Chapter

Post COVID-19 Conditions and the Cardiovascular System

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Abstract

One out of four patients affected by COVID-19 will experience persistent (>3-4 weeks) signs and symptoms (Post COVID-19 conditions or Post-Acute Sequelae of SARS-CoV-2 – PASC) and this fact will have a major significance for the healthcare and economic systems in the upcoming years. The cardiovascular system is one of the key targets for the Post COVID-19 syndrome, given the pathogenesis of the virus and prevalence of ACE-2 receptors. According to our initial personal experience via the campaign "Life after COVID" of the Bulgarian Cardiac Institute, a substantial proportion of patients having suffered from COVID-19 develop long-term cardiovascular consequences. They could range from rhythm disorder and blood pressure variation, through impairment of myocardial mechanics and heart failure, and to acute vascular manifestations of Post COVID-19 conditions, such as acute coronary syndrome, acute pulmonary embolism, and acute limb ischemia. These cardiovascular complications require special and dedicated medical attention, and we could share our personal experience on the matter.

Keywords: post COVID-19 conditions, cardio-vascular system, acute coronary syndrome, acute pulmonary embolism

1. Introduction

1.1 Definition

According to its definition, post COVID-19 conditions comprise all signs and symptoms of COVID-19 that persist after the acute phase (3 to 4 weeks), without an upper limit of duration (as for the present state of knowledge). Another term for these conditions, introduced by Antoni Fauci, is "Post-Acute Consequences of SARS-CoV-2 Infection" (PASC) [1].

1.2 Time frame

The acute phase of the disease usually lasts about 3-4 weeks from the onset of symptoms, after which replication competent SARS-CoV-2 has not been isolated in the nasopharynx [1].

Accumulated data show that the consequences for the body can be just as serious and continue for an unusually long time after the initial encounter with the virus. It is the long persistence of complaints of varying degrees and manifestations after the infection that are known as post COVID-19 conditions. There is no precise scientific definition for the reason, duration, and prognosis of PASC [2].

The acute phase of the disease does not determine the onset of Post COVID-19 syndrome, because even patients with mild or asymptomatic infection may report PASC. There is no age limit for the manifestation of post Covid-19 conditions, but the reported frequency is higher in the elderly population [3, 4].

According to the latest data from the World Health Organization, the consequences of an infectious disease can last for two to three years [5].

1.3 Pathogenetic considerations

There are several pathogenetic hypotheses for PASC. The first is direct cell damage by binding of SARC-CoV-2 to ACE 2, initiating a violent immune response leading to increased cytokine production and triggering of procoagulant states [6].

It was later found that the reason for prolonged viral replication is the fact that SARS-CoV-2 can be transmitted by a different route from the respiratory tract, namely through the gastrointestinal tract, which could be considered a second hypothesis. The gastrointestinal tract is a major immunological organ in the human body and disruption of its microbiome leads to severe dysbacteriosis. Intestinal inflammation exacerbates the expression of ACE2, and the virus stays in the gut for much longer, which in turn can modulate immune responses and cause prolonged symptoms [6, 7]. This has been demonstrated by an intestinal biopsy, which detects the presence of the virus for months [7].

COVID-19 has also been shown to provoke autoimmune reactions, leading to a more severe course of the disease and the development of post COVID-19 conditions [7].

The suboptimal immune response leads to a higher viral load associated with decreased balance in interferon production. It was found that in severe disease the body lacks IFN-beta and the level of IFN-alpha and lambda is reduced [7, 8].

Lymphopenia and unregulated inflammation have been observed in patients with severe COVID-19 and prolonged persistence of the infection as a result of decreased production of granular lymphocytes (NK cells), CD16 + monocytes, plasmacytoid dendritic cells, which are responsible for innate immunity [8].

1.4 Symptoms

The severity of symptoms can range from mild to inability to perform normal daily duties. Every system could be involved, with a typical fluctuation and changing of symptoms over time. As the pathogenesis has shown, prolonged exposure to viral load can cause multisystem inflammatory syndrome (MIS) or trigger autoimmune conditions. The involvement in PASC is multi-organ, with the most common being complaints from the nervous system [2, 9]. Post COVID-19 conditions are more common among people with chronic diseases such as hypertension, diabetes, kidney disease, obesity. Genetic pre-exposure to the disease has not yet been specified.

The main systems that are affected are the nervous, cardiovascular, pulmonary, and excretory systems, musculoskeletal system, skin (**Table 1**).

System	Symptoms	Sign
Neuropsychiatric	fatigue, dizziness, headache, dysautonomia and cognitive impairment (brain fog), anxiety, depression, sleep disturbances	Direct damage to nerve tissue by the virus in patients with severe disease. [2] Psycho-emotional changes may include a wide range of symptomatic complexes characteristic of severe patients who are being treated in intensive care, known as "Post Intensive Care Syndrome"
Pulmonary	dyspnea, decreased exercise capacity and hypoxia	Reduced difusion capacity, restrictive pulmonary physiology, destruction of the alveolar-capillary membrane, secondary bacterial infections, pulmonary fibrosis," ground-glass opacity" [2, 3]
Cardiovascular	palpitations, dyspnea and chest pain, high blood pressure, fatigue, swelling of the lower extremities, acute pain and discoloration of the arm or leg due to ischemia	Thromboembolic events. It is already known that many patients re-admitted to the hospital with chest pain and positive cardiac enzymes (Troponin, CK, CK-MB,) and high levels of D-dimer. Pulmonary embolism is very common. In patients at high cardiovascular risk or underlying ischemic heart disease, acute thrombotic occlusion of the coronary artery are diagnosed. Non-obstructive coronary heart disease has been verified in many patients: myocardial infarction with non-obstructive coronary arteries (MINOCA), endothelial dysfunction, and microcirculation of arterial vascular disease [9, 10]. Acute limb ischemia may be observed. Some patients have pericardial effusion or the development of dilated cardiomyopathy of viral origin, after myocarditis [10]
Gastrointestinal	loss of appetite, weight loss, nausea, vomiting, diarrhea, abdominal pain	increased transaminases dysbiosis in the intestinal microflora (disturbed microbiome) with, increase in pathogenic bacteria and decrease in the normal microflora in the gut [7]
Endocrine	• new or worsening control of existing diabetes mellitus • bone demineralization • subacute thyroiditis	• Hyperglycaemia is due to a stress response of the body as a result of the disease as well as due to treatment with corticosteroids. • lack of vitamin D and / or immobilization • autoimmune conditions [2, 3]
Excretory and urogenital system	impaired renal function decreased urine output, pain in the kidneys	elevated levels of waste products (urea and creatinine), requiring hemodialysis [2]
Reproductive system	Impaired spermatogenesis	The male sex is more affected in reproductive system, and one of the hypotheses for this is the higher amount of ACE 2 in the male gonads compared to the uterus [11, 12]
Musculoskeletal system	occurrence of long-lasting arthralgia/myalgia	Due to immobilization, they can lead to cachexia due to loss of muscle mass. Sarcopenia - impaired muscle function due to loss of muscle tissue [2, 13]
Ear Nose Throat	pain and "noise" in the ears, throat irritation, loss of taste and smell(anosmia)	Nasal congestion, pharyngeal erythema [14]

