**Supplemental Digital Content 1**

|  |  |
| --- | --- |
| **ICD codes**  | **ICD codes for COVID-19 related diseases**▪ Acute respiratory disease: U07.1▪ Pneumonia due to Covid-19• Other viral pneumonia: J12.89▪ Acute bronchitis due to Covid-19• Acute bronchitis due to other specified organisms: J20.8▪ Bronchitis, not otherwise specified due to Covid-19• Bronchitis, not specified as acute or chronic: J40▪ Lower respiratory infections, not otherwise specified, or an acute respiratory infection, not other specified, with associated documented Covid-19• Unspecified acute lower respiratory infection: J22• Other specified respiratory disorders: J98.8▪ Acute respiratory distress syndrome (ARDS) due to Covid-19• ARDS: J80▪ Other coronavirus as the cause of the diseases classified elsewhere: B97.29▪ Coronavirus infection, unspecified: B34.2▪ Actual exposure to someone who is confirmed COVID-19: Z20.828▪ Possible exposure to COVID-19, ruled out after evaluation: Z03.818▪ Signs and symptoms where a definitive diagnosis has not been established• Cough: R05• Shortness of breath: R06.02• Fever, unspecified: R50.9 |
| **Outcomes related codes*** A composite of death or severe COVID-19 (defined as ICD-10 diagnosis code B972A designating COVID-19 with SARS or intensive care unit admission designated by procedure code NABE)
* Discharge to Hospice
* Hospital length of stay
* Severe COVID-19 (ICD-10 code B972A or intensive care unit admission)
* Severe Sepsis (ICD-10 code R65.2)
* Severe Sepsis without septic shock (ICD-10 code R65.20)
* Severe Sepsis with septic (ICD-10 code R65.21)
* Acute Kidney Injury (ICD-10 Code N-17) according to the KIGO Definition and Staging (Appendix 3)
* Disseminated Intravascular coagulation (ICD-10 Code D65)
* Thrombosis (ICD-10 Code I82.40)
* Pulmonary Embolism (I26.9
* ARDS (ICD-10 code J80)
* Intubation (ICD -10 code T88.4)
* Invasive Mechanical Ventilation (Z99.11)
* Duration of Mechanical Ventilation 36) ECMO (Z92.81)
* Inflammatory response: serum cytokines (IL-6), High-sensitivity C-reactive Protein, ESR, ferritin, lactate dehydrogenase
* Hematologic profile: Hemoglobin concentration, Leucocytes count, Neutrophils count, Lymphocytes count, Platelets Count, aPTT, PT, Fibrinogen, D-Dimer, Ferritin
* Renal Profile: creatinine, BUN
* Metabolic Profile: pH, paO2, paCO2, lactic acid
* Lipid Profile: LDL, VLDL
* Liver profile: AST, ALT, bilirubin
* Patients on chronic renal dialysis (Z99-2)
 |
| **CPT codes**  | * Endotracheal intubation: 31500
* BIPAP/CPAP: 94660 (Non-Invasive Mechanical Ventilation (Continuous Positive Airway Pressure – CPAP – or Bilevel Positive Airway Pressure (BIPAP)
* Mechanical Ventilation: 94002
* ECMO: 33949
 |
| **Definitions** | **Acute respiratory distress syndrome diagnosis** confirmed byChest X-ray: bilateral diffuse alveolar opacities and dependent atelectasis.Chest CT typically demonstrates widespread patchy and/or coalescent opacities, usually more apparent in the dependent lung zones.**The severity of ARDS based on the Berlin definition*** Stage 1 (mild) ARDS is defined as a PaO2/FiO2 ratio of 200 to 300 with noninvasive Continuous Positive Airway Pressure (CPAP) or invasive positive end-expiratory pressure (PEEP) of at least 5 cm H2O
* Stage 2 (moderate) is a PaO2/FiO2 ratio of 100 to 200 with invasive PEEP,
* Stage 3 (severe) is a PaO2/FiO2 ratio below 100 with invasive PEEP.
 |
| **KDIGO Definition****Kidney Disease:** Improving Global Outcomes (KDIGO) definition of Acute Kidney Injury(1) Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours, or(2) Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to haveoccurred within the prior seven days, or(3) Urine volume <0.5 mL/kg/hour for six hours**KDIGO Staging**Using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, AKI is staged as follows:(1) Stage 1 – Increase in serum creatinine to 1.5 to 1.9 times baseline, or increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L), or reduction in urine output to <0.5 mL/kg/hour for 6 to 12 hours.(2) Stage 2 – Increase in serum creatinine to 2.0 to 2.9 times baseline, or reduction in urine output to <0.5 mL/kg/hour for ≥12 hours.(3) Stage 3 – Increase in serum creatinine to 3.0 times baseline, or increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L), or reduction in urine output to <0.3 mL/kg/hour for ≥24 hours, or anuria for ≥12 hours, or the initiation of renal replacement therapy, or, in patients <18 years, decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m2. |

