Medical Research Archives

ESMED European Society of Medicine

OPEN ACCESS

Published: April 30, 2023

Citation: Charra B and Bou-ouhrich Y, 2023. Pulmonary Embolism in Critically Ill COVID-19 And Non-COVID-19 Patients: Systematic Analysis of Risk Factors, Diagnostic and Management Strategies, and Prognosis, Medical Research Archives, [online] 11(4). https://doi.org/10.18103/mra.v11i4.3759

DOI
https://doi.org/10.18103/mra.v11i4.3759

ISSN: 2375-1924

RESEARCH ARTICLE

Pulmonary Embolism in Critically Ill COVID-19 And Non-COVID-19 Patients: Systematic Analysis of Risk Factors, Diagnostic and Management Strategies, and Prognosis.

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ABSTRACT

Background: Coronavirus disease of 2019 or COVID-19 is characterised by two main features: the first is the respiratory compromise which corresponds to acute respiratory distress syndrome while the second corresponds to the state of hypercoagulability responsible for thromboembolic complications particularly pulmonary embolism which is the subject of this work. Indeed, a high prevalence of pulmonary embolism has been reported throughout the pandemic period with a significant morbidity and mortality. This reflects the severity of this life-threatening emergency chiefly in the elderly, hemodynamically unstable patients, and patients with severe underlying conditions, mainly cardio-pulmonary comorbidities. The aim of our study is to point out the incidence, the risk factors, the clinical and paraclinical features, the management strategies, and the overall prognosis of pulmonary embolism in critically ill COVID-19 and non-COVID-19 patients.

Patients and methods: It is a retrospective observational study carried out over a two-year-period from January 2019 (non-COVID-19) to December 2020 (COVID-19). Over the study period, 42 cases of COVID-19 and non-COVID-19 pulmonary embolism were collected from an overall set of 611 patients admitted to the medical intensive care unit of the IBN ROCHD university hospital of Casablanca.

Results: The mean age in the COVID-19 group was 64-year-old versus 46-year-old in the non-COVID-19 group. The sex ratio was 1.2 and 0.94 in the non-COVID-19 and COVID-19 group, respectively. Clinical symptomatology was dominated by respiratory failure and chest pain in non-COVID-19 patients while in the COVID-19 group, semiology was dominated by dyspnea, cough, and chest pain. The major sign of severity in both groups was tachypnea.

The chest X-ray was performed in all our patients, it displayed radiological abnormalities in all patients mainly hyper clarity in pulmonary fields. D-dimers were performed in all patients within the two study groups. A chest computed tomography angiogram was performed for all patients and showed unilateral pulmonary embolism in 61% of cases in the non-COVID-19 group versus 61.3% in the COVID-19 group. Cardiac ultrasound was performed for all patients. It showed dilatation of right cavities in both groups (81.8% in non-COVID-19 versus 93.5% in COVID-19 patients). Venous ultrasound of the lower limbs was performed in 96.8% of COVID-19 patients and in 72.7% of non-COVID-19 patients.

With regards to management, all COVID-19 and non-COVID-19 patients received anticoagulation therapy based on standard heparin and anti-vitamin K. Mortality accounted for 54.5% in non-COVID-19 patients versus 74.2% in COVID-19 patients.

Conclusion: COVID-19 pulmonary embolism is often associated with significantly higher morbidity and mortality as compared with non-COVID-19 pulmonary embolism.

Keywords: Pulmonary embolism, Intensive care unit, COVID-19, Risk factors, Mortality.

Introduction

Pulmonary embolism (PE) occurs when there is a disruption of the blood flow within the pulmonary circulation, by a thrombus which originated somewhere else.[1] It refers to partial or complete obstruction of the pulmonary artery, or a branch of this artery, most often by a blood clot. It is a life-threatening even fatal medical emergency. PE is considered in terms of frequency, the third most common cardiovascular disease (after myocardial infarction and stroke) with approximately 35,000 hospitalizations each year.[2]

Acute infections are associated with an increased risk of venous thromboembolic events due to a transient heightened inflammatory state.[3] This pathogenesis has been linked to excessive cytokine production resulting in a cytokine storm with increased hypercoagulability.[4]

The novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease of 2019 (COVID-19), is a contagious respiratory illness responsible for a global pandemic that, as of spring 2000, has yet to be under control.[4] Its clinical spectrum may range from a mild pneumonia to acute respiratory distress syndrome due to a cytokine storm. Countries with earlier exposure to this novel virus have reported cases of pulmonary embolism in the absence of relevant risk factors and have suggested a causal relationship.[3] However, it is still unclear why infections due to COVID-19, as compared with other infections, lead to a higher incidence of thromboembolic events regardless of illness severity.[4]

Limited data of thromboembolic risk in patients with COVID-19, especially those without other risk factors motivated our research to analyse pulmonary embolism patterns in COVID-19 and non-COVID-19 patients.

The aim of our study is to work out the several features of PE in patients affected and not affected by SARS-COV2 pneumonia. This work highlights the incidence, the risk factors, the clinical and paraclinical features, the management modalities, as well as the overall prognosis of PE in critically ill COVID-19 and non-COVID-19 patients.

Patient and methods

Type and location of study

It is a retrospective observational study conducted over a two-year-period from January 2019 (non-COVID-19) to December 2020 (COVID-19). It included 42 cases of COVID-19 and non-COVID-19 embolic patients from a total of 611 patients who were admitted to the medical intensive care unit (ICU) of the IBN ROCHD university hospital of Casablanca. ***(Fig 1)***

Study population

Patients admitted to the medical ICU of IBN ROCHD university hospital of Casablanca during the study period. Patients were divided into two groups: non-COVID-19 patients having developed a PE before the pandemic between January 1 and December 31,2019 and COVID-19 patients who developed a PE during the pandemic, between January 1 and December 31, 2020.

Included in the study were COVID-19 and non-COVID-19 patients admitted to the medical ICU who were aged more than 18- year-old and in whom the diagnosis of PE was confirmed by chest computed tomography (CT) angiogram. Exclusion criteria included an ICU length of stay < 48 hours, patients less than 18-year-old, COVID-19 and non-COVID-19 patients who did not develop PE during their ICU stay, and patients with uninterpretable records.