System	Symptoms	Sign
Dermatology	hair loss, skin rash, urticaria, dry skin	disturbed cycle in hair growth, (telogen effuvium); stress after infection "COVID toes" syndrome - reddish-purple discoloration on the toes; In children, a rare condition similar to Kawasaki disease or Multisystem inflammatory syndrome in children (MIS-C) [2, 15, 16]

Table 1.
Affecting the basic systems in post COVID-19 conditions.

1.5 Duration

Many global medical centers are opening specialized clinics to provide care for people who have persistent symptoms or related illnesses after COVID-19. It is important to know that most people who have COVID-19 recover. The scientific community should focus on that part of the people in whom the effects of the disease leave lasting traces and change their lives. It is still unknown how long PASC can last. In 30% of COVID-19 survivors, symptoms may persist indefinitely. Data show that 76% of patients reported persistence of at least one of the symptoms of PASC for at least six months after the acute phase [17]. Many COVID-19 survivors cannot return to their normal lifestyle. At this stage, there is no accurate scientific data on whether these long symptoms can lead to a chronicity of the condition.

1.6 Sequelae

Understanding the pathogenesis of PASC may provide answers to additional questions to guide the medical community to the right management of the condition.

The loss of human lives, the disability of the population, the increase in the costs of health care and services burden the health systems. Persistence of post COVID-19 conditions affects various levels of medical and social life, and the negative effects on healthcare and the economy may be fully appreciated in years to come.

The psychological and social consequences of ongoing Covid19 should be considered as part of clinical care models [17].

2. COVID-19 and the cardiovascular system

The primary target for SARS-CoV-2 is the respiratory tract, but the cardiovascular system can be involved too [18, 19].

As well as the mild flu-like symptoms, COVID-19 often causes serious damage to the cardiovascular system - pulmonary vascular endothelialitis, microangiopathy, diffuse thrombosis, cardiac arrhythmias, heart failure, myocarditis, pericarditis and acute coronary syndromes [19].

Once in the nasopharynx, the SARS-CoV-2 enters the body by binding through its S-binding protein to angiotensin I-converting enzyme 2 (ACE2) receptors, found mainly in the lungs, cardiac myocytes, and endothelial cells in the vessel wall [20].

ACE2 is known to have protective effects by counteracting angiotensin II and over activating renin-angiotensin-aldosterone system (RAAS), which occurs in conditions of cardiovascular disease (CVD) such as hypertension, congestive heart failure and atherosclerosis [19, 21].

Entering through endocytosis, this RNA virus begins to replicate, causing widespread infection. Since ACE2 converts angiotensin I and II to cardioprotective peptides - angiotensin 1-9 and angiotensin 1-7, its loss on cell surface may potentiate cardiac damage, resulting in endothelial dysfunction, inflammation and thrombosis [21, 22].

ACE2 activity is known to be reduced in vessels with established atherosclerotic plaques and diabetes, while it is increased in women and young people due to the action of estrogens [21].

Decreased ACE2 activity may potentiate the so-called cytokine storm. This is an overreaction of the immune system caused by dysregulating RAAS and activating ACE2/bradykinin axis. The overproduction of cytokines and hyperinflammation leads to exacerbation of underlying cardiovascular diseases or triggering new ones.

According to the latest epidemiological data, about 80% of patients with COVID 19 have mild symptoms, about 45% have symptoms requiring hospitalization, while 5% of patients need mechanical ventilation [21–25]. The difference in course is related to the degree of viral load, host immune response, age of the patient and the presence of concomitant diseases such as hypertension, diabetes and coagulation abnormalities.

Aging is associated with slowing of body functions, increased oxidative stress, reduced role of endogenous defense mechanisms. With age, reduced efficiency of thrombolysis, lower protection afforded by physical exercise against myocardial ischemia and more frequent manifestations of heart failure are more often observed [21, 22].

It has not yet been established whether the patient's older age or greater immune response to the virus or both are responsible for myocardial damage with subsequent complications [21–24].

2.1 Cardiovascular complications in COVID-19

Direct viral infection, cytokine dysregulation and direct myocyte involvement can lead to acute myocardial injury in patients with COVID-19. Thus except for the high levels of CRP (C-reactive protein), elevated troponin levels suggest acute myocardial injury. It can be a result of myocarditis, ischemic injury, Takotsubo's cardiomyopathy, septic cardiomyopathy, acute cor pulmonale (as a result of acute pulmonary embolism) [7, 26, 27].

Acute coronary syndromes can be a manifestation of imbalance between myocardial supply and demand as a result of systemic changes – hypoxemia, tachycardia, hypotension, vasoconstriction; or acute thrombosis in the coronary arteries. Often, when the right coronary artery is affected a complete atrioventricular heart block can be seen. Other location of the coronary lesion may lead to severe ischemic cardiomyopathy, left ventricular aneurysm formation with apical thrombosis [28, 29].

The most frequent arrhythmia seen in COVID-19 patients is atrial fibrillation, which is a result of the acute respiratory failure. Electrolyte imbalance – hypokalemia and hypomagnesaemia can also lead to arrhythmic states [30].

Some of the medications used in the treatment of COVID-19 have proarrhythmogenic effects and should be used with caution, as they can provoke long QT interval, ventricular tachycardia and sudden cardiac death [30, 31].

