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RESEARCH ARTICLE

Relationship between Plasma D-Dimer Level and Pulmonary Hypertension as well as Right Ventricle Dysfunction in Patient Post Pneumonia COVID-19

Arman Christiawan[1,*], Susi Herminingsih[1], Udin Bahrudin[1] and Nur Farhanah[2]

[1]*Cardiovascular Department, Faculty of Medicine, Diponegoro University, Dr. Kariadi General Hospital, Semarang, Indonesia*
[2]*Internal Medicine Department, Faculty of Medicine, Diponegoro University, Dr. Kariadi General Hospital, Semarang, Indonesia*

Abstract:

Background:

High rate of coagulopathy and pulmonary thromboembolism in coronavirus disease 2019 (COVID-19), which is represented by an increase in plasma D-Dimer levels is believed to be related to pulmonary hypertension (PH) and right ventricle (RV) dysfunction.

Objective:

To evaluate the relationship between plasma D-Dimer levels with PH and RV dysfunction assessed from transthoracic echocardiography (TTE) in patients post COVID-19 pneumonia.

Methods:

Observational research with a cross-sectional design. Estimated mean pulmonary arterial pressure (mPAP) was calculated from Mahan's formula obtained from pulmonary artery acceleration time (PAAT) and RV function was assessed from RV free wall strain (RV FWS), tricuspid annular plane systolic excursion (TAPSE), and fractional area change (FAC). D-Dimer levels during hospitalisation were obtained from medical records and actual D-Dimer was obtained at the time of echocardiography.

Results:

Total 40 patients post-COVID-19 pneumonia underwent TTE in a median of 11 days after negative PCR. There was a significant correlation between peak D-Dimer levels with mPAP (r=0.526, p<0.001), RV FWS (r=-0.506, p=0.001), TAPSE (r=-0.498, p=0.001), and FAC (r=0.447, p=0.004). Multivariate analysis found peak D-Dimer ≥4530 µg/L independently associated with PH with odds ratio (OR) 6.6, (95% CI 1.1-10; p=0.048), but not with RV dysfunction.

Conclusion:

Peak D-Dimer level correlates with echocardiographic parameters of RV function and mPAP in patients with COVID-19 infection. Peak D-Dimer ≥4530 µg/L might increase risk of PH, but not RV dysfunction in patient post pneumonia COVID-19.

Keywords: D-Dimer, COVID-19, Pneumonia Pulmonary hypertension, Right ventricle dysfunction, Pneumonia, ARDS.

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1. INTRODUCTION

Although pneumonia and acute respiratory distress syndrome (ARDS) are the dominant clinical presentations of coronavirus disease 2019 (COVID-19) infection, it is known that there are several conditions that often complicate the course of this disease, including coagulopathy and thrombosis [1, 2]. Various meta-analyses have shown the rate of thromboembolic (TE) events in COVID-19 patients ranges from 11-48.6%, and 90% of them are pulmonary thromboembolism [3 - 6]. Helms *et al*. found that patients with COVID-19 ARDS had a 6 times higher rate pulmonary thromboembolic events compared with non-COVID-19 ARDS [7]. An autopsy study also found alveolar capillary microthrombus in pneumonia COVID-19 non-survivors were 9 times more common than for other pneumonias [8].

Pulmonary thromboembolic complications of COVID-19 have their own diagnostic challenges. CT-Pulmonary

* Address correspondence to this author at the Cardiovascular Department, Faculty of Medicine, Diponegoro University, Dr. Kariadi General Hospital, Semarang, Indonesia; E-mail: arman.chris@gmail.com

Angiography (CTPA) as gold standard modality becomes less practical and less feasible to perform during the pandemic, so clinicians often rely on other parameters, such as D-Dimer levels as surrogate markers of the thrombosis process. Previous studies showed an increase in D-Dimer levels have good diagnostic value for pulmonary thromboembolic events in COVID-19 (OR 1.99-10.7) [9, 10].

The effect of ARDS and pneumonia on pulmonary circulation and right ventricle (RV) is already well known [11]. The incidence of pulmonary thrombosis is believed to further aggravate the hemodynamic burden of the pulmonary circulation through an increase in pulmonary arterial resistance. The incidence of pulmonary hypertension (PH) in COVID-19 patients ranges from 12-15% in the general population, and increases to 42% in critically ill patients [11 - 14]. The presence of PH and RV dysfunction have been shown to affect clinical outcomes in COVID-19 patients, with the mortality rate being 7 times higher in patients with PH and 3.1 times higher in patients with RV dysfunction [14 - 16].

