

ORIGINAL RESEARCH

Patient Characteristics and Predictors of Pulmonary Embolism in Patients Infected with COVID - 19 in Upper Egypt

Ahmed Hussein 1, Ahmed M Khalaf², Laila A Alsharawy³, Gomaa Abdelrazek⁴, Mohammad Shafiq Awad⁵

¹Cardiology Unit, Department of Internal Medicine, Faculty of Medicine, Sohag University, Sohag, Egypt; ²Department of Internal Medicine, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt; ³Department of Chest Diseases, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt; ⁴Cardiology Department, Faculty of Medicine, Fayoum University, Fayoum, Egypt; ⁵Cardiology Department, Faculty of Medicine, Beni-Suef University,

Correspondence: Ahmed Hussein, Sohag University, Faculty of Medicine, Nasser City, Sohag, 82524, Egypt, Tel +2 01011145537, Fax +2 0934600349, Email ahmed_hussien@med.sohag.edu.eg

Background: A little is known about the risk factors and predictors of pulmonary embolism (PE) in Coronavirus disease 2019 (Covid-19) infected patients. Therefore, we directed this study to investigate the predictors of PE in patients infected with Covid – 19 in Upper Egypt.

Methods: We conducted a retrospective cohort study on 297 patients infected with COVID-19, aged ≥ 18 years old. Suspicion of COVID-19 infection was based on the World Health Organization (WHO) criteria and confirmed by nasal and pharyngeal swab for real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. The patient was also determined to have COVID-19 when CT results that were thought to be typical for COVID-19 and clinical data that were compatible were present.

Results: PE was diagnosed in 18.2% of patients. We found that the incidence of PE was significantly higher in older patients, females, those with higher BMI, hypertensive patients, diabetics, and patients with co-morbidities. Also, PE was significantly higher in patients presented with dyspnea, chest pain, longer duration of symptoms at hospital admission, and lower oxygen concentration. The mean serum Hb level, platelet count, TLC and absolute lymphocytic count were markedly reduced in those who had PE. All the patients who developed PE had a CO-RADS scale five on their CT chest scan. Age > 65, BMI > 25, DM, and associated co-morbidities were the independent patients' characteristics associated with the development of PE after the multivariate regression analysis.

Conclusion: PE is a common complication of Covid 19 infection. PE is associated with a variety of clinical and laboratory parameters in univariate analysis, but age > 65, BMI > 25, DM, and associated co-morbidities were the independent patients' characteristics associated with the development of PE in those infected with Covid-19.

Keywords: Covid-19, SARS-CoV-2, CO-RADS, pulmonary embolism

Introduction

The Covid-19 pandemic, which has affected millions of people globally and spread to more than 200 nations, is the most egregiously horrible in the past 100 years.² Covid-19 is brought on by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) and one of its cellular receptors is the angiotensin-converting enzyme 2 (ACE2).³ From asymptomatic or mild symptoms in about 80% of patients to a case mortality rate of about 2% in hospitalised patients, Covid-19 exhibits a variety of clinical manifestations.²⁻⁴ Utilizing laboratory tests for early risk stratification is depending on the reasoning that predictive biomarkers of disease severity enable the timely recognition of patients at more risk of progression towards adverse outcomes; this helps for early appropriate therapeutic intervention, thus focusing the allocation of limited medical care resources on patients who would get the best advantages.³ Numerous studies have shown that hospitalized individuals with severe COVID-19 types have aberrant serum coagulation profiles. Additionally, the patients with COVID-19 infection

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who died fit the clinical requirements for disseminated intravascular coagulation (DIC).⁵ In a study using computed tomography (CT) scans, pulmonary thrombi were present in the patients with SARS-CoV-2-related pneumonia.⁶ Unambiguously, increased D-dimer levels were linked to in-hospital mortality.⁷ Patients with severe COVID-19 have been shown to have a decreased risk of mortality when taking anticoagulant medication.⁸ Compared to before the pandemic, the COVID-19 pandemic has been linked to higher incidence of PE-related mortality.⁹ The risk factors and indicators of pulmonary embolism (PE) in COVID-19-infected patients are poorly understood.

