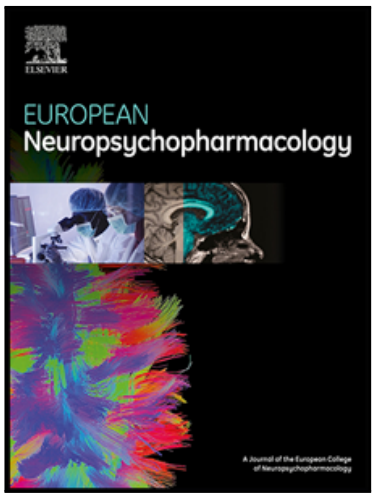

COVID-related hospitalization, intensive care treatment, and all-cause mortality in patients with psychosis and treated with clozapine

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ABSTRACT

Clozapine, an antipsychotic, is associated with increased susceptibility to infection with COVID-19, compared to other antipsychotics. Here, we investigate associations between clozapine treatment and increased risk of adverse outcomes of COVID-19, namely COVID-related hospitalisation, intensive care treatment, and death, among patients taking antipsychotics with schizophrenia-spectrum disorders. Using the clinical records of South London and Maudsley NHS Foundation Trust, we identified 157 individuals who had an ICD-10 diagnosis of schizophrenia-spectrum disorders, were taking antipsychotics (clozapine or other antipsychotics) at the time of COVID-19 pandemic in the UK and had a laboratory-confirmed COVID-19 infection. The following health outcomes were measured: COVID-related hospitalisation, COVID-related intensive care treatment and death. We tested associations between clozapine treatment and each outcome using logistic regression models, adjusting for gender, age, ethnicity, neighbourhood deprivation, obesity, smoking status, diabetes, asthma, bronchitis and hypertension using propensity scores. Of the 157 individuals who developed COVID-19 while on antipsychotics (clozapine or other antipsychotics), there were 28% COVID-related hospitalisations, 8% COVID-related intensive care treatments and 8% deaths of any cause during the 28 days follow-up period. Among those taking clozapine, there were 25% COVID-related hospitalisations, 7% COVID-related intensive care treatments and 7% deaths. In both unadjusted and adjusted analyses, we found no significant association between clozapine and any of the outcomes. Thus, we found no evidence that patients with clozapine treatment at time of COVID-19 infection had increased risk of hospitalisation, intensive care treatment or death, compared to non-

clozapine antipsychotic-treated patients. However, further research should be considered in larger samples to confirm this.

Keywords

clozapine; COVID-19

Ethics statement. The research was conducted under ethical approval reference 18/SC/0372 from Oxfordshire Research Ethics Committee C.

INTRODUCTION

Clozapine is an atypical antipsychotic, the gold standard drug for treatment-resistant schizophrenia, and the only effective treatment for many patients with schizophrenia (Siskind *et al.*, 2016). Patients with schizophrenia have a higher risk for developing pneumonia and, compared to the general population, have higher premature mortality (Chou, Tsai and Chou, 2013; Seminog and Goldacre, 2013; Hayes *et al.*, 2017; John *et al.*, 2018; Shen *et al.*, 2018; Vermeulen *et al.*, 2019). Patients receiving clozapine treatment have lower rates of overall hospitalisation and mortality compared to those receiving other antipsychotic treatments (Hayes *et al.*, 2015; Wimberley *et al.*, 2017; Cho *et al.*, 2018; Kesserwani *et al.*, 2019). However, clozapine is associated with an increased risk of developing pneumonia (Haddad, 2013; Kuo *et al.*, 2013; Stoecker *et al.*, 2017; De Leon, Sanz and De las Cuevas, 2020). This might be explained by confounding by indication, in that clozapine is predominantly prescribed in cases of treatment-resistant schizophrenia, associated in itself with higher rates of comorbidities such as smoking cigarettes, inadequate physical activity, and poor diet (Liu *et al.*, 2017). Alternatively, clozapine could increase the risk of pneumonia via immunosuppression, or via other adverse effects of clozapine which could fall on the causal pathway, such as hypersalivation (causing aspiration pneumonia), diabetes and obesity (Newcomer, 2005; Liu *et al.*, 2017; De Leon, Sanz and De las Cuevas, 2020).

