

REVIEW

A narrative review of the pathophysiology of COVID-19 infection among cancer patients: Current evidence and research perspectives

Vinod K. Ramani¹  | Radheshyam Naik²

¹Department of Preventive Oncology, Healthcare Global Enterprise Ltd., Bangalore, India

²Department of Medical Oncology, Healthcare Global Enterprise Ltd., Bangalore, India

Correspondence

Vinod K. Ramani, Department of Preventive Oncology, Healthcare Global Enterprise Ltd., KR Road, Bangalore 560027, India.
Email: drvinod.r@hcgel.com

Abstract

Introduction: The mechanism by which a suppressed immune system of a cancer patient makes them susceptible to COVID-19 is still unclear. Any delay or discontinuation of cancer care due to the pandemic is expected to have a detrimental impact on the outcome of cancer. A few studies have addressed the incidence of COVID-19 among cancer patients, but the small sample size of such studies makes it difficult to draw inference to the general population.

Methods: For our review, 'Pubmed' database and Google search engines were used for searching the relevant articles. The criterion used for review includes their relevance to the defined review question, which is the pathophysiological mechanism of COVID-19 among cancer patients and the relevant therapeutic interventions therewith. This review includes 20 studies and other relevant literature which address the determinants of COVID-19 among Cancer patients.

Results: Delay in cancer diagnosis will increase the stage progression of cancer patients and increased mortality in the future. A short delay in administering cancer related treatment to aid the odds of patient surviving the acute SARS-CoV-2 infection, should be at the discretion of the treating Physician. Oncologists dilemma in the current situation includes titrating the density of drug doses and intensity of treatment regimen, for the optimal management of metastatic and adjuvant cancer patients. Patients are thus subjected to suboptimal treatment and undetected disease recurrence, To circumvent the immunosuppressive effects of chemotherapy, Providers need to consider staggered regimen or alternate therapies such as biological/immunotherapy, targeted therapy, anti-angiogenic drugs, hormone therapy and/or antibody-based therapeutics.

Conclusion: This review provides insights on the pathogenesis of SARS-CoV-2, which could enable Physicians in formulating therapeutic strategies for the management of severe patients, more so in Oncology settings, thus reducing the mortality. The key is to balance the continuation of urgent cancer care, but rationing the elective treatment according to the circumstances.

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KEYWORDS

cancer care, COVID-19, immunosuppression

1 | INTRODUCTION

On January 30, 2020, World health organization (WHO) declared COVID-19 (2019 novel coronavirus disease) as a public health emergency of global concern.¹ WHO declared COVID-19 caused by SARS-CoV-2 virus as a pandemic on March 11, 2020.² The Chinese Center for Disease Control and Prevention (CDC) reports the overall case fatality rate (CFR) of COVID-19 as 2.3%. When compared with SARS-CoV or MERS-CoV, SARS-CoV 2 is found to be far more transmissible. It is estimated that, on average, 2.68 new secondary cases will arise from each new infected case. In China, the CFR is 2.3% among the general population when compared with 5.6% among cancer patients.³

The response of many countries toward this pandemic has been poor, due to the lack of scientific rigor in drawing inference from empirical data. Initially, the information emerging from China seemed incomplete, and countries like United States were in a state of “COVID denial” thus delaying the response. United Kingdom held the premise of herd immunity, thus exposing a large number of its population. The initial stages of response were hampered by lack of consensus regarding testing of the population/healthcare staff, usage of masks in the community, and full personal protective equipment (PPE) for medical staff. Research shows that patients with hematologic, lung, or metastatic cancers had a high frequency of severe events due to COVID-19. However, the frequency of such severe events among patients with non-metastatic cancers and other cancer types was similar to non-cancer patients.⁴

Cancer patients are more susceptible to infections when compared with the general population, due to their systemic immunosuppressive state caused by the malignancy and anticancer treatment. This could be the reason for the poor prognosis of such patients infected with COVID-19. However, smoking could increase the gene expression of angiotensin-converting enzyme 2 (ACE 2) and confound this association as a risk factor.⁵ Multidisciplinary teams involved with cancer care are expected to customize the regimen as per each patient's health condition, either continuing urgent or rationing other treatment.⁶

During the earlier coronavirus epidemics such as severe acute respiratory syndrome (SARS) and middle-east respiratory syndrome (MERS), deaths were due to respiratory failure unlike with COVID-19, which results in multiple organ dysfunction.⁵ During 2015, the MERS epidemic resulted in a mortality rate of 84% among tumor affected subjects, which was twice that in non-oncology subjects.⁷ The protracted influenza A virus subtype, H1N1 epidemic, during 2009 resulted in a 18.5% higher mortality among cancer subjects. Tumors are connected with an increased expression of immunosuppressive cytokines, augmented functional immunosuppressive leukocyte population, and decreased proinflammatory danger signals, which may

dampen the immune system and augment the probability of infectious complications.⁷