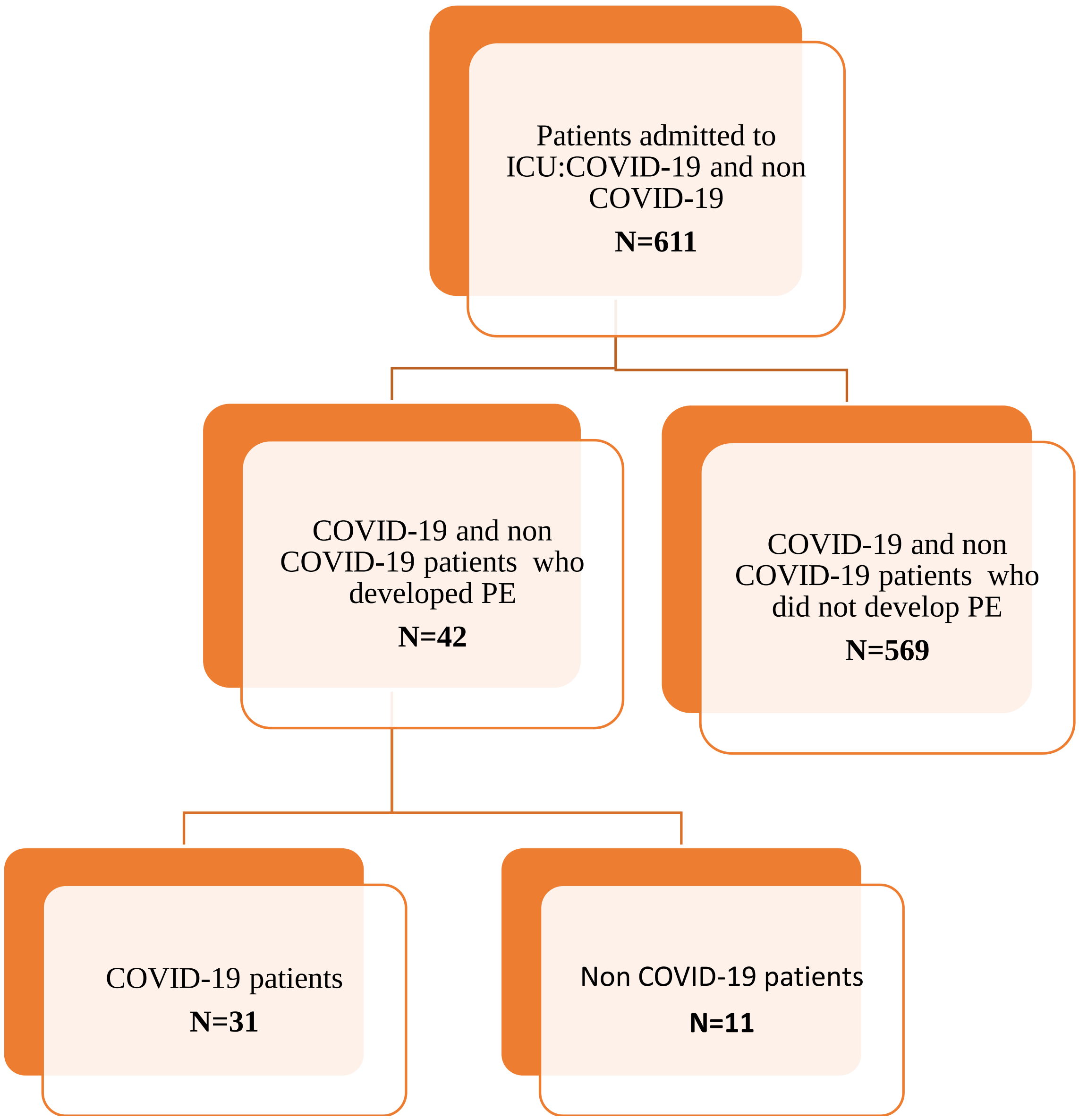

Fig 1: Study population

DATA COLLECTION

Records were taken from the archives after a list of patients was drawn up from the admission register during the study period. Data collection was done via a pre-established exploitation form which allowed us to specify the following baseline characteristics: demographic data (i.e.name, sex, age, and comorbidities), reason for admission, positive or negative COVID-19 polymerase chain reaction (PCR), severity score upon admission: IGS II, SOFA, APACHE II, clinical and biological risk factors, clinical and para-clinical features, WELLS score, Pulmonary Embolism Severity Index (PESI), therapeutic modalities, and the evolution of patient. This allowed us to gather epidemiological, clinical, para-clinical, and etiological parameters as well as treatment and monitoring data.

STATISTICAL ANALYSIS

At the end of analysis, we differentiated two main arms among the 42 patients: the COVID-19 patients comprising 31 patients (5.07%) and the non-COVID-19 patients comprising 11 patients (1.80%). Data are expressed as a percentage, mean plus or minus standard deviation, or median; and entered and coded on SPSS 25 and EXCEL 2016 software. Once validated, a global description of the population was made.

The variable of interest is mortality. Univariate analyses were performed to explain mortality according to different variables (age, sex, medical history, risk factors for PE, clinical and paraclinical data, WELLS score, and PESI. The statistical tests used were the student test for the comparison of two means and the chi-square test for the comparison of two percentages. A p-value lower than 0.05 was chosen as a threshold of significance.

Results

1) *Descriptive study*

-Epidemiology

1. Incidence:

Throughout the study period, 611 patients were admitted to ICU and were included in the study. Of these, 42 patients had developed PE with an incidence of 6.78%. Among these 42 patients: 31 patients were COVID-19 with an incidence of 5.07% and 11 patients were non-COVID-19 with an incidence of 1.80%.

2-Distribution by age

The median age was 64.55-year-old for patients with COVID-19 PE versus 46-year-old for non-COVID-19 patients; with extremes ranging from 32 to 95-year-old. The most represented age bracket in our series was that of over 65-year-old with a prevalence of 40.5%, the threshold above which the risk of PE becomes significant. ***(Tables 1 and 2)***

Table 1: Descriptive analysis of age.

COVID-19		**N**	**Mean**	**Standard deviation**
Age	*Non-COVID-19 PE*	*11*	*46,00*	*12,38*
	COVID-19 PE	*31*	*64,55*	*13,28*

Table 1: Distribution of patients by age bracket.

			COVID-19		**Total**
			Non-COVID-19 PE	*COVID-19 PE*	
Age bracket (years)	*30-45*	*N*	*5*	*4*	*9*
		%	*45,5%*	*12,9%*	*21,4%*
	46-55	*N*	*3*	*4*	*7*
		%	*27,3%*	*12,9%*	*16,7%*
	56-65	*N*	*3*	*6*	*9*
		%	*27,3%*	*19,4%*	*21,4%*
	Over 65	*N*	*0*	*17*	*17*
		%	*0,0%*	*54,8%*	*40,5%*
Total		*N*	*11*	*31*	*42*
		%	*100,0%*	*100,0%*	*100,0%*

3-Gender distribution

Female gender was slightly predominant in the COVID-19 group. The sex ratio (male/female) was 0.94 in COVID-19 patients versus 1.2 in non-COVID-19 patients. ***(Table 3)***

Table 2: Distribution of patients by sex.

			COVID-19		**Total**
			Non-COVID-19 PE	*COVID-19 PE*	
Sex	*Female*	*N*	*5*	*16*	*21*
		%	*45,5%*	*51,6%*	*50,0%*
	Male	*N*	*6*	*15*	*21*
		%	*54,5%*	*48,4%*	*50,0%*
Total		*N*	*11*	*31*	*42*
		%	*100,0%*	*100,0%*	*100,0%*

4-Diagnosis of admission

In our study, the most common reason for hospitalization in patients with COVID-19 PE was acute respiratory failure. In contrast, in non-COVID-19 patients, most patients (45.45%) were initially admitted to ICU for PE.

-Medical history

1. Medical / Toxic:

In our study, 90.5% of patients had a medical history. Patients had various comorbidities, the most common were hypertension and diabetes. Toxic habits were significantly more prevalent in non-COVID-19 patients (54.6%) as compared to covid-19 patients (3.2%). ***(Table 4)***

Table 3: Distribution of patients depending on comorbidities.

		COVID-19		***Total***
		Non-COVID-19 PE	*COVID-19 PE*	
Hypertension	*N*	*2*	*19*	*21*
	%	*18,2%*	*61,3%*	*50,0%*
Diabetes	*N*	*2*	*22*	*24*
	%	*18,2%*	*71,0%*	*57,1%*
Respiratory failure	*N*	*2*	*2*	*4*
	%	*18,2%*	*6,5%*	*9,5%*
Thromboembolism	*N*	*0*	*6*	*6*
	%	*0,0%*	*19,4%*	*14,3%*
Cancer	*N*	*2*	*0*	*2*
	%	*18,2%*	*0,0%*	*4,8%*
Pregnancy	*N*	*2*	*0*	*2*
	%	*18,2%*	*0,0%*	*4,8%*
Smoking	*N*	*4*	*1*	*5*
	%	*36,4%*	*3,2%*	*11,9%*
Alcohol	*N*	*2*	*0*	*2*
	%	*18,2%*	*0,0%*	*4,8%*

2-Surgical history

Around 16% of patients with COVID-19 PE had a history of surgery as compared to 27.3% of patients with non-COVID-19 PE. ***(Table 5)***

Table 4: Distribution of patients depending on surgical history.

