ISSN 2449-8955 European Journal of Biological Research *Research Article*

DOI: http://dx.doi.org/10.5281/zenodo.15288546

COVID-19 long-term consequences: rapidly progressing cor pulmonale and its relation to hypercoagulation

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Received: 29 August 2024; **Revised submission:** 07 January 2025; **Accepted:** 17 February 2025

https://jbrodka.com/index.php/ejbr

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ABSTRACT: Patients with COVID-19 exhibit alterations in the coagulation process and are associated with respiratory and cardiovascular diseases, including acute respiratory distress syndrome and acute cor pulmonale. we described the effects of systemic thrombolysis on acute cor pulmonale in a patient suffering from COVID-19 long-term consequences. We examined the correlation between the Rapidly progressing cor pulmonale and its relation to hypercoagulation in 45 post COVID-19 patients at Osh State University, utilizing laboratory characteristics, radiological studies, and other clinical markers. A negative moderate correlation between PTI% and PT sec, suggesting that as PTI% decreases, the PT sec increases, potentially signalling hypercoagulability and the correlation between these variables is statistically significant ($p<0.05$). Moreover, a positive moderate correlation between PTI% and fibrinogen, indicating that lower PTI% is associated with higher fibrinogen levels. This correlation was also statistically significant ($p<0.05$). The study underscores the multifaceted nature of long-term COVID-19 complications, emphasizing the need for comprehensive patient monitoring. The significant correlations involving PTI% could serve as valuable indicators for clinicians to assess the risk of hypercoagulation and inflammation in patients, potentially guiding more tailored and timely interventions. However, the predominance of insignificant correlations calls for cautious interpretation of the results. It suggests that while some relationships between these physiological parameters and long-term COVID-19 complications exist, they may not be straightforward or may be influenced by other factors not captured in this analysis. This highlights the importance of holistic patient assessment and the potential for individual variability in response to long-term COVID-19.

Keywords: Cor pulmonale; COVID-19; Right ventricular hypertrophy; Echocardiography; Long-term consequences of COVID-19; Hypercoagulation.

1. INTRODUCTION

COVID-19, caused by the severe acute respiratory syndrome coronavirus-2, emerged as a global pandemic, resulting in significant morbidity and mortality worldwide. Patients with comorbidities face a notably worse prognosis. Among the comorbidities, cardiovascular disease has drawn particular attention for its association with increased COVID-19 mortality. However, fatalities have also been reported in patients without known risk factors [1]. The mechanisms underlying mortality in these cases are not yet fully understood but are believed to involve a combination of thromboembolic and inflammatory processes [2].

Acute cor pulmonale (ACP), characterized by a sudden unexpected increase in pulmonary vascular resistance, is closely linked with acute respiratory distress syndrome (ARDS) [3,4]. Interestingly, some COVID-19 patients developed ARDS, with reports of ACP development in severe cases [5]. Cor pulmonale, a complication affecting both pulmonary and extra-pulmonary systems, is pathophysiologically classified into three mechanisms: hypoxemic, vascular, and thoraco-diaphragmatic. Symptoms include exercise intolerance, breathlessness, edema, and organ congestion [6].

The long-term consequences of COVID-19, termed post-acute sequelae, are of primary concern and require serious attention. While numerous studies have been conducted on long-term COVID-19 effects, the phenomenon of rapidly progressing right ventricular failure has not yet been fully described. Pulmonary hypertension and rapidly progressing right ventricular failure contribute significantly to morbidity and mortality in COVID-19-associated pneumonia, although the potential mechanisms remain unclear. Evidence suggests oxidative stress, platelet activation, and a prothrombotic state as potential contributors.

This study aimed to evaluate the correlation between fibrinogen levels and right ventricular size, as well as potential risk factors, in COVID-19 patients requiring hospital admission due to disease progression. It offers a practical approach for examining patients with cor pulmonale.

2. MATERIALS AND METHODS

2.1. Study design and subjects

This cross-sectional observational study was carried out among 45 previous patients who were prospectively recruited from August 2022 to March 2024 in two hospitals at International Medical Faculty, Osh State University, Osh city, Kyrgyzstan.

