Association Between FIASMAs and Reduced Risk of Intubation or Death in Individuals Hospitalized for Severe COVID-19: An Observational Multicenter Study

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Several medications commonly used for a number of medical conditions share a property of functional inhibition of acid sphingomyelinase (ASM), or FIASMA. Preclinical and clinical evidence suggest that the ASM/ceramide system may be central to severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. We examined the potential usefulness of FIASMA use among patients hospitalized for severe coronavirus disease 2019 (COVID-19) in an observational multicenter study conducted at Greater Paris University hospitals. Of 2,846 adult patients hospitalized for severe COVID-19, 277 (9.7%) were taking an FIASMA medication at the time of their hospital admission. The primary end point was a composite of intubation and/or death. We compared this end point between patients taking vs. not taking an FIASMA medication in time-to-event analyses adjusted for sociodemographic characteristics and medical comorbidities. The primary analysis was a Cox regression model with inverse probability weighting (IPW). Over a mean follow-up of 9.2 days (SD = 12.5), the primary end point occurred in 104 patients (37.5%) receiving an FIASMA medication, and 1,060 patients (41.4%) who did not. Despite being significantly and substantially associated with older age and greater medical severity, FIASMA medication use was significantly associated with reduced likelihood of intubation or death in both crude (hazard ratio (HR) = 0.71, 95% confidence interval (CI) = 0.58–0.87, $P < 0.001$) and primary IPW (HR = 0.58, 95%CI = 0.46–0.72, $P < 0.001$) analyses. This association remained significant in multiple sensitivity analyses and was not specific to one particular FIASMA class or medication. These results show the potential importance of the ASM/ceramide system in COVID-19 and support the continuation of FIASMA medications in these patients. Double-blind controlled randomized clinical trials of these medications for COVID-19 are needed.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Several medications commonly used for a number of medical conditions share a property of functional inhibition of acid sphingomyelinase (ASM), or FIASMA. Preclinical and clinical evidence suggest that the ASM/ceramide system may be central to severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Is there an association between FIASMA medication use and the composite outcome of intubation or death in patients hospitalized for severe coronavirus disease 2019 (COVID-19)?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Taking an FIASMA medication was associated with reduced likelihood of intubation or death in analyses adjusted for sociodemographic characteristics and medical comorbidities.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These results show the potential importance of the ASM/ceramide system as a treatment target in COVID-19 and support the continuation of FIASMA medications in patients with COVID-19. Double-blind controlled randomized clinical trials of these medications for COVID-19 are needed.

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Global spread of the novel coronavirus severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and its variants, the causative agents of coronavirus disease 2019 (COVID-19), has created an unprecedented infectious disease crisis worldwide.[1-4] Although the availability of vaccines has raised hope for a decline of the pandemic, the search for an effective treatment for patients with COVID-19 among all available medications is still urgently needed.

Several medications commonly used for a number of medical conditions, such as depression or high blood pressure, are functional inhibitors of acid sphingomyelinase (ASM)[5-10] or FIASMA. FIASMA medications, as detailed in **Table 1**, include, for example, certain antidepressants (e.g., fluoxetine, fluvoxamine, and escitalopram), antihistamine medications (e.g., hydroxyzine and promethazine), antipsychotics (e.g., aripiprazole and chlorpromazine), calcium channel blockers (e.g., amlodipine and bepridil), and mucolytics (e.g., ambroxol).[5-10]

Preclinical evidence indicates that SARS-CoV-2 activates the ASM/ceramide system, resulting in the formation of ceramide-enriched membrane domains that facilitate viral entry and infection by clustering ACE2, the cellular receptor of SARS-CoV-2.[5] An *in vitro* study[5] showed that several FIASMA[6] medications, including fluoxetine and amitriptyline, inhibited ASM and the formation of ceramide-enriched membrane domains, and prevented Vero cells from being infected with SARS-CoV-2. Reconstitution of ceramide in cells treated with antidepressant medications having FIASMA properties restored infection with SARS-CoV-2. In healthy volunteers, oral administration of amitriptyline blocked infection of freshly isolated nasal epithelial cells with SARS-CoV-2.[5] These preclinical data were confirmed by another study that demonstrated an inhibition of the infection of cultured epithelial cells with SARS-CoV-2 by fluoxetine.[11] A scheme of the biological mechanisms proposed by Carpinteiro *et al.*[5,10] underlying the potential inhibition by FIASMAs of cell infection with SARS-CoV-2 is summarized in **Figure 1**.

Findings from clinical and observational studies are consistent with these preclinical data. First, a randomized double-blind controlled study[12] showed significant protective effects of the FIASMA antidepressant fluvoxamine (N = 80) vs. placebo (N = 72) on COVID-19 progression in outpatients (0 of 80 patients in the fluvoxamine group vs. 6 of 72 patients in the placebo group; absolute difference, 8.7% (95% CI, 1.8%–16.4%) from survival analysis; log-rank $P = 0.009$). These results were confirmed in an open-label prospective cohort,[13] in which the incidence of hospitalization was 0% (0 of 65) in patients with COVID-19 who opted to receive fluvoxamine and 12.5% (6 of 48) in those who declined. Second, an observational multicenter retrospective study using data from Greater Paris University Hospitals showed that use of antidepressants, mostly FIASMA antidepressants, and of the FIASMA hydroxyzine, were significantly associated with reduced mortality in patients hospitalized for COVID-19.[14,15] Third, retrospective clinical investigations among hospitalized patients with COVID-19 either elderly (N = 77)[16] or with hypertension as the only comorbidity[17] (N = 96) showed that the use of amlodipine (a calcium channel blocker[18] and an FIASMA) may be associated with decreased mortality. Taken together, these results suggest that the ASM/ceramide system may provide a useful framework for better understanding SARS-CoV-2 infection and favoring the possible repurposing of FIASMA medications against COVID-19.

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

We used data from Greater Paris University Hospitals to examine the association between FIASMA medication use and the composite outcome of intubation or death among patients hospitalized for laboratory-confirmed severe COVID-19. Our primary hypothesis was that FIASMA medication use would be associated with reduced risk of intubation or death among patients hospitalized for severe COVID-19 in time-to-event analyses adjusting for sociodemographic characteristics and medical comorbidities. Additional exploratory analyses examined whether this association was specific to certain FIASMA classes (e.g., FIASMA antidepressants) or certain individual medications (e.g., fluoxetine or amlodipine).

