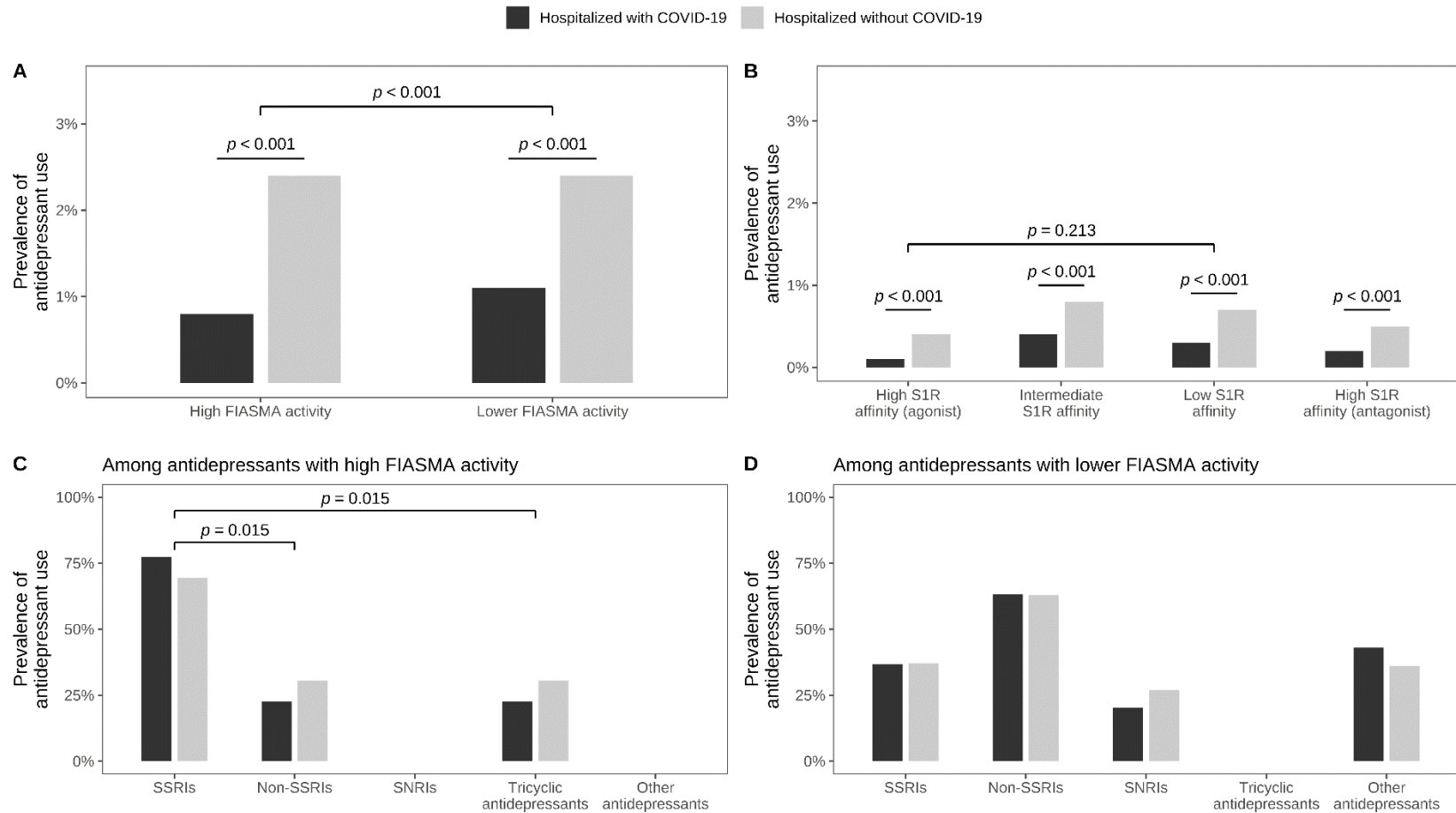