A hypercoagulable state and thrombotic events, that are related to markedly elevated D-dimer and fibrin degradation products, are thought to be secondary to systemic inflammatory response [32, 33].

Takotsubo cardiomyopathy, predominantly seen in women, is mainly a result of increased sympathetic stimulation, which is usually observed in patients with COVID-19. It can be due to physical and psychological stress. This state can mimic acute coronary syndrome, which can develop within severe sepsis, hypoxemia, or metabolic acidosis [34–36].

Acute myocarditis due to myocardial inflammation can lead to ventricular dysfunction as a result of focal or global myocarditis or necrosis [37]. Life- threatening arrhythmias can be a consequence of myocarditis. When linked with pericardial effusion, further deteriorating of the hemodynamics might lead to acute heart failure (HF) and cardiogenic shock [38, 39].

The pathogenic mechanisms and clinical manifestations of cardiovascular complications of COVID-19 are presented in **Table 2**.

Cardiovascular disease	**Pathogenic mechanism**	**Clinical manifestation**
Acute coronary syndrome with or without ST elevation	Cytokine storm, hypercoagulability, plaque instability, imbalance between cardiac supply and demand	Typical chest pain or atypical pain and/or dyspnea, elevated levels of troponin, ECG changes (ST elevation or depression) and LV WMAs associated with specific region of distribution of a coronary artery
Myocarditis	Cytokine storm, direct cellular damage (possible)	Chest pain (possible), dyspnea (possible), elevated levels of troponin, ECG changes (possible), diffuse LV WMAs not related to specific coronary artery territory distribution
Pericarditis	Cytokine storm, direct cellular damage (possible)	Chest pain, dyspnea (possible), elevated troponin, ECG changes, impaired LV diastolic function and/or pericardial effusion
TTS	Emotional stress, microvascular and endothelial dysfunction, sepsis, acidosis, hypoxemia	Chest pain and/or dyspnea, elevated troponin, ECG changes, LV WMAs not related to specific coronary artery territory distribution (circumferential pattern, apical ballooning most frequently)
PE	Hypercoagulability	Chest pain and/or dyspnea, perioral cyanosis, elevated troponin (possible), ECG changes - S1Q3T3 pattern (possible), RV enlargement and dysfunction (McConnell sign, 60/60 sign)
Decompensated chronic HF	Hypoxia, elevated metabolic demand	Dyspnea, fatique, orthopea, tachydyspnea, hepatomegalia, anasarca, elevated levels of troponin (possible), LV WMAs without de novo abnormalities
Acute myocardial injury	Cytokine storm, direct cellular damage (possible), microvascular and endothelial dysfunction, hypoxia	Chest pain and/or dyspnea (possible), elevated levels of troponin, ECG changes (possible), LV WMAs (possible) not associated with specific coronary artery territory distribution (if absence of coexistent CAD)
Arrhytmias	Electrolyte abnormalities and medications for treatment of COVID 19 that have proarrhythmic effects	Dyspnea and chest pain (possible), ECG changes

ACS, acute coronary syndrome; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; HF, heart failure; ICA, invasive coronary angiography; LV, left ventricular; PE, pulmonary embolism; RV, right ventricular; TTE, transthoracic echocardiography; TTS, Takotsubo syndrome, WMAs, wall motion abnormalities. Modified from Ref. [40].

Table 2.
Pathogenetic mechanisms and clinical presentations of cardiovascular complications seen in patients with COVID-19.

2.2 Imaging of cardiovascular complications

As COVID 19 is an infectious disease clinicians should use methods of imaging, minimizing the risk of spreading infection. Most suitable are transthoracic echocardiography and point of care ultrasound. They are the first-line cardiac imaging techniques in this clinical setting, due to its portability, bedside feasibility in emergency settings and low cost [41].

The ultrasound is a diagnostic method for imaging the heart structures, valve lesions and kinetics. According to the European Association of Cardiovascular Imaging it is recommended performing echocardiography in patients with abnormally high levels of cardiac biomarkers and/or ECG signs of myocardial damage, while acknowledging that other imaging diagnostic tests are not routinely used in the emergency context of the COVID-19 pandemic [42, 43].

Findings in echocardiography could be normal heart or uchanged from prior exams, global left ventricular dysfunction and strain, regional left ventricular dysfunction, right ventricuar dilatation, pylmonary hypertention and pericardial effusion.

CT scan and MRI can also be used for distinguising cardiovascular implication, but they have higher cost and lower availability [44].

2.3 Treatment of cardiovascular complications during acute COVID-19

Every hospital in the world should develop appropriate protocols for rapid diagnosis, triage, isolation, and management of patients with COVID-19 and concomitant cardiovascular complications. These protocols should be well-rehearsed for proper use of health services and to minimize the exposure of the medical staff [45].

Most of the patients with COVID-19 have hypertension, treated with ACE inhibitors or (ACEi) or angiotensin II receptor blockers (ARBs). The amount of cardiac ACE2 mRNA could be increased significantly by the use of ACEi and ARBs [46, 47]. However, major cardiology scientific associations, have recommended continuation of renin-angiotensin system inhibitors (RASi) in patients who have been prescribed them [47–49].

Statin therapy is important for patients with diabetes, history of stroke or chronic heart disease, and familial hypercholesterolemia. However, in cases with COVID-19 there is still not an approved opinion whether it is risky or beneficial [50, 51].

As various anti-retroviral drugs might interact with cardiac drugs, a dose modification should be performed as well as careful monitoring [52]. Even though chloroquine or hydroxychloroquine could interfere with cellular endocytosis of the virus, prolongation of the QT interval might be observed. Therefore ECG monitoring is crucial and should be done [52, 53].

Colchicine is a drug that has been shown to restrict the production of pro-inflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1 and IL-6) and chemokines (IL-8), usually observed in patients with severe COVID-19 [54, 55].

As patients with COVID-19 may have elevated levels of D-dimer and higher platelet counts, it is suggested that coagulopathy is a major clinical feature in severe cases. This makes the use of anticoagulant and/or antiplatelet therapy very reasonable [56, 57].

