Chapter

Cardio-Oncology and the COVID-19 Pandemic

Zahra Mortezaei and Narges Hosseini

Abstract

As one of the novel interesting fields of cardiology, cardio-oncology focuses on monitoring, detecting, and treating cardiovascular diseases caused due to chemotherapy or radiotherapy side effects. It has been observed that cardiovascular patients have a higher risk of viral infections and poorer treatment outcomes. COVID-19 is a disease caused by the new coronavirus, SARS-CoV-2, which emerged in Wuhan, China, in 2019 and then distributed worldwide. Recent evidence showed that the risk of COVID-19 and its mortality rate is higher in patients suffering from cardiovascular side effects of cancer therapies. Additional diagnosis complexity in cardio-oncology is another problem due to overlapping with COVID-19. Therefore, the cardio-oncology community had to re-evaluate the best clinical care in the COVID-19 pandemic. The present study aims to review previous studies focusing on the interaction between COVID-19 and cardio-oncology, which will pave the way for studying human diseases overlapping with COVID-19.

Keywords: cardio-oncology, COVID-19, cancer, cardiovascular, SARS-CoV-2, signaling pathway

1. Introduction

At the end of 2019, a novel corona virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified, which was caused respiratory-related diseases in China, and the disease caused by this virus was named COVID-19 by the World Health Organization and then in 12 March 2020 has been notified as a pandemic [1, 2]. Although COVID-19 mostly manifests in the lung, this virus invades to all part of the body such as heart, eyes, kidneys, the central nervous system (CNS), and other physiological systems (**Figure 1**) [3–7]. The virus directly affects the CNS or the peripheral nervous system (PNS), or other organs which ultimately causes disease in the CNS/PNS [3].

One of the crises in public health which emerged as a global pandemic is related to the coronavirus disease 2019 (COVID-19) increasing infectious outbreaks among broad population. During that pandemic, an unprecedented upheaval in the field of medicine has been observed. Cancer patients are vulnerable to adverse cardiac events, and therefore healthcare interactions have to be increased for them. Increasing cardiovascular disease due to cancer treatment led to the development of cardio-oncology field of research with the aim of monitoring, detecting, and