Patients who were previously healthy and had recovered from severe COVID-19 disease with indicated right-sided heart failure and pulmonary hypertension, as demonstrated by dyspnea, cyanosis with low oxygen saturation, abnormal jugular venous distension, rales, edema, and hepatomegaly, were deemed eligible to enroll in the study. On the other hand, patients on current use of anticoagulants and with chronic pulmonary condition as COPD, asthma, idiopathic pulmonary fibrosis, and congestive left-sided heart failure with low left ventricular ejection fraction <52%, and left atrial and ventricular hypertrophy, systemic autoimmune disease that can lead to increased pulmonary pressure as well as right ventricular remodeling were exclude from the study.

2.2. Physical and laboratory investigations

All patients were subjected to routine investigations, including obtaining detailed history, traditional physical examination, complete blood count, coagulogram, blood urea and serum creatinine, electrocardiography, chest radiography, echocardiography, pulmonary functioning testing, and pulse-oximetry. The dyspnea scaled according to Modified Medical Research Council Dyspnea Scale (mMRC) 2-4 grade accordingly [7]. Laboratory coagulation tests data were pooled and collected the following coagulation data:

international normalized ratio (INR) activated partial thromboplastin time (aPTT), prothrombin time (PT) and fibrinogen.

2.3. Echocardiographic investigations

Transthoracic two-dimensional echocardiography with Doppler flow was prospectively performed by experienced cardiac sonographers using the MINDRAYDC-8 echocardiograph, following a standard protocol and assessed the valvular structure and function, right and left chamber size, and diastolic and systolic cardiac functions and presence and location of systolic tricuspid regurgitation (TR) was verified by color Doppler echocardiography and. Doppler recordings of maximal velocity were obtained from apical, lower left parasternal, and subcostal transducer positions. The RV size was measured in the apical 4-chamber view. Right ventricle consistent with right ventricular volume, and interventricular septal and posterior wall thicknesses obtained by parasternal long axis view. Although, wall thickness and chamber dimension evaluated from parasternal short axis view.

2.4. Pulmonary investigations

Pulmonary hypertension (PAH) is defined a sPAP >36 mmHg by using spirometer [8,9]. This value is chosen according to the PAH definition. All measurements were standardized according to the European society of cardiology recommendations [10,11].

2.5. Statistical analysis

Correlations between the two variables were evaluated using Pearson's Product Moment formula with an 95% confidence limits. The statistical analyses and graphical presentation were achieved using R Studios (vers. 4.2.2) with significant values set at $P < 0.05$ (two-tailed).

3. RESULTS

A total of 45 patients participated in the study, with the mean age of the total sample being 44.5±9.7 years, including 28 (62%) males. The most prevalent clinical findings were dyspnea. Detailed demographic and clinical characteristics of all patients are outlined in Table 1. Complete blood tests revealed various abnormalities including erythrocytosis, leukocytosis, leukopenia, neutrophilosis, lymphopenia, thrombocytosis, and thrombocytopenia, as shown in Table 2.

Table 1. Demographic and clinical findings and pulmonary functioning test (n=45).

Findings	No of patients, n(%)
Mean age (years)	44.5±9.7
Male gender	28 (62%)
Fatigue	41 (91%)
Dyspnea Grade 2	6
Dyspnea Grade 3	28
Dyspnea Grade 4	11
Cyanosis with a low oxygen saturation	42 (93.3%)
Cough and sputum production	33 (73.3%)
Edema	16 (35.5%)
Rales and rhonchi	6 (13.3%)
Wheezes	3 (2.8%)
Hepatomegaly	8 (7.5%)

Findings	No of patients, n(%)
Hypotension	5 (4.7%)
Restrictive pattern	36 (80%)
Obstructive pattern	4 (3.8%)
Normal PFT	16 (15%)

Table 2. Hemostasiogramma (Hemostatic) and complete blood test (n=45).