2.4 Long-term cardiovascular consequences as a part of the post COVID-19 conditions

Most people recover completely from COVID-19, but some of them have persisting symptoms after their initial recovery. This is the group of "long haulers" and

the condition is called post-COVID-19 syndrome/conditions. [57, 58] The most common signs are fatigue, shortness of breath, cough, joint paint, chest pain. Every system could be affected, and the cardiovascular system is one of the frequent targets. Imaging tests taken months after recovery have shown lasting damage to the heart muscle [58–60]. This may increase the risk of heart failure or other complications such as arrhythmias and micropulmonary embolism. Careful follow-up of patients recovering from COVID-19 would be of great importance to understand the long-term impact of this illness [37, 61, 62].

3. "Life after COVID" campaign of the Bulgarian Cardiac Institute

Bulgarian Cardiac Institute is a leading organization for cardiovascular diagnosis and treatment in South-eastern Europe. The institute manages the largest and fastest growing medical group in Bulgaria. The medical establishments cover 2/3 of the patient flow and ¾ from the territory of the country. The Bulgarian Cardiac Institute is unique in the development of modern scientific, educational and medical activities in the field of cardiology, cardiac surgery, neurology, neurosurgery, vascular surgery, oncology, surgery, orthopedics, genetics, immunology, radiation therapy and radiosurgery.

Despite the growing population of patients surviving COVID-19, the long-term consequences remain a clinical challenge. Currently, just under 1% of studies focus on Post COVID-19 conditions. That is why the Bulgarian Cardiac Institute has launched a large-scale, free-of-charge, voluntary and indefinite screening campaign "Life after COVID-19". It aims to establish the effects of the infection on the cardiovascular system, diagnosis, treatment, long-term follow-up and adequate actions to improve the quality of life by providing specialized medical care.

The campaign covers citizens who have suffered from COVID-19. Those who wish to participate answer a survey with questions related to their health. When they answer in the affirmative to at least one of the questions (yes, i.e.there is a problem), we offer a free medical examination. It is held in one of the seven high-tech hospitals, with the highest third level of competence, according to national medical standards or in one of the 15 medical centers in the country, by leading specialists in the field of cardiology. The initial examination includes a detailed history, complete examination, blood pressure measurement and electrocardiogram, on the basis of which we determine whether the patient needs additional instrumental or laboratory tests and treatment. According to the results and the leading symptoms, patients are consulted with trained in Europe and USA specialists in the field of cardiac surgery, neurology, neurosurgery, vascular surgery and others. If necessary and with persistence of symptoms, despite treatment, citizens are hospitalized.

As the population of recovering from COVID-19 grows, it is crucial to identify the health problems that surround them. The campaign creates round-the-clock access to high-quality and specialized medical care at European level, based on a multidisciplinary approach and dedicated medical care.

4. Initial results of the campaign "Life after COVID"

More than 1,500 citizens took part in the survey - 77% of them were treated at home, 23% were hospitalized, of which 2% in intensive care units. Of all respondents, 80% answered in the affirmative (Yes, i.e.there is a problem) to at least one of the initial survey questions. Signs and symptoms such as fatigue (67%), palpitations (41%), shortness of breath (31%), chest pain (30%), joint pain (27%),

headache (22%), impaired concentration (17%), persistent cough (16%), dizziness (15%) were among the most frequently reported in the questionnaire responses (**Figure 1**). A significant proportion of patients had more than two symptoms.

Medical examination was offered to citizens with persistent symptoms. We analyzed data from 808 patients (57% women and 43% men). The most common pathological changes we found were destabilization of blood pressure control (51%) - hypertension (92%), hypotension (5%) or fluctuation in blood pressure (3%). Heart rhythm disorders are the next most common finding (29%), expressed in tachycardia (97%) or bradycardia (3%). Manifestations of heart failure were found in 15% of cases.

According to the anamnesis and the objective condition, additional examinations had to be performed in 65% of the examined. These examinations included:

- Instrumental methods: echocardiography (41%), holter ECG (3%), radiography (3%)

- Laboratory diagnostics (9.4%): complete blood count, NT-proBNP, D-dimer, blood glucose test

- consultations with specialists (10%): neurologist (28%), pulmonologist (22%), endocrinologist (12%), vascular surgeon (5%), rheumatologist (4%) and other

At the end of the examination, a change in therapy was required for 62% of those followed.

At the time of the secondary examination, new studies were performed in 5% and a change in therapy in 2.6%. Despite all interventions, in 6% of the cases, due to the persistence of the symptoms, the citizens were hospitalized.

Our experience shows that the care of patients with COVID-19 should not stop at the end of the acute illness. From the responders to our survey, 4/5 reported persistent signs and symptoms months later. The most common complaints were: fatigue, palpitations, shortness of breath, chest pain. Other reported symptoms included joint pain, headache, and impaired concentration. High values of blood pressure, tachycardia, and manifestations of heart failure were the leading objective changes. Our study showed that in more than half of the cases of COVID-19,

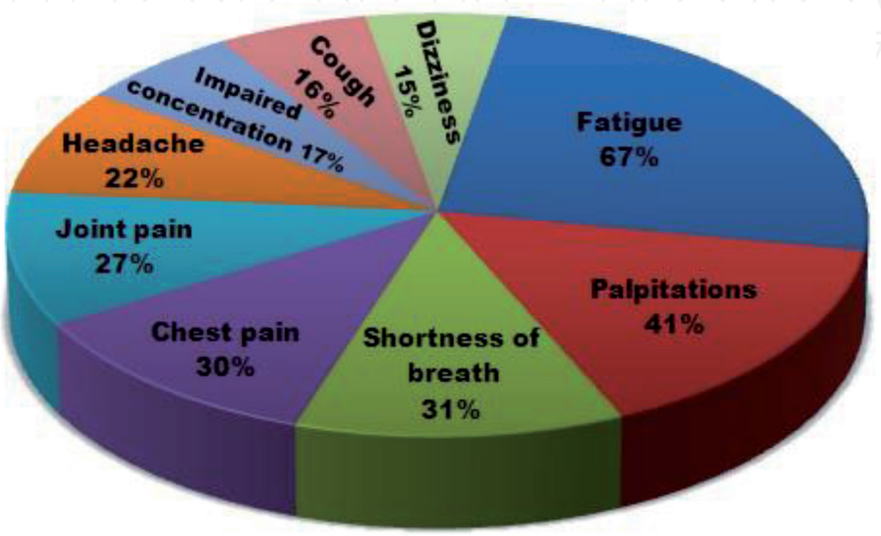


Figure 1.
The most common signs and symptoms persisting after COVID-19.

additional tests and changes in treatment were required. The range of symptoms required the inclusion of doctors with different specialties in the overall follow-up. Despite the measures taken, the symptoms may be so severe and difficult to control that re-hospitalization may be necessary.

