COVID-19 quarantine and acute pulmonary embolism

Embolia pulmonar aguda durante la cuarentena por COVID-19

To the Editor,

As the COVID-19 outbreak has increased worldwide, many countries have imposed lockdown restrictions to movement. Since 14 March 2020 in Spain, most people have been confined to home with an absolute ban on outdoor physical activity.

While the number of in-hospital positive COVID-19 patients was growing exponentially, there was a drastic decline in non–COVID-19 emergency patients with a drop of nearly 40% of ST-elevation myocardial infarction patients worldwide.[1]

Although the number of non–COVID-19 emergency patients decreased, there was an increase in the number of pulmonary embolisms (PE) in non–COVID-19 patients. In this scenario, the role of thromboprophylaxis is uncertain.[2]

From 14 March to 18 April 2020, in our center we diagnosed 17 acute PE with computed tomography pulmonary angiography.

Table 1

Characteristics of patients with acute pulmonary embolism lockdown subgroups (14 March to 18 April, 2020) vs the no-lockdown period (14 March to 18 April, 2019)

	Lockdown group N = 17	No-lockdown group N = 9	P
Female sex, %	52.9	66.7	.500
Age, y	68 [56-81]	83 [75-87]	.012
≥ 65 y, %	55.8	88.9	.114
Hypertension, %	52.9	88.9	.067
Diabetes mellitus, %	17.6	55.6	.046
Hypercholesterolemia, %	29.4	100	.001
Current smoker, %	23.5	33.3	.592
BMI, kg/m^2	25 [23-29]	29 [28-30]	.037
Heart rate, bpm	97 [85-114]	99 [75-125]	.403
Hemoptysis, %	0	11	.161
D-dimer	4695 [2310-18 649]	15 059 [6800-19 000]	.307
DVT signs or symptoms, %	29.4	55.6	.192
Previous DVT, %	23.5	0	.114
Surgery in previous 4 wk or immobilization at least 4 d, %	11.8	22.2	.161
Active malignant condition, %	17.6	22.2	.778
Mental disorders, %	35.3	44.4	.648
*PE risks factors**	3 [0.6-3]	4 [3-4]	.011
Geneva score, points	6 [6-9]	11 [6-14]	.089
Wells score, points	4.5 [3-6]	7.5 [4.5-7.5]	.159
Padua score, points	3 [1-4]	2 [1-4]	.216
Padua score for VTE including immobility as a risk factor in COVID–19-related lockdown group, points	5 [4-7]	2 [1-4]	.019
Geneva risk for PE			.038
Low (0-3 points), %	12	0	
Moderate (4-10 points), %	70	44	
High (> 10 points), %	18	56	
Wells risk for PE			.051
Low (0-1 points), %	0	0	
Moderate (2-6 points), %	82	44	
High (> 6 points), %	18	56	
Padua score risk for VTE			.102
Low (0-3 points), %	76.5	44.4	
High (≥ 4 points), %	23.5	55.6	
Padua score risk for VTE including immobility as a risk factor in the COVID–19-related lockdown group			.272
Low (0-3 points), %	23.5	44.4	
High (≥ 4 points), %	76.5	55.6	

BMI, body mass Index; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Data are expressed as No. (%), or median [interquartile range].

PE risks factors*: **Strong risk factors:** fracture of lower limb, hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months), hip or knee replacement, major trauma, myocardial infarction (within previous 3 months), previous VTE, spinal cord injury. **Moderate risk factors:** arthroscopic knee surgery, autoimmune diseases, blood transfusion, central venous lines, intravenous catheters and leads, chemotherapy, congestive heart failure or respiratory failure, erythropoiesis-stimulating agents, hormone replacement therapy, in vitro fertilization, oral contraceptive therapy, postpartum period, infection (specifically pneumonia, urinary tract infection, and human immunodeficiency virus, inflammatory bowel disease, cancer (highest risk in metastatic disease), paralytic stroke, superficial vein thrombosis, and thrombophilia. **Weak risk factors:** bed rest > 3 days, diabetes mellitus, hypertension, immobility due to sitting, increasing age, laparoscopic surgery, obesity, pregnancy, and varicose veins.

