

Cardio-oncology care in the era of the coronavirus disease 2019 (COVID-19) pandemic: An International Cardio-Oncology Society (ICOS) statement.

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Disease 2019 (COVID-19) Pandemic: An International Cardio-Oncology Society (ICOS) Statement
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Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota. Corresponding Author: Joerg Herrmann, MD, Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (herrmann.joerg@mayo.edu). 10 9 2020 11 2020 70 6 376680 480 504 18 01 2021 05 03 2021 05 03 2021 20 09 2024 This file is available for text mining. It may also be used consistent with the principles of fair use under the copyright law. The severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) has given rise to a pandemic of unprecedented proportions in the modern era because of its highly contagious nature and impact on human health and society: coronavirus disease 2019 (COVID-19). Patients with cardiovascular (CV) risk factors and established CV disease (CVD) are among those initially identified at the highest risk for serious complications, including death. Subsequent studies have pointed out that patients with cancer are also at high risk for a critical disease course. Therefore, the most vulnerable patients are seemingly those with both cancer and CVD, and a careful, unified approach in the evaluation and management of this patient population is especially needed in times of the COVID-19 pandemic. This review provides an overview of the unique implications of the viral outbreak for the field of cardiooncology and outlines key modifications in the approach to this ever-increasing patient population. These modifications include a shift toward greater utilization of cardiac biomarkers and a more focused CV imaging approach in the broader context of modifications to typical practice pathways. The goal of this strategic adjustment is to minimize the risk of SARS–CoV-2 infection (or other future viral outbreaks) while not becoming negligent of CVD and its important impact on the overall outcomes of patients who are being treated for cancer.

On December 31, 2019, Chinese officials informed the World Health Organization of a cluster of cases of pneumonia in Wuhan, central China, related to a novel coronavirus (2019-nCoV, later designated severe acute respiratory syndrome coronavirus 2 [SARS–CoV-2]). 1 The viral outbreak has been marked by the rapidity of spread to pandemic proportions (coronavirus disease 2019 [COVID-19]) and the spectrum of presentations from asymptomatic supercarrier status to life-threatening respiratory failure. 1 , 2 Individuals with SARS–CoV-2 at highest risk for morbidity and mortality include the elderly, those with cardiovascular (CV) risk factors and established CV disease (CVD), and those with cancer. 3 – 8 Accordingly, patients with both cancer and CVD are likely to be at highest risk to experience morbidity and mortality from SARS–CoV-2. The purpose of this review from the International Cardio-Oncology Society (www.IC-OS.org) is to address and provide general guidance for the assurance of cardiac safety among patients with cancer that can be practically useful for oncologists, hematologists, and cardiologists during and after this COVID-19 pandemic. Importantly, the need for such guidance is underscored by the projection that COVID-19 will remain a legitimate concern for health care systems and the practice of medicine for the foreseeable future. The expected timeline for the development of an effective vaccine is unknown, and reports are surfacing that there may be a relatively short-lasting immunity among patients who have had the SARS–CoV-2 infection (compared with other viral illnesses). 9

Therefore, this review is appropriate not only for immediate utilization but also for the new reality that this pandemic has created: cardio-oncology (C-O) care in the era of COVID-19 (Fig. 1). As a disclaimer, as the evidence base in this area is rapidly evolving, a complete understanding is still in its early stages, and many specific aspects still need to be conclusively defined.

CV injury and dysfunction are leading causes of death and disability among patients with SARS–CoV-2. For example, Guo et al demonstrated that 27.8% of patients with SARS–CoV-2 had myocardial injury (defined by an elevation in troponin), 20% had arrhythmias, and 16% needed hemodynamic support. 10 Importantly, cardiac troponin elevations indicate worse outcomes; for instance, a >60% mortality rate among patients with CVD. 2 Interestingly, elevated cardiac troponin levels are correlate with high C-reactive protein levels and an exaggerated inflammatory response, perhaps similar to that seen after chimeric antigen receptor-T cell (CAR-T) therapy. 11 This exaggerated inflammatory response/cytokine storm is postulated to be one of the primary mechanisms leading to cardiac injury and dysfunction. However, there are multiple potential mechanisms for cardiac injury with COVID-19 beyond an exaggerated inflammatory response, including acute coronary syndrome, microvascular dysfunction, thrombosis, and even myocarditis. It is interesting to note that the cellular receptor for viral entry into the human body is the

angiotensin-converting enzyme-2 receptor (ACE2), which is expressed on lung epithelial cells (type 2 pneumocytes) as well as vascular endothelial cells, pericytes, cardiomyocytes, and macrophages. Accordingly, SARS-CoV-2 may be viewed not only as a respiratory virus but also as a CV virus, which can result in both severe acute lung injury and severe CV injury. 12 – 17 Indeed, several autopsy-based studies have now conclusively reported arterial and venous thrombosis, including pulmonary thrombosis and infarction, in addition to acute lung injury. 18 – 20

These prominent thrombotic aspects are a distinguishing feature of SARS-CoV-2. The mechanisms are not fully detailed but may relate to the inflammatory response and endothelial injury. From the initial reports, there appears to be a link between markers of inflammation (interleukin-6 [IL-6]), myocardial injury (troponin), and thrombosis/fibrinolysis (D-dimer) for identifying patients who are suffering important CV consequences. 4 In fact, a D-dimer level $>1\mu\text{g/mL}$ was the only biomarker independently and most potently predictive of mortality in one of the first studies on patients hospitalized with COVID-19. 4 The value of D-Dimer levels in this regard has subsequently been confirmed in other studies. 21

While the course of COVID-19 in patients with cancer continues to be defined, current data suggest that patients with cancer are at higher risk of acquiring the infection and experiencing a more severe course and higher mortality. 6 , 22 , 23 Indeed, various factors might influence susceptibility to COVID-19 among patients with cancer, including the type and stage of cancer, its location, the immunosuppressive effects of the therapeutic choices, the degree of bone marrow suppression, the frequent visits to the health care system, and the prevalence of COVID-19 in the region.

An overview of studies on patients with cancer who had COVID-19 published in the first one-half of 2020 is provided in Table 1 . 6 , 24 – 31 The majority of these studies confirm the notion that patients with cancer have a more severe course of COVID-19 and are also at a higher mortality risk. Increasing age has been the most consistent predictor of poor outcomes in these patients, followed by male sex. The presence of comorbidities, in particular CVD, have been identified as risk factors for a more severe and even fatal course of COVID-19. No particular cancer type has been identified to pose the highest risk, although lung cancer and hematologic malignancies have been discussed. Patients with active, progressive, and metastatic cancer seem to be more vulnerable to poor outcomes. No specific type of cancer therapy has been identified to pose a risk for a complicated or fatal course of COVID-19.

Interestingly, calls to prepare for the care of patients with cancer in times of a pandemic were issued over a decade ago and were updated more recently. 32 These include preparation for a change in the delivery of cancer care, including type, timing, and setting. Such an approach may shift away from surgery, radiation therapy, and conventional infusion chemotherapy toward therapies that can be given as a tablet or injection. More recently, specific recommendations for the care of patients with cancer in times of COVID-19 have emerged. A key concept is the designation of patients with cancer as high-risk or low-risk for disease progression without cancer therapy and thus at high need or low need for urgent treatment. 33 , 34 This concept of prioritization is depicted in Figure 2 .

Contemporary cancer therapy has expanded beyond traditional chemotherapeutics, radiation therapy, and surgery to include targeted therapies as well as immunotherapy, resulting in a range of potential CV toxicities that require more complex CV monitoring. 11 , 35 – 37 Specific cancer therapies are associated with worsening CV risk factors, such as hypertension and dyslipidemia, as well as the development of CVD, including heart failure, reduced left ventricular ejection fraction (LVEF), accelerated coronary artery disease, myocardial infarction, increased thrombosis, and (uncommonly) myocarditis. Patients with cancer or those who have been previously treated may be immunocompromised and have increased susceptibility to SARS-CoV-2; however, more than half of the patients reported previously from Wuhan who had cancer were survivors and were not necessarily undergoing active therapy. This suggests that the adverse outcomes in patients with cancer may relate, in part, to a reduced cardiopulmonary reserve or the presence of CVD. Importantly, in terms of acute CVD related to cancer therapy, it remains to be seen whether patients

exposed to potentially cardiotoxic cancer therapies are at an even higher risk with COVID-19. Indeed, the CV effects of certain cancer therapies may be unmasked or heightened by the current pandemic, especially when newer cancer therapy has the potential to cause endothelial damage and reduce CV reserve.³⁸ For this very reason, a multidisciplinary C-O approach is needed for patients with cancer during COVID-19.

The central conundrum for C-O care in the era of COVID-19 is how to deliver optimal care with fewer resources and at the lowest (possible) risk. Important questions include the following: 1) Which patients need attention, and by what means? 2) Is there a need to modify published algorithms and protocols? 3) Should there be a switch from CV imaging to serum biomarkers? 4) Which innovative approaches for remote monitoring can be quickly and effectively used? The answers to many of these questions may vary, depending on the local impact of COVID-19 or any other pandemic at the time, and these questions should be approached with vibrant and ongoing communication between oncology, hematology, and C-O providers alike. In fact, it is advisable that the directors of C-O clinics and service lines be proactive in approaching and working out potential new workflows completely integrated with the cancer team (Figs. 2 and 3). Some of these newly developed strategies in response to a pandemic can be found in other areas of cardiology, such as the care of patients with acute coronary syndrome and stroke, the need for cardioversion, and imaging.^{16, 39 – 41} It is important to emphasize that postponing or neglecting any appropriate care because of the COVID-19 pandemic is as detrimental as not considering potential exposures to COVID-19 and its impact on the patient and the health care system.

