Right heart overload – possible long-term sequelae of Covid-19: a narrative review

Sobrecarga do coração direito – possíveis sequelas de longo prazo da Covid-19: uma revisão narrativa

Sobrecarga en el corazón derecho - posibles secuelas a largo plazo de Covid-19: una revisión narrativa

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ABSTRACT
The United Nations announced the COVID-19 Pandemic in March 2019, and since then, many efforts have been made to understand better the multiple consequences of the virus on one's health. Notably, such viral infection leads to an increase in the formation of thrombi and microthrombi. However, mechanisms are not precise yet, neither are these complication consequences and management. It is essential to acknowledge these aspects of the disease, so patients receive better health care when dealing with COVID-19. This article's extensive search involved PubMed, SCOPUS, Cochrane, and Google Scholar databases; authors used keywords to find relevant studies on the subject. SARS-CoV2 creates a pro-thrombotic state through direct endothelial damage and a cytokine storm, affecting the lung, among other organs, leading to hypoxia and a rise in vascular resistance. Increased vascular resistance makes patients prone to cardiac stress, with a known association with right heart failure, among other insults to the heart. This condition affects both outpatients and inpatients, hypertension being a significant risk factor. The cardiac damage can be observed by cardiac injury biomarkers, imaging, and heart failure symptoms. Considering the massive number of infected during the pandemic, we suggest that right heart failure secondary to increased vascular resistance in the COVID/post-COVID state presents as a long-term sequel of the infection. Moreover, we believe it deserves attention so that patients may receive early and adequate health care.

Keywords: pulmonary microthrombi, Covid-19, Sars-Cov2, cardiovascular manifestations, right heart failure, thromboembolism, hypercoagulation.

RESUMO
As Nações Unidas comunicaram Pandemia da COVID-19 em março de 2019 e, desde então, muitos esforços têm sido feitos para compreender melhor as múltiplas consequências do vírus na saúde. Notavelmente, tal infecção viral leva a um aumento na formação de trombos e micro trombos. No entanto, os mecanismos ainda não são precisos, nem as consequências e a gestão destas complicações. É essencial reconhecer estes aspectos da doença, para que os pacientes recebam melhores cuidados de saúde ao lidar com a COVID-19. A extensa pesquisa deste artigo envolveu os bancos de dados PubMed, SCOPUS, Cochrane e Google Scholar; os autores utilizaram palavras-chave para encontrar estudos relevantes sobre o tema. O SARS-CoV2 cria um estado pró-trombótico através de danos endoteliais diretos e uma tempestade de citocinas, afetando o pulmão, entre outros órgãos, levando à hipóxia e ao aumento da resistência vascular. O aumento da resistência vascular torna os pacientes propensos ao estresse cardíaco, com associação conhecida com insuficiência cardíaca direita, entre outros insultos ao coração. Essa condição afeta pacientes ambulatoriais e internados, sendo a hipertensão um fator de risco significativo. O dano cardíaco pode ser observado por biomarcadores de lesão cardíaca, exames de imagem e sintomas de insuficiência cardíaca. Considerando o enorme número de infectados durante a pandemia, sugerimos que a insuficiência cardíaca direita secundária ao aumento da resistência vascular no estado COVID/pós-COVID se apresenta como uma sequela da infecção em longo prazo. Além disso, acreditamos que este assunto merece atenção para que os pacientes possam receber cuidados de saúde precoces e adequados.

Palavras-chave: microtrombos pulmonares, Covid 19, Sars-Cov-2, manifestações cardiovasculares, insuficiência cardíaca direita, tromboembolismo, hipercoagulação.

RESUMEN
Las Naciones Unidas informaron sobre la pandemia de COVID-19 en marzo de 2019 y desde entonces se han realizado muchos esfuerzos para comprender mejor las múltiples consecuencias del virus para la salud. En particular, una infección viral de este tipo conduce a un aumento en la formación de trombos y microtrombos. Sin embargo, los mecanismos aún no son precisos, ni tampoco las consecuencias y el manejo de estas complicaciones. Es esencial reconocer estos aspectos de la enfermedad, para que los pacientes reciban una mejor atención sanitaria cuando se trata de COVID-19. La extensa investigación en este artículo involucró las bases de datos PubMed, SCOPUS, Cochrane y Google Académico, los autores utilizaron palabras clave para encontrar estudios relevantes sobre el tema. El SARS-CoV2 crea un estado protrombótico a través del daño endotelial directo y una tormenta de citocinas, que afecta el pulmón y otros órganos, lo que conduce a hipoxia y aumento de la resistencia vascular. El aumento de la resistencia vascular hace que los pacientes sean propensos al estrés cardíaco, con asociación conocida con insuficiencia cardíaca derecha, entre otros insultos al corazón. Esta condición afecta a pacientes ambulatorios e internados, siendo la hipertensión un factor de riesgo significativo. La lesión cardíaca puede detectarse mediante biomarcadores de la lesión cardíaca, pruebas de diagnóstico por la imagen y síntomas de insuficiencia cardíaca. Considerando el enorme número de pacientes infectados durante la pandemia, sugerimos que la insuficiencia cardíaca derecha secundaria al aumento de la resistencia vascular en el estado de COVID/post-COVID se presenta como una secuela de la infección a largo plazo. Además, creemos que este tema merece atención para que los pacientes puedan recibir una atención temprana y adecuada.

