***Supplemental Material***

**Higher intensity thromboprophylaxis regimens and pulmonary embolism in critically ill COVID-19 patients**

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**Methods**

*Data collection*

ICU admissions were recorded daily to provide real-time data to the Health authorities about bed occupancy rates and use of mechanical ventilation. The study started on March 10 when the first COVID-19 patient was admitted and ended on April 20, 2020. We collected demographics, comorbidities, including previous venous thromboembolic disease and obesity (1), patients’ characteristics on admission and on the day of CTPA; CTPA was obtained by using a commercially available 64-detector row scanner (Somatom Sensation 64; Siemens Healthcare, Forchheim, Germany) after the injection of non-ionic iodinated intravenous contrast media (400mg I/mL, Iomeron 400, Bracco, Ferentino, Italy) at the rate of 4 mL/s via a central line using; a breath-hold during inspiration using the ventilator was applied whenever possible to facilitate adequate images acquisition and reconstruction. The images were reviewed by one radiologist (PAG). Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, C-reactive protein (CRP), lactate dehydrogenase, ferritin and blood gas analyses as well as respiratory parameters. Cardiac echography and lower limb compression ultrasonography results were also collected, whenever available. The risk of pulmonary embolism (PE) was calculated using the score proposed by Wells et al. (2); acute kidney injury (AKI) was defined according to the Kidney Disease Improving Global Outcomes definitions (3). Data were entered into a computerized database and cross-checked. No missing data were reported.

*Patients management*

Patients diagnosed of COVID-19 received oral hydroxychloroquine (400 mg q12h orally on the first day followed by 200 mg q12h orally until day 10) in association with an antiviral drug (i.e. remdesivir, lopinavir-ritonavir or oseltamivir). Standard care included, as necessary, non-invasive ventilation, mechanical ventilation, vasopressor therapy, renal-replacement therapy (RRT) and extracorporeal membrane oxygenation (ECMO). All patients were monitored with an arterial catheter and a central venous catheter.

In all patients, thromboprophylaxis initially consisted of subcutaneous enoxaparin 4000 IU once daily; however, after the first cases of PE were detected, enoxaparin dose was increased to subcutaneous 4000 IU twice daily, even in those patients with AKI. We defined than the patients as receiving “standard thromboprophylaxis” (i.e. subcutaneous enoxaparin 4000 IU s once daily) or “high dose thromboprophylaxis” (i.e. subcutaneous enoxaparin 4000 IU twice daily or continuous therapeutic infusion of unfractioned heparin in case of RRT and/or ECMO). Monitoring of thromboprophylaxis or anticoagulation was based on daily anti-Xa activity (target: 0.35-0.50 for thromboprophylaxis and 0.50-0.70 for therapeutic anticoagulation); however, anti-Xa monitoring was implemented in clinical practice after the first cases of COVID-19 were admitted to the ICU. In case of thromboprophylaxis, anti-Xa activity was assessed twice a week; if the values were outside the target ranges, enoxaparin regimen was modified, accordingly. In case of therapeutic anticoagulation, anti-Xa activity was assessed at least one daily; in addition, it was assessed also after each change in anticoagulation regimens. No patient was treated with pneumatic compression.

*Statistical Analysis*

Statistical analyses were performed using the SPSS 24.0 for Windows NT software package (SPSS Inc. 2004, Chicago, USA). Descriptive statistics were computed for all study variables. Discrete variables were expressed as counts (percentage) and continuous variables as median [25th–75th percentiles]. Demographics and clinical differences between groups (PE vs. no-PE) were assessed using a Fisher’s exact test, Student’s T-test or Mann-Whitney U test, as appropriate. The discriminative ability of D-dimers to predict PE was evaluated using receiver operating characteristic (ROC) curves with the corresponding area under the curve (AUROC). We analyzed the occurrence of PE in patients receiving standard or high dose thromboprophylaxis. Odds ratios (OR) with 95% confidence intervals (CI) were computed. Adjusted OR was reported by performing a multivariate analysis, which included: age, immunosuppressive agents, hypertension, obesity, D-dimers on admission, Wells score, time from admission to CT-scan, C-reactive protein on the day of CTPA and use of prone positioning. Other variables, such as D-Dimers on the day of CTPA, tidal volume or volume ventilation on the day of CTPA, were not included because considered as the result of EP (i.e. thrombus formation and dead space). A p < 0.05 was considered as statistically significant.

**References**

1. Apovian CM. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care* 2016; 22(7 Suppl):s176-85.
2. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000; 83(3):416-20.
3. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017; 13(4):241-257.

