ORIGINAL ARTICLE

Clinical, Diagnostic and Prognostic Characterization of Patients with Suspected Pulmonary Embolism Before and During COVID-19

Caracterización clínica, diagnóstica y pronóstica de los pacientes con sospecha de tromboembolismo pulmonar antes y durante la COVID-19

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ABSTRACT

Background: Pulmonary embolism (PE) is a frequent disease generating important hemodynamic effects and high mortality rate, with great incidence in coronavirus disease (COVID-19).
Objective: The aim of this study was to characterize the clinical, diagnostic, and prognostic behavior of patients with suspected PE before and during the SARS-CoV-2 pandemic.
Methods: A prospective cohort study of adult patients with suspected PE undergoing computed tomography pulmonary angiography was carried out during two periods: a) the pre-COVID-19 phase: June 2018 to December 2019, and b) during the COVID-19 phase: June to December 2020. Bivariate analyses were conducted and ROC curves were built calculating the areas under the curve (AUC) for D-dimer PE diagnosis and clinical prediction rules.
Results: Three-hundred and two pre-COVID-19 patients and 55 patients with COVID-19 were included in the study. D-dimer showed a moderate performance for the diagnosis of PE, with AUC 0.73 (95% CI 0.62-0.84) in pre-COVID-19 phase vs. 0.75 (95% CI 0.58-0.92) in COVID-19 phase. The AUC of each of the clinical prediction rules had moderate to low performance in the pre-COVID-19 phase (AUC 0.623 to 0.697), with a non-discriminatory AUC in the COVID-19 phase (0.355 to 0.450).
Conclusions: Traditional risk factors were poorly prevalent in patients with COVID-19 and PE. Although D-dimer was higher in those with PE, the difference was not statistically significant. Clinical prediction rules for PE diagnosis showed low discriminative power in COVID-19 patients.

Key word: Pulmonary embolism - D-dimer - SARS-CoV-2 - COVID-19 - Diagnosis

RESUMEN

Introducción: El tromboembolismo pulmonar (TEP) es una patología frecuente, que genera repercusiones hemodinámicas importantes y alta tasa de mortalidad, con alta incidencia en la enfermedad por coronavirus 2019 (COVID-19).
Objetivo: Caracterizar el comportamiento clínico, de diagnóstico y pronóstico de los pacientes con sospecha de TEP antes y durante la pandemia de SARS-CoV-2.
Metodología: Estudio de cohorte prospectiva de pacientes adultos llevados a angiotomografía de tórax por sospecha de TEP durante dos periodos de tiempo: a) pre-COVID-19: junio de 2018 a diciembre de 2019, y b) COVID-19: junio a diciembre de 2020. Se condujeron análisis bivariados y se construyeron curvas ROC calculando las áreas bajo la curva para el diagnóstico de TEP del dímero D y las reglas de predicción clínica.
Resultados: Se incluyeron 302 pacientes pre COVID-19 y 55 pacientes con COVID-19. El dímero D muestra un desempeño moderado para diagnóstico del TEP con AUC 0,73 (IC 95% 0,62-0,84) en fase pre-COVID-19 vs. 0,75 (IC95% 0,58-0,92) en fase COVID-19. Las áreas bajo la curva de cada una de las reglas de predicción clínica tuvieron un desempeño moderado a bajo en la fase pre-COVID-19 (AUC 0,623 a 0,697), frente a una no discriminatoria en la fase COVID-19 (0,355 a 0,450).
Conclusiones: Los factores de riesgo tradicional fueron poco prevalentes en pacientes con COVID-19 y TEP. Aunque el dímero D fue más alto en aquellos con TEP, la diferencia no fue estadísticamente significativa. Las reglas de predicción clínicas para el diagnóstico de TEP mostraron un bajo poder discriminativo en pacientes con COVID-19.

Palabras clave: Embolismo pulmonar - Dimero D - virusSARS-CoV-2 - COVID-19 - Diagnóstico

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INTRODUCTION

A central component to determine the morbidity and mortality of the SARS-CoV-2 pandemic, recognized since the beginning of its presentation, is the associated hypercoagulable state, especially the development of pulmonary embolism (PE), with an incidence of 20% to 30% in hospitalized patients evaluated by computed tomography pulmonary angiography (CTPA). (1,2).

