pharmaceuticals

Article

Medications Modulating the Acid Sphingomyelinase/Ceramide System and 28-Day Mortality among Patients with SARS-CoV-2: An Observational Study

Nicolas Hoertel [1,2,*], Katayoun Rezaei [2], Marina Sánchez-Rico [2,3], Alfonso Delgado-Álvarez [2,3,4], Johannes Kornhuber [5], Erich Gulbins [6], Mark Olfson [7], Charles Ouazana-Vedrines [8], Alexander Carpinteiro [6,9], Céline Cougoule [10], Katrin Anne Becker [6], Jesús M. Alvarado [3], Frédéric Limosin [1,2] and on behalf of the AP-HP/Université Paris Cité/INSERM COVID-19 Research Collaboration, AP-HP COVID CDR Initiative and "Entrepôt de Données de Santé" AP-HP Consortium [†]

1 INSERM U1266, Université Paris Cité, F-75014 Paris, France
2 Service de Psychiatrie et Addictologie de l'Adulte et du Sujet Agé, DMU Psychiatrie et Addictologie, Hôpital Corentin-Celton, GHU APHP.Centre, F-92130 Issy-les-Moulineaux, France
3 Department of Psychobiology and Behavioural Sciences Methods, Faculty of Psychology, Universidad Complutense de Madrid, 28223 Madrid, Spain
4 Department of Biological and Health Psychology, Faculty of Psychology, Universidad Autónoma de Madrid, 28049 Madrid, Spain
5 Department of Psychiatry and Psychotherapy, University Hospital, Friedrich-Alexander-University of Erlangen-Nuremberg (FAU), 91054 Erlangen, Germany
6 Institute of Molecular Biology, University Hospital Essen, University of Duisburg-Essen, 47057 Essen, Germany; katrin.becker-flegler@uni-due.de (K.A.B.)
7 Department of Psychiatry, New York State Psychiatric Institute, Columbia University, New York, NY 10032, USA
8 Service de Psychiatrie de l'Adulte, DMU Psychiatrie et Addictologie, Hôpital Hôtel-Dieu, AP-HP, Université Paris Cité, F-75004 Paris, France
9 Department of Hematology and Stem Cell Transplantation, University Hospital Essen, University of Duisburg-Essen, 47057 Essen, Germany
10 Institute of Pharmacology and Structural Biology (IPBS), University of Toulouse, CNRS, 31000 Toulouse, France
* Correspondence: nico.hoertel@yahoo.fr
† Collaborators of AP-HP/Université Paris Cité/INSERM COVID-19 Research Collaboration, AP-HP COVID CDR Initiative and "Entrepôt de Données de Santé" AP-HP Consortium are cited in the Acknowledgments.

Abstract: Prior evidence indicates the potential central role of the acid sphingomyelinase (ASM)/ceramide system in the infection of cells with SARS-CoV-2. We conducted a multicenter retrospective observational study including 72,105 adult patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to 36 AP-HP (Assistance Publique–Hôpitaux de Paris) hospitals from 2 May 2020 to 31 August 2022. We examined the association between the ongoing use of medications functionally inhibiting acid sphingomyelinase (FIASMA), which reduces the infection of cells with SARS-CoV-2 in vitro, upon hospital admission with 28-day all-cause mortality in a 1:1 ratio matched analytic sample based on clinical characteristics, disease severity and other medications (N = 9714). The univariate Cox regression model of the matched analytic sample showed that FIASMA medication use at admission was associated with significantly lower risks of 28-day mortality (HR = 0.80; 95% CI = 0.72–0.88; $p < 0.001$). In this multicenter observational study, the use of FIASMA medications was significantly and substantially associated with reduced 28-day mortality among adult patients hospitalized with COVID-19. These findings support the continuation of these medications during the treatment of SARS-CoV-2 infections. Randomized clinical trials (RCTs) are needed to confirm these results, starting with the molecules with the greatest effect size in the study, e.g., fluoxetine, escitalopram, and amlodipine.

Keywords: COVID-19; SARS-CoV-2; mortality; FIASMA; ceramide; antidepressant

Citation: Hoertel, N.; Rezaei, K.; Sánchez-Rico, M.; Delgado-Álvarez, A.; Kornhuber, J.; Gulbins, E.; Olfson, M.; Ouazana-Vedrines, C.; Carpinteiro, A.; Cougoule, C.; et al. Medications Modulating the Acid Sphingomyelinase/Ceramide System and 28-Day Mortality among Patients with SARS-CoV-2: An Observational Study. *Pharmaceuticals* **2023**, *16*, 1107. https://doi.org/10.3390/ph16081107

Academic Editor: Juan Carlos Saiz

Received: 26 May 2023
Revised: 12 July 2023
Accepted: 20 July 2023
Published: 4 August 2023

1. Introduction

The COVID-19 pandemic is still regarded as a leading concern due to its deleterious effects on public health, healthcare infrastructure, and the economy [1–6]. There remains an unmet need for effective outpatient treatments for Coronavirus Disease 2019 (COVID-19), particularly for low- and middle-income countries, especially treatments that can be taken orally, have few medical contraindications [7,8], and are well-tolerated, affordable, and readily available [9–12].

Prior evidence indicates that the ASM/ceramide system may play an important role in the infection of cells with SARS-CoV-2 [13]. Acid sphingomyelinase (ASM) is an enzyme that cleaves sphingomyelin into ceramide, forming gel-like platforms in the plasma membrane. Experimental in vitro studies support the notion that SARS-CoV-2 causes the activation of the acid sphingomyelinase/ceramide pathway, which facilitates viral entry into cells through these gel-like platforms, favoring the clustering of activated SARS-CoV-2 cellular ACE2 receptors [13] (Figure 1). Therefore, it was shown that medications with the functional inhibition of acid sphingomyelinase (FIASMA), which inhibit ASM and reduce the formation of ceramide-enriched membrane platforms [12], decrease cell infection with SARS-CoV-2 and subsequent inflammation [12–15]. FIASMA medications include certain antidepressants (e.g., fluoxetine, fluvoxamine, escitalopram, amitriptyline), calcium channel blockers (e.g., amlodipine, bepridil), antihistamine medications (e.g., hydroxyzine and promethazine), and other specific medications [16]. In addition, drugs such as fluoxetine have also been shown to act directly on the virus and its replication, respectively. It remains to be determined whether different functional inhibitors of acid sphingomyelinase act on the acid sphingomyelinase/ceramide system and additional targets that are also important for infection, thereby amplifying the effects of the drugs used against the infection.

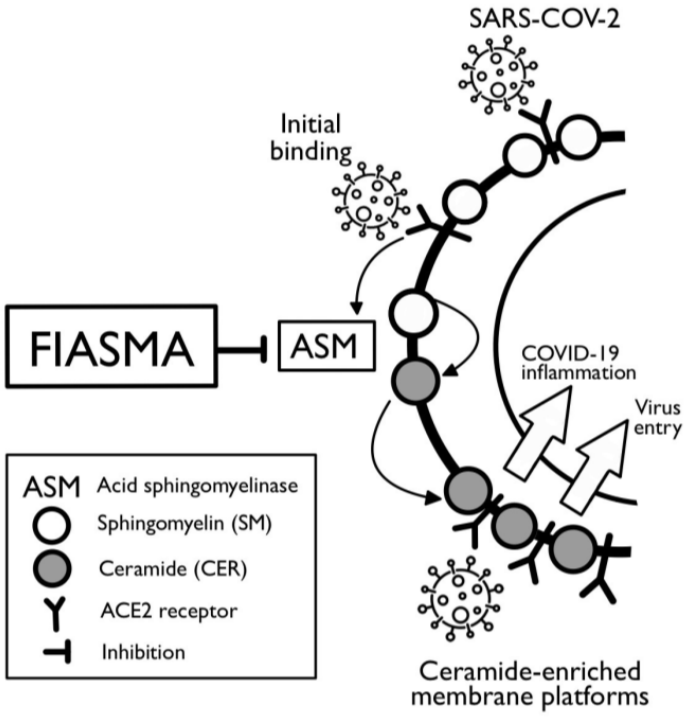

Figure 1. Biological mechanisms proposed by Carpinteiro et al. [13,15], underlying the potential effects of the functional inhibitors of acid sphingomyelinase (FIASMAs) on SARS-CoV-2 infection. SARS-CoV-2 may activate the acid sphingomyelinase/ceramide pathway, which, in turn, facilitates viral entry into cells through gel-like platforms that favor the clustering of activated SARS-CoV-2 cellular ACE2 receptors. Inhibition of the ASM by FIASMAs may result in a reduced concentration of ceramides, decreased viral entry, and subsequent inflammation.

Evidence from preclinical studies suggests that the infection of Vero E6 cells with SARS-CoV-2 can be hindered through the inhibition of the ASM/ceramide system by specific antidepressants, such as escitalopram, fluoxetine, or ambroxol [13,15,17]. The addition of ceramides to cells treated with these medications restores the infection [13]. In healthy volunteers, the infection of freshly isolated nasal epithelial cells with SARS-CoV-2 was blocked after the oral administration of amitriptyline [13]. Other studies conducted with human and nonhuman host cells confirmed the in vitro antiviral activity of several FIASMA antidepressants against different variants of SARS-CoV-2 [18–25]. Finally, the results from a K18-hACE2 mouse model of SARS-CoV-2 infection support the antiviral and anti-inflammatory properties of fluoxetine, possibly explained by the modulation of the ceramide system [17].

Several clinical trials have strengthened this preclinical evidence. Observational cohort studies of COVID-19 patients have indicated that FIASMA antidepressants and the FIASMAs amlodipine and hydroxyzine are associated with a reduced risk of mechanical ventilation or death in the acute care setting [26–32] and a decreased risk of hospital or emergency department visits among outpatients [33]. A systematic review and meta-analysis of six randomized controlled trials (RCTs) (N = 4197) found that a medium dose of the FIASMA antidepressant fluvoxamine (100 mg twice a day) was significantly associated with reduced mortality, hospitalization, and hospitalization/emergency department visits and not associated with increased serious adverse events [34]. Finally, two observational, multicenter, retrospective cohort studies conducted at Greater Paris University Hospitals showed that FIASMA medications, mostly FIASMA antidepressants, calcium channel blocker medications, and hydroxyzine, were significantly associated with a decreased likelihood of death or intubation [26,28] among inpatients with COVID-19.

Taken together, these results favor the possible repurposing of FIASMA medications against COVID-19. However, the few prior observational studies explored a limited range of FIASMA molecules (e.g., only FIASMA antidepressants [33] or the FIASMA hydroxyzine [35]), and several of them examined composite outcomes, such as intubation or death [26,28], posing challenges for the interpretation of the results.

In this report, we examined the link between the use of FIASMA medications at hospital admission and 28-day mortality among adult COVID-19 patients hospitalized at 36 Greater Paris University Hospitals. We hypothesized that FIASMA medication use would be associated with diminished mortality among COVID-19 inpatients.

2. Results

2.1. Characteristics of the Cohort

Of 72,105 adult patients hospitalized with COVID-19, 261 patients (0.4%) were excluded due to missing data (Figure 2).

Of the remaining 71,844 inpatients, 2354 patients (3.3%) were excluded because they took a FIASMA medication after their admission to hospital. Of the remaining 69,490 patients, 4857 (7.0%) received a FIASMA medication at the time of hospital admission, and 64,633 did not. Twenty-eight-day mortality occurred in 4416 (6.8%) patients. The associations of the clinical characteristics with 28-day mortality and the use of FIASMA medications at hospital admission are shown in Appendix A (Tables A1 and A2). In the matched analytic sample, no covariate substantially differed between groups (all SMDs < 0.1) (Table A3).

