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CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

The COVID-19 Pandemic and its Impact on the Cardio-Oncology Population

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Abstract

Purpose of Review The novel Coronavirus (2019-nCoV, COVID-19) is historically one of the most severe acute respiratory syndromes and pandemics to affect the globe in the twenty-first century. Originating in Wuhan, the virus rapidly spread and impacted subsets of populations with initial unclear risk factors contributing to worsening morbidity and mortality. Patients with diagnosis of cancer and undergoing treatment further represent a population at risk for worsening cardiopulmonary outcomes. This review explores specific risk factors, diagnoses, and treatment options that impact cardio-oncologic patients with COVID-19.

Recent Findings Multiple studies globally, including Italy, China, and the USA, have documented severe outcomes. Cancer patients are at increased risk of cardiac injury which itself is a risk factor for mortality. Additionally, elderly cancer patients undergoing recent anti-cancer treatment may be at greater risk for sustaining worse outcomes, although data remains suboptimal in this population. Major gaps remain regarding risk associated with type of cancer and type of anti-cancer treatment, as well as the layered risk of cardiovascular disease and cancer. Immunomodulatory therapies used to treat cytokine release syndrome secondary to anti-cancer therapies, as well as other agents being traditionally used to treat cardiovascular and cancer disease states, are being investigated for treatment of COVID-19.

Summary Hypertension, cardiovascular disease, diabetes, and cancer have been associated with more severe COVID-19 infection and worse outcomes. Patients undergoing anti-cancer therapy or those who have suffered from coronavirus infection may develop long-standing changes, not limited to pulmonary fibrosis, hyperlipidemia, and worsening atherosclerosis. Those undergoing anti-cancer therapy are at theoretically increased susceptibility for infection, with type of cancer not necessarily dictating outcome. A review of the literature of patients with cardiovascular and/or cancer disease is presented, as well as proposed strategies to attenuate risk regarding treatment, management, and surveillance in this vulnerable population.

Keywords COVID-19 · Cardio-oncology · Cancer · Cardiovascular disease

Introduction

The spread of novel Coronavirus (2019-nCoV, COVID-19) shook the world with its highly virulent transmissibility, manifesting largely as a severe acute respiratory syndrome, with more than 4.3 million people confirmed to be infected—with approximately 1.3 million cases in the USA—and over 294,000 deaths worldwide at the time of this writing [1]. Originating in China, the COVID-19 epidemic has surpassed its predecessors in the number of hospitalizations and intensive care unit admissions required to handle an infectious process within a short period of time and of such grand scale [2]. The early SARS epidemic that emerged in 2002 similarly involved human-to-human transmission, with animal vectors linked to outbreaks and confirmed in laboratory isolates [3]. Initially described as pneumonia of unknown origin, COVID-

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19 is believed to be linked to bats based on its genomic similarity to known bat coronavirus BatCoV RaTG13 [4]. Though most coronaviruses are mild, two beta-coronaviruses, severe acute respiratory syndrome (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), also took place within the last two decades [5]. These two unique predecessors preceded the pandemic that began in China in 2019. The virus, originating in Wuhan, Hubei province, China, in late December, resulted in nearly 96,000 cases initially and is now considered a worldwide pandemic [6].

Routes of transmission of the virus have been documented to include respiratory droplets, contact, fomites, and fecal-oral transmission [7, 8]. The most common symptoms at onset of illness include fever, cough, myalgia, and fatigue, with rare complaints of sputum production, headache, hemoptysis, loss of taste and/or smell, and diarrhea. In addition to clinical characteristics, patients showcased ground-glass opacities on chest computed tomography scans. However, more than half of the patients in early studies notably developed dyspnea that correlated with patchy infiltrates on chest radiographs. The mean duration of symptoms was roughly 8 days, with progression to acute respiratory distress syndrome (ARDS) occurring between days 8 and 14 [9]. Patients receiving mechanical ventilation in the Wuhan Cohort typically required ICU admission of up to 1–2 weeks following symptom development which foreshadowed the scale of the pandemic and mirrored data obtained from the MERS epidemic in 2015 [10, 11].

Epidemiology of COVID-19 and Risk Factors for Severity of Illness

Epidemiological data from China confirmed the median age of the patients impacted by the disease to be 59 years, with disease distribution disproportionately impacting males [12]. The data further hypothesized that children might be less likely to become infected, or if infected, demonstrated far milder symptoms. Italy documented nearly 22,512 cases by March of 2020, with the largest proportion of cases and fatalities impacting males greater than 60 years of age [13]. In the Lombardy study, 68% of patients had at least one existing comorbidity, with hypertension being most frequently cited. Other predisposing factors included cardiovascular disease and hypercholesterolemia. A rare subset had pre-existing lung disease, manifesting as chronic obstructive pulmonary disease. Roughly 11% of the Lombardy patients were managed with non-invasive ventilatory support [14]. The need for invasive ventilatory support varied across regions of the world, and some of the Wuhan cohort were directly transitioned to extracorporeal membrane oxygenation (ECMO) for resuscitation purposes [10].

