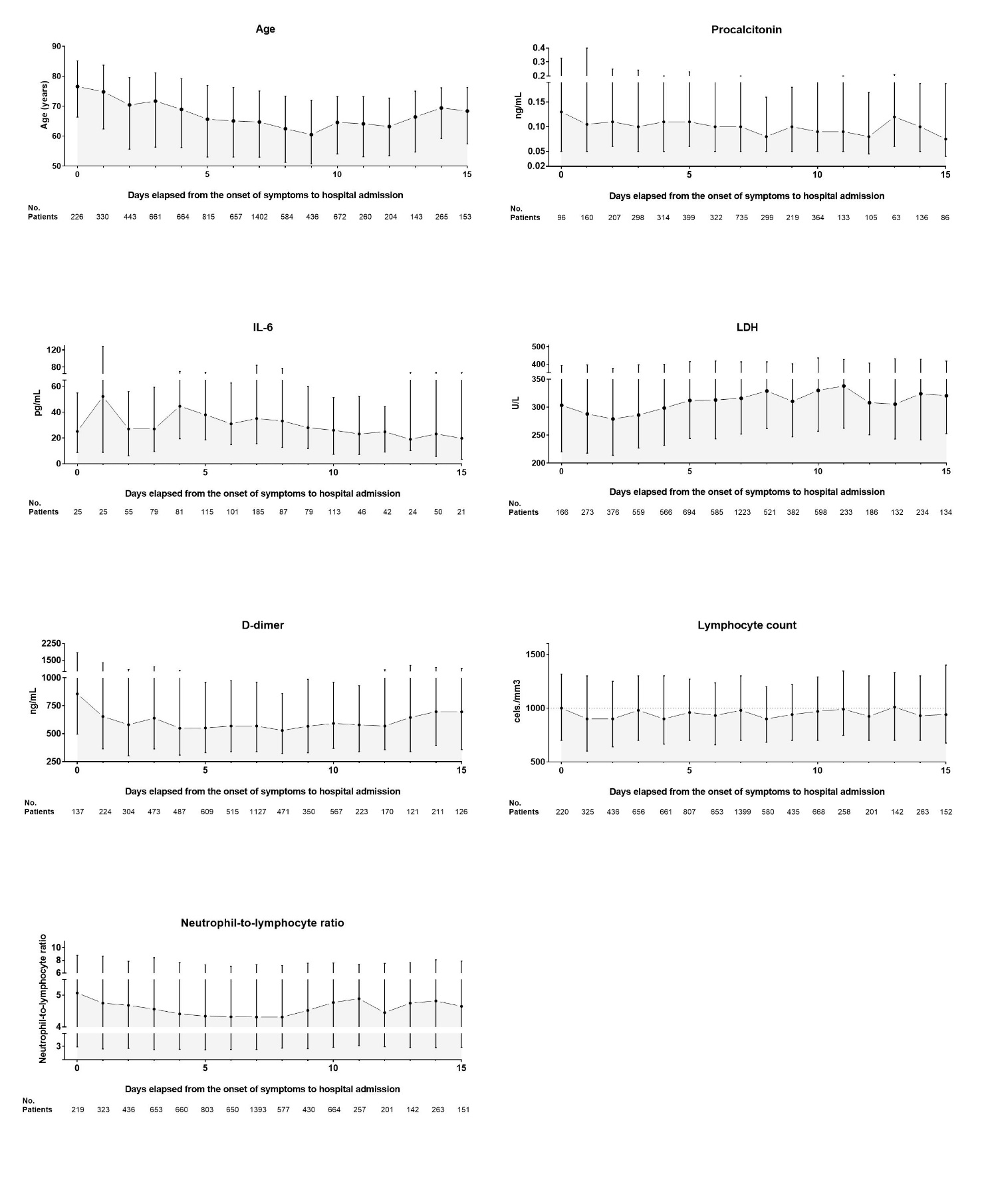
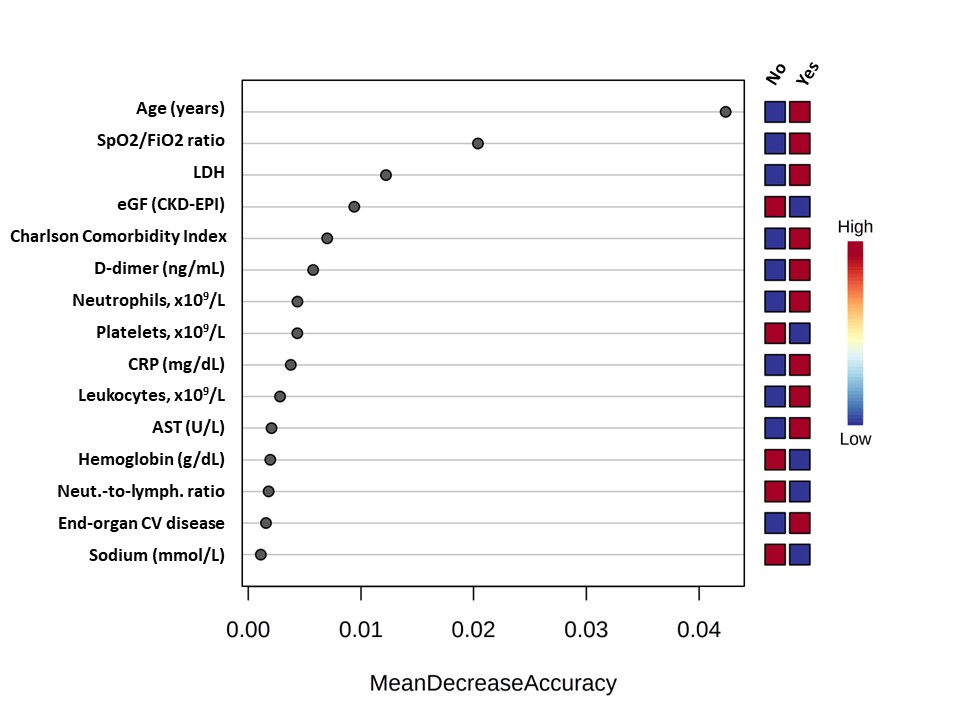
**Appendix – Figures**

**Appendix figure 1. Evolution of clinical and laboratory test values upon hospital admission according to days elapsed from symptoms onset to hospital admission.**



**Appendix figure 2. Random Forest plot.**

AST = Aspartate aminotransferase; CRP = C-reactive protein; CV = cardiovascular; eGFR (CKD-EPI) = estimated glomerular filtration rate measured using the Chronic Kidney Disease Epidemiology Collaboration equation; LDH = Lactate dehydrogenase; Neut.-to-lymph. ratio = Neutrophil-to-lymphocyte ratio; SpO2/FiO2 = Oxygen saturation to fraction of inspired oxygen ratio.



**Appendix – Tables**

|  |  |  |  |  |
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| Appendix table 1. Relevant drugs received during hospitalization | | | |  |
|  | **Total**  (n = 7915) | **Early-presenting**  (n = 2324) | **Late-presenting**  (n = 5591) | ***p*** |
| LPVr, no./total no. (%) | 5371/7855 (68.4) | 1432/867 (62.3) | 3939/5556 (70.9) | < .001 |
| Remdesivir, no./total no. (%) | 42/7781 (0.5) | 8/2280 (0.4) | 34/5501 (0.6) | .143 |
| Immunotherapies (tocilizumab, anakinra, or both), no./total no. (%) | 801/7734 (10.4) | 197/2256 (8.7) | 604/5478 (11.0) | .003 |
| Tocilizumab | 782/7832 (10.0) | 191/2293 (8.9) | 591/5539 (10.7) | .002 |
| Anakinra | 41/7735 (0.5) | 10/2256 (0.4) | 31/5479 (0.6) | .500 |
| Corticosteroids, no./total no. (%) | 2684/7825 (34.3) | 770/2290 (33.6) | 1914/5535 (34.6) | .418 |
| Hydroxychloroquine, no./total no. (%) | 7019/7869 (89.2) | 1957/2307 (84.8) | 5062/5562 (91.0) | < .001 |
| Anticoagulants (oral anticoagulants or LMWH), no./total no. (%) | 6606/7756 (85.2) | 5024/5926 (84.8) | 1582/1830 (86.4) | .079 |
| Oral anticoagulants1 | 222/7810 (2.8) | 88/2287 (3.8) | 134/5523 (2.4) | .001 |
| LMWH2 | 6621/7810 (84.8) | 1884/2282 (82.6) | 4737/5528 (85.7) | .001 |