COVID-19 first appeared in China in December 2019 and was declared a global pandemic by the WHO in March 2020 (Siskind *et al.*, 2020). It is caused by the SARS-Cov2 virus, and has pathological effects on multiple organ systems including the lungs, heart, brain, kidney, gastrointestinal tract, liver and spleen (Tabary *et al.*, 2020). The most concerning consequence of the infection is respiratory failure. The most severe cases of COVID-19 can

require hospitalisation and treatment in intensive care, and mortality is significant. Several studies have been performed to investigate the impact of COVID-19 on patients on clozapine treatment (Govind *et al.*, 2020; Vita and Barlati, 2021). In a previous study, we reported that patients on clozapine treatment may be at higher risk of COVID-19 infection (Govind *et al.*, 2020). Recently, case studies on this have been presented by Butler et al., Boland and Dratcu (Boland and Dratcu, 2020; Butler *et al.*, 2020); however, to our knowledge, the association between clozapine treatment and the adverse outcomes of COVID-19 have yet to be investigated in an epidemiological sample.

In this paper, we investigated whether clozapine treatment, compared to non-clozapine antipsychotic treatment, at time of COVID-19 infection, was associated with an increased risk of adverse outcomes of COVID-19 in patients with schizophrenia in a geographically defined population in London during the COVID-19 pandemic in the UK.

METHOD

Setting and Ethics Statement

A retrospective cohort study was carried out using data from the electronic records of the South London and Maudsley NHS Foundation Trust (SLAM). SLAM caters to all secondary mental health care needs of over 1.3 million people of four London boroughs (Lambeth, Southwark, Lewisham, and Croydon). SLAM has used a fully electronic clinical records system since 2006, and the Clinical Records Interactive Search (CRIS) platform was established to render full, de-identified clinical records available to researchers for secondary analysis within robust data security and governance framework (Stewart *et al.*,

2009). CRIS was approved for use as a de-identified data resource for secondary analysis by Oxfordshire Research Ethics Committee C (reference 18/SC/0372).

CRIS includes both structured and free-text fields from the clinical notes, and custom-built Natural Language Processing (NLP) algorithms are used to extract information from the latter, the specifications and performance metrics of which are detailed in an open online catalogue (CRIS NLP Applications Library, 2020). Data from four NLP algorithms were used in this study: diagnosis, medication, smoking and body mass index (BMI). Information regarding COVID-19 patient cases admitted to two local hospitals (King's College Hospital and Princess Royal University Hospital) were obtained via a data linkage (performed under Regulation 3(2) and Regulation 3(3) of the Health Service Control of Patient Information Regulations 2002 (COPI)).

Cohort

The cohort comprised individuals who satisfied all three of the following inclusion criteria: (1) a laboratory-confirmed COVID-19 infection between March 01, 2020, and December 20, 2020; (2) ICD-10 diagnosis of any schizophrenia-spectrum disorder (F2*); (3) recorded as taking antipsychotic medication within 3 months prior to the date of COVID-19 infection. Figure 1 shows the study design. SQL Server Management Studio version 15.0 (Microsoft Inc, USA) was used to extract the data. The day of data extraction was January 07, 2021. Patients were followed-up from the date of COVID-19 infection until they were hospitalised, entered intensive care treatment, died, or reached the end of the follow-up period (within 28 days of infection). Since we did not have access to the cause of death information,

measured all cause mortality within 28 days of COVID-19 diagnosis, in line with Public Health England (Department of Health and Social Care, 2020).

Diagnosis of schizophrenia-spectrum disorder (ICD-10: F2*) was ascertained via a diagnosis algorithm, by which NLP outputs are combined with data in the structured fields, such as the data from ICD-10 diagnosis forms in the source record (CRIS NLP Applications Library, 2020).