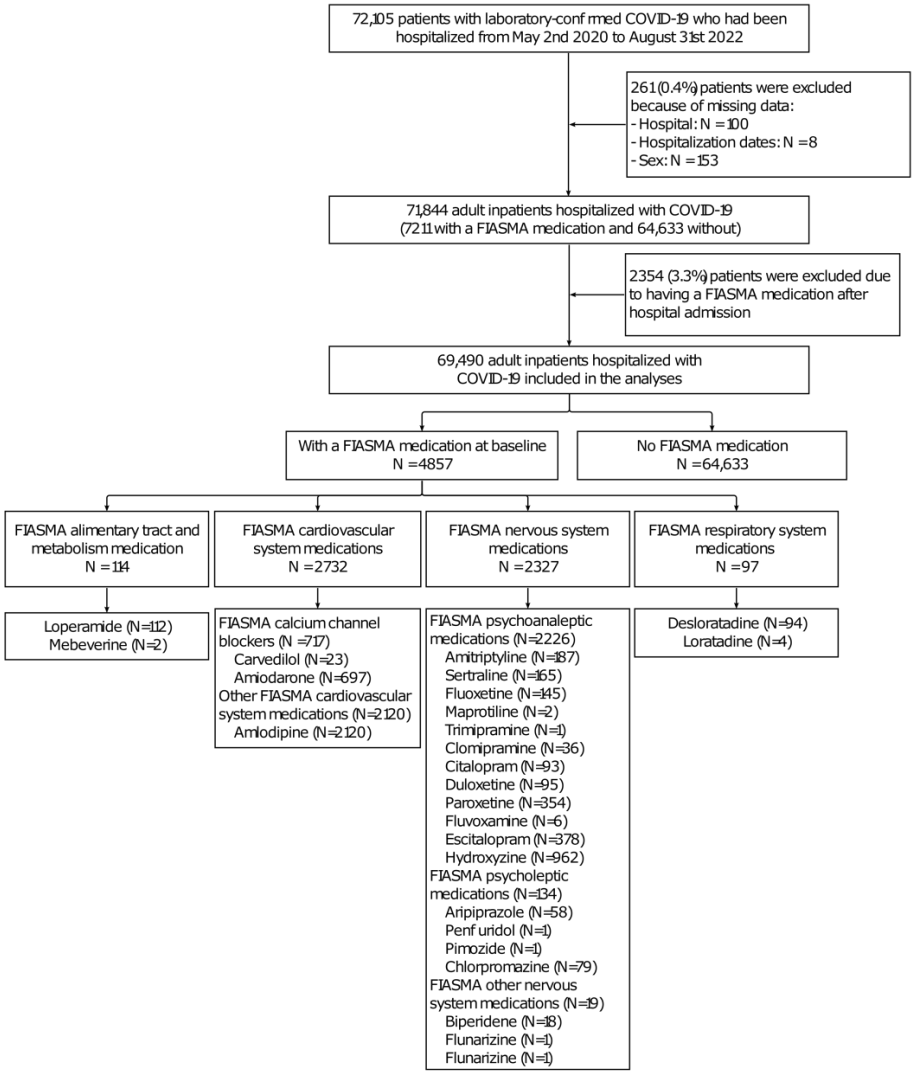

Figure 2. Study cohort.

2.2. Twenty-Eight-Day Mortality

In the matched analytic sample, 28-day mortality occurred in 625 patients (12.9%) who took a FIASMA medication at admission and in 772 patients (15.9%) who did not. The univariate Cox regression model in the matched analytic sample showed a significant association between FIASMA medication use at baseline and a reduced risk of 28-day mortality (HR = 0.80; 95% CI = 0.72–0.88; $p < 0.001$) (Figure 3; Table 1), corresponding to an ARR of death of 2.7% and an NNT of 37. This association remained significant when stratifying by age, sex, and period of hospitalization (Figure 4; Table 1; Table A4).

Table 1. FIASMA medication use at hospital admission and 28-day all-cause mortality in the matched analytic sample of adult inpatients with COVID-19.

	Number of Events/Number of Patients	**Crude Cox Regression Analysis of the Matched Analytic Sample**
	N/N (%)	**HR (95%CI; *p*-Value)**
Full sample (N = 9714)		
FIASMA medication	625/4857 (12.9%)	0.80 (0.72–0.88; <0.001)
No FIASMA medication	772/4857 (15.9%)	Ref.

Table 1. *Cont.*

	Number of Events/Number of Patients	Crude Cox Regression Analysis of the Matched Analytic Sample
	N/N (%)	**HR (95%CI; *p*-Value)**
Women (N= 4744)		
FIASMA medication	258/2372 (10.9%)	0.80 (0.68–0.94; 0.007 *)
No FIASMA medication	318/2372 (13.4%)	Ref.
Men (N= 4970)		
FIASMA medication	367/2485 (14.8%)	0.82 (0.71–0.94; 0.004 *)
No FIASMA medication	441/2485 (17.7%)	Ref.
Younger (≤70 years) (N = 3940)		
FIASMA medication	117/1970 (5.9%)	0.70 (0.55–0.88; 0.003 *)
No FIASMA medication	166/1970 (8.4%)	Ref.
Older (>70 years) (N= 5774)		
FIASMA medication	508/2887 (17.6%)	0.84 (0.74–0.94; 0.003 *)
No FIASMA medication	594/2887 (20.6%)	Ref.
Hospitalized before 24 October 2021 (N= 2037)		
FIASMA medication	372/2037 (18.3%)	0.85 (0.74–0.98; 0.021 *)
No FIASMA medication	431/2037 (21.2%)	Ref.
Hospitalized from 25 October 2021 (N= 5640)		
FIASMA medication	253/2820 (9.0%)	0.67 (0.57–0.79; <0.001 *)
No FIASMA medication	368/2820 (13.0%)	Ref.

* Two-sided *p*-value is significant ($p < 0.05$). Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference group.

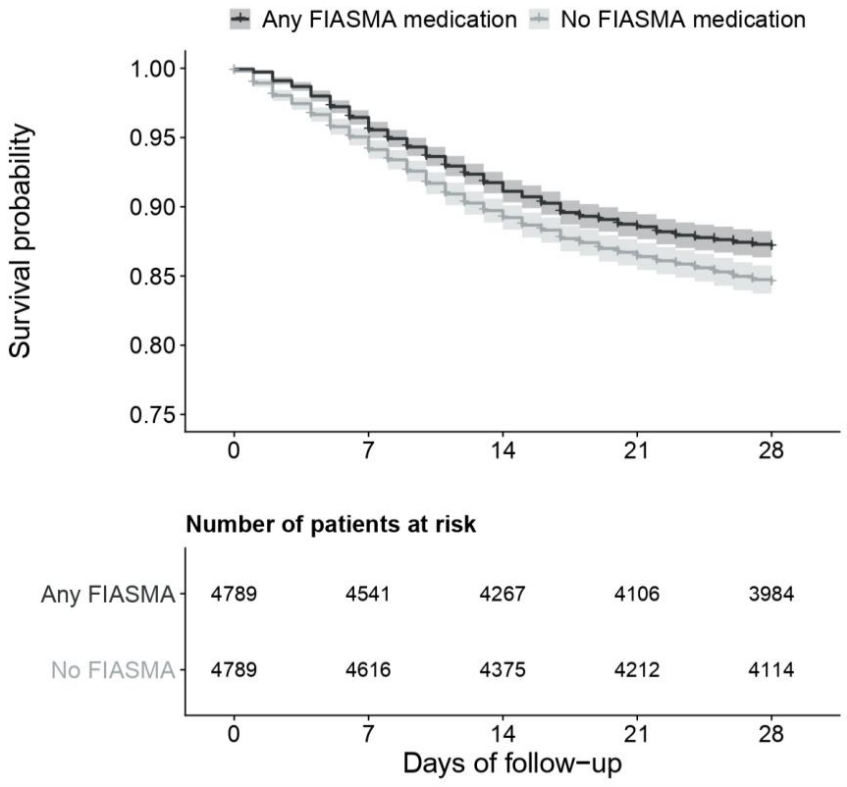

Figure 3. FIASMA medication use and 28-day mortality in the matched analytic sample (N = 9714).

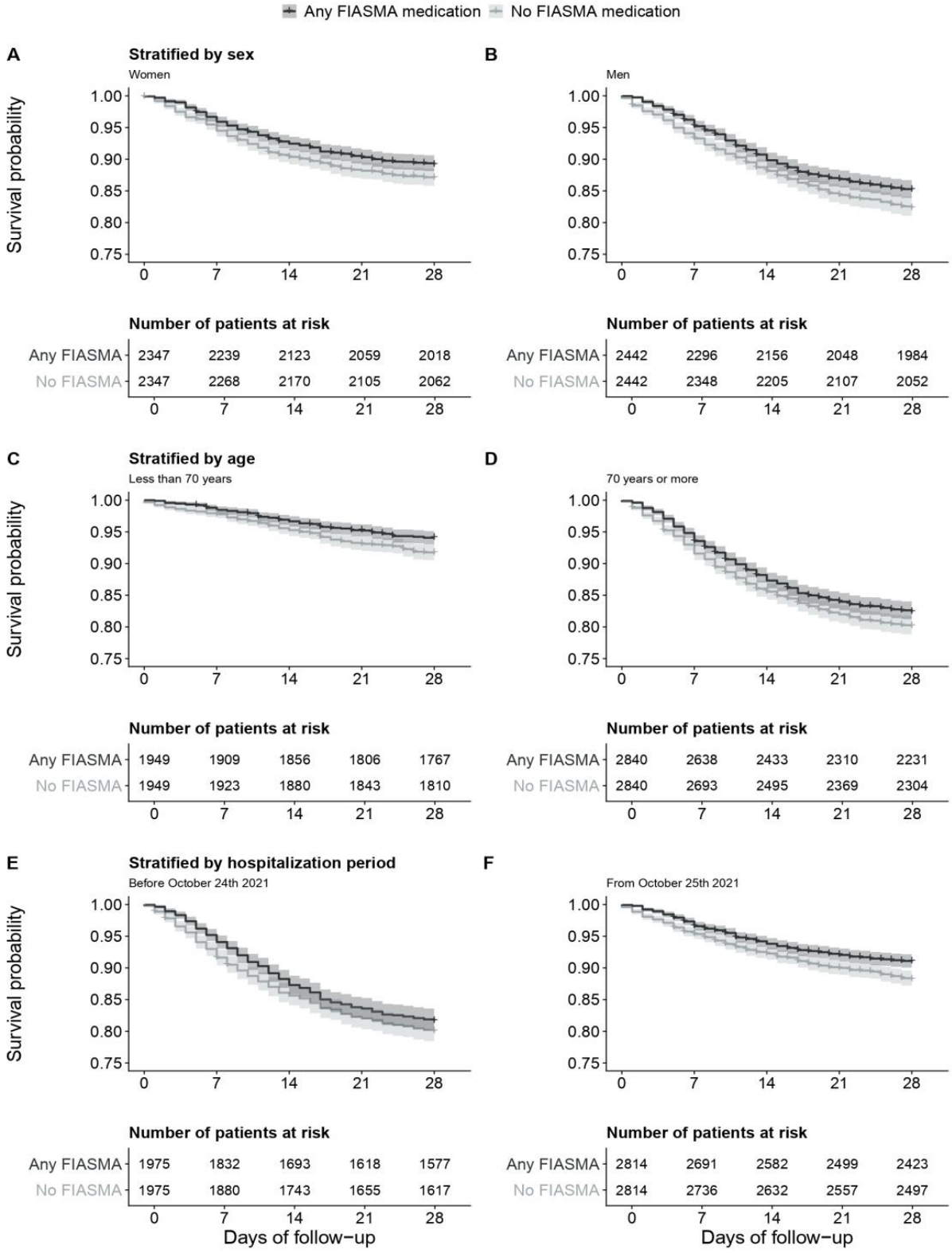

Figure 4. FIASMA medication use and 28-day mortality in the matched analytic sample, stratified by sex (**A**,**B**), age (**C**,**D**), and period of hospitalization (**E**,**F**).

Exploratory analyses indicated that the use of FIASMA cardiovascular system medications (particularly other FIASMA cardiovascular system medications) and FIASMA nervous system medications (particularly FIASMA psychoanaleptic medications) was significantly associated with reduced 28-day mortality (Table 2; Table A4). For most individual FIASMA

molecules, the hazard ratios were lower than 1. For all non-significant associations, the post hoc estimates of statistical power ranged from 3.5% to 59.6% (Table A5). Fluoxetine, amlodipine, and escitalopram were significantly associated with reduced 28-day mortality.

Table 2. Use of FIASMA medications at hospital admission and 28-day all-cause mortality in the matched analytic samples of adult inpatients with COVID-19.

