Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Mortality from coronavirus disease 2019 (Covid-19) in patients with schizophrenia: A systematic review, meta-analysis and meta-regression

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ABSTRACT

Objective: Schizophrenia has been associated with patients' poor quality of life, disability, and hospitalization. As of today, evidence that highlights the association between schizophrenia and coronavirus disease (Covid-19) outcomes remains unclear. This study sought to analyze whether patients with pre-existing schizophrenia are at higher risk for Covid-19 mortality.

Methods: Using specific keywords, we comprehensively searched PubMed, Scopus, OVID, and Cochrane Library sources until November 15th, 2021. All published studies on schizophrenia and Covid-19 were collected. We used Review Manager 5.4 and Comprehensive Meta-Analysis 3 software to conduct statistical analysis.

Results: There were 10 studies with 263,207 Covid-19 patients included in the analysis. Evaluation of the data gathered yielded an association between schizophrenia and increased mortality from Covid-19 (RR 2.22; 95%CI: 1.54–3.20, $p < 0.00001$, $I^2 = 82\%$ random-effect model). The increased risk of developing mortality from Covid-19 in patients with schizophrenia was significantly influenced by older age ($p = 0.0004$) and smoking ($p = 0.0048$).

Conclusions: This study proposes that patients with pre-existing schizophrenia are at risk of developing higher Covid-19 mortality. Patients with schizophrenia need special attention and should be prioritized to receive the SARS-CoV-2 vaccine.

Registration details: CRD42021293997.

1. Introduction

The worldwide pandemic of Covid-19 has been ongoing since early 2020, however the transmission and death rate are constantly increasing, thus it is still considered a major global challenge. As of November 2021, COVID-19 cases exceeded 250 million, with more than 5 million deaths worldwide [1]. While some patients with SARS-CoV-2 may develop mild non-debilitating self-limiting upper-respiratory symptoms, a significant percentage of patients may also develop destructive and progressive symptoms that require hospitalizations and intensive care treatment due to the threat of symptoms progression into acute respiratory distress syndrome (ARDS) and multi-organ failure [2–4]. Thus, Covid-19 remains a great threat to the global healthcare system, especially in vulnerable populations with established risk factors including older age, unhealthy lifestyle, physical comorbidities, and psychiatric illnesses [5–10].

Previously published studies have tended to focus on the general medical (e.g., hypertension, diabetes, and obesity) rather than psychiatric comorbidities as risk factors for poor Covid-19 outcomes. During this pandemic, patients with psychiatric illness also need our special attention. Individuals with schizophrenia may be at greater risk for Covid-19 complications because of a confluence of factors known to increase the risk in the general population [11]. For instance, several studies have reported that patients with schizophrenia have a dysregulated immune response which can potentially increase the fatality from SARS-CoV-2 infection [12,13]. Moreover, social determinants of risk (eg, poverty and insufficient access to timely and preventive health care) are also more commonly observed in individuals with schizophrenia [14,15]. However, to our knowledge, no meta-analysis has focused on Covid-19 outcomes in patients with schizophrenia. In this study, we aim to analyze the relationship between schizophrenia and mortality from Covid-19.

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2. Materials and methods

2.1. Eligibility criteria

We conducted a systematic review and meta-analysis study of extant observational studies. The protocol for this study has been registered in PROSPERO (CRD42021293997). We compared Covid-19 mortality rate in populations with schizophrenia vs without schizophrenia of any age, sex, and nationality. Inclusion criteria were established before article review and were as follows: (1) a diagnosis of schizophrenia using standardized diagnostic criteria (eg. DSM-5 or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]); (2) schizophrenia diagnosis was documented before Covid-19 event or present as of the index date (ie. comorbid); (3) Covid-19 ascertained according to laboratory testing, ICD-10, electronic health record (EHR), and/or clinical judgment; (4) available complete quantitative data relevant to mortality outcome; (5) discrete outcome data for schizophrenia; (6) primary research; and (7) presentation as a full-text article (which included preprints). Exclusion criteria were as follows: (1) schizophrenia that was self-reported or otherwise did not follow standardized diagnostic criteria; (2) schizophrenia outcomes grouped with those for other mental illnesses; (3) unpublished study or abstract; (4) and nonprimary research.