The proposed pathophysiological mechanisms can be described following the components of Virchow's triad (3). Firstly, the presence of a hypercoagulable state induced by a cytokine storm that has been explained by a macrophage activation syndrome; (4) secondly, endothelial injury, which has been proposed after reports of elevated von Willebrand factor and factor VIII levels; (5) and lastly, blood flow stasis, related with high levels of positive end-expiratory pressure (PEEP) that are recommended for ventilation with protective parameters and fluid restriction. (3)

Patients with severe coronavirus disease 2019 (COVID-19) present certain features that are a challenge for diagnostic evaluation with respect to usual situations (6). On the one hand, the symptoms of PE may mimic or overlap with those of COVID-19 infection, and on the other hand, the hyperinflammatory state is accompanied by elevated D-dimer levels (3). Associated with this, concerns about possible exposure of healthcare staff lead to diagnostic tests not being easily obtained with due speed, as could occur with CTPA or echocardiography.

Therefore, the present study aims to characterize the clinical, diagnostic and prognostic behavior of patients with suspected PE before and during the SARS-CoV-2 pandemic, with special consideration regarding the diagnostic accuracy of D-dimer and clinical prediction rules.

METHODS

A prospective cohort study was carried out including patients hospitalized in the emergency department or general ward who had undergone CTPA for suspected pulmonary embolism at Hospital San José de Bogotá (Colombia). The cohort was divided into two time periods: a) pre-COVID-19 phase, June 2018 to December 2019, and b) COVID-19 phase, June 2020 to December 2020. During this phase, only patients with confirmed diagnosis of COVID-19 infection by real-time polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 were included. Cases with incomplete information for study variables were excluded.

Patient identification was carried out from the daily internal medicine clinical review and from the lists of patients undergoing CTPA in the Radiology service. Patients were then interviewed to obtain a signed authorization for data use in the investigation in accordance with the Habeas Data law. An online collection form that included demographic data, clinical presentation, risk factors, physical examination, laboratory and imaging studies, as well as in-hospital clinical events was carried out.

Definition of events

Transfers to the intensive care unit and in-hospital mortality as recorded in the medical history were taken into consideration.

Clinical prediction models

The following clinical prediction rules were calculated according to the data in the clinical history:

Wells criteria for PE (7): It evaluates seven clinical characteristics according to a scoring system that divided patients into three levels of probability in the original model, and which was later simplified to two classes, probable and not probable. The two forms of classification were taken into account.

2. Geneva PE score (8): This system evaluates eight clinical characteristics to classify the pretest probability of PE.
3. PERC rule (9): System for clinical PE exclusion based on the absence of eight clinical characteristics.

Event prediction models

Not applicable.

Imaging acquisition protocol

Axial slices of the thorax from the thoracic operculum to the upper hemiabdomen were performed after the administration of contrast medium, using an Aquilion Prime (80 slices) CT scanner with multiplanar reconstructions. Once the image was obtained, it was read by a radiologist.

D-dimer

The test was performed using the D-dimer HS 500 reagent from Werfen laboratory and processed in an ACL TOP500 coagulation analyzer, which has a lower detection limit of 203 ng/mL and an upper range limit of 500 ng/mL.

Statistical analysis

Continuous variables were expressed as mean and standard deviation as central tendency measures, and median and interquartile range as measure of dispersion, according to their distribution. Qualitative variables were presented as absolute and relative frequencies. Bivariate analysis was performed using Student's t-test or the Mann-Whitney U-test for quantitative variables and the chi-square test for qualitative variables. Significant statistical difference was established for $p<0.05$.

Boxplots of D-dimer levels were represented for the two time periods. ROC curves were built of CTPA PE diagnosis for different D-dimer values, and the Wells, Geneva and PERC clinical prediction rule scores, and areas under the curve (AUC) with their respective 95% confidence intervals (95% CI) were calculated; in addition, the optimal cut-off value for D-dimer was obtained by Youden's test. Data analysis was performed using SPSS 24® software package and the R version 4.0.2 program (R Foundation, Vienna, Austria) using "pROC", "ROCit" and "cutpointr".