Palabras clave: microtrombos pulmonares, Covid 19, Sars-Cov-2, manifestaciones cardiovasculares, insuficiencia cardíaca derecha, tromboembolia, hipercoagulación.

1 INTRODUCTION

The Coronavirus disease of 2019 (COVID -19) belongs to a group of acute respiratory illnesses caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which belongs to the coronaviridae family (1).

It first originated in Wuhan, China, and rapidly spread worldwide. The World Health Organization (WHO) officially declared COVID-19 a pandemic in early January 2020 (1). Multiple research studies have suggested that the natural reservoir are the bats, and that SARS-CoV-2 is 96% similar to the bat coronavirus (2).

The new coronavirus uses the same receptor as the first SARS-CoV, the angiotensin-converting enzyme 2 (ACE2) receptor (1); this is how the virus binds to pneumocytes. Along with pneumocytes, the ACE2 receptor has also been expressed in other vital organs of the body, for example, the heart, kidneys, testicles, and blood vessels. ACE-2 is one of the human body's mechanisms to regulate blood pressure through the renin-angiotensin-aldosterone system. This receptor is crucial, especially in controlling blood pressure. Its affection in COVID-19 also explains why hypertension, cardiovascular disease, and diabetes mellitus are frequent comorbidities in patients infected by SARS-CoV2 (3).

Moreover, due to the ACE2 receptor, the virus has an important tropism to blood vessels, and a critical complication of COVID-19 is the formation of microthrombi due to a hypercoagulable state. Multiple mechanisms lead to this hypercoagulability, one being endothelial dysfunction. It involves either the direct invasion of SARS-CoV-2 or indirect inflammatory effects (4).

Another feature contributing to hypercoagulability in COVID-19 is a decrease in fibrinolysis, which impairs clot dissolution. In addition, there is a loss of vascular tone, leading to vasoconstriction and concurrent prothrombotic effects. Endothelial disruption can also lead to platelet activation and recruitment by exposing the collagen-containing subendothelial matrix (4).

D-dimer is a sensitive fibrinolysis marker; however, it is not specific. Its elevated levels have been associated with increased mortality (8). Other labs that may be abnormal are ferritin, von Willebrand Factor (VWF), C reactive protein (CRP), complement, and cytokines; those preliminarily point to a relationship between the hematologic system and the immune system

(4) in the disease´s pathophysiology. The body forms both thrombi and microthrombi. There is microthrombi formation and persistence in a great deal of the population, especially the lungs. This pulmonary vasculature obstruction causes the release of vasoactive mediators and subsequential hypoxia, causing local vasoconstriction and increase in pulmonary vascular resistance (PVR). The afterload increases because of this resistance, and the right ventricle (RV) must work beyond its capacity, resulting in cardiac stress (5).

When a critical level of afterload is reached, the RV responds with dilation, demanding increased oxygen supply that exceeds the body's aptitude, leading to hypoxia followed by ischemia, necrosis, and fibrosis of the RV wall. Then, RV contractility is decreased due to all these structural changes, further causing RV failure and even cardiogenic shock (5).

Considering that COVID-19 is a recent illness, several studies have already related it to Acute Heart Failure (AHF) (7). For instance, a study conducted with 131 patients who died from COVID-19 showed that about 49% of deaths were due to AHF complications in patients with no history of cardiovascular disease (6).

Nevertheless, there is little evidence directly linking COVID-19 to Chronic Heart Failure. It is known that SARS-CoV2 is responsible for a hypercoagulable state and that pulmonary microthrombi is a common complication of COVID-19. In addition, it is well-established that long-term pulmonary microthrombi leads to Right Heart Failure, but there is still a lack of literature linking those aspects.

This article strives to elicit and elucidate currently available data on COVID-19's association with Chronic Right Heart Failure secondary to pulmonary microthrombi and RV overload. This paper aims to make healthcare professionals aware of the significant impact of COVID-19, which doubtlessly will be more prominent in the following years following the pandemic, even overwhelming the health system if ignored.

