Submitted: 19 January, 2022 Accepted: 08 March, 2022 Published: 08 May, 2023 DOI:10.22514/sv.2022.067

Open Access

Signa Vitae

ORIGINAL RESEARCH

Pulmonary embolism at the emergency department during the COVID-19 pandemic. A comparative cohort study from a tertiary level hospital in southern Spain

Antonio Jesús Láinez-Ramos-Bossini[1,2,3,*], Beatriz Moraleda Cabrera[1,3], Francisco Garrido Sanz[1,3], Elvira Ruiz Castellano[1,3], Mónica Crespo Balbuena[1,3], Francisco Javier Pérez García[1,3], Carlos Jiménez Mascuñán[1,3], Mario Rivera Izquierdo[3,4]

[1]Department of Radiology, Virgen de las Nieves University Hospital, 18014 Granada, Spain
[2]Department of Radiology, University of Granada, 18012 Granada, Spain
[3]Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), 18012 Granada, Spain
[4]Department of Preventive Medicine and Public Health, University of Granada, 18012 Granada, Spain

***Correspondence**
ajbossini@ugr.es
(Antonio Jesús Láinez-Ramos-Bossini)

Abstract

Several studies have been published showing a significant increase in thrombotic complications in coronavirus disease 2019 (COVID-19) patients, including acute pulmonary embolism (PE). However, there is significant variability regarding published data on the number of computed tomography pulmonary angiography (CTPA) orders to rule out PE, frequency and characteristics of PE, and other factors that could have magnified the actual incidence of PE. The aim of this work is to analyze these factors during the first year of the pandemic. A longitudinal retrospective observational study was designed comparing two cohorts (preCOVID and COVID) of patients for whom an emergency CTPA was requested to rule out PE at the emergency department of our institution. Information was collected regarding the number of CTPAs requested, patient demographics, presence and extension of PE, and radiological signs of right ventricle strain/pulmonary hypertension (RVS/PH). Univariate and bivariate analyses were performed, with stratification by time intervals according to different pandemic waves in the COVID cohort. A total of 1905 patients (530 in the pre-COVID cohort and 1375 in the COVID cohort), with a mean age of 68.3 years (standard deviation, 16.5) and 981 (51.5%) women were included. No significant differences were observed regarding the incidence of PE between both cohorts. In patients with PE, no significant differences regarding age or sex were found, but a significantly higher frequency of peripheral PE was observed in the COVID cohort (42.0% *vs.* 6.5%, $p < 0.001$). Regarding signs of RVS/PH, a lower degree of septal deviation and contrast reflux to the inferior vena cava was observed in the COVID cohort, but no significant differences were observed in the right-to-left ventricular ratio. For the COVID cohort, the distribution of central *vs.* peripheral PE was similar in patients without laboratory-confirmed COVID-19 infection. Finally, the analysis of signs of RVS/PH stratifying by pandemic waves showed a lower frequency of RVS/PH signs in the 2nd and 3rd pandemic waves. In conclusion, despite a significantly higher number of CTPAs were performed during the pandemic, the incidence of PE was similar to that of the pre-pandemic period. A higher number of peripheral PE and less radiological signs of RVS/PH were observed during the pandemic. These findings could be explained by an increased incidental detection of PE during the pandemic. Our study has some limitations, mainly derived from its retrospective and single-center nature, which should be overcome in future research.

Keywords

COVID-19; Pulmonary embolism; Emergency department; Pandemic; Cohort study

1. Introduction

Acute pulmonary embolism (PE) is a potentially life-threatening condition which mandates urgent diagnosis and treatment [1]. It is the third leading cause of cardiovascular mortality in emergency departments (EDs) worldwide, following acute myocardial infarction and stroke [2]. Its incidence in the population ranges from 0.5 to 1 per 1000 individuals per year, with no significant sex differences, and increases with age [3]. Several risk factors for PE have been

This is an open access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).
 ©2023 The Author(s). Published by MRE Press.

identified, including confinement in a hospital or nursing home, active cancer, presence of a central venous catheter or pacemaker, and recent pregnancy [4]. In the context of the global Coronavirus disease 2019 (COVID-19) pandemic, an increased risk of venous thromboembolic (VTE) disease, including PE, has been reported since the first published studies [5, 6] particularly in hospitalized and Intensive Care Unit (ICU) patients [7–10], with associated increased mortality risk [11, 12]. The pathophysiological mechanism of PE in COVID-19 patients has been suggested to involve multiple factors related to inflammation, prothrombotic state, hypoxia, immobilization, diffuse intravascular coagulation and endothelial dysfunction, among others [13]. However, subsequent studies reported discrepant results regarding the incidence, clinical significance, and characteristics of PE during the pandemic. Gallastegui *et al.* [14] were among the first authors who challenged the generalized assumption that PE was unusually highly incident in hospitalized patients. In line with other authors, some of the main factors underlying discrepancies among studies lie in the heterogeneity regarding different methodological approaches [15], including but not limited to patient selection, study design, and assessment tools. Currently, unanswered questions remain in spite of several systematic reviews and meta-analyses on this topic [16–18]. It is still unclear whether PE is more frequent in COVID versus non-COVID cohorts with the same degree of disease severity.