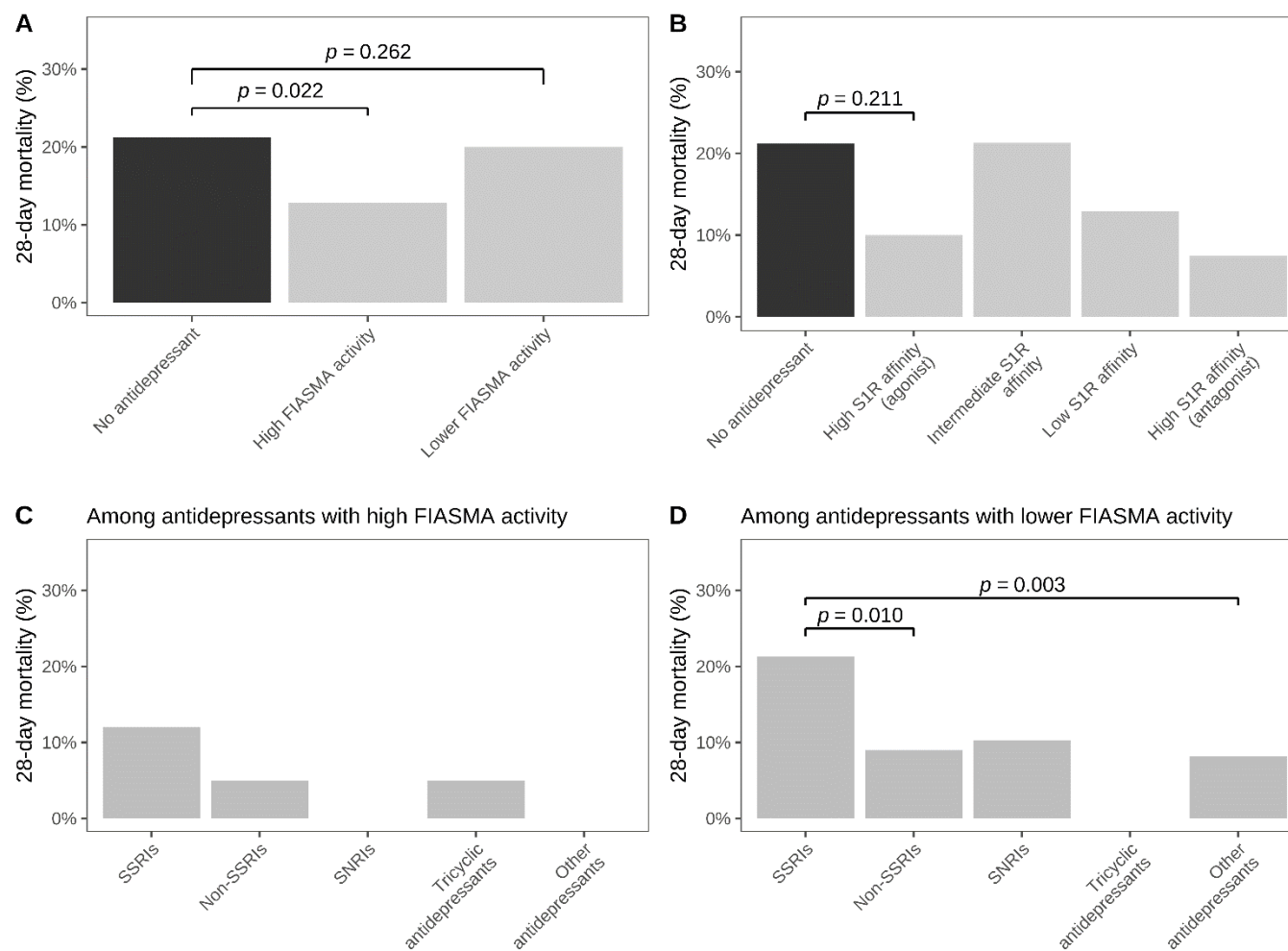