Ethical considerations

The present study was approved by the ethics and research committee of Hospital San José de Bogotá and the Health Sciences University Foundation under protocol number: 1201-3739-64. Although it was not considered necessary to sign an informed consent, data use authorization was required according to the national Habeas Data law. In view of the COVID-19 pandemic, the isolation and personal protection institutional protocols were followed.

RESULTS

The total study population consisted of 357 patients who were evaluated by CTPA due to PE suspicion. Among them, 55 were confirmed cases of COVID-19 infection and 302 were from the pre-COVID-19 phase. The clinical characteristics of the patients are summarized in Tables 1 and 2. Patients in the pre-COVID-19 phase had a mean age of 59.6±17.7 years, 173 were female (57.3%), 89.4% had dyspnea (n=270) and 39.7% reported chest pain (n=120). In 30.5% of cases these patients had cancer (n=92), 14.2% had a history of venous thrombosis (n=43), 6.6% had an autoimmune disease (n=20) and there were only 3 pregnant women. Ninety patients were diagnosed with PE (29.8%) and the most common location was at the level of the lobar branches of the pulmonary artery (43.2%).

Twenty-seven patients had D-dimer assessment (27.2%), with a median level of 3951 (IQR 11- 377)

Table 1. Clinical characteristics of the population

Characteristic	PRE-COVID-19 PHASE			COVID-19 PHASE			p value*
	All patients undergoing CTPA (n=302)	No PE (n= 212)	Confirmed PE(n=90)	All patients undergoing CTPA (n= 55)	No PE (n=43)	Confirmed PE (n=12)	
Age in years, mean (SD)	59.61 (17.69)	59.86 (18.26)	59.01 (16.36)	60.86 (15.97)	61.12 (16.18)	60.00 (15.89)	0.937
Female gender, n (%)	173 (57.3)	90 (42.5)	51 (56.7)	27 (48.2)	19 (44.2)	8 (61.5)	0.315
Comorbidities, n (%)							
Thromboembolic disease	43 (14.2)	23 (10.8)	20 (22.2)	2 (3.6)	2 (47)	0 (0.0)	-
Heart failure	40 (13.2)	33 (15.6)	7 (7.8)	3 (5.4)	3 (7.0)	0 (0.0)	-
Chronic pulmonary disease	51 (16.9)	40 (18.9)	11 (12.2)	6 (10.7)	5 (11.6)	1 (7.7)	-
Diabetes	51 (16.9)	40 (18.9)	11 (12.2)	4 (7.1)	3 (7.0)	1 (7.7)	-
Hypertension	128 (42.4)	93 (43.9)	35 (38.9)	23 (41.1)	19 (44.2)	4 (30.8)	0.692
Cancer	92 (30.5)	67 (31.6)	25 (27.8)	1 (1.8)	1 (2.3)	0 (0.0)	-
Thrombophilia	6 (2.0)	3 (1.4)	3 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	-
Autoimmune disease	20 (6.6)	14 (6.6)	6 (6.7)	3 (5.4)	2 (4.7)	1 (7.7)	0.846
Cerebrovascular disease	6 (2.0)	5 (2.4)	1 (1.1)	1 (1.8)	1 (2.3)	0 (0.0)	-
Obesity	9 (3.0)	5 (2.4)	4 (4.4)	4 (7.1)	2 (4.7)	2 (15.4)	0.705
Other risk factors, n (%)							
Immobility for more than three days	63 (20.9)	48 (22.6)	15 (16.7)	3 (5.4)	1 (2.3)	2 (15.4)	0.846
Recent surgery	50 (16.6)	34 (16.0)	16 (17.8)	1 (1.8)	0 (0.0)	1 (7.7)	0.923
Limb paralysis	3 (1.0)	2 (0.9)	1 (1.1)	1 (1.8)	1 (2.3)	0 (0.0)	-
Clinical presentation, n (%)							
Hemoptysis	22 (7.3)	16 (7.5)	84 (93.3)	2 (3.6)	1 (2.3)	1 (7.7)	0.846
Dyspnea	270 (89.4)	186 (87.7)	6 (6.7)	54 (96.4)	0 (0.0)	11 (84.6)	0.295
Chest pain	120 (39.7)	76 (35.8)	44 (48.9)	12 (21.4)	10 (23.3)	2 (15.4)	0.359
Syncope	11 (3.6)	5 (2.4)	6 (6.7)	3 (5.4)	2 (4.7)	1 (7.7)	-
Physical exam findings							
Heart rate, mean (SD)	92.96 (18.90)	92.07 (18.99)	95.06 (18.60)	89.04 (29.71)	89.57 (21,18)	87.31 (19.85)	0.255
Respiratory frequency, mean (SD)	21.46 (10.07)	20.73 (7.17)	23.19 (14.75)	20.38 (3.84)	20.49 (3.95)	20.00 (3.55)	0.767
Oxygen saturation, mean (SD)	88.42 (9.41)	88.90 (7.75)	87.26 (12.51)	88.35 (7.20)	88.67 (6.18)	87.17 (10.32)	0.293
Rales, n (%)	16 (5.3)	14 (6.6)	2 (2.2)	5 (8.9)	5 (11.6)	0 (0.0)	-
Unilateral leg swelling, n (%)	22 (7.3)	15 (7.1)	7 (7.8)	2 (3.6)	1 (2.3)	1 (7.7)	0.546
Lower extremity deep palpation pain, n (%)	18 (6.0)	10 (4.7)	8 (8.9)	1 (1.8)	1 (2.3)	1 (7.7)	0.231