The clinical presentation of acute PE encompasses a wide spectrum of signs and symptoms, and routine exams at the ED have low specificity for its detection [19]. Currently, the 'old standard' technique for the diagnosis of PE is computed tomography pulmonary angiography (CTPA), which has high sensitivity and specificity, allowing to detect even small (*i.e.*, subsegmental) embolisms. In addition, this technique may show radiological signs associated with right ventricle strain and pulmonary hypertension (RVS/PH), which have been associated with a worse prognosis [2]. For these reasons, CTPA has been suggested to have a fundamental role in the diagnostic work-up of COVID-19 patients for the diagnosis of acute PE [20]. The early-recognized, alleged association between COVID-19 and higher risk of PE in the setting of a hypercoagulability state together with the characteristic pulmonary involvement of this virus, could have motivated a greater number of CTPA orders to rule out PE during the pandemic. Accordingly, some institutions carried out universal CTPA screening to rule out PE, which has been associated with an increased incidence of PE [21]. This increase in the number of CTPAs performed may have magnified the actual incidence of PE by increasing the detection of subsegmental PEs, which are frequently asymptomatic and whose clinical impact is still unclear [2]. Conversely, the number of CTPAs could have been very infrequent in some settings, particularly during the first waves of the pandemic, due to factors such as scarcity of resources, fear to concerns pertaining to the contamination of computed tomography (CT) scanners and in-hospital transmission of disease [22], the decrease in patient visits to the ED, or differences in respiratory severity of the disease. This would imply an underestimation of PE incidence [6]. In sum, whether the number of CTPA orders increased or decreased during the pandemic, and whether such trend was homogeneous throughout the pandemic remains unknown. The subsequent impact on the incidence of PE, as well as other related factors associated with prognosis and mortality (*e.g.*, distribution of PE, associated signs of RVS/PH) is also unclear.

The aim of this work is to analyze the number of CTPAs ordered to rule out PE at our ED during the first year of the pandemic, as well as the incidence, distribution and radiological features associated with PE.

2. Methods

2.1 Study design and sample selection

A longitudinal retrospective observational (cohort) study was designed at the Virgen de las Nieves University Hospital (Granada, Spain). Two cohorts of patients were selected: the first group consisted of patients for whom an emergency CTPA scan was requested due to suspected PE during the first year of the pandemic (15 March 2020 to 14 March 2021) while the second group consisted of patients for whom an emergency CTPA scan was requested for the same reason and during the same time interval the previous year (15 March 2019 to 14 March 2020). Exclusion criteria were ordering department other than ED, age $<$18 years, suspicion other than PE, poor (non-diagnostic) CT quality due to contrast extravasation, severe artifacts, *etc.*, and chronic PE.

The cohorts were selected from our hospital's radiological information system (RIS) database by reviewing all CTPAs available at the Picture Archiving and Communication System in Medicine (PACS). In particular, we performed a keyword text search on the radiology reports including the term 'pulmonary embolism'. All electronic CT requests were manually reviewed by four authors, paying careful attention to the clinical suspicion. Then, exclusion criteria were applied.

For each case, the following variables were collected: sociodemographic information (age and sex), number and date in which the CTPA was ordered, and frequency and type of PE (*i.e.*, central-main or lobar arteries- or peripheral-segmental or subsegmental arteries- [23]). In patients with confirmed PE (PE+ group), we collected information on radiological signs of RVS/PH (diameter of pulmonary artery (PA), PA/aorta ratio, right-to-left ventricle ratio, deviation of interventricular septum, and contrast reflux to the inferior vena cava (IVC)). In the COVID cohort, patients with laboratory-confirmed COVID-19 infection were annotated, and the cohort was classified in time intervals according to the 3 epidemic waves that occurred in Spain during the study period. In this regard, we considered periods of high care pressure as those with the highest number of incident cases according to data from the Spanish Ministry of Health [24, 25] up to the end of the study period (March 2021). Accordingly, the periods were divided into First Epidemic Wave (March to April 2020), Second Epidemic Wave (September to November 2020), Third Epidemic Wave (January to February 2021) and Intermediate Periods (May to August 2020; December 2020 and March 2021). These intermediate periods correspond to lower health care pressure, as the average of incident cases were $<$50 cases/100,000 inhabitants.

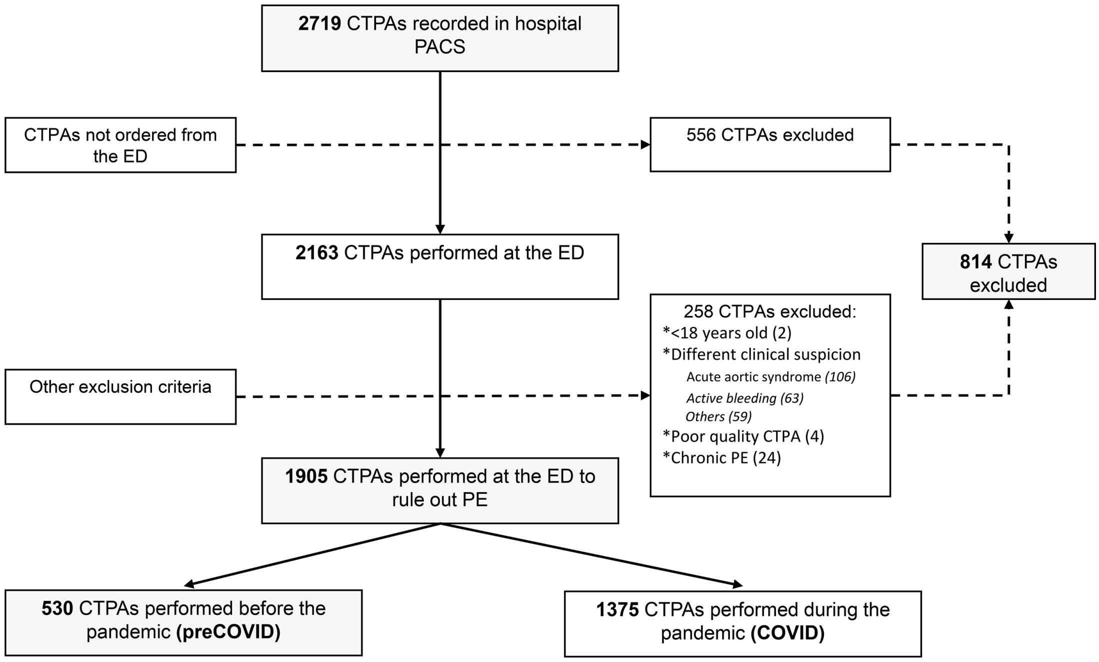

FIGURE 1. Flow diagram of the selection of cohorts in our study. CTPA, computed tomography pulmonary angiography. PACS, picture archiving and communication system. ED, emergency department. COVID, coronavirus disease 2019 sub-group. PE, pulmonary embolism. *Indicates the categories of the reason for exclusion of CTPAs.