The number of PE cases clear increased compared with 2019 (average of 8 PE cases per month in 2019, with 9 cases from 14 March to 18 April, 2019). To examine whether there was a quarantine-related effect in the increased rate of acute PE, we compared the characteristics of acute PE patients by lockdown subgroups (ie, 14 March to 18 April, 2020) vs the no-lockdown period (ie, 14 March to 18 April, 2019) (table 1) in a single-center observational case series study.

Comparison between categorical data was performed using the chi-square test or the McNemar test for paired data and the Mann-Whitney *U*-test for ordinal and continuous variables. Statistical analysis was performed with SPSS version 21 (SPSS Inc, Chicago, IL) and a value of $P < .05$ was considered the threshold for statistical significance.

Patients in the PE lockdown period were younger (median age, 68 years; interquartile range [IQR][56-81] versus 83 [75-87] years;

Table 2
Patients with acute pulmonary embolism during the COVID–19-related lockdown period (14 March to 18 Abril, 2020) and during the no-lockdown period (14 March to 18 Abril, 2019)

Year	Sex	Age	BMI	Smoker	HTA	Hyper-choleste-rolemia	Diabetes	Mental disorder	PE risk factors	COVID-19	d-dimer	RV dysfunction	DVT Doppler US	DVT Signs/ symptoms	Death
2019	Female	73	34	Yes	Yes	No	No	No	-Active lung cancer -Obesity	-	-	Yes	-	Yes	Yes
2019	Female	87	29	No	Yes	Yes	Yes	Anxiety	-Reduced mobility -Overweight	-	17 051	No	Yes	Yes	No
2019	Male	44	28	No	Yes	Yes	Yes	No	-Rheumatoid arthritis under treatment -Overweight	-	7485	No	Yes	Yes	No
2019	Female	86	29	No	Yes	Yes	No	No	-Overweight -Advanced age	-	15 059	No	Yes	Yes	No
2019	Male	87	30	Former smoker	Yes	Yes	No	No	-Vertebral fracture -Obesity	-	1474	No	-	No	Yes
2019	Female	84	31	Yes	Yes	Yes	Yes	No	-Hip fracture -Obesity	-	-	Yes	-	No	No
2019	Female	75	32	Yes	Yes	Yes	Yes	Parkinson Anxiety	- Obesity	-	6800	No	No	No	No
2019	Male	76	30	No	No	Yes	Yes	Bipolar disorder	-No active colorectal cancer -Obesity	-	19 000	Yes	Yes	No	No
2019	Female	83	25	No	Yes	Yes	No	Psychotic disorder Dementia	- Active colorectal cancer	-	71 649	No	-	Yes	No
2020	Male	56	32	No	Yes	Yes	No	Anxiety	-DVT under LMWH treatment -Obesity	No	1117	No	Yes	Yes	No
2020	Female	69	24	Yes	No	No	No	No	-Previous PE with DVT	No	2800	No	Yes	Yes	No
2020	Female	43	23	No	No	No	No	No	-Oral contraceptive	No	4695	No	No	No	No
2020	Female	34	25	No	No	No	No	Psychotic disorders	-Psychotic attack -Bedridden -Obesity	No	63 409	Yes	No	No	No
2020	Male	56	33	No	No	No	No	No	-Previous DVT -Obesity	No	2639	No	Yes	Yes	No
2020	Male	62	17	Yes	No	No	No	No	-Orchiepididymitis -Bedridden	No	-	Yes	No	No	No
2020	Male	83	21	Former smoker	No	No	No	No	-Advanced age	No	18 649	Yes	-	No	No
2020	Female	56	23	Yes	No	Yes	No	Psychotic disorders	No	No	27 361	No	Yes	No	No
2020	Male	81	28	No		No	Yes	No	-Chronic lymphocytic leukemia	Positive	6057	No	-	No	No
2020	Female	70	29	No	Yes	No	No	Depression	-Overweight	No	3685	No	No	No	No
2020	Female	68	30	No	Yes	No	Yes	No	-Active breast cancer -Obesity	No	2006	No	-	No	No
2020	Male	67	28	No	Yes	No	No	No	-Previous PE with DVT	No	15 252	Yes	No	No	No
2020	Male	85	29	No	Yes	No	No	No	-Advanced age -Overweight	No	2310	Yes	No	No	Yes
2020	Female	70	17	No	Yes	Yes	No	No	-Ventricular dysfunction with heart failure	No	800	Yes	No	No	No
2020	Female	83	23	No	Yes	Yes	Yes	Dementia	-COVID-19 infection discharged with negative PCR -Advanced age	Discharged for COVID-19 infection 1 week before	13 340	No	-	No	No
2020	Female	71	32	No	No	Yes	No	Parkinson's - Dementia	-Parkinson's Dementia disease -Obesity	No	-	Yes	-	No	No
2020	Male	65	25	Yes	Yes	No	No	No	Active pancreatic cancer under LMWH treatment	No	137 741	No	-	No	No

BMI, body mass index; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PCR, polymerase chain reaction; PE, pulmonary embolism; PHT, pulmonary hypertension; RV dysfunction, right ventricular dysfunction.