Although the gold standard method for assessing pulmonary artery pressure (PAP) is using right heart catheterization (RHC), the use echocardiographic parameters including pulmonary artery acceleration time (PAAT) in estimating PAP has been shown to be quite accurate [16 - 19]. Likewise, several parameters of RV function, especially RV free wall longitudinal strain (RV-FWLS), have good correlation with its gold standard method, which is cardiac magnetic resonance (CMR) [20]. In addition, the practicality of echocardiography during the COVID-19 pandemic make it the preferable diagnostic tool to assess cardiac function and underlying pathological abnormalities. The objective of this study is to seek relationship between D-Dimer levels as a surrogate marker of thrombosis and short-term cardiovascular complications especially PH and RV dysfunction using echocardiography.

2. MATERIALS AND METHODS

2.1. Study Population and Procedure

This retrospective, single-centre study was performed at the Dr. Kariadi Hospital, Semarang, Indonesia, between August 2021 and November 2021. Patients who recovered from more than moderate severity pneumonia COVID-19 according to World Heart Organization (WHO) classification were included in the study [21]. Due to safety concerns and local protocol, only patients with a swab that was negative for COVID-19 by Polymerase Chain Reaction (PCR) underwent further echocardiographic examination. Exclusion criteria included history of coronary artery disease, congenital heart disease, aortic and mitral valve disease more than moderate, left ventricular (LV) dysfunction (LV ejection fraction ≤40% and/or diastolic dysfunction ≥grade II), chronic lung disease, severe chronic renal failure, known hematologic disorder, and concomitant acute coronary syndrome or myocarditis during hospitalization.

After the exclusion criteria were applied, the study continued with 40 adults with COVID-19. Baseline data, medical history, and medications used during treatment were obtained from the hospital's database. Hypertension and diabetes mellitus was diagnosed using criteria from American Heart Association (AHA) and American Diabetes Association (ADA) guidelines, respectively [22, 23]. Obesity was defined as a body mass index (BMI) ≥25 kg/m^2 according to Asia-Pacific classification [24]. Laboratory parameters including, complete blood count (CBC), C-reactive protein (CRP), D-Dimer, ferritin and blood gas analysis parameters were recorded at its worst value during patient hospitalization course. Estimated glomerular filtration rate (eGFR) was derived from Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [25]. P_aO_2/FiO_2 ratio is the ratio of arterial oxygen partial pressure (P_aO_2 in mmHg) to fractional inspired oxygen (FiO_2) obtained from blood gas analysis and used as oxygenation parameter to assess severity of ARDS [26]. We also assessed patient's Brixia score, a semi-quantitative scoring of pneumonia assessed by plain chest X-ray [27].

The echocardiographic examinations were performed pre-discharge or within 2 weeks after patient was proven negative by PCR swab. The research procedures were reviewed and approved by the local hospital's ethics committee according to the ethical considerations stipulated in the Helsinki Declaration.

2.2. Echocardiographic Examination

Bedside transthoracic echocardiographic examinations were performed using the EPIQ 7C ultrasound system (Philips Medical Systems, Andover, Massachusetts, USA). Two-dimensional and Doppler echocardiography were performed on the basis of the guidelines of the American Society of Echocardiography by two experienced research echocardiographers blinded to the clinical status and laboratory data of the patients [28]. After a regular exam of the cardiac morphology and function, we assessed the following parameters.

1. Echocardiographically estimated mean PAP (mPAP), based on the pulmonary artery acceleration time (PAAT). PAAT was obtained by placing a pulsed wave (PW) Doppler volume sample at the annulus of the pulmonary valve in the parasternal short axis view, and then measuring the time interval from peak to beginning of the wave (units in ms). mPAP was then measured using Mahan's Formula, which is mPAP = 90 - (0.62 x PAAT) [29, 30]. In this study, we considered that mPAP values of ≥25 mmHg at rest, as PH.

2. RV free wall longitudinal strain (RV-FWLS) was performed using a modified apical 4-chamber (A4C) view, and RV-focused images including at least three cardiac cycles with regular ECG signals were obtained. The analysis was performed using the software QLAB chamber motion quantification (CMQ), Philips Healthcare, Andover, Massachusetts, USA). After tracing the RV endocardial border, the region of interest was automatically generated. Manual corrections were performed if needed to fit the thickness of the RV myocardial wall. In this study, impairment of RV function was defined only by RV-FWLS, of which values ≤17%, indicates RV dysfunction [20].

