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EDITORIAL

Evaluating chest pain in patients with post COVID conditions permission to think outside of the box

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Abstract
Chest pain is among the most common symptoms of post-COVID-19 Conditions (PCC) that prompts medical attention. Because the SARS-CoV-2 virus has proclivity for many organs and organ systems in the chest, ranging from the heart, lungs, great vessels, lymphatics, and peripheral nerves, clinicians evaluating patients with chest pain must consider a broad differential diagnosis and take a comprehensive approach to management.

Keywords Post-COVID conditions · Chest pain · Organ systems

Introduction

Chest pain is among the most common symptoms of post-COVID-19 Conditions (PCC) that prompts medical attention. A tenet of medicine is to focus one's attention on common conditions. The COVID-19 pandemic in some ways challenges this tenet and serves as a reminder for the medical community, perhaps like no other in the past century of the importance of keeping an open mind, the power of listening and observing, and that new knowledge does indeed have a place in contemporary medicine.

For early-, mid-, and late-career clinicians the overarching message is to develop an understanding of COVID-19- a complex viral illness of a protean nature and a proclivity for vascular endothelial cells, tissue injury, up-regulating and altering immune responses, and impairing normal reparative processes in multiple organ systems (reviewed in Becker and Khan [1–3]. Honoring the medical community's pledge to apply science and service for the betterment of humankind, a thoughtful and comprehensive, yet targeted approach to evaluating patients with chest pain and PCC encourages and necessitates, "permission to think outside of the box".

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COVID-19 and post-COVID-19 conditions

COVID-19 is a systematic viral infection. Like many viral illnesses there are localized symptoms that reflect a combination of direct organ or organ system involvement and mild, moderate, or large effects stemming from multiple stages, phases, or waves of innate and humoral immune responses. The resulting inflammatory state and in some instances marked "resetting" of innate and adaptive immune memory as determined by memory B cells, memory CD4 + T cells, and memory CD8 + T cells are major determinants of acute, subacute, and chronic disease phenotypes [4–7].

Systemic symptoms in the acute phase of infection such as fever, chills, headaches, bone pain, myalgias, fatigue, exhaustion, and arthralgias while not unique to SARS-COV-2 infections, may be more pronounced and longer-lasting than comparable viral illnesses like influenza A and B [8, 9]. This may reflect heightened immune and inflammatory responses to a new pathogen [10] and be responsible for cytokine release and resulting biomarkers in the peripheral blood that include but are not limited to elevated ferritin, C-reactive protein, erythrocyte sedimentation rate, D-dimers, lactate dehydrogenase (LDH), Interleukin (IL)-1, IL-6, fibrinogen, von Willebrand protein and Factor VIII activity [11].

Post-COVID Conditions as defined by the Center for Disease Control and Prevention (CDC) and World Health Organization (WHO) is the continuation or development of new symptoms 1 month or 3 months after the initial SARS-CoV-2 infection, respectively, with these symptoms lasting

Table 1 Percentage of adult COVID-19 case-patients and control patients with ≥ 1 post-COVID–attributable incident conditions and estimated number of COVID-19 survivors who will experience a post-COVID condition — United States, March 2020–November 2021. From Post-COVID-19 conditions among adult COVID-19 survivors aged 18-64 and ?65 years-Cerner Real World Data, United States, March 2020-November 2021. Centers for Disease Control and Prevention. Morbidity and Mortality weekly report, Vol.71, May 20, 2022