**Supplemental Digital Content 2**

**Appendix 2. Tables on Propensity Score Matching, Sampling without Replacement**

**Appendix 2.1. Comparison of baseline characteristics between preexisting statin users and non-users before and after propensity matching without replacement**

|  |  |  |
| --- | --- | --- |
| **Patient Characteristics** | **Before propensity matching** | **After propensity matching, without replacement, covariate-adjusted** |
| **Preexisting use of statins** |  |  |  | **Preexisting use of statins** |  |  |  |
| **Yes** | **No** | **Cohort** | **Std dif\*** | **p-value** | **Yes** | **No** | **Cohort** | **Std dif\*** | **Adjusted** **p-value** |
| (n = 11533) | (n = 27342) | (n = 38875) |  |   | (n = 11533) | (n = 11533) | (n = 23066) |  |   |
| **DEMOGRAPHICS** |  |  |  |  |   |  |  |  |  |   |
| **Age, [mean ± SD]** | 70.82 ± 12.25 | 58.44 ± 18.27 | 62.11 ± 17.64 | -0.70 | <0.0001 | 70.82 ± 12.25 | 64.76 ± 16.28 | 67.79 ± 14.72 | -0.41 | <0.001 |
| **Age Range, [No. (%)]** |  |  |  |  | <0.0001 |  |  |  |  | <0.001 |
|  18-30 | 19 (0.2) | 2152 (7.9) | 2171 (5.6) | -10.55 |        | 19 (0.2) | 328 (2.8) | 347 (1.5) | -3.91 |        |
|  31-50 | 688 (6.0) | 7201 (26.3) | 7889 (20.3) | -2.93 | 688 (6.0) | 1939 (18.8) | 2627 (11.4) | -1.08 |
|  51-64 | 2662 (23.1) | 7428 (27.2) | 10090 (26.0) | -1.07 | 2662 (23.1) | 3248 (28.2) | 5910 (25.6) | -0.20 |
|  65-74 | 3353 (29.1) | 4495 (16.4) | 7848 (20.2) | -0.29 | 3353 (29.1) | 2420 (21.0) | 5773 (25.0) | 0.33 |
|  75-84 | 3155 (27.4) | 3572 (13.1) | 6727 (17.3) | -0.12 | 3155 (27.4) | 2095 (18.2) | 5250 (22.8) | 0.41 |
|  >=85 | 1656 (14.4) | 2494 (9.1) | 4150 (10.7) | -0.41 | 1656 (14.4) | 1503 (13.0) | 3159 (13.7) | 0.10 |
| **BMI, [mean ± SD]** | 30.30 ± 7.33 | 30.90 ± 7.93 | 30.7 ± 7.7 | 0.07 | <0.001 | 30.30 ± 7.33 | 30.35 ± 7.77 | 30.32 ± 7.55 | 0.00 | 0.53 |
| **BMI Range, [No. (%)]** |  |  |  |  | <0.001 |  |  |  |  | <0.001 |
| <18.5 | 214 (1.9) | 625 (2.3) | 839 (2.2) | -1.12 |  | 214 (1.9) | 302 (2.6) | 516 (2.2) | -0.35 |      |
