COVID-19: RISK, CLINICAL OUTCOMES AND MECHANISM AMONG PATIENTS WITH CANCER

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Abstract

Since its first outbreak in 2019, Covid-19 caused by SARS-CoV-2 virus has killed millions of people worldwide. Among those who are affected by the disease, cancer patients are more vulnerable towards this respiratory illness. This review covers the clinical features, risks and mechanism of the disease among Covid-19 patients associated with cancer. Patients with cancer are at higher risk to Covid-19 infection and develop worse clinical outcomes. Among all cancer types, lung cancer patients are the most susceptible for infection, whereas haematological malignant patients are at higher risk of developing severe clinical symptoms and death. Cancer patients are clinically immunosuppressive causing them already susceptible to infection. Infection caused by SARS-CoV-2 virus is highly infectious and contagious causing cytokine and bradykinin storms which make patients with underlying cancer disease to have adverse outcomes and consequently death. Better care for patients with cancer should be emphasised during pandemic to reduce burden of the disease not only to the patient, but also to the overall healthcare system.

Keywords: Covid-19, Cancer patients, SARS-CoV-2

Introduction

The outbreak of new coronavirus (SARS-Cov-2) is an ongoing pandemic, with a total of nearly 235 million cases and 5 million deaths has been recorded worldwide at the time of writing(1). This brings the death rate of Covid-19 to nearly 2%. According to Centers for Disease Control and Prevention (CDC) in the United States, patients with certain underlying medical conditions are at higher risk of contracting severe Covid-19 illness and ultimately lead to adverse outcomes as well as deaths. Among this vulnerable subgroup, patients with cancer are reported to be associated with higher risk of developing adverse outcomes (2). Furthermore, older patients generally develop severe disease symptoms and consequence in comparison to the younger ones.

Therefore, this review aimed to discuss the Covid-19 clinical outcomes, risks as well as the mechanism associated with cancer patients with more focus on the elderly. Management of cancer patients contracting Covid-19 disease and issues surrounding the matters are also outlined in this review.

Clinical features

Generally, patients with cancer contracted Covid-19 are older than 60 years old with males being more prone to get infected (Table 1)(3–7). Patients with cancer presented similar symptoms of Covid-19 such as fever, cough and breathing difficulties (3, 5,7). Nevertheless, about half of the patients reported signs of chess distress and gastrointestinal symptoms (5,7). A small portion (13%) of cancer patients did not have any symptoms (7) (Table 1).

Lung and haematological malignancies appeared to be the most common cancer among all other cancer types as well as associated with higher risk of deaths and severe outcomes (will be discussed in the next section)(3, 5–7) (Table 1). Lung cancer epitomises a challenge within the Covid-19 curative and palliative care context as the Covid-19 disease shows similar symptoms such as persistent cough, shortness of breath and fatigue (2).

Risk of contracting Covid-19 among cancer patients

Patients with cancer are at higher risk of contracting Covid-19(3,5,7,8). As listed in Table 1, among the first study that included patients with cancer was a study by Liang et al. (2020). From 1590 patients studied across China, they have identified 1% of the Covid-19 positive patients have had history of cancer, which makes the incidence higher than the cancer incidence in the overall Chinese population (0.29%)(3). Furthermore, Crolley et. al. (2020) reported cancer patients are eight-fold higher risk to contract Covid-19 than the general population (at time of the report)(7).

As summarised in Table 1, cancer patients with Covid-19 are more likely to die, develop severe symptoms and requires mechanical invasion than those who do not contract the disease(3,5). Dai (2020) reported a 2-fold risk of deaths and a 3-fold risk of needing medical invasion and developing one or more severe symptoms among cancer patients(5). In a bigger sample size study, 39% of cancer patients were admitted to the intensive care unit that requires invasive ventilation or eventually death in comparison to only 8% of non-cancer patients(3). This study also showed half of the cancer patients developed one or more severe Covid-19 symptoms in comparison to only 16% of non-cancer patients(3).

Despite the higher frequency of lung cancer patients with Covid-19 infection(3,5), patients with haematological malignancies are reported to have a higher risk of death, hospitalisation, and severe symptoms than patients with solid tumour when infected with Covid-19(5,6). This observation is also supported by studies from the European continent and Hubei, China(9,10). The fact that haematologic malignancies manifest aggressive or neoplastic plasma cells, lymphocytes, or leukocytes and eventually a reduced immune function, exacerbates the outcomes of Covid-19. As shown by Dai et al., around 56% of the patients with haematological malignancies had severe immunosuppression(5), which explained the severe outcomes among these patients. From the cancer stage perspective, patients with metastatic stage (stage IV) had a six times higher risk of death, six times higher to develop critical symptoms, and 55 times higher risk of using mechanical ventilation(5). On the contrary, non-metastatic cancer patients did not have a significant variance when compared with Covid-19 patients without cancer(5).