First, a descriptive analysis of both cohorts was performed. Then, comparative analyses were carried out of the variables collected between both cohorts using chi-square tests in the case of qualitative variables and Student's *t* test for continuous variables, after verification of the normality of the variables. Subsequently, a comparative analysis was performed stratifying by healthcare pressure periods in Spain using the chi-square test for qualitative variables and one-way analysis of variance (ANOVA) for continuous variables. Finally, a comparative analysis was carried out to analyze differences within the COVID cohort based on the presence of laboratory-confirmed COVID-19 infection. Statistical analyses were performed using the SPSS software (v. 23.0, IBM Corp, Armonk, NY, United States).

3. Results

3.1 Flow diagram of the study and description of the cohorts

Of the total of 2719 CTPAs registered in the PACS of our institution, 1905 CTPAs were included after applying the exclusion criteria. Of these, 530 (27.8%) belonged in the pre-COVID cohort and 1375 (72.2%) corresponded to the COVID cohort. Fig. 1 shows the flow diagram followed for the selection of both cohorts.

The mean age of the entire sample included in the study was 68.3 years (standard deviation (SD), 16.5), and sex distribution included 981 (51.5%) women. Comparative analyses showed no significant differences between groups regarding sex or incidence of PE, although the mean age was significantly different ($p = 0.009$). In the group with confirmed PE, comparative analyses showed no significant differences regarding age or sex, but a significantly higher proportion of peripheral PE was observed in the COVID cohort. Table 1 summarizes the characteristics and contrastive analysis of the cohorts included in the study. Table 2 shows the adjusted analyses of the multivariate logistic regression models. PE was defined as the outcome (dependent variable), and the covariates included were sex, age, and cohort (*i.e.*, preCOVID or COVID). The pre-pandemic cohort showed higher odds of presenting PE, although no significant association was found (odds ratio [OR]: 1.23, 95% confidence interval [CI]: 0.97–1.57).

3.2 Radiological signs of right ventricle strain in patients with pulmonary embolism

Analysis of the radiological signs associated with RVS/PH showed increased septal deviation and contrast reflux to the IVC in the pre-COVID cohort. No significant differences were observed in the right-to-left ventricle ratio. Table 3 shows the corresponding data.

3.3 COVID cohort. Descriptive analysis and stratification by pandemic waves

Contrastive analyses within the COVID cohort showed no significant differences regarding sex or age based on the presence of COVID-19 infection. Conversely, significant differences were observed in the distribution of patients infected with COVID-19 across pandemic waves, with a higher relative frequency of COVID-19 infected patients during the periods of high healthcare pressure, which progressively decreased from the first to the third wave. There were also significant differences in the frequency of PE, which was significantly higher in the COVID-19 infection subgroup. Finally, the distribution of PE showed a similar ratio of central *vs.* peripheral PE in patients without COVID-19 infection. Table 4 illustrates the

TABLE 1. Characteristics and bivariate analyses of the two cohorts included in the study.

	Total n (%), x (s)	Pre-COVID cohort n (%), x (s)	COVID cohort n (%), x (s)	*p* value†
Total	1905 (100.0)	530 (27.8)	1375 (72.2)	-
Age*	68.3 (16.5)	69.9 (16.7)	67.7 (16.4)	0.009
Sex*				
Female	981 (51.5)	278 (52.5)	703 (51.1)	0.604
Male	924 (48.5)	252 (47.5)	672 (48.9)	
PE frequency	392 (20.6)	123 (23.2)	269 (19.6)	0.078
Age**	69.0 (16.3)	70.7 (17.0)	68.2 (15.9)	0.160
Sex**				
Female**	208 (53.1)	65 (52.8)	143 (53.2)	0.954
Male**	184 (46.9)	58 (47.2)	126 (46.8)	
PE location				
Central**	269	115 (93.5)	156 (58.0)	< 0.001
Peripheral**	122	8 (6.5)	113 (42.0)	

**Data relative to the entire sample. **Data relative to the PE+ group. †p value of the chi-squared test for qualitative variables and Student's t test for the continuous variable "age". PE, pulmonary embolism.*

TABLE 2. Multivariate analysis of the two cohorts included in the study.

	OR*	95% CI
Sex		
Female	0.93	0.75–1.17
Male	Ref	-
Age	1.00	0.97–1.01
Cohort		
Pre-pandemic	1.23	0.97–1.57
Pandemic	Ref	-

**Odds ratio (OR) for presenting pulmonary embolism for each category. CI, confidence interval.*

corresponding analyses.

The comparative analysis by stratification periods showed no significant differences in sex or PE frequency but there were significant differences in age. In addition, significant differences were found regarding the location of PE, particularly when comparing the pre-COVID cohort (relative frequency of peripheral PE of 6.5%) with each of the subgroups of the COVID cohort (relative frequency of peripheral PE ranging from 28.6% to 55.7%). Table 5 shows the main results of the comparative analysis.

