Observational Study of Chlorpromazine in Hospitalized Patients with Covid-19 Running title: Chlorpromazine in hospitalized patients with Covid-19

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Ethics approval

All procedures related to this work adhered to the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Consent to participate

AP-HP clinical Data Warehouse initiative ensures patient information and consent regarding the different approved studies through a transparency portal in accordance with European Regulation on data protection and authorization n°1980120 from National Commission for Information Technology and Civil Liberties (CNIL). Participants who did not consent to participate in the study were excluded.

Consent for publication

This study received approval from the Institutional Review Board of the AP-HP clinical data warehouse (decision CSE-20-20_COVID19, IRB00011591).

Availability of data and material

Data from the AP-HP Health Data Warehouse can be obtained with permission at https://eds.aphp.fr//.

Code availability

Not applicable.

Author's contributions

NH designed the study, performed statistical analyses, and wrote the first draft of the manuscript. MSR performed statistical analyses and critically revised the manuscript. RV contributed to statistical analyses and critically revised the manuscript for scientific content. FL, NB and ASJ contributed to study design and critically revised the manuscript for scientific content. NB, ASJ, AN, NP, CD, AG, GL, MB, and AB contributed to database build process. All authors critically revised the manuscript for scientific content.

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ABSTRACT

Introduction: Chlorpromazine has been suggested as potentially useful in patients with COVID-19 on the grounds of its potential antiviral and anti-inflammatory effects.

Objectives: To examine the association between chlorpromazine use and mortality among adult patients hospitalized for COVID-19.

Methods: We conducted an observational multicenter retrospective study at AP-HP Greater Paris University hospitals. Study baseline was defined as the date of first prescription of chlorpromazine during the hospitalization for COVID-19. The primary endpoint was death. Among patients who had not been hospitalized in ICUs, we compared this endpoint between those who received chlorpromazine and those who did not, in time-to-event analyses adjusted for patient characteristics, clinical markers of disease severity, and other psychotropic medications. The primary analysis used a Cox regression model with inverse probability weighting. Multiple sensitivity analyses were performed.

Results: Of the 14,340 adult inpatients hospitalized outside ICUs for COVID-19, 55 patients (0.4%) received chlorpromazine. Over a mean follow-up of 14.3 days (SD=18.2), death occurred in 13 patients (23.6%) who received chlorpromazine and 1,289 patients (9.0%) who did not. In the primary analysis, there was not significant association between chlorpromazine use and mortality (HR=2.01; 95%CI=0.75-5.40, p=0.163). Sensitivity analyses included a Cox regression in a 1:5 ratio matched analytic sample that showed a similar result (HR=1.67; 95%CI=0.91-3.06, p=0.100) and a multivariable Cox regression that indicated a significant positive association (HR=3.10; 95%CI=1.31-7.34, p=0.010).

Conclusion: Our results suggest that chlorpromazine prescribed at a mean daily dose of 70.8 mg (SD=65.3) was not associated with reduced mortality.

Key words: COVID-19; SARS-CoV-2; chlorpromazine; treatment; efficacy; death; mortality.

Key points:

- We examined the association between chlorpromazine use and mortality among adult patients hospitalized for COVID-19 outside ICUs.
- Chlorpromazine was prescribed at a mean daily dose of 70.8 mg (SD=65.3).
- Our results suggest that chlorpromazine use was not associated with reduced mortality.

1. Introduction

Global spread of the novel coronavirus SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), has created an unprecedented infectious disease crisis worldwide [1,2]. In the current absence of antiviral medications associated with substantial decrease in COVID-19-related mortality [3–5], the search for an effective treatment for patients with COVID-19 among all available medications is urgently needed [6–8].

Chlorpromazine, a dimethylamine derivative of phenothiazine used in the treatment of acute and chronic psychoses [9], has been suggested as potentially useful for patients with COVID-19 on the grounds of its antiviral and anti-inflammatory effects [10]. Specifically, several in-vitro studies [11–13] showed that chlorpromazine reduces viral replication of coronavirus-229E, MERS-CoV et SARS-CoV-1, possibly through the inhibition of clathrin-mediated endocytosis [14,15]. Furthermore, several mouse models of sepsis [16–19] suggest that this medication is associated with a decrease in pro-inflammatory cytokines, including IL-2, IL4, IFN alpha, TNF, and GM-CSF, and an increase of the anti-inflammatory cytokine IL-10. Short-term use of chlorpromazine is generally well tolerated [10,20], although side effects can occur, including QT interval prolongation, extrapyramidal symptoms, dry mouth, dizziness, urine retention, blurred vision, constipation, and hyperprolactinemia [10,20].

To our knowledge, no clinical study has examined to date the potential usefulness of chlorpromazine in patients hospitalized for COVID-19. Observational studies of patients with COVID-19 taking medications for other indications can help decide which treatment should be prioritized for randomized clinical trials and minimize the risk for patients of being exposed to potentially harmful and ineffective treatments.