Body system	Outcome	Age Group: 18–64 years					Age Group: ≥65 Years				
		Case patients		Controls		RR (95% CI)	Case patients		Controls		RR (95% CI)
		No.	IR*	No.	IR*		No.	IR*	No.	IR*	
Cardiac	cardiovascular disease	3,709	0.13	5,644	0.1	1.35 [1.30, 1.41]	5,175	0.54	11,140	0.39	1.39 [1.34, 1.44]
	cardiac dysrhythmia	14,658	0.61	19,489	0.37	1.66 [1.63, 1.70]	8,096	0.94	16,471	0.63	1.49 [1.45, 1.53]
	heart failure	1,172	0.04	1,566	0.03	1.52 [1.41, 1.64]	1,601	0.12	3,352	0.09	1.33 [1.25, 1.41]
	acute myocardial infarction	1,044	0.03	1,284	0.02	1.66 [1.53, 1.80]	1,442	0.11	2,367	0.07	1.71 [1.60, 1.82]
	myocarditis and cardiomyopathy	1,226	0.04	1,929	0.03	1.29 [1.20, 1.39]	1,553	0.12	3,275	0.09	1.32 [1.24, 1.40]
Respiratory	acute pulmonary embolism	1,198	0.04	1,173	0.02	2.09 [1.93, 2.26]	1,080	0.08	1,375	0.04	2.20 [2.04, 2.39]
	asthma	5,932	0.23	8,820	0.16	1.43 [1.38, 1.48]	1,676	0.14	3,521	0.1	1.35 [1.27, 1.43]
	respiratory symptom	20,264	1.22	27,693	0.57	2.14 [2.10, 2.18]	9,780	1.42	17,869	0.66	2.14 [2.09, 2.20]
Renal	renal failure	3,336	0.12	4,587	0.08	1.51 [1.44, 1.58]	4,410	0.39	7,187	0.21	1.85 [1.78, 1.92]
	chronic kidney disease	2,502	0.09	4,330	0.07	1.19 [1.13, 1.25]	4,081	0.39	9,563	0.31	1.26 [1.21, 1.31]
Hemolytic and Vascular	coagulation and hemorrhagic event	2,665	0.09	4,254	0.07	1.28 [1.22, 1.35]	2,393	0.19	4,816	0.14	1.41 [1.34, 1.48]
	thromboembolic event	1,085	0.04	1,498	0.02	1.47 [1.36, 1.59]	1,096	0.08	1,673	0.05	1.82 [1.69, 1.97]
	cerebrovascular disease	444	0.01	846	0.01	1.06 [0.95, 1.19]	972	0.07	1,878	0.05	1.44 [1.33, 1.55]
GI	gastrointestinal and esophageal event	14,296	0.62	23,950	0.49	1.27 [1.24, 1.30]	7,730	0.9	17,597	0.67	1.34 [1.30, 1.37]
Neurologic	smell and taste disturbances	545	0.02	581	0.01	1.92 [1.71, 2.16]	81	0.01	148	0	1.51 [1.15, 1.98]
	neurologic conditions	10,438	0.4	17,692	0.33	1.21 [1.18, 1.24]	8,682	0.98	17,940	0.64	1.52 [1.48, 1.56]
Mental Health	sleeping disorders	9,893	0.39	16,599	0.31	1.24 [1.21, 1.27]	4,825	0.46	10,932	0.36	1.26 [1.22, 1.30]
	other mental conditions	1,594	0.05	3,279	0.05	0.99 [0.93, 1.05]	899	0.07	1,777	0.05	1.41 [1.30, 1.53]
	substance-related disorder	1,881	0.06	4,173	0.07	0.91 [0.86, 0.96]	413	0.03	922	0.03	1.24 [1.10, 1.39]
	anxiety	12,486	0.53	23,212	0.48	1.10 [1.08, 1.13]	4,135	0.37	9,278	0.29	1.27 [1.22, 1.32]
	mood disorder	626	0.02	1,352	0.02	0.94 [0.85, 1.03]	230	0.02	448	0.01	1.42 [1.21, 1.66]
Muscular	malaise and fatigue	13,555	0.55	16,814	0.31	1.79 [1.75, 1.83]	7,882	0.84	14,405	0.47	1.77 [1.72, 1.82]
	musculoskeletal pain	24,626	1.31	36,007	0.85	1.55 [1.53, 1.58]	9,925	1.24	21,687	0.9	1.37 [1.34, 1.40]
	muscle disorder	3,156	0.11	5,416	0.09	1.19 [1.14, 1.24]	1,957	0.16	3,459	0.1	1.60 [1.51, 1.69]
Diabetes	diabetes type 1	613	0.02	943	0.02	1.32 [1.19, 1.46]	220	0.02	434	0.01	1.40 [1.19, 1.64]
	diabetes type 2	6,311	0.27	9,955	0.19	1.39 [1.35, 1.44]	3,875	0.48	8,157	0.31	1.53 [1.48, 1.59]

*IR, incidence rate per 100 person-months

for at least 2 months with no other explanation (Table 1) (www.CDC.gov;accessed March 18,2023; www.who.int; accessed March 23, 2023). Symptoms often occur in clusters that may represent phenotypes from one organ system or multiple organ systems (Table 1). Preexisting medical conditions are known to be a contributing factor (Fig. 1).