People suffering from post COVID-19 conditions constitute already a significant part of the world's population, and their numbers will continue to grow. This necessitates a long-term commitment of human and material resources and will test the health and economic system of the countries. Regardless of the obstacles we face, dedication and professionalism, good organization and a holistic approach are the main prerequisites for good results. By tracking and caring for these patients, we will not only contribute to increasing humanity's knowledge of this new, dangerous pathogen, but we will also make progress in the process of diagnosis and treatment guidelines.

5. Imaging of myocardial involvement in post COVID-19 conditions

COVID-19 is a multiorgan systemic inflammatory disease caused by SARS-CoV-2 virus. Patients with COVID-19 often exhibit cardiac dysfunction and myocardial injury [63], which we can recognize with laboratory parameters and imaging methods. The most used imaging method is transthoraic echocardiography (TTE), which gives us information about the heart function. Global longitudinal strain (GLS) by speckle tracking echocardiography is an important additive method for evaluation of LV function at global and regional level. It is more sensitive method for detecting myocardial dysfunction, compared with Left ventricular ejection fraction (LVEF) [64]. Another very informative method is MRI, however it is not used that often, due to higher expenses and need of contrast material. According to studies, almost all patients with severe COVID-19 and most of the patients with moderate illness, had a certain degree of cardiac dysfunction [63].

Conventional echocardiography usually does not show significant changes in the LVEF and LV sizes in patients with mild or moderate COVID- 19. According to one trial in China, however, in 78.3% from the patients with mild infection and 98% of the patients who were in critical condition, some echocardiographic parameters showed deviations. For example, the motion of the LV walls was abnormal and the wall thickness was slightly thickened, particularly for the septum [63]. But in patients who were with critical conditions, lower LVEF could be found [65]. These changes are in correlation with elevated serum levels of cardiac biomarkers, such as cardiac troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), pulse oxygen saturation (SpO2) and inflammatory markers, such as C-reactive protein and cytokines [63].

Although abnormalities in conventional echocardiography are found mostly in patients with severe COVID- 19, global longitudinal strain (GLS) can identify subclinical myocardial dysfunction. Moreover, measuring GLS gives us the opportunity for earlier diagnosis of myocardial injury, even before a reduction in the LVEF occurs. Studies showed that reduced LV-GLS is more frequent, occurring in 80% of the patients, while LV function parameters such as reduced EF and wall motion abnormalities were less frequent findings [66].

2D- speckle tracking echocardiography is a method, which evaluates myocardial function at global and regional level. It shows the percentage of deformation between two points in the myocardium. Studies in COVID-19 patients show that the abnormal GLS predominantly involves the basal-septal and basal-lateral segments of the LV. This pattern reminded of a "reverse tako-tsubo" morphology, and is not typical for other viral myocarditis [67]. Another interesting finding is that the

reduction of the LV-GLS is usually reversible, with normalization of the findings for one to three months [66].

Cardiac magnetic resonance (CMR) is the current gold standard to evaluate cardiac morphology and function. It has higher sensitivity for detecting occult cardiac dysfunction than hs-cTnI. With its mapping techniques, such as T1, T2, extracellular volume (ECV) and Late Gadolinium Enhancement (GLE), this method can assess quantitatively diffuse or local myocardial fibrosis and edema [68]. One study in Frankfurt with 100 patients recently recovered from COVID-19, showed that 78% of them had abnormal CMR findings, namely lower left ventricular ejection fraction, higher left ventricle volumes, raised signals in native T1 and T2 mapping, which illustrate edema and changes in LGE, showing myocardial fibrosis. Endomyocardial biopsy was performed in patients with severe findings and revealed active lymphocytic inflammation [37].

Our experience in "Life after COVID" campaign (unpublished data) shows that about two-thirds of PASC patients referred for echocardiography have the typical post COVID-19 GLS impairment, involving predominantly the basal segments. We observe such findings in severe as well as non-severe COVID-19 cases. Our management strategy in these cases includes prolongation of antiaggregant therapy, initiation of cardioprotective therapy (could include some or all of the following: beta-blocker, trimetazidine, molsidomine), antiviral therapy (hydroxychloroquine) and advice to refrain from vigorous physical activity, although maintaining moderate physical activity or inclusion in a rehabilitation program. Our initial experience with 3-month follow-up of these patients shows a resolution of the abnormality in about 80% of the cases in this time period.

From our experience, we think that global longitudinal strain is very sensitive for recognizing subclinical myocardial dysfunction and a valuable imaging method for prognosis, management, sport activity resumption advice, and long-term following of the patients recovered from COVID-19.

6. Acute coronary syndrome as part of the post COVID-19 conditions

Apart from the direct lung damage, the virus infection is associated with multiple organ damage, including the heart, causing conditions such as congestive heart failure, myocarditis, conduction abnormalities, arrhythmias, and acute coronary syndromes [69, 70]. The SARS-CoV-2 infection can frequently induce coagulation abnormalities that are associated with cardiopulmonary damage in all patients, despite presence or absence of concomitant risk factors and diseases.

The range of clinical responses to COVID-19 is extremely broad. Endothelial injury is an underlying mechanism that links the inflammation and consequent thrombosis [71, 72]. It is currently hypothesized that ACE-2 receptor is the entry gate for the virus to invade and infect tissues [73]. The vascular endothelium appears to be targeted directly by the virus as ACE-2 is expressed widely in the blood vessels and the heart. The result is exocytosis of endothelial granules containing VWF (von Willebrand factor), P-selectin, and other proinflammatory cytokines, which mediate platelets adhesion, aggregation, and leukocyte adherence to the vessel wall, with a final result of intravascular thrombosis [74].