We took advantage of the Assistance Publique-Hôpitaux de Paris (AP-HP) Health Data Warehouse, which includes data on all patients with COVID-19 who had been consecutively admitted to AP-HP Greater Paris University hospitals.

In this report, we examined the association between chlorpromazine use and mortality among adult patients who have been admitted to these medical centers with COVID-19. We hypothesized that chlorpromazine use could be associated with lower mortality in time-to-event analyses adjusting for patient characteristics, clinical markers of disease severity, and other psychotropic medications.

2. Methods

2.1. Setting

We conducted a multicenter observational retrospective study at AP-HP, which includes 39 hospitals of which 23 are acute, 20 are adult and 3 are pediatric hospitals. We included all adults aged 18 years or over who have been admitted with COVID-19 to these medical centers from the beginning of the epidemic in France, i.e. January 24th, until May 1st. COVID-19 was ascertained by a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test from analysis of nasopharyngeal or oropharyngeal swab specimens. This observational non-interventional study using routinely collected data received approval from the Institutional Review Board of the AP-HP clinical data warehouse (decision CSE-20-20_COVID19, IRB00011591). AP-HP clinical Data Warehouse initiative ensures patient information and consent regarding the different approved studies through a transparency portal in accordance with European Regulation on data protection and authorization n°1980120 from National Commission for Information Technology and Civil Liberties (CNIL). Participants who did not consent to participate in the study were excluded. All procedures related to this work adhered to the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Data sources

We used data from the AP-HP Health Data Warehouse ('Entrepôt de Données de Santé (EDS)'). This warehouse contains all the clinical data available on all inpatient visits for COVID-19 in all medical departments of any of the 39 AP-HP Greater Paris University hospitals. The data obtained included patient demographic characteristics, RT-PCR test results, medication administration data, medication lists during current and past hospitalizations in AP-HP hospitals, current diagnoses, discharge disposition, ventilator use data, and death certificates.

2.3. Variables assessed

We obtained the following data for each patient at the time of the hospitalization: sex; age, which was categorized based on the OpenSAFELY study results (i.e. 18-50, 51-70, 71-80, 81 +) [21]; hospital, which was categorized into 4 classes following the administrative clustering of AP-HP hospitals in Paris and its suburbs based on their geographical location (i.e., AP-HP Centre – Paris University, Henri Mondor University Hospitals and at home hospitalization; AP-HP Nord and Hôpitaux Universitaires Paris Seine-Saint-Denis; AP-HP Paris Saclay University; and AP-HP Sorbonne University); obesity, which was defined as having a body-mass index higher than 30 kg/m^2 or an International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis code for obesity (E66.0, E66.1, E66.2, E66.8, E66.9); self-reported current smoking status; number of medical conditions associated with increased risk of severe SARS-CoV-2 infection [22–27], based on ICD-10 diagnosis codes, including diabetes mellitus (E11), diseases of the circulatory system (I00-I99), diseases of the respiratory system (J00-J99), neoplasms (C00-D49), and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D5-D8); any medication prescribed according to compassionate use or as part of clinical trials

(e.g., hydroxychloroquine, azithromycin, remdesivir, tocilizumab, sarilumab, or dexamethasone); and clinical severity of COVID-19 at admission, defined as having at least one of the following criteria [28,29]: respiratory rate > 24 breaths/min or < 12 breaths/min, resting peripheral capillary oxygen saturation in ambient air < 90% , temperature > 40°C, or systolic blood pressure < 100 mm Hg. To take into account possible confounding by indication bias for chlorpromazine, we recorded whether patients had any current diagnosis of psychiatric disorder (F00-F04 and F06-F99) or delirium (F05 and R41.0), and whether they were prescribed clozapine, which could be associated with increased risk of COVID-19 infection [30], any antipsychotic medication other than chlorpromazine or clozapine, any antidepressant, any benzodiazepine or Z-drug, or any mood stabilizer (i.e. lithium or antiepileptic medications with mood stabilizing effects [31–34]).

All medical notes and prescriptions are computerized in Greater Paris University hospitals. Medications including their dose, frequency, date, and mode of administration were identified from medication administration data or scanned hand-written medical prescriptions, through two deep learning models based on BERT contextual embeddings [35], one for the medications and another for their mode of administration. The model was trained on the APmed corpus [36], a previously annotated dataset for this task. Extracted medications names were then normalized to the Anatomical Therapeutic Chemical (ATC) terminology using approximate string matching.

2.4. Chlorpromazine use

Study baseline was defined as the date of first prescription of chlorpromazine during the hospitalization for COVID-19. Chlorpromazine is mostly used in psychiatry to treat acute symptoms in patients with psychotic disorders but may also be prescribed in intensive care units (ICUs) either in terminal restlessness (i.e. agitation and delirium before death) or as an

aid in orotracheal intubation. Therefore, to reduce a potential indication bias due to these later medical indications, which are associated with increased mortality, patients who had been hospitalized in ICUs (receiving or not receiving chlorpromazine) were excluded from the main analyses, and chlorpromazine use was defined as receiving this medication during the hospitalization for COVID-19 before the end of the index hospitalization or death. In our study, all patients who had been intubated and ventilated were hospitalized in ICUs.