The analysis of radiological signs of RVS/PH stratified by pandemic waves showed significant differences in interventricular septal deviation and contrast reflux. No significant differences were observed in the right ventricular/left ventricular (RV/LV) ratio. Table 6 shows the main results.

4. Discussion

A number of thrombotic events including PE have been reported to be more frequent in COVID-19 patients as a consequence of a hyper-inflammatory response [26]. However, the degree of severity has been observed to be variable depending on the patient profile. For instance, patients with mild COVID-19 disease may show scarce abnormalities in laboratory parameters, while critically ill patients exhibit a hyperinflammatory and procoagulant phenotype with significantly higher levels of ferritin, C-reactive protein, fibrinogen, D-dimer, and lactic acid [27]. Considering the dramatic impact of this disease in health care systems, important efforts have been made to facilitate identification, risk stratification and optimization of treatment in COVID-19 patients. This includes consensus guidelines and recommendations that are now available to facilitate clinical decision-making [28]. For example, the need for specific prediction rules has been advocated for estimating the risk of PE in hospitalized COVID-19 patients, differentiating ICU from non-ICU patients, and taking into account anticoagulation prophylaxis, comorbidities, and the time from COVID-19 diagnosis [29]. However, it is not clear whether mild forms of COVID-19 infection lead to a significant increase in the risk of developing thrombotic complications in comparison with other diseases of similar nature and severity, particularly in the context of general wards.

Due to the rapid emergence of this pandemic, many of the studies exploring the incidence of PE in COVID-19 patients show heterogeneity, selection biases or inadequate designs. This has prompted systematic reviews and meta-analyses to shed light on the actual incidence of PE in COVID-19 patients. However, discrepancies have also been found in these pooled studies. Early meta-analyses observed an increased incidence of PE in both ICU and non-ICU patients [30], but figures were highly variable ranges (*e.g.*, 2–35%) [31]. Posterior,

TABLE 3. Radiological signs of right ventricle strain and pulmonary hypertension (RVS/PH) in patients with pulmonary embolism. Comparative analysis.

Signs of RVS/PH	Total n (%), x (s)	Pre-COVID cohort n (%), x (s)	COVID cohort n (%), x (s)	*p* value†
Total	392 (100.0)	123 (100.0)	269 (100.0)	
Right-to-left ventricle ratio				
>1	91 (23.2)*	22 (17.9)	69 (25.7)	0.091
<1	301 (76.8)*	101 (82.1)	200 (74.3)	
Septal deviation				
Normal	236 (60.2)*	60 (48.8)	176 (65.4)	0.004
Rectification	107 (27.3)*	40 (32.5)	67 (24.9)	
Inversion	49 (12.5)*	23 (18.7)	26 (9.7)	
Contrast reflux				
No/Mild	270 (68.9)*	54 (43.9)	216 (80.3)	< 0.001
Moderate	77 (19.6)*	42 (34.1)	35 (13.0)	
Severe	45 (11.5)*	27 (22.0)	18 (6.7)	

*†p value of the chi-squared test. *Data relative to the PE+ group.*

TABLE 4. COVID cohort. Contrastive analysis based on the presence of laboratory-confirmed COVID-19 infection.

	Total n (%), x (s)	COVID-19 infection n (%), x (s)	No COVID-19 infection n (%), x (s)	*p* value†
Total	1375 (100.0)	701 (51.0)	674 (49.0)	
First wave	86 (6.3)*	59 (68.6)**	27 (31.4)**	< 0.001
Second wave	373 (27.1)*	228 (61.1)**	145 (38.9)**	
Third wave	358 (26.0)*	197 (55.0)**	161 (45.0)**	
Interim	558 (40.6)*	217 (38.9)**	341 (61.1)**	
PE frequency	269 (19.6)*	207 (77.0)***	62 (23.0)***	< 0.001
Age	67.7 (16.4)	68.0 (16.0)	67.3 (16.7)	0.420
Sex				
Female	672 (48.9)*	346 (49.4)^	357 (53.0)^	0.181
Male	703 (51.1)*	355 (50.6)^	317 (47.0)^	
PE location				
Central	156 (58.0)***	124 (59.9)^^	32 (51.6)^^	< 0.001
Peripheral	113 (42.0)***	83 (40.1)^^	30 (48.4)^^	

**Data relative to the COVID cohort. **Data relative to the corresponding wave subgroup (row). ***Data relative to the PE+ subgroup of the COVID cohort. ^Proportion relative to the COVID-19 infection subgroup (column). ^^Proportion relative to the PE+ sub-cohort of the corresponding infection subgroup. †p value of the chi-squared test for qualitative variables and Student's t test for the continuous variable "age". COVID-19, coronavirus disease 2019. PE, pulmonary embolism.*

TABLE 5. Comparative analysis of cohorts, with the COVID cohort stratified according to epidemic waves. Interim: intervals between waves during the pandemic.