The SARS-CoV-2 interacts with the ACE2 functional receptor and TMPRSS2, which is a serine protease, widely distributed in multiple organs. The varying risk of infection, stroke, hypertension, or diabetes among different ethnic groups is due to the varied ACE2 gene polymorphisms. Given the correlation between ACE2 receptor density and COVID-19 uptake in human cells, its differential analyses could differentiate the clinical outcomes and severity of the patients' symptoms. The elevated susceptibility to COVID-19 among smokers is due to the increased gene expression of ACE2 induced by tobacco. Antihypertensives, such as ACE inhibitors, tend to promote the greater expression of ACE2 in the heart and lungs, and such patients may have a higher risk of COVID-19 infection when compared to the others.⁸

The initial evidence from China regarding the extrapulmonary effects of SARS-CoV-2 among humans shows that 12% of patients without underlying cardiovascular disease experienced heart damage. The laboratory result of such patients shows increased levels of cardiac troponin and D-dimer, or episode of cardiac arrest during hospitalization for COVID-19. The multiorgan failure (including myocarditis, venous thromboembolism, and acute respiratory distress syndrome [ARDS]) and consequent death could be the result of secondary hemophagocytic lymphohistiocytosis (sHLH). This multiorgan hyperinflammatory condition is due to the hyperactivation of cytotoxic T lymphocytes, macrophages, and natural killer cells.⁸ This review⁸ highlights the role of androgens in risk of SARS-CoV-2 infection, wherein high circulating androgen levels among prostate or breast cancer patients may have an increased risk of viral infection and subsequent poor prognosis.

Cancer patients are at risk of viral infection and the magnitude of effect depends on the type of cancer, recent sessions of chemotherapy, radiotherapy or surgical interventions, and presence of comorbidities (diabetes, cardiovascular disease, and metabolic syndrome). This review provides insights to the pathogenesis of SARS-CoV-2, which will enable the physician to formulate therapeutic strategies for management of severe patients, more so in oncology settings for reducing the mortality. The relative risk of treatment vs death from coronavirus infection needs to be carefully balanced.⁹

2 | METHODS

“Pubmed” database and Google search engines were used for searching the relevant articles. Search terms with Boolean operators used include “COVID 19 and Cancer”; “Morbidity of COVID 19 among

TABLE 1 Incidence of COVID-19 among cancer patients

Sl. No.	Author's name, place of study, sample size	Risk estimate	Comparison
1	Zhang et al ³ Hospital-based retrospective cohort study in Wuhan, China	This study ³ shows that severe events developed among 53.6% of cancer patients (ICU admission, requiring mechanical ventilation, or death), and death as an outcome among 28.6% of patients. Among the general population infected with COVID-19, data shows that 4.7% of confirmed cases were critically ill clinically and 2.3% were fatal	
2	Liang et al ⁵ China (575 hospitals) 1590	18 patients had history of cancer (1%, 95% CI 0.61-1.65)	Incidence of cancer overall among the Chinese population 0.29% (285.83 per 100 000 people)
3	Saini et al ¹⁰ Italy 355	20% of the perished COVID-19 patients had active cancer	
4	Yu et al ¹¹	Difference in incidence of COVID-19 among cancer patients when compared with the general population, during the same period of time (0.79% vs 0.37%, OR 2.31, 95% CI 1.89-3.02)	
5	Zheng et al ¹² Record based study in 3 hospitals, Wuhan, China 28 patients admitted for quarantine and isolation	As on February 26, 2020, severe clinical events were found among 15 patients (53.6%) requiring ICU admission or mechanical ventilation, life-threatening complications among 10 (35.7%), and death among 8 (28.6%)	For COVID-19 among general population, severe clinical events were found among 4.7% and death among 2.3% of patients
6	Tian et al ¹³ Multicentric study at Wuhan	Cancer patients were more likely to have severe COVID-19 than patients without cancer (OR: 3.61, 95% CI: 2.59-5.04, $P < .0001$)	
7	Yang et al ¹⁴ Multicentric record based study, Hubei province, China 205	The incidence of COVID-19 among cancer patients was 2.5% In-hospital case-fatality rate (CFR) in patients with COVID-19 and cancer was 20%	The incidence of COVID-19 reported in the overall Chinese population is 0.29% and in other studies is 1% The CFR for COVID-19 among the overall Chinese population is 1%
8	Miyashita et al's study ¹⁵ Aggregate data from the electronic medical records (EMR) of Mount Sinai Health System (MSHS) in New York City 5668 records from March 1 to April 6, 2020	6% (334) of COVID-19 patients, had cancer	
9	Trapani et al ¹⁶	Italian cancer mortality for 909 COVID-19 patients, which were reported from the National Medical council	16.5% were cancer patients

Cancer patients.” The results of this search yield research articles that contextually provide details of the relevant concepts. The criterion used for reviewing these articles includes their relevance to the defined review question, which includes the pathophysiological mechanism of COVID-19 among cancer patients and the relevant therapeutic interventions therewith. These studies were reviewed for the incidence of COVID-19 among their cohort of cancer patients, issues influencing delivery of healthcare systems such as screening process, laboratory investigations, referral pathways, therapeutic regimen, and other relevant concepts. This review includes 20 studies and other

relevant literature, which address the determinants of COVID-19 among cancer patients.