In the absence of curative treatment for COVID-19, all patients benefited from symptomatic care including respiratory support and supportive management of the complications of the disease (e.g. pneumonia, secondary bacterial infections, thromboembolism). This symptomatic care was not different in patients who received chlorpromazine and those who did not.

2.5. Endpoints

The primary endpoint was the time from study baseline (i.e. first prescription of chlorpromazine during the hospitalization for COVID-19) until death. Patients without an end-point event had their data censored on May 1st, 2020.

2.6. Statistical analysis

We calculated frequencies of each variable described above in patients receiving or not receiving chlorpromazine and compared them using chi-square tests.

To examine the association of chlorpromazine use with the primary endpoint, we performed Cox proportional-hazards regression models [37]. Weighted Cox regression models were used when the proportional hazards assumption was not met [38]. To help account for the nonrandomized prescription of chlorpromazine and reduce the effects of confounding, the primary analysis used propensity score analysis with inverse probability

weighting (IPW) [39,40]. The individual propensities for chlorpromazine prescription were estimated by a multivariable logistic regression model that included sex, age, hospital, obesity, smoking status, number of medical conditions, any medication prescribed according to compassionate use or as part of a clinical trial, any current diagnosis of psychiatric disorder or delirium, any prescribed psychotropic medication, including clozapine, any antipsychotic medication other than chlorpromazine or clozapine, any antidepressant, any benzodiazepine or Z-drug, and any mood stabilizer, and clinical severity. In the inverse-probability-weighted analysis, the predicted probabilities from the propensity-score model were used to calculate the stabilized inverse-probability-weighting weights [39]. Association between chlorpromazine use and the primary endpoint was then estimated using an IPW Cox regression model. In case of unbalanced covariates, an IPW multivariable Cox regression model adjusting for the unbalanced covariates was performed to examine the robustness of the results. Kaplan-Meier curves were performed using the inverse-probability-weighting weight [41,42], and their pointwise 95% confidence intervals were estimated using the nonparametric bootstrap method [41,43].

We conducted three sensitivity analyses. We performed a multivariable Cox regression model comprising as covariates the same variables as in the IPW analysis and a univariate Cox regression model in a matched analytic sample. For this later analysis, we decided *a priori* to select five controls for each exposed case, based on the same variables used for both the IPW analysis and the multivariable Cox regression. Weighted Cox regression models were used when proportional hazards assumption was not met [38]. To reduce the effects of confounding, optimal matching was used in order to obtain the smallest average absolute distance across all the characteristics listed in **Table 1** between each exposed patient and the five corresponding non-exposed matched controls [44]. We also examined whether our

findings were similar when including in the analyses the 813 patients who had been hospitalized in ICUs and were excluded from the main analyses.

Finally, we examined a potential dose-effect relationship by testing the association between the daily dose received (dichotomized at the median value) with the endpoint among patients receiving chlorpromazine.

For all associations, we performed residual analyses to assess the fit of the data, check assumptions, including the proportional hazards assumption [37], and examined the potential influence of outliers. To improve the quality of result reporting, we followed the recommendations of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative [45]. Statistical significance was fixed a priori at $p<0.05$. All analyses were conducted in R software version 2.4.3 (R Project for Statistical Computing).

3. Results

3.1. Characteristics of the cohort

Of the 17,076 hospitalized adult patients with a positive COVID-19 RT-PCR test, 1,908 patients (11.2%) were excluded because of missing data or their young age (i.e. less than 18 years of age). Of the 75 adult patients who received chlorpromazine at any time during the visit for COVID-19, 15 patients (20.0%) were excluded because they received this treatment after intubation. Of the remaining 15,153 adult inpatients, 813 patients had been hospitalized in ICUs, and were excluded from the main analyses. Among the remaining 14,340 adult patients hospitalized outside ICUs, 55 patients (0.40%) received chlorpromazine, either by intramuscular injection (5.5%) or *per os* (94.5%), at a mean daily dose of 70.8 mg (SD=65.3; median=43.8 mg; range: 10.0 mg to 300.0 mg). Of these 55 patients who received chlorpromazine during the visit, 76.3% had either a current diagnosis of psychiatric disorder

or a current prescription of another psychotropic medication (63.6% if excluding a prescription of any benzodiazepine or Z-drug and a diagnosis of delirium). The relatively high rate of chlorpromazine prescription (0.4%) [46] might be explained by the greater risk of severe COVID-19 and thus of COVID-19-related hospitalization in individuals with psychiatric disorders than in their counterparts, in line with findings from prior studies [32,47,48]. A complementary explanation may include that certain patients may have received this treatment for non-psychiatric indications. The median delay between hospital admission and the first prescription of chlorpromazine was 1 day (SD=0.48, mean=0.78, range=0-2 days) and the median delay between first prescription of chlorpromazine and the end-point event or the end of the index hospitalization or the end of the study was 5.5 days (SD=7.0, mean=6.4, range=1-36 days).