	Total n (%), x (s)	Pre-COVID n (%), x (s)	1st wave n (%), x (s)	2nd wave n (%), x (s)	3rd waven (%), x (s)	Interim n (%), x (s)	*p* value†
Total	1905 (100.0)	530 (27.8)	86 (4.5)	373 (19.6)	358 (18.8)	558 (29.3)	-
Age*	68.3 (16.5)	69.9 (16.7)	68.9 (15.8)	66.2 (16.7)	67.7 (16.3)	68.4 (16.5)	0.023
Sex*							
Female	981 (51.5)	278 (52.5)	42 (48.8)	184 (49.3)	189 (52.8)	288 (51.6)	0.847
Male	924 (48.5)	252 (47.5)*	44 (51.2)	189 (50.7)	169 (47.2)	270 (48.4)	
PE frequency*	392 (20.6)	123 (23.2)	21 (24.4)	70 (18.8)	68 (19.0)	110 (19.7)	0.334
Sex**							
Female	208 (53.1)*	65 (52.8)*	9 (42.9)*	38 (54.3)	39 (57.4)	57 (51.8)	0.828
Male	184 (46.9)*	58 (47.2)*	12 (57.1)*	32 (45.7)	29 (42.6)	53 (48.2)	
Age**	69.0 (16.3)	70.7 (17.0)	63.19 (17.6)	70.8 (16.7)	68.8 (15.4)	67.3 (16.3)	0.187
PE location**							
Central	271 (69.1)**	115 (93.5)	15 (71.4)	31 (44.3)	35 (51.5)	75 (68.2)	< 0.001
Peripheral	121 (30.9)**	8 (6.5)	6 (28.6)	39 (55.7)	33 (48.5)	35 (31.8)	

**Data relative to the subgroup in the corresponding column. **Data relative to the PE+ sub-cohort of the COVID cohort. †p value of the chi-squared test for qualitative variables and Student's t test for the continuous variable "age". PE, pulmonary embolism.*

TABLE 6. Radiological signs of right ventricle strain and pulmonary hypertension stratified by pandemic waves.

Signs of RVS/PH	Total n (%), x(s)	Pre-COVID n (%), x(s)	1st wave n (%), x(s)	2nd wave n (%), x(s)	3rd wave n (%), x(s)	Interim n (%), x(s)	*p* value†
				RV/LV ratio			
>1	91 (23.2)	22 (17.9)	9 (42.9)	16 (22.9)	17 (25.0)	83 (75.5)	0.150
<1	301 (76.8)	101 (82.1)	12 (57.1)	54 (77.1)	51 (75.0)	27 (24.5)	
				Septal deviation			
Normal	236 (60.2)	60 (48.8)	10 (47.6)	50 (71.4)	44 (64.7)	72 (65.5)	
Rectification	107 (27.3)	40 (32.5)	5 (23.8)	18 (25.7)	15 (22.1)	29 (26.4)	0.004
Inversion	49 (12.5)	23 (18.7)	6 (28.6)	2 (2.9)	9 (13.2)	9 (8.2)	
				Contrast reflux			
No/Mild	270 (68.9)	54 (43.9)	18 (85.7)	63 (90.0)	57 (83.8)	78 (70.9)	
Moderate	77 (19.6)	42 (34.1)	2 (9.5)	4 (5.7)	3 (4.4)	26 (23.6)	< 0.001
Severe	45 (11.5)	27 (22.0)	1 (4.8)	3 (4.3)	8 (11.8)	6 (5.5)	

†p value of the chi-squared test. RVS/PH, right ventricle strain and pulmonary hypertension. Pre-COVID, pre-pandemic cohort of patients. RV/LV, right ventricular/left ventricular ratio.

meta-analyses such as the one published by Mai *et al.* [16] including more than 40,000 patients found an increased risk of VTE occurrence among COVID-19 patients hospitalized in the ICU, but no overall difference in risk in COVID-19 cohorts compared to non-COVID-19 cohorts. Conversely, a more recent review by Tufano *et al.* [17] including more than 1,000,000 patients reported a risk difference (RD) for PE between COVID-19 and non-COVID-19 patients of 0.03, while the RD for PE between COVID-19 and non-COVID-19 patients was 0.021 in retrospective studies and 0.11 in ICU studies.

In Spain, few studies have been published on the incidence of PE during the COVID-19 pandemic. A study by Martínez-Chamorro *et al.* [32] comparing the number of CTPAs performed to rule out PE and the incidence of PE at the beginning of the pandemic found a greater number of CTPA orders (69.9% *vs.* 30.1%), but no significant differences in the incidence of PE. When adjusted for COVID infection, significant differences were found, with PE being more frequent in patients with COVID-19 infection. These results are in agreement with our findings; our ratio of CTPAs was very similar (72.2% *vs.* 27.8%), but no significant differences were observed in the incidence of PE (in fact, it was lower in the COVID cohort). In addition, the analysis of the COVID cohort showed that the frequency of PE was significantly higher in patients with laboratory-confirmed COVID-19 disease compared to non-COVID-19 patients (77% *vs.* 23%). Moreover, an added value of our study is the longer follow up (first year of the pandemic), with stratified analyses based on health care pressure intervals which showed interesting results. First, the incidence of PE was not significantly different across waves, although it was lower during the second and third waves compared to the first wave. Interestingly, the ratio of peripheral PE was also significantly lower in the first wave compared to the rest of the pandemic, and these were in turn significantly higher compared to the pre-COVID cohort. These findings could be explained by a lower number of CTPAs performed during the first pandemic wave. Of note, we observed statistically significant differences regarding age both in the comparative analysis between the pre-COVID and COVID cohorts and between the different pandemic waves, but this seems to be secondary to large numbers rather than actual relevant differences (less than 3 years between cohorts).