Methods

Design of the Study

We conducted a retrospective cohort study on 297 patients infected with COVID-19, aged ≥ 18 years old. We collected the patient's data records from 4 different centers at period of 3 months duration according to the illustrated flowchart (Figure 1). Based on the World Health Organization (WHO) criteria, we suspected COVID-19 infection, which was later verified by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing of nose and pharyngeal swabs. ¹⁰ The patient was also determined to have COVID-19 when CT results that were regarded characteristic for COVID-19 (ie, significant bilateral and peripheral ground-glass opacities and/or alveolar consolidation) and clinical data were in agreement. ^{11,12}

Due to the study's retrospective nature, informed consent was not required. The patient's data confidentiality was ensured. Anonymous data were taken from the recorded files after approval from the institution. The study protocol was in compliance with the 1975 Helsinki Declaration's ethical principles, and the Beni Suef's Faculty of Medicine ethics committee approved it.

The approval number is: FMBSUREC/01022022/Awad.

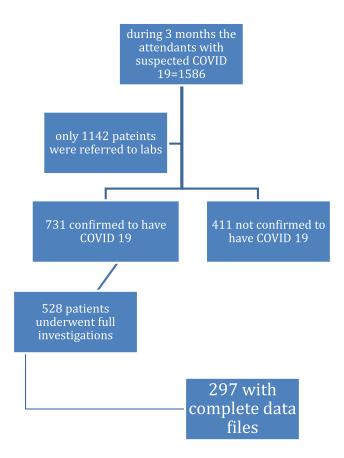


Figure I Flowchart showing the patients' inclusion in the study.

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All the Patients Underwent

- 1. A thorough medical history and examination.
- 2. Baseline complete blood count (CBC), erythrocytic sedimentation rate (ESR), C- reactive protein (CRP), D-dimer, liver enzymes, serum creatinine, serum lactate dehydrogenase (LDH), and serum ferritin.
- 3. At the initial visit, all patients got a triage-based unenhanced chest CT scan. A consultant radiologist who reviewed these scans determined the likelihood of COVID-19 using a 5-point scale (CO-RADS).
- 4. Patients with suspected PE were diagnosed according to the ESC guidelines recommendations, 13 and the patients underwent a computer tomography pulmonary angiography (CTPA). For severity scoring of PE using CTPA, we depended on the obstruction index assessed by the Qandali score, based on the obstruction site, percent of occlusion, and the number of peripheral branches involved, the maximum embolism score of each patient was $2 \times 20 = 40$.
- 5. We categorized the patients according to their risk stratification into low, intermediate-low, intermediate-high, and high-risk according to the ESC Guidelines¹³ involves the evaluation of two sets of prognostic criteria: (i) the presence of clinical, imaging, and laboratory markers of PE severity, largely associated with the presence of RV dysfunction; and (ii) presence of comorbidities and any other exacerbating factors that may negatively affect early prognosis.
- 6. A biplane Simpson's rule-based echocardiography study evaluated the left ventricular ejection fraction (LVEF). Tricuspid annular plane systolic excursion (TAPSE) was used to measure RV function. Using the calculated transtricuspid systolic pressure gradient and the addition of measured right atrial pressure in accordance with inferior vena cava dimension and inspiratory distensibility, we evaluated the Systolic pulmonary artery pressure (sPAP) from the tricuspid regurgitant jet velocity.
- 7. Resting 12 lead electrocardiogram.
- 8. All the patients were managed according to the Egyptian COVID-19 protocol. 14

Analysis of Data

SPSS v. 25 (Statistical Package for Social Science) for Windows was used to analyze the data. Mean, standard deviation (SD), and median (for non-parametric variables) were used to present the quantitative variables. The qualitative variables were reported as both percentages (%) and numbers (No.). To distinguish between cases and controls with respect to scale variables, an Independent *T*-test was employed. The categorical variables were compared between the two groups using the chi-Square test. Binary logistic regression analysis was used to predict different risk factors of the acquisition of pulmonary embolism.

Receiver operating characteristic (ROC) curve analysis was used to detect the optimal cut-off of different laboratory parameters associated with the development of pulmonary embolism. Youden's index was used to identify the optimal threshold value, and the area under the curve (AUC), a measure of their diagnostic efficacy, was calculated. P-values were used to evaluate the results' significance; results were deemed significant when P-value 0.05.