**Table 1.** Characteristics of study population, according to the diagnosis of acute pulmonary embolism (PE).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All Patients** **(n=40)** | **PE****(n=13)** | **Non-PE****(n=27)** | ***p value*** |
| **Age, years** | 61 [57-66] | 58 [53-61] | 63 [58-68] | 0.09 |
| **Male Gender, n (%)** | 28 (70) | 11 (85) | 17 (63) | 0.27 |
|  |  |  |  |  |
| **Hypertension, n (%)** | 28 (70) | 10 (77) | 18 (67) | 0.72 |
| **Coronary Artery Disease, n (%)** | 5 (13) | 2 (15) | 3 (11) | 1.00 |
| **Diabetes, n (%)** | 5 (13) | 1 (8) | 4 (15) | 1.00 |
| **COPD/Asthma, n (%)** | 10 (25) | 1 (8) | 9 (33) | 0.12 |
| **Cerebrovascular Disease, n (%)** | 1 (3) | - | 1 (4) | 1.00 |
| **Chronic Renal Disease, n (%)**  | 1 (3) | - | 1 (4) | 1.00 |
| **Liver Cirrhosis, n (%)** | 1 (3) | - | 1 (4) | 1.00 |
| **Smoking, n (%)** | 6 (15) | 2 (15) | 4 (15) | 1.00 |
| **Cancer, n (%)** | 5 (13) | - | 5 (19) | 0.15 |
| **Immunosuppressive agents, n (%)** | 2 (5) | 2 (15) | - | 0.10 |
| **Obesity, n (%)** | 16 (40) | 6 (46) | 10 (37) | 0.73 |
| **Previous venous thromboembolism, n (%)** | - | - | - | - |
|  |  |  |  |  |
| **Positive RT-PCR on NP swab, n (%)** | 38 (95) | 11 (85) | 27 (100) | 0.10 |
| **Positive RT-PCR on BAL, n (%) #** | 22 (88) | 7 (100) | 15 (83) | 0.53 |
|  |  |  |  |  |
| **Temperature on ICU admission, °C** | 38 [37.5-38.6] | 38.3 [37.4-39.0] | 38.0 [37.5-38.6] | 0.65 |
| **WBC on admission, n/mm3** | 10225 [7910-12825] | 7850 [7020-9280] | 11800 [9165-13790] | 0.003 |
| **Lymphocytes on admission, n/mm3** | 805 [658-1095] | 720 [650-830] | 880 [708-1140] | 0.19 |
| **Hemoglobin on admission, g/dL** | 12.8 [11.1-14.3] | 12.1 [10.5-13.9] | 13.0 [11.7-14.6] | 0.29 |
| **Platelets on admission, n\*103/mm3** | 247 [200-344] | 245 [213-285] | 249 [199-361] | 0.89 |
| **C-Reactive Protein on admission, mg/L** | 190 [130-253] | 150 [130-300] | 199 [135-235] | 0.93 |
| **D-Dimers on admission, ng/mL** | 1896 [1131-3248] | 1456 [1208-2744] | 2100 [1073-3509] | 0.75 |
| **LDH on admission, IU/L** | 487 [405-572] | 484 [360-560] | 490 [424-790] | 0.30 |
| **Troponin T on admission, ng/L** | 25 [16-40] | 28 [16-56] | 24 [16-36] | 0.49 |
| **PaO2/FiO2 on admission** | 130 [94-168] | 140 [118-181] | 128 [91-148] | 0.16 |
|  |  |  |  |  |
| **Onset of symptoms to CT-scan, days** | 12 [9-16] | 13 [9-16] | 12 [9-15] | 0.53 |
| **Admission to CT-scan, days** | 7 [4-8] | 5 [4-7] | 7 [4-9] | 0.82 |
| **Thromboprophylaxis at CT-scan***Standard doses**High doses* | 40 (100)*22**18* | 13 (100)*11**2* | 27 (100)*11**16* | 0.02 |
| **Wells score at CT-scan** | 3 [3-4] | 3 [3-3] | 3 [3-4] | 0.84 |
| **Temperature at CT-scan, °C** | 38.3 [37.7-38.9] | 38.5 [37.9-39.1] | 38.2 [37.7-38.7] | 0.17 |
| **WBC at CT-scan, n/mm3** | 12085 [8828-17863] | 11710 [9100-18900] | 12100 [8825-17695] | 0.82 |
| **Lymphocytes at CT-scan, n/mm3** | 925 [750-1358] | 860 [550-1680] | 990 [795-1270] | 0.67 |