2 MATERIALS AND METHOD

A comprehensive electronic literature search was done on PubMed, SCOPUS, Cochrane database, and Google Scholar from January 2019 to December 2021 to identify the articles that discussed the pulmonary microthrombi and their relationship with COVID-19 and Right Heart Failure.

Keywords used were “pulmonary microthrombi”; “COVID-19”; “SARS-CoV2”; “Cardiovascular manifestations”; “Right heart failure”; “Thromboembolism”; “Hypercoagulation”; “Outcomes.” These search terms were used as keywords and combined as MeSH terms to maximize the output. A general literature search was done, whereby a

separate literature search was performed for each section within this article, and all relevant studies were identified and summarized separately. Two independent authors identified and screened all the relevant articles; the results are summarized narratively in each section within the article. Then, the authors made connections between what is already known regarding cardiology and what is already known about COVID-19 complications and finally raised an issue that, if not addressed, will cause a massive impact on the health system.

Studies were included if they have reported outcomes on any aspects of cardiology concerning COVID-19; the main exclusion criteria were statistically insignificant studies (p value<0.05).

3 RESULTS

3.1 EPIDEMIOLOGY OF COVID-19-RELATED CARDIOVASCULAR OUTCOMES

When the COVID-19 pandemic emerged, scientists had very little and limited knowledge about the viral complications and this illness's consequences in the infected population. Among many alarming outcomes, myocardial injuries, such as the pulmonary ones were very significant, not only in patients with pre-existing comorbidities but also among healthy individuals (9,38).

First, regarding pulmonary impairment, Jimenez et al. (2021) (38) found that among hospitalized patients with COVID-19 between January 2020 and July 2020, VTE incidence was 18%. Of those, 12% had DVT, and 7,1% presented with PE. In addition, another meta-analysis, responsible for evaluating 65.503 patients on VTE prevalence related to COVID-19, found a frequency of 14,7% episodes, with a 7,8% incidence of PE (39).

Then, to elucidate cardiac harm, a systematic review and metanalyses (9) study gathered data from December 2019 to March 2020. Twenty-eight reports from 4189 patients in 22 studies were analyzed to study myocardial injury and elevation of biomarkers like troponin, creatinine kinase-MB (CKMB) fraction, and N-terminal (NT)-prohormone BNP (NT-proBNP) during patients' hospitalization. They showed a comparative study of severe and less severe cases and comorbidities, demonstrating chronic high blood pressure as the most predominant chronic condition.

Elevation of biomarkers to a higher level in more critical cases (more information in tables 1 and 2), and male patients were more affected than females (9).

Another study, this time a systematic review, was based on case reports (10) from December 2019 to January 2021 of 42 patients. Among them, more than half did not have any previous comorbidity. Those with a former disease presented with hypertension and obesity

(better elicited in Graphic 1). Troponin was elevated in 90% of patients and prohormone BNP in 87% of patients (Graphic 2). This indicates a certain level of myocardial damage secondary to COVID-19. In addition, Echocardiogram and Cardiac Magnetic Resonance Imaging (CMRI) were performed. The Echocardiogram was made in 35 patients, revealing that 74% had decreased Left Ventricular (LV) ejection fraction, and 26% revealed pericardial effusion (10).

Table 1: Most common comorbidities:

Between Severity	**CI 95%, P-Value**
HTA	Pv = 0.030
Cardiovascular	Pv =0.337
Cerebrovascular	Pv = 0.748
Diabetes	Pv = 0.324
COPD	Pv = 0.052

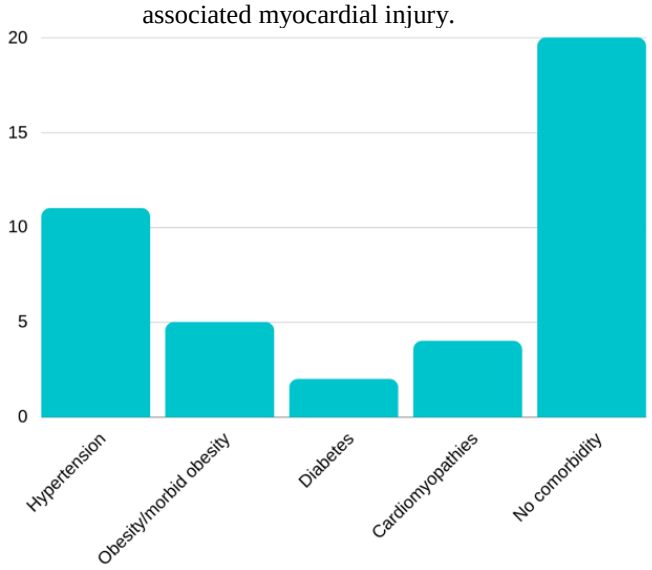
Source: Rathore et al. (2021)