2.2. Search strategy and study selection

Four databases were searched systematically for English-language articles (PubMed, Scopus, OVID, and the Cochrane Library). Keywords such as "(Covid-19 OR SARS-CoV-2 OR 2019-nCoV OR Severe acute respiratory syndrome coronavirus 2) AND (mortality OR death OR association) AND (pre-existing OR pre-existent OR pre-pandemic OR prior) AND (schizophrenia OR schizophrenic OR psychosis OR mental illness OR mental disorder OR psychiatric) NOT (psychosocial OR social OR social distancing OR lockdown OR quarantine OR sequelae)" were used to filter the intended studies from the period of 2019 until November 15th, 2021. The sample search strategies used in this study are provided in Supplementary Table 1. The initial step was the identification of eligible articles through screening of titles and abstracts by two reviewers. Additional evaluation of references from found eligible studies were also conducted to search for more potential articles. Duplicate articles were removed. Finally, full-text articles were independently screened by 2 reviewers, with discrepancies resolved through discussion. Meta-analysis of Observational Studies in Epidemiology (MOOSE) [16] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were employed for our study [17].

2.3. Data extraction and quality assessment

Two authors conducted the data extraction. The extraction form included study information including sample characteristics, hypertension, diabetes, smoking status, obesity, mood disorders, number of patients with schizophrenia, the control group in included studies, as well as the outcome of Covid-19 patients.

Our outcome of interest was Covid-19 mortality. Mortality outcome is described by the number of deaths divided by the number of patients with Covid-19.

Two authors assessed the quality of each study involved in this review independently. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of case-control and cohort studies. The assessment process included reviewing the comparability, selection, and outcome of each study, then each research was assigned a total score beginning with zero until nine. Research is graded good if it scores $\geq$7 [18].

2.4. Statistical analysis

Meta-analysis was done using Review Manager 5.4 (Cochrane Collaboration) and Comprehensive Meta-Analysis version 3 software. Application of the Mantel-Haenszel formula with random-effect models, regardless of heterogeneity was employed to calculate the risk ratio (RR) and its 95% confidence interval (95% CI) for the mortality outcome. In this meta-analysis, heterogeneity between studies was assessed by I-squared statistic (I^2; Inconsistency). An I-squared statistic with a value of <25% reflects a low degree of heterogeneity, 26–50% a moderate degree, and > 50% a high degree of heterogeneity. I^2 of at least 50% is considered substantial heterogeneity; it means that at least half of the total variability among effect sizes is due to true heterogeneity between studies. Meta-regression with a random-effects model was performed using restricted-maximum likelihood for pre-specified variables including age, gender, hypertension, diabetes, smoking, obesity, and mood disorders to assess evidence for an interaction effect between schizophrenia and these variables in influencing the Covid-19 outcome. Funnel plot analysis was utilized to assess the qualitative risk of publication bias, while Begg and Mazumdar's rank correlation method was used to assess the quantitative risk of publication bias [19].

3. Results

3.1. Study selection and characteristics

The initial database search yielded 334 studies, from which 30 were eligible after screening titles and abstracts and removal of duplicates. Of these eligible studies, 20 articles were further excluded after full-text screening. Seven articles did not contain relevant and/or complete data for the specified outcome measures, five articles did not contain discrete data for schizophrenia, five articles did not use a valid mode of ascertainment for schizophrenia or only included schizophrenia symptoms, three articles were not primary research thus resulting in the final number of 10 studies [[20–29]] which included a total of 263,207 Covid-19 patients for the analysis (Fig. 1). Out of 10 studies, seven were retrospective cohort, two were case-control studies, and the remaining one article was prospective cohort. Sample sizes ranged from 87 to 144,321. Most of the included studies used ICD-10 criteria for the diagnosis of schizophrenia and RT-PCR method for the diagnosis of Covid-19. Table 1 provides details regarding the included studies.