In addition, many patients with severe COVID-19 undergo thromboembolic events, due to this particular coagulopathy [75, 76]. One of the most and life-threatening types of this coagulation abnormality is the one involving the coronary blood flow, thus causing a heart attack. In this scenario many additional problems arise – for example: access to a Cath lab, exposure of additional medical personnel, more complications and increased mortality for the patients. Invasive coronary

angiography for COVID-19 patients is a logistic challenge and, in some cases, there is not a need for intervention since the main problem is the thrombosis and the dysfunction of the microcirculation. For this reason, we evaluated in detail a case series of ten patients referred for primary percutaneous coronary intervention (pPCI) for MI in our catheterization laboratory during the course of COVID-19 infection. The goal was to evaluate if there are any factors or parameters that could predict the presence of an interventional target – infarct related artery (IRA), prior to catheterization, and to determine their sensitivity and specificity.

During November and December 2020, 214 patients were treated in our COVID-19 department. Ten of them were referred to the Cath lab with MI defined by the fourth universal definition [77]. Most of the patients in our study were sent to our hospital due to acute coronary syndrome, while others developed ACS during their stay in the COVID-19 department.

After coronary angiography, we found that 7 patients (70%) had an IRA, and they underwent pPCI. The other 3 (30%) did not have an IRA, they did not require pPCI, and the diagnosis of myocardial infarction with no obstructive coronary arteries (MINOCA) was made, most probably due to myocarditis or microvascular dysfunction.

Comparing the patients with IRA to those without we found that the subjects who required pPCI had significantly higher high-sensitivity troponin I(hsTRI) values, had typical chest pain, and had more often ST elevation. The other studied variables did not differ significantly between the groups with or without IRA. Regarding hsTrI concentrations, all but one patient with IRA and pPCI had hsTrI>7.5 times URL, and all patients without IRA and pPCI had hsTrI $\leq$7.5 times URLN. Therefore, for hsTrI>1.5 ng/ml (>7.5 times URL) to predict the presence of IRA and the need for pPCI the sensitivity is 86%, the specificity is 100%, positive predictive value (PPV) is 100%, while the negative predictive value (NPV) is 10%.

Even though our analysis is on a small number of patients, similar incidence of arterial (coronary and cerebral) thrombosis (4%) has been described by other authors. In this study, however, the authors have not provided a guide to the right moment of interventional treatment. According to our published data search, we were not able to find another study, analyzing the predictors for the presence of IRA and the need for pPCI in COVID-19 MI patients.

So in conclusion, myocardial infarction, could complicate up to 5% of COVID-19 cases. In our study group, most of the patients (30%) with MI did not have an IRA and, did not need a coronary intervention. Patients with MI and IRA had significantly higher hsTrI values and exclusively typical chest pain compared to patients with MI but without an IRA, whose hsTrI values were lower and chest pain was atypical or non-stenocardic. ECG changes had only a minor statistical significance for distinguishing between MI patients with or without IRA. Our results suggest that using a higher cut-off value for hsTrI increases the specificity for diagnosing a MI and therefore - interventional treatment.

7. Pulmonary thromboembolism in patients after COVID-19 - predictive indicators for correct diagnosis

Infection caused by SARS-CoV-2 has been shown to lead to significant procoagulant events, in some cases involving life-threatening pulmonary thromboembolism (PE) [78]. A number of abnormalities have been described in coagulation parameters, which are a predictor of poor prognosis in patients with COVID-19 and PE [79]. Due to the lack of large prospective studies, little is known about the

pathogenesis underlying PE, caused by COVID-19 [80]. Additional conditions complicating the diagnosis are the presence of risk factors for PE in almost all patients with COVID-19, as well as the overlap of the clinical presentation between PE and COVID-19.

We, therefore designed a study to find the indicators that predict the presence of PE in patients with acute or Post-acute COVID-19 conditions. It was a single-center study, conducted at the Heart and Brain Hospital, Pleven in the period December 2020-February 2021. It included 27 consecutively hospitalized patients with recent pneumonia caused by Covid-19 and clinical presentation referring to PE. The cohort was divided into two groups - without and with a definitive diagnosis of PE, proven by CT pulmoangiography. During treatment with COVID-19, all patients received a prophylactic dose of anticoagulant and antiplatelet drug.

Our results showed that eight patients from the group had PE, and 19 had not evidence of PE. The mean age of the group was 65 years and 18 of the patients were women. The two groups did not differ significantly in age and distribution between the sexes. Statistically significant differences in electrocardiographic findings were observed in the two groups. In patients without PE, 18 (94.7%) had no evidence of S-wave greater than 1.5 mm in I, aVL. On the other hand, in the group diagnosed with PE in 3 (37.5%) this ECG criteria was not present, and in 5 (62.5%) it was present ($p = 0.004$). Similar ratios were found in terms of the presence of Q-wave in III, aVF. In patients without PE, 18 (94.7%) did not have this ECG sign, while it was present in half of the patients with PE($p = 0.017$).

In patients without PE, the median value of oxygen saturation was 92.0% (69-97), and in those with proven - 88.5% (83-95) ($p < 0.001$). Statistically significant differences between the two groups were observed in regard to the indicator - the ratio RV/LV diameters ≥1.0 ($p = 0.001$). In patients without PE there was none with an increase in the ratio ≥ 1 in favor of the right ventricle, while in the group of patients with massive form 5 (62.5%) had the ratio RV/ LV diameters ≥1.0, and 3 (37, 5%) did not have it. The same results were demonstrated for the indicator right ventricular dysfunction ($p = 0.001$). The RV/LV diameter ratios ≥1.0 as well as right ventricular dysfunction showed sensitivity 62.5%, specificity 100%, positive predictive value 100% and negative such 86.4% to verify the PE diagnosis.

D-dimer values differed significantly in the two groups. In patients without PE, the mean D-dimer value was 1546 ng/ml (109-8840), while in those with PE - 6489.75 ng/ml (570-17051) ($p = 0.021$). For our laboratory, the upper limit of the normal range is 500 ng/ml. As a result of the ROC analysis we found that the D-dimer cut-off value of 1032 ng/ml (2,064 times higher above the upper limit of the normal range) had an optimal sensitivity (Se) of 87.5%, specificity (Sp) 57.9%, positive predictive value (PPV) 46.7% and negative predictive value (NPV) of 91.7% for the diagnosis of PE ($p = 0.021$) (**Figure 2**).

