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Review

COVID-19 and cancer: Sailing through the tides

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ABSTRACT

The COVID-19 (coronavirus disease) pandemic caused by SARS-CoV-2 with its rapid expansion has led to extraordinary implications in our understanding of viral infections and their management globally. In this current scenario of unusual circumstances and public health emergency, the cancer care per se is facing unprecedented challenges. The peculiarity of the SARS-CoV-2 infections is still being uncovered as the pandemic spreads across the populations than showing signs of its curtailment. The review highlights the significance of idiosyncrasy of the SARS-Cov-2 infection especially putting forth the importance of immunosenescence, both in the COVID-19 specific immune response in the infected lungs of the elderly and in the cancer patients infected with SARS-CoV-2.The focus of the article is directed towards demystifying the unparalleled essence of a pro-protein convertase, Furin in the biology of the SARS-Cov-2 infection and its role in facilitating viral transmission through expedited cellular entry into alveolar epithelial cells in COVID-19 infected cancer patients. The risk stratification of the cancer treatment and guidelines shaped up by national and international oncology societies in providing uncompromised patient care during the COVID-19 crisis have also been addressed. The global efforts towards vaccination in developing SARS CoV-2 immunity are also discussed in this article.

1. Introducing the spiky invader: the coronavirus

The respiratory pathogen named as Severe Acute Respiratory Syndrome corona virus-2 (SARS-CoV-2), accountable for Corona virus disease (COVID-19) displays a reminiscence of an unseen threat to humanity from an old viral enemy. The global emergence of the SARS-CoV-2 infection, since its first occurrence in Wuhan, China in December 2019 has up surged as the third largest corona virus epidemic after the SARS-CoV in 2012 and Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012 [1]. Following its initial discovery, the COVID-19 has led to a global widespread affecting more than 200 countries. The overwhelming escalation in the number of coronavirus infections has forced the researchers and epidemiologists across the globe in a competitive battle to understand the underlying biology and etiology behind the spread of COVID-19.

Coronaviruses (CoVs), first identified by Tyrell and Bynoe in 1966, in patients with viral-like upper respiratory illness [2] are positive single-stranded RNA viruses that can infect humans and animals. The morphological resemblance of the core shell and glycoprotein projections from the envelope of these spherical viruses as visualized by electron microscopy towards a “crown-like” appearance gives their name as coronaviruses [3]. SARS-CoV-2 has distinctive infectious mechanisms from other CoVs of beta-CoVs subgroup, such as SARS-CoV and MERS-CoV. The most characteristic one as discovered by the genomic analyses of the new coronavirus is the ‘Spike (S) protein’ of the SARS-CoV-2 that attaches the virus to the hosts or target cell membrane via the host cell receptor ACE2 (angiotensin-converting enzyme-2), for infecting any human cell expressing it, especially the lung alveolar epithelial cells and hence the name ‘Spiky Invader’ [4].

Abbreviations: ACE-2, Angiotensin-converting enzyme-2; ACS, American college of Surgeons; ADT, Androgen Deprivation Therapy; ARDS, Acute respiratory distress syndrome; ASTRO, American Society for Radiation oncology; Ca, Cancer; CDC, Center for disease control and prevention; CoVs, Coronaviruses; COVID-19, Coronavirus disease 2019; CI, Confidence Interval; CRS, Cytokine Release Syndrome; CVD, Cardiovascular Diseases; ESMO, European society for Medical Oncology; H& N, Head & Neck; HER, Human Epidermal Growth Factor Receptor; ICU, Intensive Care Unit; IFN-γ, Interferon Gamma; IL, Interleukin; IPD, In patient department; MERS-CoV, Middle-East respiratory syndrome coronavirus; NK cell, Natural Killer Cell; Leuk, Leukemia; OPD, Outpatient Department; OR, Odds Ratio; OSCC, Oral Squamous Cell Carcinoma; PCa, Prostate Cancer; RBD, Receptor Binding Domain; RT, Radiotherapy; SARS-CoV-2, Severe Acute Respiratory Syndrome corona virus-2; TMPRSS2, Trans-membrane Serine Protease 2.

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2. COVID-19 and cancer: unusual clinical manifestations

The onset of COVID-19 infection is marked by typical symptoms including fever, cough, dyspnea, sore throat rhinorrhea, chest pain, diarrhea, muscle pain, nausea, vomiting, anosmia and dysgeusia with severe clinical manifestations reported to occur in one third of patients with COVID-19 in the form of acute respiratory distress syndrome (ARDS), acute renal failure, acute respiratory injury, septic shock, and severe pneumonia. However, it has been seen that the extremities of this disease can range from that of an asymptomatic disease to ARDS, requiring aggressive measures to death [5,6]. Currently, with no available vaccine or any approved treatment modalities until date, clear evidences pertaining to higher degrees of severity of Covid-19 symptoms with adverse outcomes are associated with elderly patients, and other co-morbidities like Hypertension, Diabetes and Cardiovascular Diseases (CVD) and even immuno-compromised conditions like Cancer [7]. The increased vulnerability and relative risk factors of the cancer patients towards severity of COVID-19 complications can be endorsed to the immunosuppressed status due to the malignancy and anticancer treatments, such as chemotherapy or surgery. For instance, one of the foremost evidences came from a study by Liang et al. involving 1590 patients with confirmed COVID-19 in China, revealing 18 patients (1%) with a history of cancer, particularly lung cancer [8]. The poorer cancer treatment outcomes in COVID-19 in this study exposed the increased risk of cancer patients towards COVID-19 related serious events, as evidenced with a ~3.5-fold increase in the risk of such COVID-19 positive cancer patients needing mechanical ventilation or ICU admission or dying compared with patients without cancer (OR 5.4, 95 % CI 1.8–16.2). Therefore, with such drastic outcomes from COVID-19 infection liked to cancer, suggesting potentially that recent antineoplastic therapy may impair immunity, more intensive attention and surveillance or treatment should be paid to COVID-19 positive cancer patients, older patients or those with other comorbidities displaying rapid clinical deterioration.