2.3. Statistical Analysis

All data were analysed using SPSS software version 24.0 (IBM Corp, Armonk, New York, USA). Quantitative variables with a normal distribution were specified as mean ± standard deviation or as median (min-max value). Categorical variables were shown as number and percentage values. The Shapiro-Wilk test was used to test normality of distribution. For comparison of quantitative data, student-t test (normally distributed data) and Mann-Whitney U test (non-normally distributed data) were used. Categorical variables were compared with the Chi-square test.

Spearman's correlation coefficient was used to assess the strength of the relationship between studied echocardiographic parameters and D-dimer as well as other laboratory values. A 2-sided $p<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analyses were conducted to determine the cut-off values for the sensitivity and specificity of D-Dimer for predicting PH and RV systolic dysfunction. The area under the curve (AUC) was reported with 95% confidence interval (CI) in addition to sensitivity and specificity.

Logistic regression analyses were performed to evaluate independent predictors of PH and RV systolic impairment. All variables with a $p<0.25$ by univariate analysis and other variables which might be a possible confounding factor were included in the multivariable analysis. The goodness-of-fit assumption was examined using the Hosmer-Lemeshow method and satisfied when p was ≥0.05.

3. RESULTS

The distribution of data based on demographic and laboratory characteristics is shown in Table **1**. The mean age of the study population was 55.4 years and predominantly male. Based on WHO criteria of COVID-19 pneumonia severity, 9 patients suffered from moderate degree, 21 with severe degree, and 10 with critical degree. From echocardiographic data, RV dysfunction was found (based on RV-FWLS) in 27 (67.5%) patients. In addition, PH was found in 19 patients (47.5%) with an estimated mPAP ≥25 mmHg obtained through PAAT.

Table 1. Demographic and clinical characteristics of the study population.