METHODS

Setting and cohort assembly

A multicenter cohort study was conducted at 36 Assistance Publique–Hôpitaux de Paris (AP-HP) hospitals from the beginning of the epidemic in France (i.e., January 24 until May 1, 2020).[14,15,19,20,21] We included all

Table 1 List of medications that have shown to *in vitro* inhibit acid sphingomyelinase[5-10]

Anti-arrhythmics	Amiodarone	Aprindine
Anticholinergic antiparkinson medications	Benztropine Biperidene	Profenamine
Antidepressants	Amitriptyline Citalopram Clomipramine Desipramine Doxepin Duloxetine Escitalopram Fluoxetine Fluvoxamine Imipramine	Lofepramine Maprotiline Mirtazapine Nortriptyline Paroxetine Protriptyline Sertraline Trimipramine Venlafaxine
Antidiarrheal medication	Loperamide	
Antihistamine medications	Astemizole Clemastine Cyproheptadine Desloratadine Hydroxyzine	Loratadine Mebhydrolin Pimethixene Promethazine Terfenadine
Antimycobacterial	Clofazimine	
Antiprotozoal medications	Emetine	Quinacrine
Antipsychotics	Aripiprazole Chlorpromazine Chlorprothixene Fluphenazine Flupenthixol Penfluridol Perphenazine	Pimozide Promazine Sertindole Thioridazin Trifluoperazine Triflupromazine
Antivertigo medications	Cinnarizine	Flunarizine
Beta blocking agents	Carvedilol	
Calcium channel blockers	Amlodipine Bepridil Fendiline	Mibefradil Perhexiline
Cough suppressant	Cloperastine	
Endocrine therapy medication	Tamoxifen	
Medications for functional gastrointestinal disorders	Alverine Camylofin	Dicycloverine Mebeverine
Medications of the nervous system	Cinnarizine	Flunarizine
Mucolytic	Ambroxol	
Muscle relaxant	Cyclobenzaprine	
Natural products	Conessine Solasodine	Tomatidine
Vasodilators	Dilazep	Suloctidil

adults aged 18 years or over who have been hospitalized in these medical centers for severe COVID-19. COVID-19 was ascertained by a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test on nasopharyngeal or oropharyngeal swab specimens. Severe COVID-19 was defined as having at least one of the following criteria at hospital admission: respiratory rate > 24 breaths/min or < 12 breaths/min, resting peripheral capillary oxygen saturation in ambient air < 90%, temperature > 40°C, systolic blood pressure < 100 mm Hg, or high lactate levels >2 mmol/L.[22]

This observational 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, April 8, 2020). AP-HP clinical Data Warehouse initiatives ensure patient information and informed consent regarding the different approved studies through a transparency portal in accordance with European Regulation on data protection and authorization no. 1980120 from National Commission for Information Technology and Civil Liberties (CNIL).

Data sources

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 tests, and RT-PCR test results, medication administration data during the hospitalization for COVID-19, current diagnoses, discharge disposition, ventilator use data, and death certificates.

Variables assessed

We obtained the following data for each patient at the time of the hospitalization: sex; age, which was categorized into four classes based on the OpenSAFELY study results[23] (i.e., 18–50, 51–70, 71–80, and 81+); hospital, which was categorized into four 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, and E66.9); self-reported current smoking status; and any medication prescribed according to compassionate use or as part of a clinical trial (e.g., hydroxychloroquine, azithromycin, remdesivir, tocilizumab, sarilumab, or dexamethasone). To take into account possible confounding by indication bias for FIASMA medications, we recorded whether patients had any current diagnosis, based on ICD-10 diagnosis codes recorded during the visit, of neoplasms and diseases of the blood (C00-D89); mental disorders (F01-F99); diseases of the nervous system (G00-G99); cardiovascular disorders (I00-I99); respiratory disorders (J00-J99); digestive disorders (K00-K95); dermatological disorders (L00-L99); diseases of the musculoskeletal system (M00-M99); diseases of the genitourinary system (N00-N99); endocrine disorders (E00-E89); and eye-ear-nose-throat disorders (H00-H95).

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,[24] one for the medications and another for their mode of administration. The model was trained on the APmed corpus, a previously annotated dataset for this task. Extracted medications names were then normalized to the Anatomical Therapeutic Chemical (ATC) terminology using approximate string matching.

Medications with functional inhibition effect on acid sphingomyelinase

FIASMA medications were defined as having a substantial *in vitro* functional inhibition effect on ASM (i.e., a residual ASM activity lower than 50%), as detailed elsewhere,[5-9] and were divided into the following classes according to their ATC code[25]: FIASMA alimentary tract and metabolism medications (e.g., loperamide); cardiovascular system medications, subdivided into calcium channel blockers (e.g., amlodipine), and other cardiovascular medications (e.g., carvedilol); nervous system

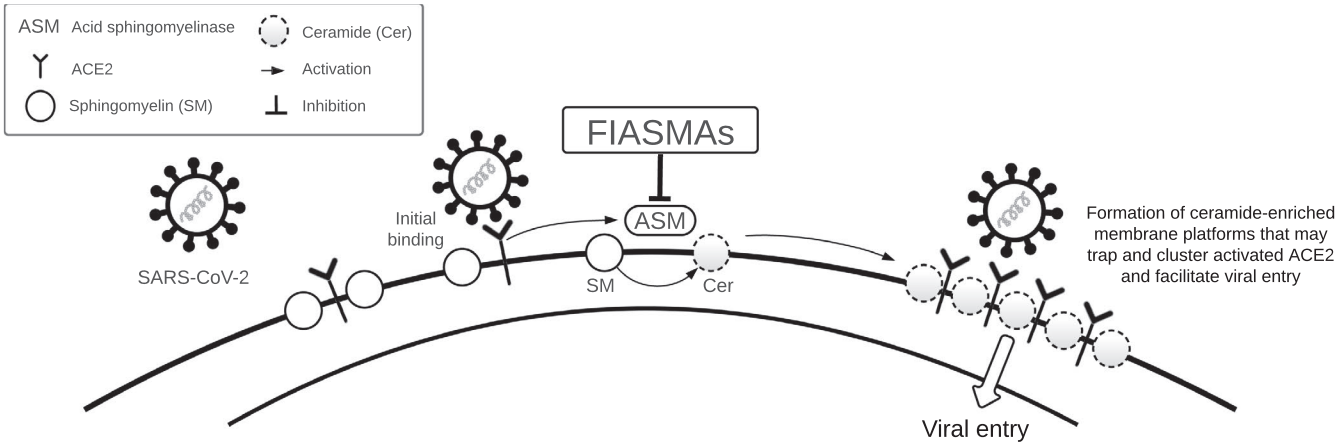

Figure 1 Biological mechanisms proposed by Carpinteiro *et al.*[5,10] underlying the potential inhibition by Functional Inhibitors of Acid Sphingomyelinase (FIASMAs) of cell infection with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Initial binding of SARS-CoV-2 spike protein to its ACE2 receptor may result in activation of the acid sphingomyelinase (ASM), formation of surface ceramide molecules that spontaneously form ceramide-enriched membrane platforms. These platforms alter membrane properties and thereby may serve to trap and cluster activated ACE2 receptors, and facilitate viral entry; inhibition of the ASM by FIASMAs may result in reduced concentration of ceramides and decreased viral entry.

medications, subdivided according to ATC codes into psycho-analeptic (e.g., amitriptyline) and psycholeptic medications (e.g., chlorpromazine); and respiratory system medications (e.g., desloratadine).