			Pulmonary embolism		***Total***
			Non-COVID-19	*COVID-19*	
Surgical history	*No*	*N*	*8*	*26*	*34*
		%	*72,7%*	*83,9%*	*81,0%*
	Yes	*N*	*3*	*5*	*8*
		%	*27,3%*	*16,1%*	*19,0%*
Total		*N*	*11*	*31*	*42*
		%	*100,0%*	*100,0%*	*100,0%*

3-Thromboembolic risk factors

In both groups, more than 95% of cases had risk factors of thromboembolism. The risk factors found in COVID-19 and non-COVID-19 patients were as follow: hospitalization <3 months (83.9% in COVID-19 PE versus 100% in non-COVID-19 PE), surgery (16.1% in COVID-19 PE versus 27.3% in non-COVID-19 PE), and heart disease (9.1% in COVID-19 PE versus 9.1% in non-COVID-19 PE). ***(Table 6)***

Table 6: Distribution of patients depending on risk factors.

		COVID-19		Total
		Non-COVID-19 PE	COVID-19 PE	
Surgery	N	3	5	8
	%	27,3%	16,1%	19,0%
Trauma > 3months	N	1	0	1
	%	9,1%	0,0%	2,4%
Antiphospholipid syndrome	N	0	0	0
	%	0,0%	0,0%	0,0%
Nephrotic syndrome	N	0	0	0
	%	0,0%	0,0%	0,0%
Cardiopathy	N	1	3	4
	%	9,1%	9,7%	9,5%
Chronic inflammatory disease of intestine	N	0	0	0
	%	0,0%	0,0%	0,0%
Age > 75- year-old	N	0	7	7
	%	0,0%	22,6%	16,7%
History of thromboembolism	N	0	0	0
	%	0,0%	0,0%	0,0%
Obesity	N	0	0	0
	%	0,0%	0,0%	0,0%
Varices	N	0	0	0
	%	0,0%	0,0%	0,0%
Cancer	N	2	0	2
	%	18,2%	0,0%	4,8%
Hospitalisation < 3months	N	11	26	37
	%	100,0%	83,9%	88,1%
Prolonged immobility	N	2	0	2
	%	18,2%	0,0%	4,8%
Obstetrical-gynaecological history	N	2	0	2
	%	18,2%	0,0%	4,8%
Congenital	N	0	0	0
	%	0,0%	0,0%	0,0%

-Clinical study

1. Functional signs

In our series, all patients with COVID-19 and non-COVID-19 PE had various functional signs. In COVID-19 PE group, the most frequent symptoms were dyspnea (90.3%) and cough (93.5%) followed by chest pain (83.87%), calf pain (32.3%), and palpitations (29%). In the non-COVID-19 PE group, the main symptom was dyspnea (100%) with a sudden onset in half of patients. Chest pain was the second most frequent symptom (around 81%). Palpitations and cough were still frequent with a rate of 63.6% and 54.5% respectively. ***(Table 7)***

Table 7: Distribution of patients depending on functional signs.

		COVID-19		Total
		Non-COVID-19 PE	COVID-19 PE	
Dyspnea	N	11	28	39
	%	100,0%	90,3%	92,9%
Chest pain	N	9	26	35
	%	81.82%	83.87%	83.33%
Cough	N	6	29	35
	%	54,5%	93,5%	83,3%
Leg swelling	N	5	0	5
	%	45,5%	0,0%	11,9%

Calf pain	*N*	*2*	*10*	*12*
	%	*18,2%*	*32,3%*	*28,6%*
Haemoptysis	*N*	*1*	*0*	*1*
	%	*9,1%*	*0,0%*	*2,4%*
Palpitations	*N*	*7*	*9*	*16*
	%	*63,6%*	*29,0%*	*38,1%*
Wheezing	*N*	*2*	*0*	*2*
	%	*18,2%*	*0,0%*	*4,8%*
Angina	*N*	*0*	*0*	*0*
	%	*0,0%*	*0,0%*	*0,0%*

2-Physical signs

All patients had at least one physical sign. In COVID-19 PE group, 90.3% of patients were tachypneic upon admission and apyretic. Just over 77% had rales in pulmonary auscultation and 54.8% had tachycardia. Deep venous thrombosis (DVT) was found in nine patients, 29.03%. In the non-COVID-19 PE group, 81.8% of patients were tachypneic and apyretic upon admission. Around 72% of patients had rales in pulmonary auscultation and around 27% had tachycardia. ***(Table 8)***

Table 8: Distribution of patients depending on physical signs.

		COVID-19		***Total***
		Non-COVID-19 PE	*COVID-19 PE*	
Tachypnea	*N*	*9*	*28*	*37*
	%	*81,8%*	*90,3%*	*88,1%*
Rales	*N*	*8*	*24*	*32*
	%	*72,7%*	*77,4%*	*76,2%*
Tachycardia	*N*	*3*	*17*	*20*
	%	*27,3%*	*54,8%*	*47,6%*
DVT	*N*	*4*	*9*	*1*
	%	*36.36%*	*29.03%*	*2,4%*
Temperature <38.2°c	*N*	*9*	*28*	*37*
	%	*81,8%*	*90,3%*	*88,1%*
Homans sign	*N*	*2*	*0*	*2*
	%	*18,2%*	*0,0%*	*4,8%*
Pleuretic friction rub	*N*	*0*	*0*	*0*
	%	*0,0%*	*0,0%*	*0,0%*
Cyanosis	*N*	*1*	*0*	*1*
	%	*9,1%*	*0,0%*	*2,4%*
Shock	*N*	*1*	*0*	*1*
	%	*9,1%*	*0,0%*	*2,4%*

3-Clinical probability of pulmonary embolism

The clinical probability of developing PE in our patients was estimated by the WELLS score. In our study, the WELLS Score was high in patients with COVID-19 PE as compared to patients with non-COVID-19 PE, 32.3% versus 18.2% respectively. ***(Table 9)***

Table 9: Distribution of patients depending on the WELLS score.

			COVID-19		Total
			Non-COVID-19 PE	COVID-19 PE	
WELLS Score	High	N	2	10	12
		%	18,2%	32,3%	28,6%
	Low	N	4	11	15
		%	36,4%	35,5%	35,7%
	Intermediate	N	5	10	15
		%	45,5%	32,3%	35,7%
Total		N	11	31	42
		%	100,0%	100,0%	100,0%

-Paraclinical data

1. Chest X-ray

In our series, all patients had a chest X-ray during their ICU stay. In the COVID-19 PE group, 38.71% had hyperclarity, just under 13% had atelectasis, and 9.68% had pleural effusion. In the non-COVID-19 PE group, 54.55% of patients had hyperclarity with a lower rate of patients with atelectasis and pleural effusion. ***(Table 10)***

Table 10: Distribution of patients depending on chest X-ray.