| **Platelets at CT-scan, n\*103/mm3** | 311 [201-428] | 331 [296-441] | 291 [198-391] | 0.24 |
| **C-Reactive Protein at CT-scan, mg/L** | 215 [145-300] | 280 [210-330] | 190 [120-265] | 0.03 |
| **aPTT at CT-scan** | 28 [25-30] | 26 [25-29] | 28 [26-30] | 0.65 |
| **INR at CT-scan** | 1.07 [1.04-1.12] | 1.08 [1.05-1.10] | 1.07 [1.03-1.12] | 0.71 |
| **D-Dimers at CT-scan, ng/mL** | 4151 [1567-9010] | 8280 [5976-11483] | 2302 [1327-5750] | <0.01 |
| **LDH at CT-scan, IU/L** | 403 [357-581] | 418 [352-489] | 396 [359-627] | 0.86 |
| **Ferritin at CT-scan, mcg/L** | 965 [666-1712] | 1180 [738-2100] | 925 [607-1361] | 0.19 |
| **Troponin T at CT-scan, ng/L** | 30 [15-51] | 38 [15-52] | 28 [16-50] | 0.69 |
| **PaO2/FiO2 at CT-scan** | 105 [82-124] | 122 [83-145] | 105 [79-120] | 0.38 |
| **FiO2 at CT-scan, %** | 60 [50-90] | 60 [50-90] | 60 [50-85] | 0.84 |
| **PaCO2 at CT-scan, mmHg** | 51 [43-59] | 59 [54-61] | 47 [42-56] | 0.09 |
| **Tidal Volume at CT-scan, mL** | 420 [375-450] | 430 [420-450] | 420 [350-439] | 0.10 |
| **Minute Ventilation at CT-scan, L/min** | 10.7 [10.0-12.0] | 11.8 [10.5-14.2] | 10.5 [9.5-11.8] | 0.02 |
| **PEEP at CT-scan, cmH2O** | 10 [10-12] | 10 [10-12] | 10 [10-12] | 0.75 |
| **Lactate at CT-scan, mmol/L** | 1.2 [1.0-1.5] | 1.0 [1.0-1.2] | 1.2 [1.0-1.5] | 0.15 |
|  |  |  |  |  |
| **Non-invasive ventilation during ICU stay, n (%)** | 21 (53) | 6 (46) | 15 (56) | 0.74 |
| **Prone Positioning during ICU stay, n (%)** | 34 (85) | 10 (77) | 24 (89) | 0.37 |
| **V-V ECMO during ICU stay, n (%)** | 9 (23) | 2 (15) | 7 (26) |  0.69 |
| **Tracheostomy during ICU stay, n (%)** | 3 (8) | 2 (15) | 1 (4) | 0.24 |
| **Vasopressors during ICU stay, n (%)** | 36 (90) | 10 (77) | 26 (96) |  0.09 |
|  |  |  |  |  |
| **Acute Kidney Injury, n (%)** | 27 (68) | 10 (77) | 17 (63) |  0.48 |
| **Renal Replacement Therapy, n (%)** | 10 (25) | 4 (31) | 6 (22) |  0.70 |
| **Hydroxychloroquine, n (%)** | 40 (100) | 13 (100) | 27 (100) |  1.00 |
| **Remdesivir, n (%)** | 4 (10) | 3 (23) | 1 (4) |  0.09 |
| **Lopinavir/Ritonavir, n (%)** | 19 (48) | 7 (54) | 12 (44) |  0.74 |
| **Oseltamivir, n (%)** | 7 (18) | 1 (8) | 6 (22) |  0.39 |
|  |  |  |  |  |
| **ICU Mortality, n (%)** | 20 (50) | 6 (46) | 14 (52) |  1.00 |
| **ICU Discharge, n (%)** | 16 (40) | 6 (46) | 10 (37) | 0.73 |
| **Follow-up after ICU admission, days** | 27 [15-33] | 32 [28-36] | 23 [14-31] | 0.01 |

ICU = intensive care unit; COPD = chronic obstructive pulmonary disease; RRT = renal replacement therapy; RT-PCR = real time polymerase chain reaction; NP = naso-pharyngeal; BAL = broncho-alveolar lavage; WBC = white blood cells; LDH = lactate dehydrogenase; aPTT = activated partial thromboplastin time; INR = international normalized ratio; PEEP = positive end-expiratory pressure; V-V ECMO = veno-venous extracorporeal membrane oxygenation;

# n = 25 (7 in the PE and 18 in the non-PE group)