

Review

# Cardiovascular Vulnerability to COVID-19 in Cancer Survivors

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**Abstract:** Coronavirus disease 2019 (COVID-19) has been declared a global pandemic by the World Health Organization on March 11, 2020. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2). Although primarily a respiratory disease, cardiovascular complications of COVID-19 have been increasingly recognized. In addition, higher fatality has been reported in COVID-19 patients with underlying cardiovascular diseases. Cancer survivors have a considerably increased risk for premature cardiovascular diseases, mainly due to cardiotoxic cancer treatments. Therefore, it is foreseeable that cancer survivors will be more vulnerable to cardiovascular complications caused by COVID-19. In this review, three scenarios for increased cardiovascular complications of COVID-19 in cancer patients are proposed. In the first scenario, cardiotoxic cancer treatment and COVID-19 synergize to exacerbate direct myocardial damage. In the second scenario, cardiotoxic cancer treatment leads to a reduced cardiac reserve in cancer survivors, making them more vulnerable to COVID-19 in a “two-hit” model. The third scenario suggests that several shared risk factors may aggravate cardiovascular complications caused by both cancer treatment and COVID-19. Taken together, cancer survivors may be more vulnerable to cardiovascular complications when challenged by the COVID-19, and special cardiovascular care should be given to these patients.

**Keywords:** COVID-19; Cancer Survivors; Cardiovascular

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## **Introduction.**

Coronavirus disease 2019 (COVID-19) has been declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. As of April 6<sup>th</sup>, 2020, there were more than 1,200,000 confirmed cases worldwide and more than 330,000 confirmed cases in the United States alone. The number of fatalities has been increasing to surpass 67,000 worldwide and 8,900 in the United States (WHO and CDC websites, accessed on April 6<sup>th</sup>, 2020). COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which is believed to be originated in bats, and moved to an intermediate host then to humans [1].

SARS-CoV-2 is transmitted primarily via respiratory droplets from both symptomatic and asymptomatic patients with a median incubation time of 4-5 days. The most reported symptoms are fever and dry cough with less frequent incidence of rhinorrhea and gastro-intestinal symptoms. The case fatality rate has been estimated to be 3.4% worldwide and 1.5 % in USA [2]. Although the case fatality rate has differed significantly, a common theme is that fatality increases markedly with increasing age [3]. In addition, the case fatality rate is significantly higher in patients with other comorbidities than in healthy patients [4]. Cardiovascular disease is a common comorbidity among COVID-19 patients and higher fatality has been reported in COVID-19 patients with underlying cardiovascular disease [5,6].

The interplay between COVID-19 and cardiovascular disease is multi-faceted. First, Angiotensin Converting Enzyme-2 (ACE2), a key enzyme in the Renin Angiotensin Aldosterone System, has been recognized as a receptor to SARS-CoV-2 [7,8]. Second, COVID-19 may compromise the cardiovascular function secondary to a systemic cytokine storm [9]. Third, COVID-19 has been shown to cause direct cardiac injury [6,10]. Even though the COVID-19 is a rapidly evolving situation, several studies, commentaries, and reviews have covered this intricate relationship between COVID-19 and the cardiovascular system [11-14]. Therefore, this review will focus on COVID-19 in cancer survivors as a very special population that may be more vulnerable to cardiovascular complications.

Cancer-related survival has significantly increased in the last two decades thanks to advanced diagnosis and treatment, leading to more than 15.5 million cancer survivors in the United States [15-18]. Unfortunately, cancer survivors suffer from multitude of adverse health conditions [19-21], with a considerably increased risk for premature cardiovascular diseases [22-24]. For instance, childhood cancer survivors have an estimated 15 times higher risk of heart failure than their siblings who did not have cancer [25]. The increased risk for cardiovascular complications in cancer survivors is mainly attributed to cardiotoxic cancer treatments, particularly in breast and childhood cancer survivors [26,27]. Nearly 50% of pediatric cancer patients receive anthracyclines such as doxorubicin (DOX), which are known to cause cardiotoxicity [28]. Other cancer treatments may cause varying degrees of cardiotoxicity (reviewed in [29,30]). Radiation therapy can also lead to cardiovascular complications including coronary artery disease, cardiomyopathy, and myocardial fibrosis [31,32]. Cancer survivors are at increased risk for morbidity and