		COVID-19	
		Non-COVID-19 PE	COVID-19 PE
Atelectasis	N	3	4
	%	27,27%	12,90%
Pleural effusion	N	2	3
	%	18,18%	9,68%
Hyperclarity pattern	N	6	12
	%	54,55%	38,71%

2-Cardiac ultrasound

In most cases, echocardiography showed dilatation of the right cavities, indicating acute pulmonary hypertension (APH) with a rate of 93% in the COVID-19 PE group versus 81.8% in the non-COVID-19 PE group. ***(Table 11)***

Table 11: Distribution of patients depending on cardiac ultrasound abnormalities.

		COVID-19		Total
		Non-COVID-19 PE	COVID-19 PE	
Dilatation of the right cavities	N	9	29	38
	%	81,8%	93,5%	90,5%
Thrombus	N	0	3	3
	%	0,0%	9,7%	7,1%
Paradoxical septal wall	N	2	1	3
	%	18,2%	3,2%	7,1%

3-Doppler ultrasound of the lower limbs

Venous doppler ultrasound of the lower limbs was performed in 96.8% of patients with COVID-19 PE and 72.7% of patients with non-COVID-19 PE. ***(Table 12)***

Table 12: Performance of lower limbs doppler ultrasound.

			COVID-19		Total
			Non-COVID-19 PE	COVID-19 PE	
Doppler Ultrasound (+ or -)	Yes	N	3	1	4
		%	27,3%	3,2%	9,5%
	No	N	8	30	38
		%	72,7%	96,8%	90,5%
Total		N	11	31	42
		%	100,0%	100,0%	100,0%

4-Chest computed tomography angiogram

Chest computed tomography (CT) angiogram was performed in all patients of both groups. In the non-COVID-19 PE group, four patients had bilateral pulmonary artery obstruction versus seven patients who had unilateral obstruction. In the COVID-19 PE group, 12 patients had bilateral pulmonary artery obstruction versus 19 patients who had unilateral obstruction and all patients had CO-RADS 6 with parenchymal involvement of ≥ 50%.

5-Electrocardiogram

All patients had electrocardiogram (ECG) which identified various abnormalities with significant rates. In the COVID-19 PE group, 54.8% had a right bundle branch block (RBBB), 22.6% had sinus tachycardia, and 12.9% had atrial fibrillation arrhythmia (AFA). We found the S1Q3 aspect in 16.13% of cases. In the non-COVID-19 PE group, 72.7% had a RBBB, 27.3% had tachycardia, and 18.2% had AFA. ***(Table 13)***

Table 13: Results of Electrocardiogram.

		COVID-19		Total
		Non-COVID-19 PE	COVID-19 PE	
S1Q3	Percentage	2	5	7
	%	18.18%	16.13%	16.6%
Tachycardia	Percentage	3	7	10
	%	27,3%	22,6%	23,8%
RBBB	Percentage	8	17	25
	%	72.7%	54.8%	59.52%
AFA	Percentage	2	4	6
	%	18,2%	12,9%	14,3%

6-Blood results

6.1-Blood count

The mean hemoglobin value was 12.55g/dl in the non-COVID-19 group versus 13.45g/dl in the COVID-19 group. The mean platelet count was 306363.64/mm³ in the non-COVID-19 group versus 266967.74/mm³ in the COVID-19 group.

6.2-Hemostasis

All patients had a systematic hemostasis test performed upon admission. ***(Table 14)***

Table 14: Results of hemostasis test.

COVID-19		N	Mean	Standard deviation
Partial thromboplastin time	Non-COVID-19 PE	11	24,80	2,57
	COVID-19 PE	31	26,48	3,44
Prothrombin ratio	Non-COVID-19 PE	11	75	23,6
	COVID-19 PE	31	74	23
D -dimers	Non-COVID-19 PE	11	893,06	2353,37
	COVID-19 PE	31	1087,38	1521,96
Fibrinogen	Non-COVID-19 PE	11	4,76	3,01
	COVID-19 PE	31	5,201	2,53

6.3-Troponin

Troponin was performed for all patients. ***(Table 15)***

Table 15: Troponin results.

COVID 19		***N***	***Mean***	***Standard deviation***
Troponin	*Non-COVID-19 PE*	*11*	*14,18*	*8,87*
	COVID-19 PE	*31*	*99,08*	*107,92*

6.4-Arterial Blood Gas

Arterial Blood Gas (ABG) was performed in 63.63% in the non-COVID-19 PE group versus 77.41% in the COVID-19 PE group where there was a significant rate of hypoxemia and hypocapnia. ***(Table 16)***

Table 16: Results of Arterial Blood Analysis.

		COVID-19		***Total***
		Non-COVID-19 PE	COVID-19 PE	
Normal	*Percentage*	*0*	*2*	*2*
	%	*0,0%*	*6,5%*	*4,8%*
Hypoxemia	*Percentage*	*7*	*24*	*31*
	%	*63,6%*	*77,4%*	*73,8%*
Hypocapnia	*Percentage*	*6*	*14*	*20*
	%	*54.54%*	*45.16%*	*47.61%*
Hypercapnia	*Percentage*	*1*	*5*	*6*
	%	*9.1%*	*16.12 %*	*14.28%*
Normocapnia	*Percentage*	*4*	*12*	*16*
	%	*36.36%*	*38.7%*	*38.1%*

-Pulmonary Embolism Severity Index

After confirmation of the diagnosis, the Pulmonary embolism Severity Index (PESI) was used to assess the severity of PE. According to PESI index, patients at risk of PE are divided into five classes; in our series only the first three classes were identified. In the non-COVID-19 PE group, 45.5% of patients were within class I (very low risk patients) and 54.5% within class II (low risk patients). In the COVID-19 PE group, 41.9% were within class I (very low risk patients), 32.3% within class II (low risk patients), and 25.8% within class III (moderate risk patients). ***(Table 17)***

Table 17: Severity of pulmonary embolism using pulmonary embolism severity index.

			COVID-19		***Total***
			Non-COVID-19 PE	COVID-19 PE	
PESI	*Class I*	*Percentage*	*5*	*13*	*18*
		%	*45,5%*	*41,9%*	*42,9%*
	Class II	*Percentage*	*6*	*10*	*16*
		%	*54,5%*	*32,3%*	*38,1%*
	Class III	*Percentage*	*0*	*8*	*8*
		%	*0,0%*	*25,8%*	*19,0%*
Total		*Percentage*	*11*	*31*	*42*
		%	*100,0%*	*100,0%*	*100,0%*

-Management

1-Resuscitation measures

Around 72.7% of non-COVID-19 patients and 93.5% of COVID-19 patients required urgent mechanical ventilation. This was mainly due to respiratory failure. Two of non-COVID-19 patients and six of COVID-19 patients required vasoactive drugs (i.e. norepinephrine). ***(Table 18)***

Table 18: Resuscitation measures.

		COVID-19		Total
		Non-COVID-19 PE	COVID-19 PE	
Mechanical ventilation	Percentage	8	29	37
	%	72,7%	93,5%	88,1%
Vasoactive drugs	Percentage	2	6	8
	%	18,2%	19,4%	19,0%

2-Treatment of pulmonary embolism

Anticoagulation therapy was started immediately after confirmation of the diagnosis of PE. Unfractionated heparin (UFH) was used in 92.8% of COVID-19 patients and non-COVID-19 patients overlapped with antivitamin K (AVK) which was used in 96.8% of COVID-19 PE and 63.6% of non-COVID-19 PE. Anticoagulation therapy was prescribed in the absence of any absolute or relative contraindication. In the non-COVID-19 PE group, no patient underwent thrombolysis. In the COVID-19 PE group, however, four patients underwent thrombolysis. No patient underwent embolectomy. ***(Table 19)***

Table 19: Treatment modalities of pulmonary embolism.