Variable	Total	PH (n=19)	No PH (n=21)	p	RV Dysfunction (n=27)	RV normal (n=13)	p
Demographic data							
Age (years)	55.4 ± 11.5	53.6 ± 13.8	55.5 ± 9.7	0.606[a]	54.1 ± 12.6	55.5 ± 9.9	0.730[a]
Male (n, %)	23 (57.5)	11 (57.9)	12 (57.1)	0.962[c]	17 (63)	6 (46.2)	0.314[c]
Body Mass Index (Kg/m^2)	26.2 ± 4.6	27.7 ± 4.2	24.9 ± 4.6	**0.048**[a]	27.1 ± 4.4	24.4 ± 4.7	0.087[a]
Obesity (n, %)	22 (55)	14 (73.7)	8 (38.1)	**0.024**[c]	17 (63)	5 (38.5)	0.145[c]
Hypertension (n, %)	17 (42.5)	10 (52.6)	7 (33.3)	0.261[c]	11 (40.7)	6 (46.2)	0.746[c]
Diabetes Mellitus (n, %)	15 (37.5)	8 (42.1)	7 (33.3)	0.567[c]	10 (37)	5 (38.5)	0.931[d]
Dyslipidemia (n, %)	8 (20)	4 (21.1)	3 (14.3)	0.689[d]	6 (22.2)	1 (7.7)	0.393[d]
Active smoker (n, %)	11 (27.5)	5 (26.3)	6 (28.6)	0.873[c]	8 (29.6)	3 (23.1)	0.955[d]
COVID-19 Vaccinated (n, %)	6 (15)	2 (10.5)	4 (19)	0.664[d]	2 (7.4)	4 (20.8)	0.275[d]
Laboratory and clinical parameters							
Hemoglobin (mg/dl)	12.6 ± 2.4	12.1 ± 2.2	13.0 ± 2.4	0.294[a]	12.9 ± 2.4	12.1 ± 2.2	0.270[a]
Leucocyte count (10^3/µl)	10.5 ± 4.2	10.9 (5.3-18.2)	8.3 (5-19.6)	0.440[b]	10.4 ± 4.2	10.6 ± 4.4	0.885[a]
Thrombocyte count (10^3/µl)	284750 ± 115750	288526 ± 130448	281333 ± 94511	0.842[a]	284370 ± 119449	285538 ± 97674	0.976[a]
Mean eGFR (mL/min)	83.2 ± 18.4	82.3 ± 20.8	84.0 ± 16.5	0.782[a]	84.1 ± 19.5	81.2 ± 16.5	0.646[a]
CRP (mg/dl)	12.0 (2.4-29.3)	13.6 (4.2-29.3)	4.8 (2.7-19.5)	**< 0.001**[b]	13.2 (2.4-29.3)	4.8 (2.7-21.6)	**0.035**[b]
CRP ≥10.1 mg/dl (n, %)		14 (73.7)	6 (28.6)	**0.004**[c]	17 (63)	3 (23.1)	**0.018**[c]
Peak D-Dimer (µg/L)	4185 (1240-20000)	7140 (1480-20000)	2590 (1240-11810)	**0.001**[b]	6490 (1470-20000)	2520 (1240-8660)	**0.008**[b]
≥4530 µg/L (n,%)		14 (73.7)	5 (23.8)	**0.002**[c]	16 (59.3)	3 (23.1)	**0.032**[c]
Fibrinogen (mg/dl)	596.6 ± 176.7	605.8 ± 178	588.2 ± 179.5	0.758[a]	570.5 ± 192.0	558.7 ± 203.7	0.859[a]
P/F ratio (worst)	137.5 ± 59.5	100.9 ± 39.0	170.7 ± 55.7	**< 0.001**[a]	114.4 ± 49.5	185.5 ± 50.0	**<0.001**[a]
≤ 121 (n, %)		15 (78.9)	3 (14.3)	**< 0.001**[c]	17 (63)	1 (7.7)	**0.001**[c]
Brixia score	9 (4-16)	12 (4-16)	8 (4-12)	**0.001**[b]	11 (4-16)	8 (4-12)	**0.007**[b]
Mechanical ventilation (n, %)	4 (10)	3 (15.8)	1 (4.8)	0.331[d]	3 (11,1)	1 (7.7)	0.608[d]
Hospital Length of Stay (days)	28.6 ± 8.5	35.1 ± 10.1	28.8 ± 6.5	**0.021**[a]	30.6 ± 9.0	24.5 ± 5.3	**0.029**[a]
Echocardiographic data							
Onset to TTE (days)	33 (29-42)	33 (29-42)	33 (29-41)	0.891[b]	34 (29-42)	32 (31-41)	0.977[b]
PCR (-) to TTE (days)	11 (7-14)	12 (7-14)	10 (8-14)	0.978[b]	11 (7-14)	10 (8-14)	0.530[b]
Left Atrium (mm)	34.4 ± 2.9	35.0 ± 3.4	33.8 ± 2.3	0.202[a]	34.5 ± 3.2	34.1 ± 2.3	0.660[a]
LVEDD (mm)	47.4 ± 6.0	46.9 ± 7.2	47.9 ± 5.0	0.607[a]	47.1 ± 6.5	48.1 ± 5.4	0.644[a]
LVEF (%)	68.35 ± 5.7	67.4 ± 5.8	69.1 ± 5.7	0.362[a]	68.0 ± 5.4	69.0 ± 6.5	0.628[a]

(Table 1) contd.....

Variable	Total	PH (n=19)	No PH (n=21)	p	RV Dysfunction (n=27)	RV normal (n=13)	p
Demographic data							
LV E/A	0.8 (0.6-1.8)	0.8 (0.6-1.8)	0.9 (0.6-1.3)	0.956[b]	0.8 (0.6-1.8)	1.0 (0.6-1.3)	0.610[b]
LV E/e'	8.7 ± 2.5	8.9 ± 2.9	8.5 ± 2.0	0.605[a]	9.3 ± 3.1	8.4 ± 2.2	0.298[a]
RV basal (mm)	34.4 ± 3.6	34.6 ± 3.6	34.3 ± 3.6	0.779[a]	34.9± 3.8	33.5 ± 3.1	0.276[a]
RV mid (mm)	31.9 ± 3.9	33.1 ± 3.8	30.8 ± 3.7	0.062[a]	32.7 ± 4.0	30.3 ± 3.3	0.073[a]
RV long (mm)	73.1 ± 4.4	73.8 ± 5.0	72.5 ± 3.7	0.342[a]	73.9 ± 4.3	71.6 ± 4.3	0.124[a]
TAPSE (mm)	17.8 ± 1.9	16.7 ± 1.6	18.8 ± 1.7	**< 0.001**[a]	16.9 ± 1.5	19.6 ± 1.4	**< 0.001**[a]
RV FAC (%)	40.3 ± 6.0	37.2 ± 5.6	43.0 ± 4.9	**0.001**[a]	37.8 ± 5.1	45.5 ± 4.0	**< 0.001**[a]
RV FWLS (%)	15.6 ± 2.5	14.1 ± 1.5	17.0 ± 2.4	**< 0.001**[a]	14.1 ± 1.3	18.6 ± 1.4	**< 0.001**[a]
PAAT (ms)	120 (93-135)	104.7 ± 6.9	126.7 ± 5.1	**< 0.001**[a]	111.4 ± 12.0	126.2 ± 6.9	**< 0.001**[a]
Estimated mPAP (mmHg)	24.7 (18.3-37)	31.9 ± 3.0	21.9 ± 2.2	**< 0.001**[a]	28.8 ± 5.3	22.1 ± 3.0	**< 0.001**[a]
Tricuspid Regurgitation (n;%)	16 (40)	11 (68.8)	5 (31.3)	**0.028**[c]	14 (87.5)	2 (12.5)	**0.027**[c]