FIASMA medication use was defined as receiving at least one FIASMA medication within the first 24 hours of hospital admission. To minimize potential confounding effects of late prescription of FIASMA medications, patients who initiated an FIASMA medication more than 24 hours after hospital admission were excluded from the analyses. Patients who received at study baseline an antipsychotic or a benzodiazepine while being hospitalized in an intensive care unit, possibly as an aid to oral intubation, were also excluded.

Primary end point

Study baseline was defined as the date of hospital admission for COVID-19. The primary end point was the occurrence of intubation and/or death. For patients who died after intubation, the timing of the primary end point was defined as the time of intubation. Patients without an end point event had their data censored on May 1, 2020.

Statistical analysis

We calculated frequencies of all baseline characteristics described above in patients receiving or not receiving an FIASMA medication and compared them using standardized mean differences (SMD). SMD are useful to evaluate between-group differences in baseline characteristic variables independently of their unit of measurement (i.e., for both continuous and categorical variables[26-28]). We considered SMD greater than 0.1 as reflecting significant differences, a threshold recommended for declaring imbalance.[27]

To examine the association between FIASMA medication use at baseline and the end point of intubation or death, we performed Cox proportional-hazards regression models.[29] To help account for the nonrandomized prescription of medications and reduce the effects of confounders, the primary analysis used propensity score analysis with inverse probability weighting (IPW).[30] The individual propensities for receiving an FIASMA medication at baseline were estimated using a multivariable logistic regression model that included sex, age, hospital, obesity, current smoking status, and medical conditions. In the inverse-probability-weighted analyses, the predicted probabilities from the propensity-score models were used to calculate the stabilized inverse-probability-weighting weights. The association between FIASMA medication use and the end point was then estimated using an IPW Cox regression model. In case of non-balanced covariates, an IPW multivariable Cox regression model adjusting for the non-balanced covariates was also performed. Kaplan–Meier curves were performed using the inverse-probability-weighting weights and their pointwise 95% confidence intervals were estimated using the nonparametric bootstrap method.[31]

We conducted two sensitivity analyses. First, we performed a multivariable Cox regression model including as covariates the same variables used in the IPW analysis. Second, we used a univariate Cox regression model in a matched analytic sample using a 1:1 ratio, based on the same variables used for the IPW analysis and the multivariable Cox regression analysis. To reduce the effects of confounding, optimal matching was used in order to obtain the smallest average absolute distance across all clinical characteristics between exposed patients and nonexposed matched controls.

We performed four additional exploratory analyses. First, we examined the relationships between each FIASMA class and each individual FIASMA medication with the composite end point of intubation or death. Second, we reproduced these analyses while comparing patients receiving any FIASMA medication at baseline to those receiving paracetamol at baseline, to mimic an active comparator, as previously done in several ongoing clinical trials.[32] This analysis sought to address a potential immortal bias, by including in the control group patients who had the same likelihood as those in the FIASMA group to survive at baseline until being prescribed a treatment. Third, because of discrepancies in the potential FIASMA *in vitro* effect of venlafaxine, mirtazapine, and citalopram,[5,6] we reproduced the main analyses while considering these molecules as FIASMAs, contrary to the main analyses. Finally, we reproduced the main analyses among all patients hospitalized for COVID-19, with and without clinical severity criteria at baseline.

For all associations, we performed residual analyses to assess the fit of the data, check assumptions, including proportional hazards assumption using proportional hazards tests and diagnostics based on weighted residuals,[29] 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. Because our main hypothesis focused on the association between FIASMA medication use at baseline and the composite end point of intubation or death, statistical significance was fixed *a priori* at two-sided *P*value < 0.05. Only if a significant association was found,