		COVID-19		Total
		Non-COVID-19 PE	COVID-19 PE	
	Percentage	10	29	39
UFH	%	90.9%	93.54%	92.8%
AVK	Percentage	7	30	37
	%	63,6%	96,8%	88,1%
Thrombolysis	Percentage	0	4	4
	%	0,0%	12,9%	9,5%
Embolectomy	Percentage	0	0	0
	%	0,0%	0,0%	0,0%

-Evolution

1-Complications

Around 45.5% of patients in the non-COVID-19 group had good outcomes versus 6.5% in the COVID-19 group. ***(Table 20)***

Table 20: Complications of pulmonary embolism in COVID-19 and non-COVID-19 patients.

			COVID-19		Total
			Non-COVID-19 PE	COVID-19 PE	
Complications	Death	Percentage	6	23	29
		%	54,5%	74,2%	69,0%
	Cardiogenic shock	Percentage	0	4	3
		%	0,0%	12,9%	9,5%
	Haemorrhagic shock	Percentage	0	2	2
		%	0,0%	6,5%	4,8%
	No complications	Percentage	5	2	7
		%	45,5%	6,5%	16,7%
Total		Percentage	11	31	42
		%	100,0%	100,0%	100,0%

2-Mortality

The mortality rate was significantly higher in the Covid-19 PE group with a rate of 74.2% as compared to 54.5% in the non-COVID-19 PE group. ***(Table 21)***

Table 21: Mortality within each study group.

			COVID-19		Total
			Non-COVID-19 PE	COVID-19 PE	
Death	No	Percentage	5	8	13
		%	45,5%	25,8%	31,0%
	Yes	Percentage	6	23	29
		%	54,5%	74,2%	69,0%
Total		Percentage	11	31	42
		%	100,0%	100,0%	100,0%

2) Analytical study

In order to determine the factors associated with high mortality rate in patients who developed COVID-19 PE, univariate analyses were performed according to different parameters (i.e. age, sex, medical history, PE risk factors, functional and physical clinical symptoms, WELLS score, and PESI index). As a result, the parameters and factors retained as significantly related to high mortality rate were: medical and toxic history (i.e. cancer, pregnancy, alcohol), risk factors (i.e. prolonged immobilization, gyneco-obstetrical history), functional clinical symptoms (i.e. palpitations), physical clinical signs (i.e. tachycardia, fever, leg swelling), high WELLS score, and high PESI score. (***Tables 22-27***)

Table 22: Analysis of baseline characteristics.

			Death		Total	P value
			No	YES		
COVID-19	Non-COVID-19 PE	Percentage	5	6	11	0,226
		%	38,5%	20,7%	26,2%	
	COVID-19 PE	Percentage	8	23	31	
		%	61,5%	79,3%	73,8%	
AGE (years)	30-45	Percentage	5	4	9	0,270
		%	38,5%	13,8%	21,4%	
	46-55	Percentage	1	6	7	
		%	7,7%	20,7%	16,7%	
	56-65	Percentage	3	6	9	
		%	23,1%	20,7%	21,4%	
	>65	Percentage	4	13	17	
		%	30,8%	44,8%	40,5%	
Sex	Women	Percentage	8	13	21	0,317
		%	61,5%	44,8%	50,0%	
	Men	Percentage	5	16	21	
		%	38,5%	55,2%	50,0%	
		%	53,8%	48,3%	50,0%	
Cancer	No	Percentage	11	29	40	0,030
		%	84,6%	100,0%	95,2%	

	Yes	Percentage	2	0	2	
		%	15,4%	0,0%	4,8%	
Pregnancy	No	Percentage	11	29	40	0,030
		%	84,6%	100,0%	95,2%	
	Yes	Percentage	2	0	2	
		%	15,4%	0,0%	4,8%	
Smoking	No	Percentage	11	26	37	0,641
		%	84,6%	89,7%	88,1%	
	Yes	Percentage	2	3	5	
		%	15,4%	10,3%	11,9%	
Alcohol	No	Percentage	11	29	40	0,030
		%	84,6%	100,0%	95,2%	
	Yes	Percentage	2	0	2	
		%	15,4%	0,0%	4,8%	
		%	30,8%	13,8%	19,0%	
Hormonal therapy	No	Percentage	12	28	40	0,550
		%	92,3%	96,6%	95,2%	
	Yes	Percentage	1	1	2	
		%	7,7%	3,4%	4,8%	
Long-term Steroids use	No	Percentage	12	28	40	0,550
		%	92,3%	96,6%	95,2%	
	Yes	Percentage	1	1	2	
		%	7,7%	3,4%	4,8%	

Table 23: Analysis of pulmonary embolism risk factors.

			Death		**Total**	**P value**
			No	Yes		
Cancer	No	Percentage	11	29	40	0,030
		%	84,6%	100,0%	95,2%	
	Yes	Percentage	2	0	2	
		%	15,4%	0,0%	4,8%	
Hospitalisation < 3 months	No	Percentage	1	4	5	NS
		%	7,7%	13,8%	11,9%	
	Yes	Percentage	12	25	37	0,572
		%	92,3%	86,2%	88,1%	
Long-term immobilization	No	Percentage	11	29	40	0,030
		%	84,6%	100,0%	95,2%	
	Yes	Percentage	2	0	2	
		%	15,4%	0,0%	4,8%	
Gyneco-obstetrics	No	Percentage	11	29	40	0,030
		%	84,6%	100,0%	95,2%	
	Yes	Percentage	2	0	2	
		%	15,4%	0,0%	4,8%	

Table 24: Analysis of functional symptoms.

			Death		Total	P value
			No	Yes		
Dyspnea	No	Percentage	0	3	3	0,229
		%	0,0%	10,3%	7,1%	
	Yes	Percentage	13	26	39	
		%	100,0%	89,7%	92,9%	
Chest pain	No	Percentage	12	24	36	0,414
		%	92,3%	82,8%	85,7%	
	Yes	Percentage	1	5	6	
		%	7,7%	17,2%	14,3%	
Palpitations	No	Percentage	5	21	26	0,036
		%	38,5%	72,4%	61,9%	
	Yes	Percentage	8	8	16	
		%	61,5%	27,6%	38,1%	
		%	100,0%	100,0%	100,0%	

Table 25: Analysis of physical symptoms.

			Death		Total	P value
			No	Yes		
Tachypnea	No	Percentage	0	5	5	0,111
		%	0,0%	17,2%	11,9%	
	Yes	Percentage	13	24	37	
		%	100,0%	82,8%	88,1%	
Pulmonary rales	No	Percentage	1	9	10	0,101
		%	7,7%	31,0%	23,8%	
	Yes	Percentage	12	20	32	
		%	92,3%	69,0%	76,2%	
Tachycardia	No	Percentage	10	12	22	0,033
		%	76,9%	41,4%	52,4%	
	Yes	Percentage	3	17	20	
		%	23,1%	58,6%	47,6%	
Fever	No	Percentage	4	1	5	0,011
		%	30,8%	3,4%	11,9%	
	Yes	Percentage	9	28	37	
		%	69,2%	96,6%	88,1%	
Shock	No	Percentage	13	28	41	0,498
		%	100,0%	96,6%	97,6%	
	Yes	Percentage	0	1	1	
		%	0,0%	3,4%	2,4%	
Leg swelling	**No**	Percentage	**9**	**28**	**37**	**0,011**
		%	69,2%	96,6%	88,1%	
	Yes	Percentage	4	1	5	
		%	30,8%	3,4%	11,9%	

Table 26: Analysis of biological risk factors.