	Patients with Medication	**Patients without Medication in the Matched Sample** [a]	**Crude Cox Regression Analysis in the Matched Analytic Sample**	**Multivariable Cox Regression Analysis of the Matched Analytic Sample Adjusted for Unbalanced Covariates**
	N/N (%)	**N/N (%)**	**HR (95%CI; *p*-Value)**	**AHR (95%CI; *p*-Value)**
FIASMA alimentary tract and metabolism medication	13/114 (11.4%)	12/114 (10.5%)	1.10 (0.50–2.41; 0.816)	1.41 (0.61–3.24; 0.420) [b]
Loperamide	13/112 (11.6%)	67/560 (12.0%)	0.98 (0.54–1.77; 0.944)	0.98 (0.54–1.78; 0.953) [c]
Mebeverine	0/2 (0.0%)	1/10 (10.0%)	NA	NA
FIASMA cardiovascular system medications	389/2732 (14.2%)	490/2732 (17.9%)	0.78 (0.68–0.89; <0.001 *)	NP
FIASMA calcium channel blockers	152/717 (21.2%)	157/717 (21.9%)	0.97 (0.77–1.21; 0.774)	NP
Carvedilol	3/23 (13.0%)	10/115 (8.7%)	1.50 (0.41–5.46; 0.537)	1.82 (0.48–6.82; 0.377) [d]
Amiodarone	151/697 (21.7%)	711/3485 (20.4%)	1.07 (0.90–1.28; 0.429)	NP
Other FIASMA cardiovascular system medications	256/2120 (12.1%)	368/2120 (17.4%)	0.67 (0.57–0.79; <0.001 *)	0.69 (0.58–0.80; <0.001 *) [e]
Amlodipine	256/2120 (12.1%)	1857/10600 (17.5%)	0.67 (0.59–0.76; <0.001 *)	0.66 (0.58–0.75; <0.001 *) [f]
FIASMA nervous system medications	266/2327 (11.4%)	332/2327 (14.3%)	0.79 (0.67–0.92; 0.004 *)	0.83 (0.71–0.98; 0.024 *) [g]
FIASMA psychoanaleptic medications	256/2226 (11.5%)	310/2226 (13.9%)	0.81 (0.69–0.96; 0.014 *)	0.93 (0.79–1.10; 0.382) [h]
Amitriptyline	28/187 (15.0%)	131/935 (14.0%)	1.06 (0.71–1.60; 0.772)	1.24 (0.82–1.87; 0.306) [i]
Sertraline	21/165 (12.7%)	138/825 (16.7%)	0.75 (0.47–1.19; 0.218)	0.82 (0.52–1.30; 0.395) [j]
Fluoxetine	9/145 (6.2%)	100/725 (13.8%)	0.44 (0.22–0.87; 0.019 *)	0.49 (0.25–0.97; 0.042 *) [k]
Maprotiline	0/2 (0.0%)	0/10 (0.0%)	NA	NA
Trimipramine	0/1 (0.0%)	1/5 (20.0%)	NA	NA
Clomipramine	7/36 (19.4%)	21/180 (11.7%)	1.73 (0.74–4.07; 0.209)	2.07 (0.86–5.00; 0.104) [l]
Citalopram	18/93 (19.4%)	69/465 (14.8%)	1.35 (0.8–2.27; 0.254)	1.42 (0.83–2.41; 0.197) [m]
Duloxetine	7/95 (7.4%)	54/475 (11.4%)	0.65 (0.30–1.44; 0.291)	0.78 (0.35–1.74; 0.548) [n]
Paroxetine	45/354 (12.7%)	253/1770 (14.3%)	0.88 (0.64–1.21; 0.420)	0.88 (0.64–1.20; 0.417) [o]
Fluvoxamine	0/6 (0.0%)	4/30 (13.3%)	NA	NA
Escitalopram	45/378 (11.9%)	323/1890 (17.1%)	0.67 (0.49–0.91; 0.012 *)	0.69 (0.51–0.95; 0.022 *) [p]
Hydroxyzine	104/962 (10.8%)	591/4810 (12.3%)	0.88 (0.71–1.08; 0.210)	1.09 (0.89–1.35; 0.396) [q]
FIASMA psycholeptic medications	10/134 (7.5%)	11/134 (8.2%)	0.91 (0.39–2.14; 0.824)	1.04 (0.43–2.50; 0.936) [r]
Aripiprazole	1/58 (1.7%)	13/290 (4.5%)	NA	NA
Penfluridol	0/1 (0.0%)	0/5 (0.0%)	NA	NA
Pimozide	0/1 (0.0%)	0/5 (0.0%)	NA	NA
Chlorpromazine	9/79 (11.4%)	29/395 (7.3%)	1.57 (0.74–3.32; 0.237)	1.87 (0.87–4.00; 0.107) [s]
Other FIASMA nervous system medications	3/19 (15.8%)’	4/19 (21.1%)	NA	NA
Biperidene	3/18 (16.7%)	13/90 (14.4%)	NA	NA
Flunarizine	0/1 (0.0%)	0/5 (0.0%)	NA	NA

Table 2. *Cont.*

	Patients with Medication	Patients without Medication in the Matched Sample [a]	Crude Cox Regression Analysis in the Matched Analytic Sample	Multivariable Cox Regression Analysis of the Matched Analytic Sample Adjusted for Unbalanced Covariates
	N/N (%)	N/N (%)	HR (95%CI; *p*-Value)	AHR (95%CI; *p*-Value)
FIASMA respiratory system medications	11/97 (11.3%)	13/97 (13.4%)	0.83 (0.37–1.86; 0.654)	1.61 (0.66–3.91; 0.297) [t]
Desloratadine	11/94 (11.7%)	62/470 (13.2%)	0.88 (0.46–1.67; 0.700)	0.92 (0.49–1.76; 0.807) [u]
Loratadine	0/4 (0.0%)	1/20 (5.0%)	NA	NA

[a] The ratio was set a priori at 1:1 for categories of molecules and at 1:5 for individual molecules. [b] Adjusted for age, hospital, period of hospitalization, any respiratory disorder, any disease of the musculoskeletal system, diseases of the genitourinary system, any eye–ear–nose–throat disorder, biological severity of COVID-19 at baseline, and clinical severity of COVID-19 at baseline. [c] Adjusted for age and any diseases of the genitourinary system. [d] Adjusted for age, sex, period of hospitalization, any neoplasm or disease of the blood, any cardiovascular disorder, any respiratory disorder, and biological severity of COVID-19 at baseline. [e] Adjusted for age. [f] Adjusted for age and any medication according to compassionate use or as part of a clinical trial. [g] Adjusted for age. [h] Adjusted for age, any respiratory disorder, and biological severity of COVID-19 at baseline. [i] Adjusted for age, any cardiovascular disorder, any respiratory disorder, any endocrine disorder, and biological severity of COVID-19 at baseline. [j] Adjusted for age, sex, any other infectious disease, and biological severity of COVID-19 at baseline. [k] Adjusted for age, sex, hospital, and biological severity of COVID-19 at baseline. [l] Adjusted for age, hospital, any medication according to compassionate use or as part of a clinical trial, any mental disorder, and biological severity of COVID-19 at baseline. [m] Adjusted for age, hospital, period of hospitalization, medications prescribed as part of a clinical trial or according to compassionate use, neoplasms and diseases of the blood, respiratory disorders, endocrine disorders, and clinical severity of COVID-19 at baseline. [n] Adjusted for age, hospital, any respiratory disorder, and biological severity of COVID-19 at baseline. [o] Adjusted for hospital. [p] Adjusted for age and any respiratory disorder. [q] Adjusted for age, any respiratory disorder, any endocrine disorder. [r] Adjusted for age and hospital. [s] Adjusted for age, any mental disorder, any disease of the musculoskeletal system, any diseases of the genitourinary system, and biological severity of COVID-19 at baseline. [t] Adjusted for age, sex, hospital, any medication as part of a clinical trial or according to compassionate use, any other infectious disease, any mental disorder, any respiratory disorder, any digestive disorder, any endocrine disorder, and biological severity of COVID-19 at baseline. [u] Adjusted for hospital, period of hospitalization, and biological severity of COVID-19 at baseline. * Two-sided *p*-value is significant ($p < 0.05$). Abbreviations: HR, hazard ratio; CI, confidence interval; NA, not applicable; NP, not performed due to the lack of unbalanced variables.

3. Discussion

In this multicenter, observational, retrospective study, the use of a FIASMA medication was significantly linked to reduced 28-day mortality, independent of sociodemographic characteristics, psychiatric and other medical comorbidities, COVID-19 severity, or other medications. The magnitude of this association (HR = 0.80; 95% CI = 0.72–0.88; $p < 0.001$) corresponded to an ARR of death of 2.7% and an NNT of 37. This association held in multiple sensitivity analysis. Additional exploratory analyses suggested that FIASMA cardiovascular system medications, particularly amlodipine, and FIASMA nervous system medications, particularly fluoxetine and escitalopram, were significantly associated with decreased 28-day mortality.

These results confirm and extend the preclinical [13,15,16,18–25,36,37], computational molecular docking [38], observational [26–35,39], and clinical [40–45] study findings suggesting that the ASM/ceramide system may play an important role in SARS-CoV-2 infection, particularly in the case of the FIASMA medications fluoxetine [17,46,47], escitalopram [27,29], and amlodipine [32,48]. These findings are also in line with studies indicating that clinical severity and inflammation markers in patients with COVID-19 are significantly associated with sphingomyelinase and ceramidase activity and the plasma levels of ceramides [3–5,17,49–51].

Th inhibition of the ASM [37,52] by FIASMA medications may result in antiviral effects (through the diminution of ceramide-enriched membrane domains resulting in decreased viral entry and subsequent inflammation) and anti-inflammatory effects (through the inhibition of this enzyme in endothelial and immune cells [9,11,12]). Because fluoxetine had the largest effect size in this study and has one of the strongest in vitro effects on the

ASM [52], is well-tolerated [53,54], and is in the World Health Organization's Model List of Essential Medicines, this molecule should be prioritized for randomized clinical trials in patients with COVID-19 [29].

The protective associations of FIASMA medications may also result from complex interactions between different biological mechanisms. These mechanisms may include anti-inflammatory properties, either through the high affinity of certain FIASMA medications for sigma-1 receptors (S1Rs) (e.g., fluoxetine and fluvoxamine) or through their effects on non–S1R-IRE1 pathways (e.g., nuclear factor κ B, peroxisome proliferator-activated receptor γ, Toll-like receptor 4, or inflammasomes) [47,55–57], reduced mast cell degranulation, decreased platelet aggregation, increased melatonin levels, interference with endolysosomal viral trafficking, and antioxidant properties [55–57]. The relative contribution of each mechanism may vary depending on disease stage, the dose prescribed, and the delay of treatment initiation.

This study has strengths, including its assessment of numerous potential confounders, such as markers of clinical severity, its substantial sample size, and the large period of observation, making relevant to different SARS-CoV-2 variants.

This study also has limitations. First, observational studies have two potential biases: unmeasured confounding and confounding by indication. Although the analyses were adjusted for numerous potential confounders, such as sex, age, psychiatric and other medical conditions, and markers of COVID-19 severity, it is still possible that some residual confounding remained unmeasured. For example, information on vaccination status and obesity was not available. In addition, we were unable to adjust our analyses for all the 36 AP-HP hospitals and all the medications, including non-FIASMA psychotropic medications, due to concerns regarding collinearity among these variables and the presence of zero events of a contingency table in some cells, including a high number of degrees of freedom. Second, a causal relationship cannot be established based on our observational study, and RCTs are necessary to confirm these results [58]. Third, information on medication discontinuation was not available, which might have contributed to an underestimation of the magnitude of the observed associations. Fourth, information on patients' nutrition, which may play a significant role in immune system functioning and overall health [59], was not available. Fifth, even though we used a multicenter study design, the results may not be generalizable to other regions or to outpatients [60]. Finally, due to the rapidly evolving nature of the COVID-19 pandemic, including the emergence of new variants, changes in preventive measures, and evolving treatment protocols, future studies would benefit from evaluating whether FIASMA are still active against infections with new virus variants [61].

4. Materials and Methods

4.1. Setting and Cohort Assembly

We conducted a multicenter retrospective cohort study at 36 AP-HP hospitals from 2 May 2020 to 31 August 2022 [29], including all adults aged 18 years or over who had been hospitalized at these medical centers with COVID-19. COVID-19 was ascertained using a positive reverse transcriptase–polymerase chain reaction (RT-PCR) test of nasopharyngeal or oropharyngeal swab specimens. The sample in this study did not overlap with the samples of the two previous studies focusing on FIASMA medications and using the AP-HP Warehouse data [26,28], which had a different inclusion period (i.e., from 24 February 2020 to 1 May 2020).

This observational study received approval from the Institutional Review Board of the AP-HP Clinical Data Warehouse (decision CSE-20- 20_COVID19, IRB00011591, 8 April 2020) [10,26–29,35,62–68]. AP-HP Clinical Data Warehouse initiatives ensure informed patient consent regarding the different studies approved through a transparency portal in accordance with the European Regulation on data protection and authorization, n°1980120, from the National Commission for Information Technology and Civil Liberties (CNIL).

4.2. Data Sources

The AP-HP Health Data Warehouse ('Entrepôt de Données de Santé (EDS)') contains all available clinical data on all inpatient visits for COVID-19 to 36 Greater Paris University Hospitals. The data included patient demographic characteristics, vital signs, laboratory test and RT-PCR test results, medication administration data during hospitalization, current medical diagnoses, and death certificates.

4.3. Variables Assessed

All variables assessed are detailed in Table A1. The sociodemographic characteristics included sex, age, hospital location, hospitalization period, psychiatric and non-psychiatric medical conditions based on the ICD-10 diagnosis codes during the visit, and medications prescribed according to compassionate use or as part of a clinical trial. The dates of medication prescriptions were recorded. Disease clinical and biological severity were also assessed. Clinical severity was defined based on at least one of the four following criteria [69,70]: resting peripheral capillary oxygen saturation in ambient air < 90%, respiratory rate > 24 breaths/min or <12 breaths/min, temperature > 40 °C, or systolic blood pressure < 100 mm Hg. Biological severity was considered to be met if the plasma lactate levels were higher than 2 mmol/L or in the case of a low lymphocyte-to-C-reactive protein ratio or high neutrophil-to-lymphocyte ratio [71] (both severity variables were binarized at the median value in the full sample).

4.4. FIASMA Medications

FIASMA medications were defined as medications displaying a residual in vitro ASM activity < 50%, as described in detail elsewhere [11,36]. We classified the medications following their Anatomical Therapeutic Chemical (ATC) codes (as detailed in Table 2).

FIASMA medication use was defined as having a prescription of at least one FIASMA medication at the time of hospital admission and at least one prior prescription of the same molecule within the last 6 months.

4.5. Study Baseline and Endpoint

The study baseline was the date of hospital admission. The endpoint was 28-day all-cause mortality. Patients without an endpoint event had their data censored at 28 days of follow-up.