One of the key traits of SARS-CoV-2 is the high level of contagiousness.^{42 – 44} The primary route of transmission from person to person is via droplets generated by a cough or sneeze of an infected person. These droplets are propelled through the air, often several meters, and can deposit on the mucous membranes of the mouth, nose, or eyes of individuals nearby. The virus also can spread when a person touches a surface or object contaminated with infectious droplets and then touches his or her mouth, nose, or eye(s). Of note, the virus can survive outside the body for several days, including on common surfaces (cardboard for 24 hours, stainless steel for 48 hours, and plastic for 72 hours).⁴⁵ Of particular concern is the fact that infected individuals may maintain high viral loads in the upper respiratory tract without any symptoms, leading to asymptomatic viral shedding and transmission. In the medical setting, the risk of viral transmission is particularly high when aerosol-generating procedures are pursued, including nebulizer treatment, highflow oxygen, bronchoscopy, open tracheal suctioning, intubation, extubation, noninvasive positive-pressure ventilation, endoscopy, and transesophageal echocardiography.

A systematic review and meta-analysis concluded that face masks are the most effective measure of protection.⁴⁶ Health care systems thus should adopt a universal face mask policy with an increased level of respiratory protection for health care personnel in high-risk exposure scenarios. Other measures include eye protection. Physical distancing may be difficult in the office setting, especially in the examination room, but any degree of one meter or more is helpful.⁴⁶ Along these lines, the indications for close contact, as required for physical examination and certain clinical studies, need to be carefully considered. Hand hygiene, especially hand washing before and after seeing and examining a patient, is key. Soap is highly effective, although evaporating disinfectant dispenser bottles are very convenient.^{47, 48} Universal gloving, as needed (eg, for neutropenic patients), should include only new gloves used once per patient.

Patients with cancer should be shielded as much as possible from infection risks, including those from SARS-CoV-19, by proper hygiene standards in the health care system, such as proper hand washing, cleaning of examination rooms, and cleaning of instruments for clinical examination.

Universal face masking is recommended, especially during periods of high virus spread and/or risk, as with any community exposure to a viral pandemic such as COVID-19.

Depending on clinical exposure risk, personal protection equipment (PPE) for health care personnel needs to be maximized, including N95 masks, eye protection, gowns, and gloves.

Physical distancing is recommended at all times, including limiting close contacts, such as those needed for physical examination and clinical testing, including echocardiography (Echo).

When cardiology input is needed in the care of a patient with cancer, the first consideration should be appropriate triage based on clinical acuity and practice environment (Fig. 2). Patients with CV emergencies still need to be treated as such, with the right protective precautions and resultant workflow modifications (Fig. 3). On the other end of the spectrum, those with routine care needs can be rescheduled or followed using non-face-to-face (virtual) formats. Telehealth (including video consultations) might be the ideal tool to connect physicians and other health care professionals with patients in this setting. The advantages and disadvantages of the various consultations types are summarized in Table 2 .

During periods of high virus spread and/or risk, C-O consultation before, during, or after cancer therapy should be performed virtually if clinically feasible; in-person consultation should be limited to emergencies for which physical examination is essential in determining clinical management.

Cardiac imaging plays an important role in treatment decisions for C-O patients and, as a result, at least 2 groups, the European Association of Cardiovascular Imaging and the American Society of Echocardiography, have produced recommendations on precautions, indications, prioritization, and protection for patients and health care personnel during the time of the COVID-19 pandemic (key points are highlighted in Table 3). 41 , 49 A key aspect to consider is not only the frequency of imaging but also the type and duration. Echo involves much closer and longer patient-staff contact than cardiac magnetic resonance imaging, nuclear scans, computed tomographic angiography, or coronary computed tomographic angiography. To decrease exposure time and risk, many imaging centers have incorporated abbreviated protocols to decrease the duration of Echo scanning: the focused cardiac ultrasound study. For instance, if the only interest is in cardiac function or LVEF, this can commonly be obtained in 5 minutes, even when both right and left ventricular function are assessed, which is recommended in the context of COVID-19. 50 A summary of the advantages and disadvantages of the various cardiac imaging techniques is provided in Table 4 . 51

Previous algorithms on the cardiac safety and monitoring of patients with cancer who are exposed to potentially cardiotoxic medications have varied greatly, but a contemporary and comprehensive consensus has recently been published by the European Society of Medical Oncology (ESMO). 35 The American Society of Clinical Oncology (ASCO) had previously published a guideline that was focused specifically on cardiac dysfunction in survivors of cancer therapy, particularly those treated with anthracyclines and trastuzumab. 52 During the current COVID-19 pandemic, the requirement for social distancing has broad impact within medical care to the degree that virtual and/or telemedicine visits are emphasized. In previous ESMO recommendations, a cardiac serum biomarker approach using troponin I was considered a valid alternative to echocardiographic imaging during anthracycline-based therapy. 53 This strategy is certainly appealing in principle, but efforts to validate this approach in a broad range of patients receiving treatment for cancer has varied significantly based on malignancy and type of cancer therapy. 54 , 55 In addition, the length and timing of the screening is important, as outlined for natriuretic peptides (NPs), ie, B-type NP (BNP) and N-terminal pro-BNP (NT-proBNP), which have been successfully used in patients with multiple myeloma (MM) undergoing treatment with carfilzomib. 56 For cardiotoxicity surveillance measures, serum biomarker measurements would appear to provide a safe and cost-effective alternative to cardiac imaging, considering the potential exposure risks of patients and health care providers to SARS-CoV-19 (Fig. 4). Serial cardiac biomarker assessments allow for the recognition of trends over time and reassurance when no change is noted. Even more, taking the high negative predictive value into consideration, patients with values below the institutional laboratory cutoff for BNP, NT-proBNP, and cardiac troponin assays (below the 99th percentile) would be expected to present a rather low-risk constellation. Thus a cardiac biomarker-based surveillance approach holds merit, particularly to identify those patients who are not expected to benefit from cardiac imaging to such a degree that justifies the potential risk of SARS-CoV-19 exposure. The section below is based on the current ESMO consensus document with updated

modifications that are in line with alterations in medical care necessitated by the current and any possible future pandemics (Table 5). 27

All cardiac imaging should be reduced in frequency to that which is critical and necessary for clinical decision making.

When performed, the cardiac imaging technique that addresses the clinical question in the most effective and efficient manner should be used, decreasing exposure time and risk as much as possible; modified, focused cardiac imaging protocols (eg, focused cardiac ultrasound study) are encouraged, especially for Echo.

A cardiac biomarker-based approach, using cardiac troponins and/or NPs, in combination with accurate symptom assessment should allow adequate monitoring of cardiac safety to avoid unnecessary cardiac imaging.

Baseline (pretherapy) assessment of cardiac function in an asymptomatic patient rarely leads to withholding of cancer therapy. However, the baseline LVEF evaluation does serve the important purpose of a point of reference in the event of evolving cardiac dysfunction/heart failure and to establish a causal association with cancer therapy. This is particularly true in patients considered at high risk for cardiotoxicity. According to ASCO practice guidelines, this includes 3 groups of patients: 1) those receiving either ≥ 250 mg/m² of doxorubicin (or its equivalent), or radiation therapy ≥ 30 grays in which the heart is in the treatment field, or any dose combination of anthracycline and chest radiation therapy; 2) those receiving sequential anthracycline and trastuzumab therapy; and 3) those receiving anthracycline or trastuzumab therapy who are either aged ≥ 60 years or have ≥ 2 CV risk factors, or an LVEF $\leq 55\%$, or a history of myocardial infarction, or moderate or greater valvular heart disease. 52 To document evidence of substantial clinical cardiotoxicity, early recognition of a decline in LVEF to $<50\%$, even if asymptomatic (American College of Cardiology/American Heart Association stage B heart failure), is important in terms of timely initiation of cardioprotective therapy as well as overall prognosis. 57 , 58 As such, current consensus guidelines support cardiac follow-up evaluations 6 to 12 months in high risk patients, especially after full completion of anthracycline-based cancer therapy. 52 In the COVID era, this practice should remain although the timing of surveillance imaging may vary based on availability and safety.

Some data indicate that a persistent increase in cardiac biomarkers, including cardiac troponin and NPs, measured repeatedly during (cardiac troponins in particular) and after (NPs) anthracycline administration, is associated with a subsequent decline in cardiac function over time and thus may serve as a gatekeeper. 55 , 59 Subject to further studies, cardiac biomarkers drawn during routine laboratory assessments in the context of oncology/hematology care may help risk-stratify patients with a more urgent need for cardiac imaging.

Routine precancer therapy cardiac function assessment should continue to be performed in individuals at high risk (eg, ASCO guidelines for high risk, 52 prior CVD, symptoms of cardiac dysfunction), whereas routine assessment of cardiac function (although recommendable) could be deferred otherwise.

Routine postanthracycline therapy imaging should still be considered in those with heart failure symptoms, prior CVD, multiple CV risk factors, and persistent elevation in serum cardiac biomarkers or if there is a need to continue anthracycline therapy with doses exceeding ≥ 250 mg/m² of doxorubicin (or its equivalent). For cancer survivors beyond the acute period, all routine cardiac surveillance should be postponed unless patients have a history of or express new signs and symptoms of heart failure.