Z XZZX		N	Mean	Standard deviation	P value
Haemoglobin	*Survivors*	*13*	*13,846*	*2,035*	*0,308*
	Death	*29*	*12,931*	*2,154*	
Platelets	*Survivors*	*13*	*356384,615*	*166461,476*	*0,134*
	Death	*29*	*241827,586*	*111537,011*	
Partial thromboplastin time	*Survivors*	*13*	*25,162*	*2,447*	*0,090*
	Death	*29*	*26,431*	*3,568*	
Prothrombin ratio	*Survivors*	*13*	*2793,3077%*	*42,566*	*0,000*
	Death	*29*	*70,7931%*	*0,2723*	

Table 27: Analysis of severity scores.

			Death		Total	P value
			No	Yes		
WELLS	*High*	*Percentage*	*2*	*10*	*12*	*0,044*
		%	*15,4%*	*34,5%*	*28,6%*	
	Low	*Percentage*	*3*	*12*	*15*	
		%	*23,1%*	*41,4%*	*35,7%*	
	Intermediate	*Percentage*	*8*	*7*	*15*	
		%	*61,5%*	*24,1%*	*35,7%*	
PESI	*Class I*	*Percentage*	*8*	*10*	*18*	*0,025*
		%	*61,5%*	*34,5%*	*42,9%*	
	Class II	*Percentage*	*5*	*11*	*16*	
		%	*38,5%*	*37,9%*	*38,1%*	
	Class III	*Percentage*	*0*	*8*	*8*	
		%	*0,0%*	*27,6%*	*19,0%*	

Discussion

PE is the obstruction of one or more pulmonary arteries supplying the lung. Thrombi form in areas of low blood flow, usually in the deep veins of the calf, and then spread to proximal veins, including and above popliteal veins, from which they are more likely to embolize.

The risk of PE is equivalent to that of thrombosis, as both diseases can occur simultaneously. PE is considered "provoked" if there is a temporary or reversible risk factor (e.g. surgery, trauma, immobilization, pregnancy, use of oral contraceptives or hormone replacement therapy) within the 6 weeks to 3 months prior to the diagnosis. It is considered "unprovoked" in the absence of any reversible risk factor.[5] The presence of a persistent risk factor may affect the decision on the duration of anticoagulation after a first episode of PE.

The development of venous thromboembolism may be related to genetic factors (e.g. constitutional thrombophilia) or to environmental or acquired factors. The risk of thrombosis is also associated with an individual risk related to the patient, such as age ≥75 years, a personal or family history of venous thromboembolism, obesity, active cancer, and cardiac or respiratory failure.

Immobilization, sepsis, pregnancy, stroke, trauma, or surgery are also risk factors for PE which may underline the risk of viral infection. The risk of PE increases proportionally with the number of underlying factors. Hospitalized patients with COVID-19 have a significantly higher risk of thrombosis as compared to non-COVID-19 patients. In our study, the main risk factor was hospitalization less than 3 months with a rate of just under 84% while Rotzinger et al. reported a rate of 94%.[6] In the second place came surgery with a rate of 16.10%.

In our series, 9.70% of patients were followed for cardiopathy. Indeed, cardiac disease usually obliges patients to remain sitting or lying down. Consequently, they remain constantly immobile. This in addition to the associated risk related to reduced blood flow. This is consistent with the Audo et al. study with a rate of 14% and the Fabré et al. study with a rate of 13%.[7,8] Likewise, 22.60% of patients hospitalized in our ICU were older than 75-year-old. Advanced age is a predictive factor of severity that magnifies the hemodynamic impact of PE. Owing to the similarity of our results with most available studies, our study highlights the existence of a direct link between these risk factors and PE.

PE is even more alarming in severe forms of COVID-19. Its incidence in patients without COVID-19 as compared to COVID-19 patients was around 13.30% versus 78% in Germany[9]; 13.6% versus 66.40% in Netherlands[10]; 4.20% versus 54% in Italy[11]; and 1.10% versus 65.80% in France[12], respectively. In our study, 42 out of 611 patients in the ICU had a confirmed PE with an incidence of 6.87%, of which 31 COVID-19 cases (5.07%) and 11 non-COVID-19 cases (1.80%). The incidence of PE in COVID-19 patients was thus higher than in non-COVID-19 patients. Our study is therefore consistent with incidences found in other studies.

Older age is also a predictive factor for fatal PE due to underlying cardiorespiratory comorbidities which worsen hemodynamic impact of PE.[13,14] Patients over 40-year-old have an increased risk of PE. This risk roughly doubles each decade.[15] Similarly, in our series, 72.8% of non-COVID-19 patients were older than 40-year-old. The average age of non-COVID-19 patients in our series (i.e.46-year-old) was much lower than that of the STEP study in France but was slightly closer to that of ABBADI in Fes.[16,17] Likewise, 54.8% of COVID-19 patients in our series were older than 65-year-old with an average age of 64.55-year-old, which is in line with a study carried out in Spain in 2020, which reported a predominance in the same age group with a rate of 47% and an average age of 63-year-old.[18] All these studies allow us to conclude that age is a risk factor for PE in both COVID-19 and non-COVID-19 patients.

In non-COVID-19 patients, a predominance of women has been reported by most series, in particular in the ICOPER (International Cooperative Of Pulmonary Embolism Registry) and PIOPED II (Prospective Investigation Of Pulmonary Embolism Diagnosis) studies. This may be related to the high incidence of phlebitis in the lower limbs due to oral contraception which is identified as the primary cause of venous thromboembolism in young women with a 2 to 6-fold increase in risk.[13,15] In patients with COVID-19 PE, a slight female predominance was noted and was consistent with the results of two studies by Danzi et al.[19] and Jafari et al.[20] but in contrast with other studies where the predominance was male.[6,21-23]

Patients had a variety of comorbidities, the most common were hypertension and diabetes in both COVID-19 and non-COVID-19 patients which is consistent with the results of numerous studies by Danzi et al.[19], Ullah et al.[22], Audo al.[7], and Le Berre et al.[24] Around 16.1% of patients with COVID-19 PE had a history of surgery compared with 27.3% of non-COVID-19 patients, which is not in line with the results of Fabré et al. in France[25] and Audo et al. in Italy[7], which showed a high rate of surgical history.

Clinical manifestations of PE are highly variable, ranging from mild respiratory distress to sudden death depending on the extent of pulmonary obstruction as well as the underlying cardiorespiratory status.[26] The diagnosis of PE should always be made, in the case of a high-risk patient, through various signs namely dyspnea, chest pain, hemoptysis, cough, and syncope. In more than 90% of cases, PE is manifested by dyspnea and/or chest pain. In our series, these two symptoms were the most frequent reason for consultation. Among our patients, 81.82% had chest pain while all of them had dyspnea. In patients with chronic heart and/or respiratory failure, worsening dyspnea may be the sole symptom revealing PE.[26] These findings correlate with the published litterature.[27-30] In our series, dyspnea and chest pain were the main clinical symptoms observed in COVID-19 patients. In second position we noted dry cough with a rate of 93.5%.

In the study by Di Castelnuovo et al. in Italy[31], they found high rates of fever (69%) and rales (85%); and the study by Fresán et al. in Spain[32] reported a predominance of fever (78%). When the first cases of COVID-19 appeared in China, the clinical picture was drawn as a respiratory viral infection whose severity depended on the degree of parenchymal involvement that causes tachypnea which was the main physical sign found in our COVID-19 patients with a rate of 90.3%. We also noted fever with a rate of 90.3%. Our results were therefore in line with other studies.