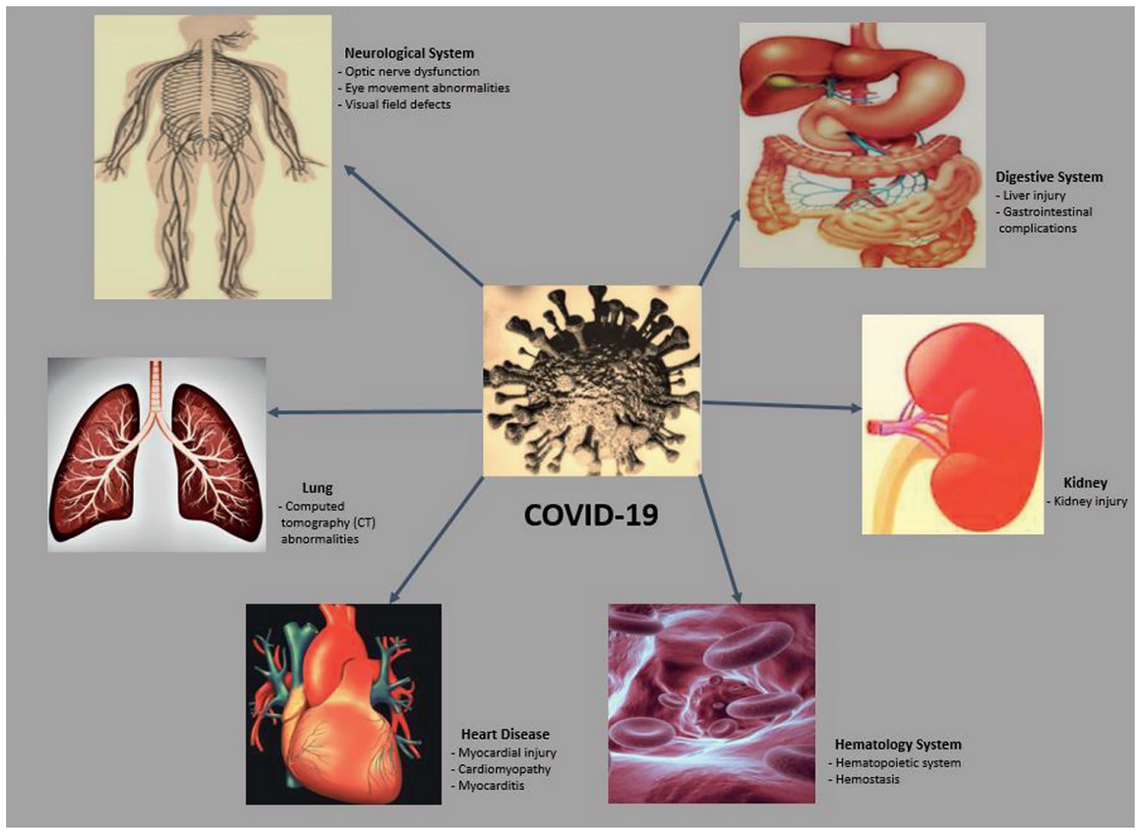

Figure 1.
COVID-19 invades most part of the body.

treating cardiovascular diseases caused due to chemotherapy or radiotherapy side effects. The aim of this research is to study the effects of cardio-oncology and COVID-19 on each other in different perspectives which can suggest strategies for future similar phases [8–11].

Cancer and cardiovascular diseases are vulnerable to COVID-19 because of an increased amount of infection risks and healthcare exposure. For example, one study among 426 hospitalized patients in Wuhan indicated that about 20% of patients have cardiac injury. Also, it has been reported that more unfavorable courses and severe outcomes of COVID-19 have been increased in cancer and cardiovascular diseases. In addition, that study indicated that irrespective of the COVID-19 pandemic, frequent use of healthcare system and anticancer therapies are required for cancer patients [12].

Due to the mentioned infection vulnerability for cancer and cardiovascular diseases, some publications focused on COVID-19 susceptibility for cancer and cardiovascular patients. Previous studies reported COVID-19 patients with cancer history and the statistics indicated that the amount of cancer patients with COVID-19 is higher than the amount of reported cancer patients before the pandemic. For example, one study reported that 6% of patients have both cancer and COVID-19. One case–control COVID-19 study among patients with cancer and those without cancer indicated that lung cancer, malignancies, or metastatic cancer are more in a risk of severe events than others. It has been shown in subsequent meta-analysis results that COVID-19 patients have an increase amount of cancer prevalence and risk of death. Some governments categorized cancer and cardiovascular patients having high risk of virus infection and severe clinical course in COVID-19 pandemic [13, 14].

There is evidences of increased mortality and morbidity rates in COVID-19 patients with comorbid cancer and cardiovascular. Cardiovascular complications such as myocarditis, arrhythmia, heart failure, and myocardial infarction have been observed due to the severe host immune response and cytokine release syndrome. In addition, there is a lot of evidence that shows cancer patients under immunosuppressive treatment have an increased risk of COVID-19 infection [15].

2. Global health system in COVID-19 pandemic

Beyond COVID-19 direct consequences, global health system has enormously been impacted by the pandemic. Since COVID-19 pandemic may affect and disturb access to clinical care, it is important to establish a clinical guideline and pathway. One of the essential and critical part of patient management is cardiac imaging. Because cardio-oncology patients are highly at both delayed care complications and COVID-19 infections risks, some countries developed strategies for cardiac imaging during oncology care in COVID-19 pandemic. In addition, for high-risk patients and to prevent an asymptomatic spread of COVID-19, some instruments have been proposed through regular COVID-19 testing and full personal protective equipment. The assessment of ST elevation myocardial infarction has been impacted during the COVID-19 affecting mortality rates. Therefore, the healthcare system must prepare for rebound effect that can increase disease incidence like heart failure [16, 17].