Note: [a]independent t-test; [b]Mann-Whitney; [c]chi-square; [d]Fisher

Abbreviations: eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, P/F ratio: PaO2/FiO2 ratio, TTE: transthoracic echocardiography, PCR: polymerase chain reaction, LA: left atrium, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, L/V E/A: early to atrial filling velocity ratio, LV E/e': early mitral inflow velocity to early diastolic mitral annulus velocity ratio, RV: right ventricle, TAPSE: tricuspid annular plane systolic excursion, FAC: fractional area change, FWLS: free wall longitudinal strain, PAAT: pulmonary artery acceleration time, mPAP: mean pulmonary arterial pressure.

Table 2. Correlation between clinical and laboratory parameters with right ventricular function and pulmonary artery pressure.

Marker	Parameter	r	p
Leucocyte count	mPAP	0.128	0.432 [b]
-	FWS	-0.050	0.759 [b]
Thrombocyte count	mPAP	-0.088	0.591 [b]
-	FWS	0.047	0.775 [a]
Mean eGFR	mPAP	0.007	0.968 [b]
-	FWS	-0.111	0.494 [a]
Peak D-Dimer	mPAP	0.526	**<0.001** [b]
-	FWS	-0.506	**0.001** [b]
Fibrinogen	mPAP	0.252	0.217 [b]
-	FWS	0.160	0.325 [a]
Ferritin	mPAP	0.292	0.279 [a]
-	FWS	-0.171	0.311 [a]
CRP	mPAP	0.435	**0.005** [b]
-	FWS	-0.498	**0.001** [b]
P/F ratio	mPAP	-0.685	**<0.001** [b]
-	FWS	0.641	**<0.001**[a]

Note:[a]Pearson; [b]Spearman

Abbreviations: eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, P/F ratio: PaO2/FiO2 ratio, FWS: free wall strain, mPAP: mean pulmonary arterial pressure.

The correlation between D-Dimer levels as well as other laboratory parameters and RV function based on the parameters of RV-FWLS and estimated mPAP is shown in Table **2**.

3.1. Predictive value of D-Dimer

ROC curve analysis was carried out to find the cut-off point of several lab parameters on the incidence of PH and RV dysfunction. The peak D-Dimer level was 4530 µg/L as the cut-off for the occurrence of RV dysfunction based on RV-FWLS parameters with AUC of 0.761 (95% CI 0.612-0.910, p=0.008), with a sensitivity of 63% and a specificity of 76.9%. The same D-Dimer number was also obtained for predictors of PH with AUC of 0.797 (95% CI 0.656-0.938, p=0.001) with a sensitivity of 73.7% and a specificity of 76.2% (Table **3**).

Table 3. ROC analysis of laboratory marker for pulmonary hypertension.

Variable	Cut-off	AUC	p	Sensitivity	Specificity
Peak D-Dimer	4530	0.797	0.001	73.7%	76.2%
P/F ratio	121.9	0.847	0.000	81.0%	78.9%
CRP	10.1	0.813	0.001	73.7%	71.4%

Note: P/F ratio: PaO2/FiO2 ratio,

Abbreviations: CRP: C-reactive protein, AUC: area under the curve, ROC: receiver operating characteristic.

Table 4. Multivariate analysis for PH and RV dysfunction.