There have been conflicting reports in relation to the risk of patients who undergone certain cancer treatments and the severity of Covid-19 outcomes. For example, some reports have shown that patients who received immunotherapy before the onset of Covid-19 had a higher risk of death and developed severe symptoms(3,5,11). On the contrary, Crolley et al. (2020) and Lee et al. (2020) have reported there is no association between the risk of death and the types of anti-cancer treatment received among cancer patients studied(6,7,12,13). Surgery is also a contributing factor towards higher mortality rates, higher admission to ICU as well as more severe symptoms among Covid-19 positive cancer patients(3,5).

On the contrary, children with cancer who are infected with Covid-19 show absence or less severe Covid-19 symptoms (14–16). For example, Millen et al. (2021) revealed 28% from 54 paediatric-oncology patients were asymptomatic during Covid-19 disease course (15), whilst 48% of paediatric cancer patients did not manifest disease symptoms in a meta-analysis on 29 studies covering 177 patients(16). The most common cancer among Covid-19 positive paediatrics cancer patients was reported to be haematology-related malignancies(16) and only 4-10% of the patients developed severe critical illness due to Covid-19 infection (16–18). No death or low death risk was observed among children cancer patients positive for SARS-CoV-2 (15) and in some minor cases, the death was due to disease progression rather than from the infectious disease itself (15).

Table 1: Summary of clinical characteristics among Covid-19 patients associated with cancer.

Reports	Dai 2020	Liang Lancet 2020	Lee 2020	Crolley 2020	Monari 2021
Subjects	641, Wuhan China	1590 cases from 575 hospitals throughout China	1044 patients with cancer, United Kingdom, UK Coronavirus Cancer Monitoring Project	2791 patients with cancer, London UK.	371 patients, Campania region, Southern Italy
No of cancer patients with Covid	105 (16%)	18 (1.1%)	1044	68	34 (9.2%)
Age (years old)	64	Cancer patient vs non-cancer patient (63.1 vs 48.7)	70 years	65	72

Gender	57% male 48% female		57% men 43% female	65% men 35% female	74% male, 26% female
Signs and symptoms	-Chest distress 14% in cancer patients vs 6% in non-cancer patients	-Rapid breathing 47% among cancer patients vs 23% non-cancer patients		-Fever 61% -Cough 54% -Shortness of breath 34% -Gastrointestinal symptoms 18% -Asymptomatic 13%	
Rate of deaths	OR 2.34	[39%] 7 of 18 cancer patients vs [8%] 124 of 1572 non cancer patients	31%	34%	
Rate of ICU admission	OR 2.84				
Rate of needing mechanical invasion					
Rate of one or more severe symptoms	OR 2.79	[50%] 9 of 18 cancer patients vs [16%] 245 of 1572 non-cancer patients			
Types of cancer occurrence with Covid-19					
Lung cancer	21%	28%	OR 0.75		11.8%
Gastrointestinal cancer	12%		OR 0.93		2.9%
Breast cancer	10%	17%	OR 0.82		2.9%
Thyroid cancer	10%				
Haematological cancer	9%	6%	-Leukaemia OR2.82 -Myeloma OR2.03 -Lymphoma OR1.63		17.6%
Bone and articular cartilage			OR2.90		
Prostatic cancer					18%
Colon cancer					15%
Pancreatic cancer					5.9%
Melanoma					2.9%
Liver cancer					2.9%
Womb cancer					2.9%

OR:Odd ratio

The mechanism

One question remains as to why cancer patients exhibit adverse effect when they contract Covid-19 and why are the effects intensified among elderly? Clinically, cancer patients exhibit common features such as neutropaenia, lymphopaenia and disruption of anatomical surfaces (such as the nasal mucosa)(9,10,19), which made them more susceptible to infections. Furthermore, the standard anticancer therapy has also made them immunocompromised. For example, treatment of docetaxel, a drug used to treat non-small cell lung cancer suppressed the immune response in patients' samples(20). Besides, cancer cells also have immunosuppressive properties. For example, tumour cells reduce the expression of human leukocyte antigen and cell surface NK activators to avoid immune detection and response(21,22).