Similar to anthracyclines, trastuzumab (and other human epidermal growth factor receptor 2 [HER2]-based therapies, such as pertuzumab) carry a black-box warning for cardiotoxicity, and

LVEF assessment is recommended before and during every 3 months therapy in all settings, ie, neoadjuvant, adjuvant, and metastatic, per the package insert. The role of cardiac biomarkers as substitutes for cardiac function imaging has not been well defined in patients with breast cancer undergoing HER2-directed therapy. Cardiac troponin elevations related to HER2-directed therapy are most commonly noted early after anthracycline exposure. 60 The absence of troponin elevation makes irreversible LVEF declines very unlikely but cannot exclude the possibility that reductions in LVEF may occur. The published literature on NPs in patients with breast cancer actively undergoing trastuzumab therapy is not robust enough to endorse its complete substitution for cardiac imaging surveillance during standard care. 35 , 62 – 74 However, there is substantial experience that serial use of either BNP or NT-proBNP can allow for adequate cardiac safety assessment during this time. 66 As stated previously, there is evidence in the general population that NPs have high negative predictive value for excluding heart failure, and assessing NPs in an asymptomatic patient may allow deferring any cardiac imaging in a high-risk COVID-19 environment. 61 , 66

Routine pretherapy cardiac function assessment should continue to be performed in individuals at high risk (eg, ASCO guidelines for high risk, 52 prior CVD, symptoms of cardiac dysfunction), whereas routine assessment of cardiac function (although recommendable) could be deferred otherwise.

During therapy with HER-2–based treatment , cardiac biomarkers may be useful to identify those patients who do not require cardiac imaging to establish cardiac safety. In patients at low CV risk who remain asymptomatic and have stable or normal cardiac biomarkers during monitoring, cardiac function imaging may be deferred. 66 , 75

Consensus recommendations, such as the 2014 American Society of Echocardiography statement, outlined that, for various tyrosine kinase inhibitors (TKIs) associated with potential cardiotoxicity, a strategy for LVEF assessment should be undertaken. 76 For vascular endothelial growth factor signaling pathway inhibitors (VSPs), the primary issue is hypertension management. 77 , 78 The use of NPs has been proposed as a more relevant tool for identifying those at risk of CV events with VSP inhibitor-based therapy. 79 , 80 In times of a viral pandemic, home-based (remote care, including telemedicine) approaches are preferred to obtain vital signs, especially serial (up to daily) blood pressure measurements in any patient on VSP-based TKIs and to focus attention on the medical management of hypertension.

For patients receiving VSP inhibitors, serial (daily) home blood pressure monitoring is paramount, and the periodic use of NPs can effectively screen for those patients at risk for the development of heart failure. Routine cardiac function imaging is not recommended.

Carfilzomib, an irreversible inhibitor of the proteasome, is a drug with a notable risk of cardiotoxicity, especially in patients with relapsed MM. 56 , 81 Interestingly, echocardiography (LVEF) is not of high value, and risk-benefit analysis does not support its use in the COVID-19 era for screening. 56 , 81 In contrast, there is demonstrated value in the measurement of NPs, even as early as mid-first cycle. 56 CVD is highly prevalent in the MM population and is associated with adverse events that affect long-term outcomes, including those after a stem cell transplantation. 82 Patients with amyloidosis (light-chain disease [AL]) with or without MM are commonly treated with bortezomib, ixazomib, and (less commonly) carfilzomib, and these patients frequently have complex CVD as well as multiple CV complications during therapy. 83 The use of cardiac biomarkers is essential in the AL amyloidosis population, and these cardiac biomarkers are used to stage and prognosticate in this disease. 84 As a result of the high prevalence of CVD in patients with MM and AL amyloidosis, these patients are considered high-risk for the development of cardiac adverse events. Furthermore, cardiac biomarkers are an essential and proven tool for assessing cardiac safety during treatment in these patients, whereas cardiac imaging is not apparently useful.

Cardiac biomarker assessments before and during cancer treatment are essential components of ensuring cardiac safety in patients with MM and AL amyloidosis. The utility of cardiac imaging for early detection of CV adverse events with ongoing cancer treatment in these patients is not

established or recommended.

The use of immune checkpoint inhibitors (ICIs) has expanded significantly but may be associated with immune-related adverse events (irAEs). Although one of the least common irAEs, myocarditis with an ICI is one of the most fatal. 37 , 85 Different degrees (high-level and lowlevel) of lymphohistiocytic myocardial inflammation can be seen, and the exact mechanisms of this presentation are not yet defined. 86 Confirmation of the diagnosis can be challenging because neither magnetic resonance imaging nor endomyocardial biopsy is sufficiently sensitive, and a diagnosis is often made based on the overall clinical picture (in keeping with proposed consensus definitions). 37 , 87 , 88 As SARS-CoV-2 can directly infect the myocardium, with a resultant inflammatory response, SARS-CoV-2 should be considered in the differential diagnosis of a patient with concern for ICI-associated myocarditis. 13 , 14 There are no data to suggest caution for the continued use of ICIs during this COVID-19 pandemic, especially considering the dramatic cancer responses and overall safety profiles that have been reported with these therapies in previously recalcitrant cancer conditions. 89 , 90 Persistent viral infections or excessive viral antigen load may cause T-cell exhaustion, with increased expression of PD-1 and PD-L1. In this setting, the effect of ICI directed against PD-1/PD-L1 is unknown. However, in contradistinction, supporting the immune response with a CTLA-4 agonist has been shown to be helpful in other models of acute infection. Although various CV adverse events have been reported with ICI therapy, including serious rhythm issues, the optimal strategy for monitoring cardiac safety before, during, and after ICI therapy for cancer has not been standardized or recommended. 37 , 38 , 91 Serial electrocardiography (ECG) and cardiac troponin and/or NP levels have been considered, but the value is unclear. 37 , 92 A complete baseline assessment, including biomarkers and an ECG, would be prudent given the range of potential CV adverse events, but it is unclear whether an assessment of LVEF is necessary or helpful.

In patients about to receive ICI therapy for cancer, baseline assessment for CVD, including cardiac biomarkers and ECG, should be completed as well as SARS-CoV-2 status. The need or value of cardiac imaging before initiating ICI therapy is not established. The optimal protocol for monitoring cardiac safety during treatment with ICIs is unknown at present. Serious cardiac adverse events related to ICI therapy have been reported, and any suspicious symptoms or clinical findings of CV toxicity should be aggressively investigated. SARS-CoV-2 has been noted to cause myocarditis, which needs to be differentiated from ICI myocarditis in patients on ICI therapy.

Adoptive immunotherapy for cancer may result in a systemic inflammatory response of varying severity, referred to as the cytokine release syndrome (CRS). 93 This has been associated with neurotoxicity and CV toxicity. 11 , 94 The value of cardiac imaging at baseline before therapy or during the monitoring phase after treatment is still quite uncertain. The measurement of cardiac biomarkers has been identified as a useful strategy for ensuring cardiac safety, although the experience remains quite limited in general. 11 In the current COVID-19 pandemic, the virus itself can lead to a severe and overwhelming CRS, thus treatment with these cancer therapies may likely lead to added CV risk for CRS. Interestingly, IL-6 antagonists, typically used to treat CAR-T therapy-associated CRS, are also currently being tested in severely ill patients with COVID-19 who display an overwhelming inflammatory response that is a harbinger of poor outcomes. 95 Recently, the Society for Immunotherapy in Cancer proposed that efforts should be made to maximize the availability of anti-IL-6 agents, including tocilizumab and sarilumab, for use on a compassionate basis to critically ill, hospitalized, COVID-19-infected patients. 96

In patients receiving CAR-T or bispecific T-cell-engager therapy, it is recommended to screen for active COVID-19 infection before initiation of treatment. A low threshold for the use of an anti-IL-6 agent, such as tocilizumab, should be considered in patients who develop CRS in the current pandemic, given the potential for unrecognized coinfection with SARS-CoV-2.

Patients on active cancer therapy that is compromising the immune system should receive maximal precautions and protection against SARS-CoV-2 exposure.

SARS-CoV-2 uses the ACE2 receptor for cellular entry, which may explain why certain organs are preferentially affected in COVID-19. 97 ACE2 is expressed on lung alveolar epithelial cells and enterocytes of the small intestine as well as on the arterial and venous endothelium. 97 As outlined above, patients with preexisting CVD and/or CV risk factors are at the highest risk of experiencing a more severe course with COVID-19, and it is hypothesized that this may be related to reduced endothelial reserve. Along these lines, several cancer therapies, including chemotherapies (eg, cisplatin, cyclophosphamide), targeted therapies (eg, VSP inhibitors), immune therapies (eg, ICIs), and radiation therapy, can activate and injure the endothelium. 98 Although this vascular injury may often go unnoticed in clinical practice, it may become more evident in the setting of a potent endothelial stressor such as COVID-19. Indeed, viral infection of endothelial cells has been observed, and the vascular injury is considered to contribute to several complicating manifestations of COVID-19. 99 Recent data suggest that statin therapy may be an important adjunct for minimizing the major adverse vascular effects and inflammation that appears to be critically important during COVID-19. 100 It is unknown whether aspirin is a beneficial or harmful adjunctive therapy unless otherwise indicated for patients presenting with classic acute myocardial infarction, stroke, or acute limb ischemia, as per standard practice guidelines. Trials are currently ongoing to address the thrombotic aspects of COVID-19, which include microthrombi in various organs, and the merit of anticoagulation strategies.