Parameter	OR (Univariate) 95% CI	p	OR (Multivariate) 95% CI	p
PH				
Obesity	4.5 (1.1-7.5)	0.028	2.8 (0.4-4.1)	0.273
Peak D-Dimer ≥4530 µg/L	8.9 (2.1-11.5)	0.003	**6.6 (1.1-10.0)**	**0.048**
CRP ≥10.1 mg/dl	7.0 (1.7-9.2)	0.006	5.7 (0.8-8.6)	0.076
P/F ratio ≤121.9	12.5 (4.3-16.7)	0.001	**10.2 (1.6-18.3)**	**0.013**
Mechanical ventilation	3.7 (0.3-8.5)	0.272	-	-
Hypertension	2.2 (0.6-4.9)	0.221	-	-
Diabetes Mellitus	1.4 (0.4-3.2)	0.568	-	-
***Nagelkerke R square: 0.621; Hosmer and Lemeshow test: 0.644**				
RV dysfunction				
Obesity	2.7 (0.6-6.3)	0.150	1.4 (0.2-3.2)	0.702
Peak D-Dimer ≥4530 µg/L	4.8 (1.1-7.7)	0.039	2.3 (0.4-3.7)	0.366
CRP ≥10.1 mg/dl	5.7 (1.2-8.6)	0.024	3.0 (0.8-7.6)	0.089
P/F ratio ≤121.9	15.4 (2.2-18.2)	0.007	**11.4 (2.3-19.2)**	**0.007**
Mechanical ventilation	1.5 (0.3-5.9)	0.737	-	-
Hypertension	1.3 (0.2-3.0)	0.746	-	-
Diabetes Mellitus	1.1 (0.2-2.6)	0.931	-	-
***Nagelkerke R square: 0.372; Hosmer and Lemeshow test: 0.550**				

Abbreviations:: PH: pulmonary hypertension, RV: right ventricle, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, P/F ratio: PaO2/FiO2 ratio, OR: odds ratio.

3.2. Multivariate Analysis

From the multivariate analysis, there are 2 independent variables that simultaneously and independently significantly influence the incidence of PH: P/F ratio ≤121.9 (multivariate odds ratio (OR) 10.2; p=0.013) and peak D-Dimer levels ≥4530 µg/L (multivariate OR 6.6; p=0.048). While the regression model for RV dysfunction from the RV-FWLS parameter, only P/F ratio ≤121.9 that was independently significant (Table **4**) (multivariate OR 11.4; p=0.007).

4. DISCUSSION

Elevated pulmonary artery pressure (PAP) and RV dysfunction are common in patients with both acute and chronic pulmonary disease [11, 31]. COVID-19 pneumonia is no exception. The present study showed, that at short-term evaluation (median 11 days after negative PCR), PH was found in 47.5% of patients, higher than prevalence in general COVID-19 populations, which ranged from 12-15% [12, 13]. This difference is understandable considering that almost 75% of our study sample were patients with a history of severe and critical COVID-19 who were admitted to the ICU. The severity of ARDS was related to the increase in PAP.

The estimation of PAP by echocardiography can be carried out in several ways, the most common is by using the gradient of the tricuspid regurgitant jet (TR), as used in other studies [29]. However, this method has limitations. Often the TR jet is not visualized, especially in early and mild PH [18, 32, 33]. In our study, TR was only found in 16 patients (40%) of the total sample, so the use of the PAAT parameter was chosen in order to describe the estimation of PA pressure in the entire sample. PAAT for mPAP estimation is easy, feasible, and reproducible in patients with or without TR. In a meta-analysis, PAAT was negatively correlated with PA pressure and had high sensitivity and specificity, especially in patients with mPAP ≥25 mmHg [18].

RV dysfunction in COVID-19 could be the result of various pathomechanical pathways. Increased pulmonary vascular resistance due to ARDS and pulmonary thromboembolism, as well as myocardial injury due to inflammatory cytokines are believed to be the main causes of RV dysfunction in COVID-19 patients [34]. The results of our study showed the prevalence of RV dysfunction is 67.5% when using the RV FWLS parameter, 2-3 times higher than the other conventional parameters which ranged from 14.5-27% [12, 35, 36]. As is well known, one of the advantages of the strain parameter is more sensitive in detecting early and subclinical dysfunction [37]. Longobardo *et al*. and Morris *et al*. found that the strain as RV function parameter has the best correlation with its gold standard method, which is CMR and the detection rate of RV dysfunction using strain is 1.5-2 times higher than conventional parameters such as TAPSE and FAC [38, 39]. Likewise, Lamia *et al*. reported that an abnormal RV FWS value was already seen even in a patient with borderline PH [40]. The free wall section can reflect the contractility of the RV independently, apart from the contribution of the septum which is a combination of LV and RV components.

