

COVID-19 AND PULMONARY THROMBOEMBOLISM: A CASE SERIES

Mailla Mylena Mendes Bergmann

<http://lattes.cnpq.br/2912254563376960>

Lilian Mara Vieira Monsalve Moraga

<http://lattes.cnpq.br/6969002944449996>

Roberto Carlos Cruz Carbonell

<http://lattes.cnpq.br/5754511048186155>

Bianca Jorge Sequeira

<http://lattes.cnpq.br/0416608225783691>

Nayara Melo Dos Santos

<http://lattes.cnpq.br/4458774232308999>

Domingos Sávio Matos Dantas

<http://lattes.cnpq.br/1525944185247908>

Luis Enrique Bermejo Galan

<http://lattes.cnpq.br/5096777417510461>

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Abstract: Objective: to perform a review and descriptive analysis of 24 cases of COVID-19 associated with pulmonary thromboembolism seen in the public service in the State of Roraima in 2021. **Methods:** retrospective review of 24 selected cases of patients who presented with COVID-19 pneumonia and developed pulmonary thromboembolism (PTE) in the year 2021. All patients selected for this study had a confirmed diagnosis of COVID-19 - either by SWAB-RT-PCR or by clinical-epidemiological diagnosis + imaging tests - and a diagnosis of PTE within a period of up to 3 months after the date of hospitalization/diagnosis. **Results:** the predominant age range among research participants was patients older than 60 years. There was a predominance of obesity (58.3%) and hypertension (50%) as the main comorbidities among patients in the selected group, followed by diabetes mellitus (41.6%). About 75% of the patients required intensive care and of these, 61.1% were admitted to the intensive care unit for a period of more than 10 days. Most study subjects were on prophylaxis with regular use of enoxaparin at a dose appropriate for their weight (79.2% of participants). **Conclusion:** there is an association between Covid-19 and the presence of coagulopathies, especially in the most critically ill patients.

Keywords: COVID, Pulmonary thromboembolism, Complications.

INTRODUCTION

The global health crisis caused by the spread of infection by the human Coronavirus, SARS-CoV-2, began in December 2019, in the city of Wuhan, China (WHO, 2021). Since then, more than 240 million cases of Covid-19 have been registered around the world, with more than 21 million of these in Brazil (JOHNS HOPKINS, 2021).

Viral infections similar in many respects to Covid-19 were previously associated with

complications of a thrombotic nature, so that questions were raised regarding the presence of such complications also associated with infection by Sars-Cov-2 (ARYAL et al., 2020). In addition, respiratory complications are largely related to the immune response caused by viral infections. Among these respiratory manifestations, one of the most worrying is PTE (SUH et al., 2021).

Complications resulting from Covid-19 have been the subject of clinical research, so that it was possible to highlight complications of a thromboembolic nature as responsible for a large portion of the morbidity and mortality associated with Covid-19 (POYIADJI et al., 2020). It is believed that factors intrinsic to SARS-CoV-2 infection (JAIN, 2020) and the length of stay to which the most critically ill patients are subject are responsible for the increase in procoagulant factors in affected patients (DI MINNO et al, 2020). Among these factors, we can emphasize those of Virchow's triad: state of hypercoagulability, venous stasis and vascular injury, all of which are exacerbated in the context of hospitalization for Covid-19 (BORGES et al., 2020).

Coagulopathies associated with this disease are present in about 50% of cases of severe SARS-CoV-2, even with the use of thromboprophylaxis. The concomitant presence of risk factors such as systemic arterial hypertension, male gender and advanced age may further contribute to the development of this type of complication (MIESBACH; MAKRIS, 2020).

It is important to highlight the scarcity of clinical studies on specific risk factors that lead to this association (LEVI, 2020). Still in 2022, we continue with uncertainties about the Covid-19 disease and with a small number of clinical trials in Brazil, even more so in Amazonian regions with their demographic peculiarities, as is the case of this work.

Added to this is the fact that pulmonary

thromboembolism is among one of the most common causes of undiagnosed mortality in critically ill patients (RECH; GIRARDI; GAZZANA, 2020), corroborating with the essential need for epidemiological descriptions of patients with Covid-19 and thromboembolism, the objective for which this case series was proposed.