mortality from infections and infection-related complications [33,34]. Indeed, influenza-induced exacerbation of pre-existing cardiovascular diseases is more common among high-risk populations, including cancer survivors [35]. Taken together, it is foreseeable that cancer survivors will be more vulnerable to cardiovascular complications caused by COVID-19. Those survivors who had been treated with cardiotoxic cancer treatments would be at the greatest risk. Therefore, the current review will briefly summarize the most commonly used cardiotoxic cancer treatments and the proposed mechanisms for their cardiotoxic effects. Then, three scenarios of increased cardiovascular vulnerability to COVID-19 in cancer survivors will be proposed.

#### **Cardiotoxic Cancer Treatment:**

The most common cardiotoxic cancer treatments are anthracyclines. Anthracyclines (e.g. doxorubicin; Adriamycin®) are chemotherapeutic agents commonly used to treat pediatric hematologic malignancies. Unfortunately, the clinical utility of these effective agents is limited by their well-known cardiotoxic effects that can progress to end-stage heart failure [36]. Anthracyclines cause both acute and chronic cardiotoxic effects in pediatric cancer patients; however, lower anthracycline doses used in the recent treatment protocols have decreased the incidence of severe cardiovascular complications [37,38]. Nevertheless, subclinical cardiotoxicity occurs in those who receive even low doses of anthracyclines [39-41]. The mechanisms of anthracycline-induced cardiotoxicity include oxidative stress [42], apoptotic and necrotic cell death [43,44], cellular senescence [45-47], mitochondrial dysfunction [48], inflammation [49], and altered myocardial energy

metabolism [50-52]. In addition to cardiotoxicity, anthracyclines are associated with endothelial dysfunction and vascular injury [53-56].

Other cardiotoxic cancer treatments include tyrosine kinase inhibitors, trastuzumab, immune check point inhibitors, cyclophosphamide, and cisplatin (reviewed in [29,30]). Sunitinib, a tyrosine kinase inhibitor, has been shown to cause heart failure in up to 8% and hypertension in up to 50% of cancer patients [57]. The proposed mechanism of sunitinib-induced cardiotoxicity is the inhibition of off-target kinases [58-60]. Trastuzumab is an epidermal growth factor receptor-2 (HER-2) monoclonal antibody that has been shown to be cardiotoxic in breast cancer patients [61]. Importantly, trastuzumab has been shown to augment anthracycline-induced cardiotoxicity [62]. Novel immune check point inhibitors have also been associated with increased risk of myocarditis [63]. Although less frequent at low doses, cyclophosphamide-induced symptomatic cardiotoxicity occurs in 5-28% of patients treated with high doses [64,65]. Cyclophosphamide-induced cardiotoxicity may be mediated by increased oxidative and nitrosative stress [66]. Cisplatin-induced cardiotoxicity has been shown to be caused by oxidative stress, mitochondrial dysfunction, increased endoplasmic reticulum stress, and apoptosis [67,68].