4.6. Statistical Analysis

We calculated the frequency of each baseline characteristic described above for the adult inpatients with COVID-19 taking or not taking a FIASMA medication at baseline and compared them using standardized mean differences (SMDs) [72–74]. We considered SMDs greater than 0.1 to reflect significant differences [73].

To examine the association between FIASMA medication use at baseline and the risk of mortality during the 28 days following admission, we used Cox proportional hazard regression models [75] in a matched analytic sample of inpatients with COVID-19 receiving or not receiving a FIASMA medication. In order to reduce the effects of confounding variables, we used a 1:1 ratio matched analytic sample based on sex, age, hospital, period of hospitalization, medications prescribed as part of a clinical trial or according to compassionate use, psychiatric and other medical comorbidities, and biological and clinical markers of COVID-19 severity. Specifically, we used the nearest matching method [76]. We performed additional multivariable Cox regression models, including all unbalanced covariates (i.e., with a SMD > 0.1) [73].

If the main association was significant, we planned to calculate both the between-group difference in absolute risk reduction/increase (ARR) and the number needed to treat (NNT), considering a weighted time-to-event design.

To test the robustness of the primary analysis, we performed sensitivity analyses and separately reproduced the above-mentioned analyses (i) in women and men, (ii) in younger

and older patients (based on the median age of the fully matched analytic sample), and (iii) in two different periods of hospitalizations (based on the median date of hospitalization in the fully matched analytic sample).

As an exploratory analysis, we reproduced the above-mentioned analyses for each class of FIASMA medications and individual FIASMA molecules. We selected, a priori, one control for each case of exposure to each class of FIASMA medications and five controls for each exposed case of exposure to each individual FIASMA molecule.

We performed residual analyses for all the associations to determine the fit of the data and checked the assumptions, including multicollinearity diagnoses, using the generalized variance inflation factor (GVIF) for all the multivariable analyses. Our proportional hazard assumption was verified using proportional hazard tests and diagnostics based on weighted residuals [75] for all the survival analyses. Finally, we examined the potential presence and influence of outliers. We also performed post hoc statistical power calculations for all the associations, assuming a 20% mortality reduction. All analyses were conducted in R software version 3.6.3 (R Project for Statistical Computing), and statistical significance was fixed a priori at a two-sided p-value < 0.05. We followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative [77].

5. Conclusions

In this multicenter, observational, retrospective study, the ongoing use of functional inhibitors of acid sphingomyelinase (FIASMA) medications at hospital admission was significantly and substantially associated with reduced 28-day mortality, independent of sociodemographic characteristics, psychiatric or other medical comorbidities, the severity of the infection, or other medications among adult inpatients with COVID-19. This association held true in multiple sensitivity analyses. Additional exploratory analyses indicated that FIASMA cardiovascular system medications, particularly amlodipine, and FIASMA nervous system medications, particularly fluoxetine and escitalopram, were also associated with reduced 28-day mortality. These findings support the continuation of these medications during the treatment of SARS-CoV-2 infections. Randomized clinical trials (RCTs) against placebos as well as recommended antiviral treatments are needed to confirm these results, starting with fluoxetine, escitalopram, and amlodipine, which displayed the most robust results in our study [17,29,33,34,78].

Author Contributions: Conceptualization: N.H.; Data collection and administration: AP-HP/Université Paris Cité/INSERM COVID-19 Research Collaboration, AP-HP COVID CDR Initiative and "Entrepôt de Données de Santé" AP-HP Consortium; Data curation: M.S.-R. and A.D.-Á. Formal analysis: M.S.-R. and A.D.-Á. Methodology: N.H. and M.S.-R. Supervision: N.H. and F.L. Visualization: M.S.-R. Writing—original draft: N.H., K.R. and M.S.-R. Writing—review and editing: A.D.-Á., J.K., E.G., M.O., A.C., C.C., K.A.B., J.M.A., C.O.-V. and F.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and received approval from the Institutional Review Board of the AP-HP Clinical Data Warehouse (decision CSE-20- 20_COVID19, IRB00011591, 8 April 2020). AP-HP Clinical Data Warehouse initiatives ensure informed patient consent regarding the different studies approved through a transparency portal in accordance with the European Regulation on data protection and authorization, n°1980120, from the National Commission for Information Technology and Civil Liberties (CNIL).

Informed Consent Statement: Patient consent was not applicable, as this study did not include factors necessitating it.

Data Availability Statement: Data from the AP–HP Health Data Warehouse can be obtained upon request at https://eds.aphp.fr//. The statistical code is available upon request.

Acknowledgments: AP–HP/Université Paris Cité/INSERM COVID-19 research collaboration, AP–HP COVID CDR Initiative, "Entrepôt de Données de Santé" AP–HP Consortium: Pierre-Yves Ancel, Alain Bau-chet, Nathanaël Beeker, Vincent Benoit, Mélodie Bernaux, Ali Bellamine, Romain Bey, Aurélie Bourmaud, Stéphane Breant, Anita Burgun, Fabrice Carrat, Charlotte Caucheteux, Julien Champ, Sylvie Cormont, Christel Daniel, Julien Dubiel, Catherine Ducloas, Loic Esteve, Marie Frank, Nicolas Garcelon, Alexandre Gramfort, Nicolas Griffon, Olivier Grisel, Martin Guilbaud, Claire Hassen-Khodja, François Hemery, Martin Hilka, Anne Sophie Jannot, Jerome Lambert, Richard Layese, Judith Leblanc, Léo Lebouter, Guillaume Lemaitre, Damien Leprovost, Ivan Lerner, Kankoe Levi Sallah, Aurélien Maire, Marie-France Mamzer, Patricia Martel, Arthur Mensch, Thomas Moreau, Antoine Neuraz, Nina Orlova, Nicolas Paris, Bastien Rance, Hélène Ravera, Antoine Rozes, Elisa Salamanca, Arnaud Sandrin, Patricia Serre, Xavier Tannier, Jean-Marc Treluyer, Damien van Gysel, Gaël Varoquaux, Jill Jen Vie, Maxime Wack, Perceval Wajsburt, Demian Wassermann, and Eric Zapletal.

Conflicts of Interest: N.H., M.S.R., J.K., E.G., A.C. and F.L. are the inventors of a patented application related to methods of treating COVID-19, filed by the Assistance Publique—Hopitaux de Paris in France. The other authors declare no conflict of interest related to this work.

Appendix A

Table A1. Associations of baseline characteristics with 28-day mortality in the cohort of adult inpatients with COVID-19 (N = 69,490).

	Full Population (N= 69,490)	**Death (N= 4416)**	**No Death (N= 65,074)**	**Crude Analysis**	**Multivariable Analysis**	
	Mean (SD)/ N (%)	**Mean (SD)/ N (%)**	**Mean (SD)/ N (%)**	**HR (95%CI; *p*-Value)**	**AHR (95%CI; *p*-Value)**	**GVIF**
Age						1.21
18–50 years	32738 (47.1%)	159 (0.49%)	32579 (99.5%)	Ref.	Ref.	
51–60 years	9286 (13.4%)	297 (3.20%)	8989 (96.8%)	6.67 (5.50–8.09; <0.001 *)	4.33 (3.57–5.26; <0.001 *)	
61–70 years	8709 (12.5%)	732 (8.41%)	7977 (91.6%)	18.05 (15.21–21.43; <0.001 *)	9.69 (8.14–11.55; <0.001 *)	
71–80 years	8477 (12.2%)	1174 (13.8%)	7303 (86.2%)	30.73 (26.04–36.27; <0.001 *)	17 (14.35–20.15; <0.001 *)	
81–90 years	7164 (10.3%)	1338 (18.7%)	5826 (81.3%)	42.94 (36.43–50.62; <0.001 *)	27.72 (23.42–32.8; <0.001 *)	
More than 90 years	3116 (4.48%)	716 (23.0%)	2400 (77.0%)	54.50 (45.89–64.72; <0.001 *)	38.44 (32.21–45.87; <0.001 *)	
Sex						1.06
Women	36001 (51.8%)	1782 (4.95%)	34219 (95.1%)	Ref.	Ref.	
Men	33489 (48.2%)	2634 (7.87%)	30855 (92.1%)	1.61 (1.52–1.71; <0.001 *)	1.34 (1.26–1.42; <0.001 *)	
Hospital						1.08
AP-HP Centre–Paris University, Henri Mondor, Doumer University Hospitals, and hospitalization at home	27967 (40.2%)	1712 (6.12%)	26255 (93.9%)	Ref.	Ref.	
AP-HP Nord and Hôpitaux Universitaires Paris Seine-Saint-Denis	27967 (40.2%)	1641 (5.87%)	26326 (94.1%)	0.94 (0.88—1.01; 0.077)	1.05 (0.98—1.13; 0.142)	
AP-HP Sorbonne University	13556 (19.5%)	1063 (7.84%)	12493 (92.2%)	1.27 (1.18–1.37; <0.001 *)	1.07 (0.99–1.16; 0.078)	
Period of hospitalization						1.07
2 May 2020–31 March 2021	28216 (40.6%)	2136 (7.57%)	26080 (92.4%)	Ref.	Ref.	
1 April 2021–27 January 2022	25576 (36.8%)	1640 (6.41%)	23936 (93.6%)	0.83 (0.78–0.88; <0.001 *)	0.95 (0.89–1.01; 0.093)	
28 January 2022–31 August 2022	15698 (22.6%)	640 (4.08%)	15058 (95.9%)	0.53 (0.48–0.57; <0.001 *)	0.50 (0.46–0.55; <0.001*)	

Table A1. *Cont.*

	Full Population (N= 69,490)	Death (N= 4416)	No Death (N= 65,074)	Crude Analysis	Multivariable Analysis	
	Mean (SD)/ N (%)	Mean (SD)/ N (%)	Mean (SD)/ N (%)	HR (95%CI; *p*-Value)	AHR (95%CI; *p*-Value)	GVIF
Medication according to compassionate use or as part of a clinical trial [a]						1.05
Yes	1777 (2.56%)	297 (16.7%)	1480 (83.3%)	2.86 (2.54–3.22; <0.001 *)	1.07 (0.95–1.21; 0.271)	
No	67713 (97.4%)	4119 (6.08%)	63594 (93.9%)	Ref.	Ref.	
Other infectious diseases [b]						1.27
Yes	5243 (7.54%)	878 (16.7%)	4365 (83.3%)	3.14 (2.91–3.38; <0.001 *)	1.08 (0.99–1.17; 0.070)	
No	64247 (92.5%)	3538 (5.51%)	60709 (94.5%)	Ref.	Ref.	
Neoplasms and diseases of the blood [c]						1.18
Yes	7502 (10.8%)	1074 (14.3%)	6428 (85.7%)	2.74 (2.56–2.94; <0.001 *)	1.11 (1.03–1.19; 0.008 *)	
No	61988 (89.2%)	3342 (5.39%)	58646 (94.6%)	Ref.	Ref.	
Mental disorders [d]						1.18
Yes	5964 (8.58%)	818 (13.7%)	5146 (86.3%)	2.50 (2.32–2.70; <0.001 *)	0.86 (0.79–0.93; <0.001 *)	
No	63526 (91.4%)	3598 (5.66%)	59928 (94.3%)	Ref.	Ref.	
Diseases of the nervous system [e]						1.15
Yes	4323 (6.22%)	658 (15.2%)	3665 (84.8%)	2.75 (2.53–2.99; <0.001 *)	1.14 (1.04–1.24; 0.005 *)	
No	65167 (93.8%)	3758 (5.77%)	61409 (94.2%)	Ref.	Ref.	
Cardiovascular disorders [f]						1.55
Yes	12527 (18.0%)	2135 (17.0%)	10392 (83.0%)	4.53 (4.27–4.81; <0.001 *)	1.06 (0.98–1.14; 0.141)	
No	56963 (82.0%)	2281 (4.00%)	54682 (96.0%)	Ref.	Ref.	
Respiratory disorders [g]						1.58
Yes	14232 (20.5%)	2649 (18.6%)	11583 (81.4%)	6.26 (5.90–6.65; <0.001 *)	2.22 (2.06–2.40; <0.001 *)	
No	55258 (79.5%)	1767 (3.20%)	53491 (96.8%)	Ref.	Ref.	
Digestive disorders [h]						1.11
Yes	4604 (6.63%)	589 (12.8%)	4015 (87.2%)	2.22 (2.04–2.42; <0.001 *)	1.01 (0.92–1.11; 0.787)	
No	64886 (93.4%)	3827 (5.90%)	61059 (94.1%)	Ref.	Ref.	
Dermatological disorders [i]						1.07
Yes	1571 (2.26%)	223 (14.2%)	1348 (85.8%)	2.36 (2.06–2.70; <0.001 *)	0.95 (0.83–1.09; 0.465)	
No	67919 (97.7%)	4193 (6.17%)	63726 (93.8%)	Ref.	Ref.	
Diseases of the musculoskeletal system [j]						1.08
Yes	3800 (5.47%)	392 (10.3%)	3408 (89.7%)	1.71 (1.54–1.90; <0.001 *)	0.80 (0.72–0.90; <0.001 *)	
No	65690 (94.5%)	4024 (6.13%)	61666 (93.9%)	Ref.	Ref.	
Diseases of the genitourinary system [k]						1.37
Yes	6275 (9.03%)	1270 (20.2%)	5005 (79.8%)	4.34 (4.07–4.63; <0.001 *)	1.46 (1.35–1.57; <0.001 *)	
No	63215 (91.0%)	3146 (4.98%)	60069 (95.0%)	Ref.	Ref.	
Endocrine disorders [l]						1.55
Yes	13922 (20.0%)	2022 (14.5%)	11900 (85.5%)	3.51 (3.31–3.73; <0.001 *)	0.72 (0.67–0.78; <0.001 *)	
No	55568 (80.0%)	2394 (4.31%)	53174 (95.7%)	Ref.	Ref.	
Eye–ear–nose–throat disorders [m]						1.05
Yes	1245 (1.79%)	151 (12.1%)	1094 (87.9%)	1.98 (1.68–2.33; <0.001 *)	0.76 (0.64–0.89; 0.001 *)	
No	68245 (98.2%)	4265 (6.25%)	63980 (93.8%)	Ref.	Ref.	
Biological severity of COVID-19 at baseline [n]						1.29
Yes	18486 (26.6%)	2930 (15.8%)	15556 (84.2%)	5.78 (5.43–6.15; <0.001 *)	1.91 (1.78–2.05; <0.001 *)	
No	51004 (73.4%)	1486 (2.91%)	49518 (97.1%)	Ref.	Ref.	