3 | BODY

3.1 | Incidence

Table 1 lists the incidence of COVID-19 among cancer patients, as reviewed from the research included in our study. Given the

frequency of hospital visits of cancer patients, it is possible that they are more likely to be diagnosed with COVID-19.

3.2 | Screening

Gorin et al¹⁷ report a precipitous drop in US national cancer screening patterns as of April 25, 2020 due to the pandemic, which was measured at 94% each for cervical cytology and breast cancer screening and 86% for colorectal cancer screening. The challenges for cancer detection as a result of delayed cancer screening include late stage of disease at the time of diagnosis, increased cancer incidence (particularly for cervical and colorectal cancer), and greater morbidity and mortality.

Peng et al¹⁸ infer that a simple advice for postponing the screening of breast cancer may not be an ideal approach. Instead, we need to adopt different approaches to diminish the barriers for resumption of screening. This includes standard procedure for mammography (PPE, sanitizers, COVID-19 rapid testing, and rearrangement of waiting areas) in hospitals and mobile units. For women with BI-RADS category 4 or 5, examinations should be prioritized and referred for diagnostic evaluation. The challenge is to regularly sterilize the equipment and the environment where screening activities are undertaken. The crisis caused by this pandemic necessitates women with previous history of breast cancer, dense breast tissue, family history, and high-risk genes such as BRCA1 and BRCA2 toward receiving priority in screening referrals.

3.3 | Signs and symptoms

In Zheng et al's¹² record based study, severe clinical events among cancer patients were found among those with patchy consolidation on chest CT (HR 5.44, 95% CI 1.5-19.75; $P = .01$) and those receiving cancer treatment within the last 14 days (HR 4.1, 95% CI 1.09-15.32; $P = .037$).

Zhang et al³ in their retrospective cohort study in China found that cancer patients present with similar clinical features when compared with those in the general population. The clinical features of COVID-19 include fatigue, fever, dry cough, dyspnea, along with blood profile changes such as lymphopenia, and high levels of highly sensitive C-reactive protein.³ The authors assess the frequent manifestation of anemia and hypoproteinemia among cancer patients, due to their nutritional deterioration that might adversely affect their immune competence and increase their susceptibility to respiratory pathogens. This study reports that lung cancer patients with COVID-19 are likely to develop severe anoxia and progress more rapidly, possibly due to their worse baseline lung function and endurance. We could thus infer that there is an increased need to treat cancer patients infected with COVID-19, with special emphasis on lung cancer patients.

However, the studies by Liang et al,⁵ Yu et al,¹¹ and Zheng et al¹² are affected either by the retrospective nature of evidence, small

sample size, and limited duration of follow-up.¹⁹ Tumor stage is another confounder that needs to be controlled during multivariate analysis. Since Zhang et al's³ study was conducted from hospitals in Wuhan, China, which is the epicenter of the COVID-19 outbreak, there was shortage of medical resources during the early stages of the outbreak. Such relatively inadequate resources or delayed admission could have contributed to the increased mortality. All these concerns limit the ability of such studies for population-based projections. The possibility of severe events among them should be validated through prospective studies. The risk of COVID-19 among cancer patients could be better analyzed using individual level data rather than the aggregate.

3.4 | Age and sex of the patient

Liang et al's⁵ study reports an increased risk among those receiving chemotherapy or surgery during the previous month following adjustment for other variables such as history of smoking, age, and other comorbidities (OR: 5.34, 95% CI 1.8-16.18, $P = .0026$). In addition, the time-dependent hazards of developing severe events were evaluated using a Cox regression model (after adjusting for age, the median time to severe events was 13 days vs 43 days, $P < .0001$; HR 3.56, 95% CI 1.65-7.69). Among cancer patients in this study,⁵ older age was the only risk factor for severe events (OR 1.43, 95% CI 0.97-2.12, $P = .072$). However, the study⁵ reports that the median age of cancer patients (63.1 years) was significantly higher than the non-cancerous patients (48.7 years), which suggests that worse COVID-19 outcomes were associated with older age. Irrespective of the cancer status, available evidence shows that COVID-19 is more lethal among older patients and those with comorbidities.¹⁵

Yu et al's¹¹ study also shows that among patients with non-small cell lung cancer, the incidence of COVID-19 was high among those aged >60 years when compared with those ≤60 years (4.3% vs 1.8%). Miyashita et al's study¹⁵ reports that following stratification by age groups, the risk of intubation was significant only in the 66 to 80 years age group (RR 1.76, 95% CI: 1.15-2.7). Cancer patients <50 years had a significantly higher mortality rate (RR 5.01, 95% CI: 1.55-16.2).