| LPVr = Lopinavir/Ritonavir; LMWH = low-molecular-weight heparin  1 Either vitamin K antagonists or direct oral anticoagulants.  2 Either at a prophylactic or anticoagulant dose. | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Appendix table 2. Outcomes during and after hospitalization | | | |  |
|  | **Total**  (n = 7915) | **Early-presenting**  (n = 2324) | **Late-presenting**  (n = 5591) | ***p*** |
| In-hospital mortality, no./total no. (%) | 1237/7915 (15.6) | 508/2324 (21.9) | 729/5591 (13.0) | < .001 |
| Moderate or severe acute respiratory distress syndrome (SpO2/FiO2 < 235 or PaO2/FiO2 < 200), no./total no. (%) | 1817/7858 (23.1) | 611/2304 (26.5) | 1206/5554 (21.7) | < .001 |
| Intensive care unit admission, no./total no. (%) | 732/7902 (9.3) | 205/2318 (8.8) | 527/5584 (9.4) | .407 |
| Length of hospital stay (days), median (IQR) | 9 (6-14)  7915 | 9 (6-15)  2324 | 9 (6-13)  5591 | < .001 |
|  | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Appendix table 3. Univariate Cox regression analysis of in-hospital mortality | | | | |
|  | HR | Lower limit  (CI 95%) | Upper limit  (CI 95%) | *p* |
| Baseline characteristics of patients hospitalized with COVID-19 | | | | |
| Days elapsed from the onset of symptoms to hospital admission | 0.935 | 0.920 | 0.950 | < .001 |
| Age (each year) | 1.077 | 1.071 | 1.082 | < .001 |
| Sex (male) | 1.319 | 1.171 | 1.485 | < .001 |
| BMI | 1.028 | 1.013 | 1.043 | < .001 |
| Current smoker | 1.013 | 0.789 | 1.302 | .917 |
| Race |  |  |  |  |
| Caucasian | 2.756 | 2.122 | 3.580 | < .001 |
| Hispanic | 0.382 | .287 | .508 | < .001 |
| African | 0.270 | 0.067 | 1.080 | .018 |
| Asian | 0.440 | 0.142 | 1.365 | .100 |
| Charlson Comorbidity Index score | 1.198 | 1.171 | 1.226 | < .001 |
| Charlson Comorbidity Index ≥ 1 | 2.396 | 2.116 | 2.714 | < .001 |
| Functional status, moderately dependent | 3.240 | 2.781 | 3.774 | < .001 |
| Hypertension | 2.397 | 2.122 | 2.707 | < .001 |
| Any vascular disease (coronary artery disease, stroke or TIA, or PAD) | 2.030 | 1.784 | 2.310 | < .001 |
| Coronary artery disease2 | 2.048 | 1.743 | 2.406 | < .001 |
| Previous stroke or transient ischemic attack | 1.791 | 1.465 | 2.190 | < .001 |
