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The Novel Coronavirus Disease (COVID-19) Threat for Patients with Cardiovascular Disease and Cancer

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Abbreviations:
ACE-2: angiotensin-converting enzyme 2
ACEi: Angiotensin converting enzyme inhibitor
ARB: Angiotensin receptor blocker
CDC: Centers for Disease Control
Coronavirus disease 2019: COVID-19
CVD: Cardiovascular disease
MERS-CoV: Middle East respiratory syndrome coronavirus
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
WHO: World Health Organization

As the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread across the globe, millions of people may be affected (1,2). While knowledge regarding the complications and fatality rate associated with SARS-CoV-2 (COVID-19) infection is evolving, preliminary data from China suggests that patients with pre-existing comorbidities, particularly cardiovascular disease (CVD) and cancer may be among those at highest risk of not just acquiring the infection but also having worse outcomes (1-3). The risk of adverse outcomes may be even higher for those afflicted with a dual diagnosis, particularly the elderly. This is extremely concerning from a public health perspective since cancer and CVD are amongst the most prevalent diseases worldwide (4), and the impact of the current pandemic of coronavirus disease 2019 (COVID-19) could be devastating for these patients.

The World Health Organization (WHO) has recently declared COVID-19 a public health emergency of international concern (2). While COVID-19 caused by SARS-CoV-2 originated in Wuhan, Hubei province of China, it is spreading rapidly and efficiently (2). SARS-CoV-2 is a novel enveloped RNA beta-coronavirus, similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), pathogens responsible for the severe acute respiratory syndrome (SARS) outbreaks in 2002-03 in Guangdong Province, China and severe respiratory disease outbreaks in 2012 in the Middle East, respectively (5). Although there are phylogenetic similarities between the coronaviruses responsible for SARS and COVID-19, the transmission is exponential with COVID-19, and additionally, it can be transmitted by people who are just mildly ill or even asymptomatic leading to 10 times as many cases as SARS in a quarter of the time (2,5,6).

While our understanding about the risk of infection with SARS-CoV-2 and its impact is limited, we examine its interaction with the two most common disease entities: cancer and CVD.

Pre-existing Cancer and Cardiovascular Disease

Patients with cancer are typically at higher risk of infection due to compromised host defenses and the sequelae of antineoplastic treatment; namely leukopenia, disruption in barriers to infection, and shifts in microbial flora. The current COVID-19 pandemic is particularly concerning, given the potential of spread from asymptomatic carriers (1-3). A report from China suggests that among those confirmed infected with SARS-CoV-2, approximately 1% of patients had cancer (3): 5-fold higher than the general incidence of cancer in China (201.7/100,000 persons) (7).

A retrospective analysis of MERS-CoV infection has demonstrated that it was more likely to occur in patients with underlying CVD. In patients with MERS-CoV infection and severe symptoms, 50% had hypertension and diabetes and up to 30% had heart disease (6). In an early single center report describing hospitalized patients infected with pneumonia due to SARS-CoV-2, 40% had pre-existing CVD, particularly coronary artery disease (CAD) and cerebrovascular disease (3). Recent emerging data from China assessing a broader population with COVID-19 describe a lower overall rate of affected patients with underlying CAD (8%), but elderly patients with comorbidities, particularly hypertension (30%) and diabetes (19%), were more likely to be infected with SARS-CoV-2 (1,8).