Our study showed a significant correlation between peak D-Dimer levels with RV-FWLS (r = -0.506; p = 0.001) and mPAP (r = 0.526; p<0.001). This is also consistent with other studies which showed that D-Dimer levels were negatively correlated with parameters of RV function, including by Akkaya *et al*. (RV FWS; r = -0.557; p<0.001) and Elsayed *et al*. (FAC; r = -0.34; p = 0.003) [36, 41]. Meanwhile, the correlation of D-Dimer levels with pulmonary arterial pressure was previously reported by Goudot *et al*. (r = -0.178; p =0 .047) [42].

In the present study peak D-Dimer levels were recorded at a median of 14 days from symptom onset. As is well known, thromboembolic complications occur as the disease severity progresses, and generally occur in the third phase or hyperinflammatory phase [43]. Studies by Pasha *et al*. and Cerda *et al*., showed that thromboembolic complications in patients with COVID-19 occurred mostly at 2-4 weeks from symptom onset [44, 45]. In contrast to the increase in D-Dimer in the first week due to the natural immune response to viral infection, D-Dimer levels in the 2nd to 4th week are more likely to represent thrombotic complications in COVID-19 patients [45].

Elevated D-Dimer levels in COVID-19 indicate a hypercoagulable state and have been associated with major thromboembolic events [46]. However, from several meta-analytical studies, it is known that the predictive ability of D-Dimer for pulmonary thromboembolic events has a high sensitivity, but low specificity, considering that in severe COVID-19 extensive endothelial injury and systemic microthrombosis occurs [4, 47]. However, it is important to recognize and diagnose pulmonary thromboembolic complications because of their therapeutic and prognostic value in patients with COVID-19. Several studies evaluated D-Dimer accuracy as a surrogate marker of pulmonary thromboembolic compared with CTPA, including Mouhat *et al*. (cut-off D-Dimer 2590 µg/L and Diaz *et al*. (cut-off D-Dimer 2903 µg/L) [41, 42]. Meanwhile, our study found that the peak D-Dimer ≥4530 µg/L was a predictor of PH in the short-term follow-up after COVID-19 pneumonia.

The hemodynamic consequences of pulmonary thromboembolism depend on the degree and location of the thrombus. Generally, thrombus in the PA main branch and extensive thrombus in the pulmonary vascular tree will result in significant hemodynamic changes [48, 50]. Previous studies showed most thrombosis in COVID-19 occurred in the peripheral pulmonary vessels (segmental or subsegmental), in contrast to the incidence of PE in the general population which is more common in the main and proximal pulmonary arteries [46, 48, 51]. This may explain why the cut-off value of D-Dimer for hemodynamic sequelae in this study was higher than the cut-off for pulmonary thrombosis diagnostic values obtained from previous studies.

The dynamics of D-Dimer levels also cannot be separated from the use of anticoagulant thromboprophylaxis. All samples of this study received enoxaparin which is a low molecular weight heparin (LMWH) with doses according to WHO and International Society on Thrombosis and Haemostasis (ISTH) guidelines [52]. During hospitalisation, 4 patients were switched to unfractionated heparin (UFH), with indications of acute kidney injury. Meanwhile, for 6 (15%) samples, the anticoagulant was uptitrated from prophylactic to therapeutic dose because of the rapid increase of D-Dimer levels and respiration worsening out of proportion to pneumonia severity. Patients on therapeutic anticoagulants had a higher mean peak D-Dimer level (16240 *vs* 5431 µg/L; p=0.001) and also a poorer P/F ratio (94.2 *vs* 145.1; p=0.05). Patients receiving therapeutic doses of anticoagulants also had significant changes in peak and pre-discharge D-Dimer levels (delta D-Dimer) compared with prophylactic doses (13991 *vs* 3961 µg/L; p=0.01). This indicates that this group of patients may indeed have thrombotic complications that respond well to higher doses of anticoagulation.

From multivariate analysis, it was seen that peak D-Dimer levels ≥4530 µg/L were associated with the incidence of PH, but not with RV dysfunction. This suggests that other mechanisms may also play a role in causing RV dysfunction in COVID-19. In contrast to PH which is directly caused by increased PA pressure due to ARDS and pulmonary thrombosis, RV dysfunction can occur from two pathomechanical pathways, which are increased pulmonary circulation afterload and impaired RV contractility due to myocardial injury.