Underlying risk factors, such as hypertension, diabetes, cardiovascular disease, and immunosuppression, have been explored as prognosticators regarding clinical outcomes of COVID-19 infections in hospitalized patients [15•]. However, the impact of the pandemic in patients with a history of cancer and pre-existing and/or cancer treatment–associated cardiovascular disease—the cardio-oncology patient—is unknown. Theoretically, this population is likely at higher risk of morbidity and mortality from COVID-19 infection, and has unique healthcare needs that put them at higher risk at exposure from community and healthcare-related transmission. Examples of these risks include needing ongoing cancer treatments in the outpatient and inpatient setting, as well as imaging-related procedures and operations for cancer-related staging and treatments. If these patients also have pre-existing cardiovascular disease and/or acquired cardiotoxicity during and after treatments, they also warrant additional evaluation. Finally, there appears to be a strong correlation with worse outcomes in hospitalized COVID-19 patients in cardiovascular and/or cancer-related comorbidities, which will be reviewed below.

Cardiovascular Disease and COVID-19

Multiple retrospective analyses including those from China, the USA, and Italy have shown that there is high cardiovascular disease (CVD) prevalence in patients that develop COVID-19 and particularly those that have more severe disease and worse outcomes. The mechanism by which cardiovascular patients have a higher risk of contracting COVID-19 and developing more severe disease is unknown, but potentially may be due to poor cardiovascular reserve, a greater associated age with the cardiovascular conditions, and dysregulated immunity and existing inflammation from their underlying diseases such as hypertension and diabetes [16]. An observational database of the Surgical Outcomes Collaborative registry, which comprised of 8910 hospitalized COVID-19 patients from 169 hospitals in Asia, Europe, and North America, found that an age greater than 65, and diagnosis of history coronary artery disease, heart failure, and/or cardiac arrhythmias were independently associated with increased risk of in-hospital death, with 5.8% ($n = 515$) of this cohort dying in the hospital [17]. Further studies analyzing risk factors and associated clinical outcomes by geography are further described below.

China

A meta-analysis of 6 Chinese studies evaluating 1527 affected patients showed that the most prevalent cardiovascular metabolic comorbidities included hypertension (17.1%), cardiac and/or cerebrovascular disease (16.4%), and diabetes (9.7%). Most importantly, patients with hypertension and cardiac and/or cerebrovascular disease significantly accounted for more ICU cases compared with non-ICU cases with prevalence of 28.8% (RR 2.03) for hypertension, and 16.7% (RR 3.30) for

cardiac and/or cerebrovascular disease [18]. Data from the World Health Organization and Chinese Center for Disease Control and Prevention confirm that patients with comorbidities have a higher case fatality rate (CFR) than those without comorbidities [19, 20]. Of the 55,924 laboratory-confirmed cases in China, there was a 3.8% CFR and higher rates were seen with those with CVD (13.2%), diabetes (9.2%), and hypertension (8.4%) [19•]. A cohort study of 201 patients from Wuhan Jinyintan Hospital showed that hypertension was significantly associated with patients progressing to Acute Respiratory Distress Syndrome (ARDS) (27.4% vs. 13.7%; $p = 0.02$) and later death (36.4% vs. 17.5%; $p = 0.05$) [21].

Italy

As of March 17, 2020, the CFR in Italy is 7.2%. from a total of 22,512 cases of which a detailed chart review of a subsample of 355 deceased patients found high underlying disease prevalence of ischemic heart disease (30%), diabetes (35.5%), atrial fibrillation (24.5%), and cancer (20.3%) [22]. A case series of patients with COVID-19 in the ICUs in the Lombardy region demonstrated that hypertension was the most common comorbidity (49%) and cardiovascular disease (21%) was the second. Furthermore, there was a statistically significant higher prevalence of hypertension among patients who died compared with those who were discharged from the ICU (63% vs. 40%; $p < 0.001$) [14].

USA

While epidemiologic data in the USA remains dynamic with limited studies to date in major urban centers, a report of 167 confirmed cases linked to a long-term facility in Washington State also conferred similar findings showing high underlying disease prevalence with hypertension (44.3%), cardiac disease (40.7%), and diabetes (22.8%) [23]. A large New York study examined a total of 5700 patients, with median age being 63 years age. The New York cohort found hypertension in 56.6% patients, obesity in 41.7% patients, and diabetes in 33.8% of patients. Of the patients who died, those with diabetes were more likely to have been mechanically ventilated or be hospitalized in the ICU [15•]. Another case series of 393 patients admitted to New York hospitals found that 50.1% of patients had hypertension and 21% had cardiovascular disease [24]. Not all studies detailed specifics of what defined cardiac disease; therefore, it is difficult to delineate COVID-19 direct associations with coronary artery disease, cardiomyopathy, or heart failure from a large sample size standpoint. However, a case series from Seattle, Washington did state that 42.9% of the 21 critically ill patients with COVID-19 had underlying congestive heart failure [25].