Findings	Patients, n(%)
Fibrinogen > 4000	32 (71%)
Fibrinogen >8000	13 (29.8%)
Activated partial thromboplastin time <	5 (11.1%)
Prothrombin time (PT)	14 (31.1%)
Complete Blood Test	
Erytrocytosis	3 (6.6%)
Leukocytosis	20 (44.4%)
Leukopenia	10 (22.2%)
Neutrophilosis	11 (24 .4%)
Lymphopenia	14 (31.1%)
Thrombocytosis	19 (42.2%)
Thrombocytopenia	10 (22.2%)

Echocardiographic findings predominantly indicated different stages of pulmonary hypertension, right ventricular hypertrophy, right ventricular dilatation, right ventricular impairment, tricuspid regurgitation, and right ventricular (RV) systolic dysfunction (defined by fractional area change). Notably, RV systolic dysfunction was significantly associated with increased levels of fibrinogen A ($\rho = -0.34$; $P = 0.003$) and CRP ($r = -0.23$; $P = 0.045$), indicating a correlation with hypercoagulation and disease severity, as presented in Table 3. Radiological patterns observed in pulmonary imaging are detailed in Table 4.

Table 3. Echocardiography (n=45).

Findings	Patients, n (%)
Global right heart impairment	45 (100%)
Tricuspid regurgitation	44 (97.8%)
Right ventricle wall thickness >2.90 cm	45 (100%)
Right ventricular dilatation	18 (40%)
right ventricular impairment	14 (31.1%)
Mild (36-50)	14 (31.1%)
Moderate (50-70)	25 (55.5%)
Severe (> 70)	6 (13.3%)

The statistical analyses provided in this research highlight the complex interplay between various physiological parameters and their potential association with long-term COVID-19 complications, such as hypercoagulation and cor pulmonale. Notably, two significant correlations were found. A negative moderate correlation between PTI% and PT sec, suggesting that as PTI% decreases (indicating worsening lung function), the PT sec increases, potentially signaling hypercoagulability as presented in Figure 1.

Table 4. Pulmonary imaging (n=45).

Findings	Patients, n (%)
Normal appearance	12 (26.7%)
Architectural distortion	33 (73.3%)
Reticulation	25 (55.5%)
Honeycombing	7 (15.5%)
Traction bronchiectasis	2 (4.4%)
Consolidation	3 (6.7%)
Ground - glass opacity	2 (4.4%)
Air bronchogromm	2 (4.4%)
Atelectasis	3 (6.7%)