Outcomes in Patients with Cancer and Cardiovascular Disease

In s small retrospective study, patients with a history of cancer infected with SARS-CoV-2 were older (63 versus 49 years), more likely to be current or former smokers, more likely to experience rapid breathing and had more abnormal lung CT scans than those without cancer. In a study of 1590 people with confirmed COVID-19 in China, 18 patients (1%) had a history of cancer, with lung cancer being most common. A greater proportion of patients with a history of

cancer had severe disease, defined as either admission to an intensive care unit for mechanical ventilation or death, compared to those without cancer (39% vs 8%, p=0.0003) (9). Among cancer patients, 3 out of 4 (75%) who had received recent chemotherapy or surgery developed severe disease compared with 6 of 14 (43%) not recently treated for cancer (odds ratio 5.34, 95% CI 1.80–16.18; p=0.0026), even after adjusting for other risk factors, including age, smoking history, and other comorbidities (9), suggesting potentially that recent antineoplastic therapy may impair immunity and impact the outcomes related to COVID-19. The mortality rate in this small study was also significantly higher in cancer patients: 5.6% compared to approximately 1% general COVID-19 related mortality (9). An updated WHO report demonstrates a similarly high mortality of 7.6% among patients with cancer (2). Data regarding the type of cancer or antineoplastic therapy is not available in these early reports; however, patients undergoing antineoplastic therapy and those with hematological malignancies and baseline lymphopenia theoretically may be at even higher risk for adverse consequences.

Early reports from China suggest that the COVID-19 mortality rate was highest among patients with CVD (13.2%) compared to other comorbidities, and was disproportionately higher for patients with cardiovascular risk factors such as diabetes (9.2%) and hypertension (8.4%) compared to around 1% for patients without such comorbidities (2,3).

Acute Cardiovascular Injury

Another coronavirus - MERS-CoV has previously been reported to cause acute myocarditis and heart failure (6). While yet unknown, the pathogenic similarities between MERS-CoV and SARS-CoV-2 make it plausible that similar cardiovascular complications may occur with COVID-19.

Many patients with COVID-19 experienced acute myocardial injury as evident by an increase in high-sensitivity cardiac troponin I levels (6). This could be secondary to direct cardiotoxicity or could represent type II myocardial injury in the context of supply-demand mismatch. Moreover, cardiac biomarker levels were significantly higher in patients admitted to the ICU and in non-survivors (<0.0001) (8), suggesting that cardiovascular complications might contribute to the severity of illness and adverse outcomes (6,8). A significant proportion of patients subsequently developed heart failure (23%). The first autopsy of a 53-year-old woman with chronic kidney disease from China demonstrated acute myocardial infarction (unpublished report). Similarly, various arrhythmias, particularly atrial fibrillation and cardiac arrest have been reported, likely precipitated by high cardio-metabolic demand (8).

Mechanism of Cardiovascular Injury

The mechanism of COVID-19-associated cardiovascular injury is not well understood; however, angiotensin-converting enzyme 2 (ACE-2) has been implicated (6,10). ACE-2 is widely expressed in the lungs and cardiovascular system and plays a vital role in the immune system. It is thought to play a critical role in the cardioprotective arm of the renin-angiotensin-aldosterone pathway.

ACE-2 serves as the cellular entry point for coronaviruses, including SARS-CoV and SARS-CoV-2 (10). The spike protein of these coronaviruses binds ACE-2, which is highly expressed in the lungs and heart, leading to not just respiratory but also potential cardiovascular damage (6). One potential explanation for the higher risk of acquiring infection, more severe symptoms and adverse outcomes with COVID-19 in patients with pre-existing CVD could be the higher than usual secretion of ACE-2 in these patients, although this is not clear (6).

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Another possible mechanism of cardiovascular injury includes excessive cytokine release triggered by an imbalanced response by type 1 and type 2 T-helper-cells, and hypoxemia secondary to respiratory dysfunction caused by COVID-19 (6).

Long-term Cardiovascular Effects

While we do not know the long-term cardiovascular impact of SARS-CoV-2 infection, a similar pathogen, SARS-CoV has been associated with dysregulation of lipid and glucose metabolism in long-term survivors. Given the structural similarities between these two pathogens, SARS-CoV-2 may also cause chronic damage to the cardiovascular system, however this remains to be seen (6).