Myocardial Injury and COVID-19

In addition to underlying CVD being a risk factor for contracting COVID-19, patients that develop acute myocardial injury have worse outcomes, even in those without baseline cardiovascular dysfunction [25–28]. Acute myocardial injury can be categorized in three varieties: elevated troponin levels above the 99th percentile upper reference limit, development of new or worsening heart failure, and myocarditis. Several studies from China found that elevated troponin levels were significantly associated with higher mortality [26–28]. A case series of 187 patients at the Seventh Hospital of Wuhan City, China, found that patients with elevated troponin T (TnT) levels had a significantly higher mortality rate to those with normal TnT levels (59.6% vs. 8.9%; $p < 0.001$). Patients with underlying CVD including those with underlying hypertension, coronary heart disease, and cardiomyopathy were more likely to have elevated TnT levels during their hospital course [26]. Lipid metabolism is also observed to be dysregulated in patients with SARS-CoV infection. Serum concentrations of free fatty acids, lysophosphatidylcholine, and phosphatidylglycerol remained elevated and contributed to chronic cardiovascular damage post infection in patients with SARS-CoV [29]. Long-term cardiovascular and atherosclerotic changes in patients who suffer from COVID-19 have not been documented yet given the recent nature of this pandemic.

A case series of 21 critically ill COVID-19 patients from Seattle also found that one-third of their patients developed new cardiomyopathy with cardiogenic shock in the absence of prior systolic dysfunction during the progression of their illness [25]. It is unclear if these patients that developed cardiomyopathy truly had myocarditis or had underlying CVD that predisposed them to this clinical course. However, COVID-19 has been shown to directly cause myocarditis in otherwise healthy individuals in several case reports [30, 31]. Thus, COVID-19 demonstrates various patterns of myocardial injury, with higher mortality risk being associated with elevated troponin levels.

In addition, in the cardio-oncology population, elevated cardiac biomarkers can pose an additional layer of complexity and challenge when dealing with management. Abnormal elevations of troponin and BNP biomarkers can be indicative of cardiotoxicity from cancer physiology or from the treatments themselves [32]. Some elevations may be non-specific and are reflective of subclinical cardiotoxicity in patients receiving anthracyclines and/or anti-HER2 agents in which stable patients can be medically managed [33, 34]. However, some patients receiving other agents such as certain tyrosine kinase inhibitors with prothrombotic risk (i.e., ponatinib) or fluoropyridines (i.e., 5-fluorouracil) may suffer cardiotoxicity in the form of coronary ischemia/vasospasm, which may warrant more invasive diagnostic/treatment strategies [35–37].

Elevated cardiac biomarkers have also been associated with worse outcomes and or cardiac hemodynamic instability, including cytokine release syndrome from chimeric antigen therapy (CAR-T), heart failure from proteasome inhibitor use (i.e., carfilzomib), or myocarditis from immune checkpoint inhibitor therapy [38–41]. Some of these disease processes may confound treatment of a cancer patient also afflicted with COVID-19, and thus, multidisciplinary assessment, particularly by a cardio-oncologist, may be essential to provide optimal care in this high-risk population.

Cancer and COVID-19

Cancer patients have shown to be at higher risk for contracting the virus likely from their immune dysregulation in setting of their malignancy and various treatments and remain at high risk for sustaining severe outcomes [19, 42]. Per the WHO Joint Mission Report, the CFR for cancer patients (7.6%) was higher than the overall CFR for 55,924 COVID-19 patients in China [19•]. Reports from Italy and Washington also support that cancer patients had similar findings [14, 22, 23]. However, the specific type of cancer was neither reported in these studies nor linked to specific outcome. Several studies have indicated that cancer patients trend toward having more severe disease. A case series of patients admitted to New York hospitals identified that 5.9% patients had cancer and 43% of these patients required invasive ventilation for support [24]. A prospective cohort study of following 1590 COVID-19 patients in China demonstrated that of the 18 patients with cancer, lung cancer was the most frequently incurred malignancy. Moreover, in this cohort, history of cancer was associated with a higher risk of severe events (ICU admission requiring ventilation or death) and faster progression to severe events (median time for cancer patients 13 days vs. 43 days for non-cancer patients). Those with a history of chemotherapy or surgery in the past month had a higher risk for severe events even when adjusted for other risk factors including age (OR 5.34, 95% CI 1.80–16.18; $p < 0.005$). Of the 18 described in the Wuhan group, roughly 10% received chemotherapy and 7.1% targeted therapy. However, age alone was also an independent risk factor for severe events in the cancer group of patients. Those with history of lung cancer versus other cancer types did not predict a more severe outcome [42].

Another study from China evaluating all cancer patients admitted to Zhongnan Hospital of Wuhan University determined that cancer patients had a 0.79% infection rate compared with the overall city's 0.37% infection rate. A total of 12 patients were affected, 58.3% had non-small cell lung carcinoma (NSCLC) with approximately 41.7% were undergoing treatment with chemotherapy and resulting mortality rate as of March 10, 2020, being 25%. Additionally, NSCLC patients that were greater than age 60 had a higher incidence of COVID-19 compared with younger patients with NSCLC [43•]. These findings are further corroborated by a study that examined all 28 cancer patients admitted to 3 hospitals in China. Lung cancer was the most common cancer type among these patients (25%). Diabetes (14.3%) and chronic cardiovascular and cerebrovascular disease (14.3%) were the most common comorbidities listed. Clinical factors that significantly predicted worse outcomes in this group of patients included age, patchy consolidation on imaging, and receipt of anti-tumor treatment in the last 14 days [44]. These studies suggest that patients with cancer are at higher risk for COVID-19, and those with older age and cancer are at an even higher risk for poor outcomes. Lung cancer has been reported to be more common in these studies, but the total sample size of cancer patients remains too low to draw any meaningful conclusions on which malignancy may be most associated with severity of COVID-19 infections. Lastly, although having recent anti-cancer treatment increases the risk for severe outcomes, it is unclear which anti-cancer agents are associated with higher risk for acquiring COVID-19 infection, severity of infection, and/or mortality. Table 1 demonstrates a literature review of studies published until April 26, 2020 that identify the prevalence of cancer among COVID-19 infected patients.