In patients with cancer who present with acute vascular events, such as acute myocardial infarction or stroke, the possibility of an infection with SARS-CoV-2 should be considered. This is especially important for patients who are being considered for invasive procedures. Myopericarditis is an important condition that should be considered in patients with SARS-CoV-2 and can mimic even ST-segment elevation myocardial infarction.

Statins should be continued in patients already on therapy and should be considered in patients undergoing therapies with potential CV toxicity.

Patients who received prior chest radiation, especially those treated >2 decades ago, are at particular risk for radiation-induced heart and lung disease and represent a patient population expected to have a significantly reduced reserve should they develop COVID-19. For patients who received radiation therapy in the more recent era, the risk is likely lower. For those who are currently undergoing or are planned to undergo radiation therapy, acute injury and inflammation may pose a risk. Furthermore, it is recommended that, once radiation therapy is started, the full course of treatment should be completed. 33

In patients receiving active radiation therapy, clinicians should be aware that symptoms related to radiation-induced pneumonitis may mimic symptoms of COVID-19.

Patients who have received prior radiation therapy may have a reduced cardiopulmonary reserve and may be especially susceptible to a complicated course of COVID-19; strict safety measures should be in place for these patients.

ACE2 is a coreceptor for SARS-CoV-2, thus there has been a debate regarding the safety of ACE inhibitors (ACE-Is) and angiotensin 2 receptor blockers (ARBs) during the COVID pandemic. 101 , 102 A higher proportion of patients with adverse outcomes had hypertension and diabetes, and it has been speculated that ACE2 levels are upregulated in these patients, putting them at greater risk. One hypothesis is that ACE2 upregulation may be related to the pathogenesis of these CV risk factors or to other related comorbidities, such as obesity. 103 – 105 Alternatively, treatment of hypertension and diabetes with ACE-Is and ARBs may increase ACE2 expression, thus increasing the risk of viral entry and propagation. 106 However, in animal models, SARS-CoV infection led to reduced ACE2 expression and acute lung injury that was rescued by blocking the renin-angiotensin-aldosterone pathway. Clinical trials are ongoing that testing whether losartan, an ARB, is protective in COVID-19. 107 Furthermore, ACE-Is and ARBs have established efficacy for the treatment of cardiomyopathy and heart failure, even in patients with cancer, and should be a preferred agent when used for cardioprotection in patients receiving cardiotoxic therapies. Current

statements by CV societies ([acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statementaddresses-concerns-re-using-raas-antagonists-in-covid-19](https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statementaddresses-concerns-re-using-raas-antagonists-in-covid-19) and [escardio.org/Councils/Council-on-Hypertension\(CHT\)/News/position-statement-of-the-esc-council-onhypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension(CHT)/News/position-statement-of-the-esc-council-onhypertension-on-ace-inhibitors-and-ang)) do not indicate that there are adequate data to recommend stopping or withholding these therapies in patients with cancer who have established indications for their use. 108 This view is supported by the observation that clinical outcomes did not differ between patients with a history of hypertension who were hospitalized for COVID-19 in Wuhan, China, and were treated either with an ACE-I/ARB or with an alternative antihypertensive regimen. 10 , 109

ACE-Is and ARBs should be continued in patients with cancer who are receiving them for established indications during the COVID-19 pandemic.

ACE-Is and ARBs, the β -blocker carvedilol, and statins should continue to be appropriate strategies for cardioprotection while patients are receiving cancer therapy during the COVID-19 pandemic.

Malignant ventricular arrhythmias have been recognized in patients with COVID-19 infection and lead to many management challenges. 40 Moreover, various investigational treatments for COVID-19, including hydroxychloroquine and azithromycin, are associated with significant QT prolongation, which can increase the likelihood of ventricular tachyarrhythmia, particularly torsades de pointes. On the basis of these considerations and emerging data, the US Food and Drug Administration determined that the benefits of chloroquine and hydroxychloroquine no longer outweigh their potential risks within the anticipated framework of use, and they revoked the emergency use authorization for these medications on June 15, 2020. It should be added that the arrhythmic risk of these medications is likely increased in patients receiving active cancer therapy because many targeted agents may have an effect on the QT interval during treatment. For example, cancer therapeutics that are known to have important effects on the QT interval include arsenic trioxide, certain TKIs (vandetanib, nilotinib, vemurafenib), as well as ribociclib (Table 6). In addition, other risk factors during cancer therapy, such as nausea and diarrhea, may further exacerbate any changes in the QT interval as a result of hypomagnesemia or hypokalemia. In patients with QT prolongation who are receiving cancer therapeutics (ie, QTc $\geq$ 500 msec or Δ QT >60 msec from baseline), caution should be exercised when initiating COVID-19 therapies that may have an important effect on the QT interval. Moreover, electrolytes should be continually repleted, and any other nonessential QT-prolonging medications should be discontinued. In patients with significant QT prolongation (>500 msec) in whom both cancer-related and COVID-19-related therapies are considered essential and cannot be altered, additional protective measures may be considered, including topical patch monitors and/or external wearable defibrillators, especially if the patient is treated in the outpatient setting. 110

QT interval and arrhythmia monitoring strategies are constantly evolving. Recent publications provide helpful guidance in monitoring for the risk of ventricular arrhythmia caused by hydroxychloroquine-azithromycin treatment for COVID-19. 111 , 112 Although a standard 12-lead ECG is the most accurate way to assess the QT interval and cardiac arrhythmias, resource utilization and management are important considerations in the setting of COVID-19. Acquisition of a 12-lead ECG requires both personnel and equipment exposure. As such, the number of requested ECGs should be limited, and only a small number of technicians and ECG machines should be designated for patients with COVID-19 to limit exposure. For inpatients, telemetry monitoring may be considered for those deemed high risk based on a validated risk score for drug-associated QT interval prolongation. 113 There is also a need for alternative tools for QT monitoring considering the tremendous cost and resource utilization required for currently recommended QT interval monitoring with serial 12-lead ECGs, typically in triplicate. 114 For example, many wearable devices and other digital technology, such as the Apple Inc smartwatch, can provide single-lead ECG data with excellent fidelity. The KardiaMobile-6L, developed by AliveCor for atrial fibrillation detection, just received emergency clearance from the US Food and Drug Administration for use as a device for QT interval monitoring of patients with COVID-19. This tool and the BodyGuardian Heart (Preventice Solutions) may be very important devices to ensure cardiac safety and also to maintain the currently required social distancing mandates. 110

All patients with cancer who are being initiated on therapies associated with QT interval prolongation require a baseline 12-lead ECG. Any subsequent monitoring that is necessary can be accurately and safely performed with topical devices that allow monitoring of arrhythmias and QT interval prolongation. Nonessential medications should be eliminated, and electrolytes should be fastidiously replaced if those issues are present.

The characteristics of cancer disease, the type of anticancer therapy, and coexisting diseases, including CVD, are important risk factors for venous thromboembolism. 115 Pulmonary embolism remains a leading cause of mortality in clinical oncology. SARS-CoV-2 appears to be an additional risk factor for thromboembolic complications (including arterial microthrombi), and D-dimer (>1 $\mu\text{g/mL}$) is one of the most important predictors for fatal outcomes. 116 – 120 Inflammation, endothelial activation, and injury are the most likely mechanisms. The clinical difficulty is that pulmonary embolism, pulmonary infarction, and SARS-CoV-2 may have the same symptoms—shortness of breath, cough, and even fever—and they can coexist. 17

In C-O patients with confirmed SARS-CoV-2 who are immobilized in bed, primary antithrombotic prophylaxis should be used.

In C-O patients with dyspnea, cough, and fever, diagnostics for the exclusion of SARS-CoV-2 and pulmonary embolism should be performed.

In patients with cancer who have confirmed pulmonary embolism, SARS-CoV-2 should be excluded.

In patients with cancer who have pneumonia and confirmed SARS-CoV-2, evaluation by computed tomography should include an assessment for pulmonary embolism.

Low-molecular-weight heparins appear to be the first choice for antithrombotic treatment; new oral anticoagulants may be considered if there are not important drugdrug interactions with other planned treatments.

In a matter of a few months, COVID-19 has had an unimaginable impact on human lives and local, national, and global economies. The pace and number of studies in this area have been unprecedented, and so has the rapidly evolving knowledge base. Specific recommendations for clinical practice will continue to evolve in the weeks and months to come. The current general observations emphasize that patients with CVD and/or cancer are among the highest risk groups for poor outcomes, especially if they contract SARS-CoV-2. Proper awareness and strategies need to be in place to manage these patients optimally and thoughtfully to ensure a safe environment. Patients who are being treated for cancer represent a complex and fragile population. The management of their comorbidities, and of CVD in particular, becomes an absolute priority, especially during COVID-19. As a result of this pandemic, the need for a proactive and integrated approach to C-O care has never been more important than it is today. It is the intent of this consensus document to provide a meaningful structure to achieve a truly integrated and safe approach for the benefit of our patients.