First positive COVID-19 RT-PCR tests were obtained after a median delay of 1.2 days (SD=12.8) from study baseline. This delay was not significantly different between patients receiving or not receiving chlorpromazine [median in the exposed group=1.0 day (SD=11.9); median in the non-exposed group=1.2 day (SD=12.8); Mood's median test Chi-square<0.01, p>0.99)].

Over a mean follow-up of 14.3 days (SD=18.2; median=7.0 days; range: 1-98 days), 1,302 patients (9.1 %) had a primary end-point event prior to the completion of data collection on May 1st. In patients who received chlorpromazine, the mean follow-up was 6.4 days (SD=7.0; median=5.5 days; range: 1-36 days), while it was of 14.3 days (SD=18.2; median=7.0 days; range: 1-98 days) in those who did not receive this medication.

The distribution of patient characteristics according to chlorpromazine use is shown in **Table 1**. In the full sample, chlorpromazine use significantly differed according to most baseline characteristics, including hospital, obesity, smoking status, number of medical conditions, any medication according to compassionate use or as part of a clinical trial, any

current psychiatric disorder, any antidepressant, any benzodiazepine or Z-drug, any mood stabilizer medication, any antipsychotic medication other than chlorpromazine or clozapine, and clinical severity. The direction of these associations indicated overall greater medical severity of patients receiving chlorpromazine than those who did not. After applying the propensity score weights, these differences were substantially reduced but were still significant for any current psychiatric disorder, any antidepressant, any benzodiazepine or Z-drug, clozapine, and any antipsychotic medication other than chlorpromazine or clozapine (**Table 1**). In the matched analytic sample comprising 330 patients (i.e., 55 patients receiving chlorpromazine and 275 patients from the matched group who did not), there were no significant differences in patient characteristics according to chlorpromazine use (**Table 1**).

3.2. Study endpoint

In the full sample, death occurred in 13 patients (23.6%) who received chlorpromazine and 1,289 patients (9.0%) who did not. This end-point event occurred in 54 patients (19.6%) from the 1:5 ratio matched control group (**Table 2**). There was a significant positive association between chlorpromazine use and the primary endpoint in the crude, unadjusted analysis (hazard ratio (HR), 3.29; 95% CI, 1.91 to 5.69, p<0.001), but not in the primary analysis with inverse probability weighting (HR, 2.01; 95% CI, 0.75 to 5.40, p=0.163) (**Fig. 2**; **Table 2**). A similar result was found in the multivariable inverse probability weighting analysis adjusting for unbalanced covariates (i.e. any current psychiatric disorder, any antidepressant, any benzodiazepine or Z-drug, clozapine, and any antipsychotic medication other than chlorpromazine or clozapine) (HR, 4.58; 95% CI, 0.40 to 52.5, p=0.221) (**Table 2**). In sensitivity analyses, the univariate Cox regression model in the 1:5 ratio matched analytic sample yielded a similar result (HR, 1.67; 95% CI, 0.91 to 3.06, p=0.100) (**Fig. 2**; **Table 2**), whereas the multivariable Cox regression model in the full sample showed a significant

positive association between chlorpromazine use and mortality (HR, 3.10; 95% CI, 1.31 to 7.34, p=0.010) (**Table 2**). Findings were similar when including the 813 patients who had been hospitalized in ICUs and were excluded from the main analyses (**Online Resource 1**).

Finally, exposure to higher rather than lower doses of chlorpromazine was not significantly associated with the endpoint (HR, 0.15; 95% CI, 0.02 to 1.34, p=0.090).

A post-hoc analysis indicated that in the full sample, we had 80% power to detect unweighted and unadjusted hazard ratios of at least 0.15/2.80 for the primary endpoint, while we had 80% power to detect unweighted and unadjusted hazard ratios of at least 0.17/2.49 in the matched analytic sample.

4. Discussion

In this multicenter retrospective observational study involving a large sample of patients hospitalized for COVID-19, chlorpromazine prescribed at a mean daily dose of 70.8 mg (SD=65.3) was not significantly associated with mortality. Although these findings should be interpreted with caution due to the observational design, the wide confidence intervals for estimates, and the fact that this is, to our knowledge, the first study examining this association in a clinical population of patients with COVID-19, they suggest that chlorpromazine prescribed at these doses was not associated with reduced mortality among patients hospitalized for COVID-19.