Table 2: Cardiac biomarkers

Between Severity	**CI 95%, P-Value**
Troponin	Pv < 0.001
CK-MB	Pv < 0.001
N T Pro BnB	Pv = 0.009
Myoglobyn	Pv = 0.052

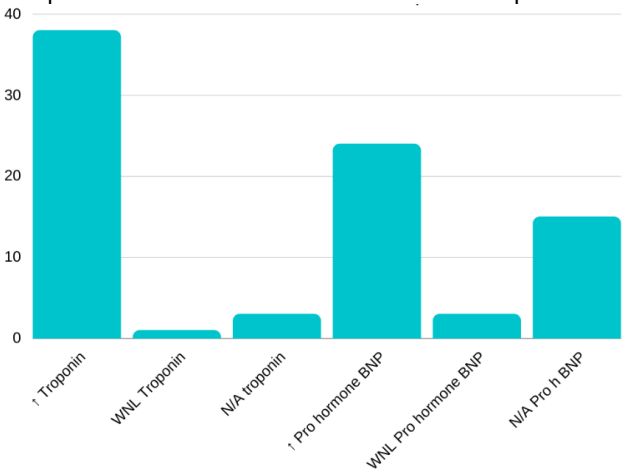
Source: Rathore et al. (2021)

Graphic 1: Related previous comorbidities in patients with COVID-19 associated myocardial injury.



Source: Rathore et al. (2021)

Graphic 2: Cardiac Biomarkers from 42 case reports/series.



Source: Rathore et al. (2021)

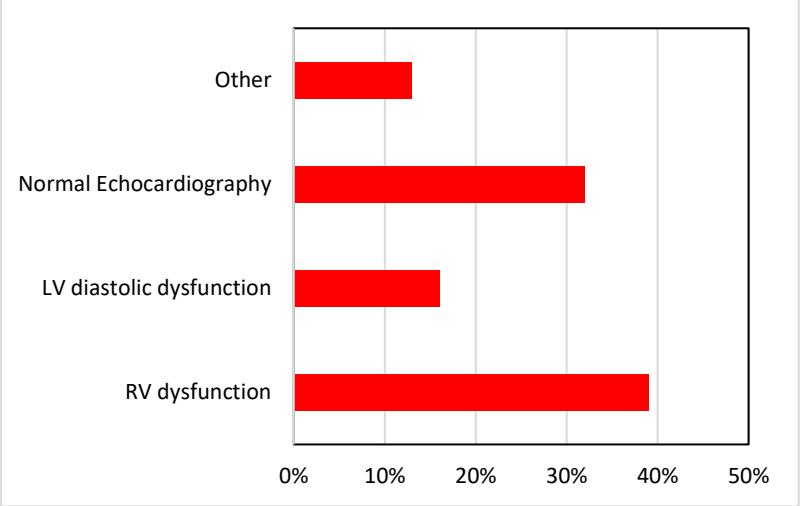
CMRI, the most reliable tool yet for noninvasive myocarditis diagnosis, demonstrated cardiac inflammation and injury. This feature was evaluated in 21 patients by a particular enhancing contrast. Even though this study is not conclusive as to whether hypertension is a risk factor, they do acknowledge from other studies that hypertension is, in fact, a risk factor for myocardial injury in COVID-19 patients (10).

Data shows that patients without any history of heart conditions also suffered from heart failure (HF). More than half of 9.1% of COVID-19 patients with acute HF had a new-onset disease. A study conducted in a hospital in Spain demonstrated that patients with acute HF faced a higher mortality rate than patients without it (12).

Further detailing the heart´s compromise, LV's systolic function was not much impaired, as Right Ventricular (RV) systolic, and LV diastolic functions were. According to a study published on the Frontiers in Cardiovascular Medicine (11), of 100 COVID-19 patients in the hospital, 39% had RV dysfunction, 16 % had LV diastolic dysfunction, and 32% had normal Echocardiography (Illustrated on Graphic 3) (11). This is crucial to this current article, as RV systolic dysfunction is one of the significant consequences of pulmonary hypertension, even though there is still little data to establish a cause-consequence relationship.

Another study, available in the JAMA Cardiology Journal (12), evaluated patients two months after recovering from their acute SARS-CoV2 illness in Germany, revealing that 78% had ongoing heart involvement.

Graphic 3: COVID-19's impact on Cardiovascular function – 100 hospitalized patients.



Source: Italia et al. (2021)

3.2 COVID-19 AND ITS HYPERCOAGULABLE STATE

During the SARS-COV-2 pandemic, manifestations regarding the clotting system, with a highlight on the prothrombotic states. It has been shown that COVID-19-associated coagulopathies manifest as a pattern that involves multiple underlying causes. Including the venous, arterial, and microcirculatory systems, manifesting as a different pattern than other infections (27). It is already known that there is a close relationship between coagulation problems and COVID-19´s severity, which also plays a role in prognosis (28).