Antipsychotic medication within 3 months prior to COVID-19 infection was identified by an NLP algorithm that targeted administrations of 29 different antipsychotic medications (Perera *et al.*, 2016; CRIS NLP Applications Library, 2020). The medications algorithm NLP outputs are combined with data from structured fields, including SLAM pharmacy dispensing data.

The COVID-19 infection data used for the inclusion criteria were collated by combining information from three sources: (1) SLAM pathology lab results data, (2) the presence of a clinician-entered alert on SLAM records indicating a positive test, and (3) data provided by local general hospitals (King's College Hospital and Princess Royal University Hospital) for COVID-19 related admissions. The COVID-19 infection dates were verified and, when needed, were rectified to the earliest mention of COVID-19-compatible symptoms or COVID-19 tests, according to the information presented in SLAM's clinical notes. To cater to scenarios where the COVID-19 test was conducted after an admission for symptomatic COVID, the COVID-19 infection date was changed to the date of hospital admission when the positive test result was within 7 days of hospital admission. The patients were removed from the analysis either if the clinical notes stated that their COVID-19 positive status was entered by mistake or they had COVID-19 infection after December 20, 2020.

Exposure of interest

People who were recorded as receiving clozapine treatment at any time within 3 months prior to the assigned COVID-19 infection date were defined as the exposed group. Those on any type or combination of antipsychotic treatment that did not include clozapine during this time constituted the unexposed group.

Main outcome measures

The outcomes of interest were: (1) COVID-related hospitalisation (2) COVID-related intensive care treatment, and (3) all-cause mortality during the follow-up period (within 28 days of COVID-19 infection). These data were collated by combining COVID-19 related information provided by local general hospitals (King's College Hospital and Princess Royal University Hospital) and the data in the SLAM records. The SLAM records data on hospitalisation and intensive care treatment were curated by reading the clinical notes of each patient from the date of COVID-19 infection until a positive mention of hospitalisation or mention of recovery from COVID-19. The SLAM records data on mortality were retrieved from structured fields in SLAM health records which are populated on weekly basis via linkage with the NHS Spine.

Potential confounding variables

We considered as potential confounding variables sociodemographic characteristics and behavioural/clinical factors. The sociodemographic information comprised age, gender,

ethnicity, and neighbourhood deprivation. The behavioural/clinical factors were smoking status, obesity, diabetes, asthma, bronchitis and hypertension.

Age was calculated at the time of COVID-19 infection from the year and month of birth. Data on gender and ethnicity came from the routinely collected data in structured fields in SLAM health records. SLAM records include ethnicity in 14 categories, which were collapsed into 3 categories, "White", "Black" and "Asian & other". The category "White" was a conflation of White British, White Irish and White Other. The category "Black" was a conflation of Black African, Black Other (which comprises Black British), Black Caribbean, Mixed Race White and Black Caribbean and Mixed Race White and Black African. The category "Asian & Other" was a conflation of Indian, Pakistani, Other Asian, and Other ethnic group. For patients with no ethnicity information, including those with ethnicity as "not stated" in the structured fields, their ethnicity data was extracted by manually reviewing the record text fields.

Neighbourhood deprivation was measured using the Index of Multiple Deprivation (IMD) 2019 applying Census-derived data to the Lower Super Output Area: a standard administrative unit containing an average of 1500 residents. The deciles of the IMD range between 1, the most deprived, and 10, the least deprived. The data from IMD deciles 1 to 3 were merged to form the "Higher level of deprivation" category. The data from IMD deciles 4 to 10 were merged to form the "Lower level of deprivation" category. A third category, "homeless", was created for the patients who were homeless.

Smoking behaviour in the year prior to COVID-19 infection was identified using an NLP algorithm (CRIS NLP Applications Library, 2020), supplemented by a manual review of record text fields. Similarly, the obesity status was derived from recorded body mass index (BMI)

scores ascertained via an NLP algorithm, supplemented by manual records text review, choosing the most recent extracted score prior to the COVID-19 infection date (CRIS NLP Applications Library, 2020). Obesity was defined as BMI is greater than or equal to 30 (World Health Organization, 1995). Data on physical illnesses (diabetes, asthma, bronchitis and hypertension) were extracted manually from relevant free-text fields of the patient records for each patient, aided by search strings.