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32091533 10.1001/jama.2020.2648 2. Shi S , Qin M , Shen B , Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China . JAMA Cardiol . 2020 ; 5 : 802 – 810 . 32211816 10.1001/jamacardio.2020.0950 PMC7097841 3. Wang D , Hu B , Hu C , Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China . JAMA . 2020 ; 323 : 1061 – 1069 . 32031570 10.1001/jama.2020.1585 PMC7042881 4. Zhou F , Yu T , Du R , Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study . Lancet . 2020 ; 395 : 1054 – 1062 . 32171076 10.1016/S0140-6736(20)30566-3 PMC7270627 5. Wu C , Chen X , Cai Y , Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China . JAMA Intern Med . 2020 ; 180 : 1 – 11 . 10.1001/jamainternmed.2020.0994 PMC7070509 32167524 6. Liang W , Guan W , Chen R , Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China . Lancet Oncol . 2020 ; 21 : 335 – 337 . 32066541 10.1016/S1470-2045(20)30096-6 PMC7159000 7. Wang H , Zhang L . Risk of COVID-19 for patients with cancer . Lancet Oncol . 2020 ; 21 : e181 . 32142621 10.1016/S1470-2045(20)30149-2 PMC7129735 8. Xia Y , Jin R , Zhao J , Shen H . Risk of COVID-19 for patients with cancer . Lancet Oncol . 2020 ; 21 : e180 . 32142622 10.1016/S1470-2045(20)30150-9 PMC7130057 9. Long QX , Tang XJ , Shi QL , Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections . Nat Med . Published online 6 18 , 2020 . doi: 10.1038/s41591-020-0965-6 32555424 10. Guo T , Fan Y , Chen M , Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19) . JAMA Cardiol . 2020 ; 5 : 1 – 8 . 10.1001/jamacardio.2020.1017 PMC7101506 32219356 11. Alvi RM , Frigault MJ , Fradley MG , Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T) . J Am Coll Cardiol . 2019 ; 74 : 3099 – 3108 . 31856966 10.1016/j.jacc.2019.10.038 PMC6938409 12. Madjid M , Safavi-Naeini P , Solomon SD , Vardeny O . Potential effects of coronaviruses on the cardiovascular system: a review . JAMA Cardiol . 2020 ; 5 : 831 – 840 . 32219363 10.1001/jamacardio.2020.1286 13. Inciardi RM , Lupi L , Zacccone G , Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19) . JAMA Cardiol . 2020 ; 5 : 819 – 824 . 32219357 10.1001/jamacardio.2020.1096 PMC7364333 14. Hu H , Ma F , Wei X , Fang Y . Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin . Eur Heart J . Published online 3 16 , 2020 . doi: 10.1093/eurheartj/ehaa290 PMC7184348 32176300 15. Hua A , O'Gallagher K , Sado D , Byrne J . Life-threatening cardiac tamponade complicating myo-pericarditis in COVID-19 . Eur Heart J . 2020 ; 41 : 2130 . 32227076 10.1093/eurheartj/ehaa253 PMC7184427 16. Zhang L , Fan Y , Lu Z . Experiences and lesson strategies for cardiology from the COVID-19 outbreak in Wuhan, China, by 'on the scene' cardiologists . Eur Heart J . 2020 ; 41 : 1788 – 1790 . 32242895 10.1093/eurheartj/ehaa266 PMC7529146 17. Danzi GB , Loffi M , Galeazzi G , Gherbesi D . Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J . 2020 ; 41 : 1858 . 32227120

10.1093/eurheartj/ehaa254 PMC7184406 18. Ackermann M , Verleden SE , Kuehnel M , Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19 . *N Engl J Med* . 2020 ; 383 : 120 – 128 . 32437596 10.1056/NEJMoa2015432 PMC7412750 19. Lax SF , Skok K , Zechner P , Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series . *Ann Intern Med* . Published online 5 14 , 2020 . doi: 10.7326/M20-2566 PMC7249507 32422076 20. Wichmann D , Sperhake JP , Lutgehetmann M , Autopsy findings and venous thromboembolism in patients with COVID-19 . *Ann Intern Med* . Published online 5 6 , 2020 . doi: 10.7326/M20-2003 33316197 21. Zhang L , Yan X , Fan Q , D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19 . *J Thromb Haemost* . 2020 ; 18 : 1324 – 1329 . 32306492 10.1111/jth.14859 PMC7264730 22. Ganatra S , Hammond SP , Nohria A . The novel coronavirus disease (COVID-19) threat for patients with cardiovascular disease and cancer . *JACC CardioOncol* . 2020 ; 2 : 350 – 355 . 32292919 10.1016/j.jacc.2020.03.001 PMC7151392 23. Yu J , Ouyang W , Chua MLK , Xie C . SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China . *JAMA Oncol* . 2020 ; 6 : 1108 – 1110 . 32211820 10.1001/jamaoncol.2020.0980 PMC7097836 24. Zhang L , Zhu F , Xie L , Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China . *Ann Oncol* . 2020 ; 31 : 894 – 901 . 32224151 10.1016/j.annonc.2020.03.296 PMC7270947 25. Dai M , Liu D , Liu M , Patients with cancer appear more vulnerable to SARS-CoV-2: a multi-center study during the COVID-19 outbreak . *Cancer Discov* . 2020 ; 10 : 783 – 791 . 32345594 10.1158/2159-8290.CD-20-0422 PMC7309152 26. Yang K , Sheng Y , Huang C , Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study . *Lancet Oncol* . 2020 ; 21 : 904 – 913 . 32479787 10.1016/S1470-2045(20)30310-7 PMC7259917 27. Rogado J , Obispo B , Pangua C , Covid-19 transmission, outcome and associated risk factors in cancer patients at the first month of the pandemic in a Spanish hospital in Madrid . *Clin Transl Oncol* . Published online 5 25 , 2020 . doi: 10.1007/s12094-020-02381-z PMC7246222 32449128 28. Mehta V , Goel S , Kabarriti R , Case fatality rate of cancer patients with COVID-19 in a New York hospital system . *Cancer Discov* . 2020 ; 10 : 935 – 941 . 32357994 10.1158/2159-8290.CD-20-0516 PMC7334098 29. Garassino MC , Whisenant JG , Huang LC , COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study . *Lancet Oncol* . 2020 ; 21 : 914 – 922 . 32539942 10.1016/S1470-2045(20)30314-4 PMC7292610 30. Kuderer NM , Choueiri TK , Shah DP , Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study . *Lancet* . 2020 ; 395 : 1907 – 1918 . 32473681 10.1016/S0140-6736(20)31187-9 PMC7255743 31. Lee LYW , Cazier JB , Starkey T , COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study . *Lancet* . 2020 ; 395 : 1919 – 1926 . 32473682 10.1016/S0140-6736(20)31173-9 PMC7255715 32. Battershill PM . Influenza pandemic planning for cancer patients . *Curr Oncol* . 2006 ; 13 : 119 – 120 . 17576451 10.3390/curroncol13040012 PMC1891185 33. Al-Shamsi HO , Alhazzani W , Alhurairi A , A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group . *Oncologist* . 2020 ; 25 : e936 – e945 . 32243668 10.1634/theoncologist.2020-0213 PMC7288661 34. Mauri D , Kamposioras K , Tolia M , Alongi F , Tzachanis D , International Oncology Panel and European Cancer Patient Coalition Collaborators. Summary of international recommendations in 23 languages for patients with cancer during the COVID-19 pandemic . *Lancet Oncol* . 2020 ; 21 : 759 – 760 . 32410877 10.1016/S1470-2045(20)30278-3 PMC7220173 35. Curigliano G , Lenihan D , Fradley M , Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations . *Ann Oncol* . 2020 ; 31 : 171 – 190 . 31959335 10.1016/j.annonc.2019.10.023 PMC8019325 36. Mahmood SS , Fradley MG , Cohen JV , Myocarditis in patients treated with immune checkpoint inhibitors . *J Am Coll Cardiol* . 2018 ; 71 : 1755 – 1764 . 29567210 10.1016/j.jacc.2018.02.037 PMC6196725 37. Ball S , Ghosh RK , Wongsasengsak S , Cardiovascular toxicities of immune checkpoint inhibitors: JACC Review Topic of the Week . *J Am Coll Cardiol* . 2019 ; 74 : 1714 – 1727 . 31558256 10.1016/j.jacc.2019.07.079 38. Herrmann J , Yang EH , Iliescu CA , Vascular toxicities of cancer therapies: the old and the new—an evolving avenue . *Circulation* . 2016 ; 133 : 1272 – 1289 . 27022039 10.1161/CIRCULATIONAHA.115.018347 PMC4817363 39. Khosravani H , Rajendram P , Notario L , Chapman MG , Menon BK . Protected code stroke: hyperacute stroke management during the