Prevention

Awareness about local SARS-CoV2 cases and concerning symptoms, excellent hand hygiene, as well as avoidance of sick contacts and large gatherings are key measures to curb widespread infection. The WHO and Centers for Disease Control (CDC) have advised that every individual should frequently and thoroughly wash their hands, avoid touching their face and practice respiratory hygiene (11). While these are important for the entire population in affected areas, high-risk patients including, the elderly and those with pre-existing CVD and cancer should strictly follow these guidelines given that they may be more likely to acquire the infection and develop severe disease.

Management Considerations for COVID-19 in Patients with Cancer and Cardiovascular Disease

SARS-CoV-2 infection can cause severe acute respiratory illness due to lung involvement. However, myocardial damage caused by the infection can undoubtedly increase the

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difficulty and complexity of patient management, particularly in vulnerable patients already affected by both cancer and CVD.

Patients with COVID-19 symptoms, such as cough, fever, or shortness of breath in areas where COVID-19 has been reported, or those with a history of travel to highly affected regions (including, China, Italy, South Korea, Iran) or with exposure to a known case of COVID-19, should be evaluated (not necessarily in person if clinically stable) based on CDC guidelines to determine if they meet criteria to be a "Person Under Investigation (PUI)." This requires testing and quarantine as per the local and federal guidelines (11). It is important to note that although majority of adult patients with COVID-19 present with symptoms, patients with cancer may have weakened immune systems and hence may not have typical symptoms. The symptoms may be more subtle despite underlying complex and severe disease, and hence heightened awareness is required among patients and clinicians.

While majority of the patients present with respiratory symptoms, the National Health Commission of China reports that some patients present with cardiovascular symptoms such as heart palpitations and chest tightness rather than respiratory symptoms (6). Hence, any patient with suspicious symptoms in endemic regions should be evaluated to determine if they meet criteria as a PUI.

Hemodynamic monitoring and supportive care are the key components of management. While there is currently no evidence to support the widespread use of routine cardiac biomarker or echocardiographic monitoring, these might be considered in select high-risk patients with pre-existing CVD, a history of exposure to cardiotoxic antineoplastic therapy, and either significant cardiovascular symptoms or lack of improvement with usual care. There is evidence that patients with severe illness from COVID-19 have highly elevated inflammatory markers and suffer from

a cytokine storm with elevated IL-6; the use of agents that block IL-6 including tocilizumab and sarilumab to treat severely ill patients with CODIV-19 is an active area of investigation (12). Similarly, remedesivir, an investigational antiviral agent is also under study through a clinical trial for patients with COVID-19 in high-risk or severely ill patients (13).

Management Considerations for Cancer and Cardiovascular Disease in SARS-CoV-2 High Transmission Areas (Figure 2)

While patients with cancer and recent cancer therapy were more severely affected by COVID-19, there is thus far no guidance for patients in the United States to defer cancer treatment. As the landscape of COVID-19 continues to change rapidly, for patients with stable cancer in areas with high transmission of SARS-CoV-2, postponing antineoplastic therapy or elective surgery may need to be considered. This decision should be made on a case-by-case basis after careful discussion with the treating physicians, based not only on cancer type and status, but also considering the overall health of the patient and the type of antineoplastic therapy needed. For patients undergoing cancer therapy or with a recent history of stem-cell transplantation in areas of high transmission, it is reasonable to consider "self-quarantine" to avoid exposure. Also, as testing for SARS-CoV-2 becomes more widely available, close contacts of such high-risk patients should have a low threshold to "self-quarantine" or obtain testing if they have any concerning symptoms.

Due to similarities between respiratory and cardiac symptoms, clinicians should maintain a high suspicion for acute myocardial infarction or heart failure in patients with COVID-19 to avoid underdiagnosis of CVD. Although the management of acute cardiovascular complications does not necessarily change for patients with or without COVID-19, in areas of high transmission, high suspicion should be maintained and patients with suggestive symptoms or

known exposure should be isolated promptly, even without a confirmatory test to minimize the spread of the infection among CV team members and other patients.