Results

Baseline Characteristics of the Studied Population

The disease was found to affect females (60.6%), middle-age (the mean patient's age was 49±15.9 years), overweight and obese patients (mean body mass index (BMI) was 28.9±5.2) more commonly. The most common patient's symptoms at admission were fever 68.7%, cough 68.7%, and dyspnea 77.8%, with a mean symptoms' duration of 9.3±5.3 days. We found only 27.3% of patients were presented with loss of taste and smell, and 14.1% presented with gastrointestinal (GIT) symptoms. The most common laboratory abnormalities at admission were elevated ESR, CRP, serum ferritin, and D- dimer, besides TR's presence. PE was diagnosed in 18.2% of patients (Tables 1–3).

Table I Patients Distribution Regarding Their Baseline Demographic Characteristics

Parameters	All Patients No=297	No PE No = 243 (81.8%)	PE No = 54 (18.2%)	P-value
Age (years, mean ± SD)	49±15.9	47.5±16.1	55.9±13.6	0.004
Age categories				
18-40 years	108(36.4%)	99(91.7%)	9(8.3%)	0.005
41-65 years	135(45.5%)	108(80%)	27(20%)	
>65	54(18.2%)	36(66.7%)	18(33.3%)	
Sex				0.002
Males	117(39.4%)	108(92.3%)	9(7.7%)	
Females	180(60.6%)	135(75%)	45(25%)	
ВМІ	28.9±5.2	28.1±5.1	33±3.8	<0.001
19–25	63(21.2%)	63(100%)	0(0)	
26–30	138(46.5%)	120(87%)	18(13%)	<0.001
>30	96(32.3%)	60(62.5%)	36(37.5%)	
HTN				<0.001
Yes	105(35.4%)	72(68.6%)	33(31.4%)	
DM				0.001
Yes	54(18.2%)	33(61.1%)	21(38.9%)	
Associated co-morbidities				<0.001
Yes	102(22.8%)	63(61.8%)	39(38.2%)	
Smoking				0.002
Yes	54(18.2%)	54(100%)	0	

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; No, Number; P value, probability value; PE, pulmonary embolism; SD, standard deviation.

Table 2 Patients Distribution Regarding Their Baseline Clinical Presentations

Parameters	All Patients No=297	No PE No=243 (81.8%)	PE No=54 (18.2%)	P-value
Fever				0.021
Yes	204 (68.7%)	174 (85.3%)	30 (14.7%)	
Cough				0.111
Yes	204 (68.7%)	162 (79.4%)	42 (20.6%)	
Dyspnea				<0.001
Yes	231(77.8%)	177 (76.6%)	54 (23.4%)	
Taste and smell loss	81(27.3%)	81(100%)	0	<0.001
GIT symptoms	42 (14.1%)	42 (100%)	0	0.001
Chest pain				<0.001
Yes	66 (22.2%)	39 (59.1%)	27 (40.9%)	
SBP	126±16	128.5±15.7	116.8±12.9	<0.001
HR	99±9	96±7	III±6	<0.001
Temperature	37.7±0.6	37.7±0.5	37.5±0.7	0.011
SPO2	94.9±2	95.6±1.7	91.9±1.4	<0.001
Duration of symptoms at hospital admission	9.3±5.3	8.1±4.5	14.3±6.1	<0.001

Abbreviations: GIT, gastrointestinal; HR, heart rate; No, Number; P value, probability value; PE, pulmonary embolism; SBP, systolic blood pressure; SPO2; oxygen saturation.

Table 3 Patients Distribution Regarding Their Laboratory Investigations

Parameters	All Patients No=297	No PE No=243 (81.8%)	PE No=54 (18.2%)	P-value
RV basal diameter (mm)	3.4±0.6	3.3±0.5	4±0.6	<0.001
TAPSE	19.4±3	19.9±2.8	17.2±2.8	<0.001
sPAP	39.9±14.1	36.3±12	52±13.9	<0.001
Hb (gm/dl)	12.9±1.5	13.1±1.5	12.4±1.2	0.003
Platelets×10 ³	222.2±95.5	232.2±94.4	177.2±90.1	0.002
Total leucocytic count	6796.9±3063.7	7306.1±2912.8	4505.6±2718.4	<0.001
Absolute Lymphocytic count	1.2±0.4	1.3±0.5	0.8±0.3	0.002
ESR I	45.2±27.5	44.2±28.9(median=39)	49.9±18.9(48)	0.166
Serum Ferritin	578.9±1517 (median=180)	541.9±1381 (median=177)	745.7±2027(median=210)	0.373
C-reactive protein	29.7±29.5 (median=16)	28±28.2(median=15)	37.3±34.9(median=18)	0.227
D- dimer	863.5±686.5(median=600)	702.9±620.7(median=450)	1586.1±471.9(median=1375)	<0.001
CO-RADS				
3	18(6.1)	18(100)	0(0)	<0.001
4	117(39.4)	117(100)	0(0)	
5	162(54.5)	108(66.7)	54(33.3)	

Abbreviations: ESR I, erythrocytic sedimentation rate first hour; Hb, hemoglobin; No, Number; P value, probability value; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle.