However, clinical data from China report that about 15–20 % of patients have severe diseases with interstitial pneumonia, progressing to acute respiratory distress syndrome (ARDS) [9,10]. Pneumonia includes decreased oxygen saturation, with severe bilateral ground glass abnormalities, patchy consolidation, and alveolar exudates [9,10]. In such patients with ARDS, a spike in the levels of pro-inflammatory cytokines mediated characterizes the virus induced aberrant host immune response, which resembles the clinical and serological features of cytokine release syndrome (CRS). Cytokine Release Syndrome (CRS), a pathogen responsive innate immune activity, leading to an unrestrained release of cytokines like IL-6, IFN- γ or cytokine storm, was first documented in the year 1989, during the usage of anti-T cell antibody muromonab-CD3 in the treatment of solid organ transplantation [11]. CRS can influence fatal consequences leading to detrimental effects such as leakage from capillaries, tissue toxicity and edema, multiple organ failure and shock. The consequence of CRS include epithelial and endothelial cell apoptosis and vascular leakage, suboptimal T cell response (impaired virus clearance), accumulation of alternatively activated macrophages and altered tissue homeostasis, acute lung injury, and acute respiratory distress syndrome (ARDS) [12]. Usually, CRS is initiated by macrophages, dendritic cell, NK cell, and T cell, in response to pathogen-associated molecular patterns. CRS has been also observed in settings of T cell-engaging immunotherapy like CAR-T cell therapy [13] or anti-PD-1 therapy. Moreover, as compared to healthy controls, COVID-19 patients exhibit significantly higher levels of the exhausted marker PD-1 in their T cells [14]. Recent study also highlighted a significant decrease in T cells (especially CD8 + T cells) and increase in IL-6, IL-10, IL-2, and IFN-γ levels in the peripheral blood of severe COVID-19 cases compared to mild cases. Furthermore, the neutrophil-to-CD8 + T cell ratio were identified as the most powerful prognostic factor for severe COVID-19 [13,15]. IFN-γ may initiate cytokine storm in SARS patients [16], while several cytokines including IL-6 may trigger CRS in COVID-19. Additionally, lympho-cytopenia may serve as the risk factor related to cytokine storm and disease severity [15]. It is not likely that cancer patients are still receiving immune-checkpoint inhibitors during this phase of the viral illness such as CRS. Over all, these recent results point out a major role of the host immune response, particularly of CRS, as a determining co-factor in the severe life-threaten form of COVID-19. Thus, treatment of CRS involves the use of both antiviral to control the underlying infection and immunosuppressive agents to dampen the aberrant pro-inflammatory response of the host.

Unfortunately, there are currently no treatments directed at halting the cytokine storm remaining anti-IL-6 antibody, tocilizumab (under investigation) [17] and acute lung injury to stop the progression from manageable hypoxia to frank respiratory failure and ARDS in patients with COVID-19 infection [18]. Preventing progression from early acute hypoxia and cytokine release syndrome to frank hypoxic respiratory failure and ARDS could have a huge impact on the foreseeable overflow of the ICU units. To exacerbate further, the SARS-CoV-2 infections have also put forth an unusual clinical representation encompassing hypoxia development superfluous to patient's symptoms called silent hypoxia [19]. Silent hypoxia, the state of clinical deception by SARS-CoV-2 in symptomatically not connecting with the alarmingly low oxygen levels such as shortness of breath or signs of hypoxic unconsciousness in the COVID-19 patients has baffled the treating physicians all over the world [20,21]. Happy or Silent hypoxia, a misnomer, is described as a scenario where patients who normally become breathless with oxygen saturation levels (SpO_2) falling below 90 are happy and not in a state of breathlessness even with oxygen levels dipping 90 up to 70 % as observed in COVID-19 patients with lung involvement. Nicholas D Caputo.et al. also reiterates that prolonged and unaddressed hypoxia can lead to poor patient outcomes [22]. Astonishingly, these patients will still persist with functionally active lungs even with the high SARS-CoV-2 viral load affecting the lungs with no clues as to how the lungs move that they are able to blow off the carbon dioxide well so that they don't develop the shortness of breath. The patients with silent hypoxia generally seek medical care post 5–7 days of COVID-19 infection with the worst time of hypoxia, whether silent of not occurring at day 10 of infection. This "silent hypoxia" may be a clinical sign that providers can look for to determine if patients are at increased risk of sudden decompensation. Till date, there are no specific criteria to determine or outline the risk factors silent or happy hypoxia leaving some inconclusive correlations with severities of COVID-19 such as ARDS, with patients ending up on ventilators. In such situations, the lungs are very stiff, requiring higher pressures and higher oxygen levels to improve the hypoxemia while the mechanisms behind onset of hypoxemia in these individuals remains far from being lucid.

3. The idiosyncrasies' of the COVID-19 specific lung immunity and cancer: Biological insights of the SARS-CoV-2

The COVID-19 pandemic, a deadly outcome of the invading SARS−COV-2 has delineated the vulnerabilities of the global ageing populations to the emerging viral infections. The silent spread of SARS−COV-2 asymptomatically poses a severe life risk to the older people who are at higher risk for more severe complications due to the well-defined hall marks of aging which affect cellular systems and indirectly affect the immunity to viral infections. The race is gushingly on to design effective COVID-19 vaccines and flow of billions of dollars is being channeled out towards anti−COVID-19 therapeutics to end the pandemic threatening a substantial population of planet especially the elderly. The pandemic response towards this virus remains disillusioned with the lack of unambiguous understanding of means to generate a protective immunity in the older adults to prevent the unprecedented spike in frailty and mortality. A comprehensive insight into the host responses and its variability against the SARS CoV-2 is likely to yield better clinical management and treatment of the elderly infected

patients.

The incidence of severity of COVID-19 associated symptoms has been reported to have more extreme consequences in the elderly than the young. This vulnerability of the aging population towards COVID-19 infection could be attributed to the reduced ability of the immune system to generate antigen specific responses to pathogens and vaccination cumulatively amounting to the higher incidences of infection. One of the most profound and well acknowledged changes displayed by the aging immune system is termed immunosenescence, influencing both innate and adaptive immunity [23–25]. Age-associated regression or involution of thymus involving a decrease in tissue mass and cellularity resulting in loss of tissue organization leading to a net reduction in naive T cell output is believed to contribute radically toward immunosenescence [26–28]. This decline in naive T cell output due to age-dependent altered thymic activity is assumed to impact the properties on the peripheral T cell pool such alterations in phenotype and function, loss of diversity, and replicative senescence [29–33].