Sud's²⁰ study reports that among <70 year individuals, the survival decrement is substantial for most tumors even for small delays (2 months). For individuals aged ≥70 years, the risk of death from nosocomial infection was much higher and exceeds the average decrement of a moderate delay, in particular for indolent cancer types (eg, prostate cancer) or cancers with poor overall prognosis (eg, upper gastrointestinal tract cancers). The population level impact of diagnostic delays in terms of lives and life-years lost could be mitigated by prioritizing referred patients according to their age and the type of tumor and its stage.

In Yang et al's¹⁴ study, "male sex" (OR: 3.86, 95% CI: 1.57-9.50, $P = .0033$) was identified as risk factor for death among the study subjects. Symptoms might be relatively mild among female patients. In young patients, COVID-19 mortality is generally low but the baseline

fragility of cancer patients might explain the relatively higher rate in this age group. We need to infer the results after adjusting for age and gender.²¹ These issues mandate the need for conducting either an age-stratified analysis or an age-gender paired analysis.

3.5 | Pathology

Xu et al's¹² study discusses the pathological findings of a demised COVID-19 patient. The over-activation of T cells was the cause of severe immune injury in this case study, and the same was manifested by high cytotoxicity of CD8 T cells and an increase of Th17. Lung tissue shows hyaline membrane formation and pulmonary edema, which are signs of ARDS, which could be prevented by the use of corticosteroids along with ventilator support among severe patients. No significant histological changes specific to SARS-CoV-2 were observed in the liver and heart of the deceased patient, which shows that the infection may not impair these organ systems. The common feature among many COVID-19 patients is lymphopenia, which, in turn, has an impact on disease severity and mortality.

3.6 | Biochemical investigations

Tian et al¹³ report the validation of known risk factors such as older age, elevated procalcitonin, D-dimer, interleukin 6, and reduced lymphocytes ($P = .024$, $P < .0001$, $P = .00033$, $P < .0001$, $P = .0028$) among cancer patients. The authors also report the following risk factors of COVID-19 severity among cancer patients: advanced tumor stage (OR: 2.6, 95% CI: 1.05-6.43, $P = .039$), elevated tumor necrosis factor α (OR: 1.22, 95% CI: 1.01-1.47, $P = .037$), elevated N-terminal pro-B-type natriuretic peptide (OR: 1.65, 95% CI: 1.03-2.78, $P = .032$), reduced CD4+ T cells (OR: 0.84, 95% CI: 0.71-0.98, $P = .031$), and reduced albumin-globulin ratio (OR: 0.12, 95% CI: 0.02-0.77, $P = .024$).

TABLE 2 Result of delay in presentation

Sl. No.	Backlog of referrals	Additional lives lost	Life-years lost
1	25%	181	3316
2	50%	361	6632
3	75%	542	9948

TABLE 3 Increase in the number of deaths up to year 5 after diagnosis²³

Sl. No.	Tumor type	Increase in the number of deaths	Total years of life lost (95% CI)
1	Breast	7.9-9.6%	9261 (8843-9631)
2	Colorectal	15.3-16.6%	27 043 (26 234-29 968)
3	Lung	4.8-5.3%	20 413 (19 833-20 909)
4	Esophagus	5.8-6.0%	5027 (4861-5213)

3.7 | Patient referral pathway

Sud et al's²⁰ study estimates that for cancers with stage I-III, delay in treatment of 2 to 6 months duration during the period of lockdown in United Kingdom (March to June 2020) will lead to the progression of early stage tumors among a large proportion of patients from curable to the incurable stage. A 2-week wait pathway exists in United Kingdom for referral from primary care for urgent specialist evaluation for individuals with red-flag symptoms suggestive of specific types of cancer. The authors based on their study on 20 tumor types opine that a 2-month delay in the 2 week-wait investigatory referrals results in a loss of 0 to 0.7 life-years per referred patient depending on the age and type of tumor. Table 2 depicts the delays in presentation via the 2-week wait pathway over the 3-month lockdown period in United Kingdom (with an average presentational delay of 2 months per patient).