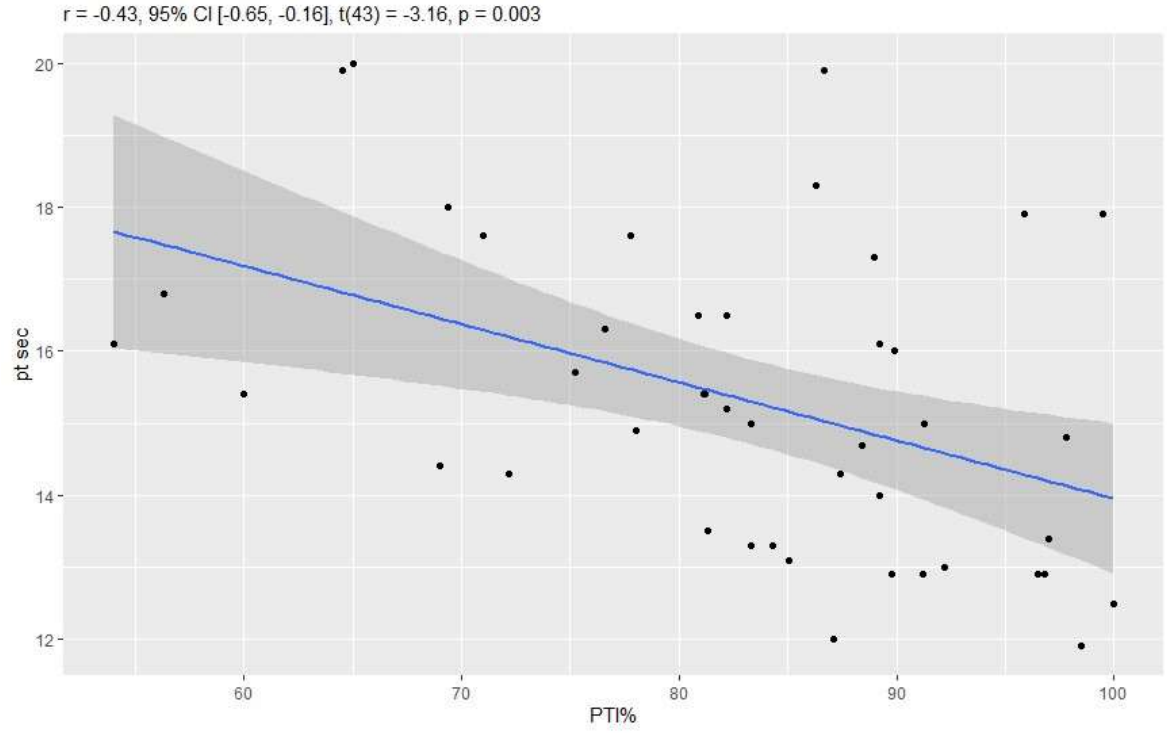


Figure 1. PTI% relationship with pt sec.

The correlation between PTI% and pt sec of -0.43. The relationship between the outcomes shows a negative moderate correlation effect. Correlations between the two variables were evaluated using Pearson's Product Moment formula with a 95% confidence limits for these were calculated. The statistical analyses and graphical presentation were achieved using R Studios (vers. 4.2.2) with significant values set at $P < 0.05$ (two-tailed). As can be seen in Figure 1, the correlation between the two variables was significant (p value < 0.05).

A positive moderate correlation between PTI% and fibrinogen, indicating that lower PTI% (worse lung function) is associated with higher fibrinogen levels, a marker of inflammation as shown in Figure 2. On the other hand, most of the variables exhibited insignificant correlations such as correlations between PAP/mmHg, RVS, RBS, PTI%, and various clinical parameters including appt numbers, PT sec, INR, platelet, and fibrinogen levels. These findings suggest a weak or non-existent linear relationship between these variables in the context of pulmonary heart disease and hypercoagulation related to long-term COVID-19.