Myocardial injury can occur due to various factors, including a cardio-depressant effect of inflammatory cytokines [50 - 52]. Our study showed CRP levels were not only negatively correlated with RV function parameters, but also with LVEF (r = -0.428; p = 0.011). In previous studies, inflammatory parameters such as interleukin 6 (IL-6), interleukin 1(IL-1), and tumour necrosis factor-alpha (TNF-α) directly affected contractility and triggered apoptosis [53, 55]. A study showed that the IL-6 level was the most significant inflammatory parameter that affects RV function in COVID-19 patients [54]. Myocardial injury characterized by elevated troponin levels has been shown to be associated with a decrease in both LV and RV function as measured using the strain parameter up to 2 months post-infection [56, 57]. However, it cannot be proven objectively in the present study, since measurement of high-sensitivity troponin (hs-Tn) and specific inflammatory biomarkers (IL-6, IL-1, TNF-α) are not routinely carried out in our institution.

The PaO2/FiO2 ratio (P/F ratio) is a simple parameter that is routinely used to evaluate oxygenation capacity in patients with ARDS and closely reflects the severity of lung injury [53 - 55]. Our study shows that there is a significant correlation between the P/F ratio and mPAP (r = 0.685; p<0.001) and RV-FWLS (r = 0.641; p<0.001). Multivariate analysis also showed that P/F ratio ≤121.9 was the most powerful and consistent parameter that affected both PH and RV dysfunction. This finding confirms the hypothesis that one of the cardiovascular sequelae of post-COVID-19 pneumonia is type 3 PH. In early stages, ARDS directly affects pulmonary vascular hemodynamics through vascular compression due to aatelectasis and alveolar edema and hypoxia-induced vasoconstriction that results in increasing of PA pressure, meanwhile in the chronic phase, hemodynamic changes can be persistent and progressive due to remodeling of the surrounding lung and vascular tissue [58 - 62]. In the present study, the incidence of PH and RV dysfunction was more common in patients with a history of mechanical ventilation (MV), although not statistically significant. This can be attributed to the very small number of patients (n=4; 15%) with a history of MV in the present study. High Flow Nasal Cannula (HFNC) was widely used in our study sample (42.5%). Several studies reported minimal hemodynamic effects of HFNC on PVR and RV afterload. HFNC increases alveolar recruitment by providing a high level of oxygen flow, not by giving positive end-expiratory pressure

(PEEP), so that the resulting positive airway pressure is also low, <4 cmH_20 [53, 54].

This study has some limitations. First, a relatively small number of patients were included. Second, there was no known baseline echocardiographic data of patients before COVID-19. Third, the possibility of extrapulmonary thrombosis complications cannot be completely ruled out. Last, there was no examination of specific inflammatory parameters such as IL-6, IL-1, and TNF-α as well as cardiac biomarkers such as hs-Tn and N-terminal pro-brain natriuretic peptide (NT-proBNP) because these biomarkers were not routinely measured in our institution.

CONCLUSION

The present study showed that PH and RV dysfunction were common in short-term evaluation of post-COVID-19 pneumonia patients. Peak D-Dimer levels during hospitalization are correlated with mPAP and RV function as measured by echocardiography at a median of 11 days after patients recovered from COVID-19 pneumonia. We found that peak D-Dimer levels ≥4530 μg/L might increase the risk of PH, but not RV dysfunction after COVID-19 pneumonia.

LIST OF ABBREVIATIONS

(COVID-19)	=	Coronavirus disease 2019
(PH)	=	Pulmonary Hypertension
(PAAT)	=	Pulmonary Artery Acceleration Time
(TAPSE)	=	Tricuspid Annular Plane Systolic Excursion
(FAC)	=	Fractional Area Change
(AHA)	=	American Heart Association
(ADA)	=	American Diabetes Association
(BMI)	=	Body Mass Index

ETHICAL STATEMENT

The research procedures were revised and approved by the local hospital's ethics committee according to the ethical considerations stipulated in the Helsinki Declaration.

CONSENT FOR PUBLICATION

All patients included in this evaluation had signed an individual informed consent form.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

We decided not to publicly shared the supporting datasets of this study, but still available from the corresponding author, [A.C], on special request.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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Declared none.

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