| 18.5-24.9 | 2540 (22.0) | 5558 (20.3) | 8098 (20.8) | -0.80 | 2540 (22.0) | 2594 (22.5) | 5138 (22.3) | -0.02 |
| 25-29.9 | 3603 (31.2) | 8152 (29.8) | 11755 (30.2) | -0.84 | 3603 (31.2) | 3475 (30.1) | 7078 (30.7) | 0.04 |
| 30+ | 5176 (44.9) | 13007 (47.6) | 18183 (46.8) | -0.95 | 5176 (44.9) | 5158 (44.7) | 10334 (44.8) | 0.00 |
| **Gender, [No. (%)]** |  |  |  |  | 0.01 |  |  |  |  | 0.74 |
|  Female | 5431 (47.1) | 13262 (48.5) | 18693 (48.1) | -0.92 |    | 5431 (47.1) | 5456 (47.3) | 10887 (47.2) | 0.00 |    |
|  Male | 6102 (52.9) | 14080 (51.5) | 20182 (51.9) | -0.86 | 6102 (52.9) | 6077 (52.7) | 12179 (52.8) | 0.00 |
| **Race, [No. (%)]** |  |  |  |  | <0.001 |  |  |  |  | <0.001 |
|  Asian | 248 (2.2) | 457 (1.7) | 705 (1.8) | -0.62 |        | 248 (2.2) | 245 (2.1) | 493 (2.1) | 0.01 |        |
|  Black Not Hispanic | 2296 (19.9) | 5478 (20.0) | 7774 (20.0) | -0.90 | 2296 (19.9) | 2443 (21.2) | 4739 (20.5) | -0.06 |
|  Other | 397 (3.4) | 1291 (4.7) | 1688 (34.0) | -1.25 | 397 (3.4) | 552 (4.8) | 949 (4.1) | -0.33 |
|  White Not Hispanic | 5422 (47.0) | 9201 (33.7) | 14623 (37.6) | -0.54 | 5422 (47.0) | 4266 (37.0) | 9688 (42.0) | 0.24 |
| Hispanic | 2980 (25.8) | 10250 (37.5) | 13230 (34.0) | -1.32 | 2980 (25.8) | 3765 (32.6) | 6745 (29.2) | -0.23 |
| Unknown | 190 (1.6) | 665 (2.4) | 855 (2.2) | -1.34 | 190 (1.6) | 262 (2.3) | 452 (2.0) | -0.32 |
| **Smoking status, [No. (%)]** |  |  |  |  | <0.001 |  |  |  |  | <0.001 |
| Non-smoker | 8984 (77.9) | 20832 (76.2) | 29816 (76.7) | -0.87 |     | 8984 (77.9) | 8871 (76.9) | 17855 (77.4) | 0.01 |     |
| Smoker | 522 (4.5) | 1919 (7.0) | 2441 (6.3) | -1.40 | 522 (4.5) | 646 (5.6) | 1168 (5.1) | -0.21 |
| Unknown | 2027 (17.6) | 4591 (16.8) | 6618 (17.0) | -0.84 | 2027 (17.6) | 2016 (17.5) | 4043 (17.5) | 0.01 |
| **Payer Type, [No. (%)]** |  |  |  |  | <0.0001 |  |  |  |  | <0.001 |
| Blue Cross | 281 (2.4) | 1029 (3.8) | 1310 (3.4) | -1.39 |          | 281 (2.4) | 374 (3.2) | 655 (2.8) | -0.29 |          |