Hence, the ratio of naive T cells versus memory T cells is a determining factor in deciding the magnitude of COVID-19 specific adaptive immune response in the infected lungs [34]. The declining levels of naive T cells in the aging lung are a predominant clue for the increased incidence of COVID-19 infections with severity of symptoms in the elderly. The population of naive T cells is initially present in considerable levels in infants and young children to be able to respond to the naive SARS CoV-2 viral antigens but the adults over the age of 30–70 years do not have the same and hence they remain always naïve to the SARS-CoV-2 virus. The elderly patients tested positive for COVID-19 have almost negligible levels of such naive T cells owing to immunosenescence. However, the distributions of the memory T cells predominate in the tissues and with age [34]. The memory T cells mostly infiltrate the lungs where more often than not, the tissue resident memory T cells are present as they do not circulate and have not been exposed to the SARS CoV-2 earlier and thus lack the recall function, a characteristic of memory T cells. Hence, the SARSCoV-2 stimulated memory T cells exhibit a minimal or altered population not enough to generate a protective neutralizing antibody response. A reduction in the number of naïve T cells accompanied by diminishing communication between T cells and antigen-presenting cells, needed to convert naïve T cells to memory cells marks the onset of aging. Thus, a decreased number of SARS-CV-2 specific memory T cells due to immunosenescence, a hallmark of aging in the elderly along with the associated comorbidities contribute to the COVID-19 linked severe illness borne by aging adults. The matters are even put to worse in elderly patients with the age dependent decline in the co-stimulatory signals from the antigen-presenting cells, including macrophages, B cells, NK, and dendritic cells obligatory to activate T cells. Interestingly, the majority of occurrence of the COVID-19 extremities is seen in elderly and the age predominance of the COVID-19 infection can be endorsed to the immune defense less state of the infected lungs deprived of naive T cells (Fig. 1a). Hence, the decrease in the naïve T cells with age as shown by red circles in Fig. 1**a** does not lead to total increase or visible presence of SARS CoV-2 specific effector T cells as represented by yellow circles (Fig. 1a). However, resident memory cells not specific to SARS CoV-2 shown in blue circles in Fig. 1**a** remain increased in numbers. In addition to the compromised SARS CoV-2 specific adaptive immune response, the SARS-CoV-2 results in a delayed dysregulated innate immune response owing to an inadequate production of Type 1 IFN which marks the hallmark of a cytokine mediated effective innate response mandatory for microbial killing against any pathogenic invasion. Put together, such an immune compromise state of the lungs predisposes it as primary site of COVID-19 infection.

The earlier precedence in literature has strongly advocated the increased susceptibility of cancer patients to COVID-19 infection than those without cancer due to their immunosuppressive state ensued by malignancy and anti-cancer therapies like chemotherapy and surgery [35]. The immune evasive mechanisms adopted by tumor cells engages

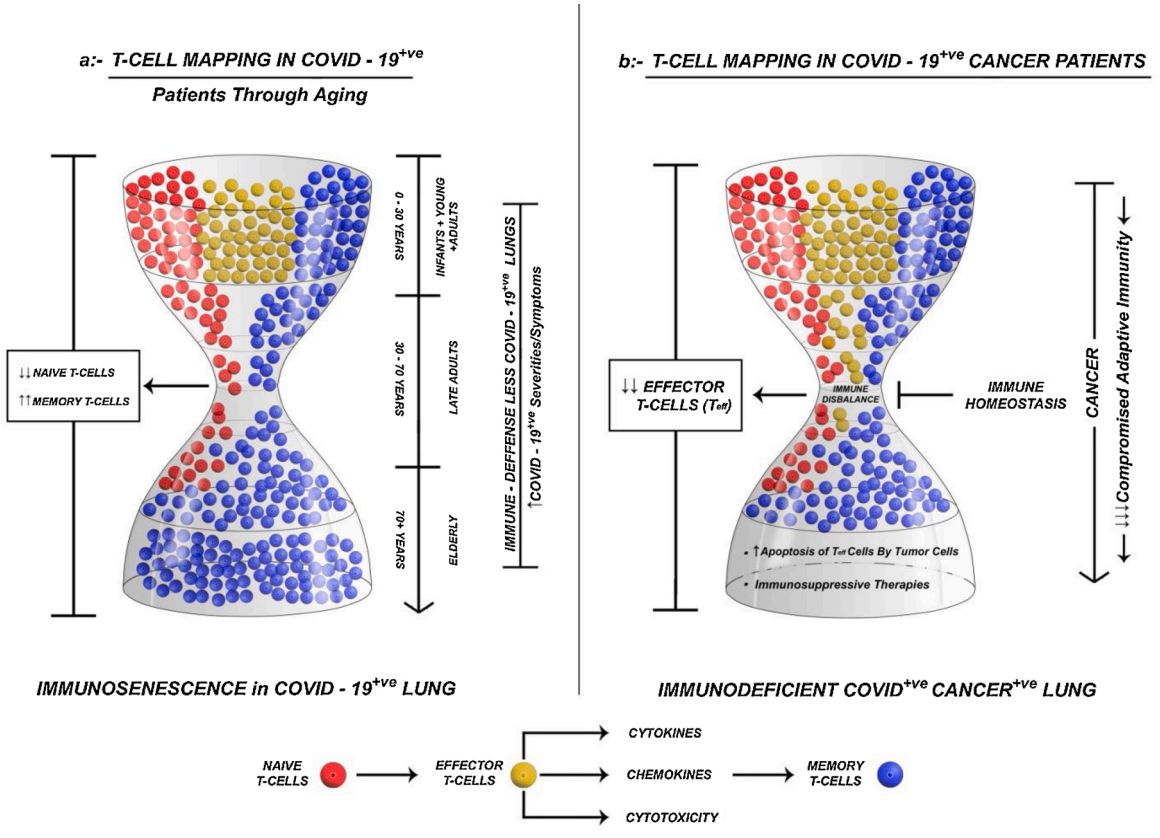

Fig. 1. T-Cell mapping in COVID-19 positive- elderly (Fig. 1a) and cancer patients (Fig. 1b).

strategies to target the immune system especially the effector T cells (T_{eff}) which are tuned by naive T cells to secrete cytokines, chemokines and to gain anti-tumor cytoxicity [36]. The anti-effector T cell mechanisms adopted by the tumor cells [36] ultimately result in the apoptosis of the effector T cells (T_{eff}) leading to an immune disbalance or aberrant immune homeostasis, a state of compromised adaptive immune system contributed also by the immunosuppressive strategies adopted to combat cancer (Fig. 1b). As a consequence, the effector T cells represented by yellow circles (Fig. 1 **b**) show diminishing levels ending up in immunosuppressive state. For instance, to make things worse, cancer treatment outcomes such as lymphopenia is commonly seen in cancer patients is by itself an independent poor prognosis indicator in COVID-19 patients. Thus, under the state of adaptive immune defense less state, it brings cancer as a co morbid condition in the list of highest risk factors for COVID-19 infection.