In COVID-19 pandemic, to assess cardio-oncology care pathways, the success of cardiotoxicity monitoring and COVID-19 mitigation effects, big data analysis is essential. For developing new strategies to overcome ongoing research barriers and to address patient risks in COVID-19 pandemic, some innovations should be inspired. Cardio-oncology in the COVID-19 pandemic has implemented clinical cares and monitoring protocols such as telemedicine systems, teleconsultation, cardiac imaging, limited clinical visits, and biomarker reliance [17].

For the purpose of better understanding similarities and relations between cardio-oncology and COVID-19, some common biological pathways between them will be discussed below [18].

3. Common signaling pathways and their effects

Considering that the virus survival depends on its host cell, cellular functions including signaling pathways can be important to discuss [2]. In coronavirus disease, viruses bind to host proteins and use different cellular pathways as their targets. Corona infection effects on multiple signal transduction pathways with important roles such as mitogen-activated protein kinase (MAPK) pathway, phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling pathway, toll-like receptor (TLRI) signaling, and nuclear factor kappa-B (NF-κB) pathway cascades. Also, the virus can cause a series of hypercytokinemia [19].

3.1 MAPK pathway

Controlling several cell functions (proliferation, apoptosis, and differentiation) are done by MAPK signaling pathways. The MAPK pathways have three pathways

in mammals that are Jun amino-terminal kinases/stress-activated protein kinases (JNK/SAPK), p38 MAPK, and MAPK/extracellular signal-regulated kinase (ERK). Environmental stimuli initially activate the p38 MAPK pathway, which has a significant impact on the inflammatory processes and immune response [19]. The host activates the immune system during viral infections to fight pathogenic microorganisms. As a result, if one of the immune responses is out of control, it can lead to significant damage during an infection such as COVID-19 [20]. It has been shown that Raf/MEK/ERK pathway inhibitors can be used as antiviral candidates for COVID-19 treatment [20].

Among severe infected COVID-19 patients, increased amount of cardiac injury has been observed. Clear mechanism of cardiac injury is not completely identified, but it is suggested to be involved in a combination of immune-mediated and viral damages by cytotoxic and cytokines/chemokines immune responses. In SARS-CoV-2 infection, cytokine storm contributors and the host immune responses are complex. In immune hyperactivity and dysregulation, T lymphocytes depletion may contribute [21].

Activation of the p38 pathway cause increases the level of pro-inflammatory cytokines such as IL-1, IL-1, and tumor necrosis factor (TNF), which play an important role in the cytokine storm stimulated by COVID-19 infection. Maybe shift balance toward harmful p38 signaling with angiotensin II if ACE2 is lost during viral infection. ACE2 activity was found in both the heart and lung. Excessive activation of p38 MAPK in infected cardiomyocytes, which causes promote fibrosis and apoptosis, can be one of the causes of cardiac dysfunction in patients with coronavirus. The cells can reduce p38 signaling which expands the viral lifespan and also causes inflammation. As a result, if p38 is suppressed, the infection of COVID-19 is reduced. Losmapimod is the most important p38 inhibitor that can be useful for patients with COVID-19 [19].

Another pathway that is effective in this infection is the c-jun NH2-terminal kinase (JNK) pathway, which may lead to an increase in lung damage and an increase in pro-inflammatory factors. This pathway is involved in tissue cytokine production, apoptotic pathway, metabolism, and inflammation [19].

3.2 Notch signaling pathway

Notch signaling pathway has a main role in development and controlling cell fate. This signaling pathway plays a role in maintaining the homeostasis of the cardiovascular system, and it can be a new target to reduce the progression of atherosclerosis and also is a main regulator of cardiovascular function and as well as involved in biological processes with viral infections. This article reported than may be able to use this signaling pathway to combat heart and lung disease caused by SARS-CoV-2 infection [22].