| Charity | 20 (0.2) | 277 (1.0) | 297 (0.8) | -3.45 | 20 (0.2) | 71 (0.6) | 91 (0.4) | -1.35 |
| Commercial  | 33 (0.3) | 183 (0.7) | 216 (0.6) | -1.93 | 33 (0.3) | 68 (0.6) | 101 (0.4) | -0.74 |
| Medicaid | 583 (5.1) | 3426 (12.5) | 4009 (10.3) | -2.01 | 583 (5.1) | 1173 (10.2) | 1756 (7.6) | -0.71 |
| Medicare | 8382 (72.7) | 10797 (39.5) | 19179 (49.3) | -0.25 | 8382 (72.7) | 5914 (51.3) | 14296 (62.0) | 0.35 |
| Others | 2174 (18.9) | 11177 (40.9) | 13351 (34.3) | -1.83 | 2174 (18.9) | 3805 (33.0) | 5979 (25.9) | -0.57 |
| Self-pay | 28 (0.2) | 342 (1.3) | 370 (1.0) | -3.21 | 28 (0.2) | 75 (0.7) | 103 (0.4) | -1.03 |
| Worker's compensation | 32 (0.3) | 111 (0.4) | 143 (0.4) | -1.33 | 32 (0.3) | 53 (0.5) | 85 (0.4) | -0.51 |
| **COMORBIDITIES, [No. (%)]** |  |  |  |  |   |  |  |  |  |   |
| Atrial fibrillation | 2605 (22.6) | 3437 (12.6) | 6042 (15.5) | -0.27 | <0.001 | 2605 (22.6) | 1893 (16.4) | 4498 (19.5) | -0.15 | <0.001 |
| Chronic obstructive pulmonary disease | 2309 (20.0) | 2847 (10.4) | 5156 (13.3) | -0.01 | <0.001 | 2309 (20.0) | 1539 (13.3) | 3848 (16.7) | -0.17 | <0.001 |
| Congestive heart failure | 2802 (24.3) | 3452 (12.6) | 6254 (16.1) | -0.31 | <0.001 | 2802 (24.3) | 1888 (16.4) | 4690 (20.3) | -0.19 | <0.001 |
| Diabetes mellitus | 6934 (60.1) | 9949 (36.4) | 16883 (43.4) | -0.28 | 0.0001 | 6934 (60.1) | 5501 (47.7) | 12435 (53.9) | -0.24 | <0.001 |
| Malignancy | 465 (4.0) | 899 (3.3) | 1364 (3.5) | -0.47 | <0.001 | 465 (4.0) | 409 (3.5) | 874 (3.8) | -0.02 | 0.05 |
| Peripheral artery disease | 743 (6.4) | 901 (3.3) | 1644 (4.2) | -0.04 | <0.001 | 743 (6.4) | 484 (4.2) | 1227 (5.3) | -0.10 | <0.001 |
| Previous myocardial infarction | 1365 (11.8) | 1828 (6.7) | 3193 (8.2) | -0.18 | <0.001 | 1365 (11.8) | 960 (8.3) | 2325 (10.1) | -0.11 | <0.001 |
| Renal disease | 3222 (27.9) | 3885 (14.2) | 7107 (18.3) | -0.15 | <0.001 | 3222 (27.9) | 2159 (18.7) | 5381 (23.3) | -0.21 | <0.001 |
| Stroke (cerebral infarction) | 170 (1.5) | 351 (1.3) | 521 (1.3) | -0.35 | 0.13 | 170 (1.5) | 158 (1.4) | 328 (1.4) | -0.00 | 0.50 |