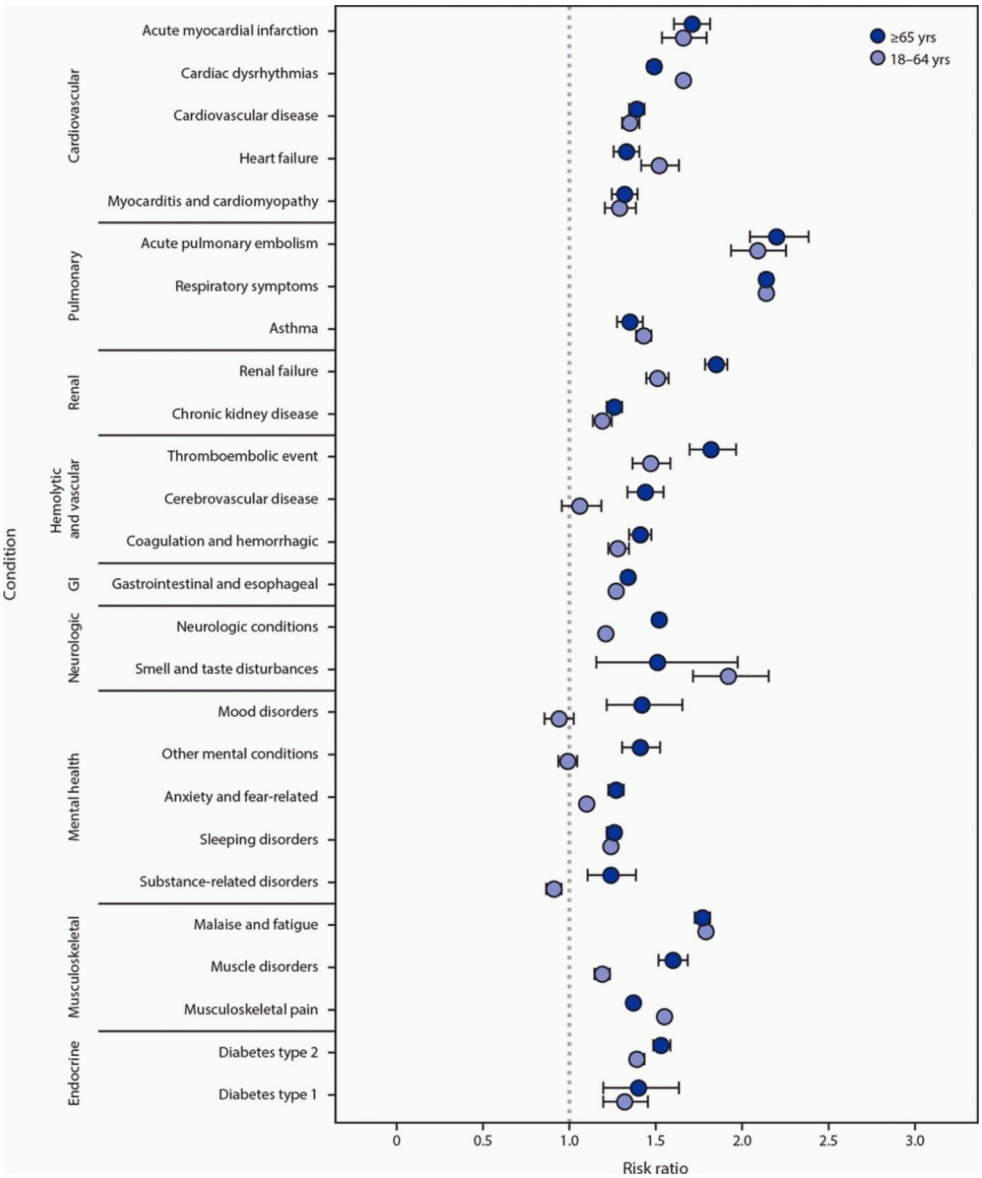


Figure 1 Risk ratios for developing post-COVID conditions among adults aged 18-64 years and ≥ 65 years- United States, March 2020-November 2021. From MMWR May 27, 2022, Vol.71; 713–717. With permission.

Developing systems-based nomenclatures for PCC is a priority for the scientific and medical communities [1, 12].

A pragmatic approach to patients with chest pain following COVID-19

Patients with chest pain following COVID-19 can be separated into groups based on the severity or acuity of their initial illness. Patients with severe or critical COVID-19 (Group1) (World Health Organization Ordinal Scale 4–7) [13, 14] often experience life-threatening conditions that cause *persisting* or *recurring* symptoms 4 to 8 weeks following hospital discharge, including chest pain. The most common conditions that fall into this category include multi-lobar pneumonia, acute respiratory distress syndrome (ARDS), prolonged invasive mechanical ventilation, barotrauma and pneumothorax, pneumomediastinum, alveolar hemorrhage, spontaneous pulmonary hematoma, empyema (often from a secondary bacterial pneumonia and need for chest tube placement), veno-venous or venous-arterial extracorporeal membrane oxygenation, acute myocardial infarction (coronary artery dissection or coronary artery thrombosis with or without plaque rupture), cardiac arrest with cardiopulmonary resuscitation, myocarditis, pericarditis, cardiac tamponade, pulmonary embolism, pulmonary embolism with infarction, pulmonary embolism with pleuritis, aortic dissection, aortitis, aortic thrombosis, aortic aneurysm rupture, aortic ulcer, aortic intramural hematoma, transverse colitis, and esophageal rupture [15–21]). Acute chest syndrome in patients with sickle cell disease (SCD) and COVID-19 must never be overlooked, including for

those in whom the diagnosis of SCD has not been secured previously. Pulmonary fat embolism, veno-occlusive crisis and pulmonary infarction from microvascular platelet-fibrin thrombosis are frequent contributors [22]. Rib infarctions have also been reported [23].

While some patients in Group 1 develop PCC, the point of transition from recovery following an acute and complicated initial illness to more classical pathophysiological signatures of PCC is difficult to discern in the absence of clear diagnostic markers or signatures that distinguish prolonged recovery from PCC or a combination of both. It is also important for clinicians to be aware that patients with severe COVID-19 are at heightened risk for future cardiovascular events following hospital discharge [20]. Accordingly, a high index of suspicion for cardiovascular causes of chest pain must be maintained even among patients who appear to be recovering uneventfully from their initial infection [24]. Symptom severity often correlates with functional difficulties and limitations as well as overall health [25].

Patients with mild-to-moderate symptoms at the time of initial infection (Group 2) (WHO Ordinal Scale 0–3) [13] can also experience PCC and present to their primary care provider or cardiologist for evaluation of chest pain. Our COVID-19 Recovery Clinic established in March 2020 has seen many such patients who often have a period of quiescence following their initial infection and then develop chest pain [1]. Accompanying symptoms frequently include fatigue, dyspnea, and an elevated heart rate at rest (> 90 beats per minute) that increases suddenly after modest physical activity. The episodes of tachycardia and dyspnea may worsen their chest pain and culminate in exhaustion that can persist for hours or sometimes days.