Table A1. *Cont.*

	Full Population (N= 69,490)	Death (N= 4416)	No Death (N= 65,074)	Crude Analysis	Multivariable Analysis	
	Mean (SD)/ N (%)	Mean (SD)/ N (%)	Mean (SD)/ N (%)	HR (95%CI; *p*-Value)	AHR (95%CI; *p*-Value)	GVIF
Clinical severity of COVID-19 at baseline [o]						1.18
Yes	9015 (13.0%)	1592 (17.7%)	7423 (82.3%)	4.07 (3.82–4.32; <0.001 *)	1.52 (1.42–1.63; <0.001 *)	
No	60475 (87.0%)	2824 (4.67%)	57651 (95.3%)	Ref.	Ref.	

[a] Any medication prescribed as part of a clinical trial or according to compassionate use (e.g., hydroxychloroquine, azithromycin, remdesivir, dexamethasone, molnupinavir, tocilizumab, sarilumab, bamlanivimab or etesevimab). [b] Assessed using ICD-10 diagnosis codes for certain infectious and parasitic diseases (A00-B99). [c] Assessed using ICD-10 diagnosis codes for neoplasms (C00-D49) and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89). [d] Assessed using ICD-10 diagnosis codes for mental, behavioral, and neurodevelopmental disorders (F01-F99). [e] Assessed using ICD-10 diagnosis codes for diseases of the nervous system (G00-G99). [f] Assessed using ICD-10 diagnosis codes for diseases of the circulatory system (I00-I99). [g] Assessed using ICD-10 diagnosis codes for diseases of the respiratory system (J00-J99). [h] Assessed using ICD-10 diagnosis codes for diseases of the digestive system (K00-K95). [i] Assessed using ICD-10 diagnosis codes for diseases of the skin and subcutaneous tissue (L00-L99). [j] Assessed using ICD-10 diagnosis codes for diseases of the musculoskeletal system and connective tissue (M00-M99). [k] Assessed using ICD-10 diagnosis codes for diseases of the genitourinary system (N00-N99). [l] Assessed using ICD-10 diagnosis codes for endocrine, nutritional, and metabolic diseases (E00-E89). [m] Assessed using ICD-10 diagnosis codes for diseases of the eye and adnexa (H00-H59) and diseases of the ear and mastoid process (H60-H95). [n] Defined as having at least one of the following criteria: a high neutrophil-to-lymphocyte ratio or low lymphocyte-to-C-reactive protein ratio (both variables were dichotomized at the median of the values observed in the full sample) or plasma lactate levels higher than 2 mmol/L. [o] Defined as having at least one of the following criteria: a 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. * Two-sided *p*-value is significant ($p < 0.05$). Abbreviations: OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; GVIF, generalized variance inflation factor; NA, not applicable; Ref., reference group.

Table A2. Associations of baseline characteristics with 28-day mortality in the cohort of adult inpatients with COVID-19 (N = 9714).

	Full Population (N= 9714)	Death (N = 1409)	No Death (N = 8305)	Crude Analysis	Multivariable Analysis	
	Mean (SD)/ N (%)	Mean (SD)/ N (%)	Mean (SD)/ N (%)	HR (95%CI; *p*-Value)	AHR (95%CI; *p*-Value)	GVIF
Age						
18–50 years	1326 (13.7%)	29 (2.2%)	1297 (97.8%)	Ref.	Ref.	1.21
51–60 years	1023 (10.5%)	66 (6.5%)	957 (93.5%)	3.27 (2.09–5.12; <0.001)	2.46 (1.57–3.85; <0.001)	
61–70 years	1704 (17.5%)	208 (12.2%)	1496 (87.8%)	6.23 (4.17–9.31; <0.001)	4.40 (2.94–6.59; <0.001)	
71–80 years	2175 (22.4%)	347 (16.0%)	1828 (84.0%)	8.42 (5.69–12.46; <0.001)	6.86 (4.62–10.18; <0.001)	
81–90 years	2383 (24.5%)	505 (21.2%)	1878 (78.8%)	11.72 (7.96–17.26; <0.001)	11.78 (7.97–17.42; <0.001)	
More than 90 years	1103 (11.40%)	254 (23.0%)	849 (77.0%)	12.74 (8.57–18.95; <0.001)	15.01 (10.03–22.45; <0.001)	
Sex						
Women	4663 (48.0%)	569 (12.2%)	4094 (87.8%)	Ref.	Ref.	1.06
Men	5051 (52.0%)	840 (16.6%)	4211 (83.4%)	1.40 (1.25–1.55; <0.001)	1.41 (1.27–1.58; <0.001)	
Hospital AP-HP Centre—Paris University, Henri Mondor, Doumer University Hospitals, and hospitalization at home	4118 (42.4%)	576 (14.0%)	3542 (86.0%)	Ref.	Ref.	1.08

Table A2. *Cont.*

	Full Population (N= 9714)	Death (N = 1409)	No Death (N = 8305)	Crude Analysis	Multivariable Analysis	
	Mean (SD)/ N (%)	Mean (SD)/ N (%)	Mean (SD)/ N (%)	HR (95%CI; *p*-Value)	AHR (95%CI; *p*-Value)	GVIF
AP-HP Nord and Hôpitaux Universitaires Paris Seine-Saint-Denis	2885 (29.7%)	419 (14.5%)	2466 (85.5%)	1.02 (0.90–1.16; 0.763)	1.05 (0.92–1.20; 0.463)	
AP-HP Sorbonne University	2711 (27.9%)	414 (15.3%)	2297 (84.7%)	1.09 (0.96–1.24; 0.162)	1.04 (0.91–1.18; 0.564)	
Period of hospitalization						
2 May 2020–31 March 2021	3242 (33.4%)	650 (20.0%)	2592 (80.0%)	Ref.	Ref.	1.07
1 April 2021–27 January 2022	3259 (33.5%)	527 (16.2%)	2732 (83.8%)	0.79 (0.70–0.89; <0.001)	0.94 (0.84–1.06; 0.298)	
28 January 2022–31 August 2022	3213 (33.1%)	232 (7.2%)	2981 (92.8%)	0.35 (0.30–0.40; <0.001)	0.46 (0.39–0.53; <0.001)	
Medication according to compassionate use or as part of a clinical trial [a]						
Yes	1051 (10.8%)	204 (19.4%)	847 (80.6%)	1.41 (1.22–1.64; <0.001)	1.11 (0.95–1.29; 0.181)	1.05
No	8663 (89.2%)	1205 (13.9%)	7458 (86.1%)	Ref.	Ref.	
Other infectious diseases [b]						
Yes	1863 (19.2%)	339 (18.2%)	1524 (81.8%)	1.31 (1.16–1.48; <0.001)	0.99 (0.87–1.13; 0.875)	1.27
No	7851 (80.8%)	1070 (13.6%)	6781 (86.4%)	Ref.	Ref.	
Neoplasms and diseases of the blood [c]						
Yes	3347 (34.5%)	518 (15.5%)	2829 (84.5%)	1.11 (1.00–1.24; 0.056)	1.14 (1.02–1.28; 0.023)	1.18
No	6367 (65.5%)	891 (14.0%)	5476 (86.0%)	Ref.	Ref.	
Mental disorders [d]						
Yes	2656 (27.3%)	401 (15.1%)	2255 (84.9%)	1.06 (0.94–1.19; 0.356)	0.89 (0.78–1.00; 0.052)	1.18
No	7058 (72.7%)	1008 (14.3%)	6050 (85.7%)	Ref.	Ref.	
Diseases of the nervous system[e]						
Yes	1804 (18.6%)	289 (16.0%)	1515 (84.0%)	1.13 (0.99–1.28; 0.068)	1.07 (0.93–1.23; 0.33)	1.15
No	7910 (81.4%)	1120 (14.2%)	6790 (85.8%)	Ref.	Ref.	
Cardiovascular disorders [f]						
Yes	5578 (57.4%)	972 (17.4%)	4606 (82.6%)	1.70 (1.52–1.90; <0.001)	1.02 (0.90–1.16; 0.712)	1.55
No	4136 (42.6%)	437 (10.6%)	3699 (89.4%)	Ref.	Ref.	
Respiratory disorders [g]						
Yes	4952 (51.0%)	1094 (22.1%)	3858 (77.9%)	3.64 (3.21–4.13; <0.001)	2.58 (2.24–2.96; <0.001)	1.58
No	4762 (49.0%)	315 (6.6%)	4447 (93.4%)	Ref.	Ref.	
Digestive disorders [h]						
Yes	1717 (17.7%)	249 (14.5%)	1468 (85.5%)	1.00 (0.87–1.14; 0.956)	0.97 (0.84–1.12; 0.685)	1.11
No	7997 (82.3%)	1160 (14.5%)	6837 (85.5%)	Ref.	Ref.	
Dermatological disorders [i]						
Yes	650 (6.7%)	107 (16.5%)	543 (83.5%)	1.13 (0.93–1.38; 0.221)	1.04 (0.85–1.28; 0.703)	1.07
No	9064 (93.3%)	1302 (14.4%)	7762 (85.6%)	Ref.	Ref.	
Diseases of the musculoskeletal system [j]						
Yes	1684 (17.3%)	204 (12.1%)	1480 (87.9%)	0.79 (0.68–0.92; 0.002)	0.88 (0.76–1.03; 0.112)	1.08
No	8030 (82.7%)	1205 (15.0%)	6825 (85.0%)	Ref.	Ref.	
Diseases of the genitourinary system [k]						
Yes	2663 (27.4%)	536 (20.1%)	2127 (79.9%)	1.66 (1.49–1.85; <0.001)	1.24 (1.10–1.40; <0.001)	1.37
No	7051 (72.6%)	873 (12.4%)	6178 (87.6%)	Ref.	Ref.	
Endocrine disorders [l]						
Yes	5722 (58.9%)	922 (16.1%)	4800 (83.9%)	1.33 (1.19–1.49; <0.001)	0.77 (0.68–0.87; <0.001)	1.55
No	3992 (41.1%)	487 (12.2%)	3505 (87.8%)	Ref.	Ref.	

Table A2. *Cont.*

	Full Population (N= 9714)	Death (N = 1409)	No Death (N = 8305)	Crude Analysis	Multivariable Analysis	
	Mean (SD)/ N (%)	Mean (SD)/ N (%)	Mean (SD)/ N (%)	HR (95%CI; *p*-Value)	AHR (95%CI; *p*-Value)	GVIF
Eye–ear–nose–throat disorders [m]						
Yes	603 (6.21%)	86 (14.3%)	517 (85.7%)	0.99 (0.79–1.23; 0.903)	0.82 (0.66–1.03; 0.089)	1.05
No	9111 (93.8%)	1323 (14.5%)	7788 (85.5%)	Ref.	Ref.	
Biological severity of COVID-19 at baseline [n]						
Yes	5009 (51.6%)	1030 (20.6%)	3979 (79.4%)	2.71 (2.41–3.05; <0.001)	1.66 (1.46–1.89; <0.001)	1.29
No	4705 (48.4%)	379 (8.1%)	4326 (91.9%)	Ref.	Ref.	
Clinical severity of COVID-19 at baseline [o]						
Yes	3370 (34.7%)	757 (22.5%)	2613 (77.5%)	2.31 (2.08–2.56; <0.001)	1.58 (1.42–1.76; <0.001)	1.18
No	6344 (65.3%)	652 (10.3%)	5692 (89.7%)	Ref.	Ref.	