Our study has several limitations. First, there are two possible major inherent biases in observational studies: unmeasured confounding and confounding by indication. In the analyses, we tried to minimize the effects of confounding in several different ways. First, because this treatment may be prescribed in intensive care units (ICUs) either in terminal restlessness (i.e. agitation and delirium before death) or as an aid in orotracheal intubation, patients who had been hospitalized in ICUs were excluded from the main analyses. Second,

we used a Cox regression model with inverse probability weighting to minimize the effects of confounding by indication [39,40]. We also performed sensitivity analyses, including a multivariable Cox regression model and a univariate Cox regression model in a matched analytic sample. None of these analyses showed a significant association between chlorpromazine use and reduced mortality. Finally, although some amount of unmeasured confounding may remain, our analyses adjusted for numerous potential confounders.

Additional limitations include missing data for some baseline characteristic variables, including clinical markers of severity of COVID-19, potential underreporting of ICD-10 diagnosis codes, particularly for current psychiatric disorders and delirium, and potential for inaccuracies in the electronic health records, which may be explained by the overwhelming of all hospital units during the COVID-19 peak incidence. Second, patients who received chlorpromazine were prescribed a relatively low dose, i.e., 70.8 mg (SD=65.3), and its antiviral properties might be observable at higher doses. Third, despite the multicenter design, our results may not be generalizable to other settings or regions. Fourth, because information on the specific medical departments where each patient was hospitalized, except for ICUs, was not available in our data, we were only able to adjust for hospital in our analyses and not on potential differences across departments in the management of patients with COVID-19. Fifth, information on the reason for prescribing chlorpromazine, and in particular if it was for terminal restlessness or as an aid in orotracheal intubation, the duration and adherence to its prescription, the prescription record of all patients before the admission, and the date that COVID-19 symptoms appeared, was not available. Although we excluded patients who had been hospitalized in ICUs from the main analyses to reduce a potential bias related to medical indications associated with increased mortality, we cannot rule out that this treatment might have been prescribed for agitation or terminal restlessness among patients hospitalized in other units, including geriatric units. However, most patients (76.3%) who received

chlorpromazine had either a current diagnosis of psychiatric disorder or a current prescription of another psychotropic medication, and the median delay between hospital admission and the first prescription of chlorpromazine was 1 day (SD=0.48, mean=0.78 day), suggesting that most of these patients were prescribed chlorpromazine for psychiatric symptoms. Sixth, our findings might support the true impact of medical care in COVID-19 rather than of the specific medication used [49]. Finally, the primary IPW analysis did not successfully balance several covariates between the chlorpromazine group and the control group, including any current psychiatric disorder, any antidepressant, any benzodiazepine or Z-drug, clozapine and any antipsychotic medication other than chlorpromazine or clozapine, which might have led to biased results. However, a similar non-significant result was found in the multivariable IPW analysis adjusting for these unbalanced covariates as well as in the univariate Cox regression model in a matched analytic sample, in which all covariates were adequately balanced between the two groups, suggesting the robustness of our findings.

In this multicenter observational retrospective study, chlorpromazine use prescribed at a mean daily dose of 70.8 mg (SD=65.3) was not associated with reduced mortality among adult patients hospitalized for COVID-19. Double-blind controlled randomized clinical trials, such as the *reCoVery study* [10], are needed to confirm these results.