3.2. Quality of study assessment

The NOS scale was used to evaluate the quality of cohort and case-control studies, which indicated all included studies had good quality (Table 2). All studies were deemed fit to be included in the meta-analysis.

3.3. Schizophrenia and mortality from Covid-19

The pooled estimate indicated that the risk of mortality from Covid-19 was significantly higher for individuals with pre-existing schizophrenia when compared with those without schizophrenia (RR 2.22; 95%CI: 1.54–3.20, $p < 0.00001$, random-effect model) (Fig. 2). The meta-analysis for Covid-19 mortality exhibited a high degree and considerable heterogeneity ($I^2 = 82\%$).

3.4. Meta-regression

Meta-regression was performed to identify risk factors which influence the relationship between schizophrenia and mortality from Covid-19. Our meta-regression revealed that variability in mortality from Covid-19 in patients with schizophrenia was explained by known patient factors associated with predictors of Covid-19 outcome (Supplementary Table 2). Specifically, statistically significant associations were present

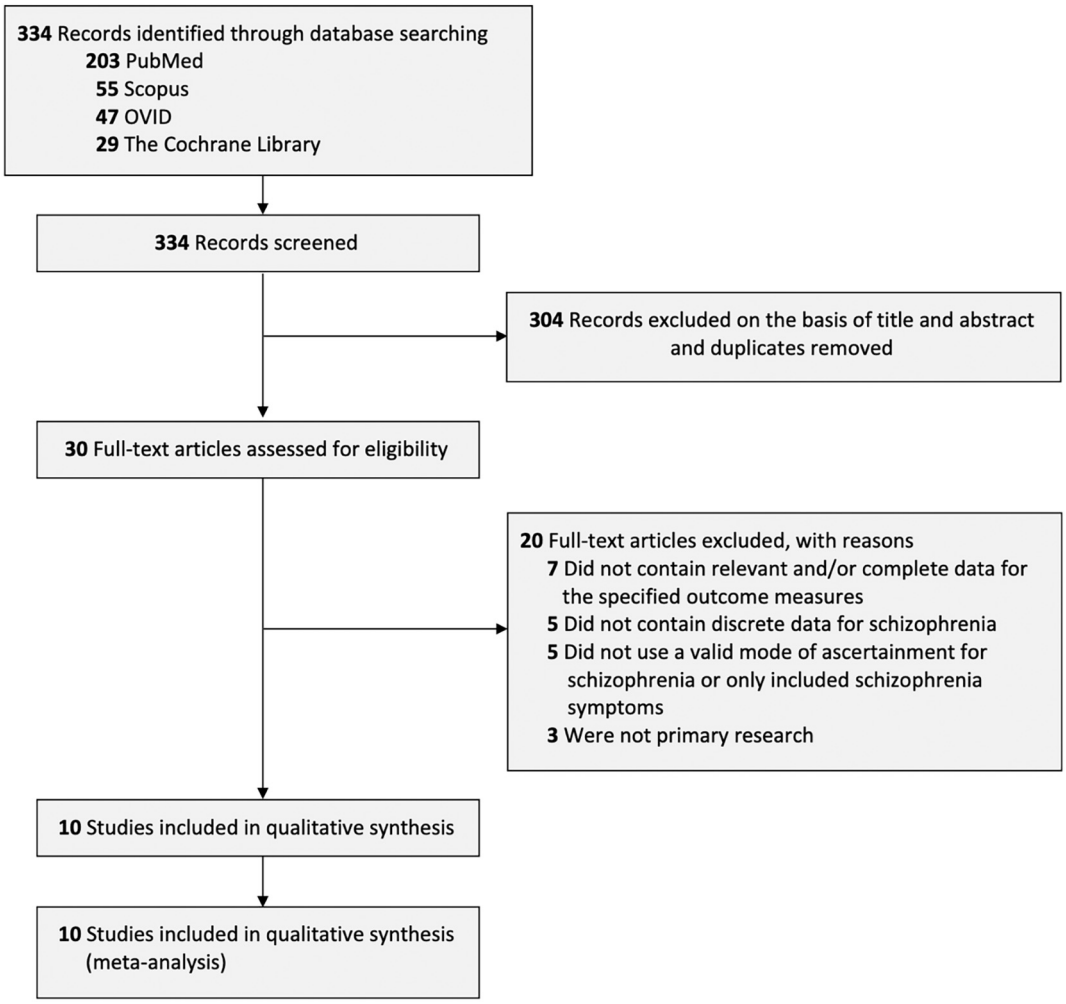

Fig. 1. PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

for age (beta coefficient: -0.0334; 95% CI: −0.0519, −0.0150; p = 0.0004) (Supplementary Fig. 1A), and smoking (beta coefficient: 0.0269; 95% CI: 0.0082, 0.0456; p = 0.0048) (Supplementary Fig. 1B). Our meta-regression also revealed that mortality from Covid-19 in patients with schizophrenia was not significantly influenced by gender (p = 0.9285) (Supplementary Fig. 1C), hypertension (p = 0.1243) (Supplementary Fig. 1D), diabetes (p = 0.1302) (Supplementary Fig. 1E), obesity (p = 0.4539) (Supplementary Fig. 1F), or mood disorder (p = 0.2981) (Supplementary Fig. 1G).

3.5. Publication bias

We used Funnel plot analysis for the mortality from Covid-19 outcome (Supplementary Fig. 2). This analysis showed a relatively symmetrical inverted-plot, indicating no publication bias. The result from the Begg and Mazumdar rank-correlation test was not statistically significant for mortality from Covid-19 (p = 0.928), confirming the results from funnel plot analysis in which no sign of publication bias was found.