Thus, in summary, a fiasco in achieving an early command on the SARS CoV-2 infection in the lungs or the respiratory tract probably leads to a high viral burden amounting to dysregulated, potentially lethal, inflammatory responses and immunopathology, and subsequently acute respiratory distress syndrome. Hence, in the elderly and cancer patients will remain particularly prone to COVID-19 owing to immunosenescence and their propensity to mount exaggerated inflammatory responses. It is imperative to say that the COVID-19 vaccines on the go in the clinical trials and launching stages may or may not have a deeply protective and penetrating in the elderly population or in the cancer patients as aging as well as cancer causes the body's immune system to lose some of its vigor due to immunosenescence. It would be wise to vaccinate the young and the healthy populations towards reaching a status of herd immunity so that the elderly do not get infected as the best strategy for subduing the pandemic might fail in exactly the elderly /cancer victims group that needs it most.

4. Furin, a possible prognostic indicator for COVID-19 positive cancer patients??: Molecular traits of the SARS-CoV-2

The SARS-CoV-2 or 'the spiky invader' as it is named due to the involvement of surface glycoprotein, spike "S" protein in human infections, has acquired certain dissimilar but unique characteristic deviations from other Coronaviruses (CoVs) such as SARS-CoV and MERS-CoV. Structural studies of this heavily glycosylated, cell-surface spike (S) protein have exposed the presence of two functional domains, indispensable for host cellular entry, termed as S1 and S [37]. Furthermore, the recent literature also highlights the role of the receptor binding domain (RBD) on the S1 subunit of spike protein and its interaction and binding with host cellular receptor, ACE2, found on the lungs, arteries, heart, kidney, and intestines as principal mechanism responsible for entry of SARS-CoV-2 into lung alveolar epithelial cells [38–41]. Another prerequisite of the viral entry as revealed is the activation or cleavage of the 'S' protein by the host proteases before the binding of the RBD to the host receptor [37]. In this regard, one of the most pivotal observations came from work by Hoffmann and colleagues in March 2020, showing that the pandemic SARS-CoV-2 harbors a functional polybasic cleavage site (RRAR) at the junction of S1 and S2 subunits or the S1/S2 cleavage site which is not found in closely related coronaviruses [4,42]. The cleavage of S1/S2 site consequently permitting the effective activation of 'S' protein is brought about by a ubiquitously expressed calcium dependent membrane bound host protease or proprotein convertase named 'Furin'. The host cell protease Furin-dependent cleavage of the SARS-CoV-2 spike protein at the S1/S2 site is mandatory for spike-driven viral entry and infection of the lung cells as well as for the fusion of infected cells with non-infected cells, accounting for cell to cell transmission within the primary site of viral infection [43]. The identification of the unique furin cleavage site on the S protein of SARS-CoV-2 renders it the ability to infect organs or tissues insensitive to other coronaviruses, leading to systematic infection of SARS-CoV-2 in the body. Following this activation, the S protein then mediates viral attachment to a new host cell but still needs to be activated by another host protease enzyme -receptor transmembrane serine protease 2 (TMPRSS2) in order to efficiently enter the cell [43]. Activation by TMPRSS2, a male sex hormone, androgen-induced serine protease is only possible if the S protein has previously been cleaved by Furin thereby facilitating the entry of the virus into target cell such as the Type 2 alveolar epithelial cells of the lungs [44]. The cleavage of the S or spike protein by Furin exposes the open ended Receptor Binding Domain of S1 or RBD-S1 which is complementary it its binding to the ACE2 receptor on the host cell (Refer Fig. 2). The predisposition of COVID-19 infections towards the darker sex can predominantly be attributed to the hormone regulated expression of TMPRSS2, expediting the risk factor of heightened viral load resulting in high COVID-19 associated mortality rates in males. Hypothetically, acquisition of the Furin cleavage motif (PRRARS|V) might have been presumed to a 'gain of function' that empowered a bat CoV to forge into the humans and begin its current epidemic spread.

The proprotein convertase, furin has a ubiquitous expression and distribution in tissues with augmented expression of furin documented in various cancer types such as lung, head and neck, colon and gynecologic cancers and sarcomas [45,46]. The expression of TMPRSS2 is ubiquitous in all lung tissue types but ACE2 shows a tissue specific pattern specially in the subsegmental bronchial branches where predominant expression of ACE 2 is seen in the transient secretory cell type [47]. In addition to its heightened expression, furin participates in many of the cancer hallmark and tumorigenic processes like cell proliferation, migration and invasion or neovascularization aiding in tumour formation and progression [46]. Interestingly, furin is considered as a pro-oncogenic trigger in the KRAS and BRAF mutant colorectal cancer [48]. Interestingly, hypoxic conditions have also been reported to upregulate furin expression [49,50] and further favoring the relocalisation of intracellular furin to the cell surface, thereby increasing cancer cell invasion [51]. Owing to the concentrated expression of furin in the lungs [4] this fact is taken advantage by the SARS-CoV-2 that engages furin in the activation of its receptor binding domain of its S protein and subsequent binding to ACE2 receptor for viral entry into host cell. Multiple studies indicate the that the over expression of host furin in many cancer cells, is a gain of function in tumor cells in attaching many viral particles due to more activation by furin and increased exposed RBD sites available for ACE2 interaction leading to heightened entrapment of SARS-CoV-2 in tumor cells (Fig. 3b) as compared to normal or healthy cells with ubiquitous expression of furin (Fig. 3a,). For instance, the literature documentations have raised concern for the increased susceptibility of the oral cancer patients towards SARS-CoV-2 infection due to higher levels of expression of furin found in 90 % of oral squamous cell carcinoma (OSCC) and in all squamous cell carcinoma of the oesophagus thereby exposing oral cavity as the most vulnerable tissue for SARS-CoV-2 infection. To make things worse the expression of furin was seen to be higher in samples obtained after radiation in post radiotherapy recurrent laryngeal cancers possibly suggesting a radiation induced over expression of furin in recurrent or resistant cancers [52]. Oral mucosa in pathological states such as chronic periodontitis/oral cancer have been reported to exhibit activating levels of p38 mitogen-activated protein kinase, leading to elevated levels of protease furin [53]. The increased cellular entry of a large number of viruses at a time actually leading to increased viral load in the patients with oral cancer or any of the furin over-expressing cancers in due course signify a very poor prognosis of COVID-19 in cancer patients. However, owing to paucity of observational as well as epidemiological evidences, a precise and thorough analytical study still eludes the clinician researchers in attributing a definitive prognostic indicator status for furin in COVID-19 positive cancer patients and a lot needs to be validated in a larger patient volume and different geographical locations.