*Difference between populations with final PE diagnosis before and during COVID-19.
CTPA: Computed tomography pulmonary angiography. PE: Pulmonary embolism. SD: Standard deviation

Table 2. Laboratory results, clinical prediction rules and clinical outcome in patients evaluated to confirm the presence of pulmonary embolism

Characteristic	PRE-COVID-19 PHASE			COVID-19 PHASE			p value*
	All patients undergoing CTPA (n=302)	No PE (n= 212)	Confirmed PE(n=90)	All patients undergoing CTPA (n= 55)	Suspected PE (n=43)	Confirmed PE (n=12)	
Laboratory							
D-dimer, median (IQR)	2205 (3885)	1483 (3274)	3951 (11 377)	1698 (4272)	1538 (2774)	5112 (16 513)	0.794
Risk scales							
Original Wells	3.59 (2.11)	3.19 (2.09)	4.53 (1.84)	3.55 (1.29)	3.61 (1.19)	3.34 (1.59)	0.026
High PE probability, n (%)	90 (29,8)	129 (60.8)	.	23 (41.8)	19 (44.2)	4 (33.3)	0.655
Simplified Wells	1.95 (1.01)	1.80 (1.02)	2.32 (0.89)	1.57 (0.70)	1.56 (0.70)	1.62 (0.76)	0.010
Probable PE, n (%)	119 (39.4)	129 (60.8)	54 (60.0)	26 (47.3)	20 (46.5)	6 (50.0)	0.173
Original Geneva score	6.32 (2.22)	6.04 (2.23)	6.96 (2.05)	4.30 (2.19)	4.42 (2.06)	3.92 (2.62)	0.003
Low PE probability, n (%)	29 (9.6)	25 (11.8)	4 (4.4)	21 (38.2)	13 (30.2)	8 (66.7)	0.054
Intermediate PE probability, n (%)	264 (87.4)	182 (85.8)	82 (91.1)	32 (58.2)	29 (67.4)	3 (25.0)	0.331
High PE probability, n (%)	7 (2.3)	3 (1.4)	4 (4.4)	2 (3.6)	1 (2.3)	1 (8.3)	0.845
PERC score	2.39 (0.97)	2.25 (0.97)	2.72 (0.89)	2.11 (0.80)	2.09 (0.71)	2.15 (1.06)	0.072
High PE probability, n (%)	295 (97.7)	206 (95.3)	89 (98.9)	55 (100.0)	43 (100.0)	12 (100.0)	-
Original PESI score	-	-	107.9 (31.7)	-	-	89.4 (18.9)	0.011
Clinical events							
CCU admission , n (%)	35 (11.6)	18 (6.0)	17 (5.6)	33 (10.9)	24 (55.8)	9 (69.2)	0.001
Mortality, n (%)	13 (5.6)	11 (3.6)	5 (1.7)	9 (3.0)	9 (20.9)	0 (0.0)	0.900

* Difference between populations with final PE diagnosis before and during COVID-19.
CTPA: Computed tomography pulmonary angiography. PE: Pulmonary embolism. IQR: Interquartile range. PESI: Pulmonary embolism severity index. CCU: Coronary Care Unit

ng/dL (Table 2). Median troponin level was 12 (IQR 25) ng/dL, mean hemoglobin level 13.3±2.8 g/dL and mean creatinine level 0.77±0.17 mg/dL Mean prothrombin time was 12.4±0.73 seconds and 35.8±14.7 seconds for thromboplastin. None of the patients diagnosed with PE died.