Regarding the estimation of clinical probability in COVID-19 patients, the original version of the simplified WELLS score was used. Around 35.50% had a low probability, 32.30% had an intermediate probability, and 32.32% had a high probability. Our results were consistent with the Adriana M. Girardi study[33] where most COVID-19 patients had a low probability (38%) whereas other studies such as the Brittany Kirsch® study[34] reported that 40% of patients had an intermediate probability while 35% had a low probability. Likewise, the Jori E. May study[35] showed that most patients had an intermediate probability (37%).

Plasma D-dimer test is the first step of the diagnostic strategy in case of a low clinical probability of PE. In our study, D-dimer assay was performed in all patients while it was performed in 60% and in 83.3% in the OUSSARI and SABREI series respectively.[36] It has the advantage to easily and rapidly rule out a deep thrombosis in case of low clinical probability and thus sparing the patient from expensive and ionizing examinations (i.e. chest CT angiogram). The results in our series were all positive above the threshold value of 500ug/l. The particularly high levels of d-dimers in the COVID-19 cohort may be related to the pro-inflammatory and hypercoagulable state.

Troponin measurement was performed in all COVID-19 and non-COVID-19 patients. A meta-analysis confirmed that in patients with PE, an elevated troponin level is associated with high mortality.[37] This association was independent of other clinical and ultrasound severity criteria.

The electrocardiogram (ECG) was performed in all our patients. Several electrical abnormalities could be observed in PE such as sinus tachycardia, complete or incomplete right bundle branch block, S1Q3 aspect, supraventricular arrhythmias (including atrial fibrillation), and anterior repolarization disorders.[38] The S1Q3 aspect is considered the most pathognomonic sign but its prevalence does not exceed 20% in most studies.[39] In our series, it was found in 18.18% of non-COVID-19 patients and 16.13% of COVID-19 patients. The presence of complete or incomplete right bundle branch block, related to ischemia of the right branch of the His trunk due to an acute rise in the right afterload, is a more prevalent sign in massive PE.[40] All these electrical signs are not specific, and a normal ECG cannot rule out the diagnosis. Therefore, combination of clinical and electrical signs has a great diagnostic value.

Trans-thoracic echocardiography is a simple and non-invasive examination which can easily be performed at the bedside, which makes it useful to potentially indicate an emergency thrombolysis if the patient's hemodynamic state does not allow transport for chest CT scan. However, it should be stressed that a normal cardiac ultrasound does not rule out a PE because of low sensitivity. Cardiac repercussions of PE which can be assessed by echocardiography appear only in severe cases. Following abnormalities could be shown: dilatation of the right cavities, increase in the right ventricle /left ventricle ratio (RV/LV), hypokinesia of the free wall of the right ventricle, and tricuspid insufficiency.[35]

Echocardiography allowed us to find out cardiac abnormalities in our patients. These abnormalities found in COVID-19 and non-COVID-19 patients were not significantly different. Dilatation of the right cavities indicating acute pulmonary hypertension was the most predominant finding with a rate of 93% in the COVID-19 group and 81.1% in the non-COVID-19 group. Visualization of a mobile thrombus in the right cavities and/or in the pulmonary artery remains a rare sign and does not exceed 10% of patients with PE.[41] Our series recorded similar findings in COVID-19 patients with a rate of 9.7%. (***Fig2***)

Fig 2: Cardiac ultrasound showing dilatation of right cavities.

The performance of a complete ultrasound with exploration of the distal veins improves the diagnosis of PE.[42,43] Moreover, studies approve that existence of a concomitant deep venous thrombosis (DVT) is associated with an increased risk of mortality.[44] In our study, 96.8% of COVID-19 patients and 72.7% of non-COVID-19 patients had a lower limbs doppler ultrasound which showed DVT in 29.03% of cases in the COVID-19 group and in 36.36% of cases in the non-COVID-19 group, which is much lower than the study

carried out by Abbadi in Fes showing a DVT in more than half of the cases.[17]
The chest CT angiogram has become the examination of choice in high clinical probability of PE, or in case of non-high clinical probability associated with a positive D-dimer assay. The approach combining clinical probability, plasma D-dimer assay, and chest CT angiogram has been widely validated.[45] Chest CT angiogram was performed in all our patients. This rate is close to that reported by the ABBADI series[17], but is in contrast with that reported by the OULDZEIN series[30] and the HASSOUNI series[46] which used chest CT angiogram in only 61% and 21.5% of cases, respectively. (***Fig 3***)

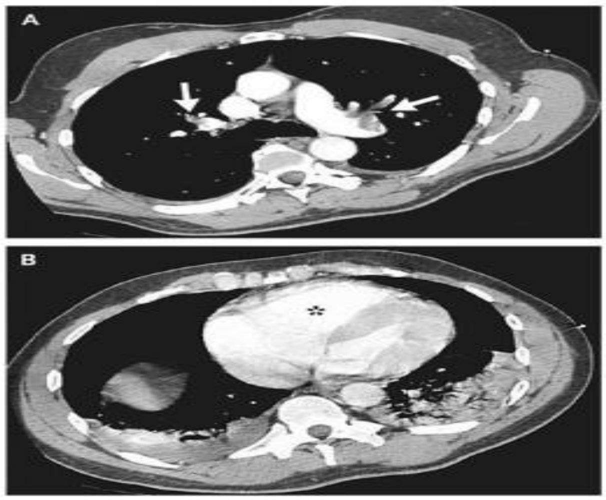

Fig 3: Chest computed tomography angiogram showing pulmonary embolism.

In our series, Arterial blood gas (ABG) was performed in 63.63% of non-COVID-19 patients and in 77.41% of COVID-19 patients. ABG typically shows hypoxia-hypocapnia.[47] This was the case in our study. Although, the increase in dead space should lead to an increase in PaCO2, this is usually compensated by hyperventilation secondary to hypoxemia. However, PaCO2 may be elevated or normalized if PE occurs in a patient with respiratory failure. In patients with massive PE, a mixed acidosis is frequently observed and is due to excessive increase in dead space, respiratory muscles fatigue, and tissue hypoperfusion secondary to shock.
Acute PE is still associated with high morbidity and mortality despite various treatment options currently available. Prospective studies report in-hospital mortality rates ranging from 1 to 15% depending on the severity of the initial clinical presentation.[48,49] The Pulmonary Embolism Severity Index (PESI) is used to predict mortality at one month after a PE episode. Once the diagnosis of PE has been made, an analysis of severity using PESI is essential to classify patients into five classes: Class 1: Very low risk patient, Class 2: Low risk patient, Class 3: Moderate risk patient, Class 4: High risk patient, Class 5: Very high risk patient.
In our series, non-COVID-19 patients had a PESI index which showed a very low risk of mortality in 45.5% and a low risk in 54.5%. In COVID-19 patients, the PESI showed a very low risk of mortality in 41.90%, a low risk in 32.30%, and a moderate risk of mortality in 25.80%. The table below compares the results of our study with those of other authors. (***Table 28 and 29***)

Table 28: Comparison of pulmonary embolism severity index between our non-COVID-19 patients and other studies.

	Our study	*Abbadi* [17]	*D Aujesky* [49]	*Ouassari* [29]	*L.Aazri* [50]	*MDB Jean-Marc* [51]
Class I	*45,50%*	*20,0%*	*8%*	*11%*	*12%*	*21%*
Class II	*54,50%*	*12,5%*	*64%*	*18%*	*17%*	*45%*
Class III	*0,00%*	*27,5%*	*28%*	*31%*	*29%*	*27%*
Class IV	*0%*	*22,5%*	*0%*	*25%*	*22%*	*7%*
Class V	*0%*	*17,5%*	*0%*	*15%*	*19%*	*0%*

Table 29: Comparison of pulmonary embolism severity index between our COVID-19 patients and other studies.