[a] Any medication prescribed as part of a clinical trial or according to compassionate use (e.g., hydroxychloroquine, azithromycin, remdesivir, dexamethasone, molnupinavir, tocilizumab, sarilumab, bamlanivimab or etesevimab). [b] Assessed using ICD-10 diagnosis codes for certain infectious and parasitic diseases (A00-B99). [c] Assessed using ICD-10 diagnosis codes for neoplasms (C00-D49) and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89). [d] Assessed using ICD-10 diagnosis codes for mental, behavioral, and neurodevelopmental disorders (F01-F99). [e] Assessed using ICD-10 diagnosis codes for diseases of the nervous system (G00-G99). [f] Assessed using ICD-10 diagnosis codes for diseases of the circulatory system (I00-I99). [g] Assessed using ICD-10 diagnosis codes for diseases of the respiratory system (J00-J99). [h] Assessed using ICD-10 diagnosis codes for diseases of the digestive system (K00-K95). [i] Assessed using ICD-10 diagnosis codes for diseases of the skin and subcutaneous tissue (L00-L99). [j] Assessed using ICD-10 diagnosis codes for diseases of the musculoskeletal system and connective tissue (M00-M99). [k] Assessed using ICD-10 diagnosis codes for diseases of the genitourinary system (N00-N99). [l] Assessed using ICD-10 diagnosis codes for endocrine, nutritional, and metabolic diseases (E00-E89). [m] Assessed using ICD-10 diagnosis codes for diseases of the eye and adnexa (H00-H59) and diseases of the ear and mastoid process (H60-H95). [n] Defined as having at least one of the following criteria: a high neutrophil-to-lymphocyte ratio or low lymphocyte-to-C-reactive protein ratio (both variables were dichotomized at the median of the values observed in the full sample) or plasma lactate levels higher than 2 mmol/L. [o] Defined as having at least one of the following criteria: a 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. Abbreviations: OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; GVIF, generalized variance inflation factor; NA, not applicable.

Table A3. Characteristics of patients receiving or not receiving a FIASMA medication at baseline in the full sample and in the 1:1 ratio matched analytic sample of patients hospitalized with COVID-19.

	Exposed to Any FIASMA Medication (N = 4857)	Not Exposed to FIASMA Medication (N= 64633)	Non-Exposed Matched Group (N= 4857)	Exposed to Any FIASMA Medication vs. Not exposed	Exposed to Any FIASMA Medication vs. Non-Exposed Matched Group
				Crude Analysis	Matched Analytic Sample Analysis Using a 1:1 Ratio
	N (%)	N (%)	N (%)	SMD	SMD
Age				0.900	0.082
18–50 years	722 (14.9%)	32016 (49.5%)	604 (12.4%)		
51–60 years	500 (10.3%)	8786 (13.6%)	523 (10.8%)		
61–70 years	811 (16.7%)	7898 (12.2%)	893 (18.4%)		
71–80 years	1104 (22.7%)	7373 (11.4%)	1071 (22.1%)		
81–90 years	1181 (24.3%)	5983 (9.26%)	1202 (24.7%)		
More than 90 years	539 (11.1%)	2577 (3.99%)	564 (11.6%)		
Sex				0.064	0.033
Women	2372 (48.8%)	33629 (52.0%)	2291 (47.2%)		
Men	2485 (51.2%)	31004 (48.0%)	2566 (52.8%)		

Table A3. *Cont.*

	Exposed to Any FIASMA Medication (N = 4857)	Not Exposed to FIASMA Medication (N= 64633)	Non-Exposed Matched Group (N= 4857)	Exposed to Any FIASMA Medication vs. Not exposed	Exposed to Any FIASMA Medication vs. Non-Exposed Matched Group
				Crude Analysis	Matched Analytic Sample Analysis Using a 1:1 Ratio
	N (%)	N (%)	N (%)	SMD	SMD
Hospital				0.293	0.042
AP-HP Centre—Paris University, Henri Mondor, Doumer University Hospitals, and hospitalization at home	2049 (42.2%)	25918 (40.1%)	2069 (42.6%)		
AP-HP Nord and Hôpitaux Universitaires Paris Seine-Saint-Denis	1410 (29.0%)	26557 (41.1%)	1475 (30.4%)		
AP-HP Sorbonne University	1398 (28.8%)	12158 (18.8%)	1313 (27.0%)		
Period of hospitalization				0.410	0.024
2 May 2020–31 March 2021	1604 (33.0%)	26612 (41.2%)	1638 (33.7%)		
1 April 2021–7 January 2022	1620 (33.4%)	23956 (37.1%)	1639 (33.7%)		
28 January 2022–31 August 2022	1633 (33.6%)	14065 (21.8%)	1580 (32.5%)		
Medication according to compassionate use or as part of a clinical trial [a]				0.384	0.079
Yes	585 (12.0%)	1192 (1.84%)	466 (9.59%)		
No	4272 (88.0%)	63441 (98.2%)	4391 (90.4%)		
Other infectious diseases [b]				0.384	0.008
Yes	939 (19.3%)	4304 (6.66%)	924 (19.0%)		
No	3918 (80.7%)	60329 (93.3%)	3933 (81.0%)		
Neoplasms and diseases of the blood [c]				0.654	0.010
Yes	1685 (34.7%)	5817 (9.00%)	1662 (34.2%)		
No	3172 (65.3%)	58816 (91.0%)	3195 (65.8%)		
Mental disorders [d]				0.558	0.006
Yes	1335 (27.5%)	4629 (7.16%)	1321 (27.2%)		
No	3522 (72.5%)	60004 (92.8%)	3536 (72.8%)		
Diseases of the nervous system [e]				0.428	0.017
Yes	918 (18.9%)	3405 (5.27%)	886 (18.2%)		
No	3939 (81.1%)	61228 (94.7%)	3971 (81.8%)		
Cardiovascular disorders [f]				0.973	0.012
Yes	2774 (57.1%)	9753 (15.1%)	2804 (57.7%)		
No	2083 (42.9%)	54880 (84.9%)	2053 (42.3%)		
Respiratory disorders [g]				0.698	0.059
Yes	2404 (49.5%)	11828 (18.3%)	2548 (52.5%)		
No	2453 (50.5%)	52805 (81.7%)	2309 (47.5%)		
Digestive disorders [h]				0.371	0.008
Yes	851 (17.5%)	3753 (5.81%)	866 (17.8%)		
No	4006 (82.5%)	60880 (94.2%)	3991 (82.2%)		
Dermatological disorders [i]				0.227	0.018
Yes	314 (6.46%)	1257 (1.94%)	336 (6.92%)		
No	4543 (93.5%)	63376 (98.1%)	4521 (93.1%)		
Diseases of the musculoskeletal system [j]				0.422	0.009
Yes	850 (17.5%)	2950 (4.56%)	834 (17.2%)		
No	4007 (82.5%)	61683 (95.4%)	4023 (82.8%)		
Diseases of the genitourinary system [k]				0.554	0.028
Yes	1362 (28.0%)	4913 (7.60%)	1301 (26.8%)		
No	3495 (72.0%)	59720 (92.4%)	3556 (73.2%)		
Endocrine disorders [l]				0.928	0.039
Yes	2815 (58.0%)	11107 (17.2%)	2907 (59.9%)		
No	2042 (42.0%)	53526 (82.8%)	1950 (40.1%)		
Eye–ear–nose–throat disorders [m]				0.270	0.042
Yes	326 (6.71%)	919 (1.42%)	277 (5.70%)		
No	4531 (93.3%)	63714 (98.6%)	4580 (94.3%)		

Table A3. *Cont.*

	Exposed to Any FIASMA Medication (N = 4857)	Not Exposed to FIASMA Medication (N= 64633)	Non-Exposed Matched Group (N= 4857)	Exposed to Any FIASMA Medication vs. Not exposed	Exposed to Any FIASMA Medication vs. Non-Exposed Matched Group
				Crude Analysis	Matched Analytic Sample Analysis Using a 1:1 Ratio
	N (%)	N (%)	N (%)	SMD	SMD
Biological severity of COVID-19 at baseline [n]				0.527	0.082
Yes	2405 (49.5%)	16081 (24.9%)	2604 (53.6%)		
No	2452 (50.5%)	48552 (75.1%)	2253 (46.4%)		
Clinical severity of COVID-19 at baseline [o]				0.558	0.034
Yes	1646 (33.9%)	7369 (11.4%)	1724 (35.5%)		
No	3211 (66.1%)	57264 (88.6%)	3133 (64.5%)		

[a] Any medication prescribed as part of a clinical trial or according to compassionate use (e.g., hydroxychloroquine, azithromycin, remdesivir, dexamethasone, molnupinavir, tocilizumab, sarilumab, bamlanivimab or etesevimab). [b] Assessed using ICD-10 diagnosis codes for certain infectious and parasitic diseases (A00-B99). [c] Assessed using ICD-10 diagnosis codes for neoplasms (C00-D49) and diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89). [d] Assessed using ICD-10 diagnosis codes for mental, behavioral, and neurodevelopmental disorders (F01-F99). [e] Assessed using ICD-10 diagnosis codes for diseases of the nervous system (G00-G99). [f] Assessed using ICD-10 diagnosis codes for diseases of the circulatory system (I00-I99). [g] Assessed using ICD-10 diagnosis codes for diseases of the respiratory system (J00-J99). [h] Assessed using ICD-10 diagnosis codes for diseases of the digestive system (K00-K95). [i] Assessed using ICD-10 diagnosis codes for diseases of the skin and subcutaneous tissue (L00-L99). [j] Assessed using ICD-10 diagnosis codes for diseases of the musculoskeletal system and connective tissue (M00-M99). [k] Assessed using ICD-10 diagnosis codes for diseases of the genitourinary system (N00-N99). [l] Assessed using ICD-10 diagnosis codes for endocrine, nutritional, and metabolic diseases (E00-E89). [m] Assessed using ICD-10 diagnosis codes for diseases of the eye and adnexa (H00-H59) and diseases of the ear and mastoid process (H60-H95). [n] Defined as having at least one of the following criteria: a high neutrophil-to-lymphocyte ratio or low lymphocyte-to-C-reactive protein ratio (both variables were dichotomized at the median of the values observed in the full sample) or plasma lactate levels higher than 2 mmol/L. [o] Defined as having at least one of the following criteria: a 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. SMD > 0.1 (in bold) indicate significant differences. Abbreviation: SMD, standardized mean difference.

Table A4. Between-group difference in absolute risk reduction (ARR) and number needed to treat (NNT) for all significant associations.

	ARR	NNT
Any FIASMA medication	2.7%	37.0
FIASMA cardiovascular system medications	7.0%	14.3
Other FIASMA cardiovascular system medications	7.0%	14.3
Amlodipine	7.0%	14.3
FIASMA nervous system medications	3.5%	28.5
Fluoxetine	5.7%	17.5
Escitalopram	9.9%	10.1

Table A5. Achieved power assuming a 20% reduction in mortality between groups.

	Power to Detect a 20% Reduction in Mortality
	%
FIASMA medication	99.5
FIASMA alimentary tract and metabolism medication	7.8
Loperamide	9.3
Mebeverine	2.3

Table A5. *Cont.*

	Power to Detect a 20% Reduction in Mortality
	%
FIASMA cardiovascular system medications	95.2
FIASMA calcium channel blockers	55.4
Carvedilol	3.5
Amiodarone	71.1
Other FIASMA cardiovascular system medications	88.1
Amlodipine	98.2
FIASMA nervous system medications	84.1
FIASMA psychoanaleptic medications	80.7
Amitriptyline	15.9
Sertraline	16.7
Fluoxetine	13
Maprotiline	NA
Trimipramine	2.4
Clomipramine	4.9
Citalopram	9.5
Duloxetine	8.1
Paroxetine	29.1
Fluvoxamine	2.9
Escitalopram	36.1
Hydroxyzine	59.6
FIASMA psycholeptic medications	7.2
Aripiprazole	3.8
Penfluridol	NA
Pimozide	NA
Chlorpromazine	5.3
Other FIASMA nervous system medications	5.2
Biperidene	4
Flunarizine	NA
FIASMA respiratory system medications	8.3
Desloratadine	8.8
Loratadine	NA

References

1. Chevance, A.; Gourion, D.; Hoertel, N.; Llorca, P.-M.; Thomas, P.; Bocher, R.; Moro, M.-R.; Laprévote, V.; Benyamina, A.; Fossati, P.; et al. Ensuring Mental Health Care during the SARS-CoV-2 Epidemic in France: A Narrative Review. *L'Encephale* **2020**, *46*, 193–201. [CrossRef] [PubMed]
2. Hoertel, N.; Blachier, M.; Blanco, C.; Olfson, M.; Massetti, M.; Rico, M.S.; Limosin, F.; Leleu, H. A Stochastic Agent-Based Model of the SARS-CoV-2 Epidemic in France. *Nat. Med.* **2020**, *26*, 1417–1421. [CrossRef] [PubMed]
3. Marín-Corral, J.; Rodríguez-Morató, J.; Gomez-Gomez, A.; Pascual-Guardia, S.; Muñoz-Bermúdez, R.; Salazar-Degracia, A.; Pérez-Terán, P.; Restrepo, M.I.; Khymenets, O.; Haro, N.; et al. Metabolic Signatures Associated with Severity in Hospitalized COVID-19 Patients. *Int. J. Mol. Sci.* **2021**, *22*, 4794. [CrossRef] [PubMed]
4. Torretta, E.; Garziano, M.; Poliseno, M.; Capitanio, D.; Biasin, M.; Santantonio, T.A.; Clerici, M.; Lo Caputo, S.; Trabattoni, D.; Gelfi, C. Severity of COVID-19 Patients Predicted by Serum Sphingolipids Signature. *Int. J. Mol. Sci.* **2021**, *22*, 10198. [CrossRef] [PubMed]
5. Mühle, C.; Kremer, A.; Vetter, M.; Schmid, J.; Achenbach, S.; Schumacher, F.; Lenz, B.; Cougoule, C.; Hoertel, N.; Carpinteiro, A.; et al. COVID-19 and Its Clinical Severity Are Associated with Alterations of Plasma Sphingolipids and Enzyme Activities of Sphingomyelinase and Ceramidase. *medRxiv* **2022**. [CrossRef]
6. Hoertel, N.; Blachier, M.; Sánchez-Rico, M.; Limosin, F.; Leleu, H. Impact of the Timing and Adherence to Face Mask Use on the Course of the COVID-19 Epidemic in France. *J. Travel Med.* **2021**, *28*, taab016. [CrossRef]
7. Lim, S.; Tignanelli, C.J.; Hoertel, N.; Boulware, D.R.; Usher, M.G. Prevalence of Medical Contraindications to Nirmatrelvir/Ritonavir in a Cohort of Hospitalized and Nonhospitalized Patients With COVID-19. *Open Forum Infect. Dis.* **2022**, *9*, ofac389. [CrossRef]