The 55 patients in the COVID-19 group had a mean age of 60.9±16.0 years, 27 were female (48.2%), 96.4% had dyspnea and 21.4% manifested chest pain. In 1.8% of cases patients had a history of cancer, 3.6% had venous thrombosis, 5.4% had an autoimmune disease, and no pregnant women were included (Table 1). Diagnosis of PE was confirmed in 12 patients (21.8%), p vs pre-COVID-19 group=0.23

Figure 1 shows a boxplot representation revealing that in the COVID-19 phase median D-dimer was higher in patients with confirmed PE than in those without this disease, while in the pre-COVID-19 phase there was no significant difference between patients with and without PE.

The ROC curve of D-dimer performance for PE diagnosis is presented in Figure 2, with a moderate performance, similar in both phases: AUC 0.73 (95% CI 0.62-0.84) in the pre-COVID-19 phase vs. 0.75 (95% CI 0.58-0.92) in the COVID-19 phase. The optimal cutoff value calculated by Youden's test was 23 850 pg./mL in the COVID-19 phase versus 19 460 pg./mL in the pre-COVID-19 phase.

Figure 3 and Table 3 present the AUC of each of the pretest clinical prediction rules with their respective 95% CI in both phases of the study: in the pre-COVID-19 phase the performance was moderate to low (AUC 0.623 to 0.697), while in the COVID-19 phase it was nondiscriminatory (AUC 0.355 to 0.450). The best discriminatory ability was obtained by the Wells score with an AUC of 0.697 (95% CI 0.635-0.760) in the pre-COVID-19 phase.

The pulmonary embolism severity index (PESI) score was significantly lower in the COVID-19 group: 90.00±18.95 vs. 107.88±31.65, p=0.001.

Transfer to intensive care was higher in patients with COVID-19 infection: 69.2% vs. 18.9% (p=0.001). In-hospital mortality was 5.6% (n=5) in pre-COVID-19 patients and 0% in the COVID-19 period (p=0.90).

DISCUSSION

Since the symptoms of PE largely overlap with those of COVID-19 in the context of an inflammatory and prothrombotic state, due to endothelial dysfunction and hypercoagulability, diagnostic evaluation of patients in the search for this complication is usually necessary. (3) The present work indicates a trend towards a non-significant decrease in the rate of PE diagnosis from 29.8% in the pre-COVID-19 period to 21.8% in the COVID-19 period in the study patients. This condition could be attributed to a lower clinical