Statistical analysis

The data were analysed using STATA for Windows version 15.1. Since the data on the date of COVID-19 infection which is the time zero date was not precise, we used logistic regression instead of Cox proportional hazard models for the analysis. In the unadjusted analysis, we used logistic regression to calculate odds ratios comparing clozapine treated patients to those treated with other antipsychotics for each of the outcomes described above. Covariate adjustment was made via propensity scores within a logistic regression model as direct adjustment for all covariates was not feasible due to limited sample size. The propensity scores were predicted from a separate logistic regression model using clozapine treatment as the outcome and the sociodemographic (age, gender, ethnicity, neighbourhood deprivation), behavioural/clinical factors (smoking status, BMI, diabetes, asthma, bronchitis, hypertension) as predictor variables. The logit (log-odds) of the probability of clozapine treatment (propensity score) was included as a single covariate along with the exposure (indicator of clozapine treatment) in the logistic regression models for adjusted analysis. STATA was also used to estimate power for the analysis.

RESULTS

There were 157 patients ascertained with a laboratory-confirmed COVID-19 infection and schizophrenia-spectrum disorders (F2*) who were receiving any type of antipsychotic treatment during the study period. The follow-up period was 28 days after COVID-19 infection. The study sample comprised of patients treated with these antipsychotic medications: clozapine (36%), olanzapine (50%), risperidone (31%), aripiprazole (35%), amisulpride (12%), paliperidone (18%), flupentixol (13%), haloperidol (17%), zuclopenthixol (11%), quetiapine (10%), fluphenazine (3%), piportil (3%), sulpiride (3%), lurasidone (3%), trifluoperazine (1%), chlorpromazine (1%), pipotiazine (3%), penfluridol (1%) and droperidol (1%). The percentages refer to the proportion of the cohort on each antipsychotic and not all patients were on monotherapy. The mean age of the study sample was 50.6 years (SD=16.01), and men accounted for 53.5% of the sample. The study sample had a relatively high proportion of patients from minority ethnic groups: 61.2% Black, 10.8% any Asian and Other ethnic background and 28.0% White. Table 1 summarises the demographic features of all the SLAM patients who were eligible for inclusion based on the inclusion criteria (*N*=157). Of the individuals who were receiving clozapine, 56% were male, 58% were Black, 88% were current smokers, and 63% were obese.

Of the 157 individuals, 44 (28%) had an episode of COVID-related hospitalisation, 13 (8%) received COVID-related intensive care treatment and 13 (8%) died of any cause during the 28 days follow-up period. The majority of deaths were in people not admitted to intensive care: only 23% of those reporting being in intensive care, according to SLaM notes and data linkage to the two hospitals, died. Among those taking clozapine, 25% had COVID-related hospitalisations, 7% had COVID-related intensive care treatments and 7% died. Among

those not taking clozapine, there were 30% COVID-related hospitalisations, 9% COVID-related intensive care treatments and 9% deaths.

The logistic regression analysis was performed on the 157 individuals for each of the three outcomes, and Table 2 shows the odds ratio for each in the unadjusted and propensity score adjusted models. In unadjusted analyses, receiving clozapine treatment was not significantly associated with any outcome. Furthermore, no significant association was observed for any of the outcomes after covariate adjustment. The unadjusted odds ratio for COVID-related hospitalisation was 0.76 (95% CI: 0.36-1.59), COVID-related treatment in intensive care was 0.76 (95% CI: 0.22-2.60) and all-cause mortality was 0.76 (95% CI: 0.22-2.60). Since the number of patients who had COVID-related treatment in intensive was the same as the number of patients who died after COVID-19 infection, the unadjusted analysis for these two outcomes produced the same results. The adjusted odds ratio for COVID-related hospitalisation was 1.12 (95% CI: 0.48-2.60), COVID-related treatment in intensive care was 0.71 (95% CI: 0.18-2.77) and all-cause mortality was 1.38 (95% CI: 0.33-5.71). Post-hoc power calculations indicated that the sample size was sufficient to detect with 80% power (alpha 0.05) an odds ratio of 2.78 for COVID-related hospitalisation and 3.95 for all-cause mortality. Given the known strong association between obesity and the risk of adverse outcomes in COVID-19 infection, we ran another model where we directly included obesity as a covariate in the propensity score adjusted model. We did not see any material change in the results indicating propensity score adjustment has done a good job in accounting for the imbalance of obesity between the groups.