| Peripheral artery disease | 2.107 | 1.714 | 2.590 | < .001 |
| Congestive heart failure | 2.519 | 2.123 | 2.989 | < .001 |
| Atrial fibrillation | 2.299 | 1.983 | 2.664 | < .001 |
| Diabetes mellitus | 1.715 | 1.514 | 1.943 | < .001 |
| Diabetes with diabetes-related complications | 2.153 | 1.774 | 2.613 | < .001 |
| Insulin-dependent diabetes | 1.886 | 1.549 | 2.297 | < .001 |
| COPD | 2.161 | 1.846 | 2.530 | < .001 |
| Asthma | 0.770 | 0.615 | 0.963 | .018 |
| Obstructive sleep apnea | 1.184 | .968 | 1.449 | .109 |
| Chronic kidney disease | 2.494 | 2.096 | 2.966 | < .001 |
| Advanced chronic kidney disease | 2.526 | 2.123 | 3.006 | < .001 |
| Patient on dialysis | 1.739 | 1.118 | 2.706 | .024 |
| Chronic liver disease (any stage) | 1.436 | 1.118 | 1.843 | .005 |
| Advanced chronic liver disease | 1.411 | .874 | 2.278 | .182 |
| Malignancy | 1.816 | 1.562 | 2.112 | < .001 |
| Solid tumor | 1.685 | 1.425 | 1.992 | < .001 |
| Metastatic solid tumor | 1.577 | 1.148 | 2.166 | .005 |
| Blood cancer | 2.060 | 1.556 | 2.726 | < .001 |
| HIV infection | 0.686 | 0.326 | 1.443 | .290 |
| Systemic rheumatic diseases | 1.544 | 1.146 | 2.080 | .004 |
| Solid organ transplantation | 1.569 | 1.064 | 2.315 | .034 |
| Chronic use of glucocorticoids | 2.146 | 1.761 | 2.615 | < .001 |
| Chronic use of anticoagulants | 2.529 | 2.199 | 2.908 | < .001 |
| Chronic use of antiplatelet therapy | 1.947 | 1.708 | 2.219 | < .001 |
| Chronic use of statins | 1.668 | 1.490 | 1.868 | < .001 |
| Chronic use of ACE inhibitors | 1.664 | 1.460 | 1.896 | < .001 |
| Chronic use of ARBs | 1.478 | 1.304 | 1.674 | < .001 |
| Symptoms, vital signs, and laboratory tests at admission | | | | |
| Dyspnea | 1.672 | 1.478 | 1.892 | < .001 |
| Cough | 0.763 | .672 | .867 | < .001 |
| Anosmia or dysgeusia | 0.318 | .220 | .461 | < .001 |
| Arthralgia or myalgia | 0.549 | .479 | .629 | < .001 |
| Headache | .441 | .348 | .558 | < .001 |
| Abdominal pain | 1.024 | .817 | 1.283 | 0.838 |
| Diarrhea | .702 | .608 | .810 | < .001 |
| Crackles | 1.511 | 1.341 | 1.703 | < .001 |