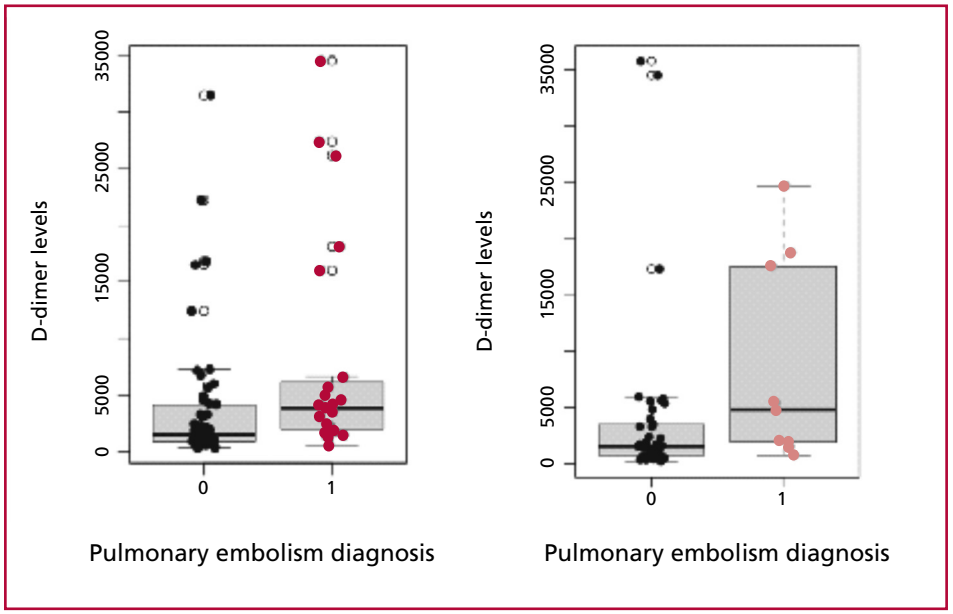

Fig. 1. D-dimer boxplot between patients undergoing computed tomography pulmonary angiography diagnosed with (1) or without (0) pulmonary embolism. a) pre-COVID-19 phase, b) COVID-19 phase

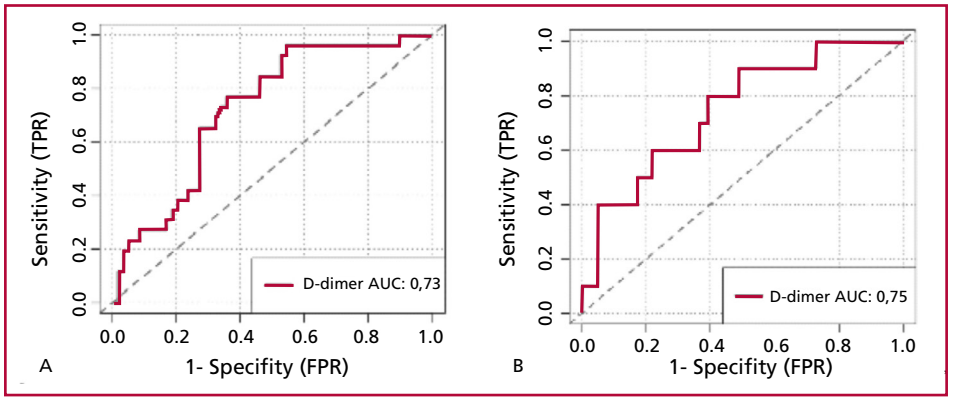

Fig. 2. D-dimer ROC curves for the diagnosis of pulmonary embolism in patients undergoing computed tomography pulmonary angiography. a) pre-COVID-19 phase, b) COVID-19 phase

TPR; True positive rate. FPR: False positive rate

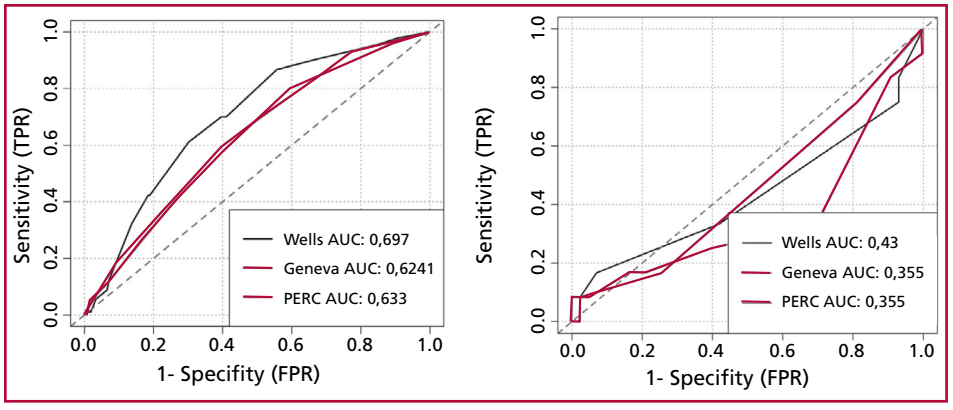

Fig. 3. ROC curves of the different rules of clinical prediction for pulmonary embolism diagnosis in patients undergoing computed tomography pulmonary angiography. a) pre-COVID-19 phase, b) COVID-19 phase