The homeostatic system is one of the most important mechanisms responsible for regulating control between hemorrhage and thrombosis. Its role is to balance fibrinolysis and thrombosis (29). Interference with such balance to favor thrombus formation happens when there is an imbalance in any of the Virchow triad´s components, represented by endothelial injury, blood stasis, and a hypercoagulability state. In other words, any pathology that causes either endothelial damage, stasis of blood, or is responsible for a hypercoagulable condition will cause an imbalance in such equilibrium (30).

In the context of COVID-19, it is known that SARS-COVID-2 can directly affect the endothelium in a pathologic spectrum that includes direct injury to it and indirect injury caused by cytokines, pro-inflammatory substances (e.g., cytokine storm) (31), and endothelium inflammation (endothelitis) (32).

For instance, direct injury to the endothelium happens with the coronavirus´ mechanisms of infection. As clarified earlier, it includes cell binding and viral entry via ACE2 receptor (33), which is part of the endothelium of many organs (34). It is one of the RAAS receptors and promotes effects on the first phase of coagulation, platelet activation.

Notably, Zhang et al. (2021) (35) analyzed platelet function and coagulation factors in COVID-19 patients. His research found that the mechanism consists of direct activation of platelets followed by an inflammatory response involving the ACE2 receptor; this enhances platelet prothrombotic activity.

Furthermore, the literature well described that SARS-CoV2 generates a hypercoagulable state, making it possible for the virus to interfere in the most various aspects of coagulation homeostasis. The natural balance responsible for homeostasis mainly consists of platelet activation, fibrin formation, and fibrinolysis. Accordingly, there were reports of increased factor VIII, elevated fibrinogen, alteration in prothrombotic microparticles, and NETS (33).

COVID-19 related coagulopathies brought clinical outcomes that generate several impacts in disease management and prognosis. Especially during the early pandemic, a high prevalence of DVT was reported, particularly in hospitalized patients with severe disease (36).

Other consequences are related to pulmonary thrombus and microthrombus formation. Several reports showed thrombotic microangiopathy in COVID-19 patients. It is more common in the lung but also affects other topography, such as the mesentery, myocytes, and skin (37).

3.3 PULMONARY THROMBOSIS ON COVID-19

Microthrombi was found on extrapulmonary organs at the beginning of the COVID-19 outbreak (13). Since then, several studies have highlighted the possibility of a thrombotic event as an initial presentation on acute infection by SARS-CoV2, with Pulmonary Embolism (PE) and Deep Venous Thrombosis (DVT) being the most common thrombotic events with an incidence of 20% to 30% in critically ill patients (14).

A Dutch cohort of 184 patients observed cumulative incidence of thromboembolic events at a rate of 49%, most of which were PE (15). In the same way, in an Italian cohort of 388 subjects, the cumulative incidence of thromboembolic events was 21% (16), as in a French cohort, 20.6% incidence of PE was found among COVID-19 ICU patients (17).

Thrombus formation in the setting of SARS-CoV2 infection happens due to several factors. There is upregulation of procoagulation mechanisms at the same time as natural anticoagulants downregulation. In addition, there is resistance to fibrinolysis and endothelial damage (18).

Notably, Magro et al. (2020, 2021) found microthrombi in lungs, kidneys, brain, heart, skin, and liver. He associated them with thrombotic vasculopathy and complement system

activation. The virus can directly activate the complement system, or the inflammatory response can activate it (19, 20).

Indeed, preliminary evidence suggests that severely affected patients with COVID-19 requiring mechanical ventilation already have thrombosis in their microcirculation (21). Organs with a high capillary density, the lungs, for example, are the most affected, and the thrombi may lead to severe hypoxemia. Microvascular thrombosis can also damage other areas, such as the liver and the brain (22), leading to multiple organ failure (23).

Distinctly, Zeng et al. (2020) published the first COVID-19 case that presented a complicated heart condition; a 63-year-old male with no history of heart disease and pneumonia that evolved with enlarged LV on Echocardiography, decreased LV ejection fraction, diffuse myocardial dyskinesia, and pulmonary hypertension (24). After that, many studies have highlighted the implications of COVID-19 on the heart (25, 26).

3.4 RIGHT HEART FAILURE SECONDARY TO COVID-19´S PULMONARY SEQUELAE

Since the COVID-19 pandemics, new clinical outcomes have been observed and widely described in the literature. Among them, secondary acute heart failure (AHF) by infection is a topic that has been profoundly studied because it is a relatively common complication, measuring up to 19,1% of the patients. Besides, it is independently associated with an increased risk of mortality in patients with COVID-19 (40). Fortunately, it is an outcome that has been observed in those who had more severe presentations of the infection and needed supplementary oxygen therapy (41).