Furthermore, to reduce the rate of transmission among patients with stable cancer and CVD, substituting in-person visits with telehealth visits and deferring any non-urgent procedures should be strongly considered (14).

Many patients with pre-existing CVD, hypertension, or diabetes, as well as patients with cancer undergoing cardiotoxic chemotherapy, may be on an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Whether treatment with an ACEi or ARB increases the risk associated with COVID-19 is controversial and speculative at this time (6).

Future Directions

Cancer and CVD are complex diseases and represent the two most common causes of morbidity and mortality worldwide. The COVID-19 pandemic and its impact on patients with CVD as well as cancer has once again proven that these patients are particularly vulnerable. Not only are these patients potentially at higher risk of acquiring infection, but depressed immunity in patients with cancer and poor baseline physiologic reserve combined with direct cardiotoxicity in patients with CVD, increases the likelihood of severe disease and adverse outcomes. As a community, we need to pay close attention to this growing patient population, particularly in such times of increased susceptibility.

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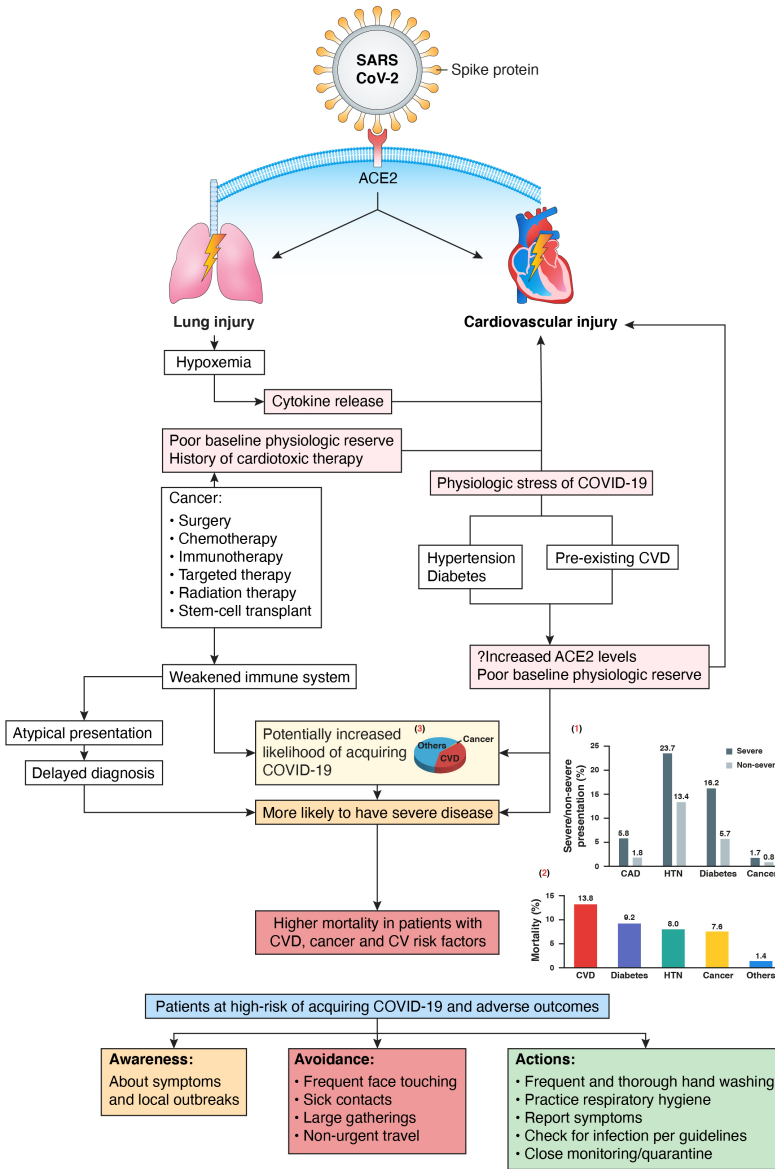
Figure Legends

Figure 1. The potential mechanism of COVID-19 associated cardiovascular injury and its impact on patients with cancer and cardiovascular disease

This figure demonstrates that patients with cancer, cardiovascular disease and certain cardiovascular risk factors are at increased risk of acquiring COVID-19 and for developing adverse outcomes. The graphs in the figure are based on data from 3 studies (1-3).