DISCUSSION

Summary of findings

We investigated if receiving clozapine treatment, compared to non-clozapine antipsychotic treatment, may be associated with increased risk of hospitalisation, intensive care treatment or all-cause mortality (within 28 days from infection) in COVID-19 positive patients with schizophrenia-spectrum disorders. We found no evidence that receiving clozapine treatment substantially increases the risk of these outcomes, compared to receiving any other types of antipsychotic treatment.

Comparison with previous studies

To our knowledge, no previous research has specifically investigated the associations between receiving clozapine treatment, as compared to receiving treatment with other antipsychotics, and hospitalisation, intensive care treatment or mortality from COVID-19.

Strengths and limitations

As a strength of this study, SLAM is a near-monopoly service provider of all aspects of secondary mental health care to residents within a defined geographic catchment, allowing relatively comprehensive ascertainment of people with the disorders of interest receiving specialist care during the COVID-19 pandemic in the UK. The CRIS database provided the platform to ascertain the relevant sample and access information on a range of potential confounders. However, it is important to bear in mind that not all people with schizophrenia-spectrum disorders will have been receiving specialist mental healthcare at that time, so that generalisability is limited. The CRIS database does not include all

antipsychotic medication data on patients who are discharged to the GP services and therefore even though these patients qualified for the inclusion criteria, they would have been missed. Also, some patients would have been missed because the cohort was extracted using results from NLP algorithms; the precision and recall scores for the diagnosis algorithm was 100% and 65% respectively; The precision and recall scores for the antipsychotics part of the medication algorithm was 88% and 90%, respectively (CRIS NLP Applications Library, 2020). Furthermore, not all COVID-19 infection episodes will have been ascertained, particularly during the early stages of the pandemic when access to tests was very limited.

The COVID-related hospitalisation and intensive care treatment data came from combining information provided by local general hospitals and supplementing that by reading the anonymised clinical notes of each patient. For the COVID-19 infections that were diagnosed in the catchment area, given that lockdown restrictions precluded travel away from one's primary residence, it is unlikely the patients would have travelled to other areas during this period and therefore, their diagnosis should have been recorded at local hospitals. Our data linkage included King's College Hospital and Princess Royal University Hospital, which are two large healthcare providers in the area. To cover diagnoses that were made in hospitals not included in our linkage, we included data from clinician-entered alerts on SLAM records. There maybe be some bias attributed to clozapine-treated patients being in more contact with the SLAM services (Govind *et al.*, 2020). This would have resulted in complications from COVID-19 infections being more likely to be recorded in patients taking clozapine than in those taking other antipsychotics, biasing the results towards unfavourable outcomes in clozapine patients.

Another important limitation of the analysis results from type II error. We acknowledge this analysis is underpowered, but since the sample included all eligible patients so could not be increased any further, there was no rationale to conduct a power calculation prior to the study. We calculated the post-hoc power calculation to give the context in terms of the probability of a Type II error and to show that a large association was unlikely.

Although all deaths occurred within 28 days of COVID-19 infection, and thus meet the Public Heath England criteria for COVID-related deaths (Public Health England, 2020), it is possible that some deaths may have been unrelated to COVID.