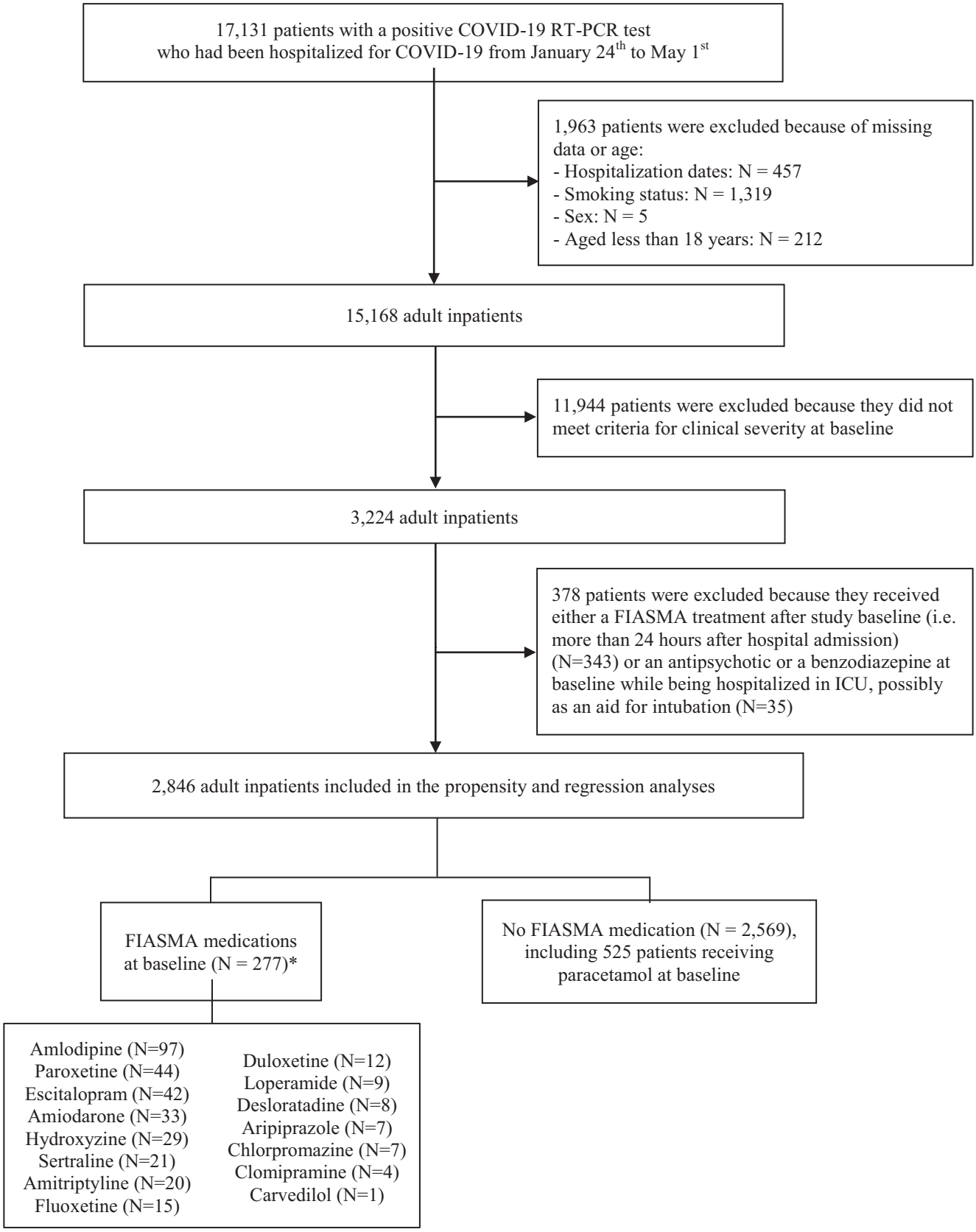

Figure 2 Study cohort. *A participant may receive two or more FIASMA medications at baseline. COVID-19, coronavirus disease 2019; FIASMA, Functional Inhibitors of Acid Sphingomyelinase; ICU, intensive care unit; RT-PCR, reverse-transcriptase–polymerase-chain-reaction.

Table 2 Characteristics of patients hospitalized for severe COVID-19 receiving or not receiving an FIASMA medication at baseline (*N* = 2,846)

	Exposed to any FIASMA medication (*N* = 277)	Not exposed to FIASMA medication (*N* = 2,569)	Non-exposed matched group (*N* = 277)	Exposed to any FIASMA medication vs. not exposed	Exposed to any FIASMA medication vs. not exposed	Exposed to any FIASMA medication vs. non-exposed matched group
				Crude analysis	Analysis weighted by inverse-probability-weighting weights	Matched analytic sample analysis using a 1:1 ratio
	N (%)	N (%)	N (%)	SMD	SMD	SMD
Age						
18 to 50 years	29 (10.5%)	493 (19.2%)	29 (10.5%)	**0.369**	0.097	0.095
51 to 70 years	88 (31.8%)	1,027 (40.0%)	99 (35.7%)			
71 to 80 years	63 (22.7%)	457 (17.8%)	55 (19.9%)			
More than 80 years	97 (35.0%)	592 (23.0%)	94 (33.9%)			
Sex						
Women	131 (47.3%)	933 (36.3%)	118 (42.6%)	**0.224**	0.034	0.094
Men	146 (52.7%)	1,636 (63.7%)	159 (57.4%)			
Hospital						
AP-HP Centre - Paris University, Henri Mondor University Hospitals and at home hospitalization	62 (22.4%)	660 (25.7%)	70 (25.3%)	**0.171**	0.087	0.097
AP-HP Nord and Hôpitaux Universitaires Paris Seine-Saint-Denis	76 (27.4%)	813 (31.6%)	68 (24.5%)			
AP-HP Paris Saclay University	63 (22.7%)	561 (21.8%)	68 (24.5%)			
AP-HP Sorbonne University	76 (27.4%)	535 (20.8%)	71 (25.6%)			
Obesity[a]						
Yes	67 (24.2%)	515 (20.0%)	63 (22.7%)	**0.100**	0.008	0.034
No	210 (75.8%)	2,054 (80.0%)	214 (77.3%)			
Smoking[b]						
Yes	46 (16.6%)	310 (12.1%)	40 (14.4%)	**0.130**	0.025	0.060
No	231 (83.4%)	2,259 (87.9%)	237 (85.6%)			
Medication according to compassionate use or as part of a clinical trial[c]						
Yes	83 (30.0%)	723 (28.1%)	80 (28.9%)	0.040	0.020	0.024
No	194 (70.0%)	1,846 (71.9%)	197 (71.1%)			

(Continued)

Table 2 (Continued)

	Exposed to any FIASMA medication (*N* = 277)	Not exposed to FIASMA medication (*N* = 2,569)	Non-exposed matched group (*N* = 277)	Exposed to any FIASMA medication vs. not exposed	Exposed to any FIASMA medication vs. not exposed	Exposed to any FIASMA medication vs. non-exposed matched group
				Crude analysis	Analysis weighted by inverse-probability-weighting weights	Matched analytic sample analysis using a 1:1 ratio
	N (%)	N (%)	N (%)	SMD	SMD	SMD
Other infectious diseases[d]						
Yes	55 (19.9%)	301 (11.7%)	50 (18.1%)	**0.225**	0.040	0.046
No	222 (80.1%)	2,268 (88.3%)	227 (81.9%)			
Neoplasms and diseases of the blood[e]						
Yes	46 (16.6%)	293 (11.4%)	41 (14.8%)	**0.150**	0.055	0.050
No	231 (83.4%)	2,276 (88.6%)	236 (85.2%)			
Mental disorders[f]						
Yes	70 (25.3%)	270 (10.5%)	60 (21.7%)	**0.392**	0.061	0.085
No	207 (74.7%)	2,299 (89.5%)	217 (78.3%)			
Diseases of the nervous system[g]						
Yes	49 (17.7%)	243 (9.5%)	41 (14.8%)	**0.242**	0.047	0.078
No	228 (82.3%)	2,326 (90.5%)	236 (85.2%)			
Cardiovascular disorders[h]						
Yes	147 (53.1%)	873 (34.0%)	144 (52.0%)	**0.392**	0.099	0.022
No	130 (46.9%)	1,696 (66.0%)	133 (48.0%)			
Respiratory disorders[i]						
Yes	195 (70.4%)	1,509 (58.7%)	203 (73.3%)	**0.246**	0.030	0.064
No	82 (29.6%)	1,060 (41.3%)	74 (26.7%)			
Digestive disorders[j]						
Yes	42 (15.2%)	192 (7.5%)	35 (12.6%)	**0.244**	0.015	0.073
No	235 (84.8%)	2,377 (92.5%)	242 (87.4%)			
Dermatological disorders[k]						
Yes	14 (5.1%)	57 (2.2%)	14 (5.1%)	**0.152**	0.010	<0.001
No	263 (94.9%)	2,512 (97.8%)	263 (94.9%)			
Diseases of the musculoskeletal system[l]						
Yes	22 (7.9%)	121 (4.7%)	22 (7.94%)	**0.133**	0.027	<0.001
No	255 (92.1%)	2,448 (95.3%)	255 (92.1%)			