METHODOLOGY

This study in question performed one analysis with hindsight in positive angiotomography for pulmonary thromboembolism (PTE) in patients diagnosed with the Covid-19 disease, treated at the General Hospital of Roraima, the main hospital in the State of Roraima. This one is located in the extreme north of Brazil, within the Amazon region and in the border region with Venezuela and British Guiana.

A retrospective and analytical study was carried out of all patients who were hospitalized with a diagnosis of COVID-19, in the hospital unit of the infectology service of the General Hospital of Roraima. The search focused on the temporality of hospitalizations between February and September 2021. The search in the medical records of patients who evolved with pulmonary thromboembolism (PTE), and the analysis resulted in 24 patients with positive TEP angiotomography, who fulfilled the clinical criteria and laboratory diagnosis of the disease.

The patients involved in the present series were hospitalized at the service, responsible for treating most cases of Covid-19 in the state, during the pandemic. Patients with complete information records were selected, and who had a positive SWAB-RT-PCR for COVID-19 or an epidemiological clinical diagnosis associated with an imaging exam, in addition to a positive angiotomography for PTE within a period of up to 3 months from the date of the diagnosis of COVID.

As a primary outcome, pulmonary

thromboembolism was considered. The variables for the analysis were: age, nationality, origin, gender, ethnicity, vaccination against Covid-19 prior to hospitalization, smoking, alcoholism, presence of pregnancy, deep vein thrombosis during hospitalization, presence of comorbidities, length of stay in the ward, length of stay in the ICU (when applicable), performance or not of non-invasive ventilation sessions, time required for invasive mechanical ventilation (when applicable), performance or not of prophylaxis for thromboembolism, plasmatic D-dimer level at the time of diagnostic angiotomography for PTE and region of the lung affected by the thrombus, to be analyzed according to the result of the angiotomography.

Data were tabulated in Microsoft Excel, version 16.54, and statistical analysis was performed using the same program. Only descriptive statistical analysis was used to present the data, since the sample size did not allow inferential analysis. The methodological design of the present study was approved by the Research Ethics Committee of "Universidade Federal de Roraima" (Opinion: 5,085,195).

RESULTS AND DISCUSSION

This study descriptively presents a significant list of patients in whom it was possible to safely diagnose the concomitance of infection by Covid-19 and the presence of pulmonary thromboembolism, since diagnostic angiotomography was performed in all patients involved in this series of cases, with demonstration of the thrombus in several pulmonary arteries. Such data is even more relevant when considering the logistical difficulties of performing this test (POVEDA; GILABERT, 2020), especially in the pandemic context in which this data was collected. From the data collected in the medical records, it was possible to relate the following results:

Variable	Absolute frequency (n)	Relative frequency (%)
age range		
20-30 years	03	12.5%
31-40 years	05	20.8%
41-50 years	03	12.5%
51-60	06	25%
Over 60 years old	07	29.2%
Nationality		
Brazilian	24	100.0%
race/color		
brown	07	29.2%
White	04	16.6%
not informed	13	54.2%
Sex		
Feminine	09	37.5%
Masculine	15	62.5%
Vaccination against COVID-19		
Yes	05	20.8%
No	07	29.2%
Uninformed	12	50%
Smoking		
Yes	04	16.7%
No	11	45.8%
Uninformed	09	37.5%
Alcoholism		
No	08	33.4%
social use	03	12.5%
high	02	8.3%
consumption	11	45.8%
Uninformed		

Table 1. Socio-environmental characteristics of the research participants.

In the series presented, 66.7% of the patients are aged over 41 years, with a predominance of patients in the age group above 60 years, in agreement with studies that show an increase in the prevalence of the association between Covid-19 and PTE with the increase of age (WICHMANN et al., 2020). Still with regard to socio-environmental factors, there was a relative balance between the number of participants of both sexes, in agreement with other studies and meta-analysis data (DI MINNO et al., 2020). Among those participants whose medical records contained vaccination data (12 participants), 41.6% had taken at least one dose of vaccine against

Covid-19, an important relationship when considering the lack of knowledge about the thromboembolic potential of the multiple vaccines available at the time. of carrying out this study. (AL-MAQBALI et al., 2021) Smoking, a known risk factor for PTE (TAPSON, 2005), was confirmed by 4 of the 15 (26.6%) patients in whose medical records it was possible to find this information.