Obesity is a recognised risk factor for more severe COVID-19 outcomes, but obesity information had to be extrapolated using the nearest BMI score, not all of which were recent. While these BMI scores are likely to give some indication of obesity of the patient, we cannot rule out that clozapine-treated patients may have more up-to-date BMI scores due to increased monitoring. Compared to those receiving treatment with other antipsychotics, a significantly high proportion of clozapine-treated patients were obese. This may be attributable to clozapine having the highest potential to induce weight gain compared to other antipsychotics (Allison *et al.*, 1999).

Since the smoking data encompasses patients who have mentions of cigarette smoking in their clinical records from any time within a year prior to COVID-19 infection, some patients' smoking status may have been misclassified. Given the impact of smoking on clozapine metabolization and clozapine plasma levels, it is important to note that clozapine-treated patients are more likely to be questioned about their smoking habits and therefore have recent information on it.

Implications

To our knowledge, this is the first study to investigate whether clozapine-treated patients are at increased risk of adverse outcomes of COVID-19, such as hospitalisation, treatment in intensive care or ventilation, or all-cause mortality, than patients on other antipsychotics. Within the limits of statistical power, we did not find evidence of substantial increased risk; however, larger and/or multi-site studies would be needed to rule out smaller effects.

Author Contributions

Conceived and design of the study: RG, DFF, RDH, JHM

Performed the analysis: RG

Interpreted the results, paper writing & critical review: all authors (RG, DFF, MP, MK, JTT, RS, RDH, JHM)

Gave final approved of the version to be published: all authors (RG, DFF, MP, MK, JTT, RS, RDH, JHM)

Role of Funding

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Conflict of interest

RDH has received research funding from Roche, Pfizer, Janssen, and Lundbeck. DFF has received research funding from Janssen and Lundbeck. JHM has received research funding from Lundbeck. JTT has received research funding from Bristol-Meyers-Squibb. RS declares research support in the last 36 months from Janssen, GSK and Takeda.