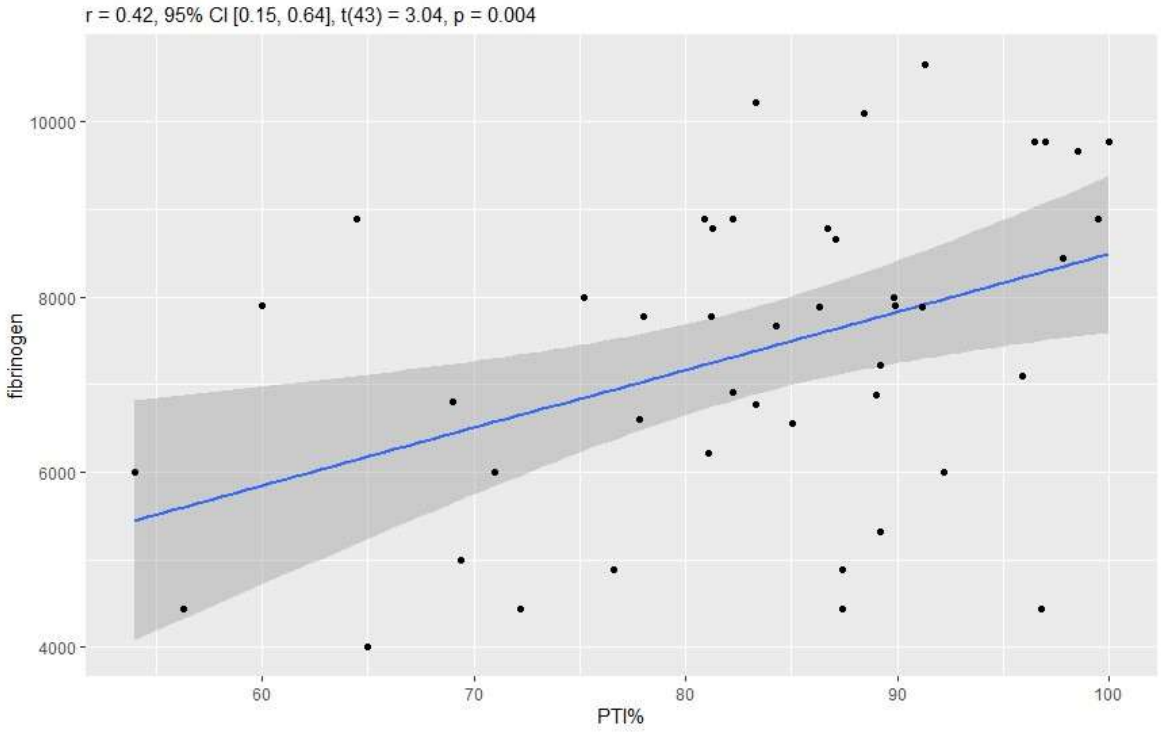


Figure 2. PTI% relationship with fibrinogen.

The correlation between PTI% and fibrinogen is 0.42. The relationship between the outcomes shows a positive moderate correlation effect. Correlations between the two variables were evaluated using Pearson's Product Moment formula with a 95% confidence limits for these were calculated. The statistical analyses and graphical presentation were achieved using R Studios (vers. 4.2.2) with significant values set at $P < 0.05$ (two-tailed). As can be seen in Fig. 2, the correlation between the two variables was significant (p value < 0.05).

4. DISCUSSION

To the best of our knowledge, the sudden onset of right ventricular failure, often accompanied by elevated fibrinogen levels in individuals previously infected with coronavirus, represents a unique pathology in modern medicine. However, specific guidelines for its diagnosis and treatment are currently lacking. The primary pathogenic mechanism seems to involve blood clotting, a hallmark feature of COVID-19 infection. Prolonged hypercoagulability likely contributes to the development of thromboembolism [12] in small pulmonary artery branches, oxidative stress [13], and subsequent elevation of pulmonary circulation pressure, leading to right ventricular remodeling and failure.

Assessing fibrinogen levels appears closely linked with right ventricular hypertrophy and dilation, providing a reliable screening method for detecting right ventricular heart failure. Typically, patients with right ventricular failure exhibit elevated fibrinogen levels, indicating ongoing hypercoagulation and ventricular remodeling [12].

COVID-19 is characterized by alterations in the coagulation process, reduced fibrinolysis, and microvascular thrombosis of lung vessels. Additionally, this disease is associated with ARDS and ACP [5, 14-16]. A significantly reduced level of fibrinolysis plays a crucial role in the hypercoagulable state and thromboembolic risk in COVID-19 patients [16]. Furthermore, the vaccination that most people relied on during the pandemic may have contributed to thrombotic problems in COVID-19 individuals [17].

In our study, we observed a negative moderate correlation between PTI% and PT sec, suggesting that as PTI% decreases, PT sec increases, potentially indicating hypercoagulability (Fig. 1). We also found a positive moderate correlation between PTI% and fibrinogen, indicating that lower PTI% is associated with higher

fibrinogen levels, a marker of inflammation (Fig. 1). This finding is supported by the findings of study by Wool and Miller [18]. A review study by Bazan and Fares in 2018 also highlighted the association between hypercoagulability and higher fibrinogen level in pulmonary hypertension or cor pulmonale [12].

Long-term COVID-19 complications may include hypercoagulation and cor pulmonale. Analysis suggests a decrease in pressure-time index and an increase in pulmonary artery pressure and residual volume in cases of cor pulmonale. The pressure-time index serves as a measure of left ventricular mass index and ventricular load, aiding in the monitoring of hypertension and chronic obstructive pulmonary disease (COPD). A study by González et al also pointed out that higher pressure-time index is associated with exacerbation of COPD and more risk of hospitalization [19]. This suggests that higher rates of hospitalization of previously COVID positive patients is an indication of its long term complications. However, the relationship between pressure-time index and activated partial thromboplastin time (APTT) appears nonexistent. Similarly, there seems to be no correlation between APTT and residual volume. Increased residual volume correlates positively with prolonged coagulation times and negatively with platelet count, suggesting possible airflow obstruction due to clots, possibly indicative of pulmonary embolism.