4. Discussion

According to our pooled analysis, pre-existing schizophrenia as a comorbidity was associated with increased mortality from Covid-19. Further regression analysis showed that age and smoking significantly influenced Covid-19 mortality in patients with schizophrenia. Meanwhile, other factors such as gender, hypertension, diabetes, obesity, and mood disorder did not significantly affect the relationship between schizophrenia and mortality from Covid-19.

The results from our meta-analysis were in-line with the previous study by Fond et al. [30] which showed that patients with mental health disorders, including schizophrenia had higher mortality from Covid-19 (pooled adjusted OR, 1.38 [95% CI, 1.15–1.65]; I^2 = 0%). However, this prior meta-analysis did not focus on patients with schizophrenia and, in fact, included half as many studies of patients with schizophrenia as the current meta-analysis.

Several reasons can be proposed to explain the higher mortality from Covid-19 in patients with pre-existing schizophrenia. First, people with schizophrenia may be late in seeking treatment or have restricted healthcare access which may add to worse outcomes [25]. This may occur due to the stigma that patients with schizophrenia often receive. They often experience discrimination when accessing healthcare and are less likely to receive a proper work-up and treatment. This would put the patients at a greater risk for misdiagnosis for their physical problems, resulting in a poor quality of healthcare overall [15,31]. Moreover, the cognitive impairment and negative symptoms of schizophrenia may also contribute to the delay in treatment seeking following Covid-19 symptom onset in patients with schizophrenia. Aside from underdiagnosis and unoptimized treatment given by the clinicians, mortality could also increase due to the fact that these patients did not adhere well to their given treatments, leading to a more fatal outcome [15].

A second possible explanation for increased mortality in patients with schizophrenia could be reduced vaccination rates. In an Israeli study, only 50.6% of patients with schizophrenia were vaccinated,

Table 1
Characteristics of included studies.