While our experience is somewhat weighted toward a group of patients with PCC and autonomic dysfunction [26], we remain vigilant as a group and take a thorough and systems-based approach to all patients (see Fig. 1and Table 2). In addition to the 26 conditions summarized by the CDC, we would add coronary artery microvascular dysfunction to the list having seen several patients with this condition following COVID-19 [27], [28]. It is also important for clinicians to remember that these patients may have preexisting medical conditions that worsen after contracting COVID-19. Last, patients can develop non-COVID related illnesses.

Table 2 Percentage of adult COVID-19 case-patients and control patients with ?1 post-COVID?attributable incident conditions and estimated number of COVID-19 survivors who will experience a post-COVID condition ? United States, March 2020?November 2021.

Age group, yrs	No. of patients (column %)		No. of patients with ≥ 1 incident condition (column %*)		Absolute risk	No. of
	Case-patients	Control patients	Case-patients	Control patients		
18–64	254,345 (72.0)		90,111 (35.4)	154,011 (14.6)	20.8	1/5
≥65	98,819 (28.0)	589,188 (35.9)	44,840 (45.4)	108,850 (18.5)	26.9	1/4
Total	**353,164 (100)**		**134,951 (38.2)**	**262,861 (16.0)**	**22.2**	**1/4–5**

We have worked closely and collaboratively with colleagues in cardiology, vascular medicine, pulmonary medicine, neurology, rheumatology, immunology, interventional radiology, dermatology, and physical medicine and rehabilitation to consider all potential etiologies of chest pain-being mindful that there can be more than one cause. These group discussions are designed with the express intent to "think outside the box". The subsequent sections represent the cumulative output.

A clinician's lens for assessing Post-COVID Condition chest pain

The approach to patient-centered care must always include a wide-angle lens. This better assures equity, inclusion, empathy and underscores the "power of why" as a foundation for many healthcare providers who view medicine as an art and a science without a ceiling [2].

Sternum: basic anatomy

The sternum represents the most anterior aspect of the chest and consists of three component parts- the manubrium, body, and xiphoid process. Each has distinct articulation points that include the clavicle, sternoclavicular joint (SCJ), manubrial-sternal joint (MSJ), chondral cartilage, sternocostal joint (SCoJ), and xipho-sternal joint. The joints themselves comprise primarily synovial and cartilaginous joint types. Common congenital variants of the sternum include pectus excavation, pectus carinatum, sternal bands, bars and clefts, sternal foramen, and episternal ossicles. The most common degenerative and inflammatory conditions are osteoarthritis (SCJ, MSJ), rheumatoid arthritis (SCJ, MSJ), seronegative arthritis (SCJ, MSJ), septic arthritis (SCJ), and osteomyelitis. Metabolic conditions and disorders include Paget's disease and renal osteodystrophy [29, 30] (Fig. 2).

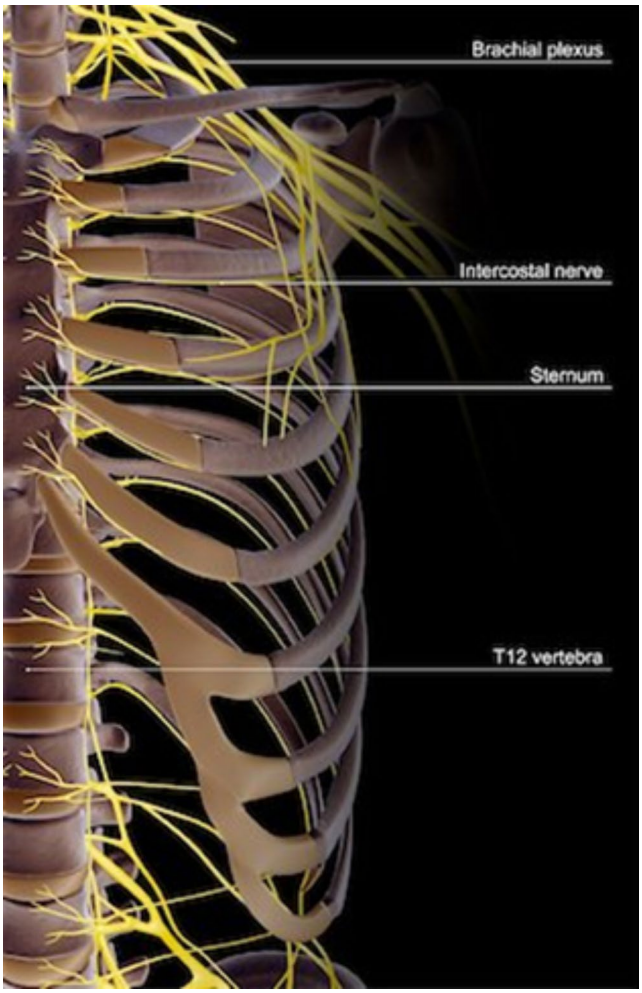


Figure 2 Anatomy of the anterior chest showing the location of the brachial plexus, intercostal nerves, ribs, and sternum (from Masterfile).