Several publications indicate that myocardial injury is the most common cardiovascular manifestation in COVID-19 due to oxygen supply and demand mismatch. Also, there is microvascular and endothelial dysfunction and destabilization of atherosclerotic plaques. Everything is triggered by the exacerbated inflammatory response of the disease. Nevertheless, there are other less studied etiologies of AHF during COVID infections, and the clinical manifestations depend on its cause and outcome (42). Therefore, it is crucial to study these other etiologies for future management and reduction of morbidity and mortality.

A prospective study of the spectrum of the cardiac manifestations in 100 consecutive patients demonstrated that the most common echocardiographic pattern among patients with COVID-19 infection was right ventricle (RV) dilatation, corresponding to 39% of the group (43). Furthermore, a retrospective analysis of 72 patients in a quaternary center of New York visualized a more significant amount of RV systolic dysfunction when compared with the left

ventricle (LV) (44). These findings usually indicate a poor prognosis and affect the clinical outcome (45).

The own anatomy of the RV, with its thin wall, compared with the LV's, allows the dilatation when there is a sharp increase of the afterload generated by the high pulmonary resistance. As the ventricle expands, there is a reorganization of its anatomy, resulting in tricuspid regurgitation. The developed valvopathy feeds back the RV overload (45). Acute RV overload leads to a decline in its output and systemic blood pressure, provoking a decrease in the coronary perfusion of the heart and generating more myocardial damage (44).

In addition to AHF, there is also Chronic Heart Failure (CHF) secondary to COVID-19, which happens due to increase in RV's afterload due to a diseased lung. Many conditions can increase pulmonary vascular resistance, but COVID-19 infection is multifactorial and related to parenchymal lung disease, pulmonary vascular disease, and elevated left atrial pressure, all leading to cardiac injury (44).

For instance, Poissy et al. (2020) demonstrated a 20,4% increase in the frequency of Pulmonary Embolism (PE) in patients with COVID-19, even with the use of prophylactic antithrombotic treatment. Also collaborating towards the same hypothesis, a series of autopsies in the United States have shown that an essential mechanism contributing to deaths related to SARS-Cov2 was thrombotic microangiopathy that was restricted to the lungs (46). These pieces of information corroborate with studies that explain the state of hypercoagulability, associated with abnormalities of homeostasis, increased inflammation, and endothelial dysfunction (47), findings that may further overload of the right ventricle, leading to right heart failure (42).

The clinical presentation involving right heart failure is of great morbidity to the patient due to its high impact in the long-term quality of life. Typically, there is intense fatigue associated with ankle edema, liver congestion, shortness of breath, and abdominal ascitic distension. Some patients may even evolve to develop anasarca depending on the severity (49). Episodes of acute dyspnea and chest pain are common. Other features are hypotension, cardiogenic shock, and hypoxia (42).

By the beginning of November 2021, nearly 250 million people had been infected by the new coronavirus disease, according to the World Health Organization (WHO). Of those people, more than 5 million died from complications of the disease (50). This data shows how prevalent in the world COVID-19 has become. Furthermore, most still survived despite the high number of people who died. A significant portion of the population who has one day had the disease will have to live with its long-term sequelae, such as pulmonary embolism and right heart failure.

It is crucial to be aware and screen for those complications to better monitor the health of the pandemic survivors, offer early forms of beneficial interventions, and avoid soon overloading the medical system with millions of patients presenting with unexpected complications (60).

Health professionals should pay special attention to thrombus-related complications. The hypercoagulable state during and after COVID-19 infection predisposes patients to significant events that must be monitored closely. The most common complications seen were TE (adjusted relative risk 1.44, 95% CI 1.42–1.47) and PE (1.49, 95% CI 1.46–1.52) compared with pre-COVID era data. Other events leading to thromboembolic complications were also observed (e.g., Atrial Fibrillation), but the incidence increase was not as significant as PE increase (51). Notably, Acute Respiratory Distress Syndrome (ARDS) and mechanical ventilation are also associated with increased PVR, which may precipitate Right Ventricular Disease (RVD) (61).

Altogether, an increase in PVR leads to chronic pressure in the RV, which is initially compensated and causes myocyte hypertrophy and fibrosis. If the pressure is maintained, the RV responds with myocyte loss, replacement, and fibrosis leading to a decompensated state.

Hypertrophied RV contracts and relaxes in an isovolumetric way in the initial compensated phase, with increased RV systolic pressure and higher end-diastolic volume. When the RV becomes decompensated, there is a concomitant rise in PVR and Right atrial (RA) pressure (RAP). As the PVR is constantly elevated, Cardiac Output (CO) drops, followed by a reduction in Pulmonary Arterial Pressure (PAP) (61).