Although no formal studies have assessed the direct impact of COVID-19 on cardio-oncology patients, a study has shown that both CVD patients and cancer patients do have an increased risk for cardiac injury which in of itself is an independent predictor of mortality [28]. Additionally, since the data suggests that CVD and cancer are potentially independent risk factors for virus acquisition and severe outcomes, it is reasonable to assume that if patients have both risk factors, then they may posit higher cumulative risk. There is also concern that cancer treatments may induce disease states such as hypertension and cardiovascular disease—both frequently associated risk factors for worse outcomes in COVID-19 patients [19•]. An example of such a clinical scenario could involve metastatic renal carcinoma patients who develop hypertension from anti-VEGF tyrosine kinase therapy, or cardiomyopathy from anti-HER2, and anthracycline therapy of breast cancer [45, 46]. However, the definition of "cardiovascular disease" that patients have been classified with in these studies is not always clearly delineated; thus, risk stratification of these patients in regard to COVID-19 risk requires more refined investigation and long-term follow-up regarding outcomes.

The elevated risk that cancer patients face during the COVID-19 pandemic poses many challenges. Some of these include providing ongoing cancer treatments especially if patients are undergoing curative therapy, enrolling patients into experimental drug trials, continuing close cardiotoxicity surveillance, and providing treatments to patients who have an optimal window of adequate functional status [47, 48]. Given concerns for hospital-acquired COVID-19 infections, this additional risk factor can impact continuation of therapy or

Table 1 COVID-19 Studies with cancer and cardiovascular disease epidemiology (through April 22, 2020)

Author	Country	Clinical setting	Number of institutions	Date of publication	Number of patients in study with COVID-19	Cancer[a] *n* (%)	Predominant cancer *n* (%)	HTN *n* (%)	CVD[b] *n* (%)	Mortality in cancer patients *n* (%)
Wu C, et al.	China	Hospitalized	1	March 13,2020	201	1(0.5)	Not specified	39 (19.4)	8 (4.0)	Not reported
Guo T, et al.	China	Hospitalized	1	March 27, 2020	187	13(7)	Not specified	61 (32.6)	29 (15.5)	Not reported
Zhou F, et al.	China	Hospitalized	2	March 9, 2020	191	2(1)	Not specified	58 (30.4)	15 (8)	0
Shi S, et al.	China	Hospitalized	1	March 25, 2020	416	9(2.2)	Not specified	127 (30.5)	61 (14.7)	Not reported
Liang W, et al.	China	Hospitalized	575	February 14, 2020	1590	18(1.1)	Lung - 5 (28)	Not reported	Not reported	Not reported
Onder G, et al.	Italy	Not specified	Not specified	March 23, 2020	355	72 (20.3)	Not specified	Not specified	117 (33)	100 (Study only reviewed cases that died)
Grasselli G, et al.[c]	Italy	Intensive care units	72	April 6, 2020	1043	81(8)	Not specified	509 (49)	223 (21)	Not reported
McMichael T, et al.	USA	Long-term care facility	1	March 27, 2020	167	15(9)	Not specified	74 (44.3)	68 (40.7)	Not reported
Goyal P, et al.	USA	Hospitalized	2	April 17, 2020	393	23(5.9)	Not specified	197 (50.1)	82 (21)	Not reported
Richardson, et al.	USA	Hospitalized	17	April 22, 2020	5700	320(6)	Not specified	3026 (56.6)[c]	966 (18)[d]	Not reported

[a] Cancer was defined in studies as either cancer, tumor, malignant neoplasm, or carcinoma. There was variability in whether cancer was active or in remission

[b] There were various definitions utilized for cardiovascular disease across all studies not limited to cardiomyopathy, coronary artery disease, and ischemic heart disease

[c,d] History regarding these comorbidities may not have been available for all patients enrolled in the study; hence, percentage does not correlate the with total number of patients in the study

HTN hypertension, *CVD* cardiovascular disease

initiation of regimens for aggressive malignancy that require hospitalization for closer monitoring [43, 47, 48]. Moreover, patients that may rely on drugs or stem cell donations for treatment may necessitate access to unique global sources and are rendered at a disadvantage due to travel restrictions and quarantine policies [49]. In response to these climactic changes, The National Comprehensive Cancer Network and National Cancer Institute have provided guidance to providers on providing care to oncology patients, resource allocation, and managing drug trials [50].