P = .012), with a lower prevalence of diabetes mellitus (17.6% vs 55.6%; P = .046), hypercholesterolemia (29.4% vs 100%; P = .001), and lower body mass index) (median body mass index = 25 [23-29] vs 29 [28-30]; P = .037).

There were numerous environmental and patient-related predisposing venous thromboembolism (VTE) risk factors that we summarize in table 1, as described in the European Society of Cardiology guidelines for acute PE.[3]

Patients in the COVID–19-related lockdown period had a lower number of PE risk factors (median PE risk factors, 3 [0.6-3] vs 4 [3-4]; P = .011) (table 1). COVID–19-related lockdown patients also had a significantly lower PE risk when assessed with the Wells and Geneva risk scores as categorical (low, moderate, and high risk) variables.

Sixteen patients had VTE risk factors added to prolonged immobility due to quarantine; 11 patients had moderate or strong risk factors for PE (table 2). Only 1 patient with chronic lymphocytic leukemia had a positive nasal-pharyngeal swab sample polymerase chain reaction (PCR) for COVID-19 at diagnosis. One patient, who had previous COVID-19 severe pneumonia and negative nasal-pharyngeal swab sample at discharge, developed acute PE 1 week later.

When asked about previous daily activity, most patients reported a previously active lifestyle followed by a sedentary lifestyle during the quarantine with prolonged immobility.

Six patients had mental disorders that could worsen immobility during the quarantine and predispose them to PE,[4] but we found no significant difference between the groups corresponding to the COVID-19-related lockdown period and the non–COVID-19 period in the prevalence of mental disorders (35.3% vs 44.4%; P = .648).

In an attempt to explain that immobility due to the hard lockdown could be one of the triggers for PE, we calculated the Padua score, which stratifies patients as being at high (≥ 4 points) or low (< 4 points) risk for VTE. We considered the hard lockdown quarantine as a "reduced mobility" risk factor; immobility in this score is penalized with 3 points. There was no significant difference in the baseline Padua prediction score for VTE (median Padua score, 3 [1-4] vs 2 [1-4]; P = .216). The COVID–19-related lockdown group had a significantly higher score in the subanalysis including immobility as a risk factor during the lockdown (median Padua score, 5 [4-7] vs 2 [1-4]; P = .019). We found a significant increase in high-risk patients in the lockdown subgroup considering lockdown as immobility (Padua score without immobility: 23.5% patients at high risk, Padua score with immobility: 76.5% patients at high risk; P = .004). When we compared the Padua score as a categorical risk variable, we found no significant difference between the lockdown period group and the no-lockdown group.

We hypothesized that a rigorous quarantine in patients with strong risk factors could predispose them to acute PE. Immobility causes an 6-fold increase in the risk of deep vein thrombosis (or PE in patients with previous events compared with patients without deep vein thrombosis or PE history).[5]

The increasing number of COVID–19-related acute PE cases described recently suggests that COVID-19 infection could be an added risk factor for acute PE during quarantine. In our series, the low prevalence of COVID-19 infection on nasal smear PCR tests does not suggest a causative relationship. A single effect, either of quarantine immobility or undiagnosed COVID-19 infection, cannot be excluded and would require a large study including COVID-19 serology-based testing with high sensitivity and specificity.

In the emergency department, elevated D-dimer with dyspnea in COVID-19 quarantine patients might be misleading. Clinicians should pay attention to a possible PE in the setting of a COVID-19 infection.

In nations imposing a hard lockdown, all patients with VTE risk factors might be counseled for mechanical prophylaxis and to stay active at home. Pharmacological prophylaxis could be advised in patients at high risk, especially previous VTE and active malignancy, which must be weighed against the risk of bleeding.

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