coronavirus disease 2019 (COVID-19) pandemic . *Stroke* . 2020 ; 51 : 1891 – 1895 . 32233980 10.1161/STROKEAHA.120.029838 PMC7258750 40. Lakkireddy DR , Chung MK , Gopinathannair R , Guidance for cardiac electrophysiology during the coronavirus (COVID-19) pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association . *Circulation* . 2020 ; 21 : e823 – e831 . 10.1161/CIRCULATIONAHA.120.047063 PMC7243667 32228309 41. Skulstad H , Cosyns B , Popescu BA , COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel . *Eur Heart J Cardiovasc Imaging* . 2020 ; 21 : 592 – 598 . 32242891 10.1093/ehjci/jeaa072 PMC7184341 42. Rothe C , Schunk M , Sothmann P , Transmission of 2019-nCoV infection from an asymptomatic contact in Germany . *N Engl J Med* . 2020 ; 382 : 970 – 971 . 32003551 10.1056/NEJMc2001468 PMC7120970 43. Ksiazek TG , Erdman D , Goldsmith CS , A novel coronavirus associated with severe acute respiratory syndrome . *N Engl J Med* . 2003 ; 348 : 1953 – 1966 . 12690092 10.1056/NEJMoA030781 44. Drosten C , Gunther S , Preiser W , Identification of a novel coronavirus in patients with severe acute respiratory syndrome . *N Engl J Med* . 2003 ; 348 : 1967 – 1976 . 12690091 10.1056/NEJMoA030747 45. van Doremalen N , Bushmaker T , Morris DH , Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1 . *N Engl J Med* . 2020 ; 382 : 1564 – 1567 . 32182409 10.1056/NEJMc2004973 PMC7121658 46. Chu DK , Akl EA , Duda S , Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis . *Lancet* . 2020 ; 395 : 1973 – 1987 . 32497510 10.1016/S0140-6736(20)31142-9 PMC7263814 47. Cook TM . Personal protective equipment during the coronavirus disease (COVID) 2019 pandemic—a narrative review . *Anaesthesia* . 2020 ; 75 : 920 – 927 . 32246849 10.1111/anae.15071 48. Ma QX , Shan H , Zhang HL , Li GM , Yang RM , Chen JM . Potential utilities of mask-wearing and instant hand hygiene for fighting SARS-CoV-2 . *J Med Virol* . Published online 3 31 , 2020 . doi: 10.1002/jmv.25805 PMC7228401 32232986 49. Kirkpatrick JN , Mitchell C , Taub C , Kort S , Hung J , Swaminathan M . ASE statement on protection of patients and echocardiography service providers during the 2019 novel coronavirus outbreak . *J Am Coll Cardiol* . 2020 ; 75 : 3078 – 3084 . 32272153 10.1016/j.jacc.2020.04.002 PMC7194625 50. Szekely Y , Lichter Y , Taieb P , The spectrum of cardiac manifestations in coronavirus disease 2019 (COVID-19)—a systematic echocardiographic study . *Circulation* . Published online 5 29 , 2020 . doi: 10.1161/circulationaha.120.047971 PMC7382541 32469253 51. Seraphim A , Westwood M , Bhuva AN , Advanced imaging modalities to monitor for cardiotoxicity . *Curr Treat Options Oncol* . 2019 ; 20 : 73 . 31396720 10.1007/s11864-019-0672-z PMC6687672 52. Armenian SH , Lacchetti C , Barac A , Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline . *J Clin Oncol* . 2017 ; 35 : 893 – 911 . 27918725 10.1200/JCO.2016.70.5400 53. Curigliano G , Cardinale D , Suter T , Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines . *Ann Oncol* . 2012 ; 23 (suppl 7) : vii155 – vii166 . 22997448 10.1093/annonc/mds293 54. Plana JC , Galderisi M , Barac A , Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging . *J Am Soc Echocardiogr* . 2014 ; 27 : 911 – 939 . 25172399 10.1016/j.echo.2014.07.012 55. Lenihan DJ , Stevens PL , Massey M , The utility of point-of-care biomarkers to detect cardiotoxicity during anthracycline chemotherapy: a feasibility study . *J Card Fail* . 2016 ; 22 : 433 – 438 . 27079675 10.1016/j.cardfail.2016.04.003 56. Cornell RF , Ky B , Weiss BM , Prospective study of cardiac events during proteasome inhibitor therapy for relapsed multiple myeloma . *J Clin Oncol* . 2019 ; 37 : 1946 – 1955 . 31188726 10.1200/JCO.19.00231 PMC9798911 57. Yancy CW , Jessup M , Bozkurt B , 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America . *J Am Coll Cardiol* . 2017 ; 70 : 776 – 803 . 28461007 10.1016/j.jacc.2017.04.025 58. Yancy CW , Jessup M , Bozkurt B , 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines . *J Am Coll Cardiol* . 2013 ; 62 : e147 – e239 . 23747642 10.1016/j.jacc.2013.05.019 59. Feola M , Garrone O , Occelli M , Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left

ventricular ejection fraction, troponin I and brain natriuretic peptide . *Int J Cardiol* . 2011 ; 148 : 194 – 198 . 19945181 10.1016/j.ijcard.2009.09.564 60. Cardinale D , Colombo A , Torrisi R , Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation . *J Clin Oncol* . 2010 ; 28 : 3910 – 3916 . 20679614 10.1200/JCO.2009.27.3615 61. Demissei BG , Hubbard RA , Zhang L , Changes in cardiovascular biomarkers with breast cancer therapy and associations with cardiac dysfunction . *J Am Heart Assoc* . 2020 ; 9 : e014708 . 31959034 10.1161/JAHA.119.014708 PMC7033834 62. Goel S , Liu J , Guo H , Decline in left ventricular ejection fraction following anthracyclines predicts trastuzumab cardiotoxicity . *JACC Heart Fail* . 2019 ; 7 : 795 – 780 . 31401102 10.1016/j.jchf.2019.04.014 63. Demissei BG , Finkelman BS , Hubbard RA , Detailed phenotyping reveals distinct trajectories of cardiovascular function and symptoms with exposure to modern breast cancer therapy . *Cancer* . 2019 ; 125 : 2762 – 2771 . 31042319 10.1002/cncr.32149 PMC6722325 64. Bouwer NI , Liesting C , Kofflard MJM , NT-proBNP correlates with LVEF decline in HER2-positive breast cancer patients treated with trastuzumab . *Cardiooncology* . 2019 ; 5 : 4 . 32154011 10.1186/s40959-019-0039-4 PMC7048136 65. Ponde N , Bradbury I , Lambertini M , Cardiac biomarkers for early detection and prediction of trastuzumab and/or lapatinib-induced cardiotoxicity in patients with HER2-positive early-stage breast cancer: a NeoALTTO sub-study (BIG 1–06) . *Breast Cancer Res Treat* . 2018 ; 168 : 631 – 638 . 29280043 10.1007/s10549-017-4628-3 PMC5843537 66. Zardavas D , Suter TM , Van Veldhuisen DJ , Role of troponins I and T and N-terminal prohormone of brain natriuretic peptide in monitoring cardiac safety of patients with early-stage human epidermal growth factor receptor 2-positive breast cancer receiving trastuzumab: a herceptin adjuvant study cardiac marker substudy . *J Clin Oncol* . 2017 ; 35 : 878 – 884 . 28199174 10.1200/JCO.2015.65.7916 67. Thavendiranathan P , Amir E . Left ventricular dysfunction with trastuzumab therapy: is primary prevention the best option? *J Clin Oncol* . 2017 ; 35 : 820 – 825 . 28029315 10.1200/JCO.2016.71.0038 68. Kitayama H , Kondo T , Sugiyama J , High-sensitive troponin T assay can predict anthracycline- and trastuzumab-induced cardiotoxicity in breast cancer patients . *Breast Cancer* . 2017 ; 24 : 774 – 782 . 28434150 10.1007/s12282-017-0778-8 69. Altundag K Robust predictive markers are needed for early detection of trastuzumab-related cardiac dysfunction in breast cancer . *Breast Cancer* . 2017 ; 24 : 794 . 28275991 10.1007/s12282-017-0767-y 70. Ky B , Putt M , Sawaya H , Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab . *J Am Coll Cardiol* . 2014 ; 63 : 809 – 816 . 24291281 10.1016/j.jacc.2013.10.061 PMC4286181 71. Sawaya H , Sebag IA , Plana JC , Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab . *Circ Cardiovasc Imaging* . 2012 ; 5 : 596 – 603 . 22744937 10.1161/CIRCIMAGING.112.973321 PMC3703313 72. Sawaya H , Sebag IA , Plana JC , Early detection and prediction of cardiotoxicity in chemotherapy-treated patients . *Am J Cardiol* . 2011 ; 107 : 1375 – 1380 . 21371685 10.1016/j.amjcard.2011.01.006 PMC3703314 73. Goel S , Simes RJ , Beith JM . Exploratory analysis of cardiac biomarkers in women with normal cardiac function receiving trastuzumab for breast cancer . *Asia Pac J Clin Oncol* . 2011 ; 7 : 276 – 280 . 21884439 10.1111/j.1743-7563.2011.01422.x 74. Fallah-Rad N , Walker JR , Wassef A , The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy . *J Am Coll Cardiol* . 2011 ; 57 : 2263 – 2270 . 21616287 10.1016/j.jacc.2010.11.063 75. Dang CT , Yu AF , Jones LW , Cardiac surveillance guidelines for trastuzumab-containing therapy in early-stage breast cancer: getting to the heart of the matter . *J Clin Oncol* . 2016 ; 34 : 1030 – 1033 . 26834055 10.1200/JCO.2015.64.5515 PMC5070558 76. Plana JC , Galderisi M , Barac A , Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging . *Eur Heart J Cardiovasc Imaging* . 2014 ; 15 : 1063 – 1093 . 25239940 10.1093/ehjci/jeu192 PMC4402366 77. Maitland ML , Bakris GL , Black HR , Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors . *J Natl Cancer Inst* . 2010 ; 102 : 596 – 604 . 20351338 10.1093/jnci/djq091 PMC2864290 78. Touyz RM , Herrmann SMS , Herrmann J . Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events . *J Am Soc Hypertens* . 2018 ; 12 : 409 – 425 . 29703600 10.1016/j.jash.2018.03.008 PMC6168784 79. Witteles RM . Biomarkers as predictors of cardiac toxicity from targeted cancer therapies . *J Card*