However, Sud's²⁰ model includes patients who had a 2-week wait referral and thus omits a considerable proportion of patients with cancer who are diagnosed through other routes (emergency admissions, routine referrals). Hamilton²² comments that during February 2020, the conversion rate was 7.1% across all 2-week wait pathways. Thus, 13 patients without cancer were tested for each patient with cancer. This counters Sud's²⁰ opinion that post-lockdown in United Kingdom, the diagnostic services will be at reduced capacity and at above-normal demand. Maringe et al²³ report that the general practitioner (GP) initiated urgent 2-week wait referrals for patients with suspected cancer has decreased by ~80% in response to UK's physical distancing norms.

Maringe et al,²³ in their population-based modeling study at United Kingdom, used a routes-to-diagnosis framework for estimating the impact of diagnostic delays over a 12-month period since March 16, 2020 (commencement of physical distancing measures), on net survival up to 1, 3, and 5 years after diagnosis. Table 3 depicts the increase in number of deaths up to year 5 after diagnosis.

3.8 | Outcome of infection

The results from Liang et al's⁵ prospective cohort study show that the risk of COVID-19 among cancer patients is higher than those without cancer. However, given the contagious nature of the virus, everyone (not just cancer patients) exposed to an infectious source are equally susceptible.²⁴ This study⁵ also reports worse outcomes among cancer patients due to COVID-19 (39% vs 8%; $P = .0003$).

Miyashita et al's¹⁵ study reports that the frequency of intubation among cancer patients was significantly more (unadjusted RR 1.89, 95% CI: 1.37-2.61), but the death rate was not significantly different

from other patients. Yang et al¹⁴ in their multicentric hospital based study report that pneumonia occurred among 25% of cancer patients with COVID-19.

The potential etiology in severe cases of COVID-19 is the cytokine-associated lung injury.¹² The impaired immune system of cancer patients could impair the overwhelming lung inflammation found in non-cancerous COVID-19 patients, explaining the equivocal COVID-19 mortality rates among the cancer group.

3.9 | Cancer treatment and other therapeutics

In their study, Liang et al⁵ report an increased risk of adverse events following chemotherapy or surgery, which most likely predisposes them to an immunocompromised state and hematological toxicity. Yang et al¹⁴ report that “receiving chemotherapy within 4 weeks before symptom onset” (OR: 3.51, 95% CI: 1.16-10.59, $P = .026$) was identified as risk factor for death among the study subjects.

Zhang et al's³ study reports that among COVID-19 infected cancer patients, severe clinical events were significantly associated with antitumor therapy within the last 14 days. Although >50% of cancer patients ($n = 28$)³ were treated with steroids, there was no reduction in the incidence of severe events. In case of viral pneumonia, the immunosuppressive effect of steroids is speculated to delay the clearance of virus. There is an increased risk of opportunistic infections due to steroid therapy, especially among patients who are in need of mechanical ventilation. This study³ reports that nosocomial infection resulted in 28.6% of patients. The Chinese CDC confirms COVID-19 transmission among patients within healthcare settings.²⁵ Human-to-human transmission has been confirmed in familial clusters or travel-related clusters.²⁶

Trapani et al¹⁶ report that morbidity among COVID-19 patients could be affected by an aging population and the burden of NCDs including those with cancer. This, in turn, will determine a different CFR. This study reports no specific pattern of increased risk of severe outcomes among cancer patients. Immunotherapy is a speculated risk factor for severe COVID-19, and some of the patients in the study who required hospitalization did not receive the same.

The American association for cancer research (AACR) reports²⁷ that during the early stages of the pandemic, the impact of immunotherapy (among cancer patients) on SARS-CoV-2 was uncertain. It was believed that immunotherapy agents could worsen the immune response to SARS-CoV-2, by blocking certain immune checkpoints. However, these studies did not account for the presence of inflammatory lung disease (ILD) among cancer patients infected with SARS-CoV-2. ILD is common among current or former smokers, which make them predisposed to worse outcomes of COVID-19. Smokers are likely to receive programmed cell death 1 (PD-1) checkpoint inhibitors compared with nonsmokers, who are likely to receive targeted therapies. Given this difference in treatment and the unclear confounding effect of ILD pathology, it was initially assumed that immunotherapy caused worse outcomes among cancer patients. Other studies show that immunotherapy may lead to cytokine storm in patients with

COVID-19. Research suggests that the antidiabetic drug “Metformin” decreases certain inflammatory cytokines and may be a potential treatment in these cases.

Further research will enable oncologists in learning whether immunotherapy should be postponed in cancer patients with severe COVID-19 infections. The National Cancer Institute has initiated a 2 year prospective study on 2000 cancer patients infected with COVID-19 at 650 sites, which will provide more information in this regard.

Also, the pandemic has hastened pre-planned measures to improve clinical trial accruals, such as halting onsite auditing, shipping investigational agents directly to the sites, and avoiding routine visit of patients to the clinic for laboratory tests (which could be done close to their homes). Minor deviations to the protocols are being allowed with a greater focus on major outcomes.