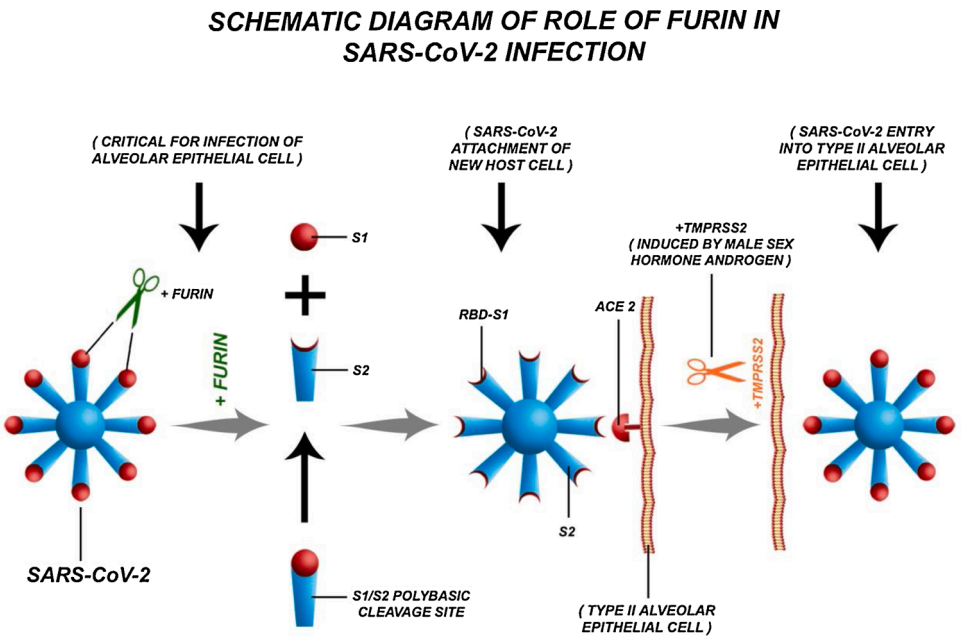

Fig. 2. Schematic diagram of the role of furin in SARS-CoV-2 infection.

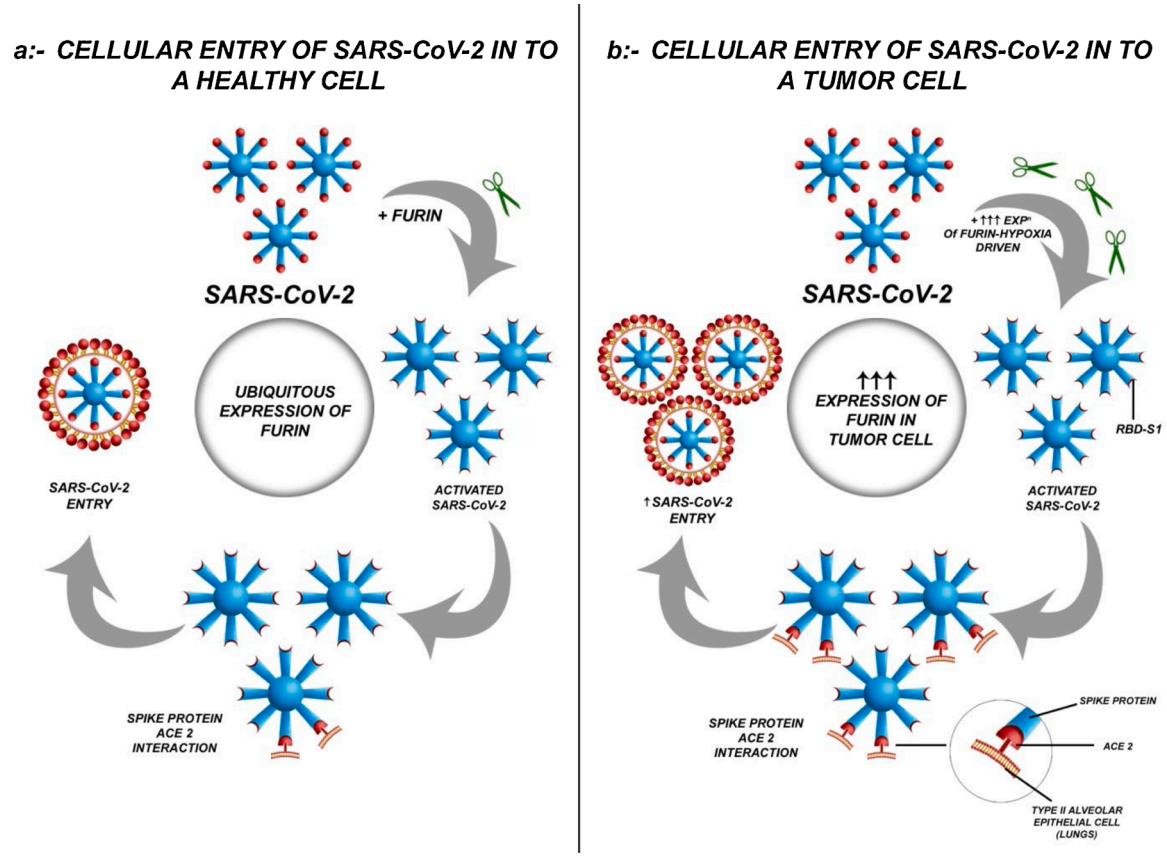

Fig. 3. Cellular entry of the SARS-CoV-2 in to a healthy cell (Fig. 3a) and a tumor cell (Fig. 3b).