PE and Patient's Baseline Demographic and Clinical Characteristics

We found that the incidence of PE vs non-PE was significantly higher in older patients (mean age 55.9 ± 13.6 vs 47.5 ± 16.1 ; P= 0.004), females (25% vs 7.7%; p=0.002), those with higher BMI (33 ±3.8 vs 28.1 ± 5.1 ; p < 0.001), hypertensive patients (31.4% vs 10.9%; p <0.001), diabetics (38.9% vs 13.6%; p = 0.001), and patients with co-morbidities (chronic obstructive pulmonary disease, atrial fibrillation, malignancy, rheumatologic diseases, chronic kidney disease, cardio-vascular disease, autoimmune diseases, and hematological disorders) (38.2% vs 7.7%; p <0.001). Surprisingly, we noticed that none of the 54 smokers developed PE while 22.2% of the non-smokers developed it (Table 1).

Furthermore, the incidence of PE was significantly higher in patients presented with dyspnea (p = <0.001), chest pain (p = <0.001), longer duration of symptoms at hospital admission (p = <0.001), and lower oxygen concentration (p = <0.001). While no one presented with GIT symptoms or taste and smell loss developed PE. Patients presented with fever showed a significantly lower incidence of PE (p = 0.021) (Table 2).

PE and Patient's Laboratory Investigations

We found that the mean serum Hb level (12.4 ± 1.2 vs 13.1 ± 1.5 ; p= 0.003), platelet count (177.2 ± 90.1 vs 232.2 ± 94.4 ; p= 0.002), TLC (4505.6 ± 2718.4 vs 7306.1 ± 2912.8 ; p< 0.001), and absolute lymphocytic count (0.8 ± 0.3 vs 1.3 ± 0.5 ; p= 0.002), were significantly lower in patients developed PE compared to those without PE. While the mean D-dimer level was significantly higher in those developed PE 1586.1 ± 471.9 ng/mL (median=1375) vs 702.9 ± 620.7 ng/mL (median=450); p< 0.001). All the patients who developed PE had a CO-RADS scale five on their CT chest scan.

As regards the echocardiographic parameters, the patients who developed PE had a significantly higher mean RV basal diameter (4±0.6 vs 3.3±0.5; p<0.001) and sPAP (52±13.9 vs 36.3±12; p<0.001) and significantly lower mean TAPSE (17.2±2.8 vs 19.9±2.8; p<0.001) compared to those did not developed PE (Table 3).

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The Pulmonary Embolism's Risk Stratification in Affected Patients

We found that 12 (22.2%) patients had a low-risk PE, while 9 (16.7%) patients had intermediate-low risk PE, 20 (37%) patients had intermediate-high risk PE, and 13 (24.1%) patients had a high- risk PE (Table 4). Subsegmental PE was present in nine of the patients who developed PE.

Independent Predictors of PE

Age > 65 (OR 5.015, 95% CI 1.423: 17.674, p = 0.012), BMI > 25 (OR 9.053, 95% CI 2.581: 31.754, p = 0.001), DM (OR 32.537, 95% CI 6.004: 76.321, p <0.001), and associated co-morbidities (OR 46.476, 95% CI 8.689: 48.591, p <0.001) were the independent patients' characteristics associated with the development of PE after the multivariate regression analysis (Table 5).

The ROC Curve Analysis

The ROC curve analysis demonstrated that the following laboratory parameters were associated with the development of PE in univariate analysis; 1- TLC at a cut off ≤ 2800 (p- value = <0.001). 2- Absolute Lymphocytic count at a cut off ≤ 0.66 (p- value = <0.001). 3- D- dimer at a cut off >1000 ng/mL (p- value = <0.001). 4- platelet count at a cut off $\leq 180 \times 10^3$ (p- value = 0.003). 5- ESR at a cut off >35 (p- value = 0.0108) (Table 6 and Table 7).