(Continued)

Table 2 (Continued)

	Exposed to any FIASMA medication (*N* = 277)	Not exposed to FIASMA medication (*N* = 2,569)	Non-exposed matched group (*N* = 277)	Exposed to any FIASMA medication vs. not exposed	Exposed to any FIASMA medication vs. not exposed	Exposed to any FIASMA medication vs. non-exposed matched group
				Crude analysis	Analysis weighted by inverse-probability-weighting weights	Matched analytic sample analysis using a 1:1 ratio
	N (%)	N (%)	N (%)	SMD	SMD	SMD
Diseases of the genitourinary system[m]						
Yes	76 (27.4%)	353 (13.7%)	70 (25.3%)	**0.344**	0.055	0.049
No	201 (72.6%)	2,216 (86.3%)	207 (74.7%)			
Endocrine disorders[n]						
Yes	134 (48.4%)	908 (35.3%)	135 (48.7%)	**0.266**	0.037	0.007
No	143 (51.6%)	1,661 (64.7%)	142 (51.3%)			
Eye-Ear-Nose-Throat disorders[o]						
Yes	12 (4.3%)	47 (1.8%)	12 (4.33%)	**0.145**	0.008	<0.001
No	265 (95.7%)	2,522 (98.2%)	265 (95.7%)			

SMD > 0.1 (in bold) indicate significant differences.

AP-HP, Assistance Publique–Hôpitaux de Paris; COVID-19, coronavirus disease 2019; FIASMA, Functional Inhibitors of Acid Sphingomyelinase Activity; SMD, standardized mean difference.

[a]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, and E66.9). [b]Current smoking status was self-reported. [c]Any medication prescribed as part of a clinical trial or according to compassionate use (e.g., hydroxychloroquine, azithromycin, remdesivir, tocilizumab, sarilumab, or dexamethasone). [d]Assessed using ICD-10 diagnosis codes for certain infectious and parasitic diseases (A00-B99). [e]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). [f]Assessed using ICD-10 diagnosis codes for mental, behavioral, and neurodevelopmental disorders (F01-F99). [g]Assessed using ICD-10 diagnosis codes for diseases of the nervous system (G00-G99). [h]Assessed using ICD-10 diagnosis codes for diseases of the circulatory system (I00-I99). [i]Assessed using ICD-10 diagnosis codes for diseases of the respiratory system (J00-J99). [j]Assessed using ICD-10 diagnosis codes for diseases of the digestive system (K00-K95). [k]Assessed using ICD-10 diagnosis codes for diseases of the skin and subcutaneous tissue (L00-L99). [l]Assessed using ICD-10 diagnosis codes for diseases of the musculoskeletal system and connective tissue (M00-M99). [m]Assessed using ICD-10 diagnosis codes for diseases of the genitourinary system (N00-N99). [n]Assessed using ICD-10 diagnosis codes for endocrine, nutritional and metabolic diseases (E00-E89). [o]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).

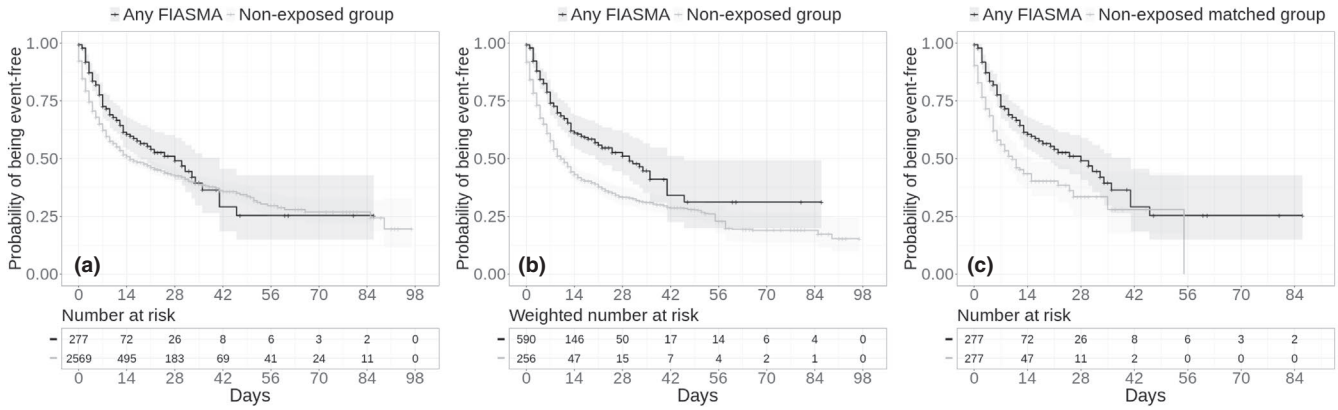

Figure 3 Kaplan-Meier curves for the composite endpoint of intubation or death in the full sample crude analysis ($N = 2846$) (**a**), in the full sample analysis with IPW ($N = 2846$) (**b**), and in the matched analytic sample using a 1:1 ratio ($N = 554$) (**c**) among patients hospitalized for severe COVID-19, according to FIASMA medication use at baseline. The shaded areas represent pointwise 95% confidence intervals. COVID-19, coronavirus disease 2019; IPW, inverse probability weighting; FIASMA, Functional Inhibitors of Acid Sphingomyelinase Activity.

we planned to perform additional exploratory analyses as described above. All analyses were conducted in R software version 3.6.3 (R Project for Statistical Computing).