Healthcare-Related Exposure

As referenced above, a unique source of transmission in the cardio-oncology population is healthcare exposure. Healthcare-related exposure is being given greater importance as an attributable vector. Past experience with SARS-CoV demonstrated that the virus can be transmitted via aerosolizing procedures, such as endotracheal intubation, placing anesthesiologists at great risk for acquiring the infection [51, 52]. During the outbreak of COVID-19, implementation of infection control and establishment of safe personal protective equipment (PPE) remained and remains key. Intense aerosolizing procedures, such as emergent intubations, cardiopulmonary resuscitation, or bronchoscopies, should require stringent PPE to maintain adequate protection. Despite attempting to roll out these precautions, review of the WHO-China Joint Mission on COVID confirmed that nearly 3387 healthcare workers tested positive for COVID-19 infection, resulting in 22 deaths [53]. While initial understanding of the pathogen remained poor, long-time exposure to large-scale infected patients directly increased the risk of infection for healthcare workers and risk of being an asymptomatic carrier [54]. Fatigue, lack of available healthcare workers, limited resources, and intensity of response led to several healthcare workers succumbing to infection. Though unsettling, it is doubly important to place value on healthcare-related exposure as an established risk factor when dealing with cancer patients with pre-existing risk factors.

Coronavirus Structure and Foundation for Treatment Strategies

Coronaviruses are a large collection of single-stranded enveloped, non-segmented positive-sense RNA viruses that fall within the family of Coronaviridae and the order nidovirales [55]. Six specific coronaviruses have been identified as human-susceptible, among which alpha and beta subsets demonstrated lower pathogenicity and caused milder respiratory symptoms respectively. Genomic analysis of SARS-COV-2 showcased 96.2% shared sequencing with bat CoV

RATG13, thus positing that the bat variant served as the natural host of the virus [4]. However, the severe acute syndromes belong to the B-genus, with envelope-anchored spike protein mediating viral entry into host cells by first binding to a host receptor and subsequently fusing membranes [56]. The COVID-19 infection has a well-defined capsular structure with 14 binding residues, with 8 conserved from prior SARS-CoV infections. The viral genome contains several open reading frames, with majority of the viral RNA-encoding non-structural proteins (NSPs) that play a role in the pathogenesis of disease. Recent research studies focusing on NSP2 and NSP3 demonstrated an in vivo role that these subunits may play in infectious capability and differentiation of COVID-19 [57].

Mechanistically, COVID-19 is found to be linked to Angiotensin-Converting Enzyme 2, a membrane-bound aminopeptidase highly expressed in lung, intestinal, and heart tissue. Beyond being implicated in hypertension and diabetes, ACE-2 further functions as a receptor for coronaviruses [58•]. COVID-19 translocates into lung parenchyma via damaging epithelial cells, resulting in respiratory symptoms, with symptom severity worsening in patients with cardiovascular disease. ACE2 secretion is noted to be elevated in CVD patients due to increased reliance on angiotensin-receptor blockers for management of hypertension. At the receptor level, the receptor-binding domain of SARS-CoV spike protein specifically recognizes ACE2, which contributes to both cross-species and human-to-human transmission [59, 60]. Documented variability is demonstrated between various strains of SARS-CoV in terms of binding affinity and viral attachment, which is preserved across both humans and animal models of disease transmission [61]. The preserved domains across MERS/SARS may contribute to the heightened inflammatory response and cytokine milieu that leads to severe pneumonia [62].

On a molecular level, specific associations and descriptive characteristics of the patients identified cytokine abnormalities in ICU-level patients versus non-ICU–level admissions. Compared with non-ICU patients, ICU patients had higher plasma levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-a [63•]. Though this cytokine thumbprint is being linked to COVID-19 infection, ARDS similarly showcases elevations in inflammatory markers, questioning origin and role of virally mediated hyperinflammation [64].

Potential Overlapping Mechanisms in COVID-19 and Cardiovascular Disease and Anti-cancer Treatments

Multiple treatments are being assessed in various trials including antivirals, anti-inflammatories, immunotherapies, and cardiovascular medications for the treatment of COVID-19. Although some these therapies have potential to provide benefit, there are numerous potential cardiac toxicities and drug-drug interactions that may be harmful to cardio-oncology patients, which is critically relevant since a high percentage of COVID-19 patients have cardiovascular comorbidities [65–68]. An appraisal of these agents and their potential cardiotoxicities—of which there is no current proven efficacy at this time—is beyond the scope of this review. However, some agents are actively used in the treatment of cardiovascular disease and/or cancer-related conditions, and the unique disease states of the cardio-oncology population may yield insights into the mechanisms of COVID-19 pathophysiology.

For instance, the idea of using medications that have already been well-studied and target host responses by boosting host immunity was in discussion during prior significant outbreaks and epidemics including Ebola and influenza [69, 70]. ACE inhibitors (ACEI), angiotensin-receptor blockers (ARB), and statins are of particular importance during this current pandemic.