Regarding pulmonary artery pressure (PAP), a positive correlation with coagulation times is observed but deemed clinically insignificant. No significant correlations are found between PAP and APTT, international normalized ratio (INR), or fibrinogen levels. A negative correlation exists between PAP and platelet count, though it lacks clinical significance. These observations align with several reports from China and Italy documenting a high incidence of acute right ventricular dysfunction in severe COVID-19 patients. For instance, Rauch et al. published a series of 29 ICU patients hospitalized from March to April 2020 [20], reporting five cases with elevated troponin and echocardiographic features consistent with myopericarditis. Ferrante's study on 332 COVID-19 patients hospitalized from February to April 2020 reported an incidence of 37% of myocardial injury, independently associated with an increased risk of death. Overall, these findings suggest that ongoing damage to the pulmonary circulation might be a critical trigger of myocardial injury and RV dysfunction in COVID-19 [21].

In our study, we found that global right heart impairment was present in 100% of cases, tricuspid regurgitation in 98%, right ventricular wall thickness (>2.90 cm) in 100%, right ventricular dilatation in 40%, and right ventricular impairment in 30%. Pulmonary hypertension (sPAP >36 mmHg) was categorized as mild (36-50) in 31% of patients, moderate (50-70) in 56%, and severe (>70) in 13% of patients. Our study findings go in line with other studies which have indicated the need of performing echocardiographic examinations to trace out the level of damage caused to the right ventricle [22, 23].

An early indicator for detection of hypercoagulation from the data extrapolated is an increase in PT second value and a decrease in platelets. A study by Boccatonda et al. also pointed that the patients who were COVID positive had decreased level of platelets which is linked with other clinical parameters [24]. It seems that primary thrombosis could be active since the platelets are decreasing and the PT values are prolonged. However, most of the platelet values are in normal range (150-450). Factor VII may be decreased to form clots for the platelets which could result in a prolonged PT result. A study by Wang et al correlated the impact of prolonged PT value in increasing the complexity among COVID patients leading to deaths [25].

The study underscores the multifaceted nature of long-term COVID complications, emphasizing the need for comprehensive patient monitoring. The significant correlations involving PTI% could serve as valuable indicators for clinicians to assess the risk of hypercoagulation and inflammation in patients, potentially guiding more tailored and timely interventions. However, the predominance of insignificant correlations calls for

cautious interpretation of the results. It suggests that while some relationships between these physiological parameters and long-term COVID complications exist, they may not be straightforward or may be influenced by other factors not captured in this analysis. This highlights the importance of holistic patient assessment and the potential for individual variability in response to long-term COVID.

5. CONCLUSION

The research analysis offers valuable insights into the relationship between various physiological parameters and the risk of hypercoagulation and cor pulmonale in the context of long-term COVID. Despite the largely insignificant correlations, the significant findings related to PTI% suggest a potential pathway for further investigation. Clinicians and researchers should consider these findings as part of a broader effort to understand and mitigate the impact of long-term COVID complications on patient health. Future studies should aim to explore these relationships further, incorporating a wider range of variables and larger patient cohorts to validate these findings and uncover additional insights into the pathophysiology of post-COVID conditions.

Acknowledgements: We would like to express our gratitude to all those who contributed to this research. Special thanks to our Dean for their support, and to hospital director for providing the necessary resources and facilities. We are also grateful to our colleagues for their invaluable assistance and insightful discussions throughout the study. Lastly, we extend our appreciation to the participants and their families for their cooperation and contribution to this research.

Author Contributions: All authors contributed equally in this manuscript. All authors read and approved the final version of the manuscript.

Ethical Approval: The University Ethical Committee at the International Medical Faculty, Osh State University approved the study (No. IMFRC/COVID-19/13/2022). All enrolled participants provided written informed consent.

Conflict of Interest: The authors declare no potential conflict of interest.

Source of Funding: This work has not received any financial support.

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