With regard to comorbidities, among the patients who had them (50%), there was a predominance of obesity (n=12) in line with meta-analysis data on the subject, which describe a high prevalence of this comorbidity (DI MINNO et al., 2020). In addition, 50% of patients with systemic arterial hypertension were also found, 41.6% diagnosed with diabetes mellitus, 8.3% with asthma and 8.3% diagnosed with chronic obstructive pulmonary disease, and in some patients, there was coexistence of comorbidities. Among the patients, the association between deep venous thrombosis and PTE was investigated, and only 12.5% of the patients had such an association.

The importance of knowledge about the risk of thrombotic events in patients is highlighted, aiming to choose the best prophylactic approach to which these individuals must be subject during hospitalization. (KLOK et al., 2020) For the stratification of previous risk for the development of venous thromboembolism in hospitalized patients, the Padua risk score was used, with the results described below.

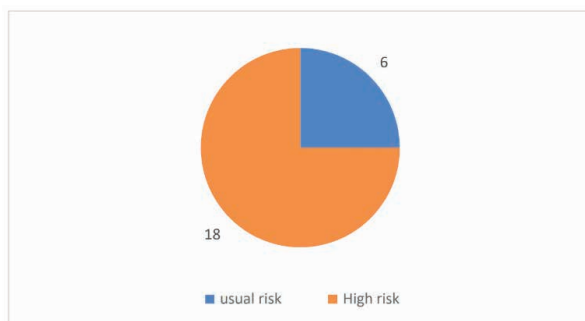


Figure 1. The risk stratification for PTE using the Padua score.

The instrument considers factors such as age greater than 70 years, presence of comorbidities, active carcinoma, history of previous deep vein thrombosis (DVT) or PTE, reduced mobility, obesity, recent surgery or trauma, hormone therapy, rheumatological disease or current infection. (BARBAR et al., 2010) From this, it was possible to determine that 75% of the patients hospitalized in this series showed high risk for thromboembolism.

According to the hospitalization profile, the results are presented below:

Variable	Absolute frequency (n)	Relative frequency (%)
place of hospitalization		
outpatient	02	8.3%
Nursery	04	16.7%
Infirmery + ICU	18	75%
Hospital stay period		
10 – 20 days	03	13.6%
21 – 30 days	07	31.8%
31 – 40 days	04	18.2%
41 – 50 days	04	18.2%
Over 50 days	03	13.6%
Uninformed	01	4.6%
Length of stay in the ICU		
01 - 10 days	05	27.8%
11 – 20 days	07	38.9%
Over 20 days	04	22.2%
Uninformed	02	11.1%

Table 2. Hospitalization profile of study participants.

According to the data collected, approximately 75% of the patients in the series presented required intensive care, and of these, 61.1% were hospitalized in the Intensive Care Unit (ICU) for a period longer than 10 days. With regard to the total period of hospitalization, 75% of the patients were hospitalized for a period greater than 20 days, and 12.5% had more than 50 days of hospitalization.

It is important to remember that there are reports of patients with moderate manifestations of pneumonia due to Covid-19

who presented late manifestations of PTE (VECHI; MAIA; ALVES, 2020), so it is not possible to associate ICU admission as the exclusive determining factor of presentation of TEP.

The use of invasive mechanical ventilation was necessary for 70.8% of the participants surveyed, and the period of use of this modality of ventilatory support was greater than 10 days in 58.8% of the cases. Such relationships are described in the images below.

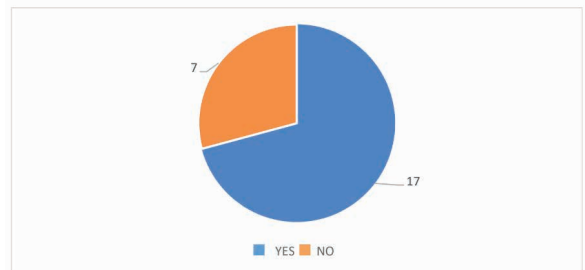


Figure 2. The patients who had pulmonary thromboembolism and its relationship with the use of invasive mechanical ventilation.

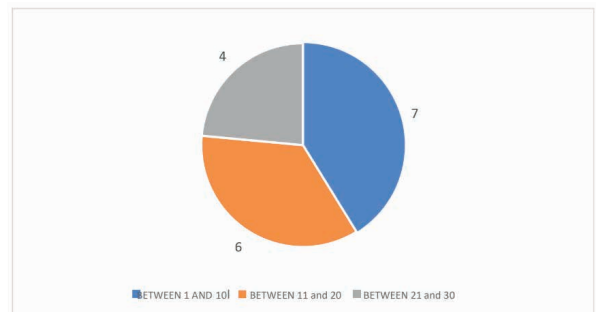


Figure 3. The period (days) in which patients with pulmonary thromboembolism who used invasive mechanical ventilation.