Discussion

We found that COVID 19 mainly affects females, middle-aged, overweight and obese patients. The most common patient's symptoms at admission were fever, cough, and dyspnea, with a mean symptoms' duration of 9.3±5.3 days. We found only 27.3% of patients were presented with loss of taste and smell, and 14.1% presented with GIT symptoms. The

Table 4 Pulmonary Embolism's Risk Stratification in Affected Patients

Category	No (%) 54 Patients		
Low risk PE	12 (22.2%)		
Intermediate-low risk PE	9 (16.7%)		
Intermediate-high risk PE	20 (37%)		
High risk PE	13 (24.1%)		

Abbreviations: No, Number; PE, pulmonary embolism.

Table 5 Multivariable Binary Logistic Regression Analysis for the Prediction of Pulmonary Embolism from Different Patients' Characteristics

Variables	P-value	OR	95% C.I. for OR	
			Lower	Upper
Gender (female)	0.133	4.027	0.653	24.835
Associated comorbidities	<0.001	46.476	8.689	48.591
DM	<0.001	32.537	6.004	76.321
Age>65	0.012	5.015	1.423	17.674
BMI>25	0.001	9.053	2.581	31.754
HTN	0.141	0.396	-0.115	1.360

Abbreviations: BMI, body mass index; C.I, confidence interval; DM, diabetes mellitus; HTN, hypertension; OR, odds ratio; P value, probability value.

Table 6 Cut off, Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Different Laboratory Parameters Associated with Pulmonary Embolism Occurrence

Items	TLC	Absolute Lymphocytic Count	D- Dimer	Ferritin	Platelets	ESR	CRP
AUC (95% CI)	0.790 (0.697–0.866)	0.771 (0.675–0.849)	0.889 (0.810–0.943)	0.579 (0.476–0.678)	0.719 (0.620–0.805)	0.642 (0.539–0.736)	0.593 (0.489–0.690)
P-value	<0.001	<0.001	<0.001	0.1747	0.003	0.0108	0.2298
Cut off	≤2800	≤0.66	>1000	>167	≤180×10³	>35	>15
Sensitivity% (95% CI)	38.89% (17.3–64.3)	27.78% (9.7–53.5)	83.33% (58.6–96.4)	94.44% (72.7–99.9)	83.33% (58.6–96.4)	83.33% (58.6–96.4)	83.33% (58.6–96.4)
Specificity% (95% CI)	97.53% (91.4–99.7)	98.77% (93.3–100)	85.19% (75.6 -92.1)	46.91% (35.7 -58.3)	74.07% (63.1–83.2)	48.15% (36.9–59.5)	51.85% (40.5–63.1)
PPV (95% CI)	77.8% (44.2–93.9)	83.3% (38.3–97.6)	55.6% (41.6–68.7)	28.3% (23.8–33.3)	41.7% (31.9–52.1)	26.3% (21.0–32.4)	27.8% (22.1–34.3)
NPV (95% CI)	87.8% (83.2–91.2)	86% (82.2–89.1)	95.8% (89.1–98.5)	97.4% (84.8–99.6)	95.2% (87.6–98.3)	92.9% (81.9–97.4)	93.3% (83.0–97.6)

Abbreviations: AUC, Area under the curve; CI, Confidence interval; NPV, Negative predictive value; PPV, Positive predictive value; TLC, total leucocytic count.

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Table 7 Cut off, Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Body Mass Index and Duration of Latency Till Seeking Medical Consultation Associated with Pulmonary Embolism Occurrence

Items	вмі	Duration	
AUC (95% CI)	0.792 (0.699–0.867)	0.829 (0.740–0.897)	
P-value	<0.001	<0.001	
Cut off	>31	>10	
Sensitivity% (95% CI)	66.67% (41.0–86.7)	72.22% (46.5–90.3)	
Specificity% (95% CI)	79.01% (68.5–87.3)	79.01% (68.5 -87.3)	
PPV (95% CI)	41.4% (29.3–54.6)	43.3% (31.5–56)	
NPV (95% CI)	91.4% (84.6–95.4)	92.8% (85.8–96.5)	

Abbreviations: AUC, Area under the curve; CI, Confidence interval; NPV, Negative predictive value; PPV, Positive predictive value; TLC, total leucocytic count.

most common laboratory abnormalities at admission were elevated ESR, CRP, serum ferritin, and D- dimer, besides TR's presence.