Study	Sample size	Design	Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	Smoking (%)	Obesity (%)	Mood disorders (%)	Schizophrenia (%)	Mode(s) of ascertainment
Barcella et al. [20] 2021	144,321	Prospective cohort	40.3 ± 20.8	48.4%	8.6%	4.6%	N/A	N/A	2.9%	0.7%	ICD-10 diagnosis for schizophrenia; ICD-10 diagnosis for Covid-19
Bitan DT et al. [21] 2021	51,078	Retrospective cohort	51.5 ± 15.4	60.9%	20%	17.1%	45.4%	27.3%	N/A	50%	ICD-9 or ICD-10 diagnosis for schizophrenia; RT-PCR for Covid-19
Fond et al. [22] 2021 (a)	1092	Case-control	63.1 ± 18.5	54.3%	36%	23.4%	11.5%	31.4%	N/A	1.3%	ICD-10 diagnosis for schizophrenia; RT-PCR for Covid-19
Fond et al. [23] 2021 (b)	50,750	Retrospective cohort	70.3 ± 19.2	56.8%	N/A	27.8%	4.3%	14.2%	N/A	1.6%	ICD-10 diagnosis for schizophrenia; ICD-10 diagnosis for Covid-19
Jeon et al. [24] 2021	3551	Retrospective cohort	55.4 ± 16.2	41.7%	25.7%	15.1%	N/A	N/A	8%	4.8%	ICD-10 diagnosis for schizophrenia; RT-PCR for Covid-19
Nemani et al. [25] 2021	7348	Retrospective cohort	54 ± 18.6	47%	45.4%	25.7%	23.1%	N/A	7.6%	1%	ICD-10 diagnosis for schizophrenia; RT-PCR for Covid-19
Poblador-Plou et al. [26] 2020	4412	Retrospective cohort	67.7 ± 20.7	41.2%	34.4%	11.9%	N/A	25.5%	16.5%	0.9%	ICD-9-CM diagnosis for schizophrenia; EHR of laboratory test for Covid-19
Rivas-Ramirez AR et al. [27] 2021	87	Retrospective cohort	51.5 ± 14.8	47.1%	11.4%	4.5%	N/A	N/A	6.8%	20.6%	ICD-10 diagnosis for schizophrenia; RT-PCR for Covid-19
Rodriguez-Molinero A et al. [28] 2020	418	Retrospective cohort	65.4 ± 16.6	56.9%	51.9%	23.6%	8.6%	17.7%	15%	0.9%	ICD-10 diagnosis for schizophrenia; RT-PCR for Covid-19
Tyson et al. [29] 2021	150	Case-control	77.6 ± 10.5	50%	N/A	34%	N/A	20.6%	41.3%	4%	ICD-10 diagnosis for schizophrenia; RT-PCR for Covid-19

Table 2
Newcastle-Ottawa quality assessment of observational studies.

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Result
Barcella et al. [20] 2021	Cohort	***	**	***	8	Good
Bitan DT et al. [21] 2021	Cohort	***	**	**	7	Good
Fond et al. [22] 2021 (a)	Case-control	***	**	**	7	Good
Fond et al. [23] 2021 (b)	Cohort	***	**	***	8	Good
Jeon et al. [24] 2021	Cohort	***	**	***	8	Good
Nemani et al. [25] 2021	Cohort	***	**	***	8	Good
Poblador-Plou et al. [26] 2020	Cohort	***	**	**	7	Good
Rivas-Ramirez AR et al. [27] 2021	Cohort	***	**	**	7	Good
Rodriguez-Molinero A et al. [28] 2020	Cohort	***	**	***	8	Good
Tyson et al. [29] 2021	Case-control	***	**	**	7	Good

[a] (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study.
[b] (1) comparability of cohorts on the basis of design or analysis, (maximum two stars).
[c] (1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow up of cohorts.

compared to 52.8% in the comparison group [21]. However, vaccinated patients with schizophrenia had reduced hospitalizations and mortality [21,32]. Thus, results from that study and the current meta-analysis demonstrate the importance of prioritizing Covid-19 vaccination in patients with schizophrenia.

