort study. Lancet Psychiatry 2020; 7: 1025–1031. DOI: 10.1016/S2215-0366(20)30421-1

[74] Ayling K, Jia R, Coupland C et al. Psychological predictors of self-reported COVID-19 outcomes: Results from a prospective cohort study. Ann Behav Med 2022; 56: 484–497. DOI: 10.1093/abm/kaab106

[75] Chevance A, Gourion D, Hoertel N et al. Ensuring mental health care during the SARS-CoV-2 epidemic in France: A narrative review. Encephale 2020; 46: 193–201. DOI: 10.1016/j.encep.2020.04.005

[76] Knowles M, Aref-Adib G, Moslehi S et al. Containing COVID: the establishment and management of a COVID-19 ward in an adult psychiatric hospital. BJPsych Open 2020; 6: e140. DOI: 10.1192/bjo.2020.126

[77] Bocher R, Jansen C, Gayet P et al. Responsiveness and sustainability of psychiatric care in France during COVID-19 epidemic. Encephale 2020; 46: S81–S84. DOI: 10.1016/j.encep.2020.05.004

[78] Percudani M, Corradin M, Moreno M et al. Mental health services in Lombardy during COVID-19 outbreak. Psychiatry Res 2020; 288: 112980. DOI: 10.1016/j.psychres.2020.112980

[79] Hoertel N, Sanchez-Rico M, Muela P et al. Risk of death in individuals hospitalized for COVID-19 with and without psychiatric disorders: An observational multicenter study in France. Biol Psychiatry Glob Open Sci 2022. DOI: 10.1016/j.bpsgos.2021.12.007

[80] Steardo L Jr., Steardo L, Verkhratsky A. Psychiatric face of COVID-19. Transl Psychiatry 2020; 10: 261. DOI: 10.1038/s41398-020-00949-5

[81] Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: Double trouble. Neuron 2020; 107: 234–256. DOI: 10.1016/j.neuron.2020.06.002

[82] Benedetti F, Aggio V, Pratesi ML et al. Neuroinflammation in bipolar depression. Front Psychiatry 2020; 11: 71. DOI: 10.3389/fpsyt.2020.00071

[83] Bonnet U, Juckel G, Scherbaum N et al. Are persons treated with antidepressants and/or antipsychotics possibly better protected against severe COVID 19. Pharmacopsychiatry 2021; 54: 142–143. DOI: 10.1055/a-1408-8298

[84] Javelot H, Petrignet J, Addiego F et al. Towards a pharmacochemical hypothesis of the prophylaxis of SARS-CoV-2 by psychoactive substances. Med Hypotheses 2020; 144: 110025. DOI: 10.1016/j.mehy.2020.110025

[85] Stip E, Rizvi TA, Mustafa F et al. The large action of chlorpromazine: Translational and transdisciplinary considerations in the face of COVID-19. Front Pharmacol 2020; 11: 577678. DOI: 10.3389/fphar.2020.577678

[86] Bonnet U, Claus B, Schaefer M et al. Impact of psychiatric and related somatic medications on the duration and severity of COVID-19: A retrospective explorative multi-center study from the German Metropolitan Ruhr-area. Pharmacopsychiatry 2022; 55: 30–39. DOI: 10.1055/a-1559-3904

[87] Rivas-Ramirez AR, Tendilla-Beltran H, Gomez-Mendoza LE et al. Patients with schizophrenia have decreased COVID-19 prevalence among hospitalised patients with psychiatric and neurological diseases: A retrospective analysis in Mexican population. Int J Clin Pract 2021; 75: e14528. DOI: 10.1111/ijcp.14528

[88] Moga S, Teodorescu A, Ifteni P et al. Inflammatory response in SARS-CoV-2 infection of patients with schizophrenia and long-term antipsychotic treatment. Neuropsychiatr Dis Treat 2021; 17: 3053–3060. DOI: 10.2147/NDT.S325062

[89] Oskotsky T, Maric I, Tang A et al. Mortality risk among patients with COVID-19 prescribed selective serotonin reuptake inhibitor antidepressants. JAMA Netw Open 2021; 4: e2133090. DOI: 10.1001/jamanetworkopen.2021.33090

[90] Clelland CL, Ramiah K, Steinberg L et al. Analysis of the impact of antidepressants and other medications on COVID-19 infection risk in a chronic psychiatric in-patient cohort. BJPsych Open 2021; 8: e6. DOI: 10.1192/bjo.2021.1053

[91] Bonnet U, Juckel G. COVID-19 outcomes: Does the use of psychotropic drugs make a difference? Accumulating evidence of a beneficial effect of antidepressants-a scoping review. J Clin Psychopharmacol 2022; 42: 284–292. DOI: 10.1097/JCP.0000000000001543

[92] Obiora E, Hubbard R, Sanders RD et al. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: A nested case-control and survival analysis in a population-based cohort. Thorax 2013; 68: 163–170. DOI: 10.1136/thoraxjnl-2012-202374

[93] Hoertel N, Sanchez-Rico M, Gulbins E et al. Association between benzodiazepine receptor agonist use and mortality in patients hospitalised for COVID-19: A multicentre observational study. Epidemiol Psychiatr Sci 2022; 31: e18. DOI: 10.1017/S2045796021000743

[94] Kornhuber J, Hoertel N, Gulbins E. The acid sphingomyelinase/ceramide system in COVID-19. Mol Psychiatry 2022; 27: 307–314. DOI: 10.1038/s41380-021-01309-5

[95] Hoertel N, Sanchez-Rico M, Gulbins E et al. Association between FIASMA psychotropic medications and reduced risk of intubation or death in individuals with psychiatric disorders hospitalized for severe COVID-19: An observational multicenter study. Transl Psychiatry 2022; 12: 90. DOI: 10.1038/s41398-022-01804-5

[96] Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020; 395: 1054–1062. DOI: 10.1016/S0140-6736(20)30566-3

[97] Barcella CA, Polcwiartek C, Mohr GH et al. Severe mental illness is associated with increased mortality and severe course of COVID-19. Acta Psychiatr Scand 2021; 144: 82–91. DOI: 10.1111/acps.13309

[98] D'Andrea G, Pascale R, Vatamanu O et al. Exposure to psychotropic medications and COVID-19 course after hospital admission: Results from a prospective cohort study. J Psychosom Res 2023; 167: 111199. DOI: 10.1016/j.jpsychores.2023.111199

[99] Docherty AB, Harrison EM, Green CA et al. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. BMJ 2020; 369: m1985. DOI: 10.1136/bmj.m1985

[100] Richardson S, Hirsch JS, Narasimhan M et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020; 323: 2052–2059. DOI: 10.1001/jama.2020.6775

[101] Petrilli CM, Jones SA, Yang J et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ 2020; 369: m1966. DOI: 10.1136/bmj.m1966

[102] Racki V, Marcelic M, Stimac I et al. Effects of haloperidol, risperidone, and aripiprazole on the immunometabolic properties of BV-2 microglial cells. Int J Mol Sci 2021; 22. DOI: 10.3390/ijms22094399

[103] Mosiolek A, Pieta A, Jakima S et al. Effects of antidepressant treatment on peripheral biomarkers in patients with major depressive disorder (MDD. J Clin Med 2021; 10. DOI: 10.3390/jcm10081706