SARS-CoV-2 Infection and Cardioncology

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The coronavirus disease-2019 (COVID-19) is a highly transmissible viral illness caused by SARS-CoV-2, which has been defined by the World Health Organization as a pandemic, considering its remarkable transmission speed worldwide. SARS-CoV-2 interacts with angiotensin-converting enzyme 2 and TMPRSS2, which is a serine protease both expressed in lungs, the gastro-intestinal tract, and cardiac myocytes. Patients with COVID-19 experienced adverse cardiac events (hypertension, venous thromboembolism, arrhythmia, myocardial injury, fulminant myocarditis), and patients with previous cardiovascular disease have a higher risk of death. Cancer patients are extremely vulnerable with a high risk of viral infection and more negative prognosis than healthy people, and the magnitude of effects depends on the type of cancer, recent chemotherapy, radiotherapy, or surgery and other concomitant comorbidities (diabetes, cardiovascular diseases, metabolic syndrome). Patients with active cancer or those treated with cardiotoxic therapies may have heart damages exacerbated by SARS-CoV-2 infection than non-cancer patients.

SARS-CoV-2 Cardioncology Cardiometabolic Risk Factors

1. Introduction

In December 2019, a previously unknown coronavirus called Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) [1] caused severe acute respiratory syndrome in Whuan, the capital of Hubei, in China. In March 2020, the World Health Organization (WHO) defined the SARS-CoV-2 infection as a pandemic, due to its high rate of virulence and propagation in the world, which could potentially affect millions of people [2]. The full spectrum of the disease, termed coronavirus disease-2019 (COVID-19), ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death. To 28 October 2020, the virus spread to over 150 countries and affected more than 44 million individuals, causing over one million deaths. Coronaviruses are a large family of zoonotic, enveloped, and non-segmented RNA-based viruses, which cause illness ranging from common cold to severe respiratory diseases [3][4]. Other similar coronavirus-related infections in humans are Severe Acute Respiratory Syndrome (SARS-Cov) [5] and Middle East respiratory syndrome-related coronavirus (MERS-Cov) [6]. The mortality rate for 10,000 total cases were 10 and 37% for SARS-Cov and MERS-Cov, respectively [6][7]. Notably, patients affected by SARS-Cov and MERS-Cov had cardiovascular complications such as myocardial infarction and fulminant myocarditis [8]. SARS-CoV-2 infection causes multiorgan damages involving lungs and the cardiovascular system [9] and patients with chronic diseases such as cancer, hypertension, diabetes, cardiovascular diseases, liver steatosis, asthmatic bronchitis, and chronic inflammatory diseases are particularly vulnerable [10][11][12].

Cardiovascular diseases such as ischemic heart disease, stroke, heart failure, and peripheral arterial disease are the leading cause of global mortality [13]. In 2017, cardiovascular diseases caused an estimated 17.8 million deaths worldwide [13]. Improvements in cancer survival in the past few decades have resulted in a large and growing population of long-term cancer survivors; about half of patients diagnosed with cancer in high-income settings are now expected to survive for 10 years or longer [14]. The increase in survival is associated with a high risk of cardiovascular diseases related to anticancer therapies. The cardiotoxic effects of chemotherapy, radiotherapy, and immune checkpoint inhibitors expose cancer survivors to high cardiac and vascular vulnerability [14]. Very recent data indicate that patients with underlying cardiovascular diseases or cancer have a high risk of SARS-CoV-2 infection and a poorer prognosis than healthy people [9].

Figure 1. Cardiovascular adverse outcomes in patients with cancer during Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection are exacerbated by four interrelated risk factors: cancer itself, which causes immunosuppressive effects; cardiotoxic, pro-fibrotic, and pro-inflammatory anticancer therapies; history of cardiovascular diseases (hypertension, coronary heart disease, or diabetes); direct cardiac effects of SARS-CoV-2 infection.

2. Cardiovascular Outcomes in Non-Cancer Patients with COVID-19

Reports suggest that SARS-CoV-2 and MERS-CoV could have the same effects in humans with similar multiorgan damages leading to cardiovascular adverse events (more frequently heart failure and myocarditis) and severe pneumonia [9]. In Figure 2, we summarized the risk and prognostic factors in COVID-19 and the most frequent seen cardiovascular adverse events. In brief, risk factors of SARS-CoV-2 infection are active cancer, previous cardiotoxic anticancer therapies, metabolic syndrome, prior cardiovascular diseases, type 2 diabetes mellitus, hypertension, coagulopathy, shock, smoke, low or no physical activity, gene polymorphism of ectoenzyme

angiotensin-converting enzyme 2 (ACE2). Prognostic factors of SARS-CoV-2 infection are d-Dimer greater than 1 µg/mL, older age, high Sequential Organ Failure Assessment score (also called sepsis-related organ failure assessment score, involving the health status of respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems), high levels of high-sensitivity cardiac troponin I, lactate dehydrogenase, and interleukin-6 as well as low levels of lymphocytes (lymphopenia) [15]. Patients with COVID-19 have multiple cardiovascular adverse outcomes involving fulminant myocarditis, venous thromboembolism, hypertension, arrhythmia, heart failure, cardiogenic shock, and acute coronary syndrome [1][9].