RESULTS

Characteristics of the cohort

Of the 17,131 patients hospitalized for COVID-19, ascertained with a positive COVID-19 RT-PCR test, 1,963 patients (11.5%) were excluded because of missing data or young age (i.e., < 18 years old of age). Of these 15,168 patients, 3,224 (21.3%) met criteria for severe COVID-19 at hospital admission. Of these 3,224 patients, 378 (11.7%) were excluded because they started an FIASMA medication more than 24 hours after hospital admission ($N = 343$) or because they initiated an antipsychotic or a benzodiazepine in an intensive care unit, possibly as an aid for intubation ($N = 35$). Of the remaining 2,846 adult patients, 277 (9.7%) received an FIASMA medication within the first 24 hours of hospitalization, with a mean delay between hospital admission and first FIASMA medication prescription of 0.11 days (SD = 0.38; interquartile range (IQR) = 0.00–0.19; **Figure 2**).

RT-PCR test results were obtained after a median delay of 0.9 days (SD = 9.4; IQR = 0.5–1.7) from hospital admission date. This median delay was similar (i.e., 0.9 days) in the exposed (SD = 11.4; IQR = 0.5–1.4) and nonexposed (SD = 9.3; IQR = 0.5–1.7) groups. Over a mean follow-up of 9.2 days (SD = 12.5; median = 6 days; IQR = 2–11), 1,168 patients (41.0%) had an end point event at the time of data cutoff on May 1, 2020. Among patients who received an FIASMA medication at baseline, the mean follow-up was 12.0 days (SD = 12.9, median = 8 days; IQR = 4–14), whereas it was of 8.9 days (SD = 12.4, median = 5 days; IQR = 1–11) in those who did not.

All patient characteristics, except for current smoking status, diseases of the musculoskeletal system, and Eye-Ear-Nose-Throat disorders were significantly associated with the end point of intubation or death. A multivariable Cox regression model showed that sex, the hospital in which the patient was treated, obesity, medications according to compassionate use or as part of a clinical trial, cardiovascular disorders, respiratory disorders, neoplasms and diseases of the blood, other infectious diseases, and diseases of the genitourinary system were significantly and independently associated with the composite risk of intubation or death (**Table S1**).

The distributions of patient characteristics according to FIASMA medication use are shown in **Table 2**. In the full sample, FIASMA medication use at baseline substantially differed according to all patient characteristics, except for medications according to compassionate use or as part of a clinical trial, and the direction of the associations indicated an older age and greater medical severity of patients receiving FIASMA medication at baseline.

In the matched analytic sample and in the full sample after applying the propensity score weights, there were no substantial differences in any characteristic (**Table 2**; **Figure S1**).

Study end point

The end point of intubation or death occurred in 104 patients (37.5%) who received an FIASMA medication at baseline and in 1,060 patients (41.4%) who did not. Both the crude unadjusted analysis (hazard ratio (HR) = 0.71; 95% confidence interval (CI) = 0.58–0.87; $P < 0.01$) and the primary analysis with IPW (HR = 0.58; 95% CI = 0.46–0.72; $P < 0.01$) showed a significant association between FIASMA medication use at baseline and reduced risk of intubation or death (**Figure 3**; **Table 3**). A post hoc analysis indicated that we had 80% power in the crude analysis to detect a HR of at least 0.82/1.21.

In sensitivity analyses, the multivariable Cox regression model also showed a significant association (HR = 0.66; 95% CI = 0.53–0.83; $P < 0.01$), as did the univariate Cox regression model in the matched analytic sample using a 1:1 ratio (HR = 0.55; 95% CI = 0.43–0.73; $P < 0.01$; **Table 3**).

Additional exploratory analyses showed that the use of FIASMA nervous system medications, and specifically FIASMA psychoanaleptic medications, was significantly associated with decreased risk of intubation or death across all analyses (**Table 4**, **Table S2**). Using FIASMA cardiovascular system medication, and specifically FIASMA calcium channel blocker medications, was also significantly associated with reduced risk of intubation or death in the

Table 3 Association between FIASMA medication use at baseline and risk of intubation or death among patients hospitalized for severe COVID-19 (*N* = 2,846)

	Number of events / Number of patients	Crude Cox regression analysis	Multivariable Cox regression analysis	Analysis weighted by inverse-probability-weighting weights	Number of events /Number of patients in the matched groups	Univariate Cox regression in a 1:1 ratio matched analytic sample
	N / N (%)	HR (95% CI; *P* value)	HR (95% CI; *P* value)	HR (95% CI; *P* value)	N / N (%)	HR (95% CI; *P* value)
No FIASMA medication	1,064 / 2,569 (41.4%)	Ref	Ref	Ref	137 / 277 (49.5%)	Ref
Any FIASMA medication	104 / 277 (37.5%)	0.71 (0.58–0.87; 0.001*)	0.66 (0.53–0.83; <0.001*)	0.58 (0.46–0.72; <0.001*)	104 / 277 (37.5%)	0.55 (0.43–0.73; <0.001*)

CI, confidence interval; COVID-19, coronavirus disease 2019; FIASMA, Functional Inhibitor of Acid Sphingomyelinase; HR, hazard ratio.
*Two-sided *P* value is significant (*P* < 0.05).

primary IPW analysis, multivariable analysis, and the IPW analysis adjusted for unbalanced covariates. HRs were lower than 1 for most individual FIASMA molecules, but none of them reached statistical significance across all main and sensitivity analyses, except for hydroxyzine and escitalopram (**Table S2**), possibly due to restricted statistical power. Patients receiving any FIASMA medication at baseline, and specifically an FIASMA calcium channel blocker medication, an FIASMA nervous system medication, and specifically an FIASMA psycho-analeptic medication had a significantly reduced risk of intubation or death compared with patients who received paracetamol at baseline (**Table S3**). Reproducing the main analyses while considering venlafaxine, mirtazapine, and citalopram as FIASMA antidepressants did not alter the significance of our results (**Table S4**). Finally, including in the main analyses all patients with and without clinical severity criteria at baseline did not alter the significance of our results (**Table S5**).

DISCUSSION

In this multicenter retrospective observational study involving 2,846 adult patients hospitalized for severe COVID-19, we found that FIASMA medication use at hospital admission was significantly and substantially associated with reduced risk of intubation or death, independently of sociodemographic characteristics and medical comorbidities. This association remained significant in multiple sensitivity analyses. Additional exploratory analyses suggest that this association was not explained by one specific FIASMA class or one specific FIASMA medication.