5. Risk stratification: A simple handle in triaging of cancer patients during COVID-19 pandemic :International Health Care recommendations

The pandemic poses several challenges for oncology health care settings. Healthcare professionals have to think about how to reduce their patients' exposure to health-care facilities.

The challenges faced by physician's or surgeons treating cancers are unique, because most of the procedures cannot be delayed beyond a certain point of time due to biology of the disease and adverse impact on survival. Due to the protracted nature of COVID-19 pandemic, surgical as well as medical oncologist's world over are facing ethical and moral

dilemmas in day to day practice while taking decisions regarding any oncological emergency? The pace at which COVID -19 is going through in India "Without treatment, some cancers could hinder, others could metastasize." Should patients risk exposure to SARS-CoV-2 in order to receive treatment for cancer?

Hence specific guidelines have to be tailored based on the extent of disease in that particular region. An in-depth analysis of the recommendations and the prevalent conditions in Europe and the USA helped us reach a consensus for directing cancer management for patients in our country. The face of this pandemic is ever changing, and these recommendations may need to remain in a constant state of flux, serving as a skeleton for cancer health care setting.

Herein, we address the question of risk categorization for patients with cancer requiring treatment in SARS-CoV-2 endemic areas that can be used to channelize decision making process on delaying or continuing cancer treatment in COVID-19 pandemic. Risk categorization – strategy for the delivery of cancer therapies in the context of a pandemic will be strongly influenced by both the magnitude of potential treatment benefit and therapeutic intent. The proposed strategy is mainly focused on categorizing the patients into low, intermediate and high risk group of disease progression with cancer treatment delay and it is considered to be safe to delay the treatment for >2 to 3 months with low risk of disease progression in patients with hematological cancers [54]. Surgery and radiotherapy can also be delayed for the same risk group. This can be applicable for non-melanoma skin cancer, non-locally advanced breast cancer, low or intermediate-risk Prostate Cancer, low-grade lymphoma and other low-risk cancer diseases [54].

On the contrary, treatment hindrance is not recommended in patients who are at high risk of disease progression with treatment delay including patients with rapidly progressive tumors with increase mortality risk, brain, leukemia, lymphoma, colon cancer, ovarian malignancy, and small cell lung cancer (Fig. 4).These suggested severity-driven recommendations might provide a clear glimpse to Onco-physicians/surgeons to channelize the treatment plan about positive COVID-19 cancer patients, risk of procedures, and solutions to deliver optimal care to the patients in these extra-ordinary circumstances.

5.1. Combating COVID-19 in oncology settings

The need of the hour in the current stage of this unstoppable contagion is to focus on how the healthcare professionals can ensure a balance of uncompromised cancer care long with reduction of their patients' exposure to health-care facilities. The COVID-19 crisis has brought unprecedented challenges in the management of those who are afflicted, by overwhelming healthcare systems and causing great stress to the healthcare workforce providing care to immune-compromised cancer patients, amidst this pandemic, has been extremely challenging. As the pandemic accelerates, health care providers and their safety has become the prime area of concern. According to Remuzzi et al. 20 % of health-care workers were infected, and some have died [55]. In this global response, the safety of health-care workers must be ensured, thus strict measures (minimize chance for exposures, adhere to standard and transmission-based precautions, precautions while performing aerosol-generating procedures, implement engineering controls, train and educate health care personnel, implement environmental infection control etc) and an adequate supply of leaky proof quality approved PPE is obligate to their preparedness to face the war against the COVID-19 positive patients [53].

The current situation investigates two fundamental prospects regarding welfare of patients. First, frequent visits by cancer patients to hospital for treatment and disease surveillance, which in turn can possibly expose them to infection. Second, cancer treatments themselves can predispose patients to the more serious harmful effects of COVID-19.

For outpatient department (OPD) it is recommended that patients with no history of epidemiological exposure and no symptoms such as fever can be allowed to enter the hospital; otherwise, patients should be