With regard to laboratory diagnostic data, d-dimer testing was performed in all patients, with the vast majority of patients showing significantly elevated values of this marker, as shown by the list below. The description of the values of this marker is of particular importance when considering the association between high d-dimer values and worse outcomes in pneumonia caused by Covid-19 (BOMPARD et al., 2020).

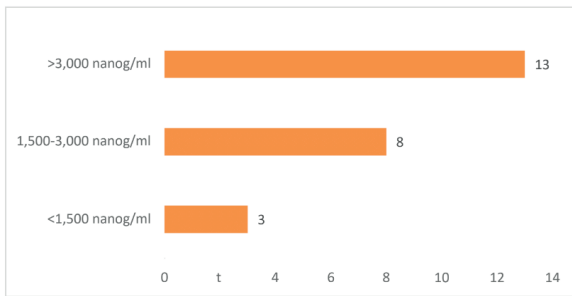
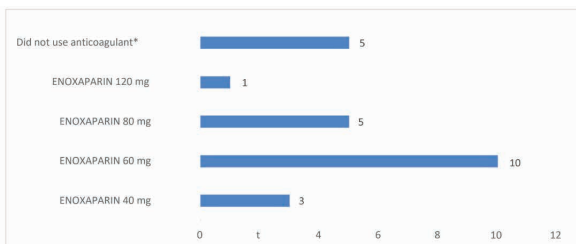


Figure 4. The maximum d-dimer value of patients during hospitalization.

It was possible to assess in this list of cases that 87.5% of patients had d-dimer > 1,500 nanog/ml, with 54.2% of participants presenting values greater than 3,000 nanog/ml. Such high values may be related to an increase in intravascular coagulation resulting from a systemic inflammatory response syndrome or as a consequence of the Sars-CoV-2 infection itself. (LÉONARD-LORANT et al., 2020) In view of these results, the use of thromboprophylaxis was also investigated, with a description of the drug and doses used. Such data are described below.



* Patients who did not use prophylactic Enoxaparin during hospitalization had some contraindication to the use of this drug.

Figure 5. Drug used as prophylaxis for pulmonary thromboembolism during hospitalization, daily dose.

Most subjects were using prophylaxis with regular use of enoxaparin in a dose appropriate for weight (79.2% of participants). Recent randomized clinical studies sought to analyze the impact of heparin dose on significant morbidity and mortality outcomes, such as

death, use of mechanical ventilation and ICU stay. The RAPID study, which had 465 participants from 6 countries, including Brazil, showed that there was a statistically significant impact on the absolute number of deaths from different causes in the group of patients who used a therapeutic dose of heparin up to 2 days after hospitalization hospital. The use of a therapeutic dose of heparin adequate for weight was able to reduce the percentile of deaths from different causes from 7.6% to 1.8% between the groups with prophylactic and therapeutic doses, respectively.

Thus, even if a therapeutic dose of heparin was given to the patients analyzed in this series, the most prevalent outcomes among the patients analyzed (ICU admission – 75% and need for MV – 70.1%) would not have had a significant change with the early therapeutic intervention with enoxaparin regarding the scope of the randomized study described above.

As for the associated bacterial infections in the patients studied, the relationship was found as described in the figure below:

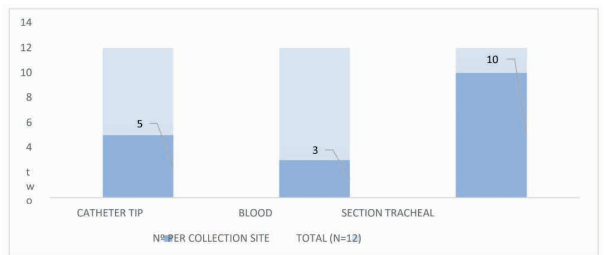


Figure 6. The culture sites where secondary bacterial infections were detected during hospitalization.