## SUPPLEMENTARY MATERIAL

**Figure S1. Prevalence of antidepressant use in inpatients hospitalized with and without COVID-19 by FIASMA activity (A), S1R affinity (B) and antidepressant class by FIASMA activity (C-D) (N = 82,586).**



**Figure S2. Antidepressant use and 28-day all-cause mortality in a matched analytic sample of patients hospitalized with COVID-19 by FIASMA activity (A), S1R affinity (B) and antidepressant class by FIASMA activity (C-D) (N=1,482).**



**Table S1. Comparing characteristics between patients hospitalized with COVID-19 and patients hospitalized without COVID-19 in a 1:1 ratio matched analytic sample (N=82,586).**

|   | With COVID-19<br>(N=41,293) | Without COVID-19<br>(N=41,293) | With COVID-19 vs.<br>without COVID-19 |
|---|-----------------------------|--------------------------------|---------------------------------------|
|   | Median (SD) / N (%)         | Median (SD) / N (%)            | SMD                                   |
| Age   | 53.7 (21.4)                 | 53.6 (21.6)                    | 0.003                                 |
| Sex   |                             |                                | <0.001                                |
| <i>Women</i>  | 20561 (50.0%)               | 20552 (50.0%)                  |                                       |
| <i>Men</i>  | 20732 (50.0%)               | 20741 (50.0%)                  |                                       |
| Hospital  |                             |                                | 0.006                                 |
| <i>AP-HP Centre—Paris University,<br/>    Paris Saclay University, Henri<br/>    Mondor University Hospitals and at<br/>    home hospitalization<br/>    and Hôpitaux</i> | 17192 (50.1%)               | 17136 (49.9%)                  |                                       |
| <i>AP-HP Nord and Universitaires<br/>    Paris Seine-Saint-Denis</i>  | 16454 (50.1%)               | 16418 (49.9%)                  |                                       |
| <i>AP-HP Sorbonne University</i>  | 7647 (49.7%)                | 7739 (50.3%)                   |                                       |
| Hospitalization period  |                             |                                | 0.003                                 |
| <i>May 2<sup>nd</sup> 2020 - December 5<sup>th</sup> 2020</i>   | 16195 (50.0%)               | 16224 (50.0%)                  |                                       |
| <i>December 6<sup>th</sup> 2020 - March 15<sup>th</sup><br/>    2021</i>  | 9598 (49.9%)                | 9629 (50.1%)                   |                                       |
| <i>March 16<sup>th</sup> 2021 - November 2<sup>nd</sup><br/>    2021</i>  | 15500 (50.1%)               | 15440 (49.9%)                  |                                       |
| Number of medical conditions  |                             |                                | 0.023                                 |
| <i>0-4</i>  | 29155 (50.1%)               | 29089 (49.9%)                  |                                       |
| <i>5-7</i>  | 4397 (49.7%)                | 4443 (50.3%)                   |                                       |
| <i>8-9</i>  | 2284 (49.2%)                | 2362 (50.8%)                   |                                       |
| <i>10-12</i>  | 2409 (49.5%)                | 2454 (50.5%)                   |                                       |
| <i>13-17</i>  | 2049 (49.7%)                | 2073 (50.3%)                   |                                       |
| <i>18+</i>  | 999 (53.4%)                 | 872 (46.6%)                    |                                       |

SMD>0.1 indicate substantial differences.

Abbreviation: SMD, standardized mean difference.

**Table S2. Prevalence of antidepressant use in a matched analytic sample of adult patients hospitalized with and without COVID-19 (A), and antidepressant use and 28-day all-cause mortality in a matched analytic sample of patients hospitalized with COVID-19 (B), using the nearest neighbor matching method.**

| <b>A. Matched analytic sample of adult patients hospitalized with and without COVID-19</b> | <b>Patients hospitalized with COVID-19<br/>(N = 41,293) – N (%)</b> | <b>Patients hospitalized without COVID-19<br/>(N = 41,293) – N (%)</b> | <b>Hospitalized with COVID-19 versus without COVID-19 in a 1:1 ratio matched analytic sample – OR (95% CI; p-value)</b> | <b>Hospitalized with COVID-19 versus without COVID-19 in a 1:1 ratio matched analytic sample adjusted for unbalanced covariates – AOR (95% CI; p-value)</b> |
|--|---|--|---|---|
| No antidepressant  | 40521 (98.1%)   | 39259 (95.1%)  | Ref.  | Ref.  |
| Any antidepressant   | 772 (1.9%)  | 2035 (4.9%)  | 0.37 (0.34 - 0.40; <0.001***)   | -   |
| <b>B. Matched analytic sample of patients hospitalized with COVID-19</b>                   | <b>Median dose (IQR)</b>  | <b>Deaths / Patients (%)</b>   | <b>Crude logistic regression in the matched analytic sample – OR (95% CI; p-value)</b>                                  | <b>Multivariable logistic regression in the matched analytic sample adjusted for unbalanced covariates – AOR (95% CI; p-value)</b>                          |
| No antidepressant  | -   | 196 / 741 (26.5%)  | Ref.  | Ref.  |
| Any antidepressant   | 30.0 (19.0-49.5)  | 95 / 741 (12.8%)   | 0.41 (0.31 - 0.54; <0.001***)   | 0.42 (0.32 - 0.55; <0.001***) <sup>a</sup>  |

<sup>a</sup> Adjusted for age, number of medical conditions and any antipsychotic medication.