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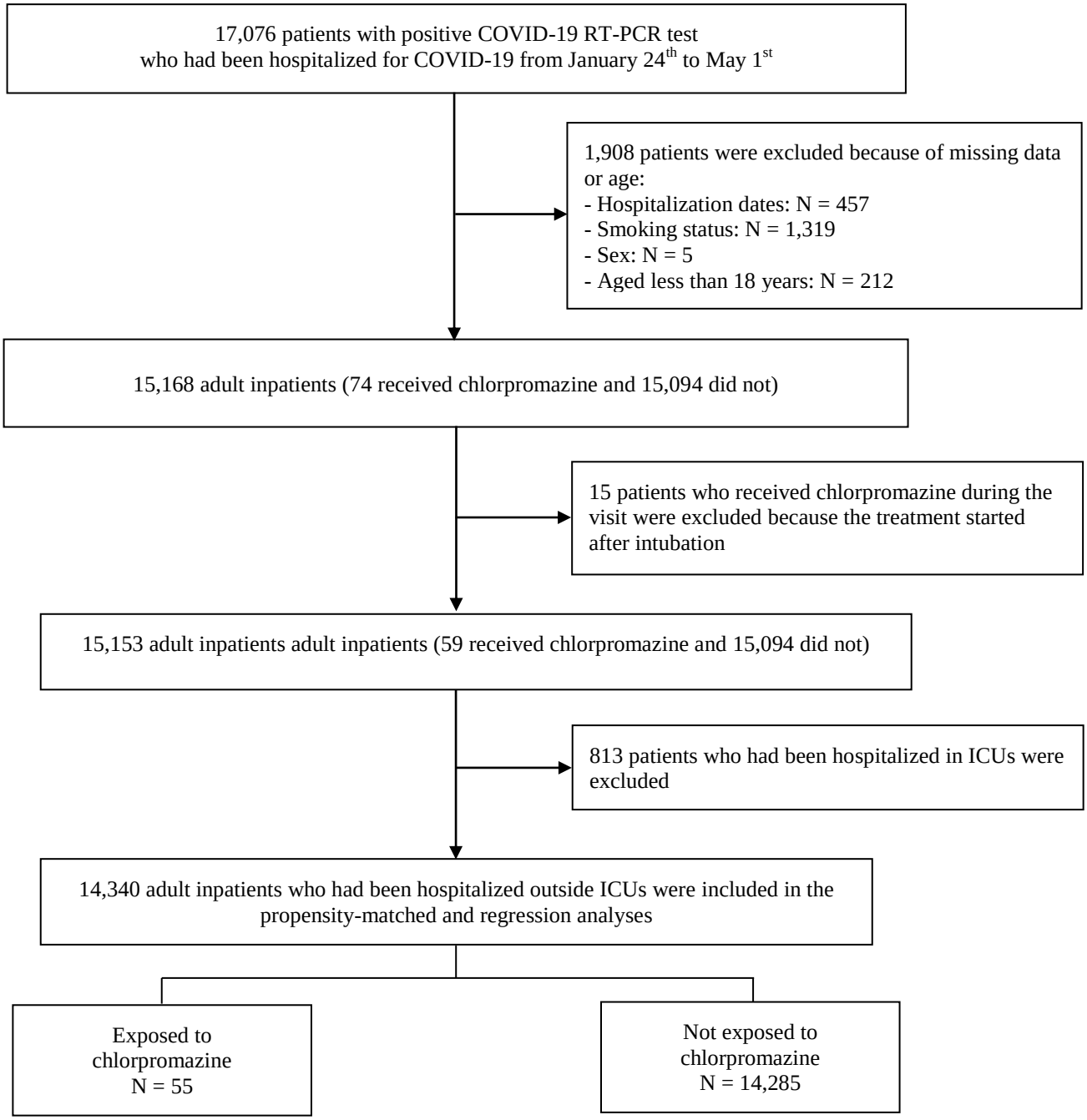
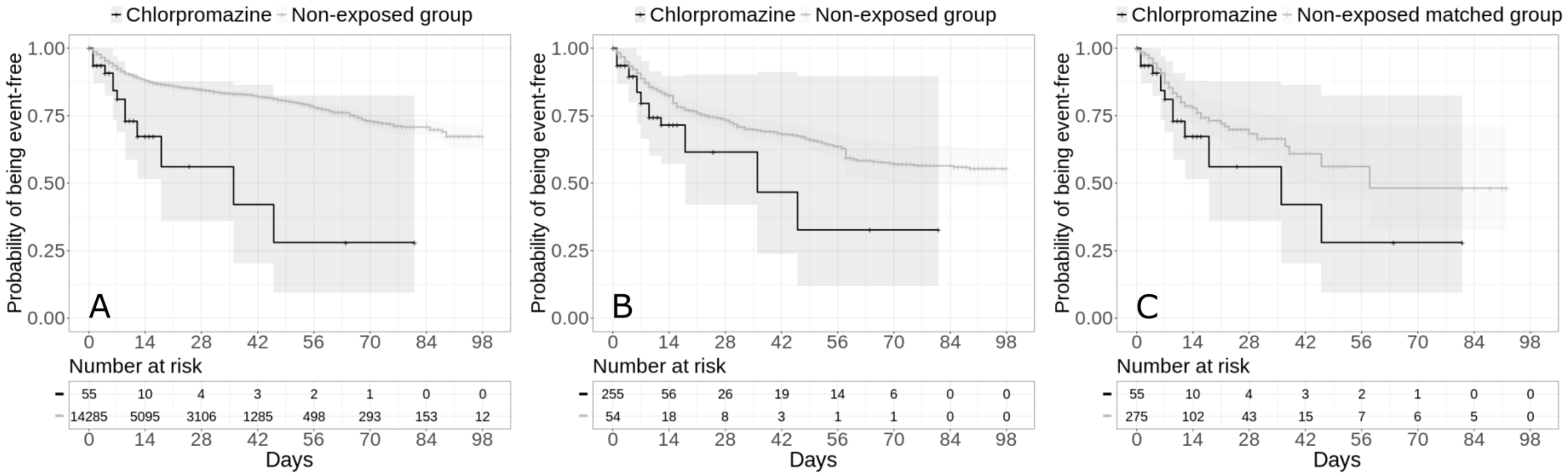
Fig. 1



Study cohort.

Fig. 2. Kaplan-Meier curves for mortality in the full sample crude analysis (N=14,340) (A), in the full sample analysis with inverse-probability weighting analysis (N=14,340) (B), and in the matched analytic sample using a 1:5 ratio (N=330) (C) of hospitalized patients with COVID-19 according to chlorpromazine use.