Chest wall vasculature

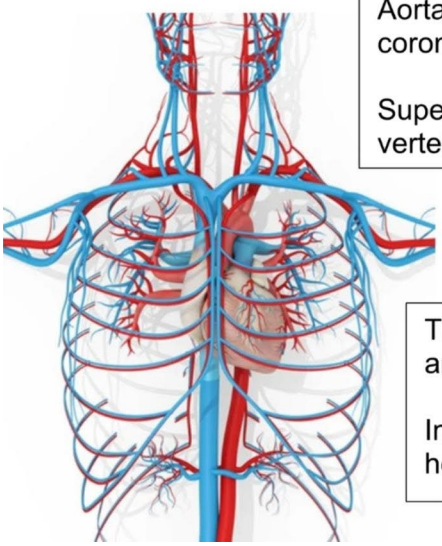
The vascular architecture of the chest wall is well-defined and may offer clues to understanding potential causes of chest pain among patients with COVID-19-a virus known to have a proclivity for vascular endothelial cells and other organ systems with a high concentration of angiotensin-converting enzyme (ACE) 2 receptors [31].

The anterior chest or torso is richly supplied by superficial and deep arteries and arterioles (reviewed in Palmer) [32] The internal thoracic arteries and deep epigastric arteries are the primary source of the cutaneous, intercostal, and intermuscular circulation. Parasternal perforating vessels from the right and left internal thoracic arteries interconnect with the lateral thoracic vessels and course below the ribs along with veins and nerves that collectively make up the intercostal bundles. There are anterior and posterior intercostal arteries with interconnecting vessels that branch to perfuse the pectoralis major muscle and integument through large cutaneous perforating vessels (Fig. 3).

Inflammation of the chest wall vasculature is a consideration among patients with PCC and chest pain.

Pericardial circulation

Vascular channels including arteries, veins, and nerves are located within adipose tissue beneath the visceral pericardium and on the mediastinal aspect of the parietal pericardium [33]. The arteries of the pericardium arise from the internal thoracic arteries and their musculophrenic branches and from the descending aorta. There are also branches and anastomoses of the coronary arteries with pericardial fat originating from the internal thoracic, anterior mediastinal,



Aorta, brachiocephalic, carotid, vertebral, subclavian, pulmonary, coronary, and pericardial arteries.

Superior vena cava, brachiocephalic, pulmonary, subclavian, vertebral,

Thoracic, intercostal, descending aorta, celiac, mesenteric, hepatic, and renal arteries.

Inferior vena cava, intercostal, pulmonary, celiac, mesenteric, portal, hepatic, and renal veins.

Figure 3 Large, medium, and small (arterial and venous) vessels of the neck, chest, mediastinum, and upper abdomen.

pericardial, bronchial, superior, and inferior phrenic, intercoastal and esophageal branches of the aorta [34]. Inflammation of these vessels could be a cause of chest pain among patients with COVID-19. As with several other anatomical locations in the chest or torso, imaging modalities to determine tissue and vascular inflammation are not readily available. This limits a clinician's ability to secure a diagnosis.

Epicardial and Pericardial Fat

Early pathological descriptions of COVID-19 decedents identified SARS-COV-2 virus in adipocytes [35]. Indeed, the presence of fatty tissue reservoirs has been postulated to be a potential contributor to post-COVID conditions [36]. In either case, adipocytes are known to have a high metabolic capacity and produce a wide variety of inflammatory mediators.

Epicardial and pericardial fatty tissue found underneath the visceral pericardium or on top of the parietal pericardium, respectively, is not evenly distributed but rather confined to areas coursing with epicardial and pericardial vessels [37]. Epicardial fat pads that contain parasympathetic ganglia are found in three discrete areas- the junction of the right atrium and right superior pulmonary vein, the junction of the inferior vena cava and the right atrium, and between the superior vena cava and aortic root [38]. Any or each of the epicardial and pericardial fatty tissues could be a site of inflammation and resulting chest pain among patients with COVID-19.

Fat necrosis can be identified by MRI using the Dixon method [39]. The presence of epicardial fat deposits by cardiac MRI or CT has been postulated to be a marker of inflammation-particularly chronic inflammation [40]. Might these tools be capable of shedding light on one or more causes of chest pain in patients with PCC? Further investigation is warranted.

Lymphatic system

The lymphatic system, also referred to as the lymphatic vasculature consists of a network of thin walled, highly permeable initial lymphatics that first drain into pre-collecting lymphatic vessels, merging into larger secondary collecting lymphatics. The unidirectional valves control the transport of lymph back to the blood circulation. Lymph is transferred to pre-nodal collecting lymphatics, also called afferent lymphatics, leading to lymph nodes. The lymph exits lymph nodes through post-nodal collecting lymphatics, eventually draining into the thoracic duct and the right lymphatic duct, which, in turn, discharge lymph into the large veins at the base of the neck (reviewed in Singhal) [41] (Fig. 4).

Inflammation, NETs, and coagulation of pulmonary lymphatic vessels draining from the lungs have been described in patients with severe COVID-19 pneumonia [42]. Damage to germinal centers within the lymphatic system could contribute to impaired immune responses, lymphatic dysfunction, and an inflammatory state [43]. Because the vascular endothelium and lymphatic system glycocalyx's share many similarities and the glycocalyx is known to be a common site of injury in COVID-19, prolonged dysfunction may be a consideration among patients with PCC and chest pain [44]. MRI and lymphangiography are the preferred imaging modalities for evaluating the lymphatic system of the mediastinum and chest.