Among the patients in this series, 12 had secondary bacterial infection recorded by culture, all of them admitted to the ICU. Of the 18 patients who were admitted to the ICU, only 33.3% had no recorded secondary infection. Most positive cultures were performed in tracheal secretions: 83.3% of patients with positive cultures had at least

one culture of infected tracheal secretions. Only 4 of these patients had infection in more than one culture site. Other studies that evaluated nosocomial infection among hospitalized patients with Covid-19 showed a predominance of cases in intensive care patients (GARCIA-VIDAL, 2021).

An analysis of the prevalence of infectious agents present in the list of patients described was also carried out.

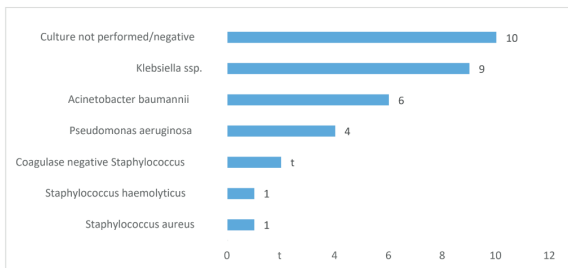


Figure 7. The profile of secondary bacterial infections of patients during hospitalization.

With regard to infectious agents, there was a predominance of *Klebsiella* ssp. (*Klebsiella pneumoniae* and *Klebsiella ozaenae*) which totaled 9 positive cultures in this series, followed by *Acinetobacter baumannii*, with 6 positive cultures, and *Pseudomonas aeruginosa*, with 4 cultures. There was a record of infection by multiple bacterial agents in 58.3% of the cases, especially the association *Klebsiella* ssp. + *Pseudomonas aeruginosa*, responsible for 33.3% of multi-agent cases. There was some similarity between this case series and that reported by Garcia-Vidal (2021) with regard to the most common microbiota and infectious site reported in both studies.

Antibiotic	Absolute frequency (n)
clarithromycin	01
caspofungin	01
Ampicillin + sulbactam	01
Tigecycline	01
Ciprofloxacin	01
Levofloxacin	01
Linezolid	01
Polymyxin B	02
Metronidazole	02
Fluconazole	03
Piperacillin + tazobactam	05
Vancomycin	05
Teicoplanin	05
Amikacin	06
Cefepime	09
Ceftriaxone	09
Meropenem	09

Table 3. The use of antibiotic therapy among patients in the series.

All hospitalized patients mentioned in this series of cases were using antibiotic therapy during hospitalization, although 45.5% of them did not have a culture or only presented negative cultures during hospitalization. Among the most used antibiotics are cefepime, meropenem and ceftriaxone. Most patients used more than one antibiotic during hospitalization (72.7%). One of the patients treated on an outpatient basis also used empirical antibiotic therapy. Such data are most likely due to the difficulty of clinically differentiating the evolution of Covid-19 from bacterial pneumonia, so that many of the antibiotic regimens are implemented empirically not only in the services where this case series took place, but also in other parts of the country. world.

There was a predominance of favorable outcomes, with only one death in this case series, representing a 4% percentile of the patients surveyed. One of the patients was lost to follow-up and transferred to another

service.

CONCLUSION

The great proportions that the Covid-19 pandemic took made it essential to carry out studies that could help in the understanding of this condition and its complications. This series of cases, although numerically limited, was able to demonstrate the existence of a relationship between the results of the researched cases and studies carried out by other clinical researches.

The importance of clinical research on the relationship between Sars-Cov-2 and the presence of pulmonary thromboembolism is reaffirmed by the high morbidity and mortality associated with the latter. This way, the present casuistry proposes to contribute to the medical and academic community, composing part of the literature on the subject.