\* Two-sided p < 0.05; \*\* p < 0.01; \*\*\* p < 0.001.

Abbreviations: OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; NA, not applicable; -, irrelevant.

**Table S3. Associations of baseline characteristics with 28-day mortality in the matched analytic sample of inpatients with COVID-19 receiving or not receiving an antidepressant at baseline (N=1,482).**

|   | Full population<br>(N=1,482) | Death<br>(N=252)    | No death<br>(N=1230) | Crude analysis              | Multivariable analysis      |                                     |
|---|------------------------------|---------------------|----------------------|-----------------------------|-----------------------------|-------------------------------------|
|   | Mean (SD)/<br>N (%)          | Mean (SD)/<br>N (%) | Mean (SD)/<br>N (%)  | OR (95%CI ; p-value)        | AOR (95%CI ; p-value)       | Collinearity<br>diagnosis<br>(GVIF) |
| Age   | 76.2 (15.4)                  | 82.5 (9.76)         | 75.0 (16.0)          | 1.87 (1.57 - 2.24; <0.001*) | 1.06 (1.05 - 1.08; <0.001*) | 1.24                                |
| Sex   |                              |                     |                      |                             |                             | 1.09                                |
| <i>Women</i>  | 931 (62.8%)                  | 145 (15.6%)         | 786 (84.4%)          | Ref.                        | Ref.                        |                                     |
| <i>Men</i>  | 551 (37.2%)                  | 107 (19.4%)         | 444 (80.6%)          | 1.31 (0.99 - 1.72; 0.057)   | 1.67 (1.22 - 2.29; 0.001*)  |                                     |
| Hospital  |                              |                     |                      |                             |                             | 1.23                                |
| <i>AP-HP Centre—Paris<br/>University, Paris Saclay<br/>University, Henri Mondor<br/>University Hospitals and at<br/>home hospitalization<br/>and Hôpitaux</i> | 626 (42.2%)                  | 100 (16.0%)         | 526 (84.0%)          | Ref.                        | Ref.                        |                                     |
| <i>AP-HP Nord and<br/>Universitaires Paris Seine-<br/>Saint-Denis</i>   | 373 (25.2%)                  | 64 (17.2%)          | 309 (82.8%)          | 1.09 (0.77 - 1.54; 0.625)   | 1.11 (0.75 - 1.66; 0.592)   |                                     |
| <i>AP-HP Sorbonne University</i>  | 483 (32.6%)                  | 88 (18.2%)          | 395 (81.8%)          | 1.17 (0.86 - 1.61; 0.323)   | 1.10 (0.77 - 1.58; 0.602)   |                                     |
| Hospitalization period  |                              |                     |                      |                             |                             | 1.08                                |
| <i>May 2<sup>nd</sup> 2020 - December 5<sup>th</sup><br/>2020</i>   | 519 (35.0%)                  | 69 (13.3%)          | 450 (86.7%)          | Ref.                        | Ref.                        |                                     |
| <i>December 6<sup>th</sup> 2020 - March<br/>15<sup>th</sup> 2021</i>  | 497 (33.5%)                  | 101 (20.3%)         | 396 (79.7%)          | 1.66 (1.19 - 2.32; 0.003*)  | 1.53 (1.06 - 2.21; 0.023*)  |                                     |
| <i>March 16<sup>th</sup> 2021 - November<br/>2<sup>nd</sup> 2021</i>  | 466 (31.4%)                  | 82 (17.6%)          | 384 (82.4%)          | 1.39 (0.98 - 1.97; 0.062)   | 1.53 (1.04 - 2.24; 0.030*)  |                                     |
| Number of medical conditions  |                              |                     |                      |                             |                             | 1.45                                |
| <i>0-4</i>  | 268 (18.1%)                  | 35 (13.1%)          | 233 (86.9%)          | Ref.                        | Ref.                        |                                     |
| <i>5-7</i>  | 316 (21.3%)                  | 45 (14.2%)          | 271 (85.8%)          | 1.11 (0.69 - 1.78; 0.679)   | 0.94 (0.55 - 1.60; 0.826)   |                                     |
| <i>8-9</i>  | 206 (13.9%)                  | 24 (11.7%)          | 182 (88.3%)          | 0.88 (0.50 - 1.53; 0.645)   | 0.66 (0.35 - 1.22; 0.182)   |                                     |
| <i>10-12</i>  | 239 (16.1%)                  | 47 (19.7%)          | 192 (80.3%)          | 1.63 (1.01 - 2.63; 0.045*)  | 1.49 (0.86 - 2.59; 0.156)   |                                     |
| <i>13-17</i>  | 303 (20.4%)                  | 66 (21.8%)          | 237 (78.2%)          | 1.85 (1.18 - 2.90; 0.007*)  | 1.30 (0.77 - 2.21; 0.327)   |                                     |
| <i>18+</i>  | 150 (10.1%)                  | 35 (23.3%)          | 115 (76.7%)          | 2.03 (1.21 - 3.40; 0.008*)  | 1.43 (0.77 - 2.64; 0.258)   |                                     |
| Any psychiatric disorder <sup>1</sup>   |                              |                     |                      |                             |                             | 1.36                                |
| <i>Yes</i>  | 775 (52.3%)                  | 137 (17.7%)         | 638 (82.3%)          | 1.11 (0.84 - 1.45; 0.470)   | 0.79 (0.56 - 1.12; 0.181)   |                                     |
| <i>No</i>   | 707 (47.7%)                  | 115 (16.3%)         | 592 (83.7%)          | Ref.                        | Ref.                        |                                     |
| Any medication according to   |                              |                     |                      |                             |                             | 1.21                                |