| Wheezing | 1.626 | 1.342 | 1.971 | < .001 |
| Vital signs (no./total no. (%) or median (IQR)) | | | | |
| Temperature on admission | 1.059 | 0.999 | 1.122 | 0.550 |
| Systolic blood pressure | 1.000 | 0.998 | 1.003 | 0.784 |
| Heart rate | 0.999 | 0.996 | 1.003 | 0.704 |
| Altered mental status | 3.397 | 2.940 | 3.925 | < .001 |
| Respiratory rate ≥ 20 breaths/min | 2.571 | 2.293 | 2.883 | < .001 |
| SpO2/FiO2 | 0.995 | 0.995 | 0.996 | < .001 |
| qSOFA ≥ 2 | 3.385 | 2.903 | 3.947 | < .001 |
| Admission studies (no./total no. (%) or median (IQR)) | | | | |
| Lymphocyte count, x 109/L | 0.990 | 0.961 | 1.019 | 0.489 |
| Neutrophil count, x 109/L | 1.034 | 1.028 | 1.039 | < .001 |
| Neutrophil-to-lymphocyte ratio | 1.008 | 1.007 | 1.010 | < .001 |
| Platelet count, x 109/L | 0.998 | 0.998 | 0.999 | < .001 |
| Hemoglobin, g/dL | 0.887 | 0.861 | 0.913 | < .001 |
| Sodium (mmol/L) | 0.985 | 0.971 | 0.999 | 0.033 |
| Creatinine (mg/dL) | 1.330 | 1.285 | 1.375 | < .001 |
| eGFR (CKD-EPI) | 0.972 | 0.970 | 0.974 | < .001 |
| LDH (U/L) | 1.001 | 1.001 | 1.001 | < .001 |
| AST (U/L) | 1.001 | 1.001 | 1.002 | < .001 |
| ALT (U/L) | 0.999 | 0.998 | 1.001 | 0.197 |
| AST/ALT ratio | 1.257 | 1.219 | 1.296 | < .001 |
| Creatine kinase (U/L) | 1.000 | 1.000 | 1.000 | 0.211 |
| Venous lactate > 2 mmol/L | 1.480 | 1.259 | 1.741 | < .001 |
| Procalcitonin (ng/mL) | 1.217 | 1.171 | 1.264 | < .001 |
| Ferritin (ng/mL) | 1.000 | 1.000 | 1.000 | < .001 |
| CRP (mg/dL) | 1.038 | 1.033 | 1.043 | < .001 |
| Interleukin 6 (pg/mL) | 1.001 | 1.000 | 1.001 | 0.027 |
| D-dimer (ng/mL) | 1.000 | 1.000 | 1.000 | < .001 |
| Fibrinogen (mg/dL) | 1.000 | 1.000 | 1.000 | 0.592 |
| Activated partial thromboplastin time (s) | 1.012 | 1.008 | 1.017 | < .001 |
| Lung infiltrates on chest x-ray | 1.395 | 1.133 | 1.718 | 0.002 |
| ACE = Angiotensin-converting enzyme; ARB = Angiotensin II receptor blocker; BMI = Body mass index, calculated as the ratio of weight (kg)/height2 (m); COPD = Chronic obstructive pulmonary disease; HIV = Human immunodeficiency virus. | | | | |