Fail . 2016 ; 22 : 459 – 464 . 27038641 10.1016/j.cardfail.2016.03.016 80. Hall PS , Harshman LC , Srinivas S , Witteles RM . The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients . JACC Heart Fail . 2013 ; 1 : 72 – 78 . 24621801 10.1016/j.jchf.2012.09.001 81. Chari A , Stewart AK , Russell SD , Analysis of carfilzomib cardiovascular safety profile across relapsed and/or refractory multiple myeloma clinical trials . Blood Adv . 2018 ; 2 : 1633 – 1644 . 29991494 10.1182/bloodadvances.2017015545 PMC6039655 82. Li W , Garcia D , Cornell RF , Cardiovascular and thrombotic complications of novel multiple myeloma therapies: a review . JAMA Oncol . 2017 ; 3 : 980 – 988 . 27632640 10.1001/jamaoncol.2016.3350 83. Gertz MA , Dispenzieri A , Sher T . Pathophysiology and treatment of cardiac amyloidosis . Nat Rev Cardiol . 2015 ; 12 : 91 – 102 . 25311231 10.1038/nrcardio.2014.165 84. Kumar SK , Gertz MA , Dispenzieri A . Validation of Mayo Clinic staging system for light chain amyloidosis with high-sensitivity troponin . J Clin Oncol . 2019 ; 37 : 171 – 173 . 30433848 10.1200/JCO.18.01398 85. Wang DY , Salem JE , Cohen JV , Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis . JAMA Oncol . 2018 ; 4 : 1721 – 1728 . 30242316 10.1001/jamaoncol.2018.3923 PMC6440712 86. Brown SA , Ray JC , Herrmann J . Precision cardio-oncology: a systems-based perspective on cardiotoxicity of tyrosine kinase inhibitors and immune checkpoint inhibitors . J Cardiovasc Transl Res . 2020 ; 13 : 402 – 416 . 32253744 10.1007/s12265-020-09992-5 PMC8855704 87. Awadalla M , Mahmood SS , Groarke JD , Global longitudinal strain and cardiac events in patients with immune checkpoint inhibitor-related myocarditis . J Am Coll Cardiol . 2020 ; 75 : 467 – 478 . 32029128 10.1016/j.jacc.2019.11.049 PMC7067226 88. Zhang L , Awadalla M , Mahmood SS , Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis . Eur Heart J . 2020 ; 41 : 1733 – 1743 . 32112560 10.1093/eurheartj/ehaa051 PMC7205467 89. Khalil DN , Smith EL , Brentjens RJ , Wolchok JD . The future of cancer treatment: immunomodulation, CARs and combination immunotherapy . Nat Rev Clin Oncol . 2016 ; 13 : 273 – 290 . 26977780 10.1038/nrclinonc.2016.25 PMC5551685 90. Martins F , Sofiya L , Sykietis GP , Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance . Nat Rev Clin Oncol . 2019 ; 16 : 563 – 580 . 31092901 10.1038/s41571-019-0218-0 91. Hu JR , Florido R , Lipson EJ , Cardiovascular toxicities associated with immune checkpoint inhibitors . Cardiovasc Res . 2019 ; 115 : 854 – 868 . 30715219 10.1093/cvr/cvz026 PMC6452314 92. Neilan TG , Rothenberg ML , Amiri-Kordestani L , Myocarditis associated with immune checkpoint inhibitors: an expert consensus on data gaps and a call to action . Oncologist . 2018 ; 23 : 874 – 878 . 29802220 10.1634/theoncologist.2018-0157 PMC6156187 93. Herrmann J Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia . Nat Rev Cardiol . 2020 ; 17 : 474 – 502 . 32231332 10.1038/s41569-020-0348-1 PMC8782611 94. Ganatra S , Carver JR , Hayek SS , Chimeric antigen receptor T-cell therapy for cancer and heart: JACC Council perspectives . J Am Coll Cardiol . 2019 ; 74 : 3153 – 3163 . 31856973 10.1016/j.jacc.2019.10.049 PMC8211027 95. Mehta P , McAuley DF , Brown M , COVID-19: consider cytokine storm syndromes and immunosuppression . Lancet . 2020 ; 395 : 1033 – 1034 . 32192578 10.1016/S0140-6736(20)30628-0 PMC7270045 96. Ascierto PA , Fox BA , Urba WJ , Insights from immuno-oncology: the Society for Immunotherapy of Cancer statement on access to IL-6-targeting therapies for COVID-19 . J Immunother Cancer . 2020 ; 9 : e000878 . 10.1136/jitc-2020-000878 PMC7204613 32300051 97. Hamming I , Timens W , Bulthuis MLC , Lely AT , Navis GJ , van Goor H . Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis . J Pathol . 2004 ; 203 : 631 – 637 . 15141377 10.1002/path.1570 PMC7167720 98. Herrmann J Vascular toxic effects of cancer therapies . Nat Rev Cardiol . 2020 ; 17 : 503 – 522 . 32218531 10.1038/s41569-020-0347-2 PMC8782612 99. Varga Z , Flammer AJ , Steiger P , Endothelial cell infection and endotheliitis in COVID-19 . Lancet . 2020 ; 395 : 1417 – 1418 . 32325026 10.1016/S0140-6736(20)30937-5 PMC7172722 100. Zhang XJ , Qin JJ , Cheng X , In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19 . Cell Metab . Published online 6 24 , 2020 . doi: 10.1016/j.cmet.2020.06.015 PMC7311917 32592657 101. Hoffmann M , Kleine-Weber H , Schroeder S , SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor . Cell . 2020 ; 181 : 271 – 280.e8 . 32142651 10.1016/j.cell.2020.02.052 PMC7102627 102. Danser AHJ , Epstein M , Batlle D . Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers . Hypertension . 2020 ; 75 : 1382 – 1385 . 32208987 10.1161/HYPERTENSIONAHA.120.15082 PMC7225046 103. Gupte M , Boustany-Kari CM ,

Bharadwaj K , ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet . *Am J Physiol Regul Integr Comp Physiol* . 2008 ; 295 : R781 – R788 . 18650320 10.1152/ajpregu.00183.2008 PMC2536864 104. Palmer BR , Jarvis MD , Pilbrow AP , Angiotensin-converting enzyme 2 A1075G polymorphism is associated with survival in an acute coronary syndromes cohort . *Am Heart J* . 2008 ; 156 : 752 – 758 . 18926157 10.1016/j.ahj.2008.06.013 105. Fan Z , Wu G , Yue M , Hypertension and hypertensive left ventricular hypertrophy are associated with ACE2 genetic polymorphism . *Life Sci* . 2019 ; 225 : 39 – 45 . 30917908 10.1016/j.lfs.2019.03.059 106. Ferrario CM , Jessup J , Chappell MC , Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2 . *Circulation* . 2005 ; 111 : 2605 – 2610 . 15897343 10.1161/CIRCULATIONAHA.104.510461 107. Kuba K , Imai Y , Rao S , A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury . *Nat Med* . 2005 ; 11 : 875 – 879 . 16007097 10.1038/nm1267 PMC7095783 108. Rico-Mesa JS , White A , Anderson AS . Outcomes in patients with COVID-19 infection taking ACEI/ARB . *Curr Cardiol Rep* . 2020 ; 22 : 31 . 32291526 10.1007/s11886-020-01291-4 PMC7154066 109. Vaduganathan M , Vardeny O , Michel T , McMurray JJV , Pfeffer MA , Solomon SD . Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19 . *N Engl J Med* . 2020 ; 382 : 1653 – 1659 . 32227760 10.1056/NEJMSr2005760 PMC7121452 110. Castelletti S , Dagradi F , Goulene K , A wearable remote monitoring system for the identification of subjects with a prolonged QT interval or at risk for drug-induced long QT syndrome . *Int J Cardiol* . 2018 ; 266 : 89 – 94 . 29887480 10.1016/j.ijcard.2018.03.097 111. Roden DM , Harrington RA , Poppas A , Russo AM . Considerations for drug interactions on QTc in exploratory COVID-19 (coronavirus disease 2019) treatment . *Circulation* . 2020 ; 141 : e906 – e907 . 32267732 10.1161/CIRCULATIONAHA.120.047521 112. Sapp JL , Alqarawi W , MacIntyre CJ , Guidance on minimizing risk of drug-induced ventricular arrhythmia during treatment of COVID-19: a statement from the Canadian Heart Rhythm Society . *Can J Cardiol* . 2020 ; 36 : 948 – 951 . 32299753 10.1016/j.cjca.2020.04.003 PMC7195336 113. Tisdale JE , Jaynes HA , Kingery JR , Development and validation of a risk score to predict QT interval prolongation in hospitalized patients . *Circ Cardiovasc Qual Outcomes* . 2013 ; 6 : 479 – 487 . 23716032 10.1161/CIRCOUTCOMES.113.000152 PMC3788679 114. Menna P , Salvatorelli E , Minotti G . Cancer drugs and QT prolongation: weighing risk against benefit . *Expert Opin Drug Saf* . 2017 ; 16 : 1099 – 1102 . 28699784 10.1080/14740338.2017.1354987 115. Connolly GC , Francis CW . Cancer-associated thrombosis . *Hematology Am Soc Hematol Educ Program* . 2013 ; 2013 : 684 – 691 . 24319253 10.1182/asheducation-2013.1.684 116. Iba T , Levy JH , Levi M , Connors JM , Thachil J . Coagulopathy of coronavirus disease 2019 . *Crit Care Med* . Published online 5 27 , 2020 . doi: 10.1097/CCM.0000000000004458 PMC7255402 32467443 117. Connors JM , Levy JH . COVID-19 and its implications for thrombosis and anticoagulation . *Blood* . 2020 ; 135 : 2033 – 2040 . 32339221 10.1182/blood.2020006000 PMC7273827 118. Connors JM , Levy JH . Thromboinflammation and the hypercoagulability of COVID-19 . *J Thromb Haemost* . 2020 ; 18 : 1559 – 1561 . 32302453 10.1111/jth.14849 PMC9770920 119. Iba T , Levy JH , Connors JM , Warkentin TE , Thachil J , Levi M . The unique characteristics of COVID-19 coagulopathy . *Crit Care* . 2020 ; 24 : 360 . 32552865 10.1186/s13054-020-03077-0 PMC7301352 120. Bikdeli B , Madhavan MV , Jimenez D , COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review . *J Am Coll Cardiol* . 2020 ; 75 : 2950 – 2973 . 32311448 10.1016/j.jacc.2020.04.031 PMC7164881