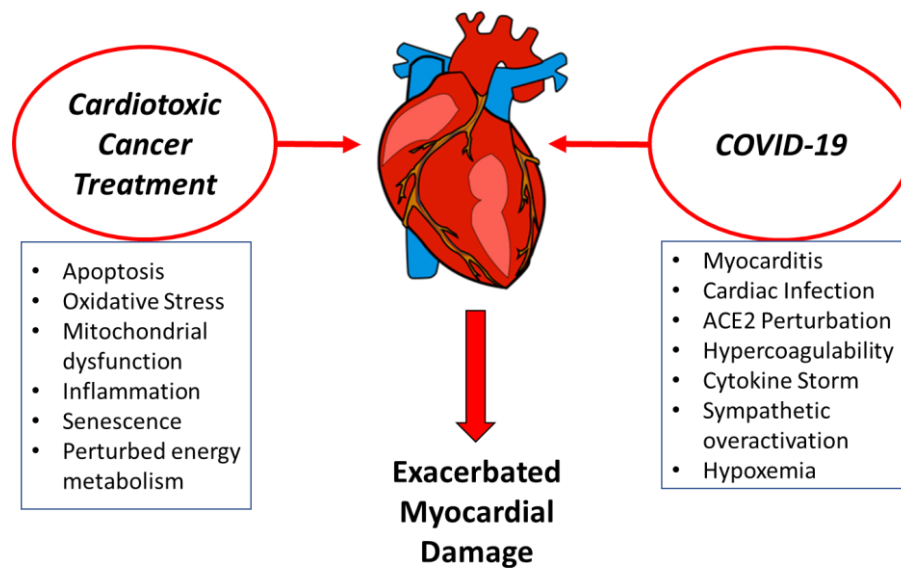
Radiation therapy has also been shown to cause several cardiovascular adverse effects, including: pericarditis, pericardial fibrosis, myocardial fibrosis, coronary artery disease, and microvascular damage (reviewed in [69]). Similar to anthracyclines, radiation-induced cardiovascular toxicity is mediated by oxidative stress [70,71], apoptotic cell death [72], inflammation [73,74], and cellular senescence [75].

## **Scenarios for increased cardiovascular complications of COVID-19 in cancer survivors:**

Cardiovascular complications of COVID-19 has been increasingly recognized [11-14,76]. Cancer survivors who had been treated with cardiotoxic treatments are at a potentially higher risk for cardiovascular complications than the general population when challenged by COVID-19. Herein, three possible scenarios for this potential increased risk will be discussed.

### **1- Exacerbated myocardial damage:**

Myocardial damage, evidenced by elevated cardiac biomarkers, has been observed in 7.2% of patients in a study of 138 hospitalized COVID-19 patients in Wuhan, China [77]. The National Health Commission of China has estimated that 12% of patients without previous cardiovascular disease had elevated troponin levels or cardiac arrest during hospitalization [78]. The rise in cardiac markers has generally tracked the increase in inflammatory markers such as interleukin-6 [79], suggesting that myocardial injury may be secondary to a cytokine storm [76]. On the other hand, there are reports of patients presenting with primarily cardiac symptoms that may be due to viral myocarditis [80] or stress cardiomyopathy [76]. Unfortunately, higher rates of heart failure and acute cardiac injury were observed in fatal COVID-19 cases as compared to those who survive [79]. It is important to note that the SARS-CoV-2 receptor, ACE2, is highly expressed in the heart and can lead to ACE2-dependent myocardial infection [8]. Thus, COVID-19-mediated myocardial injury may exacerbate cancer treatment-induced latent cardiotoxicity in cancer survivors.