According to our study, 18.2% of COVID-19 hospitalised patients got PE, which is a much greater frequency than that of the general population as described in the most recent PE ESC guidelines¹³ and comparable to a study conducted by Scudiero et al who reported incidence of 14% of cases developed PE¹⁵ and a meta-analysis by Jiménez et al reported the incidence at 17%. 16 While some studies found a decreased prevalence of PE in patients with covid 19 infection, including those by Hobohm et al, Miró et al, and Fauvel et al (1.9%, 0.5%, and 8.3%, respectively). ^{17–19} An earlier study on diabetes patients in upper Egypt revealed a greater incidence of cardiovascular risk factors and cardiovascular risk factor clustering in those populations, which may help to explain the significantly elevated risk of PE in covid-19 infected individuals in our study.²⁰ We tested many variables suggested to be associated with PE, including patient's characteristics and laboratory findings, and we found that Age > 65, BMI > 25, DM, and associated co-morbidities were the independent patients' characteristics associated with the development of PE in those infected with Covid-19 after multivariate regression analysis, while female gender, hypertension, long duration of symptoms, dyspnea, chest pain, and low oxygen concentration were significantly associated with PE in univariate analysis. The echocardiographic parameters TAPSE, sPAP, and RV basal diameter were all significantly associated with the development of PE in univariate analysis. Also, low hemoglobin level, low platelet count, low total leucocytic count, low absolute lymphocytic count, higher D-dimer, and higher CO-RADS score were strongly associated with PE in univariate analysis. TAPSE and sPAP were found to be independently associated with the development of PE by Scudiero et al. 15 whereas D-dimer, cardiac injury, and late hospitalisation following the onset of symptoms showed a significant association with PE at univariable analyses, which is consistent with our findings.

Kho et al did yet another study²¹ suggested that patients who exhibit sudden deterioration, a protracted illness with non-resolving symptoms, increased dyspnoea, ongoing oxygen needs, or noticeably elevated D-dimer values should be checked for PE, especially if COVID-19 infection is present. In this setting, TTE and to a lesser extent the ECG are unreliable PE predictors. We discovered a D-dimer cutoff of >1000 ng/mL, which is more than double the typical threshold value (500 ng/mL) often taken into account for PE diagnosis in the general population¹³ while Scudiero F, et¹⁵ found a higher D-dimer cutoff (1743 ng/mL) for PE diagnosis, but Silva et al²² recommended the adoption of a D-dimer threshold of 500 ng/mL because larger thresholds reduce this strategy's utility as a screening test while increasing specificity. D-dimer is frequently abnormal in COVID-19 due to the inflammatory response brought on by the SARS-CoV-2 infection and the hypoxia-inducible transcription factor-dependent signalling cascade.²³ These results highlight the significance of clinical features, echocardiographic measures, computed tomography, and lab data for the diagnosis and prognostic classification of PE in COVID 19-infected patients.²⁴ We discovered that 61% of patients with covid-19 infection who developed PE were at intermediate-high or high risk (37% and 24.1%,

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respectively). Our findings corroborated those of Hobohm et al, Miró et al, and Hajra et al^{17,18,25} As we know, Patients who have COVID 19 infection make it difficult to do echocardiographic evaluations, necessitating special safety measures.²⁶ However, the most recent ESC recommendations suggested echocardiography as the primary imaging modality for early PE detection.¹³

Limitations of Our Study

There are some restrictions to be aware of with our study. First, the study's retrospective design. Secondly, the comparative analysis of the data gathered in the current study was restricted by the relatively small number of patients.

Conclusion

A common consequence of COVID 19 infection is PE. Several clinical and laboratory factors are connected to PE in univariate analysis, but age > 65, BMI > 25, DM, and associated co-morbidities were the independent patients' characteristics associated with the development of PE in those infected with Covid-19.

Abbreviations

ACE, angiotensin converting enzyme; AUC, area under the curve; Covid-19, coronavirus disease 2019; CT, computerized tomography; CTPA, computerized tomography pulmonary angiography; DIC, disseminated intravascular coagulopathy; DM, diabetes mellitus; PE, pulmonary embolism; ROC curve, receiver operating characteristic curve; RV, right ventricle; BMI, body mass index; sPAP, systolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic excursion; TLC, total leucocytic count; WHO, World Health Organization.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The need for informed consent was waived due to the retrospective design of the study. The study protocol was approved by: Beni Suef's Faculty of Medicine ethics committee. The approval number is: FMBSUREC/01022022/Awad. Date of approval, February 2022.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in All these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

There are no conflicts of interest among the authors in this study.

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