One of the most interesting results of our study relates to the frequency of peripheral and central PE, both before and during the pandemic, and across the waves of the pandemic. We observed that, whilst the ratio of peripheral PE was anecdotal prior to the pandemic (6.5%) —in agreement with previous studies—, this proportion was significantly higher during the pandemic (42.0%). These findings parallel those reported by a retrospective study conducted in COVID-19 patients in France by Grillet *et al.* [33] who found a PE incidence of 23%, with a more frequent peripheral distribution (51%), and also are in line with the results of the meta-analysis conducted by Jiménez *et al.* [34] in hospitalized patients. In Spain, Mestre-Gómez *et al.* [35] conducted a retrospective study with 91 patients who underwent a CT scan to rule out PE in a tertiary hospital from Madrid. The authors found a 31.9% PE incidence, with a significantly more predominant distribution of peripheral *vs.* central location (69% *vs.* 31%). Similarly, Benito *et al.* [36] reported a higher incidence of PE in hospitalized COVID-19 patients, with a predominance of peripheral (78.1%) *vs.* central (21.9%) distribution. These findings could be explained by two main hypotheses. On the one hand, this could be due to a higher number of incidental PEs resulting from the 3-fold increase in the number of CTPAs performed during the pandemic. On the other hand, COVID-19 disease could be specifically associated with a higher risk of small size pulmonary emboli rather than with central/massive PE forms. Interestingly, some authors have raised the hypothesis that pulmonary in situ clot formation is an added mechanism of PE in COVID-19 patients, since the prevalence of deep vein thrombosis (DVT) has been found to be low in COVID-19 patients as compared with PE [37–39]. A combination of both hypotheses (*i.e.*, increased incidental detection of subsegmental PEs and increased formation of peripheral PE in COVID-19 patients) also seems reasonable.

A particularly innovative aspect of our study is the analysis of signs of RHS/PH. Early reports such as the study by Argulian *et al.* [40] suggested right ventricular dilation in patients hospitalized due to COVID-19, yet potential biases secondary to small sample size and retrospective nature limited its validity. Potential causes for such finding included increased susceptibility of PE, PH and acute respiratory syndrome [41]. It seems that disease severity plays a role in the development or aggravation of PH. Accordingly, patients with severe COVID-19 were reported to have a higher proportion of pulmonary hypertension as compared to mild COVID-19 disease (22% *vs.* 2%) [42]. A study by van den Heuvel *et al.* [43] including 51 COVID-19 patients admitted to hospital. One of the subgroup analyses carried out in this study compared COVID-19 patients with PE (n = 9) *vs.* those with no PE (n = 42), and found that none of the patients with PE had right ventricular dysfunction, and right ventricular dimensions were normal, although a higher tricuspid annular plane systolic excursion and increased right ventricular systolic excursion velocity were found in PE patients, presumably due to small sample size and limited severity of embolism. A retrospective study conducted by Tilliridou *et al.* [44] including a total of 1286 CTPAs performed to rule out PE in three hospitals from Scotland. They compared CTPA frequency and PE severity in April and May 2020 versus 2019. The authors assessed PE severity with the Modified Miller score and also assessed the presence of right heart strain (RHS). The authors found a 17% reduction in the number of CTPA performed and an increase in the proportion of PEs detected (26% *vs.* 15%). Although there was no difference in PE severity in 2020 compared to 2019, the authors observed an increased frequency of RHS in May 2020 (29 *vs.* 12%, $p = 0.029$). Of note, the authors only used a RV/LV >1.2 as radiological indicator of RHS. In our study, the comparison between the pre-COVID and COVID cohorts showed no significant differences in the RV/LV ratio, but significant differences were observed in septal modification (with the presence of signs of RHS/PH being more frequent in the pre-COVID cohort). In addition, stratified analyses based on pandemic waves showed that RHS/PH signs were less frequent in the second and third waves, paralleling the pattern of distribution of peripheral PE, and suggesting a causal association (*i.e.*, more peripheral PEs with less RHS/PH signs were present throughout the pandemic).

The main limitations of our study lie in its retrospective observational design and single-centered nature, as well as the relatively short follow-up period. In addition, it should be noted that the radiological signs of RHS/PH are indirect signs that do not always correlate with clinical symptoms. For example, contrast reflux is associated with rapid contrast injections or other pathologies such as mitral regurgitation [45]. On the other hand, the quantification of reflux is variable in the literature, ranging from classifications with 4 categories [46] to 6 categories [47, 48]. These limitations should be overcome in future studies, which shall address the incidence and characteristics of PE considering present challenges, such as the influence of vaccination and changes in virus dynamics with new variants such as Omicron.

5. Conclusions

Despite a significantly higher number of CTPAs were ordered in our institution during the first year of the pandemic, the incidence of PE was similar to that of the pre-pandemic era. A higher number of peripheral PE and less radiological signs of RVS/PH were observed during the pandemic. Although PE was more frequent in patients with laboratory-confirmed COVID-19, our overall findings suggest that a high number of incidental PEs were detected during the pandemic.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

AJLRB, BMC and FGS—designed the research study and wrote the first draft of the manuscript; AJLRB, BMC and FGS—conducted the research and advised on methodology; ERC, MCB, FJPG and CJM—extracted the data; MRI—mentored the work. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study complies with the principles of the Declaration of Helsinki. A completely anonymized database was used for the analyses. No identification data were used. The need for informed consent has been waived owing to its retrospective nature. The study was approved by the Provincial Research Ethics Committee of Granada (ref. TEPA18).

ACKNOWLEDGMENT

The authors wish to thank Benítez Sánchez of the University of Granada for his statistical assistance.

FUNDING

This work was supported by the 'Artificial Intelligence for the diagnosis and prognosis of COVID-19' project (CV20-29480), funded by the Consejería de Transformación Económica, Industria, Conocimiento y Universidades, Junta de Andalucía, and the FEDER funds.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Antonio Jesús Láinez-Ramos-Bossini is serving as one of the Guest editors of this journal. We declare that Antonio Jesús Láinez-Ramos-Bossini had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MC.