Muscular-skeletal chest Pain

Muscular-skeletal chest wall pain includes a wide range of causes including cervicothoracic angina, intercostal myalgia, segmental thoracic dysfunction, pectoral myalgia, fibrositis, costochondritis, Tietze syndrome, fibromyalgia, and sternoclavicular disease (reviewed in Stochkendahl) [45]. The neurovascular bundle inflammation described with COVID-19, coupled with cytokine-mediated arthralgias and arthritis, autoimmune profile, and skeletal inflammation [46] detected in some patients by magnetic resonance imaging (MRI) suggests that many of the muscular-skeletal causes of chest pain should be included in the differential diagnosis in patients with PCC and chest pain. The overall clinical context must be considered carefully.

Polychondritis, relapsing polychondritis, and dermatomyositis have been described in autoimmune diseases and viral infections such as HIV, Hepatitis C, and herpes simplex. The COVID-19 experience and its impact on rare and complex connective tissue diseases has been captured in the European Network of Rare and Complex Connective Tissue and Musculoskeletal Disease (ERN-ReCONNECT) [47]. While cutaneous features and muscle weakness are expected in dermatomyositis, the phenotype is heterogeneous. Muscle biopsies from patients with COVID-19 show abnormal presence of Myxovirus resistance protein A in muscle fibers and capillaries. Myxovirus resistance protein A is one of the IFN1-inducible proteins, is overexpressed in biopsy muscle specimens from DM patients and may be a more sensitive marker of DM, suggesting that autoimmune myositis may be caused by COVID-19 [48, 49].

What is the mechanism for myalgias, arthralgia, and bone pain in viral illnesses?

In most infections muscle, joint, and bone pain have been attributed to immune responses. Many inflammatory

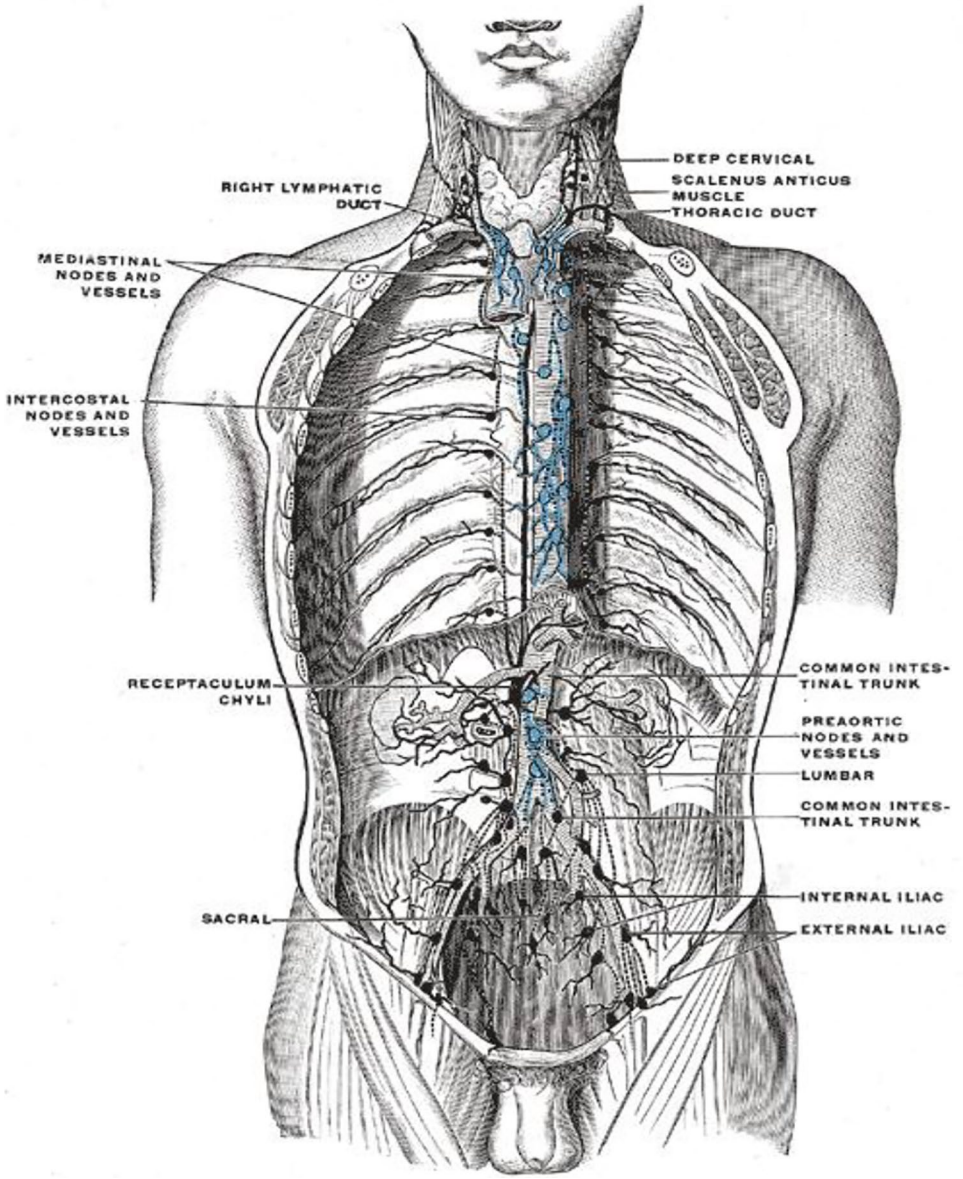


Figure 4 Lymphatic system of the chest. Courtesy of Greys Anatomy plates.