3.10 | Other issues

The computerized tomography (CT) imaging findings of COVID-19 infection are characterized by ground-glass opacity and patchy consolidation, which are common for both cancer patients and the general population. Shi et al²⁸ report that ground-glass opacity can be detected on CT lungs even before the onset of symptoms. During the subsequent 2 weeks, this sign is found to increase and decreases gradually by the third week. During imaging, signs of patchy consolidation in the lung tend to appear during the first or second week after the onset of symptoms. In some scenarios, this could rapidly evolve into bilateral extensive consolidation leading to poor prognosis. The same appears as a white lung on CT.

Childhood cancers are known to be aggressive, needing immediate treatment with intensive multiagent chemotherapy. In this context, Kotecha et al¹¹ opine that postponement of therapy may not be an option for children. However, the immunosuppressed state of childhood cancers contributes to their vulnerability for infections. Younger children (≤ 5 years) are reported to manifest severe clinical events of COVID-19 when compared with older children (≥ 6 years), given the immature nature of their immune system.

4 | DISCUSSION

The current COVID-19 pandemic has resulted in reprioritization of resources by the Global health systems, and has increased the challenges faced by cancer patients. This includes disruption of treatment and care, such as rescheduling of surgeries and radiotherapy, redesigning chemotherapy regimens, and interruption of supply chain systems for essential medicines (including palliative care). The redeployment of healthcare staff for the national COVID-19 response will result in lost opportunities for diagnosing cancer at an early stage. As concerns regarding coinfection exist among immunocompromised cancer patients, the continuity of care will be interrupted. The pandemic can cause distress in the community, and cancer patients could

be compounded by a variety of psychological problems such as panic disorder, anxiety, and depression.

A significant public health measure being implemented by many countries include social distancing measures, such as national lockdowns, which tend to reduce the COVID-19 related deaths in an ad hoc manner and results in the spread of non-avoidable mortality over a long period of time (flatten the curve). As a result of the same, clinical activities including oncology care have been relegated to second priority.²⁹ Current public health measures, which are conceptualized for controlling the spread of the disease, are aimed at decreasing elective procedures and preventable hospital admissions.³⁰ Many cancer patients tend to stay indoors and tend to indirectly benefit from this auto-distancing measure.

Given the prevailing media induced fear of COVID-19 infection, individuals may not seek screening and early diagnostic services for cancer care. This delays many modalities of diagnostic process such as biopsy procedures. The pathways and models of care in healthcare institutes have changed due to COVID-19 specific care. Despite the travel restrictions during the lockdown, patients have to visit an oncology institute for treatment and should endure the formalities of a COVID-19 check-up.

Oncologists dilemma in the current situation includes titrating the dose density and intensity of treatment, for the optimal management of metastatic and adjuvant cancer patients. Patients are thus subjected to suboptimal treatment and undetected disease recurrence.²⁹ The COVID-19 prioritized health system causes a less organized multidisciplinary teamwork, upward stage migration at diagnosis, and reduced follow-up care, which, in turn, has an impact on the cancer morbidity and mortality. The death count of cancer patients could have been added to those due to the toll of COVID-19. Smoking status and other systemic comorbidities can skew the mortality rate. Clinical trials on cancer patients could be subject to protocol deviations as the survival endpoints could be potentially affected by COVID-19 related deaths. However, the rationale of research findings may be influenced by the varying stages of COVID-19 disease and heterogeneity of cancer types.

The exposure assessment among cancer patients includes the incidence of COVID-19 infection. The blunted immune status among cancer patients due to chemotherapy-induced myelosuppression is characterized by suppressed induction of proinflammatory danger signals, impaired dendritic cell maturation, overexpressed immunosuppressive cytokines, and enhanced functional immunosuppressive leukocyte population.³¹ This is contrary to the sequence of severe events in a COVID-19 patient wherein the instigating processes include an overwhelming inflammation and cytokine-associated lung injury. CD4⁺ T cells enhance the ability of cytotoxic T cells to clear the pathogens, however, severe COVID-19 cases manifest with features of immunosuppression (reduced CD4⁺ T cells). Until effective drugs targeting SARS-CoV-2 become available, the inherent immunity of the patient will determine the prognosis following supportive care.