\*Standardized difference

**Appendix 2.2 Clinical outcomes before and after propensity score matching without replacement between statin users and non-users**

|  |  |  |
| --- | --- | --- |
| **OUTCOMES** | **Before propensity matching, unadjusted multivariate analysis****(n = 38875)** | **After propensity score matching without replacement, unadjusted multivariate analysis****(n = 23066)** |
| **Preexisting use of Statins** |  |  |  | **Preexisting use of Statins** |  |  |  |
| **Yes** | **No** | **Cohort** | **Std dif\*** | **p-value** | **Yes** | **No** | **Cohort**  | **Std dif\*** | **p-value** |
| (n = 11533) | (n = 27342) | (n = 38875) |  |  | **(**n = 11533) | (n = 11533) | (n = 23066) |  |  |
| **PRIMARY, [No.(%)]** |  |  |  |  |   |  |  |  |  |  |
| All-cause mortality | 2032 (17.6) | 3611 (13.2) | 5643 (14.5) | -0.12 | <0.001 | 2032 (17.6) | 2095 (18.2) | 4127 (17.9) | 0.01 | 0.27 |
| **SECONDARY, [No.(%)]** |  |  |   |  |   |  |  |  |  |   |
| In-hospital mortality from COVID-19 | 1430 (12.4) | 2727 (10.0) | 4157 (10.7) | -0.65 | <0.001 | 1430 (12.4) | 1596 (13.8) | 3026 (13.1) | -0.10 | <0.001 |
| Discharge to hospice | 927 (8.0) | 1454 (5.3) | 2381 (6.1) | -0.45 | <0.001 | 927 (8.0) | 817 (7.1) | 1744 (7.6) | 0.12 | <0.001 |
| ICU admission | 4139 (35.9) | 9510 (34.8) | 136469 (35.1) | -0.02 | 0.03 | 4139 (35.9) | 4831 (41.9) | 8970 (38.9) | 0.12 | <0.001 |
| Mild/Moderate ARDS with COVID-19 | 7394 (64.1) | 17832 (65.2) | 25226 (64.9) | -0.90 | 0.11 | 7394 (64.1) | 6702 (58.1) | 14096 (61.1) | 0.09 | <0.001 |
| Severe ARDS with COVID-19 | 2646 (22.9) | 6059 (22.2) | 8705 (22.4) | -0.85 | 0.11 | 2646 (22.9) | 2870 (24.9) | 5516 (23.9) | -0.08 | <0.001 |
| Critical ADRS with COVID-19 | 1493 (12.9) | 3451 (12.6) | 4944 (12.7) | -0.86 | 0.11 | 1493 (12.9) | 1961 (17.0) | 3454 (15.0) | -0.27 | <0.001 |
| Mechanical ventilation | 1737 (15.1) | 3986 (14.6) | 5723 (14.7) | -0.01 | 0.22 | 1737 (15.1) | 2261 (19.6) | 3998 (17.3) | 0.12 | <0.001 |
| Extracorporeal membrane oxygenation | 3 (0.0) | 26 (0.1) | 29 (0.1%) | 0.02 | 0.02 | 3 (0.0) | 8 (0.1) | 11 (0.0) | 0.01 | 0.13 |
| Severe sepsis | 416 (3.6) | 911 (3.3) | 1327 (3.4) | -0.01 | 0.17 | 416 (3.6) | 527 (4.6) | 943 (4.1) | 0.04 | <0.001 |
| Severe sepsis without septic shock | 58 (0.5) | 140 (0.5) | 198 (0.5) | 0.00 | 0.90 | 58 (0.5) | 80 (0.7) | 138 (0.6) | 0.02 | 0.06 |
| Severe sepsis with septic shock | 358 (3.1) | 772 (2.8) | 1130 (2.9) | -0.01 | 0.13 | 358 (3.1) | 447 (3.9) | 805 (3.5) | 0.04 | 0.001 |
| Acute kidney injury | 454 (3.9) | 812 (3.0) | 1266 (3.3) | -0.05 | <0.001 | 454 (3.9) | 469 (4.1) | 923 (4.0) | 0.00 | 0.61 |
| Thrombosis | 32 (0.3) | 99 (0.4) | 131 (0.3) | 0.01 | 0.18 | 32 (0.3) | 64 (0.6) | 96 (0.4) | 0.04 | 0.001 |
| Pulmonary embolism | 43 (0.4) | 102 (0.4) | 145 (0.4) | 0.00 | 0.99 | 43 (0.4) | 45 (0.4) | 88 (0.4) | 0.00 | 0.83 |
| Disseminated intravascular coagulation | 24 (0.2) | 52 (0.2) | 76 (0.2) | -0.00 | 0.71 | 24 (0.2) | 28 (0.2) | 52 (0.2) | 0.00 | 0.57 |
| Hospital length of stay | 9.87 ± 8.94 | 9.30 ± 9.76 | 9.47 ± 9.53 | -0.06 | <0.001 | 9.87 ± 8.94 | 11.25 ± 11.69 | 10.56 ± 10.43 | 0.13 | <0.001 |
| Duration of mechanical ventilation | 8.90 ± 8.94 | 10.46 ± 10.91 | 9.99 ± 10.3 | 0.15 | <0.001 | 8.90 ± 8.94 | 11.09 ± 11.39 | 10.14 ± 10.46 | 0.20 | <0.001 |