8. Hoertel, N.; Boulware, D.R.; Sánchez-Rico, M.; Burgun, A.; Limosin, F. Prevalence of Contraindications to Nirmatrelvir-Ritonavir among Hospitalized Patients With COVID-19 at Risk for Progression to Severe Disease. *JAMA Netw. Open* **2022**, *5*, e2242140. [CrossRef]
9. 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. [CrossRef]
10. Hoertel, N.; Sánchez-Rico, M.; Herrera-Morueco, J.J.; De La Muela, P.; Gulbins, E.; Kornhuber, J.; Carpinteiro, A.; Becker, K.A.; Cougoule, C.; Limosin, F.; 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. [CrossRef]
11. Hoertel, N.; Sánchez-Rico, M.; Cougoule, C.; Gulbins, E.; Kornhuber, J.; Carpinteiro, A.; Becker, K.A.; Reiersen, A.M.; Lenze, E.J.; Seftel, D.; et al. Repurposing Antidepressants Inhibiting the Sphingomyelinase Acid/Ceramide System against COVID-19: Current Evidence and Potential Mechanisms. *Mol. Psychiatry* **2021**, *26*, 7098–7099. [CrossRef] [PubMed]
12. Kornhuber, J.; Hoertel, N.; Gulbins, E. The Acid Sphingomyelinase/Ceramide System in COVID-19. *Mol. Psychiatry* **2022**, *27*, 307–314. [CrossRef] [PubMed]
13. Carpinteiro, A.; Edwards, M.J.; Hoffmann, M.; Kochs, G.; Gripp, B.; Weigang, S.; Adams, C.; Carpinteiro, E.; Gulbins, A.; Keitsch, S.; et al. Pharmacological Inhibition of Acid Sphingomyelinase Prevents Uptake of SARS-CoV-2 by Epithelial Cells. *Cell Rep. Med.* **2020**, *1*, 100142. [CrossRef]
14. Petrache, I.; Pujadas, E.; Ganju, A.; Serban, K.A.; Borowiec, A.; Babbs, B.; Bronova, I.A.; Egersdorf, N.; Hume, P.S.; Goel, K.; et al. Marked Elevations in Lung and Plasma Ceramide in COVID-19 Linked to Microvascular Injury. *JCI Insight* **2023**, *8*, e156104. [CrossRef] [PubMed]
15. Carpinteiro, A.; Gripp, B.; Hoffmann, M.; Pöhlmann, S.; Hoertel, N.; Edwards, M.J.; Kamler, M.; Kornhuber, J.; Becker, K.A.; Gulbins, E. Inhibition of Acid Sphingomyelinase by Ambroxol Prevents SARS-CoV-2 Entry into Epithelial Cells. *J. Biol. Chem.* **2021**, *296*, 100701. [CrossRef] [PubMed]
16. Kornhuber, J.; Tripal, P.; Reichel, M.; Mühle, C.; Rhein, C.; Muehlbacher, M.; Groemer, T.W.; Gulbins, E. Functional Inhibitors of Acid Sphingomyelinase (FIASMAs): A Novel Pharmacological Group of Drugs with Broad Clinical Applications. *Cell. Physiol. Biochem.* **2010**, *26*, 9–20. [CrossRef] [PubMed]
17. Péricat, D.; Leon-Icaza, S.A.; Sanchez Rico, M.; Mühle, C.; Zoicas, I.; Schumacher, F.; Planès, R.; Mazars, R.; Gros, G.; Carpinteiro, A.; et al. Antiviral and Anti-Inflammatory Activities of Fluoxetine in a SARS-CoV-2 Infection Mouse Model. *Int. J. Mol. Sci.* **2022**, *23*, 13623. [CrossRef]
18. Schloer, S.; Brunotte, L.; Goretzko, J.; Mecate-Zambrano, A.; Korthals, N.; Gerke, V.; Ludwig, S.; Rescher, U. Targeting the Endolysosomal Host-SARS-CoV-2 Interface by Clinically Licensed Functional Inhibitors of Acid Sphingomyelinase (FIASMA) Including the Antidepressant Fluoxetine. *Emerg. Microbes Infect.* **2020**, *9*, 2245–2255. [CrossRef]
19. Fred, S.M.; Kuivanen, S.; Ugurlu, H.; Casarotto, P.C.; Levanov, L.; Saksela, K.; Vapalahti, O.; Castrén, E. Antidepressant and Antipsychotic Drugs Reduce Viral Infection by SARS-CoV-2 and Fluoxetine Shows Antiviral Activity Against the Novel Variants in Vitro. *Front. Pharmacol.* **2022**, *12*, 755600. [CrossRef]
20. Chen, Y.; Wu, Y.; Chen, S.; Zhan, Q.; Wu, D.; Yang, C.; He, X.; Qiu, M.; Zhang, N.; Li, Z.; et al. Sertraline Is an Effective SARS-CoV-2 Entry Inhibitor Targeting the Spike Protein. *J. Virol.* **2022**, *96*, e01245-22. [CrossRef]
21. Khater, S.E.; El-khouly, A.; Abdel-Bar, H.M.; Al-mahallawi, A.M.; Ghorab, D.M. Fluoxetine Hydrochloride Loaded Lipid Polymer Hybrid Nanoparticles Showed Possible Efficiency against SARS-CoV-2 Infection. *Int. J. Pharm.* **2021**, *607*, 121023. [CrossRef]
22. Brunotte, L.; Zheng, S.; Mecate-Zambrano, A.; Tang, J.; Ludwig, S.; Rescher, U.; Schloer, S. Combination Therapy with Fluoxetine and the Nucleoside Analog GS-441524 Exerts Synergistic Antiviral Effects against Different SARS-CoV-2 Variants In Vitro. *Pharmaceutics* **2021**, *13*, 1400. [CrossRef] [PubMed]
23. Dechaumes, A.; Nekoua, M.P.; Belouzard, S.; Sane, F.; Engelmann, I.; Dubuisson, J.; Alidjinou, E.K.; Hober, D. Fluoxetine Can Inhibit SARS-CoV-2 In Vitro. *Microorganisms* **2021**, *9*, 339. [CrossRef] [PubMed]
24. Schloer, S.; Brunotte, L.; Mecate-Zambrano, A.; Zheng, S.; Tang, J.; Ludwig, S.; Rescher, U. Drug Synergy of Combinatory Treatment with Remdesivir and the Repurposed Drugs Fluoxetine and Itraconazole Effectively Impairs SARS-CoV-2 Infection in Vitro. *Br. J. Pharmacol.* **2021**, *178*, 2339–2350. [CrossRef] [PubMed]
25. Zimniak, M.; Kirschner, L.; Hilpert, H.; Geiger, N.; Danov, O.; Oberwinkler, H.; Steinke, M.; Sewald, K.; Seibel, J.; Bodem, J. The Serotonin Reuptake Inhibitor Fluoxetine Inhibits SARS-CoV-2 in Human Lung Tissue. *Sci. Rep.* **2021**, *11*, 5890. [CrossRef]
26. Hoertel, N.; Sánchez-Rico, M.; Gulbins, E.; Kornhuber, J.; Carpinteiro, A.; Lenze, E.J.; Reiersen, A.M.; Abellán, M.; Muela, P.; Vernet, R.; et al. Association Between FIASMAs and Reduced Risk of Intubation or Death in Individuals Hospitalized for Severe COVID-19: An Observational Multicenter Study. *Clin. Pharmacol. Ther.* **2021**, *110*, 1498–1511. [CrossRef]
27. Hoertel, N.; Sánchez-Rico, M.; Vernet, R.; Beeker, N.; Jannot, A.-S.; Neuraz, A.; Salamanca, E.; Paris, N.; Daniel, C.; Gramfort, A.; 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. [CrossRef]
28. Hoertel, N.; Sánchez-Rico, M.; Gulbins, E.; Kornhuber, J.; Carpinteiro, A.; Abellán, M.; De La Muela, P.; Vernet, R.; Beeker, N.; Neuraz, A.; 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. [CrossRef]