REFERENCES

[1] Moore AJE, Wachsmann J, Chamarthy MR, Panjikaran L, Tanabe Y, Rajiah P. Imaging of acute pulmonary embolism: an update. Cardiovascular Diagnosis and Therapy. 2018; 8: 225–243.
[2] Láinez-Ramos-Bossini AJ, Moreno-Suárez S, Pérez-García MC, Gálvez-López R, Sanz FG, Rivera-Izquierdo M. Acute pulmonary embolism: appropriateness of emergency department management according to clinical guidelines. To be published in Radiologia. 2020. [Preprint]
[3] Raskob GE, Angchaisuksiri P, Blanco AN, Büller H, Gallus A, Hunt BJ, *et al.* Thrombosis: a major contributor to global disease burden. Seminars in Thrombosis and Hemostasis. 2014; 40: 724–735.
[4] Serhal M, Barnes GD. Venous thromboembolism: a clinician update. Vascular Medicine. 2019; 24: 122–131.
[5] Casey K, Iteen A, Nicolini R, Auten J. COVID-19 pneumonia with hemoptysis: acute segmental pulmonary emboli associated with novel coronavirus infection. American Journal of Emergency Medicine. 2020; 38: 1544.e1–1544.e3.
[6] Hanff TC, Mohareb AM, Giri J, Cohen JB, Chirinos JA. Thrombosis in COVID-19. American Journal of Hematology. 2020; 95: 1578–1589.
[7] Roncon L, Zuin M, Barco S, Valerio L, Zuliani G, Zonzin P, *et al.* Incidence of acute pulmonary embolism in COVID-19 patients: systematic review and meta-analysis. European Journal of Internal Medicine. 2020; 82: 29–37.
[8] Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, *et al.* Incidence of venous thromboembolism in hospitalized patients with COVID-19. Journal of Thrombosis and Haemostasis. 2020; 18: 1995–2002.
[9] Wu T, Zuo Z, Yang D, Luo X, Jiang L, Xia Z, *et al.* Venous thromboembolic events in patients with COVID-19: a systematic review and meta-analysis. Age and Ageing. 2021; 50: 284–293.
[10] Zhang R, Ni L, Di X, Wang X, Ma B, Niu S, *et al.* Systematic review and meta-analysis of the prevalence of venous thromboembolic events in novel coronavirus disease-2019 patients. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2021; 9: 289–298.e5.
[11] Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. EClinicalMedicine. 2020; 29: 100639.
[12] Akhter MS, Hamali HA, Mobarki AA, Rashid H, Oldenburg J, Biswas A. SARS-CoV-2 infection: modulator of pulmonary embolism paradigm. Journal of Clinical Medicine. 2021; 10: 1064.
[13] Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. Journal of Clinical Virology. 2020; 127: 104362.
[14] Gallastegui N, Zhou JY, Drygalski AV, Barnes RFW, Fernandes TM, Morris TA. Pulmonary embolism does not have an unusually high incidence among hospitalized COVID19 patients. Clinical and Applied Thrombosis/Hemostasis. 2021; 27: 107602962199647.
[15] Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. Thrombosis Research. 2020; 196: 67–74.
[16] Mai V, Tan BK, Mainbourg S, Potus F, Cucherat M, Lega J, *et al.* Venous thromboembolism in COVID-19 compared to non-COVID-19 cohorts: a systematic review with meta-analysis. Vascular Pharmacology. 2021; 139: 106882.
[17] Tufano A, Rendina D, Abate V, Casoria A, Marra A, Buonanno P, *et al.* Venous thromboembolism in COVID-19 compared to non-COVID-19 cohorts: a systematic review with meta-analysis. Journal of Clinical Medicine. 2021; 10: 4925.
[18] Sridharan GK, Vegunta R, Rokkam VRP, Meyyur Aravamudan V, Vegunta R, Khan SR, *et al.* Venous thromboembolism in hospitalized COVID-19 patients. American Journal of Therapeutics. 2020; 27: e599–e610.
[19] Láinez-Ramos-Bossini AJ, Moreno-Suárez S, Pérez-García MDC, Gálvez-López R, Garrido-Sanz F, Rivera-Izquierdo M. Use of clinical probability scores and D-dimer in suspected pulmonary embolism. Results from a Spanish retrospective study. European Journal of Emergency Medicine. 2020; 27: 468–469.
[20] Pontone G, Scafuri S, Mancini ME, Agalbato C, Guglielmo M, Baggiano A, *et al.* Role of computed tomography in COVID-19. Journal of Cardiovascular Computed Tomography. 2021; 15: 27–36.
[21] Suh YJ, Hong H, Ohana M, Bompard F, Revel M, Valle C, *et al.* Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. Radiology. 2021; 298: E70–E80.
[22] Kaminetzky M, Moore W, Fansiwala K, Babb JS, Kaminetzky D, Horwitz LI, *et al.* Pulmonary embolism at CT pulmonary angiography in patients with COVID-19. Radiology: Cardiothoracic Imaging. 2020; 2: e200308.
[23] Alonso Martinez J, Annicchericho Sánchez F, Urbieta Echezarreta M, García I, Álvaro J. Central versus peripheral pulmonary embolism: analysis of the impact on the physiological parameters and long-term