Regarding D-dimer as a binary variable (cut-off 1032 ng/ml), we found that in the group without PE, in 11 (57.9%) of patients the D-dimer was ≤1032 ng/ml, while in 8 (42.1%) it was >1032 ng/ml. Of the patients with massive PE, only 1 (12.5%) had a D-dimer ≤1032 ng/ml, and the remaining 7 (87.5%) were > 1032 ng/ml (Fisher's exact tests, $p = 0.043$).

When performing binary logistic regression, part of the ECG criteria - S-wave over 1.5 mm in I lead and aVL ($p = 0.007$), Q-wave in III and aVF ($p = 0.020$), as well as the D-dimer as quantitative variable ($p = 0.025$) proved to be independent predictors of PE.

Our results show that against the background of acute and Post-acute COVID-19 conditions ECG and EchoCG criteria remain predictive of PE. As for the D-dimer values, we found that a cut-off concentration with optimal Se, Sp, PPV and NPV for diagnosis of PE, is two times higher than the upper limit of normal, with high Se and

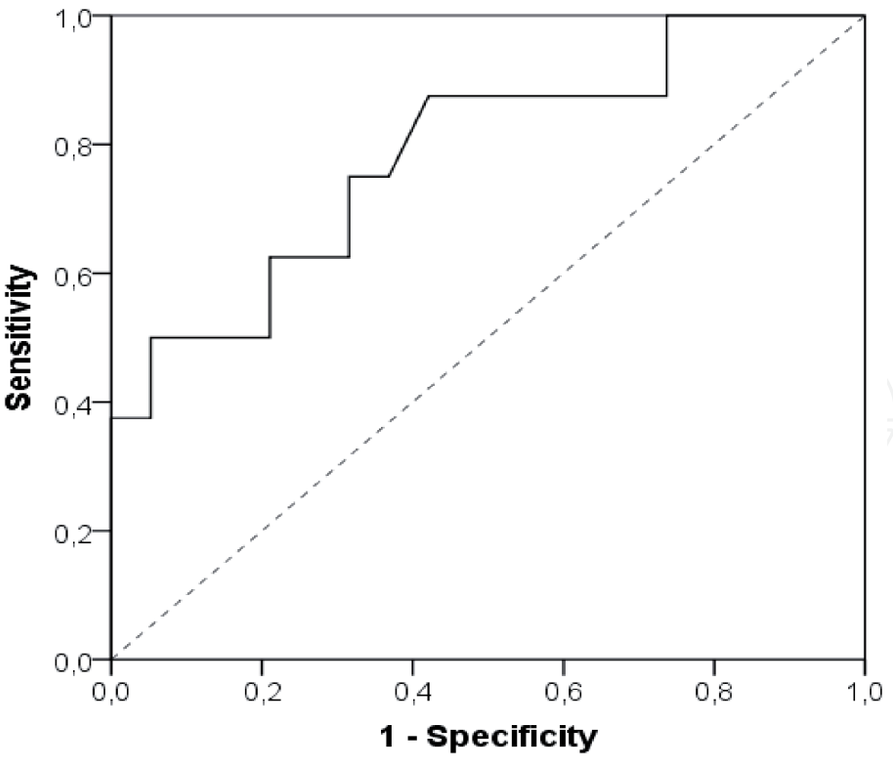


Figure 2.
ROC analysis for D-dimer values and the probability of PE.

NPV. We suggest that a higher D-dimer cut-off value should be applied in COVID-19 and post-COVID-19 patients in order to confirm/dismiss the diagnosis PE.

8. Acute limb ischemia as part of the post COVID-19 conditions

The vascular bed, being rich in ACE2 receptors, is not devoid of complications during the acute or post-acute COVID-19 conditions. Our analysis is to report our experience in the Department of Vascular Surgery of Heart and Brain Center of Clinical Excellence, Pleven, Bulgaria, focusing on management of COVID-19 patients who developed severe acute ischemia with impending lower and upper limb loss.

We carried out a retrospective data collection of COVID-19 patients with severe acute ischemia of the lower or upper limbs between December 2020, and April 2021. We included only those COVID-19 patients suffering from acute lower limb ischemia. Primary outcomes of the analysis were early reoperations, amputation and postoperative mortality.

Admitted to our department were 16 patients (13 male, 3 female) with acute ischemia of the lower limbs and 2 patients (both male) with acute ischemia of the upper limbs. The median age was 70 years (range 50–85 years). All patients tested positive for COVID-19 and all had general clinical symptoms. In all patients, the limb was at risk, and the only alternative was a major amputation. Seven of the cases had previous claudication symptoms and peripheral artery disease (PAD). Computed tomography-angiography (CT-A) showed acute thrombosis over atherosclerotic occlusive disease. The rest of the patients [11] had no clinical evidence of PAD. The occlusion was related to acute thrombosis of the arteries or distal embolization and confirmed by (CT-A).

Generally, based on the patient's overall stability, degree of ischemia, and limb viability, a determination needs to be made whether intervention is appropriate,

	All procedures	Generally good condition	Mortality
All patients	18	11 (61.1%)	7 (38.9%)
Open surgery	15	8 (53.3%)	7 (46.7%)
PTA/Stent	3	3 (100%)	0 (0%)
Re-operation	4	3 (75%)	1 (25%)
Amputation	6	3 (50%)	3 (50%)

Table 3.
Operative vascular procedures at the Vascular Surgery Department of Heart and Brain Center of Clinical Excellence, Pleven, Bulgaria

and if so, whether an endovascular or open approach should be used. It is crucial to consider the severity of systemic illness when considering intervention. Because of the severe pulmonary complications associated with COVID-19, critically ill patients may not be candidates for revascularization. Similar to damage control in trauma patients, the principle of "life over limb" is justified.

Laboratory parameters in our group showed increased levels of serum D-Dimer, C-reactive protein (CRP), and a decreased platelet count. All 18 patients underwent urgent revascularization, (embolectomy, open surgery procedures, percutaneous transluminal angioplasty with catheter balloon and stenting or primary amputation). Postoperatively, all patients received heparin therapy with low molecular weight heparin, combined with clopidogrel 75 mg and, in some cases, acetylsalicylic acid 100 mg.