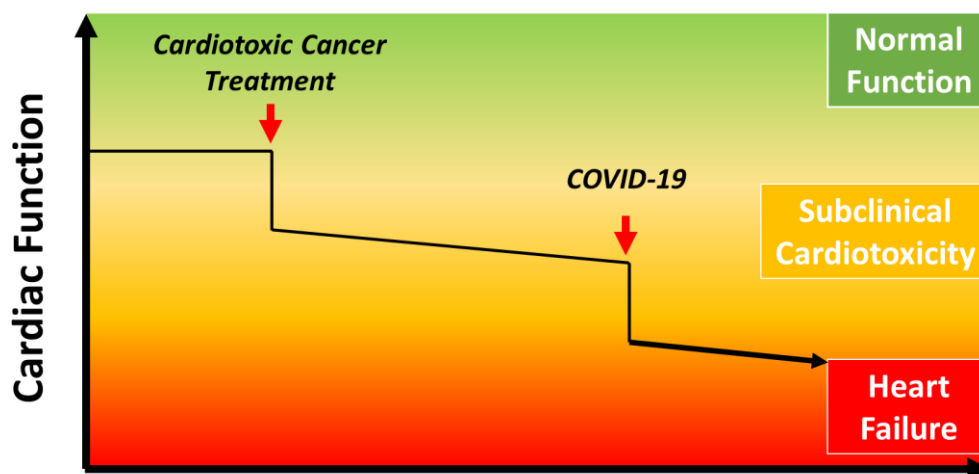


**Figure 1. Exacerbated Myocardial Damage by COVID-19 in Cancer Survivors.** Cardiotoxic cancer treatment and COVID-19 may synergize to exacerbate myocardial damage through a variety of mechanisms.

## 2- Reduced cardiac reserve:

Although the incidence of severe cardiac dysfunction and heart failure has been declining in cancer survivors due to the use of lower doses of anthracyclines in modern protocols. Anthracycline-induced subclinical cardiac dysfunction still affects up to 65% of DOX-treated pediatric cancer patients [15,41]. It has been suggested that anthracycline-treated childhood cancer survivors have lower cardiac reserve as compared to control subjects [24]. The subclinical cardiotoxicity and reduced cardiac reserve predispose anthracycline-treated survivors to other cardiovascular risk factors later in life in a “two-hit” manner [81]. Childhood cancer survivors have been shown to be a higher risk of cardiovascular complications when challenged by other stressors in their adult life. For instance, female survivors who had been treated with cardiotoxic therapy were more

vulnerable to pregnancy-associated cardiovascular complications when compared to the general population [82-84]. Preclinical studies have also demonstrated that mice treated with doxorubicin at a young age were more vulnerable to cardiovascular complications when challenged by myocardial infarction [85] and hypertension [86] in their adult life. It is obvious that COVID-19 represents a stressful condition characterized by cytokine storm, sympathetic stimulation, acute respiratory distress syndrome, hypoxemia, and hypercoagulability [14]. High cardiac reserve in healthy individuals may be sufficient to overcome these challenges; however, the prognosis may be much worse in patients with reduced cardiac reserve, such as cancer survivors.



**Figure 2. A “two-hit” model for exacerbated cardiac dysfunction due to COVID-19 in cancer survivors.** Cardiotoxic cancer treatment causes latent subclinical cardiotoxicity in cancer survivors. A subsequent challenge by COVID-19 will further deteriorate the cardiac function leading to severe cardiac dysfunction and heart failure.

### 3- Increased cardiovascular risk factors:

There are several risk factors that are common between COVID-19 and cancer treatment-induced cardiotoxicity. These shared risk factors may increase the risk of



cardiovascular complications of COVID-19 in cancer survivors who had been treated with cardiotoxic agents.