Third, people with schizophrenia may have susceptibility because of immune system dysregulation. Various lines of research, including genome-wide association studies, suggest dissimilarity in HLA (major histocompatibility complex) proteins and deficient T-cell mediated immune responses in patients with schizophrenia [33]. This immune system dysregulation in patients with schizophrenia was evident in the context of Covid-19 infection, in which these patients typically presented with higher levels of inflammatory biomarkers, cytokines, and chemokines, such as procalcitonin, serum ferritin, erythrocyte sedimentation rate, IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α, GDF-15, and CRP [34–36]. The increase of these substances would lead to a systemic proinflammatory state and eventually cause a cytokine storm that may result in more critical symptoms, multi-organ failure, and even death [37–39].

Apart from proinflammatory cytokines, the fourth possible explanation for the increased mortality rate of schizophrenic patients from Covid-19 is the disrupted modulation of the coagulation pathway. Recent research has highlighted the involvement of coagulation dysregulation in SARS-CoV-2 infection, through mechanisms such as cytokine

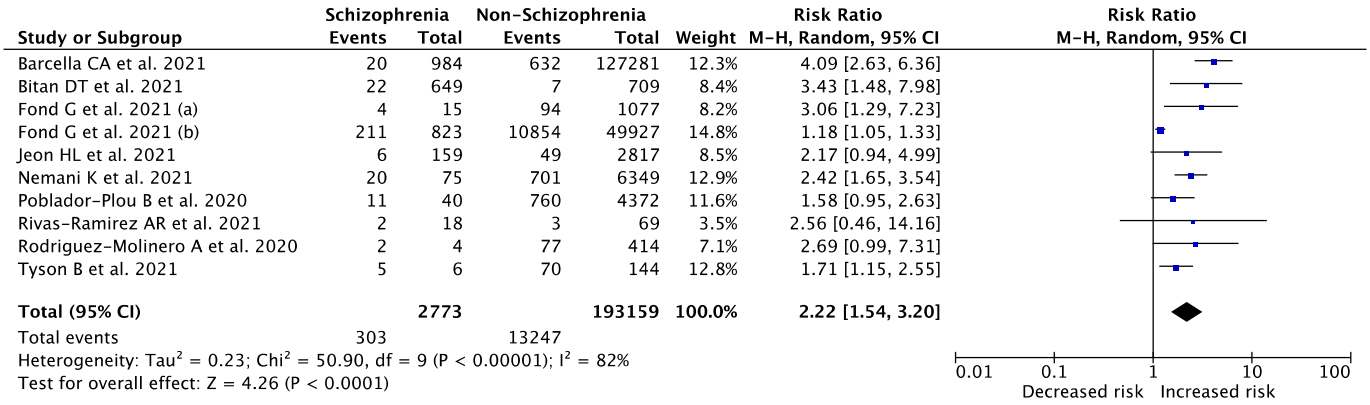

Fig. 2. Forest plot that demonstrates the association of pre-existing schizophrenia with mortality from Covid-19.

release, systemic inflammation, endothelial activation, tissue damage, hypoxic vasoconstriction, and fibrinolysis impairment that lead to fatal thromboembolic events [36,40]. This theory was supported by a study in China that reported higher levels of D-dimer in the non-survivor group compared to the survivor group ($p < 0.0001$), thus demonstrating a significant association of hypercoagulability state and death in patients with COVID-19 [38]. These findings were then linked to evidence of hypercoagulability in schizophrenic patients. In several studies, patients with mental illness, including schizophrenia, had higher concentrations of D-dimer level (with a median value of 2061 ng/mL, according to a study conducted in New York City community hospital) as well as plasminogen activator inhibitor (PAI-1) compared to controls, which made them more susceptible to thrombotic complications [41]. Patients with schizophrenia were also reported to have 3 times the risk for deep vein thrombosis and 2.6 times the risk for pulmonary embolism [42]. Our results would fit with the possibility of a hypercoagulable state in patients with schizophrenia additionally affected with Covid-19, leading to thromboembolism and death. Several risk factors for thromboembolic events are common in patients with schizophrenia. These risk factors include smoking rate which is higher among patients with psychiatric conditions; metabolic syndrome caused by illness and treatment (with a higher risk in low potency antipsychotics (AOR 20.8 (95% CI: 1.7–259.0))); unhealthy lifestyle affected by illness and the use of physical restraint [42,43].