In China, 12% of patients without underlying cardiovascular diseases experienced heart damages with increased levels of cardiac troponin levels and d-dimer or cardiac arrest during hospitalization for COVID-19 [1]; it was the first evidence of extra-pulmonary effects of SARS-CoV-2 in humans. Moreover, high levels of pro-inflammatory markers were seen in these patients, confirming the inflammatory nature of the coronavirus-associated clinical outcomes [1]. Another evidence of cardiovascular effects of SARS-CoV-2 infection was described by Chen et al., where 150 patients with COVID-19 admitted to Intensive Care Units (ICU) correlated with multiple clinical factors i.e., older age, high levels of hypersensitive C-reactive protein (hs-CRP), serum creatinine, NT-proBNP, and cTnI, as well as a history of hypertension and coronary heart diseases [10]. Chen et al. clearly demonstrated a correlation between SARS-CoV-2 and heart, and they concluded that two independent determinants of poor prognosis in COVID-19 patients were the past medical history of coronary heart disease and increased levels of cardiac troponin-I [16]. Another study on 138 patients with COVID-19 demonstrated that 16.7% of total patients and 44.4% of ICU patients developed arrhythmia, respectively, and 7.2% of total patients experienced acute cardiac injury in addition to other COVID-19 related complications. Moreover, 58% of patients had hypertension and 25% had heart diseases [17]. Indeed, ICU patients had higher biomarkers of myocardial injury compared to non-ICU patients (increases in 30% of median creatine kinase (CK)- myocardial band (MB) and 60% of hypersensitive circulating troponin levels ($p < 0.001$; $p = 0.004$, respectively) [17]. In another study [1] on 41 patients with COVID-19, Huang et al. demonstrated that 12.2% of patients developed acute cardiac injury with increased levels of high-sensitivity cardiac troponin I (hs-cTnI) and 80% of them were admitted to the ICU and had hypertension with a mean systolic blood pressure of 145 mmHg (19% more than non-ICU COVID-19 patients, $p < 0.001$) [1].

Figure 2. A representative scheme of the general cardio-metabolic risk factors, prognostic factors involved in coronavirus disease-2019 (COVID-19), and cardiovascular outcomes.

3. Non-Pharmacological Strategies to Reduce Cardiovascular Events in Cancer Patients with COVID-19

A proper management of preventive measures should be promoted in cancer patients, considering their systemic immunosuppressive state and cardiovascular vulnerability [18][19][20].

(1) First of all, cancer patients should be stimulated to perform daily physical activity, compatibly with their state of health, following WHO recommendations [21]. Cancer survivors doing daily physical exercises reduced cancer mortality by 27% compared with sedentary patients [22]. An appropriate physical activity reduced cardio-metabolic comorbidities in cancer patients and inflammation markers involved in heart failure and VTE [23].

(2) Patients with cancer should follow World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations [23]. Briefly, WCRF/AICR principles are:

-Reduce total body fat, especially visceral fat; pay attention to body weight;

-Do daily exercise, at any time of the day; reduce the time spent on television;

-Limit consumption of energy-dense foods and avoid sugary drinks;

-Eat mostly foods of plant origin and follow a diet rich in whole grains, vegetables (non-starchy), fruit, and legumes;

-Limit the consumption of red meats (beef, pork, sheep), cured meats, and preserved meats;

-Limit alcohol consumption;

-For cancer prevention, do not use supplements. Try to meet nutritional needs through diet alone;

-For mothers: if you have the opportunity to breastfeed, this has benefits for the baby and the mother.

A recent meta-analysis of observational studies demonstrated that the adherence to WCRF/AICR recommendations reduced risks of cancer incidence and mortality in breast, lung, upper aerodigestive tract, stomach, prostate, and colorectal cancers [24][25][26], and they also improved hemostatic factors implicated in chronic disease development [27]. A special note on fiber intake and mortality should be made: there is an inverse association between fiber intake from foods and risk of death for respiratory diseases, infection, and cardiovascular diseases [28]. A recent report on 219,123 men and 168,999 women in the USA demonstrated that dietary fiber intake was associated with a lower risk of total death (multivariate RR comparing the highest vs. the lowest quintile = 0.78, 95% CI: 0.73–0.82, p-trend, <0.001 in men; 0.78. 95% CI: 0.73–0.85, p-trend, <0.001 in women). Dietary fiber intake (derived from whole grains, as suggested in WCRF/AICR recommendations) also lowered the risk of death from cardiovascular disease and respiratory diseases by 24%–56% in men and 34%–59% in women [29]. However, to date, no studies associated fiber intake with risk of mortality rate in patients with COVID-19.

(3) Cancer patients should reduce contact with external people as much as possible, promoting self-quarantine status, telemedicine, and minimizing medical examinations after a proper consult with your oncologist and cardiologist. To reduce the rate of transmission among patients with stable cancer and cardiovascular diseases, substituting in-person visits with telehealth visits and deferring any non-urgent procedures should be strongly considered.

(4) In cancer patients treated with cardiotoxic anticancer drugs, following the American Heart Association Scientific Statement on Cardio-Oncology Rehabilitation [30] to reduce cardiovascular outcomes in cancer patients and survivors should be strongly promoted. In brief, this statement from the American Heart Association provides an overview of the existing knowledge and rationale for the use of cardiac rehabilitation to provide structured exercise and ancillary services to cancer patients and survivors in order to reduce risk of mortality.

(5) In cancer patients with high cardiovascular risk, a proper hemodynamic analysis and control of biomarkers of heart damage associated to echocardiographic studies should be promoted as a primary strategy of cardiovascular prevention during COVID-19.

(6) Control of glycemic homeostasis in these patients should be promoted in hospital practice involved in the management of COVID-19, considering that almost all the observational studies available correlate diabetes or hyperglycemia with a poor prognosis of COVID-19 [31].

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