|  |              |             |             |                             |                             |      |
|--|--------------|-------------|-------------|-----------------------------|-----------------------------|------|
| compassionate use or as part of a medical trial          |              |             |             |                             |                             |      |
| Yes  | 298 (20.1%)  | 39 (13.1%)  | 259 (86.9%) | 4.03 (3.00 - 5.42; <0.001*) | 3.75 (2.67 - 5.26; <0.001*) |      |
| No   | 1184 (79.9%) | 213 (18.0%) | 971 (82.0%) | Ref.                        | Ref.                        |      |
| Any benzodiazepine or Z-drug within 24h from admission   |              |             |             |                             |                             | 1.11 |
| Yes  | 644 (43.5%)  | 179 (27.8%) | 465 (72.2%) | 1.51 (1.15 - 1.99; 0.003*)  | 1.64 (1.20 - 2.24; 0.002*)  |      |
| No   | 838 (56.5%)  | 73 (8.71%)  | 765 (91.3%) | Ref.                        | Ref.                        |      |
| Any antipsychotic medication within 24h from admission   |              |             |             |                             |                             | 1.08 |
| Yes  | 781 (52.7%)  | 154 (19.7%) | 627 (80.3%) | 0.91 (0.64 - 1.30; 0.603)   | 1.17 (0.78 - 1.74; 0.449)   |      |
| No   | 701 (47.3%)  | 98 (14.0%)  | 603 (86.0%) | Ref.                        | Ref.                        |      |
| Any mood stabilizer medication within 24h from admission |              |             |             |                             |                             | 1.02 |
| Yes  | 282 (19.0%)  | 45 (16.0%)  | 237 (84.0%) | 0.69 (0.48 - 0.99; 0.045*)  | 0.84 (0.56 - 1.26; 0.400)   |      |
| No   | 1200 (81.0%) | 207 (17.2%) | 993 (82.8%) | Ref.                        | Ref.                        |      |
| Biological severity of COVID-19 <sup>2</sup>             |              |             |             |                             |                             | 1.25 |
| Yes  | 782 (52.8%)  | 168 (21.5%) | 614 (78.5%) | 2.01 (1.51 - 2.67; <0.001*) | 1.3 (0.93 - 1.84; 0.129)    |      |
| No   | 700 (47.2%)  | 84 (12.0%)  | 616 (88.0%) | Ref.                        | Ref.                        |      |
| Clinical severity of COVID-19 <sup>3</sup>               |              |             |             |                             |                             | 1.11 |
| Yes  | 540 (36.4%)  | 128 (23.7%) | 412 (76.3%) | 2.05 (1.56 - 2.70; <0.001*) | 1.62 (1.18 - 2.2; 0.002*)   |      |
| No   | 942 (63.6%)  | 124 (13.2%) | 818 (86.8%) | Ref.                        | Ref.                        |      |