survival. North American Journal of Medical Sciences. 2016; 8: 134–142.
[24] Ministerio de Sanidad, Consumo y Bienestar Social - Situación actual Coronavirus. Available at: https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/situacionActual.htm (Accessed: 18 January 2022).
[25] Láinez Ramos-Bossini AJ, Láinez Millán B, Ruiz Santiago F, Rivera Izquierdo M. Impact of the COVID-19 pandemic on osteoporotic vertebral fracture incidence and follow-up at the emergency department. A retrospective study of a tertiary hospital in southern Spain. Signa Vitae. 2022; 18: 15–23.
[26] Tomerak S, Khan S, Almasri M, Hussein R, Abdelati A, Aly A, *et al.* Systemic inflammation in COVID-19 patients may induce various types of venous and arterial thrombosis: a systematic review. Scandinavian Journal of Immunology. 2021; 94: e13097.
[27] Doyle AJ, Hunt BJ, Sanderson B, Zhang J, Mak SM, Benedetti G, *et al.* A comparison of thrombosis and hemorrhage rates in patients with severe respiratory failure due to coronavirus disease 2019 and influenza requiring extracorporeal membrane oxygenation. Critical Care Medicine. 2021; 49: e663–e672.
[28] Flaczyk A, Rosovsky RP, Reed CT, Bankhead-Kendall BK, Bittner EA, Chang MG. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. Critical Care. 2020; 24: 559.
[29] Rindi LV, Al Moghazi S, Donno DR, Cataldo MA, Petrosillo N. Predictive scores for the diagnosis of pulmonary embolism in COVID-19: a systematic review. International Journal of Infectious Diseases. 2022; 115: 93–100.
[30] Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Research and Practice in Thrombosis and Haemostasis, 2020; 4: 1178–1191.
[31] Lu Y, Pan L, Zhang W, Cheng F, Hu S, Zhang X, *et al.* A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. International Journal of Infectious Diseases. 2020; 100: 34–41.
[32] Martínez Chamorro E, Revilla Ostolaza TY, Pérez Núñez M, Borruel Nacenta S, Cruz-Conde Rodríguez-Guerra C, Ibáñez Sanz L. Pulmonary embolisms in patients with COVID-19: a prevalence study in a tertiary hospital. Radiología. 2021; 63: 13–21.
[33] Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography. Radiology. 2020; 296: E186–E188.
[34] Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, *et al.* Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. Chest. 2021; 159: 1182–1196.
[35] Mestre-Gómez B, Lorente-Ramos RM, Rogado J, Franco-Moreno A, Obispo B, Salazar-Chiriboga D, *et al.* Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. Journal of Thrombosis and Thrombolysis. 2021; 51: 40–46.
[36] Benito N, Filella D, Mateo J, Fortuna AM, Gutierrez-Alliende JE, Hernandez N, *et al.* Pulmonary thrombosis or embolism in a large cohort of hospitalized patients with Covid-19. Frontiers in Medicine. 2020; 7: 557.
[37] McFadyen JD, Stevens H, Peter K. The emerging threat of (micro) thrombosis in COVID-19 and its therapeutic implications. Circulation Research. 2020; 127: 571–587.
[38] Thachil J, Srivastava A. SARS-2 coronavirus-associated hemostatic lung abnormality in COVID-19: is it pulmonary thrombosis or pulmonary embolism? Seminars in Thrombosis and Hemostasis. 2020; 46: 777–780.
[39] Birocchi S, Manzoni M, Podda GM, Casazza G, Cattaneo M. High rates of pulmonary artery occlusions in COVID-19. A meta-analysis. European Journal of Clinical Investigation. 2021; 51: e13433.
[40] Argulian E, Sud K, Vogel B, Bohra C, Garg VP, Talebi S, *et al.* Right ventricular dilation in hospitalized patients with COVID-19 infection. JACC: Cardiovascular Imaging. 2020; 13: 2459–2461.
[41] Cao Y, Zhang M, Guo Y, Zhang Y. The overlooked chamber in coronavirus disease 2019. ESC Heart Failure. 2020; 7: 3483–3486.
[42] Mishra AK, Lal A, Sahu KK, George AA, Martin K, Sargent J. An update on pulmonary hypertension in coronavirus disease-19 (COVID-19). Acta Bio Medica: Atenei Parmensis. 2020; 91: e2020155.
[43] van den Heuvel FMA, Vos JL, Koop Y, van Dijk APJ, Duijnhouwer AL, de Mast Q, *et al.* Cardiac function in relation to myocardial injury in hospitalised patients with COVID-19. Netherlands Heart Journal. 2020; 28: 410–417.
[44] Tilliridou V, Kirkbride R, Dickinson R, Tiernan J, Yong GL, van Beek EJ, *et al.* Pulmonary embolism severity before and during the COVID-19 pandemic. The British Journal of Radiology. 2021; 94: 20210264.
[45] Collins MA, Pidgeon JW, Fitzgerald R. Computed tomography manifestations of tricuspid regurgitation. The British Journal of Radiology. 1995; 68: 1058–1060.
[46] Bailis N, Lerche M, Meyer HJ, Wienke A, Surov A. Contrast reflux into the inferior vena cava on computer tomographic pulmonary angiography is a predictor of 24-hour and 30-day mortality in patients with acute pulmonary embolism. Acta Radiologica. 2021; 62: 34–41.
[47] Aviram G, Cohen D, Steinvil A, Shmueli H, Keren G, Banai S, *et al.* Significance of reflux of contrast medium into the inferior vena cava on computerized tomographic pulmonary angiogram. The American Journal of Cardiology. 2012; 109: 432–437.
[48] Aviram G, Rogowski O, Gotler Y, Bendler A, Steinvil A, Goldin Y, *et al.* Real-time risk stratification of patients with acute pulmonary embolism by grading the reflux of contrast into the inferior vena cava on computerized tomographic pulmonary angiography. Journal of Thrombosis and Haemostasis. 2008; 6: 1488–1493.

How to cite this article: Antonio Jesús Láinez-Ramos-Bossini, Beatriz Moraleda Cabrera, Francisco Garrido Sanz, Elvira Ruiz Castellano, Mónica Crespo Balbuena, Francisco Javier Pérez García, et al. Pulmonary embolism at the emergency department during the COVID-19 pandemic. A comparative cohort study from a tertiary level hospital in southern Spain. Signa Vitae. 2023; 19(3): 57-65. doi: 10.22514/sv.2022.067.