proteins, cytokines, and chemokines are released from osteoblasts for the purpose of stimulating bone remodeling. These include but are not limited to macrophage colony-stimulating factor, IL-6, and IL-11 [50]. There are bacteria and viruses that can infect bones either through direct contact or by hematogenous spread, typically beginning in the metaphyseal region of the tubular bones. Bacteria such as staphylococcus aureus, staphylococcus epidermis, pseudomonas aeruginosa, Serratia marcescens, and Escherichia coli possess receptors that permit direct binding to adhesive matrix proteins ([51]. Viral illnesses can cause infectious bone and joint degeneration by promoting osteoclastogenesis [52, 53].

An existing literature considers constitutional symptoms including pain to be neurogenic in origin [54]. Specifically, the central and peripheral nervous systems' nociceptors are stimulated and transduced into pain impulses transmitted by first-order neurons (nerve fibers C and Ay). The stimulus itself can prompt the release of inflammatory cytokines that further stimulate nociceptors. First-order neurons synapse with second-order neurons to form spinothalamic tracts that course to the thalamus, synapsing with third-order neurons projecting to the somatosensory cortex and limbic system [55].

Inflammatory responses are governed by several coordinated processes and trigger granulopoieses in the bone marrow [56]. S100A8/A9-NLRP3-IL-1β signaling induces the accumulation of inflammasome- primed neutrophils within the bone marrow. In turn, the primed neutrophils secrete IL-1β triggering additional granulopoiesis. The

entire process is localized to the bone marrow limiting systemic release and off-target effects. Bone marrow NLRP3 inflammasome-IL-1β signaling also stimulate megakaryocyte development and platelet production [57]. Emergency granulopoiesis is stimulated by G-CSF [58].

Arthritis, arthralgia, and muscular-skeletal pain are common with viral illnesses, including SARS-COV-2 (and other Coronaviruses), parvovirus, influenza, hepatitis, and human immunodeficiency virus [54]. In some cases, the severity of symptoms correlates with viral load, the concentration of pro-inflammatory cytokines and detection of immune complexes in inflamed joints [59]. The joints involved depend on the viral pathogen and at times can be difficult to distinguish from traditional autoimmune arthritis, particularly in cases where the viral pathogen and immune response induce autoimmunity and inflammatory molecular mimicry.

The autoantigen atlas of COVID-19 identified many proteins with structural and functional roles in the musculoskeletal system. They include various isoforms of actin, actinin, collagen, filamin, fibronectin, fibulin, dynactin, dynein, lamin, myosin, nestin, nexilin, profilin, plectin, plastin, proteoglycan, septin, spectrin, talin, tropomyosin, tubulin, vinculin, and vimentin. These proteins are major components of the extracellular matrix, basement membrane, cell cytoskeleton, cytoskeletal motors, muscle filaments, and contractile motors of muscle cells [60].

Tachycardia and chest pain

Many of our patients in the COVID-19 Recovery Clinic who have heart racing alone or as a part of a symptom cluster that includes chest pain also experience fatigue and exhaustion after physical activity. In many instances high heart rates appear to proceed or precipitate other limiting symptoms, including in patients with PCC and chest pain in the absence of coronary artery disease, microvascular dysfunction, or pulmonary conditions (i.e., normal CT chest, pulmonary CT angiography, ventilation-perfusion scan, pulmonary function studies, maximum inspiratory pressure, and maximum expiratory pressure). The work of Hsueh and colleagues identified the posterior insular cortex as a potential mediator of bottom-up cardiac interoceptive processing and found that optogenetic inhibition of this brain region attenuated the behaviors that were induced by cardiac pacing [61]. In other words, pacing the heart to high heart rates under experimental conditions stimulate areas of the brain associated with the central autonomic network such as the insular cortex, gustatory area and agranular insular area, prefrontal cortex, including the infralimbic area, prelimbic area and anterior cingulate area, and brainstem, including the pons and medulla. These areas are responsible for human emotions such as anxiety, blood pressure regulation, environmental responses, complex cognitive behavior, decision making, sensory processing to include pain, and sleep patterns that govern REM (rapid eye movement)- restful sleep.

Neuropathic pain

COVID-19 has been associated with both peripheral and central nervous system complications either through direct invasion of the nervous system or post viral immune responses [62]. Several viruses are known to cause post viral neuropathic pain- the most common of which is herpes zoster with a prevalence of approximately 6 to 10% in the year following initial infection [63]. Other virus that can cause neuropathic pain include human immunodeficiency virus, enterovirus, poliovirus, Zika virus, Epstein Barr virus, cytomegalovirus, hepatitis, and influenza A [64]. Chest pain of potential neuropathic origin has been reported in up to 20% of patients with PCC [65, 66]. The overall prevalence may be higher among patients with 5 or more symptoms attributable to PCC [67]-a phenotype considered to represent severe PCC.