There has been a theoretical uncertainty in regard to the safety of ACEI/ARB use in patients with COVID-19 based on the ACE2 viral entry mechanism [71, 72]. The virus gains cellular entry by attaching to the ACE2 receptor [72]. ACE2 expression and activity have shown to be increased in by ACEI/ARB use [73]. Although there is theoretical risk that ACE2 upregulation may increase the susceptibility of infection, other conflicting evidence indicates that upregulation of ACE2 in fact has a more protective effect. Studies in mouse models have shown that ACE2 is protective against acute lung injury and blocking the renin-angiotensin-aldosterone system pathway decreases lung failure [74, 75]. Based on the review of the literature to date, the Heart Failure Society of America recommends continuation of ACEI/ARB use for patients that are prescribed them for heart failure, hypertension, and ischemic disease [76••]. Abrupt discontinuation of medications is not recommended and can worsen clinical stability especially in patients with existing cardiovascular conditions [71].

Additionally, statins have long been shown to have anti-inflammatory properties through multiple studies. For instance, simvastatin has been shown to decrease pulmonary inflammation in human subjects [77]. Although the benefits for cardiovascular patients have been numerous from a lipid lower standpoint, it is important to note that the ability of statins to decrease inflammation also improves mortality [78]. A retrospective analysis of patients from the Veterans Administration showed that statin use, ACEI use, or ARB use each independently improved 30 day mortality of patients > 65 years old who were hospitalized for pneumonia [79]. However, in the era of the COVID-19 pandemic, studies are needed to evaluate its role in COVID-19–related illness.

Although cancer patients have been considered immunosuppressed as a result of their underlying malignancy and cytoreduction therapies, patients that undergo immunotherapy

including immune checkpoint inhibitors (ICIs) or CAR-T cell therapy may have different immuno-physiology that responds to COVID-19 differently [80]. Anti-PD-1/PD-L1 and anti-CTLA-4 ICIs have been approved by the FDA for use in a variety of cancers. These drugs primarily work by enhancing a patient's immune response to tumors through inhibiting negative regulators of T cell function [81]. CAR-T cell therapy involves reprogramming a patient's own T cells to directly target their specific tumor [82].

An adverse effect that can occur with either anti-PD-1 therapy or CAR-T cell therapy involves cytokine release syndrome (CRS) which is similar to the cytokine storm phenomenon that occurs in patients with severe COVID-19 [80, 82, 83]. CRS occurs as a result of hyperimmune activation in response to tumor death, whereas cytokine storm in COVID-19 patients occurs as a result of T cell hyperactivation from immune dysregulation [80, 84]. Similar markers are elevated in both phenomena, including IL-6, TNF-alpha, and IFN-λ, of which IL-6 has also been shown to be a mortality predictor in COVID-19 patients [27, 64, 80, 84]. COVID-19 patients that develop cytokine storm syndrome are at risk of developing ARDS and multi-organ failure [84, 85]. Immunosuppression with tocilizumab, an IL-6 inhibitor, is used to treat CRS associated with CAR-T cell therapy [80, 86]. Additionally, tocilizumab immunosuppression is used to treat immune-related adverse events (irAEs) from PD-1 inhibitors that are refractory to steroids; irAEs also occur as a result of hyperimmune activation [80, 87]. Moreover, the cytokine storm observed with COVID-19 has also been noted to be similar to that of secondary hemophagocytic lymphohistiocytosis (HLH) which is also treated with immunosuppression [64].

Current trials are underway with using tocilizumab and sarilumab (another IL-6 inhibitor) to treat COVID-19 patients [88–90]. Although immunotherapy may be thought to reinstate a cancer patient's immunocompetence, there is potential for synergy from CRS and the COVID-19 cytokine storm pathogenesis which can further worsen a patient's mortality risk. Further unfavorable synergy between ICI immune-related adverse events (irAEs) can also be seen potentially between the pneumonitis that ICIs can cause and the lung involvement with COVID-19 [80]. Pneumonitis occurs in < 10% of patients being treated with anti-CTLA-4 and anti-PD-1 ICIs and is potentially life-threatening [81]. Therefore, if combined with lung injury from COVID-19, there is a theoretical potential for poor outcomes.

There are potential cancer treatments that may counteract the pathogenesis of COVID-19, such as CCR5 treatments and tyrosine kinase inhibitors (TKIs) [91–93]. The CCR5 receptor is a G protein–coupled receptor selectively expressed on macrophages, T cells, eosinophils, dendritic cells, and microglia and is implicated in chemokine-mediated signaling [94]. This receptor has historically been targeted for HIV antiviral therapy, in the setting of disrupting viral entry, specifically through small molecule inhibition with maraviroc and vicriviroc, and monoclonal antibody treatment with leronlimab [95]. Moreover, multiple cancers have been shown to overexpress CCR5 which has been linked to a cancer's metastatic potential. CCR5 therapies are currently being studied in metastatic colorectal and breast cancers [91, 94]. Due to its immune system restorative properties, leronlimab is being investigated for compassionate use in the treatment of COVID-19 patients [96, 97]. Studies examining receptor blockade in leronlimab preliminarily have shown decreases in IL-6, restoration of CD4/CD8 ratios, and reduction in overall COVID-19 viremia [98]. These collective findings suggest possible therapeutic role in establishing immune reconstitution in patients that are critically ill and may provide dual benefit in patients with shared cancer diagnoses.