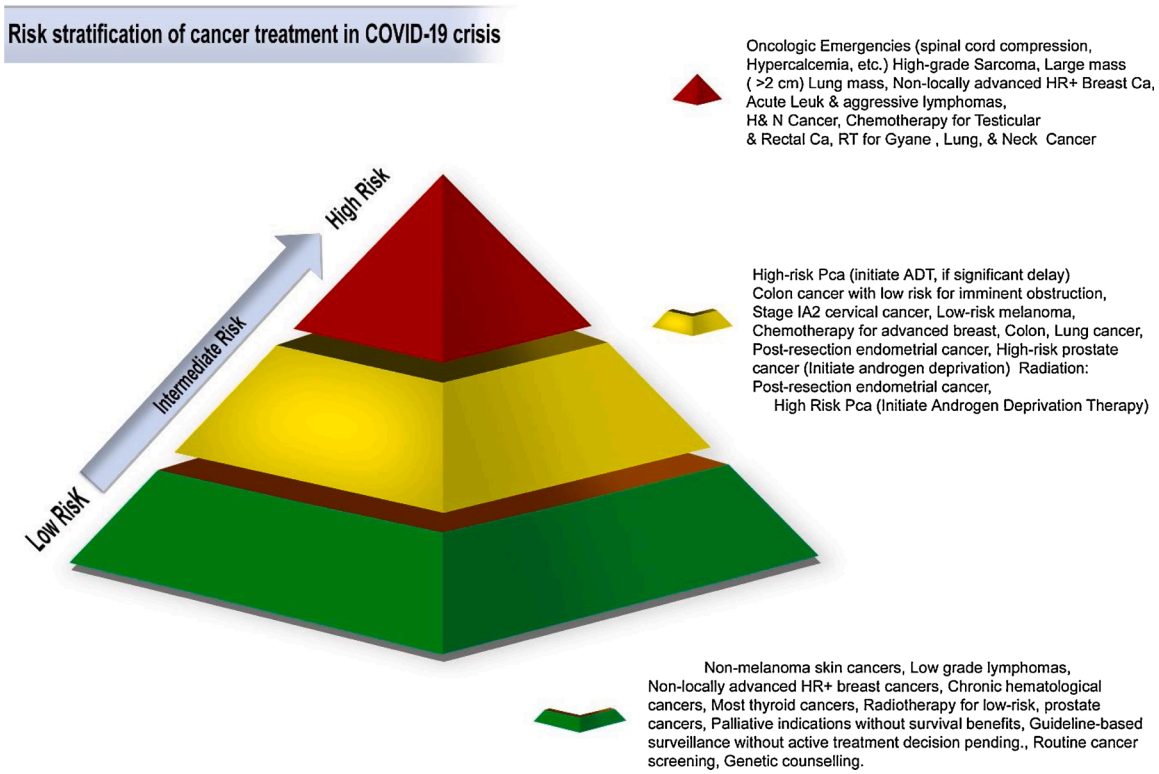

Fig. 4. Risk stratification of cancer treatment during COVID-19 crisis. COVID-19: coronavirus 2019; Ca: Cancer, H& N: Head & Neck, PCa: Prostate Cancer, RT: Radiotherapy, Leuk: Leukemia hormone receptor–positive; ADT: Androgen Deprivation Therapy, HER: human epidermal growth factor receptor–negative.Adopted from [51] with permission.

transferred to the isolation ward, where concerned doctor can attend the patient [56]. This practice may allow minimizing the risk of alleviating exposure and possible further transmission link. For in-patient department (IPD) the infection control regulations and control measures for COVID-19 must be strictly implemented. The number of medical or para-medical staff in the ward should be restricted. According to the risk of exposure of different positions, stratified protection measures should be taken to reduce the risk of nosocomial infection. Based on other hospital experiences, three areas are recommended (a clean area, a potential contaminated area and a contaminated area), two channels (a medical staff channel and a patient channel) and an isolation room.

Studies by Liang et al. have proposed three important strategies may be used to mitigate the COVID-19 crisis, for prevention of infection affecting cancer patients. Given the undisguised vulnerability of the cancer patients undergoing chemotherapy or surgery and the current evolving situation, pragmatic approaches such as delaying adjuvant chemotherapy or elective surgery in stable cancers, implementing strict personal precautions for cancer survivors, and execution of intensive care COVID-19 positive cancer patients with comorbidities are suggested approaches needed to deal with the challenges of treating cancer patients, without jeopardizing their care during the COVID-19 infection crisis [8].

Surgery is the major component in cancer management the Centers for Disease Control and Prevention (CDC) and the American College of Surgeons (ACS) have advised rescheduling elective surgeries if possible. Evidence suggests that patients who received surgery and concomitantly contracted COVID-19 were at much higher risk of severe clinical events than those who did not have surgery [8]. In spite of these advisories, it is important for clinicians and patients to have risk assessment discussions prior to making treatment decisions especially in the context of chemotherapy & radiotherapy, key components of cancer treatment [55]. Considering varied clinical scenarios, the American Society for Radiation Oncology (ASTRO) recently published brief guidelines for radiation oncologists dealing with COVID-19 pandemic. As noted by ASTRO, if considered reasonable, hypo-fractionated schedules are encouraged. Additionally, in patients with rapidly progressing disease or potentially curable tumors where Radio Therapy significantly impacts survival, treatment should be prioritized as benefits outweigh risks (57). Treatment decisions should be taken in the context of a multidisciplinary tumor board, which may take place virtually. The decision-making should balance risk and benefits of treatment in the context of the specific pandemic level, on a case by case discussion, always including patients' preferences. The capacity of a specified health facility in terms of ensuring social distancing, healthcare worker availability, inpatient versus outpatient care, catchment area would also be important factors to consider. Hence, training, reassurance, psychological upliftment and support of the primary health care workers are a much needed priority. Providing remote care, prioritizing treatment and deferring intervention wherever possible, along with ascertaining the protection of patients and care providers from COVID-19, are the formidable challenges to be handled by the physicians besides maintaining their own physical and mental well-being.

Table below summarizes the different types of cancer associated with COVID-19 and provides a glimpse of the strong connection between COVID-19 and cancer (Table 1).

6. The roads less travelled in the COVID-19 Era??

COVID-19 with its present day prevalence has put forth more unanswered and leading questions than treatment solutions to be offered to cancer patients. Hence, answering these questions might open up unexplored routes for prevention of unusual modes of transmission for the immunologically defenseless cancer patients in clinical or cancer health care settings.

Table 1
Summary of different types of cancer associated with COVID-19.

CANCER	AUTHOR	YEAR	PMID
Oral Cancer	David Forner et al Y Li et al Lavinia barbieri et al	2020	• PMID: 32,599,499 • PMID: 32,105,052
Esophagus	C M Jones et al	2020	• PMID: 32,322,892PMID: 32,299,723
Head & Neck Cancer	Francesca De Felice et al Andrew G Shuman et al J Luo et al	2020	• PMID: 32,247,204 • PMID: 32,329,948
Lung Cancer	Yan Xu et al	2020	• PMID: 32,561,401PMID: 32,077,441
Gall Bladder	S Bennett et al	2020	• PMID: 33,173,390
Kidney Cancer	Michael Staehler et al Yasser Ged et al	2020	• PMID: 32,943,372 • PMID: 32,494,029
Bladder Cancer	Tina Wang et al Francesco Esperto et al	2020	• PMID: 32,455,894 • PMID: 32,549,074
Prostate Cancer	Neil A Bhowmick et al	2020	• PMID: 32,508,311
Ovarian Cancer	Vincenzo Dario Mandato	2020	• PMID: 32,275,775
Breast cancer	Jennifer Y Sheng et al	2020	• PMID: 32,603,252
Cervical Cancer	Maria Del Pilar Estevez-Diz et al	2020	• PMID: 32,582,375
Colorectal cancer	Xianghai Ren et al	2020	• PMID: 32,395,542

6.1. The second era of COVID-19 pandemic: Vaccination as the possible way out of the SARS-Cov-2 tunnel

One of the path breaking solutions to the biggest health emergency, COVID-19 pandemic has been the consequence of indomitable efforts made by the immunologists and vaccine biologists to develop a multitude of four different kinds of vaccine which have raised the hopes towards achieving global immunity against SARS-CoV-2. The efforts have reached unexpected success in the launch of four vaccines currently showing great promise to mitigate the best immunological response against the SARS-CoV-2 virus generating highly protective anti-SARS-CoV-2 antibodies. The vaccine biologists and developers of these vaccines (Covishield, viral vector vaccine; Covaxin, whole virus vaccine; Moderna and Pfizer, mRNA vaccines) aim to stop the transmission through a single goal i.e. to stimulate an immune response to an antigen in the virus which is typically the characteristic spike protein in case of SARS-CoV-2 (Fig. 5).