ACE2: angiotensin converting enzyme-2 receptor; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CAD: coronary artery disease; COVID-19: Coronavirus disease 2019; CVD: cardiovascular disease; HTN: hypertension; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2.

Figure 2. Proposed management pathway for patients with cancer and CVD in SARS-CoV-2 high transmission areas

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CDC: Center for Disease Control; CVD: cardiovascular disease; COVID-19: coronavirus disease-2019; SOB: shortness of breath; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2.

SARS CoV-2 — Spike protein

ACE2

Lung injury

Cardiovascular injury

Hypoxemia

Cytokine release

Poor baseline physiologic reserve
History of cardiotoxic therapy

Physiologic stress of COVID-19

Cancer:
• Surgery
• Chemotherapy
• Immunotherapy
• Targeted therapy
• Radiation therapy
• Stem-cell transplant

Hypertension
Diabetes

Pre-existing CVD

?Increased ACE2 levels
Poor baseline physiologic reserve

Weakened immune system

Atypical presentation

Delayed diagnosis

Potentially increased (3)
likelihood of acquiring
COVID-19

Others Cancer
CVD

(1)

More likely to have severe disease

Higher mortality in patients with
CVD, cancer and CV risk factors

(2)

Patients at high-risk of acquiring COVID-19 and adverse outcomes

Awareness:
About symptoms
and local outbreaks

Avoidance:
• Frequent face touching
• Sick contacts
• Large gatherings
• Non-urgent travel

Actions:
• Frequent and thorough hand washing
• Practice respiratory hygiene
• Report symptoms
• Check for infection per guidelines
• Close monitoring/quarantine

(1) Severe/non-severe presentation (%) — Severe, Non-severe
CAD 5.8 1.8
HTN 23.7 13.4
Diabetes 16.2 5.7
Cancer 1.7 0.8

(2) Mortality (%)
CVD 13.8
Diabetes 9.2
HTN 8.0
Cancer 7.6
Others 1.4

```mermaid
SARS-CoV-2 High Transmission Area
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SARS-CoV-2 High Transmission Area

Patient with cancer/CVD presenting with sore throat, cough, fever, myalgias, SOB or atypical CV symptoms

Patient with Cancer

Patient with CVD

- Suspect COVID-19 and promptly isolate the patient
- Test as per CDC guidelines

- Consider Telehealth visits for stable patients
- Continue anti-neoplastic therapy after discussing risks/benefits with clinician
- Patient education: Need for heightened awareness and precautions
- For patients undergoing antineoplastic therapy or recent SCT, consider "self-quarantine"
- Low threshold for "self-quarantine" and COVID-19 testing for close contact of high-risk cancer patients

Active CV Symptoms

Stable CVD

- Hemodynamic monitoring
- Supportive care
- Consider cardiac biomarkers and echocardiogram in high-risk patients with pre-existing CVD, cardiotoxic drug exposure,CV symptoms, and/or failure to improve with usual care
- Careful monitoring of patients with cardiomyopathy/HF who need fluid resuscitation

- If any suspicious symptoms or exposure, isolate the patient to minimize the exposure to other patients and CV team and test as per CDC guidelines
- Management of CVD per guidelines

- Consider Telehealth visits
- Consider postponing elective procedures
- Educate about risk of COVID-19 and precautions

Could consider investigational therapy for severely ill patients
- Tocilizumab (IL-6 monoclonal antibody) (12)
- remdesivir (investigational anti-viral agent under clinical trial) (13)