 \*Standardized difference

**Appendix 2.3. Logistic Regression of clinical outcomes before and after propensity score matching without replacement in daily statin users**

|  |  |  |
| --- | --- | --- |
| **OUTCOMES** | **Before propensity matching, covariate-adjusted effect size in prehospital statin users****(n = 11533)** | **After propensity score matching without replacement and covariate-adjusted effect size in prehospital statin users****(n = 11533)****(Same as Figure 2 below)** |
|  | **Odds Ratio** | **95% CI** | **Adjusted** **p-value** | **Odds Ratio**  | **95% CI** | **Adjusted** **p-value** |
| **PRIMARY, [No.(%)]** |  |  |   |  |  |  |
| All-cause mortality | 0.78 | 0.73-0.83 | <0.001 | 0.69 | 0.64-0.74 | <0.001 |
| **SECONDARY, [No.(%)]** |  |  |   |   |  |  |
| In-hospital mortality from COVID-19 vs. Normal or Other discharge | 0.74 | 0.69-0.80 | <0.001 | 0.63 | 0.58-0.69 | <0.001 |
| Discharge to hospice vs. Normal or Other Discharge | 0.87 | 0.78-0.98 | 0.01 | 0.79 | 0.68-0.88 | <0.001 |
| ICU admission | 0.84 | 0.80-0.88 | <0.001 | 0.69 | 0.66-0.74 | <0.001 |
| Severe ARDS with COVID-19 vs. Mild/Moderate | 0.9 | 0.85-0.96 | 0.0008 | 0.78 | 0.73-0.84 | <0.001 |
| Critical ARDS with COVID-19 vs. Mild/Moderate | 0.73 | 0.67-0.78 | <.0001 | 0.57 | 0.52-0.61 | <0.001 |
| Mechanical ventilation | 0.74 | 0.70-0.79 | <0.001 | 0.60 | 0.56-0.65 | <0.001 |
| Extracorporeal membrane oxygenation | 0.29 | 0.08-1.07 | 0.06 | 0.37 | 0.08-1.60 | 0.18 |
| Severe sepsis | 0.76 | 0.67-0.86 | <0.001 | 0.66 | 0.57-0.75 | <0.001 |
| Severe sepsis without septic shock | 0.73 | 0.53-1.01 | 0.06 | 0.67 | 0.47-0.96 | 0.03 |
| Severe sepsis with septic shock | 0.76 | 0.67-0.88 | <0.001 | 0.66 | 0.57-0.76 | <0.001 |
| Acute kidney injury | 0.90 | 0.80-1.02 | 0.10 | 0.80 | 0.69-0.92 | 0.002 |
| Thrombosis | 0.59 | 0.39-0.90 | 0.01 | 0.46 | 0.30-0.72 | <0.001 |
| Pulmonary embolism | 0.89 | 0.61-1.30 | 0.55 | 0.99 | 0.64-1.54 | 0.98 |
| Disseminated intravascular coagulation | 0.94 | 0.55-1.58 | 0.80 | 0.79 | 0.44-1.40 | 0.79 |
|  | **Estimate, Standard Error** | **(95% CI)** | **Adjusted p-value** | **Estimate, Standard Error** | **(95% CI)** | **Adjusted p-value** |
| Hospital length of stay | -0.66, 0.11 | (-0.88, -0.44) | <0.001 | -1.88, 0.14 | (-2.15, -1.60) | <0.001 |
| Duration of mechanical ventilation | -1.19, 0.32 | (-1.83, -0.56) | <0.001 | -1.80, 0.35 | (-2.50, -1.11) | <0.001 |

**Appendix 2.4 Propensity Score-Matched, Sampling without Replacement and Covariate-Adjusted Odds Ratio in Preexisting Statin Users (n=11533) (same as right column above)**



 \*Normal or Other Discharge is the reference category, ‡Mild/Moderate ARDS with COVID-19 is the reference category, CI – confidence interval. NOTE: Figure 2 is the same as the comparison table above