FIGURE 1. Cardio-Oncology Care in the Era of Coronavirus Disease 2019 (COVID-19). This is an overview of the changes in medical practice for patients with cancer in the setting of a viral pandemic such as COVID-19. These include proper preparation, execution of modified workflows, and maintenance of excellent care. Some modified practices evolving before and during peak times of a pandemic will likely remain in place to address persistent residual risk and resurges and/or those recognized to contribute to practice optimization in general. CV indicates cardiovascular; PPE, personal protection equipment.

Workflow Outline for Cardio-Oncology in Times of a Viral Pandemic. Initial triage should take cardiovascular (CV) disease (CVD) acuity into consideration as well as the broader scope of the patient's cancer care and the specific viral pandemic practice environment. COVID-19 indicates

coronavirus disease 2019.

Outline of High-Risk and Low-Risk Cardiovascular (CV) Conditions. All cases should be addressed on an individual basis. The type of clinical encounter is driven by the clinical presentation. Coronavirus disease 2019 (COVID-19) screening should be obtained for any patient to be seen in person and, ideally, for all patients proceeding with cancer therapy. Repeat and serial testing might be required. CVD indicates cardiovascular disease.

Action Grid for Cardiac Biomarker Profile. This is an outline of recommendations based on the constellation of troponin and natriuretic peptide values and within the context of the clinical presentation. CV indicates cardiovascular. *NP indicates natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-BNP [NT-proBNP]); troponin, troponin I or troponin T (normal vs abnormal levels are based on the institutional reference range). ϕ Asymptomatic indicates the absence of symptoms of heart failure (HF) or acute coronary syndrome (ACS); symptomatic, symptoms of HF or ACS. #A consultation can happen in person or by telemedicine. Discussion should include initiation of cardioprotective therapy. ‡High-risk cancer therapy is that known to be associated with HF or left ventricular dysfunction (LVD). β Cardioprotective therapy indicates that an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and/or carvedilol with or without a statin (if the patient is receiving anthracycline-containing chemotherapy) is recommended.

Studies on Coronavirus Disease 2019 (COVID-19) in Patients With Cancer (Status as of June 2020)

Cancer (OR, 5.39; 95% CI, 1.8–16.2; P = .003)

COPD (OR, 3.4; 95% CI, 1.4–8.4; P = .008)

Anticancer therapy within 14 d (OR, 4.1; 95% CI, 1.1–15.3; P = .04)

Patchy consolidation (OR, 5.4; 95% CI, 1.5–19.8; P = .01)

Cancer (HR 2.5; 95% CI, 1.7–3.8; P < .01)

Hem. malignancy (HR 6.3; 95% CI, 2.7–14.9; P < .01)

Lung cancer (HR 2.6; 95% CI, 1.3–5.0; P < .01)

Met. cancer (HR 2.5; 95% CI, 1.2–5.1; P = .01)

Immunotherapy (HR 4.8, 95% 1.7–13.5; P < .01)

Surgery (HR, 6.2; 95% CI, 2.4–15.8; P < .01)

On chemotherapy (OR, 3.5; 95% CI, 1.2–10.6; P = .03)

Men (OR, 3.9; 95% CI, 1.6–9.5; P = .003)

Current or former smoker (OR, 3.2; 95% CI, 1.1–9.1)

Former smoker (OR, 1.6; 95% CI, 1.0–2.5)

Cancer not in remission, but stable (OR, 1.8; 95% CI, 1.1–3.0) or progressing (OR, 5.2; 95% CI, 2.8–9.8)

ECOG status 2 (OR 3.9, 95% CI 2.1–7.2) ECOG status 3 (OR 5.7, 95% CI 2.8–11.5)

Azithromycin + hydroxychloroquine (OR, 2.9; 95% CI, 1.8–4.8)

Men (OR, 1.7; 95% CI, 1.2–2.3; P = .006)

Age (OR, 9.4; 95% CI, 6.6–10.0; P < .0001)

CVD (OR, 2.3; 95% CI, 1.5–3.6; p = .002)

HTN (OR, 1.95; 95% CI 1.4–2.8; P = .002)

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CVC, cardiovascular disease; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group; Hem. malignancy, hematologic malignancy; HR, hazard ratio; HTN, hypertension; ICU, intensive care unit; Met. cancer, metastatic cancer; MV, mechanical ventilation; NA, not available; NSCLC, nonsmall cell lung cancer; OR, odds ratio; SCLC, small cell lung cancer.

Efficient way for providers to seek specialty opinion

Low logistic demand, depending on institutional resources

Disproportional time commitment (and reimbursement)

Risk of incomplete coverage of the consultation reason

Inability to perform a physical examination

Flexibility for patients and providers regarding location and scheduling

Direct overall assessment of patient's condition

Thorough medication reconciliation with visual confirmation

Inability to perform a complete physical examination

Key Points With Regard to Cardiac Imaging in Response to Coronavirus Disease 2019 (COVID-19)

Cardiac imaging should be performed if appropriate and only if it is likely to substantially change patient management

Use the imaging modality with the best capability to meet the request considering the safety of medical staff regarding exposure (avoid unnecessary repetitions)

Elective nonurgent and routine follow-up examinations may be postponed or cancelled

Because of the risk of widespread contamination from transportation of critically ill or high-risk patients, a portable machine should be brought to the patient

Prolonged duration of a cardiac imaging study will increase the likelihood of contamination

A focused cardiac ultrasound study is recommended to reduce the duration of exposure and reduce the risk of contamination; to minimize exposure risk and use of resources, point-of-care ultrasound may be an option at selected centers

Echocardiography should only be performed in patients with COVID-19 when there is a clear indication that this testing will alter management

The risk of contamination of equipment and personnel is very high during a transesophageal echocardiography; consider other alternatives

Chest computed tomography (CT) is frequently used to confirm COVID-19–related pneumonia and might provide possible synergies for cardiac imaging

Coronary CT angiography can be used to exclude or confirm an acute coronary syndrome in COVID-19 pneumonia, in which elevated troponins are common

Modified from: Skulstad H, Cosyns B, Popescu BA, et al. COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel. *Eur Heart J Cardiovasc Imaging* . 2020; 21:592–598 41 ; and Kirkpatrick JN, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE statement on protection of patients and echocardiography service providers during the 2019 novel coronavirus outbreak. *J Am Coll Cardiol* . 2020; 75:3078–3084. 49

Strengths and Limitations of Different Imaging Modalities for Diagnosis and Monitoring of Cardiotoxicity a

Abbreviations: 2D Echo, 2-dimensional echocardiography; CCTA, coronary computed tomography angiogram; CMR, cardiac magnetic resonance; TEE, transesophageal echocardiography.

Modalities are scored as follows: +++, excellent diagnostic accuracy or features/high cost; ++, intermediate diagnostic accuracy or features/intermediate cost; +, reasonable diagnostic accuracy or features/low cost; 0, unable to diagnose.

Nuclear imaging modalities include single-photon emission computed tomography and multigated acquisition.

CCTA is the only noninvasive test that provides anatomic information with regard to the presence of coronary disease, and it also allows for imaging of the lung parenchyma, which shows characteristic changes in coronavirus disease 2019 and in the pulmonary vasculature and aorta (triple rule out); furthermore, it can identify pericardial effusion.

Modified from: Seraphim A, Westwood M, Bhuvana AN, et al. Advanced imaging modalities to monitor for cardiotoxicity. *Curr Treat Options Oncol*. 2019; 20:73.51

Best Practices for the Prevention and Management of Cardiac Complications in Patients With Cancer in the Coronavirus Disease 2019 (COVID-19) Era

Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomized trials without heterogeneity

Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

Retrospective cohort studies or case-control studies

Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc), optional

Moderate evidence against efficacy or for adverse outcome, generally not recommended

Strong evidence against efficacy or for adverse outcome, never recommended

Abbreviations: CV, cardiovascular; ESMO, European Society of Medical Oncology; FDA, US Food and Drug Administration; HF, heart failure; ICOS, International Cardio-Oncology Society; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MRI, magnetic resonance imaging; T-DM1, trastuzumab emtansine. Modified from Rogado J, Obispo B, Pangua C, et al. Covid-19 transmission, outcome and associated risk factors in cancer patients at the first month of the pandemic in a Spanish hospital in Madrid. Clin Transl Oncol . Published online May 25, 2020. 27

Cardiovascular Adverse Effects From Cancer Therapies