TPR; True positive rate. FPR: False positive rate

threshold for the prescription of CTPA in the face of symptoms, and the acknowledgement of PE as a frequent and important complication, as well as the difficult interpretation of elevated D-dimer in this population, underestimating its true incidence. (10) Other studies have reported similar incidences, such as those of Grillet et al. (23%, 23/100 patients) (1) and Poyiadji et al. (22%, 72/377), (11) or a very low rate as that described by Fauvel et al. in a multicenter cohort of 24 French hospitals, 8.3%, 103/1240). (12) The opposite case reporting a higher incidence is seen in several other studies, such as that of Léonard-Lorant et al. (30%, 32/106 patients), (2) Ventura-Díaz et al. (30%, 72/242), (13) Ramadan et al. (28.7%, 47/367) (14) and Ooi et al. (38%, 32/84). (15)

In the two periods evaluated, female sex predominated among patients diagnosed with PE (56.7% in the pre-COVID-19 phase vs. 61.5% in the COVID-19 period), without statistically significant difference. Population studies indicate that women are more commonly affected. (16,17) This finding has not been repeated in any of the previously reported studies or systematic reviews. (18) Traditional risk factors (previous thrombosis, major surgeries and immobilization) did not show a relationship with PE development, similar to that documented by the work of Fauvel et al.'s group. (12)

D-dimer higher levels were consistently documented in patients in whom the presence of PE was confirmed compared with those in whom it was ruled out, both in the pre-COVID-19 phase (medians of 3951 vs. 1483 μg/L, p=0.001) as in the COVID-19 phase (medians of 5112 vs. 1538 vs. μg/L, p=0.014). The boxplot graph confirms this finding, though with some overlap of values between both groups (Figure 1). A systematic review including 11 studies with 567 patients found that D-dimer levels were higher in patients with PE (7625 μg/L) than in those without PE (1750 μg/L). (18) In our study, a similar AUC was documented in both periods evaluated (0.73 in the pre-COVID-19 phase and 0.75 in the COVID-19 phase), which was the same as the one documented in the already mentioned systematic review (0.737), while the optimal cutoff value of 23 850 μg/ L was quite high compared with that reported in the review of 4453 μg/L. (18)

We found a low clinical prediction rule performance in patients hospitalized for COVID-19 infection, with an AUC of 0.434 for the original Wells score, 0.355 for the Geneva score, and 0.450 for the PERC prediction rule score. This finding had already been suggested for patients in critical condition in several clinical trials. (19-21) Two studies evaluating this aspect in patients hospitalized for COVID-19 infection undergoing CTPA found that the Wells and Geneva scores showed no predictive value for the occurrence of PE, either considering a standard or age-adjusted cutoff point. (22,23)

There were no cases of mortality in the group of patients with COVID-19 infection in whom PE was diagnosed, a result that could be attributed to the identification of milder cases (lower PESI) after a more careful diagnostic evaluation in this population. It is recognized that in patients with COVID-19 infection, the presence of embolic complications is associated with a marked increase in mortality, with an OR of 1.74 (95% CI 1.01-2.98, p=0.04) in a meta-analysis that included 42 studies with 8271 patients. (24) A high requirement for transfer to the intensive care unit (ICU) could be documented in patients with COVID-19 infection, a finding that was more notorious in those diagnosed with PE (69% of cases required intensive care). This contrasts with a study that found no significant difference in ICU admissions, need for intubation or intubation duration among patients who developed PE, and in which 72% (52/72) of PE was diagnosed in patients who did not require critical care. (11)

Limitations

The present study has several limitations: its single-center nature makes it impossible to generalize the results to other populations and presents the risk of selection. In addition, it underestimates the true incidence of PE, given that CTPA was not systematically performed in all hospitalized patients with COVID-19 infection. On the other hand, the small number of patients limited the power to determine significant differences between the groups evaluated. We consider as a strength the possibility of having a historical registry of patients undergoing CTPA that could serve as a comparator for behavior before and during the pandemic.

CONCLUSIONS

Traditional risk factors were poorly prevalent in patients with COVID-19 and confirmed diagnosis of PE. Although there was a trend towards higher D-dimer levels among those with confirmed PE, the difference was not statistically significant. The clinical prediction rules usually applied for PE diagnosis showed low discriminative power in patients with COVID-19.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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