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Figure 1: Study design

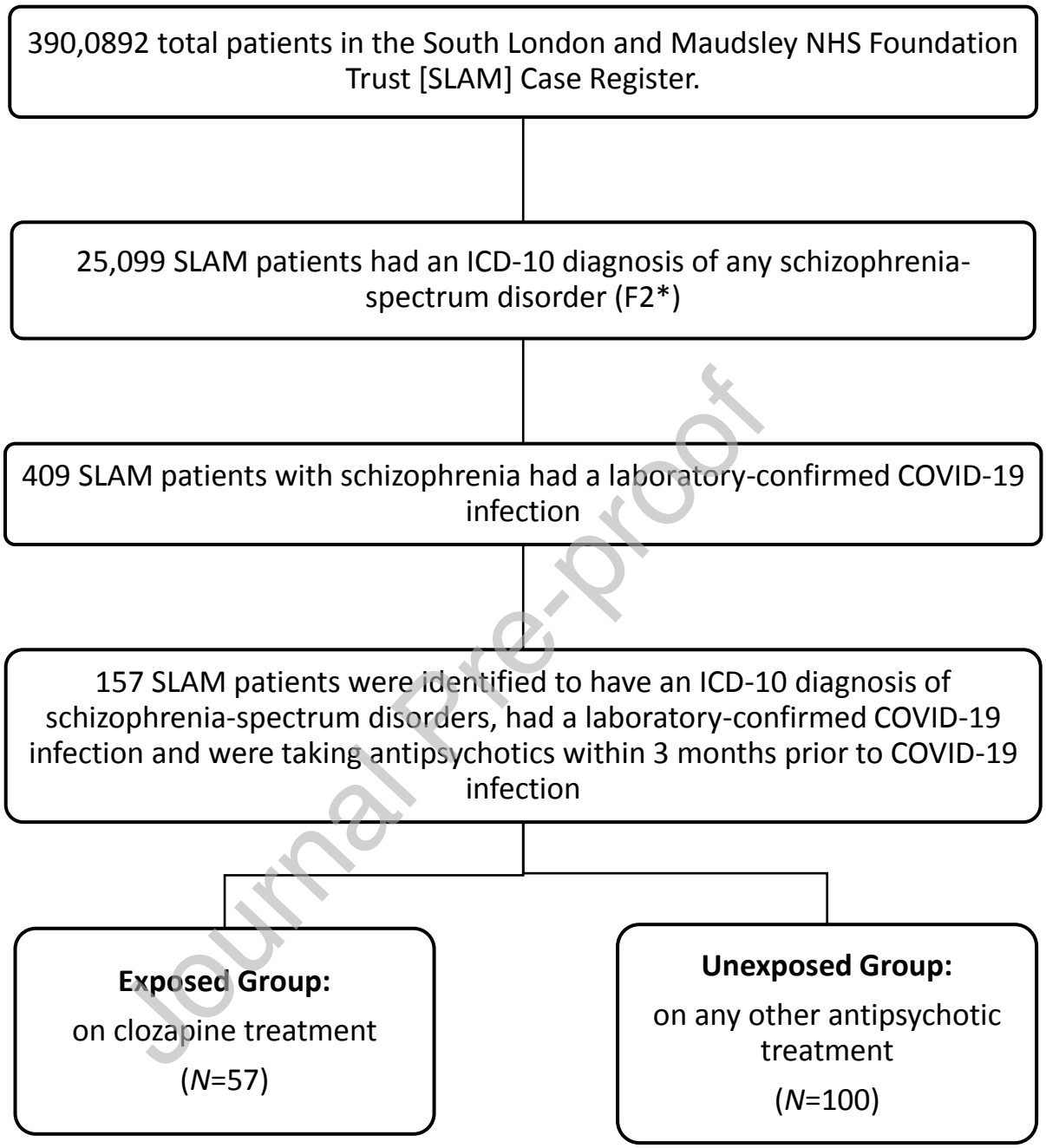

Table 1: Sample description of the 157 SLAM patients who qualified for the inclusion criteria, presented according to those who were and were not receiving clozapine-treatment

	On Clozapine treatment (%)	Not on Clozapine-treatment (%)
Total Patients in cohort	36.3 (n=57)	63.7 (n=100)
Males	56.1	52.0.0
Age		
< 50 years	52.6	40.0
> 50 years	47.4	60.0
Ethnicity		
White	28.1	28.0
Black	57.9	63.0
Asian & Other	14.0	9.0
Neighbourhood Deprivation		
Lower level of deprivation	56.1	45.0
Higher level of deprivation	35.1	49.0
Homeless	8.8	6.0
Current smoker	87.7	58.0
Obesity	63.2	35.0
Diabetes	43.9	42.0
Asthma	28.1	16.0
Bronchitis	8.8	13.0
Hypertension	45.6	45.0
Outcomes		
COVID-19 hospitalisation	24.6	30.0
COVID-19 treatment in intensive care	7.0	9.0
All-cause mortality	7.0	9.0

Table 2: Logistic regression analysis of the association between receiving clozapine treatment and each outcome (COVID-related hospitalisation, COVID-related treatment in intensive care and death) between the date of COVID-19 infection and January 07, 2021, inclusive in 157 individuals [a]

clozapine treatment risk factor for outcome:	COVID-19 hospitalisation Odds Ratio (95% CI)	COVID-19 treatment in intensive care Odds Ratio (95% CI)	All-cause mortality Odds Ratio (95% CI)
Unadjusted	0.76 (0.36-1.59)	0.76 (0.22-2.60) [b]	0.76 (0.22-2.60) [b]
Adjusted for confounding effects using propensity scores [c]	1.12 (0.48-2.60)	0.71 (0.18-2.77)	1.38 (0.33-5.71)

a: Of the 157 individuals, 44 patients had COVID-related hospitalisation, 13 patients had COVID-related treatment in intensive care, 13 patients died after COVID-19 infection

b: Since the number of patients who had COVID-related treatment in intensive were the same as the number of patients who died after COVID-19 infection, the unadjusted analysis for these two outcomes produced the same results.

c: list of confounding variables: gender, age, ethnicity, neighbourhood deprivation, smoking status, obesity, diabetes, asthma, bronchitis and hypertension

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