	Our study	H Xu [52]	OM Muñoz [53]	YWH George [54]
Class I	41,90%	32%	55%	42%
Class II	32,30%	28%	23%	21%
Class III	25,80%	32%	5%	23%
Class IV	0%	8%	15%	12%
Class V	0%	0%	2%	2%

PE is a medical emergency requiring early management to reduce the risk of death or recurrence. The purpose of management is to create sufficient hypocoagulability to prevent further thrombosis, to allow physiological fibrinolysis, to prevent embolic migration, and to decrease the rate of mortality from an acute thrombotic event.

Early mortality in PE is related to failure of the right ventricle (RV) due to an acute rise of RV afterload.[55] In cases of low cardiac output and normal blood pressure, fluid filling should be cautious. Excessive fluid loading on this suffering ventricle is generally not tolerated. This should not generally exceed 500 ml in the absence of obvious hypovolemia. Crystalloids and/or colloids could be used.[56] Along with fluid filling, the use of vasopressors is often necessary, and norepinephrine appears to improve right ventricular function. This beneficial effect is attributed both to its direct inotropic effect and to improvement of right coronary perfusion due to the increase in aortic pressure.

Nasal oxygen therapy is usually sufficient to correct hypoxemia. It was used in most of our patients. Mechanical ventilation is only indicated if there is an altered consciousness due to low blood flow and/or in the event of cardiocirculatory arrest. Tidal volume should be reduced to 7 ml/Kg with no positive expiratory pressure to avoid a surge in intrathoracic pressures.[57]

Anticoagulation is used to slow down excessive coagulation. It is used in the treatment and prophylaxis of deep vein thrombosis and pulmonary embolism.[58] Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) and antivitamin K are the most commonly used.

LMWH have revolutionized the management of patients with venous thrombosis. Compared with UFH, they have shown at least similar efficacy with a reduced risk of bleeding. Their intra- and inter-individual variability is reduced, allowing them to be prescribed according to the patient's body weight. They should be prescribed during initial anticoagulation in non-high-risk patients.[59,60] Currently, two LMWHs have been validated for the treatment of PE, Enoxaparin and Tinzaparin.[61,62]

UFH is usually administered intravenously, has a short half-life, and does not have renal clearance. It is prescribed in the acute phase of PE in case of severe renal failure. Regular biological monitoring by partial thromboplastin time is critical during UFH treatment.

Fondaparinux has low inter- and intra-individual variability, allowing fixed-dose administration without the need for biological monitoring because of the low risk of heparin induced thrombocytopenia (HIT). Fondaparinux has been shown to be at least as effective in terms of recurrence, bleeding, and death, as UFH or enoxaparin.[63]

Overall, continuous intravenous UFH remains the preferred initial anticoagulation modality in high-risk patients because of its greater manageability.[64] In patients without shock and with intermediate-risk PE, the use of LMWH should be the preferred initial anticoagulation modality during the first 24-48 hours of hospitalization. In the absence of fibrinolytic treatment and/or after clinical improvement, continuation of LMWH followed by antivitamin K or prescription of a direct oral anticoagulant (e.g. Rivaroxaban, Apixaban, Edoxaban, Dabigatran) are two possible options. Duration of anticoagulation depends primarily on the reversibility of the thromboembolic risk factor at the time of diagnosis as well as on the benefit/risk ratio, which must be assessed regularly throughout the treatment period.

Thrombolysis is indicated in case of proven PE complicated by shock or arterial hypotension defined by a systolic blood pressure lower than 90 mmHg or as an acute drop of more than 40 mmHg from baseline. Surgical embolectomy under extracorporeal circulation is only indicated in exceptional cases of massive PE with a refractory shock and/or formal contraindication to thrombolysis. However, this procedure has a high mortality rate (i.e. 30 to 40%).[56] Percutaneous embolectomy using a catheter is an alternative method to surgery.[65] Its success rate is around

80%, and is associated with a mortality rate varying from 0 to 25% according to series.[66]

Interruption of the inferior vena cava by a vena cava filter is used to reduce the risk of recurrence of PE in the short term. However, it increases the risk of deep vein thrombosis and post-phlebitic syndrome in the long term.[67] It is indicated in cases of absolute contraindication to anticoagulation therapy and in patients who have undergone surgical embolectomy.[68]

Immediate management in our study was essentially based on the administration of curative doses of UFH in 92.2% of cases. Antivitamin K was prescribed from the first day for 88.10% of patients. Monitoring was based on prothrombin ratio and international normalized ratio (INR) every two days in order to reach effective anticoagulation. This was in line with recommendations.[69] Direct oral anticoagulants were not prescribed in our series. Likewise, surgical and percutaneous procedures were not performed in our study whereas thrombolysis was performed in 9.50% of our patients. Overall, anticoagulation with heparin, alone or combined with antivitamin K, remains the most common management strategy.

PE is responsible for 5 to 10% in-hospital mortality. However, this varies significantly with the severity of obstruction, underlying comorbidities, the presence of clinical symptoms of severity, and the type of treatment undertaken.[58] The mortality rate of non-COVID-19 PE in our series was around 55%, which is much higher than other series where it ranged from 0% to 22%.[16,17,29,30,36,46] According to the literature, COVID-19 PE even under anticoagulation therapy has a poor prognosis. The mortality rate in our COVID-19 PE was as high as 74.2% which is in line with most other studies. For instance, Rotzinger et al. and Jafari et al. reported a very high mortality rate, 83% and 81% respectively.[6,20]

The risk of venous thromboembolism is significant in hospitalized patients but can be significantly reduced with an appropriate prophylaxis. UFH, LMWH, fondaparinux, warfarin, along with mechanical prophylaxis have been shown to be effective in a range of clinical settings. Unfortunately, prophylactic measures appear to be grossly under or misused, as shown by American and international studies.[65]

Conclusion

PE refers to partial or complete obstruction of a pulmonary artery. COVID-19 is associated with a state of hypercoagulability leading to thromboembolic complications. PE is therefore a serious complication to be sought and prevented in COVID-19 patients. The diagnostic approach is based on the assessment of clinical probability along with paraclinical examinations namely D-dimer assay, cardiac ultrasounds, and chest CT angiogram. Management is complex and is often associated with significant morbidity and mortality. Prophylaxis is therefore of paramount.

Limitations of the study:

-The retrospective nature of the study.

-Single center study which may undermine its generalizability.

-Difference in sample size between the two arms with disparities in some baseline confounders (e.g. age).

-Age brackets were different from those recommended by the world health organization (WHO) and were based on local study population.

-Association with other clinical conditions like sepsis may have impacted the overall prognosis in both arms.

Statements and Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial interests to disclose.

Data availability: The datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

Ethics approval: This was an observational study. The Research Ethics Committee confirmed that no ethical approval was required.

Consent to publish: The manuscript contains no individual personal details, images, nor videos.

CRediT author statement: Pr Boubaker Charra: Conceptualization, Methodology, Resources, Supervision, Project administration, and Validation. **Dr Yassine Bou-ouhrich**: Methodology, Investigation, Formal analysis, Writing Original Draft, Writing Review&Editing, Data curation, and Visualization.

Acknowledgements: We thank the staff of the medical intensive care unit of the Ibn Rochd University Hospital for their contribution to the study.

Disclosure of Conflicts of interest: The authors have no conflict of interest to disclose.

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