We found that FIASMA medication use among patients hospitalized for severe COVID-19 was significantly and substantially associated with reduced risk of intubation or death, with a 42% risk reduction in the main analysis. This association was not specific to one FIASMA psychotropic class or medication. These findings are in line with prior preclinical[5,11] and clinical[14-17] evidence that FIASMA antidepressant medications may substantially prevent cells from being infected with SARS-CoV-2 *in vitro*,[5,11] and that several FIASMA medications, such as fluoxetine, hydroxyzine, and amlodipine at their usual respective antidepressant, antihistaminic, and antihypertensive doses, may reduce mortality among patients hospitalized for COVID-19.[14-17]

Several other mechanisms could be proposed to explain this association besides the involvement of the ASM/ceramide system.[33] First, antiviral effects (i.e., inhibition of viral replication), of FIASMA medications might underlie this relationship, as suggested by *in vitro* studies for fluoxetine,[5] chlorpromazine,[34] and amlodipine.[17] However, inhibition of viral replication was not observed with several other FIASMA medications, including paroxetine and escitalopram.[35]

Second, several FIASMA medications, such as escitalopram or hydroxyzine, have high affinity for Sigma-1 receptors (S1R),[36,37] which have been suggested to have potential value in regulating inflammation by inhibiting cytokine production in COVID-19.[38] The S1R has been shown to restrict the endonuclease activity of an endoplasmic reticulum stress sensor called Inositol-Requiring Enzyme1 (IRE1) and to reduce cytokine expression, without inhibiting classical inflammatory pathways.[12,38] Because several FIASMA medications are S1R agonists in our sample, this

Table 4 Association of each FIASMA class prescribed at baseline with the composite endpoint of intubation or death among patients hospitalized for severe COVID-19 (*n* = 2,846)

	Number of events / Number of patients	Crude Cox regression analysis	Multivariable Cox regression analysis	Analysis weighted by inverse-probability-weighting weights	Analysis weighted by inverse-probability-weighting weights adjusted for unbalanced covariates	Number of events /Number of patients in the matched control groups	Univariate Cox regression in 1:2 ratio matched analytic samples	Cox regression in 1:2 ratio matched analytic samples adjusted for unbalanced covariates
	N / N (%)	HR (95% CI; *P* value)	HR (95% CI; *P* value)	HR (95% CI; *P* value)	HR (95% CI; *P* value)	N / N (%)	HR (95% CI; *P* value)	HR (95% CI; *P* value)
No FIASMA medication	1,064 / 2,569 (41.4)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
FIASMA alimentary tract and metabolism medication	2 / 9 (22.2)	0.39 (0.10–1.56; 0.182)	0.25 (0.05–1.33; 0.104)	0.15 (0.02–1.21; 0.075)	NA	11 / 18 (61.1)	0.24 (0.05–1.12; 0.070)	NA
FIASMA cardiovascular system medications	54 / 125 (43.2)	1.07 (0.81–1.41; 0.650)	0.82 (0.64–1.06; 0.135)	0.61 (0.45–0.81; <0.001*)	0.61 (0.46–0.83; 0.001*)[a]	129 / 250 (51.6)	0.80 (0.58–1.10; 0.169)	0.83 (0.62–1.13; 0.238)[b]
FIASMA calcium channel blockers	38 / 97 (39.2)	0.88 (0.61–1.27; 0.510)	0.70 (0.49–0.98; 0.037*)	0.56 (0.39–0.79; <0.001*)	0.68 (0.49–0.94; 0.020*)[c]	97 / 194 (50.0)	0.74 (0.48–1.16; 0.190)	0.75 (0.51–1.11; 0.149)[d]
Other FIASMA cardiovascular system medications	19 / 34 (55.9)	1.66 (1.21–2.28; 0.002*)	1.27 (0.96–1.69; 0.100)	NA	NA	37 / 68 (54.4)	0.91 (0.52–1.59; 0.748)	0.80 (0.44–1.46; 0.469)[e]
FIASMA nervous system medications	61 / 175 (34.9)	0.62 (0.48–0.80; <0.001*)	0.65 (0.49–0.88; <0.001*)	0.51 (0.38–0.69; <0.001*)	0.49 (0.37–0.64; <0.001*)[f]	173 / 350 (49.4)	0.60 (0.44–0.82; 0.002*)	0.61 (0.45–0.83; 0.002*)[g]
FIASMA psychoanaleptic medications	59 / 169 (34.9)	0.62 (0.47–0.80; <0.001*)	0.65 (0.48–0.87; <0.001*)	0.51 (0.37–0.70; <0.001*)	0.48 (0.36–0.63; <0.001*)[h]	169 / 338 (50.0)	0.58 (0.42–0.80; <0.001*)	0.60 (0.44–0.82; 0.001*)[i]
FIASMA psycholeptic medications	4 / 13 (30.8)	0.68 (0.28–1.64; 0.387)	0.59 (0.26–1.35; 0.210)	NA	NA	8 / 26 (30.8)	0.82 (0.25–2.73; 0.746)	0.80 (0.21–2.98; 0.735)[j]
FIASMA respiratory system medications	3 / 7 (42.9)	1.02 (0.33–3.18; 0.970)	0.68 (0.25–1.81; 0.439)	NA	NA	7 / 14 (50.0)	0.84 (0.22–3.26; 0.798)	NA

CI, confidence interval; FIASMA, Functional Inhibitor of Acid Sphingomyelinase; HR, hazard ratio; NA, not applicable.
[a]Adjusted for age, cardiovascular disorders, and diseases of the genitourinary system. [b]Adjusted for hospital, current smoking status, medication prescribed as part of a clinical trial or according to compassionate use, cardiovascular disorders, respiratory disorders, and diseases of the genitourinary system. [c]Adjusted for cardiovascular disorders, diseases of the genitourinary system, and endocrine disorders. [d]Adjusted for hospital, current smoking status, diseases of the nervous system, respiratory disorders, and diseases of the genitourinary system. [e]Adjusted for hospital, obesity, current smoking status, medication prescribed as part of a clinical trial or according to compassionate use, respiratory disorders, and diseases of the genitourinary system. [f]Adjusted for hospital. [g]Adjusted for age, sex, current smoking status, and mental disorders. [h]Adjusted for hospital. [i]Adjusted for age, sex, current smoking status, and mental disorders. [j]Adjusted for age, sex, hospital, obesity, current smoking status, medication prescribed as part of a clinical trial or according to compassionate use, mental disorders, and endocrine disorders.*Two-sided *P*value is significant ($P < 0.05$).

mechanism might have overlapped their inhibition effect on ASM. However, when examining the association between the endpoint and several FIASMA medications with low or no affinity for S1R (e.g., amlodipine, paroxetine, duloxetine, and aripiprazole),[36,39,40,41,42] the main results remained statistically significant (**Table S6**), suggesting that inhibition of ASM could underlie this association independently of S1R.