<sup>1</sup> Assessed using ICD-10 diagnosis codes for any psychiatric disorder (F00-F99).

<sup>2</sup> Defined as having at least one of the following criteria: 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.

<sup>3</sup> Defined as having at least one of the following criteria: respiratory rate > 24 breaths/min or < 12 breaths/min, resting peripheral capillary oxygen saturation in ambient air < 90% , temperature > 40°C, or systolic blood pressure < 100 mm Hg.

\* 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.

**Table S4. Characteristics of patients receiving or not receiving an antidepressant at baseline in the full sample and in the 1:1 ratio matched analytic sample of patients hospitalized with COVID-19.**

|   | With any<br>antidepressant<br>(N=741) | Without<br>antidepressants in the<br>full sample<br>(N=40,521) | Without<br>antidepressants in the<br>matched control<br>group (N=741) | Any antidepressant<br>vs. without<br>antidepressants in<br>the full sample | Any antidepressant<br>vs. without<br>antidepressants in the<br>matched analytic<br>sample |
|---|---------------------------------------|--|---|--|---|
|   | Mean (SD)/N (%)                       | Mean (SD)/N (%)  | Mean (SD)/N (%)   |  | SMD   |
| Age   | 77.0 (15.2)                           | 53.2 (21.2)  | 75.5 (15.5)   | 1.288  | 0.099   |
| Sex   |                                       |  |   | 0.303  | 0.064   |
| <i>Women</i>  | 477 (64.4%)                           | 20065 (49.5%)  | 454 (61.3%)   |  |   |
| <i>Men</i>  | 264 (35.6%)                           | 20456 (50.5%)  | 287 (38.7%)   |  |   |
| Hospital  |                                       |  |   | 0.403  | 0.036   |
| <i>AP-HP Centre—Paris University, Paris<br/>    Saclay University, Henri Mondor<br/>    University Hospitals and at home<br/>    hospitalization<br/>    and Hôpitaux</i> | 307 (41.4%)                           | 16855 (41.6%)  | 319 (43.0%)   |  |   |
| <i>AP-HP Nord and Universitaires Paris<br/>    Seine-Saint-Denis</i>  | 187 (25.2%)                           | 16267 (40.1%)  | 186 (25.1%)   |  |   |
| <i>AP-HP Sorbonne University</i>  | 247 (33.3%)                           | 7399 (18.3%)   | 236 (31.8%)   |  |   |
| Hospitalization period  |                                       |  |   | 0.252  | 0.065   |
| <i>May 2<sup>nd</sup> 2020 - December 5<sup>th</sup> 2020</i>   | 267 (36.0%)                           | 15910 (39.3%)  | 252 (34.0%)   |  |   |
| <i>December 6<sup>th</sup> 2020 - March 15<sup>th</sup> 2021</i>  | 252 (34.0%)                           | 9334 (23.0%)   | 245 (33.1%)   |  |   |
| <i>March 16<sup>th</sup> 2021 - November 2<sup>nd</sup> 2021</i>  | 222 (30.0%)                           | 15277 (37.7%)  | 244 (32.9%)   |  |   |
| Number of medical conditions  |                                       |  |   | 1.322  | 0.038   |
| <i>0-4</i>  | 129 (17.4%)                           | 29003 (71.6%)  | 139 (18.8%)   |  |   |
| <i>5-7</i>  | 161 (21.7%)                           | 4232 (10.4%)   | 155 (20.9%)   |  |   |
| <i>8-9</i>  | 103 (13.9%)                           | 2178 (5.37%)   | 103 (13.9%)   |  |   |
| <i>10-12</i>  | 120 (16.2%)                           | 2289 (5.65%)   | 119 (16.1%)   |  |   |
| <i>13-17</i>  | 153 (20.6%)                           | 1895 (4.68%)   | 150 (20.2%)   |  |   |
| <i>18+</i>  | 75 (10.1%)                            | 924 (2.28%)  | 75 (10.1%)  |  |   |
| Any psychiatric disorder <sup>1</sup>   |                                       |  |   | 1.122  | 0.003   |
| <i>Yes</i>  | 388 (52.4%)                           | 3059 (7.55%)   | 387 (52.2%)   |  |   |
| <i>No</i>   | 353 (47.6%)                           | 37462 (92.5%)  | 354 (47.8%)   |  |   |
| Any medication according to<br>compassionate use or as part of a medical<br>trial   |                                       |  |   | 0.696  | 0.027   |