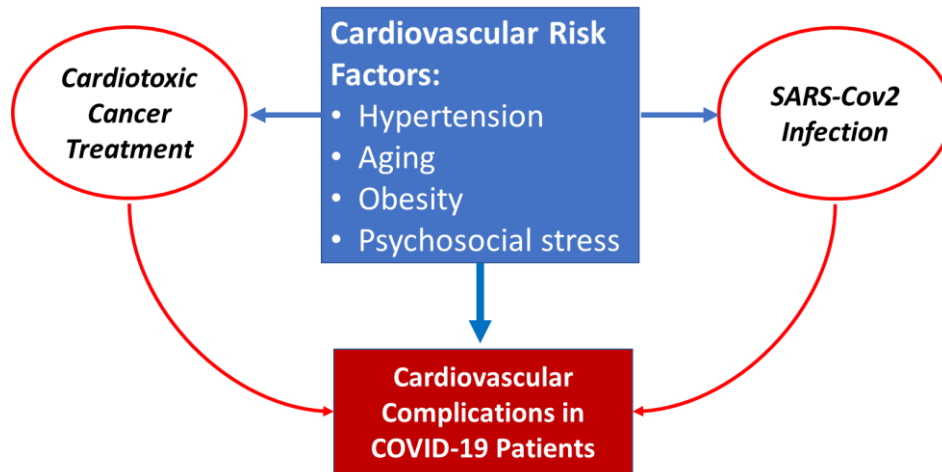
**a) Hypertension:** Hypertension was reported in 12.8% of a series of 44,672 confirmed COVID-19 patients in China. The case-fatality rate was 6% in hypertensive patients, while the overall case-fatality rate was 2.3% in this study [14]. Other studies have reported hypertension in 15-31% of COVID-19 hospitalized patients [77,87]. Hypertension was associated with a nearly 2.5-fold significantly increased risk of severe COVID-19 disease [88]. Intriguingly, hypertension is the most significant cardiovascular risk factor for all adverse cardiac events, including heart failure and cardiac death, in anthracycline-treated childhood cancer survivors with a 12 times higher risk for heart failure in hypertensive than in normotensive anthracycline-treated survivors [81].

**b) Aging:** Higher fatality rate and more severe complications of COVID-19 have been associated with advanced age [3]. Senolytics and other anti-aging drugs have been proposed for the treatment or prevention of corona virus infection [89]. Importantly, several clinical studies have demonstrated that cancer survivors show systemic signs of premature aging [19,90-92], which may put them at a greater risk for COVID-19 severe complications and even fatality. Recent publications demonstrated that DOX lead to the accumulation of senescent cells and clearance of senescent cells after DOX exposure mitigated DOX-induced cardiotoxicity [45-47]. Other pediatric cancer treatments such as radiation therapy also cause senescence [93] and lead to cardiovascular and other health complications [94]. Natural aging has been shown to predispose experimental animals to

worse outcomes when subjected to different cardiovascular challenges such as hypertension [95] and myocardial infarction [96].

**c) Psychosocial Stress:** Heightened psychosocial stress [97-99], posttraumatic stress disorder, and depression have been reported in COVID-19 survivors [100,101]. Results of correlation analysis indicated that economic effects, and effects on daily life, as well as delays in academic activities, were positively associated with anxiety symptoms [102]. Headline stress disorder has also been reported during the outbreak of COVID-19 [103]. Psychosocial stress is a significant cardiovascular risk factor [104-107] and an enormous burden in up to 63% of cancer survivors [108-112]. Observational studies demonstrate that psychosocial stress is associated with higher rates of cardiovascular complications in cancer survivors [113-116]. Therefore, the increased rates of psychological disorders among COVID-19 patients and among the general population during the COVID-19 pandemic may exacerbate cardiovascular complications in cancer survivors.

**d) Obesity and metabolic syndrome:** School closure due to COVID-19 pandemic will likely double out-of-school time this year for many US kids; thus exacerbating the risk factors for weight gain associated with summer recess [117]. Obesity has been suggested as a risk factor for higher mortality in COVID-19 patients [118]. Obesity has both been shown to be prevalent among cancer survivors [119,120], and to be a risk factor for cardiovascular disease in cancer survivors [121]. The increased risk for obesity is more prevalent in the general population during the COVID-19 pandemic, increasing the risk of cardiovascular diseases in general.



**Figure 3. Cardiovascular risk factors exacerbate cardiovascular complications of COVID-19 in cancer survivors.** Several risk factors may exacerbate both COVID-19 and cancer treatment-induced cardiovascular complications.

#### **Conclusions:**

COVID-19 represents an unprecedented challenge to the health care system all over the world. Although primarily a respiratory condition, COVID-19 has caused severe cardiovascular complications that are associated with higher fatality. Cancer survivors who have been treated with cardiotoxic cancer therapies may be at higher risk for severe cardiovascular complications. Therefore, special cardiovascular care should be given to cancer survivors challenged by the COVID-19.

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