TKIs like sunitinib and erlotinib that specifically inhibit AAK1, a protein regulator that allows passage of the virus into cells, have theorized utility [92]. Sunitinib is an anti-vascular endothelial growth factor (VEGF) TKI which is used in first-line for treatment of advanced renal cell carcinoma [99]. Erlotinib is an anti-epidermal growth factor receptor (EGFR) TKI which is used in first-line treatment for metastatic EGFR-mutant non-small cell lung cancer [100]. Both these TKIs have shown to reduce the infectivity of Dengue and Ebola through in vivo studies with murine models which showed decreased viremia and mortality with treatments. Moreover, in vitro studies in cultured cells and hepatitis C in this same study showed that use of these TKIs reduced intracellular trafficking and inhibited viral entry [101]. However, the high doses required to achieve this effect may potentially exhibit harm to patients [92, 93]. Regardless, there is potential for cancer patients receiving these therapies to achieve dual benefit as referenced before, but warrant further investigation. Further studies are warranted in tracking the outcomes of cancer patients with COVID-19 and the type of treatments they received.

Role for Anticoagulation in COVID-19

Patients with underlying hypertension, diabetes, and cancer are at higher risk for developing thrombotic events. Coagulopathy in coronavirus infection is now associated with high mortality and manifests with high D-dimer elevations [102]. Lung inflammation and impaired pulmonary gas exchange contributes to cytokine storm, which leads to spike in D-dimer and pro-inflammatory response, with impaired endothelial function. Tissue factor (TF), expressed by tumor cells, contributes to thrombosis, metastasis, tumor growth, and tumor angiogenesis, leading to release of pro-coagulant microparticles into the circulation and triggering thromboembolism in patients with cancer [103]. TF on circulating tumor cells leads to coating of cells with fibrin that traps them within

microvasculature, thereby contributing to worsening endothelial dysfunction [104]. In patients with pre-existing cancer diagnoses, shared COVID infection as well as hypoxia places them at even greater risk of developing and incurring thrombotic events [105]. Early heparin initiation is posited to delay the spike in inflammatory biomarkers and may reduce contributions to pro-coagulopathic state [106]. A retrospective study from China examined 449 patients classified as having severe COVID-19 infection, of which 272 had one or more chronic underlying diseases, such as hypertension and heart disease. Patients were assigned to receive various forms of heparin, with those treated with heparin having a lower mortality rate (40% vs. 64.2%, $p = 0.029$) [107]. Data regarding initiation and choice of anticoagulation remains limited, and further randomized clinical trials are necessary to determine prophylactic and treatment strategies for cardio-oncology patients infected with COVID-19, as they represent a population with elevated theoretical risk for suffering from thromboembolic events.

Care of the Cardio-Oncology Patient in the COVID-19 Era

The COVID-19 pandemic has added a significant layer and complexity of how patient care is being delivered due to concerns of bidirectional transmission, with no protective algorithm widely in place to dictate ongoing management of cancer patients [108••]. Initiating cancer treatments, such as targeted immunotherapies and chemotherapy, require special consideration in the COVID-19 era. As previously described, compromised immune systems render patients with cancer at higher risk for acquiring COVID-19 infection and the sequelae that may ensue. Cancer treatment centers and cardio-oncologists must now consider not only the patient but also the integral healthcare workers who are regularly interfacing with high-risk exposures. Devising strategies to ensure robust testing services and clearance mechanisms to protect patient and healthcare personnel is one of many methods now employed to continue ongoing treatments [48, 109, 110]. Though there are no clear evidence-based modifications in systems of care to reduce transmission risk while balancing high-standard cardio-oncology care, various strategies are proposed (Table 2). Life-prolonging surgeries and procedures can slowly be pursued and continued, although the risks of delaying any such advanced treatments—including bone marrow transplantation and chimeric antigen receptor treatment—need to be weighed carefully. COVID-19 screening and testing prior to these surgeries/procedures, while not infallible, should be considered if available due to rising concern for asymptomatic carriers. Following completing anti-cancer treatments, patients may additionally benefit from receiving immune system restorative treatments, such as filgastrim.

Additionally, the transition to telemedicine to conduct interval cardiovascular and oncologic appointments can potentially protect patients from unnecessarily harmful nosocomial exposures [111, 112]. Certain chronic conditions (i.e., hypertension, stable/compensated congestive heart failure) may not necessarily require a face-to-face visit, whereas highly symptomatic patients should still be seen in the cardio-oncology clinic, preferably on the same day as their cancer outpatient visits. Deferring primary prevention assessments, for example, cholesterol monitoring, unless otherwise indicated can augment protective mechanisms in place. Cardiovascular-related blood draws, if necessary, should be coincided with cancer-related treatments.

In addition, the specter of cardiotoxicity related to certain cancer treatments also requires a reexamination of risk and benefit with respect to frequent cardiac monitoring due to previously mentioned concerns. Peri-chemotherapeutic events and development of cardiomyopathy, ischemia, and life-threatening arrhythmias are further worsened by simultaneous COVID infection. Reducing reliance on frequent cardiac imaging in otherwise asymptomatic patients and providing in-mail ambulatory rhythm monitors for patients symptomatic with possible arrhythmias will further assist in mitigating exposure risk. Limited cardiac-imaging protocols (i.e., focused just on ventricular function and/or pericardial disease) if necessary for symptomatic patients or those necessitating cardiotoxicity surveillance can also be devised to reduce exposure time in the healthcare setting. In addition, for patients at low risk of cardiotoxicity and/or with prior serial-documented normal cardiac function, it can be considered to defer serial cardiac imaging in certain treatments (i.e., anti-HER2 without anthracyclines, BRAF-MEK treatments), in multidisciplinary discussions with oncology if the patient is asymptomatic [113].