Small Fiber neuropathy

Small fiber neuropathy has been described following COVID-19 and can present weeks to months following initial infection. The common symptoms include localized, generalized, or migrating burning, deep aching, tingling, or squeezing pain [68] that occurs along with fatigue, muscle pain or fasciculations, or dysautonomia [69]. A multi-system cluster has also been described [70].

Assessment of chest Pain

Our approach to the comprehensive evaluation of patients with PCC and chest pain is summarized below:

Step one:

1. Perform a thorough past medical history, social history, family history, 10- system review of systems, and symptoms at the time of initially confirmed COVID-19, persisting or recurring symptoms, current symptoms, prior diagnostic tests, and conduct a detailed physical examination.
2. Perform vital signs (blood pressure, heart rate, and pulse oximetry) in the supine, sitting, and standing positions.

3. Perform a surface 12- lead electrocardiogram, complete blood count, cytokine 13 panel, a comprehensive autoimmune panel, and a paraneoplastic antibody screen.

Step 2: Based on the overall findings from step 1 and a moderate-to-high clinical index of suspicion, the following diagnostic tests *should* be considered:

1. Cardiac MRI with and without gadolinium.
2. CT angiogram of the coronary arteries, thoracic aorta, or pulmonary arteries-all three could be conducted together if dictated by clinical suspicion(s).
3. Ventilation- perfusion (V/Q) scan.
4. Cardiac PET-CT scan.
5. 7-day cardiac event monitor.
6. Tilt Table test.
7. Pulmonary function studies to include response to bronchodilator, MIP (maximum inspiratory pressure), and MEP (maximum expiratory pressure).

Step 3: Based on the findings from diagnostic tests performed during steps 1 and 2 of the evaluation, the following specialized diagnostic tests *could* be considered:

1. Bone scan.
2. FDG-PET scan.
3. Skin biopsy.
4. Muscle biopsy.
5. Nerve biopsy.
6. MRI of the neck, chest, or cervical and thoracic spine.
7. Dedicated lymphangiogram.

Treatment

The treatment of patients with PCC and chest pain is determined only after considering the patient, the past medical history, and the collective results and interpretation of carefully selected diagnostic tests. Cardiac, vascular, pulmonary, rheumatologic, neurologic, musculoskeletal, and oncologic findings may require additional testing for confirmation of a particular diagnosis or condition. Appropriate treatment and a plan of care should then follow.

In patients with resting tachycardia or inappropriate sinus tachycardia and accompanying chest pain, low dose cardio-selective β-blockers should be considered and titrated according to heart rate, blood pressure, and symptoms. Our threshold is low for prescribing β-blockers for several reasons. As a pharmacological class of drug, they (1) reduce sympathetic tone, (2) reduce inflammation, (3) attenuate heart-brain signaling, (4) lesson autonomic imbalance that contributes to many symptoms in PCC, (5) improve endothelial function, (6) reduce oxidative stress, and (7) may play a role in reducing future cardiovascular events in patients with COVID-19 and PCC [71, 72]. Ivabradine has been used successfully in patients with PCC, including postural orthostatic tachycardia syndrome, inappropriate sinus tachycardia and in patients who experience worsening of fatigue even with low dose, β- selective agents [73]. It is important to emphasize that clinicians evaluating and managing patients with PCC should be part of a multidisciplinary team of providers to limit unnecessary testing and treatments that are outside one's area of expertise.

We recommend follow-up every 12 weeks, either in the clinic or utilizing telehealth, to assess patient progress, response to treatment, and to detect the emergence of new symptoms that may offer insight for making a unifying diagnosis of PCC, non-COVID related illnesses, and other potential causes of chest pain.

Management

Several guidelines including those from the CDC have provided strategies for managing PCC. However, while empirical evidence is still lacking, the consensus is to closely monitor patients with symptoms and adopt a symptom-based approach for targeted management. Appropriate diagnostic tests and treatments should be guided by clinical symptoms and the best available evidence. A dedicated COVID-19 Recovery Clinic is an ideal environment for patient assessment, management, and for participating in clinical trials to scientifically address a large gap in the understanding of PCC and its heterogeneous phenotypes. In addition to the CDC, other institutions like the National Institute for Health and Care Excellence (NICE) have released guidelines for health care practitioners to identify, assess, investigate, manage and monitor patients with ongoing or recurring symptoms after COVID-19 [74, 75].

Conclusions and future directions

Chest pain is common among patients with COVID-19- both in the acute phase and in those with PCC. An understanding of the former informs the latter and prepares clinicians to take a comprehensive approach to assessment and management. PCC include the remnants and recrudescence of acute conditions that occur in the setting of moderate-to-severe-to-critical infection, as well as new or worsening symptoms that follow mild infections or reinfections. We encourage practicing clinicians to be prepared and to "think outside of the box". Patients will be grateful beneficiaries of both, but

providers must remember that thinking outside of the box to secure a diagnosis and select the best available treatment is *not* a license to practice medicine that lacks a clear biological premise, precedent, or evidence of benefit. In such circumstances, we strongly encourage all providers to identify clinical research opportunities and to be active supporters of scientific initiatives designed specifically for establishing optimal care [76]. Your patients, your community, and society will be the beneficiaries [77, 78].

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