Finally, RV dilation further compresses the LV cavity in the presence of an intact pericardium. LV filling is impaired, and biventricular diastolic pressures are equalized. Patients with Chronic Right Heart Failure usually require a higher preload. However, the reduced LV filling is due mainly to RV dilation and the ventricular interdependence phenomena explained above, which reduces RV forward output. In other words, there is an increased transmural pressure caused by RV dilation and associated pericardial constraint that gets in the way of proper LV filling. This association leads to reduced overall CO, lowered coronary blood flow. For this reason, patients present with exacerbated peripheral and abdominal congestive symptoms, such as peripheral edema, ascites, and dyspnea (61).

Therefore, COVID-19 may cause AHF through an inflammatory mechanism with acutely increased RV afterload, as seen in ARDS. In addition, CHF also happens due to thrombotic complications. Those are mainly in the lungs and lead to chronic thromboembolic pulmonary hypertension and RV overload (61).

Aktaa et al. (2021), in the Thrombosis research magazine, described an increase in TE incidence from 1090 per 100,000 (before the pandemic) to 1590 per 100,000 (post-pandemic) as depicted by Graphic 4. Overall, it represents an absolute risk change of 45,9% [95% CI 45.1-46.6%], demonstrating this subject's importance (51).

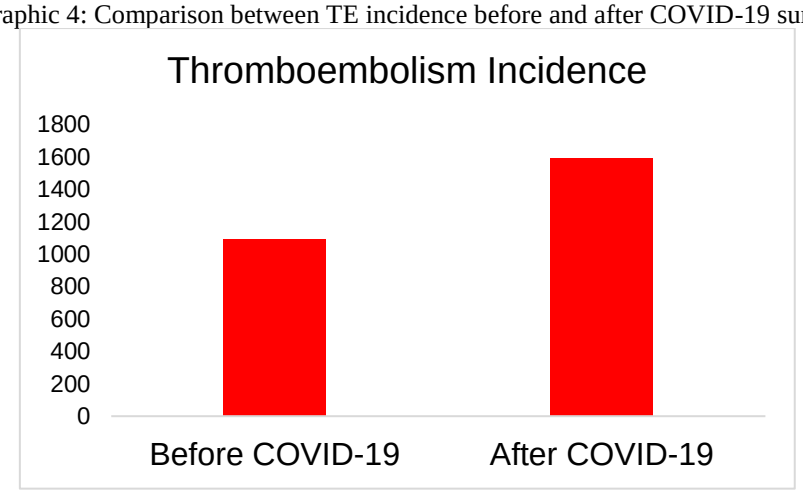
It was also notable that, during the pandemic, there was an increase in mortality from TE compared to historical baselines (44% vs. 33%) (51), as shown below in Graphic 5.

As COVID-19 became prevalent worldwide, researchers related the viral disease with thromboembolic events even further, especially DVT and PE. Suh et al. (2020) meta-analysis included 3342 patients actively infected by SARS-CoV2, demonstrating a PE occurrence of 16,5% and a DVT presence of 14,8% of all cases. In addition, it was demonstrated that more than half of patients with PE lacked DVT (52).

At the beginning of the pandemic, TE and PE were primarily shown in Intensive Care Unit (ICU) patients, but as time passed, more cases have been reported in outpatient settings (53, 54, 55).

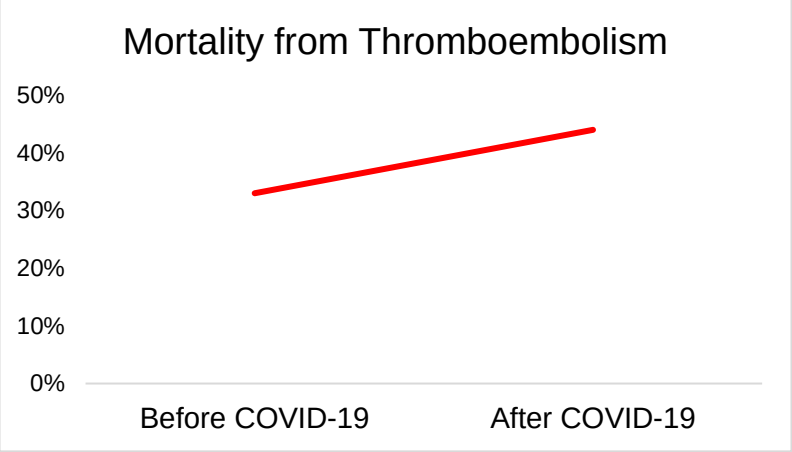
Currently, long-term outcomes of SARS-CoV2 infection are very obscure; nonetheless, the thrombotic implications stated in this paper lead to many serious sequelae. Heart failure is acute and chronic and can become a severe public health issue if not detected early and adequately managed (56).