Conclusion

The COVID-19 pandemic has caused an unprecedented global impact on healthcare delivery, and its trajectory continues to remain unclear. Vulnerable patient populations include those with cardiovascular disease and cancer, and the cardio-oncology patient, having possessed both these risk factors, may unfortunately be at significantly increased risk of experiencing worse outcomes related to COVID-19 infection. As of this writing, there are no known studies focusing on the cardio-oncology population, and there remain many opportunities to not only study the epidemiology of this unique but also significant group of patients. Clinical trials are ongoing, but rigorous, randomized high-quality science is warranted to study the efficacy of previously mentioned treatments; they also may potentially reveal critical mechanistic insights into COVID-19's pathophysiology, which overlap with cardiovascular and cancer disease states [114]. In addition, the abrupt

Table 2 Proposed special considerations of the cardio-oncology patient during the COVID-19 pandemic

Cardio-oncology aspect of care	Theoretical areas of concern	Proposed Strategies to Mitigate COVID-19 Exposure
Initiating/ongoing cancer treatments (i.e., chemotherapy, targeted therapies, immunotherapy, BMT, CAR-T), and timing of oncologic-related surgery	• Compromised immune systems induced by cancer treatments may make patient more susceptible to COVID-19 • Cancer treatments may require healthcare facility/inpatient stay exposing patient to asymptomatic carriers (i.e., HCW) • Delaying of potential critical, life-prolonging surgery as it may be deemed as "elective" • Ensuring COVID-19 testing adequacy by healthcare providers	• Implementation of universal PPE and social distancing during cancer treatments in outpatient/inpatient settings, and with family members/caretakers • Weighing risk-benefit of postponing/delaying timing of cancer treatments/surgery to minimize exposure to inpatient healthcare setting • Preoperative/procedural screening and testing for COVID-19 • Telemedicine for routine follow-up cardio-oncology/oncology visits unless clinically symptomatic • Research efforts investigating earlier utilization of immune system restorative measures post anti-tumor therapy • Consideration of delaying myeloablative therapies and immunotherapies for patients in clinical remission if possible • Consideration of minimizing surveillance/staging imaging during and after treatments
Cardiotoxicity experienced during cancer treatments (i.e., cardiomyopathy, arrhythmias, and ischemic events)	• Further delay of cancer treatments and cardio-oncology evaluation because of COVID-19 may increase cardiac and cancer-related comorbidity and mortality • Cardiac imaging and testing may cause further exposure to asymptomatic carriers	• Inpatient admission and evaluation as clinically indicated for severe symptoms • Telemedicine for patients who are asymptomatic or minimally symptomatic, or CVD risk factor modification (i.e., visits for HTN and/or dyslipidemia) • Preemptive aggressive treatment for suspected symptoms related to CAD, arrhythmias, or CHF and deferring of imaging unless clinically necessary • Mail ambulatory rhythm monitors to home to evaluate suspected/known arrhythmias
Cardiotoxicity surveillance in cancer patients during and after treatment	• Some cancer treatments (i.e., anti-HER2, BRAF-MEK treatments, clinical trials) require frequent surveillance of cardiac function (i.e., every 3 months) • Patients with known cardiotoxicity, or with known treatments that can cause long-term cardiotoxicity (i.e., anthracyclines, radiation) may not get timely surveillance imaging	• Minimize cardiac imaging to patients who are symptomatic • Multidisciplinary discussion with hematologist/oncologist about reducing frequency of cardiotoxicity screening, especially if prior serial testing unremarkable • Limited imaging protocols to evaluate LVEF to minimize acquisition time • Defer primary prevention assessment (i.e., dyslipidemia management) unless critical to care of patient • Telemedicine visits for patients who do not require face-to-face assessment for medical issues (i.e., blood pressure/lipid management/stable CHF) • Defer asymptomatic long-term cancer survivor surveillance (i.e., assessment of ventricular and valvular function) if no symptoms

BMT bone marrow transplantation, *CAR-T* chimeric antigen receptor therapy, *HCW* healthcare workers, *PPE* personal protective equipment, *CVD* cardiovascular disease, *CAD* coronary artery disease, *CHF* congestive heart failure, *LVEF* left ventricular ejection fraction

and possibly permanent alteration of cardiovascular and cancer systems of care—with the dramatic rise of telemedicine and other changes—to mitigate transmission risk in the COVID-19 era also warrants close study to evaluate clinical outcomes. Much remains unknown about how the pandemic will affect the cardio-oncology population and how they will be cared for, but what is certain is that ongoing, close multidisciplinary care and communication between the cardiac and cancer care providers of these patients remains more critical than ever in order to guarantee the best care possible.

Compliance with Ethical Standards

Conflict of Interest Ishan Asokan, Soniya V. Rabadia, and Eric H. Yang declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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