The shaded areas represent pointwise 95% confidence intervals.

Table 1. Characteristics of patients receiving or not receiving chlorpromazine in the matched and unmatched analytic samples.

	Exposed to chlorpromazine N = 55	Not exposed to chlorpromazine N = 14,285	Non-exposed matched group using a 1:5 ratio N = 275	Exposed to chlorpromazine vs. Not exposed to chlorpromazine (crude analysis)	Exposed to chlorpromazine vs. Not exposed to chlorpromazine (analysis weighted by inverse-probability-weighting weights)	Exposed to chlorpromazine vs. Non-exposed matched group (matched analytic sample analysis)
	N (%)	N (%)	N (%)	Chi-square test (p-value)	Weighted Chi-square test (p-value)	Chi-square test (p-value)
Characteristics						
Age				4.83 (0.185)	0.60 (0.896)	3.31 (0.346)
18 to 50 years	16 (29.1%)	5639 (39.5%)	58 (21.1%)			
51 to 70 years	21 (38.2%)	4320 (30.2%)	104 (37.8%)			
71 to 80 years	10 (18.2%)	1710 (12.0%)	46 (16.7%)			
More than 80 years	8 (14.5%)	2616 (18.3%)	67 (24.4%)			
Sex				1.25 (0.264)	<0.01 (0.987)	0.16 (0.694)
Women	25 (45.5%)	7699 (53.9%)	136 (49.5%)			
Men	30 (54.5%)	6586 (46.1%)	139 (50.5%)			
Hospital				21.42 (<0.001*)	1.34 (0.719)	3.65 (0.302)
AP-HP Centre – Paris University, Henri Mondor University Hospitals and at home hospitalization	12 (21.8%)	6763 (47.3%)	91 (33.1%)			
AP-HP Nord and Hôpitaux Universitaires Paris Seine-Saint-Denis	28 (50.9%)	3914 (27.4%)	118 (42.9%)			
AP-HP Paris Saclay University	4 (7.27%)	1707 (11.9%)	26 (9.45%)			
AP-HP Sorbonne University	11 (20.0%)	1901 (13.3%)	40 (14.5%)			
Obesity [α]				5.28 (0.022*)	0.64 (0.425)	0.67 (0.413)

Yes	13 (23.6%)	1780 (12.5%)	49 (17.8%)			
No	42 (76.4%)	12505 (87.5%)	226 (82.2%)			
Smoking [β]				8.31 (0.004*)	0.42 (0.518)	1.46 (0.227)
Yes	11 (20.0%)	1187 (8.31%)	35 (12.7%)			
No	44 (80.0%)	13098 (91.7%)	240 (87.3%)			
Number of medical conditions [μ]				17.95 (<0.001*)	1.98 (0.372)	0.34 (0.844)
0	28 (50.9%)	10791 (75.5%)	138 (50.2%)			
1	6 (10.9%)	796 (5.57%)	24 (8.73%)			
2 or more	21 (38.2%)	2698 (18.9%)	113 (41.1%)			
Medication according to compassionate use or as part of a clinical trial [π]				5.55 (0.018*)	1.02 (0.313)	0.86 (0.355)
Yes	12 (21.8%)	1564 (10.9%)	43 (15.6%)			
No	43 (78.2%)	12721 (89.1%)	232 (84.4%)			
Delirium[£]				<0.01 (>0.99)	<0.01 (0.974)	<0.01 (>0.99)
Yes	1 (1.82%)	217 (1.52%)	5 (1.82%)			
No	54 (98.2%)	14068 (98.5%)	270 (98.2%)			
Any current psychiatric disorder[¥]				50.23 (<0.001*)	13.12 (<0.001*)	<0.01 (>0.99)
Yes	14 (25.5%)	644 (4.51%)	69 (25.1%)			
No	41 (74.5%)	13641 (95.5%)	206 (74.9%)			
Any antidepressant				32.9 (<0.001*)	4.91 (0.027*)	<0.01 (>0.99)
Yes	14 (25.5%)	859 (6.01%)	69 (25.1%)			
No	41 (74.5%)	13426 (94.0%)	206 (74.9%)			
Any benzodiazepine or Z-drug				78.29 (<0.001*)	10.40 (0.001*)	<0.01 (>0.99)
Yes	24 (43.6%)	1248 (8.74%)	120 (43.6%)			
No	31 (56.4%)	13037 (91.3%)	155 (56.4%)			
Any mood stabilizer medication				23.21 (<0.001*)	0.24 (0.622)	<0.01 (>0.99)