REFERENCES

- AL-MAQBALI, Juhaina Salim et al. A 59-year-old woman with extensive deep vein thrombosis and pulmonary thromboembolism 7 days following a first dose of the Pfizer- BioNTech BNT162B2 mRNA covid-19 vaccine. **American Journal of Case Reports**, v. 22, jun. 2021.
- ARYAL, Madan Raj et al. Venous Thromboembolism in COVID-19: Towards an Ideal Approach to Thromboprophylaxis, Screening, and Treatment. **Current Cardiology Reports**, v. 22, n. 7, p. 52, jul. 2020.
- BARBAR, Saber et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score: Padua Prediction Score. **Journal of Thrombosis and Haemostasis**, v. 8, n. 11, p. 2450–2457, nov. 2010.
- BOMPARD, Florian et al. Pulmonary embolism in patients with COVID-19 pneumonia. **European Respiratory Journal**, v. 56, n. 1, p. 2001365, jul. 2020.
- BORGES, Nicolas Henrique et al. Tromboembolismo Pulmonar em um Paciente Jovem com COVID-19. **Arquivos Brasileiros de Cardiologia**, v. 115, n. 6, p. 1205– 1207, dez. 2020.
- DI MINNO, Alessandro et al. COVID-19 and Venous Thromboembolism: A Meta- analysis of Literature Studies. **Seminars in Thrombosis and Hemostasis**, v. 46, n. 07, p. 763–771, out. 2020.
- FRANCO-LÓPEZ, Ángeles; POVEDA, Jorge Escribano; GILABERT, Nuria Vicente. Tromboembolismo Pulmonar en los pacientes con COVID-19. Angiografía con tomografía computarizada: resultados preliminares. **Journal of Negative and No Positive Results**, v. 5, n. 6, p. 616–630, abr. 2020.
- GARCIA-VIDAL, Carolina et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. **Clinical Microbiology and Infection**, v. 27, n. 1, p. 83–88, jan. 2021.
- JAIN, Uday. Effect of COVID-19 on the Organs. **Cureus**, v. 12, n. 8, 3 ago. 2020.
- JOHNS HOPKINS. **COVID-19 Map**. Johns Hopkins University of Medicine. Disponível em: <<https://coronavirus.jhu.edu/map.html>>. Acesso em: 20 out. 2021.
- KLOK, Frederikus A. et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. **Thrombosis Research**, v. 191, p. 145–147, jul. 2020.
- LÉONARD-LORANT, Ian. et al. Acute Pulmonary Embolism in Patients with COVID- 19 at CT Angiography and Relationship to d -Dimer Levels. **Radiology**, v. 296, n. 3, p. E189–E191, set. 2020.

LEVI, Marcel. COVID-19 coagulopathy vs disseminated intravascular coagulation. **Blood Advances**, v. 4, n. 12, p. 2850–2850, 23 jun. 2020.

MIESBACH, Wolfgang; MAKRIS, Michael. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. **Clinical and Applied Thrombosis/Hemostasis**, v. 26, jan. 2020.

POYIADJI, Neo et al. Acute Pulmonary Embolism and COVID-19. **Radiology**, v. 297, n. 3, p. E335–E338, dez. 2020.

RAWSON, Timothy Miles; WILSON, Richard C.; HOLMES, Alison. Understanding the role of bacterial and fungal infection in COVID-19. **Clinical Microbiology and Infection**, v. 27, n. 1, p. 9–11, jan. 2021.

RECH, Taatiana Helena; GIRARDI, Adriana Muradás; GAZZANA, Marcelo Basso. Incidence of pulmonary embolism in patients with COVID-19. **Intensive Care Medicine**, v. 46, n. 7, p. 1500–1501, jul. 2020.

SHOLZBERG, M. et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. **The BMJ**, v. 375, p. n2400, 14 out. 2021.

SILVA ANDRADE, Bruno Silva et al. Long-COVID and Post-COVID Health Complications: An Up-to-Date Review on Clinical Conditions and Their Possible Molecular Mechanisms. **Viruses**, v. 13, n. 4, p. 700, abr. 2021

SUH, Young Joo et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID- 19: A Systematic Review and Meta-Analysis. **Radiology**, v. 298, n. 2, p. E70–E80, fev. 2021.

TAPSON, Victor F. The Role of Smoking in Coagulation and Thromboembolism in Chronic Obstructive Pulmonary Disease. **Proceedings of the American Thoracic Society**, v. 2, n. 1, p. 71–77, abr. 2005.

VECHI, Hareton Teixeira; MAIA, Lucas Rodrigues; ALVES, Manoella do Monte. Late acute pulmonary embolism after mild Coronavirus Disease 2019 (COVID-19): a case series. **Revista do Instituto de Medicina Tropical de São Paulo**, v. 62, p. e63, ago. 2020.

WICHMANN, Dominic Wichmann et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. **Annals of Internal Medicine**, v. 173, n. 4, p. 268–277, ago. 2020.

WORLD HEALTH ORGANIZATION. **WHO-convened Global Study of Origins of SARS-CoV-2: China Part**. Wuhan, CH: WHO-China, 2021.