Graphic 4: Comparison between TE incidence before and after COVID-19 surge.



Source: Aktaa et al. (2021)

Graphic 5: Comparison between mortality attributed to PE – before and after the COVID-19 surge



Source: Aktaa et a. (2021)

3.5 DIAGNOSTIC AND STRATIFICATION TOOLS

Many tests are available to diagnose and determine the gravity of various cardiac conditions, including the ones related to COVID-19. In many situations involving myocardial injury, the presentation may be asymptomatic and is only detected by cardiac biomarkers, with the most sensitive and readily available one being highly sensitive cardiac troponin (42).

When observed 416 patients with COVID-19, the mortality rate was higher in those with a myocardial injury compared with those who did not (51,2% vs. 4,5%). The mortality was markedly higher in patients with elevated troponin-T (TnT) levels than in patients with normal TnT levels (59.6% vs. 8.9%). However, despite its help in investigating the AHF, this biomarker can be elevated by other non-cardiac conditions (40), and the medical team needs to be aware of the differential diagnoses.

According to an executive summary of guidelines for managing general AHF, laboratory tests always need to be solicited in the context are blood count, platelet count, urea and electrolytes, blood glucose, C-Reactive-Peptide (CRP), and D-Dimer. International Normalized Ratio of thromboplastin time (INR) and blood gases can also be considered depending on the gravity, previous diseases, and other laboratory exams (48).

Other routine exams that can be used are the electrocardiogram (ECG) and the chest X-ray. ECG may be normal, but it can also detect explicit abnormalities that are not expected, like tachyarrhythmias, sinus tachycardia, and McGinn-With Sign (S1Q3T3) (42). When AHF is considered, a normal ECG is uncommon (48).

Besides that, radiologic investigation can show acute PE, regional oligemia, and non-specific signs such as cardiomegaly, pleural effusion, or both (42). Although, an undeniable

barrier is the overlapping of the clinical and radiological presentations of COVID-19 and AHF (41).

Echocardiography with doppler evaluates and monitors global ventricle and valvular function (48). A transthoracic echocardiogram (TTE) study is essential to demonstrate wall abnormalities and decreased systolic fraction. However, it is not indicated in all cases and should only be solicited when it may influence management strategy and equipment contamination precautions (42).

In a cohort of 749 patients, all COVID-19 diagnosed, 72 underwent TTE. The primary reasons for ordering were to understand better a patient's hemodynamics or concern for an acute cardiac event due to observing abnormalities in cardiac biomarkers, like TnT or NT-proBNP. Management changes occurred in 12 patients (16,7%) as a direct result of the TTE, including initiation of anticoagulation treatment for those presumed to have PE (44). These findings demonstrate how TTE is a valuable tool when well indicated.

4 CONCLUSION

Since the Covid-19 Pandemic began, it has been challenging to understand the disease's multiple acute and chronic consequences. One of them is thrombi/microthrombi formation, caused by mechanisms, such as direct endothelial damage, cytokine storm, and a pro-inflammatory state. Those happen mainly in the lungs but also the kidneys, brain, heart, skin, and liver.

A hyper-thrombotic state at the pulmonary circulation level eventually leads to hypoxia and an uprise in vascular resistance, stressing the right heart and finally causing right heart failure. It is possible to visualize the cardiac stress using biochemical markers of myocardial injury and imaging exams. At the Echocardiogram, alterations in the systolic function of the right ventricle are the main finding, followed by left ventricle systolic and diastolic dysfunctions.

The main risk factors for myocardial lesions secondary to COVID-19 are hypertension, obesity, diabetes, and cardiomyopathies. However, more than 50% of patients with identified myocardial lesions had no comorbidity.

During the pandemic, there was a rise in the incidence of pulmonary embolism of 45,9% compared to data from before COVID-19. This event can happen both in an inpatient or outpatient setting.

Indeed, more than 250 million people have recovered from COVID-19 so far. It is then expected that the health system faces several long-term issues in those who have had the disease, such as the pulmonary and cardiac damage accounted for in this article.

Once installed, chronic right heart failure causes a massive lifelong impact on the patient. Typical symptoms include intense fatigue associated with ankle edema, liver congestion, shortness of breath, abdominal ascitic distension, hypoxia, and cardiogenic shock.

For this reason, it is crucial to be aware and screen early for those complications to better assess patients and prevent irreversible outcomes. In addition, understanding its consequences on global health is essential, so health systems prepare for possible long-term COVID-19 consequences.

As SARS-CoV2 is a new disease, continuous scientific work is essential to create a reasonable approach to acute and chronic COVID-19 insults, leading to better screening, diagnosis, and treatment.

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