29. Hoertel, N.; Sánchez-Rico, M.; Kornhuber, J.; Gulbins, E.; Reiersen, A.M.; Lenze, E.J.; Fritz, B.A.; Jalali, F.; Mills, E.J.; Cougoule, C.; et al. Antidepressant Use and Its Association with 28-Day Mortality in Inpatients with SARS-CoV-2: Support for the FIASMA Model against COVID-19. *J. Clin. Med.* **2022**, *11*, 5882. [CrossRef]
30. Oskotsky, T.; Marić, I.; Tang, A.; Oskotsky, B.; Wong, R.J.; Aghaeepour, N.; Sirota, M.; Stevenson, D.K. Mortality Risk Among Patients With COVID-19 Prescribed Selective Serotonin Reuptake Inhibitor Antidepressants. *JAMA Netw. Open* **2021**, *4*, e2133090. [CrossRef]
31. Darquennes, G.; Le Corre, P.; Le Moine, O.; Loas, G. Association between Functional Inhibitors of Acid Sphingomyelinase (FIASMAs) and Reduced Risk of Death in COVID-19 Patients: A Retrospective Cohort Study. *Pharmaceuticals* **2021**, *14*, 226. [CrossRef] [PubMed]
32. Loas, G.; Van De Borne, P.; Darquennes, G.; Le Corre, P. Association of Amlodipine with the Risk of In-Hospital Death in Patients with COVID-19 and Hypertension: A Reanalysis on 184 COVID-19 Patients with Hypertension. *Pharmaceuticals* **2022**, *15*, 380. [CrossRef] [PubMed]
33. Fritz, B.A.; Hoertel, N.; Lenze, E.J.; Jalali, F.; Reiersen, A.M. Association between Antidepressant Use and ED or Hospital Visits in Outpatients with SARS-CoV-2. *Transl. Psychiatry* **2022**, *12*, 341. [CrossRef] [PubMed]
34. Deng, J.; Rayner, D.; Ramaraju, H.B.; Abbas, U.; Garcia, C.; Heybati, K.; Zhou, F.; Huang, E.; Park, Y.-J.; Moskalyk, M. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors in COVID-19 Management: A Systematic Review and Meta-Analysis. *Clin. Microbiol. Infect.* **2023**, *29*, 578–586. [CrossRef] [PubMed]
35. Sánchez-Rico, M.; Limosin, F.; Vernet, R.; Beeker, N.; Neuraz, A.; Blanco, C.; Olfson, M.; Lemogne, C.; Meneton, P.; Daniel, C.; et al. Hydroxyzine Use and Mortality in Patients Hospitalized for COVID-19: A Multicenter Observational Study. *J. Clin. Med.* **2021**, *10*, 5891. [CrossRef] [PubMed]
36. Gulbins, E.; Palmada, M.; Reichel, M.; Lüth, A.; Böhmer, C.; Amato, D.; Müller, C.P.; Tischbirek, C.H.; Groemer, T.W.; Tabatabai, G.; et al. Acid Sphingomyelinase–Ceramide System Mediates Effects of Antidepressant Drugs. *Nat. Med.* **2013**, *19*, 934–938. [CrossRef]
37. Kornhuber, J.; Tripal, P.; Reichel, M.; Terfloth, L.; Bleich, S.; Wiltfang, J.; Gulbins, E. Identification of New Functional Inhibitors of Acid Sphingomyelinase Using a Structure-Property-Activity Relation Model. *J. Med. Chem.* **2008**, *51*, 219–237. [CrossRef]
38. Naz, A.; Asif, S.; Alwutayd, K.M.; Sarfaraz, S.; Abbasi, S.W.; Abbasi, A.; Alenazi, A.M.; Hasan, M.E. Repurposing FIASMAs against Acid Sphingomyelinase for COVID-19: A Computational Molecular Docking and Dynamic Simulation Approach. *Molecules* **2023**, *28*, 2989. [CrossRef]
39. Clelland, C.L.; Ramiah, K.; Steinberg, L.; Clelland, J.D. Analysis of the Impact of Antidepressants and Other Medications on COVID-19 Infection Risk in a Chronic Psychiatric in-Patient Cohort. *BJPsych Open* **2022**, *8*, e6. [CrossRef]
40. Lenze, E.J.; Mattar, C.; Zorumski, C.F.; Stevens, A.; Schweiger, J.; Nicol, G.E.; Miller, J.P.; Yang, L.; Yingling, M.; Avidan, M.S.; et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA* **2020**, *324*, 2292. [CrossRef]
41. Reis, G.; Dos Santos Moreira-Silva, E.A.; Silva, D.C.M.; Thabane, L.; Milagres, A.C.; Ferreira, T.S.; Dos Santos, C.V.Q.; de Souza Campos, V.H.; Nogueira, A.M.R.; de Almeida, A.P.F.G.; 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. [CrossRef] [PubMed]
42. Seftel, D.; Boulware, D.R. Prospective Cohort of Fluvoxamine for Early Treatment of Coronavirus Disease 19. *Open Forum Infect. Dis.* **2021**, *8*, ofab050. [CrossRef] [PubMed]
43. Calusic, M.; Marcec, R.; Luksa, L.; Jurkovic, I.; Kovac, N.; Mihaljevic, S.; Likic, R. Safety and Efficacy of Fluvoxamine in COVID-19 ICU Patients: An Open Label, Prospective Cohort Trial with Matched Controls. *Br. J. Clin. Pharmacol.* **2022**, *88*, 2065–2073. [CrossRef] [PubMed]
44. Hoertel, N.; Rico, M.S.; Vernet, R.; Beeker, N.; Jannot, A.-S.; Neuraz, A.; Salamanca, E.; Paris, N.; Daniel, C.; Gramfort, A.; et al. Association between SSRI Antidepressant Use and Reduced Risk of Intubation or Death in Hospitalized Patients with Coronavirus Disease 2019: A Multicenter Retrospective Observational Study. *medRxiv* **2020**. [CrossRef]
45. Kirenga, B.J.; Mugenyi, L.; Sánchez-Rico, M.; Kyobe, H.; Muttamba, W.; Mugume, R.; Mwesigwa, E.; Kalimo, E.; Nyombi, V.; Segawa, I.; et al. Association of Fluvoxamine with Mortality and Symptom Resolution among Inpatients with COVID-19 in Uganda: A Prospective Interventional Open-Label Cohort Study. *Mol. Psychiatry* **2023**, *3*, 1–8. [CrossRef]
46. Németh, Z.K.; Szűcs, A.; Vitrai, J.; Juhász, D.; Németh, J.P.; Holló, A. Fluoxetine Use Is Associated with Improved Survival of Patients with COVID-19 Pneumonia: A Retrospective Case-Control Study. *Ideggyógy. Szle.* **2021**, *74*, 389–396. [CrossRef]
47. Creeden, J.F.; Imami, A.S.; Eby, H.M.; Gillman, C.; Becker, K.N.; Reigle, J.; Andari, E.; Pan, Z.K.; O'Donovan, S.M.; McCullumsmith, R.E.; et al. Fluoxetine as an Anti-Inflammatory Therapy in SARS-CoV-2 Infection. *Biomed. Pharmacother.* **2021**, *138*, 111437. [CrossRef]
48. Solaimanzadeh, I. Nifedipine and Amlodipine Are Associated with Improved Mortality and Decreased Risk for Intubation and Mechanical Ventilation in Elderly Patients Hospitalized for COVID-19. *Cureus* **2020**, *12*, e8069. [CrossRef]
49. Khodadoust, M.M. Inferring a Causal Relationship between Ceramide Levels and COVID-19 Respiratory Distress. *Sci. Rep.* **2021**, *11*, 20866. [CrossRef]
50. Dei Cas, M.; Ottolenghi, S.; Morano, C.; Rinaldo, R.; Roda, G.; Chiumello, D.; Centanni, S.; Samaja, M.; Paroni, R. Link between Serum Lipid Signature and Prognostic Factors in COVID-19 Patients. *Sci. Rep.* **2021**, *11*, 21633. [CrossRef]

51. Matta, J.; Wiernik, E.; Robineau, O.; Carrat, F.; Touvier, M.; Severi, G.; De Lamballerie, X.; Blanché, H.; Deleuze, J.-F.; Gouraud, C.; et al. Association of Self-Reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic. *JAMA Intern. Med.* **2022**, *182*, 19. [CrossRef] [PubMed]
52. Kornhuber, J.; Muehlbacher, M.; Trapp, S.; Pechmann, S.; Friedl, A.; Reichel, M.; Mühle, C.; Terfloth, L.; Groemer, T.W.; Spitzer, G.M.; et al. Identification of Novel Functional Inhibitors of Acid Sphingomyelinase. *PLoS ONE* **2011**, *6*, e23852. [CrossRef] [PubMed]
53. Tham, A.; Jonsson, U.; Andersson, G.; Söderlund, A.; Allard, P.; Bertilsson, G. Efficacy and Tolerability of Antidepressants in People Aged 65 Years or Older with Major Depressive Disorder—A Systematic Review and a Meta-Analysis. *J. Affect. Disord.* **2016**, *205*, 1–12. [CrossRef]
54. Cipriani, A.; Furukawa, T.A.; Salanti, G.; Chaimani, A.; Atkinson, L.Z.; Ogawa, Y.; Leucht, S.; Ruhe, H.G.; Turner, E.H.; Higgins, J.P.T.; et al. Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-Analysis. *Lancet* **2018**, *391*, 1357–1366. [CrossRef] [PubMed]
55. Sukhatme, V.P.; Reiersen, A.M.; Vayttaden, S.J.; Sukhatme, V.V. Fluvoxamine: A Review of Its Mechanism of Action and Its Role in COVID-19. *Front. Pharmacol.* **2021**, *12*, 652688. [CrossRef]
56. Hashimoto, Y.; Suzuki, T.; Hashimoto, K. Mechanisms of Action of Fluvoxamine for COVID-19: A Historical Review. *Mol. Psychiatry* **2022**, *27*, 1898–1907. [CrossRef] [PubMed]
57. Lenze, E.J.; Reiersen, A.M.; Santosh, P.J. Repurposing Fluvoxamine, and Other Psychiatric Medications, for COVID-19 and Other Conditions. *World Psychiatry* **2022**, *21*, 314–315. [CrossRef] [PubMed]
58. Le Strat, Y.; Hoertel, N. Correlation Is No Causation: Gymnasium Proliferation and the Risk of Obesity. *Addict. Abingdon Engl.* **2011**, *106*, 1871–1872. [CrossRef]
59. Dhanavade, M.J.; Sonawane, K.D. Role of Nutrition in COVID-19: Present Knowledge and Future Guidelines. *Curr. Nutr. Food Sci.* **2022**, *18*, 516–517. [CrossRef]
60. Hoertel, N.; Chevance, A.; Limosin, F. Inclusion and Exclusion Criteria and Psychological Research. In *The SAGE Encyclopedia of Abnorma l and Clinical Psychology*; SAGE Reference: Los Angeles, CA, USA, 2017; Volume 7, ISBN 978-1-4833-6583-1.
61. Butler, C.C.; Hobbs, F.D.R.; Gbinigie, O.A.; Rahman, N.M.; Hayward, G.; Richards, D.B.; Dorward, J.; Lowe, D.M.; Standing, J.F.; Breuer, J.; et al. Molnupiravir plus Usual Care versus Usual Care Alone as Early Treatment for Adults with COVID-19 at Increased Risk of Adverse Outcomes (PANORAMIC): An Open-Label, Platform-Adaptive Randomised Controlled Trial. *Lancet* **2023**, *401*, 281–293. [CrossRef]
62. Hoertel, N.; Sánchez-Rico, M.; Vernet, R.; Jannot, A.-S.; Neuraz, A.; Blanco, C.; Lemogne, C.; Airagnes, G.; Paris, N.; Daniel, C.; et al. Observational Study of Haloperidol in Hospitalized Patients with COVID-19. *PLoS ONE* **2021**, *16*, e0247122. [CrossRef] [PubMed]
63. Hoertel, N.; Sánchez-Rico, M.; Vernet, R.; Jannot, A.-S.; Neuraz, A.; Blanco, C.; Lemogne, C.; Airagnes, G.; Paris, N.; Daniel, C.; et al. Observational Study of Chlorpromazine in Hospitalized Patients with COVID-19. *Clin. Drug Investig.* **2021**, *41*, 221–233. [CrossRef] [PubMed]
64. Hoertel, N.; Sánchez-Rico, M.; Vernet, R.; Beeker, N.; Neuraz, A.; Alvarado, J.M.; Daniel, C.; Paris, N.; Gramfort, A.; Lemaitre, G.; et al. Dexamethasone Use and Mortality in Hospitalized Patients with Coronavirus Disease 2019: A Multicentre Retrospective Observational Study. *Br. J. Clin. Pharmacol.* **2021**, *87*, 3766–3775. [CrossRef] [PubMed]
65. Hoertel, N.; Sánchez-Rico, M.; Gulbins, E.; Kornhuber, J.; Vernet, R.; Beeker, N.; Neuraz, A.; Blanco, C.; Olfson, M.; Airagnes, G.; 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. [CrossRef] [PubMed]
66. Sánchez-Rico, M.; De La Muela, P.; Herrera-Morueco, J.J.; Geoffroy, P.A.; Limosin, F.; Hoertel, N.; AP-HP/Université de Paris/INSERM COVID-19 Research Collaboration/AP-HP COVID CDR Initiative/Entrepôt de Données de Santé AP-HP Consortium. Melatonin Does Not Reduce Mortality in Adult Hospitalized Patients with COVID-19: A Multicenter Retrospective Observational Study. *J. Travel Med.* **2022**, *29*, taab195. [CrossRef]
67. Hoertel, N.; Sánchez-Rico, M.; De La Muela, P.; Abellán, M.; Blanco, C.; Leboyer, M.; Cougoule, C.; Gulbins, E.; Kornhuber, J.; Carpinteiro, A.; 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.* **2023**, *3*, 56–67. [CrossRef]
68. Sánchez-Rico, M.; Rezaei, K.; Delgado-Álvarez, A.; Limosin, F.; Hoertel, N.; Alvarado, J.M. Comorbidity Patterns and Mortality Among Hospitalized Patients with Psychiatric Disorders and COVID-19. *Rev. Bras. Psiquiatr.* **2023**. [CrossRef]
69. Haut Conseil de la Santé Publique. Statement on the Management at Home or in a Care Facility of Suspected or Confirmed COVID-19 Patients. 2020. Available online: https://www.hcsp.fr (accessed on 1 May 2020).
70. Lagunas-Rangel, F.A. Neutrophil-to-Lymphocyte Ratio and Lymphocyte-to-C-Reactive Protein Ratio in Patients with Severe Coronavirus Disease 2019 (COVID-19): A Meta-Analysis. *J. Med. Virol.* **2020**, *92*, 1733–1734. [CrossRef]
71. Neuraz, A.; Lerner, I.; Digan, W.; Paris, N.; Tsopra, R.; Rogier, A.; Baudoin, D.; Cohen, K.B.; Burgun, A.; Garcelon, N.; et al. Natural Language Processing for Rapid Response to Emergent Diseases: Case Study of Calcium Channel Blockers and Hypertension in the COVID-19 Pandemic. *J. Med. Internet Res.* **2020**, *22*, e20773. [CrossRef]
72. Stuart, E.A.; Lee, B.K.; Leacy, F.P. Prognostic Score–Based Balance Measures Can Be a Useful Diagnostic for Propensity Score Methods in Comparative Effectiveness Research. *J. Clin. Epidemiol.* **2013**, *66*, S84–S90. [CrossRef]

73. Austin, P.C. Using the Standardized Difference to Compare the Prevalence of a Binary Variable between Two Groups in Observational Research. *Commun. Stat. Simul. Comput.* **2009**, *38*, 1228–1234. [CrossRef]
74. Zhang, Z.; Kim, H.J.; Lonjon, G.; Zhu, Y.; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance Diagnostics after Propensity Score Matching. *Ann. Transl. Med.* **2019**, *7*, 16. [CrossRef] [PubMed]
75. Terry, M.T.; Grambsch, P.M. *Modeling Survival Data: Extending the Cox Model*; Springer: New York, NY, USA, 2000; ISBN 0-387-98784-3.
76. Ho, D.E.; Imai, K.; King, G.; Stuart, E.A. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. *J. Stat. Softw.* **2011**, *42*, 1–28. [CrossRef]
77. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *Ann. Intern. Med.* **2007**, *147*, 573–577. [CrossRef]
78. Sonawane, K.D.; Barale, S.S.; Dhanavade, M.J.; Waghmare, S.R.; Nadaf, N.H.; Kamble, S.A.; Mohammed, A.A.; Makandar, A.M.; Fandilolu, P.M.; Dound, A.S.; et al. Structural Insights and Inhibition Mechanism of TMPRSS2 by Experimentally Known Inhibitors Camostat Mesylate, Nafamostat and Bromhexine Hydrochloride to Control SARS-Coronavirus-2: A Molecular Modeling Approach. *Inform. Med. Unlocked* **2021**, *24*, 100597. [CrossRef]