|  |             |               |             |       |        |
|--|-------------|---------------|-------------|-------|--------|
| <i>Yes</i>   | 317 (42.8%) | 5375 (13.3%)  | 327 (44.1%) |       |        |
| <i>No</i>  | 424 (57.2%) | 35146 (86.7%) | 414 (55.9%) |       |        |
| Any benzodiazepine or Z-drug within 24h from admission   |             |               |             | 1.286 | 0.003  |
| <i>Yes</i>   | 391 (52.8%) | 1618 (3.99%)  | 390 (52.6%) |       |        |
| <i>No</i>  | 350 (47.2%) | 38903 (96.0%) | 351 (47.4%) |       |        |
| Any antipsychotic medication within 24h from admission   |             |               |             | 0.633 | <0.001 |
| <i>Yes</i>   | 141 (19.0%) | 379 (0.94%)   | 141 (19.0%) |       |        |
| <i>No</i>  | 600 (81.0%) | 40142 (99.1%) | 600 (81.0%) |       |        |
| Any mood stabilizer medication within 24h from admission |             |               |             | 0.643 | <0.001 |
| <i>Yes</i>   | 149 (20.1%) | 496 (1.22%)   | 149 (20.1%) |       |        |
| <i>No</i>  | 592 (79.9%) | 40025 (98.8%) | 592 (79.9%) |       |        |
| Biological severity of COVID-19 <sup>2</sup>             |             |               |             | 0.407 | 0.022  |
| <i>Yes</i>   | 387 (52.2%) | 13168 (32.5%) | 395 (53.3%) |       |        |
| <i>No</i>  | 354 (47.8%) | 27353 (67.5%) | 346 (46.7%) |       |        |
| Clinical severity of COVID-19 <sup>3</sup>               |             |               |             | 0.527 | 0.006  |
| <i>Yes</i>   | 271 (36.6%) | 5817 (14.4%)  | 269 (36.3%) |       |        |
| <i>No</i>  | 470 (63.4%) | 34704 (85.6%) | 472 (63.7%) |       |        |

<sup>1</sup> Assessed using ICD-10 diagnosis codes for any psychiatric disorder (F00-F99).

<sup>2</sup> Defined as having at least one of the following criteria: 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.

<sup>3</sup> Defined as having at least one of the following criteria: respiratory rate > 24 breaths/min or < 12 breaths/min, resting peripheral capillary oxygen saturation in ambient air < 90% , temperature > 40°C, or systolic blood pressure < 100 mm Hg.

SMD>0.1 indicate substantial differences.

Abbreviation: SMD, standardized mean difference.



**Table S5. Association of antidepressant use with urinary infection in the matched analytic sample of inpatients with COVID-19 receiving or not receiving an antidepressant at baseline (N=1,482).**

|                         | <b>Number of events /<br/>Number of patients (%)</b> | <b>Crude logistic regression</b> |
|-------------------------|--|----------------------------------|
|                         | <b>N / N (%)</b>                                     | <b>OR (95%CI; p-value)</b>       |
| <b>Full sample</b>      |  |                                  |
| Without antidepressants | 31 / 741 (4.2%)                                      | Ref.                             |
| Any antidepressant      | 38 / 741 (5.1%)                                      | 1.24 (0.76 - 2.01; 0.389)        |

Urinary infection was defined as having any ICD-10 code for acute pyelonephritis (N10) or cystitis (N30).

Abbreviations: OR, odds ratio; CI, confidence interval.