Furthermore, the severity of the Covid-19 clinical symptoms has been attributed to a dysregulated immune response (cytokine storm)(23,24). Cytokine storm is caused by a surge of cytokines that can lead to adverse complications such as sepsis, shock, organ failure, tissue injury and eventually death(25–27). Covid-19 symptomatic patients showed increased levels of cytokines (IL-6, TNF-alpha) and chemokines (CXL10, CCL2) indicative of cytokine storm syndrome(28) which led to hyperinflammation and consequently acute respiratory distress syndrome and multiple organ failure. Furthermore, in another study patients who have been admitted to ICU showed to have higher levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1α, MIP-1, and TNF-α, again suggesting association between cytokine storm and severity of the disease, a similar cytokine storm observed in sepsis(29). Moreover, pro-inflammatory cytokine such as IL-6 and thrombosis (D-dimer) has been shown to be associated with clinically ill Covid-19 patients as well as in-hospital mortality. This observation was also seen in previous MERS and SARS epidemics(23,26).

Another propose mechanism is termed as "bradykinin storm", an observation that was based on RNA-sequencing data from bronchoalveolar lavage samples collected from patients in Wuhan China(30). The analysis revealed an increased expression of ACE2 and bradykinin. While ACE2 mediates the binding of SARS-CoV-2 virus, bradykinin is an important factor in vasopressor system that tightens blood vessels and raise blood pressure. Excessive expression of bradykinin leads to swelling and inflammation of the surrounding tissue. Bradykinin is degraded by ACE and notably ACE expression is reduced in these samples suggesting bradykinin is likely responsible for the severe lung symptoms present in Covid-19 patients(31,32).

One of the initial findings showed that ACE2 expressions are lower in children than in adults suggesting a possible explanation for a reduced infection rate and mild disease symptoms in children versus poorer symptoms observed in older population(33). However, more studies revealed that there was no link between ACE2 expression and viral load in children indicating the severity of the disease is not due to these two factors(18,34,35). It is rather in the different immune response towards the virus that contributes the severity of the disease.

When virus infects lung epithelial cells in a youthful immune system, they are actively recognised by macrophages and dendritic cells which then release cytokines and present antigens to T cells(36). Subsequently, T cells directly kill infected cells or activate other lymphocytes to prevent the spread of the virus. However, in older individuals with aged immune system accompanied by defective macrophages and less effective T cells, viral alert signals become slow, thus resulting in rapid viral replication and eventually producing elevated inflammatory cytokines. Viral components and cytokines enter the bloodstream, causing fluid accumulation in the alveolus, decreasing lung capacity, and infecting microvascular pericytes in other organs. This cytokine storm triggers blood vessels clotting, resulting in severe hypoxia, coagulopathy, and organ failure that were observed in elderly Covid-19 patients(2,5).

Management of cancer patients with Covid-19

Due to high virus replication and adverse effect caused by Covid-19, healthcare systems are under pressure to cope with large numbers of patients that need care and treatment. The situation for cancer patients is even worse as they are at higher risk of Covid-19 infection as well as developing severe disease effect that need a greater level of intensive care (5,7). As a result, an international steering committee of multidisciplinary expert panels has developed a consensus to provide healthcare professionals with insight and strategies to overcome clinical and technical obstacles associated cancer patients during pandemic (37). This consensus covers 28 statements that include patient management and follow up, prevention of cancer patients from infection, prioritisation of cancer care, treatment of cancer patients who contract Covid-19, continuous cancer treatment and clinical trial activities in the pandemic era. These statements will serve as an effective knowledge repository that will be enriched through the accumulation of information on SARS-CoV-2 biology, disease characteristics, cancer risks and its factors as well as preparation for optimal cancer care in future pandemic (37).

Conclusion

The Covid-19 pandemic has brought inevitable challenges to patients with underlying cancer illness. This subgroup of patients is at greater risk of contracting the Covid-19 disease and develop severe clinical outcomes and further complicating the overburden healthcare system. Proper management of the patients should be emphasised to prevent the deterioration of their health and consequently, more lives can be saved

during the pandemic. As we continue to face the ongoing challenges posed by the Covid-19 pandemic, it has become increasingly clear that we must be better prepared to handle similar outbreaks in the future. Consequently, a proactive approach to pandemic preparedness and a better equipped healthcare system are urgently required to manage and minimise the impact of future pandemics especially to those who are more vulnerable to the disease.

Competing interests

Author declared no competing interest.

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