Yes	9 (16.4%)	495 (3.47%)	230 (83.6%)			
No	46 (83.6%)	13790 (96.5%)	45 (16.4%)			
Clozapine				1.30 (0.255)	12.60 (<0.001*)	<0.01 (>0.99)
Yes	1 (1.82%)	29 (0.20%)	5 (1.82%)			
No	54 (98.2%)	14256 (99.8%)	270 (98.2%)			
Any antipsychotic medication other than chlorpromazine or clozapine				83.48 (<0.001*)	15.98 (<0.001*)	<0.01 (>0.99)
Yes	14 (25.5%)	435 (3.05%)	70 (25.5%)			
No	41 (74.5%)	13850 (97.0%)	205 (74.5%)			
Clinical severity [γ]				18.78 (<0.001*)	1.72 (0.424)	1.01 (0.605)
Yes	14 (25.5%)	2130 (14.9%)	94 (34.2%)			
No	22 (40.0%)	3180 (22.3%)	67 (24.4%)			
Missing	19 (34.5%)	8975 (62.8%)	114 (41.5%)			

[α] Defined as having a body-mass index higher than 30 kg/m^2 or an International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis code for obesity (E66.0, E66.1, E66.2, E66.8, E66.9).
[β] Current smoking status was self-reported.
[μ] Assessed using ICD-10 diagnosis codes for diabetes mellitus (E11), diseases of the circulatory system (I00-I99), diseases of the respiratory system (J00-J99), neoplasms (C00-D49), and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D5-D8).
[π] Any medication prescribed as part of a clinical trial or according to compassionate use (e.g., hydroxychloroquine, azithromycin, remdesivir, tocilizumab, sarilumab, or dexamethasone).
[£] Assessed using ICD-10 codes (F05 and R41.0).
[¥] Assessed using ICD-10 codes (F00-F04 and F06-F99).
[γ] Clinical severity of COVID-19 at admission was defined as having at least one of the following criteria: respiratory rate > 24 breaths/min or < 12 breaths/min, resting peripheral capillary oxygen saturation in ambient air < 90% , temperature > 40°C, or systolic blood pressure < 100 mm Hg .
* p-value is significant (p<0.05).

Table 2. Associations between chlorpromazine use and the endpoint of death in the full sample and in the matched analytic sample.

	Death
Full sample	
Number of events / Number of patients (%)	1,302 / 14,340 (9.1%)
Chlorpromazine	13 / 55 (23.6%)
No chlorpromazine	1,289 / 14,285 (9.0%)
Crude analysis – HR (95% CI; p-value)	3.29 (1.91 – 5.69; <0.001*)
Multivariable analysis – HR (95% CI; p-value)	3.10 (1.31 – 7.34; 0.010*)
Propensity score analysis with inverse probability weighting – HR (95% CI; p-value)	2.01 (0.75 – 5.40; 0.163)
Propensity score analysis with inverse probability weighting, adjusted for unbalanced covariates[α] – HR (95% CI; p-value)	4.58 (0.40 – 52.48; 0.221)
Matched analytic sample	
Number of events / Number of patients (%)	67 / 330 (20.3%)
Chlorpromazine	13 / 55 (23.6%)
No chlorpromazine	54 / 275 (19.6%)
Crude analysis – HR (95% CI; p-value)	1.67 (0.91 – 3.06; 0.100)

CI: Confidence interval; HR: hazard ratio.
[α] Adjusted for any current psychiatric disorder, any antidepressant, any benzodiazepine or Z-drug, clozapine and any antipsychotic medication other than chlorpromazine or clozapine.
* p-value is significant ($p<0.05$).

ONLINE RESOURCES

Online resource 1. Associations between chlorpromazine use and the endpoint of death in the full sample and in the matched analytic sample, while including in the analytic samples the 813 patients who had been hospitalized in ICUs.

	Death
Full sample	
Number of events / Number of patients (%)	1,595 / 15,153 (10.5%)
Chlorpromazine	15 / 59 (25.4%)
No chlorpromazine	1,580 / 15,094 (10.5%)
Crude analysis – HR (95% CI; p-value)	3.16 (1.90 – 5.25; <0.001*)
Multivariable analysis – HR (95% CI; p-value)	3.03 (1.43 – 6.39; 0.004*)
Propensity score analysis with inverse probability weighting – HR (95% CI; p-value)	2.12 (0.90 – 5.02; 0.087)
Propensity score analysis with inverse probability weighting, adjusted for unbalanced covariates[α] – HR (95% CI; p-value)	4.06 (0.30 – 55.79; 0.295)
Matched analytic sample	
Number of events / Number of patients (%)	76 / 354 (21.5%)
Chlorpromazine	15 / 59 (25.4%)
No chlorpromazine	61 / 295 (20.7%)
Crude analysis – HR (95% CI; p-value)	1.81 (1.02 – 3.20; 0.041*)

CI: Confidence interval; HR: hazard ratio; ICUs: intensive care units.
[α] Adjusted for any current psychiatric disorder, any antidepressant, any benzodiazepine or Z-drug, clozapine and any antipsychotic medication other than chlorpromazine or clozapine.
* p-value is significant (p<0.05).