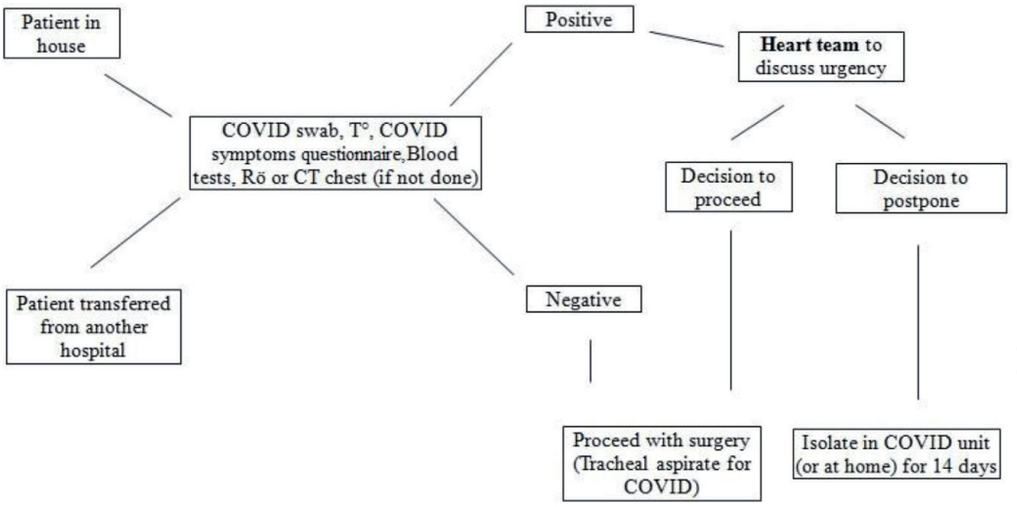
Ten of the patients suffered from early (1st or 2nd day) postoperative re-thrombosis. All of them underwent reoperation (embolectomy), but 6 of them suffered from re-re-thrombosis and eventually required above-the-knee amputation and one patient required above-the-elbow amputation. Unfortunately, 7 patient died from multiple organ failure (MOF). 11 patients left the hospital in generally good condition. One patient with femoral-popliteal thrombosis left with symptoms of claudication but without critical limb ischemia. After one month this patient underwent endovascular revascularization with percutaneous transluminal angioplasty (PTA) and stent implantation (**Table 3**).

9. Conclusions

In our experience, the incidence of acute limb ischemia increased significantly during the COVID-19 pandemic in Bulgaria. Successful revascularization and survival was lower than expected, which we believed was due to a virus-related hypercoagulable state. The use of prolonged systemic heparin might improve surgical treatment efficacy, limb salvage, and overall survival.

10. Cardiac surgery during the COVID-19 pandemic

The COVID-19 pandemic posed serious challenges not only to modern cardiac surgery, but to medicine in general. As a result of the epidemic situation, the planned admission to hospitals and elective operations were stopped, and some of the health facilities were transformed into COVID-19 centers. Our hospital has developed a special algorithm for admission of patients in need of urgent or emergent cardiac surgery.



The epidemic situation has led to a reduction in hospital admissions. One of the reasons is certainly the fear of intra-hospital infection and transmission of COVID-19. The other reason is the postponement of elective operations. According to statistics, the number of hospitalized patients with acute coronary syndrome has decreased by 30%. If we consider that the mortality from COVID-19 is about 3% and the mortality from untreated STEMI reaches 30%, then the fear seems unjustified [81]. Important in this case, from a cardiac surgery point of view, is the definition of the concepts of elective and emergency admission and treatment, as well as treatment in accelerated and urgent order, as well as the nosological units to the respective groups:

- True elective (isolated MR, isolated AS)
- Accelerated elective (AS combined with CAD)
- Urgent (CAD withLM disease or LM equivalent)
- Emergent (Infective endocarditis, Acute myocardial infarction)
- Salvage life saving (Aortic dissection Stanford type A, mechanical complications after AMI)

While the first two groups may remain on the waiting list, for the next three the waiting time is shortened according to the disease (24 hours, 6 hours and as soon as possible in case of urgent, emergency and life-saving surgery, respectively). The functioning of such a system requires particularly good communication and collaboration between GPs, specialized outpatient and inpatient care, proper categorization of patients and optimal timing of treatment.

Unfortunately, there is still no formal international protocol or guidelines for optimal timing of cardiac surgery in patients with active COVID-19 infection. Since the beginning of the pandemic, 18 patients with identified COVID-19 infection pre- or postoperatively have undergone cardiac surgery (4.9% of all operated patients). The results of the operative treatment are excellent, as the intraoperative and early (up to 7th day) postoperative mortality is zero. Late postoperative mortality was 44%, with no patients dying from cardiovascular disease. It is noteworthy, contrary to expectations, that it is not the complexity of surgical treatment that is the leading risk factor for the complicated postoperative period in patients with

proven COVID-19, but the development of viral pneumonia. Interstitial changes typical of COVID-19 pneumonia (ground-glass opacities, vascular enlargement, bilateral abnormalities, lower lobe involvement, and posterior predilection) have been demonstrated by CT scan in 75% of the deaths, with respiratory failure being the leading cause of death.

The question how long after recovery from a COVID-19 infection can a patient be transferred to surgery also remains open. Several studies on the subject are currently conducted. The data collected so far from 116 countries on 140,231 patients may finally show some resolve [82]. 2.2% of the patients included in the study were diagnosed preoperatively with COVID-19 infection. Mortality is highest in the first 7 weeks after the illness.

Thus, with surgical treatment 0-2 weeks, 3-4 weeks, and 5-6 weeks after COVID-19, the 30-day mortality was 4.1%, 3.9% and 3.6%, respectively. In surgical treatment after the seventh week, the results were the same as in patients without COVID-19 infection (1.5%). The estimated 30-day postoperative mortality in patients without COVID-19 infection was 1.5%. It should be borne in mind, however, that these are not specific studies in the field of cardiac surgery, but concern surgery in general. Probably the specific risk for cardiac surgery patients would be higher if we consider the complicated procedure of cardiac surgery, the aging of the population and the polymorbidity of the Bulgarian population. The role of the Heart team is crucial and the preparation of precise general hospital protocols and individual approach to each patient are extremely important for achieving good results.

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