7. Conclusion

The COVID-19 pandemic has acquired the peak as century's greatest public health crisis. The health crisis encircling COVID-19 continues to evolve and remain dynamic with weekly changes in guidelines and policies as we write. The crisis has put forth extraordinary challenges in the management of patients and healthcare work force as cancer care and COVID-19 persist to collide, facing an overwhelming escalation in the number of COVID-19 cases. From the onset of COVID-19 in December 2019, the understanding of the idiosyncrasy of SARS-CoV-2 which has been gathered over the last few months, have proven to be quintessential for its infection of human cells and provided deep insights into the biology and the immunopathology surrounding the viral transmission and its pathogenesis and might divulge targets for anti−COVID-19 interventions too.

The plan of combat during this delicate scuffle of balancing COVID-19 risks in cancer patients and their treatment solutions needs cautious handling of patient risk stratification and evidence based triaging, astute implementation of the public health strategies thoroughly and wise utilization of hospital resources. Under the increased propensity of the cancer patients likely to be diagnosed with COVID-19 with severe

Key unresolved issues ??

1). What will be the overall impact of the COVID-19 outbreak on cancer patients in India and rest of the world?

2). What is the direct evidence-based clinical correlation between immune suppression, cancer and SARS-CoV-2 infection?

3). Do patients with hematological malignancies treated with greater immune suppression than solid tumors have higher likeli ood of acquiring SARS-CoV-2 infection?

4). How does SARS-CoV-2 infection impact the prognosis of COVID-19 positive prostate or breast cancer patients compared to the age or gender matched non-cancer COVID-19 positive patients?

5). Should cancer curative modalities like chemotherapy or radiotherapy be delayed or modified ? OR Light chemotherapy sessions to COVID-19 positive cancer patients or in general cancer patients is a stop gap answer to aggressive chemotherapy regimens to restore immunity levels in such patients?

6). Is it clinically wise to post pone screening tests (mammogram for breast ca, HPV for cervical ca etc.) to prevent COVID-19 spread at the cost of increments in the number of new cancer cases?

7). In view of the lack of any vaccine or anti-COVID-19 drugs how will it changes in the routine screening programs,diagnosis and treatment practices influence the prognosis and overall survival of cancer patients?

8). What should be the appropriate patient care management of a COVID-19 positive case pre and post-chemotherapy,immunotherapy or targeted therapy?

9). How should the cancer health care settings take preventive measure to curb the rate of nosocomial infections in cancer patients?

10). How much can telemedicine contribute towards the maintenance of survival standard of the cancer patients by limiting access & therapies? Can this ensure overall quality of life of cancer patients by excluding the OPD and hospital flow of cancer patients to keep a check on the COVID-19 spread?

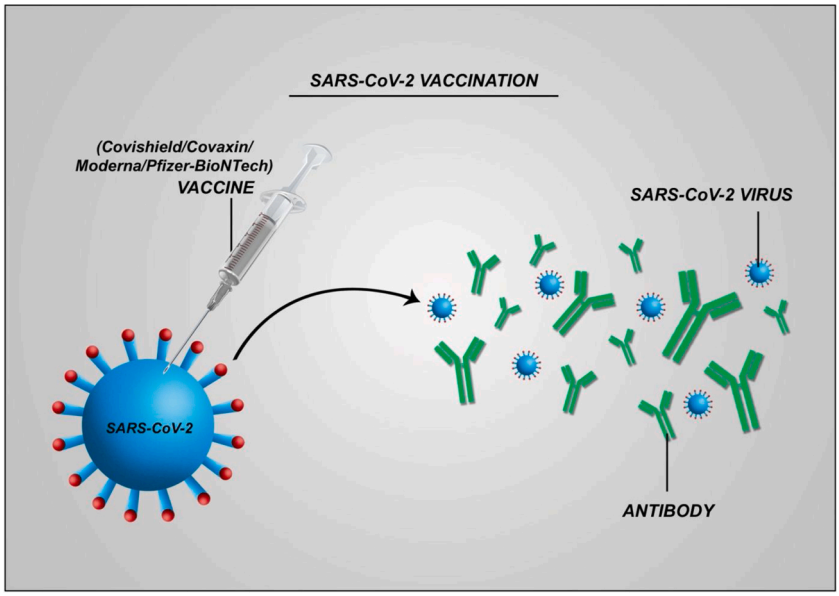

Fig. 5. Developing anti−COVID-19 global immunity through SARS−COV-2 vaccines.

symptoms, the oncologists and treating physicians should necessitate to weigh up the equilibrium between the risks versus cancer care benefits carefully relying on evidence based clinical judgments towards continuing or withholding cancer therapy in COVID-19 cases. The COVID-19 experience in the older populations unleashes the key insights to barge into profound, long lasting solutions to the future of global aging health with regards to pathogenic invasions like SARS-CoV-2 and its accumulated morbidities associated with accelerated aging.

The modern day cancer therapy faces a dual task of encountering COVID-19 in addition to ensuing efforts to develop cancer care policies and procedures towards uncompromised patient care for combating the next outbreak or similar health crisis in the future. Hence, in times to come, the oncologists eagerly await the forthcoming detailed studies shedding light on the clinical impact of COVID-19 on concurrent cancer and on different types of cancer to unravel the means to carry out suitable and curative cancer treatment modalities in the settings of COVID-19 infection.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

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