Fifth, it is possible that antipsychotic medications could interfere with the coagulation cascade, through a variety of mechanisms. For example, antipsychotic adverse effects could lead to thromboembolism through sedation, obesity, enhanced platelet aggregation, increased antiphospholipid antibodies, and hyperprolactinemia [44]. Prolactin is a platelet aggregation co-activator, and its release is inhibited by dopamine. As several antipsychotics are dopamine D2-receptor antagonists, repressed secretion of dopamine would lead to the increase of prolactin [44]. Other than causing thromboembolism, antipsychotic drugs such as clozapine, risperidone, and haloperidol could also worsen the clinical outcome of Covid-19 by increasing the susceptibility to infections. According to research, clozapine increased infection vulnerability through increasing agranulocytosis and blood dyscrasia, while risperidone increased global immunosuppression, and haloperidol increased the risk of acute respiratory failure in patients with schizophrenia and COPD [34]. Given these considerations, clinicians should take care when prescribing antipsychotics to patients with active Covid-19 infection.

Lastly, comorbid illnesses in patients with schizophrenia could influence the pathophysiology and morbidity/mortality of Covid-19 infection. Common medical conditions found in patients with mental illness include glucose-regulation abnormalities, insulin resistance, type 2 diabetes mellitus, hyperlipidemia, hypertension, cardiac arrhythmias, obesity, malignant neoplasms, HIV/AIDS, hepatitis C, osteoporosis, hyperprolactinemia, irritable bowel syndrome, and *Helicobacter pylori* infection [45–48]. These conditions are associated with the use of antipsychotic medications, lifestyle factors, and inability to adapt to healthier lifestyles [49]. Higher mortality has been observed in patients with Covid-19 and certain risk factors, such as older age, male sex, pre-existing hypertension, diabetes, coronary heart disease, and chronic kidney disease [37,49]. The risk of comorbid conditions appears particularly high among patients younger than 50 years old [50]. Thus it can be concluded that patients with schizophrenia and pre-existing comorbidities are susceptible to mortality from Covid-19.

This study is not free from limitations. Our analyses are based on a relatively small number of studies. Notable heterogeneity was also identified across studies on the outcome of interest, mortality. Finally, other factors such as schizophrenia duration, antipsychotic use, symptom severity, and Covid-19 vaccination status could not be analyzed because of limited data in the included studies. More studies that focus on the course of Covid-19 in patients with schizophrenia with larger sample sizes are still needed to confirm the results from our study. Finally, in some of the included studies, it is not possible to determine whether Covid-19 was the underlying cause of death or not, therefore some of the deaths in these studies may be with Covid-19 rather than due to Covid-19. However, since this limitation also applies to the control group, we can assume null bias regarding this point.

In conclusion, our study suggests that patients with schizophrenia are at increased risk of death from Covid-19. This may be due to comorbid conditions, immune response dysregulation, hypercoagulability, antipsychotic use, and lack of vaccination. Clinicians should prioritize patients with schizophrenia for Covid-19 vaccines. In patients with schizophrenia who have Covid-19, clinicians should screen for hypercoagulability and take precautions when prescribing antipsychotics.

Author statement

All authors have approved the final version of this article.

Availability of data and materials

Data analyzed in this study were a re-analysis of existing data, which are openly available at locations cited in the reference section.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2022.01.010.

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