3.3 WNT/B-catenin pathway

This signaling pathway is activated in response to cardiac injury and has important roles in cardiac remodeling and hypertrophy [23]. It has been shown that WNT/b-catenin pathway upregulation can be associated with COVID-19, acute respire distress syndrome [24], and cytokine storm [25].

As a result, it can be said that this virus can effect on the functioning of heart cell by disrupting the signaling pathways.

As mentioned before, COVID-19 affects different organs, including lungs and most probably also the heart. Increase in COVID-19 mortality rates has been seen in cardiovascular diseases. It has been shown in studies that various organ systems to

express the primary SARS-CoV-2 entry receptor, angiotensin-converting enzyme 2 (ACE2) [26]. ACE2 plays a major role in the regulation of cardiovascular and renal functions, and also in SARS-CoV-2 infection [27].

In one previous study, single-cell nuclei RNA sequencing in 40 failing explanted hearts and 15 healthy donor hearts has been used. As a result, low expression of ACE2 in cardiomyocytes and high pericytes expression have been observed. Therefore, SARS-CoV-2 infection in human heart can attack primarily pericytes and cause capillary endothelial cell dysfunction. The results of that can be microcirculation disorders and expanding cardiac damages' observed markers [26].

Expression of ACE2 in human hearts has been published in the European Heart Journal and by Nicin et al. used single-nuclei RNA sequencing for analyzing the expression of ACE2 and ACE in two patients with heart failure with reduced ejection fraction (HFrEF), five patients with aortic stenosis (AS), and two samples from one healthy donor heart with different cell types of the human heart. Finally, they reported an increased amount of ACE2 expression in cardiomyocytes of patients with heart disease compared with healthy controls [26, 28].

It has been shown that monitoring of SARS-CoV-2-infected patients for cardiovascular complications can be important because of ARB (angiotensin II receptor blocker)/ACE inhibitor therapy (driver of cardiovascular pathologies) [28]. One study showed that increase in level of ACE2 was related with cardiovascular male patients, and this can be a major risk factor for COVID-19 infection and complications [29]. Many cases of heart complications have been reported due to COVID-19 infection, and chemotherapy and cancer appear to be risk factors for COVID-19 [24].

In one study, cardiac complications were investigated in a cancer patient who was undergoing chemotherapy with anthracyclines and had corona disease. This patient was a 49-year-old woman with breast cancer who did not have any other medical history. The patient was admitted for coronavirus disease, and she had received chemotherapy 10 days before being admitted. At the time of admission, she had a normal electrocardiogram (normal QTc interval and narrow QRS complex), but on the second day, she had bad respiratory function, and abnormal electrocardiogram (QRS widening and QTc interval lengthening) was also reported from the patient, and finally the patient she died due to cardiorespiratory arrest [30].

In a series of recent studies, it has been reported that cancer patients with COVID-19 had a higher prevalence of severe events compared to the general population and showed a death rate more than 10 times higher than all patients in China [30].

4. Conclusions

In COVID-19 pandemic, in the field of medicine, an unprecedented upheaval has been observed. For example, it has been observed that cancer and cardiovascular diseases are vulnerable to COVID-19. Also, unfavorable courses and severe outcomes of COVID-19 have been observed in cancer and cardiovascular diseases. In addition, COVID-19 patients have an increased risk of cancer prevalence and death. Establishing clinical guidelines in COVID-19 pandemic is essential for high-risk patients. For example, monitoring protocols and clinical cares have been implemented for cardio-oncology care during COVID-19 pandemic. In order to better understand the effects of cardio-oncology and COVID-19 on each other, some common biological pathways like mitogen-activated protein kinase (MAPK) pathway, PI3K/AKT/mTOR pathway, JAK–STAT signaling pathway, TLRI signaling, and NF-κB pathway have been explained.

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