During the course of cytokine storm in a COVID-19 patient with ARDS, there is overproduction of early response proinflammatory cytokines (tumor necrosis factor, interleukins 6 and 1 β). This causes

vascular hyperpermeability, multiorgan failure, and eventual death. TNF- α facilitates apoptosis of cells lining the lung epithelial and endothelial cells, ultimately causing vascular leakage, alveolar edema, and hypoxia.²⁷ TNF- α has been identified as a mediator inducing hemorrhagic necrosis in tumors and airway hyper-responsiveness in viral infections. Therapeutic strategies should target the overactive cytokine response or use immunomodulating agents, titrating its dose for maintaining an adequate inflammatory response for clearing the pathogen.³²

Inflammation could be further augmented via proteinase-activated receptors (PAR) principally PAR-1, which mediate thrombin-induced platelet aggregation and the interplay between coagulation, inflammation, and the fibrotic response. These pathophysiological aspects cause fibroproliferative lung disease as in patients with severe COVID-19.³² Among cancer patients, the myocardial damage is exacerbated by the synergism of cardiotoxic cancer treatment and COVID-19 infection. This could be mediated through pro-oxidative, proapoptotic, and proinflammatory effects. Highly cardiotoxic anticancer therapies include anthracyclines, human epidermal growth factor receptor 2 (HER2) blocking antibodies, tyrosine kinase inhibitors, proteasome inhibitors, and immune-checkpoint inhibitors. Quagliariello et al's⁸ review reports the cumulative incidence of adverse cardiac events following combinatorial anticancer therapies as 16.4%, 23.8%, and 28.2% after 1, 2, and 3 years of cancer, respectively.

The coagulation pathways are also activated during the immune response, due to the defective balance between the procoagulants and anticoagulants. SARS-CoV-2 causes platelet adhesion and coagulation by reducing the availability of angiotensin II, increasing plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), and urokinase expression.⁸ It activates the damage-associated molecular patterns (DAMP) in endothelial cells, leading to the activation of monocytes by increasing the phosphatidylserine residues. The virus hastens the coagulation process by reducing glycocalyx and anti-thrombin factors on the cells, thus changing the extracellular matrix in the endothelium.⁸ These processes predispose the development of microthrombosis, onset of disseminated intravascular coagulation (DIC), and multi-organ failure, as seen with severe COVID-19 patients. Raised D-dimer concentration is a poor prognostic feature, and DIC is common among non-survivors.³² Biomarkers of organ damage include NT-pro BNP and decreased albumin-globulin ratio, which are associated with the severity of COVID-19 and validated in Tian et al's¹³ study. The coexistence of venous thromboembolism exacerbates the ventilation-perfusion mismatch, and the synergism of coagulation and inflammation results in poor outcome.

In this context, we need to assess the attenuation role of PAR antagonists, low molecular weight heparin, and other coagulation protease inhibitors. We could possibly ameliorate disease progression and severity of COVID-19 by using antithrombin and antifactor Xa direct oral anticoagulants. When we factor the bleeding risk for these anticoagulants, the benefits should be initially weighed, and subsequently the usage of reversal drugs (for these inhibitors) should be considered.³²

Cancer patients are reported to face higher risk of venous thromboembolism, atrial arrhythmias, and bleeding events. Quagliariello et al⁸ report a study, which indicates that 25% of cancer patients hospitalized in the ICU for COVID-19 had venous thromboembolism. Here again, the anticancer therapies tend to synergize with SARS-CoV-2 toward exacerbating intravascular coagulative damages.

The risk:benefit ratio of systemic antitumor therapy has to be evaluated, which includes the performance status of the patient, age, comorbidities, and the number of hospital visits required for therapy.⁷ With intent to limit the number of hospital visits, Cancer core Europe³³ recommends converting intravenous treatment to oral or subcutaneous regimens where possible, and cytotoxic chemotherapy to less toxic monotherapy. To circumvent the immunosuppressive effects of chemotherapy, providers need to consider staggered regimen or alternate therapies such as biological/immunotherapy, targeted therapy, antiangiogenic drugs, hormone therapy, and/or antibody-based therapeutics. Targeted therapies (eg, tyrosine kinase and PIK-mTOR pathway inhibitors) and immune-checkpoint inhibitors are not favored in severe cases of COVID-19.³³ Once the disease has been stabilized, physicians should also consider pausing the treatment. Tang³⁴ opines that timely diagnosis and treatment is warranted for tumors such as lung and pancreatic cancer, acute leukemia, and aggressive lymphoma. Therapeutic interventions could be delayed for others such as breast and thyroid cancer. The authors³⁴ opine that cancer patients have worse clinical outcomes of COVID-19 than those without cancer. Tian et al¹³ also opine that cancer patients with COVID-19 are more likely to deteriorate into severe illness than those without cancer.

Sud et al²⁰ opine that substantial mortality will result from diagnostic delays, more so when the additional diagnostic capacity for catching-up with the backlog is further delayed. Healthcare delivery will be challenged by the new requirement for PPE, physical distancing, and infection control. Pathways of care could be better adapted and referrals could be prioritized through pluralistic information exchange between primary care, diagnostic, and treatment services. Patient education is important for preventing the deferment of presenting with cancer symptoms to the primary care physician.