Finally, this association may be partly mediated by the anti-inflammatory effects of FIASMA medications, which could be explained by inhibition of ASM in endothelial cells and the immune system, and might be independent of Sigma-1 receptors. First, a recent meta-analysis[43] of studies conducted in individuals with major depressive disorder following antidepressant treatment, mostly including selective serotonin reuptake inhibitors (SSRIs), supports that, overall, antidepressants may be associated with decreased plasma levels of 4 of 16 tested inflammatory mediators, including IL-10, TNF-α, CCL-2, which are associated with COVID-19 severity,[44] as well as IL-6, which is highly correlated with disease mortality.[44,45] Second, prior *in vitro* and *in vivo* studies[46-48] suggest that some antipsychotics may have anti-inflammatory effects via glia activation, but that this activity may not be shared by all antipsychotics. However, this anti-inflammatory effect was observed for both FIASMA antipsychotics (e.g., chlorpromazine) and non-FIASMA ones (e.g., haloperidol and risperidone). If the association between FIASMA psychotropic medication use and reduced risk of intubation or death is confirmed, future studies aiming at disentangling these potentially interrelated mechanisms would be needed.

Our study has several limitations. First, there are two possible major inherent biases in observational studies: unmeasured confounding and confounding by indication. However, in the case of FIASMA medications, including several antidepressants and cardiovascular system medications, confounding by indication may typically result in increased adverse medical outcomes associated with these medications,[49] not better outcomes as suggested by our findings. We tried to minimize the effects of confounding in several different ways. First, we used an analysis with inverse probability weighting to minimize the effects of confounding by indication,[30] resulting in nonsubstantial between-group differences in clinical characteristics (all SMD < 0.1) in both the IPW primary analysis and the Cox regression analysis in the matched analytic sample. Second, we performed multiple sensitivity analyses, which showed similar results. Finally, although some amount of unmeasured confounding may remain, our analyses adjusted for numerous potential confounders. Other limitations include missing data for some baseline characteristic variables (i.e., 11.5%), which might be explained by the overwhelming of all hospital units during the COVID-19 peak incidence, and different results might have been observed during a lower COVID-19 incidence period. However, imputation of missing data did not alter the significance of our results (data available on request). Second, inflation of type I error might have occurred in exploratory analyses due to multiple testing. Third, data on several FIASMA medications were not available because no patients hospitalized for severe COVID-19 in AP-HP hospitals received them at study baseline during the first epidemic wave. Fourth, this study cannot establish a causal relationship between FIASMA medication use and reduced risk of intubation or death. Fifth, data to approximate the time to onset or duration of the potential effect of FIASMA medications and data on medications taken by patients prior to their hospital admission were not available. Although this may constitute a bias (i.e., considering patients taking an FIASMA medication just before hospital admission as not taking it instead of excluding them from the analyses), the direction of this bias is likely to be toward the null hypothesis, as it may have led to underestimate the association between FIASMAs and reduced risk of intubation or mortality by including individuals taking FIASMAs just before hospital admission in the control group. Sixth, data cutoff is nearly a year ago and represents only the first few months of the COVID-19 pandemic. Furthermore, the relatively limited sample size reduced our ability to examine with adequate statistical power each individual FIASMA medication. Future studies would benefit in replicating our analyses while including a greater number of patients hospitalized for severe COVID-19 at a more recent time of the pandemic when care has substantially progressed as compared with its beginning. Finally, despite the multicenter design, our results may not be generalizable to outpatients or other regions.

In conclusion, in this multicenter observational retrospective study, FIASMA medication use was significantly and substantially associated with reduced risk of intubation or death among adult patients hospitalized for severe COVID-19. These findings show the potential importance of the ASM/ceramide system framework in COVID-19 treatment. They also support the continuation of FIASMA medications in patients with COVID-19. Double-blind controlled randomized clinical trials (RCTs) of these medications in patients with COVID-19 are needed, starting with FIASMA molecules such as fluoxetine, fluvoxamine, escitalopram, or hydroxyzine, which have high *in vitro* inhibition effect on ASM and are ease of use, including high safety margin, good tolerability, widespread availability, and low cost such that primary care physicians and other providers could prescribe them as soon as onset of symptoms, if their usefulness against COVID-19 was confirmed in RCTs.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

N.H., M.S.R., M.A., P.d.I.M., E.G., J.K., A.C., and F.L. are inventors on a patent application related to methods of treating COVID-19, filled by Assistance Publique – Hopitaux de Paris in France. N.H. has received personal fees and nonfinancial support from Lundbeck, outside the submitted work. F.L. has received speaker and consulting fees from Janssen-Cilag, Euthérapie-Servier, and Lundbeck, outside the submitted work. E.L. has received grant support (non-federal) from COVID Early Treatment Fund, Mercatus Center

Emergent Ventures, the Skoll Foundation, the Taylor Family Institute for Innovative Psychiatric Research, the Center for Brain Research in Mood Disorders, the Patient-Centered Outcomes Research Institute, Janssen, and the Barnes Jewish Foundation, and has received consulting fees from Janssen and Jazz Pharmaceuticals. A.R. has received grant or research support from the McDonnell Center for Systems Neuroscience, the McDonnell Center for Cellular and Molecular Neurobiology, and the Taylor Family Institute for Innovative Psychiatric Research. A.R. and E.L. are inventors on a patent application related to methods of treating COVID-19, which was filed by Washington University in St. Louis. Other authors declare no conflict of interest related to this work.

AUTHOR CONTRIBUTIONS

N.H., M.S.R., E.G., J.K., A.C., E.J.L, A.M.R., M.A., P.d.l.M, R.V., C.B., C.G., N.B., A.N., P.G., J.M.A., P.M., and F.L. wrote the manuscript. N.H, M.S.R., and F.L. designed the research. N.H., M.S.R., M.A., P.d.l.M., and R.V. performed the research. M.S.R., M.A., P.d.l.M., and N.H. analyzed the data. R.V., N.B., and A.N. contributed to analytical tools.

DISCLAIMER

The information contained in this study is provided for research purpose and should not be used as a substitute or replacement for diagnosis or treatment recommendations or other clinical decisions or judgment. The views presented in this manuscript are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or the National Institute on Drug Abuse or any US Government Agency.

DATA AVAILABILITY STATEMENT

Data can be available upon request from AP-HP Health Data Warehouse (Entrepôt de Données de Santé (EDS)) at https://eds.aphp.fr//.

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APPENDIX 1
EDS APHP Covid consortium

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