Maringe et al²³ report that the COVID-19 pandemic measures in United Kingdom have reduced the number of people accessing health care and the availability of diagnostic services. Referral routes to diagnosis are characterized by differences in both stages at presentation and survival. When compared with routing from a general physician and secondary care referral routes, diagnosis by the 2-week wait referral and emergency presentation are associated with later stage of disease. The author²³ opines that the pandemic has, however, resulted in an increased diagnostic efficiency of the healthcare system.

Given the novel nature of this COVID-19 pandemic, there is a lack of universal guideline for treatment of cancer. Oncologists need data and models that will enable evidence-based assessment of the risk/benefit ratio of anticancer therapies during the COVID-19 pandemic.³³ The need-of-the-hour is to prioritize health conditions such as acute leukemia and other aggressive diseases, and continue

adjuvant and neoadjuvant therapies while delaying palliative therapies for poor prognosis patients. Intensive therapeutic interventions should be prioritized for those with comorbidities or the elderly age group. Medical staffs performing laparoscopic procedures are exposed to aerosolized specimen from patients, and such procedures need to be prioritized in cancer surgeries. Endoscopic diagnostic procedures, particularly bronchoscopy, should be limited to the absolute necessity with application of strict personal protective measures. Virtual psychological interventions should be an essential part of the management.

The impact of the pandemic can be overcome by promoting at-home screening tests, which also promotes access to primary health care during the post-pandemic times as well. The emerging findings regarding home-based patient screening indicates that it is both accessible and acceptable to the patients across diverse population groups,¹⁷ thus reducing the embarrassment these tests accompany in a physician's office. To facilitate the concept of self-screening for breast, cervical, and colorectal cancers, the transformation of health care institutions initiated by this pandemic needs to be sustained. This includes changes in the workflow, training of providers, and patient engagement. At a time when resources (staff, logistics) are devoted for the fight against the COVID-19 pandemic, an organized national screening program, such as in United Kingdom, generally yields reductions in cancer-related mortality when compared with opportunistic screening as in United States and India.

5 | CONCLUSION

The reprioritization of healthcare services due to the COVID-19 pandemic has affected the screening and diagnosis of cancer. The inherent fear of contracting this contagious pathogen from a healthcare facility dissuades patients/beneficiaries from accessing cancer care. The combination of perceived risk (for clinicians and patients) and redeployment of staff will result in diagnostic delays, which could affect survival. Delay in diagnosis will increase the stage progression of cancer patients, and increased mortality in the future. Once the pandemic has passed its peak, this inaccessibility might cause a surge in demand for cancer-related services. The need-of-the-hour is provision of stronger personal protection measures for cancer patients and providers, to prevent cross-infection.

Although global research is focused on evolving treatment regimens and inventing vaccine for COVID-19, it is imperative to minimize the risk of exposure to SARS-CoV-2. Healthcare facilities need to prioritize infection control measures for preventing the spread of this virus via respiratory droplets. Surveillance for newer risk factors such as elevated TNF- α and NT-proBNP, and decreased CD4+ T cells or albumin-globulin ratio would aid in assessing the progression of COVID-19 (apart from the established factors such as old age, decreased lymphocytes, elevated IL-6, procalcitonin, and D-dimer). Public health messaging should accurately convey the consequence of severe illness from COVID-19 vs the risk of not seeking healthcare advice if patients are symptomatic.

Some late-stage cancer patients in remission or receiving palliative care may need home healthcare services, primary care consultation, or supportive care medications for the disease. Disruption of such services due to the existent pandemic could hasten morbidity and also cause premature death among such patients. A better approach is to promote telephone consultations, home delivery of oral medications, and collection of biological samples. Routine diagnostic investigations could be addressed through outreach programs.

Any delay or discontinuation of cancer care due to the pandemic could have a detrimental impact on the outcome of cancer. The key is to balance the continuation of urgent cancer care, but rationing the elective treatment according to the circumstance. We need to be mindful of the equivocal prognosis due to these ad hoc adaptations, while simultaneously prioritizing patients with substantial improvement in the quality of life or overall survival gain. The pandemic preparedness plan should include evidence-based continuity of care for cancer patients, for countering the collateral damage due to reallocation of resources. During the course of this pandemic, it is an exhaustive challenge to secure the supply chain of cancer medicines and devices. The absence of a tailored approach of care to cancer patients seems more detrimental than SARS-CoV-2 infection in a cancer patient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Vinod K. Ramani, Radheshyam Naik

Funding acquisition: Vinod K. Ramani

Writing—original draft: Vinod K. Ramani

All authors have read and approved the final version of the manuscript.

ORCID

Vinod K. Ramani  <https://orcid.org/0000-0002-6531-9579>

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