



PROGNOSTIC FACTORS FOR SEVERITY IN CANCER PATIENTS WITH COVID-19: A DIFFICULT UNDERSTANDING ON THE IMMUNOLOGICAL BACKGROUND OF MALIGNANCY AND COVID-19

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ABSTRACT COVID-19, malignancy and anti-cancer treatment share a complex inter connected immunological relation and several factors play to determine the disease severity and mortality rate in COVID-19. Overall the cancer patients remain at greater risk of developing severe disease and most of the published data have demonstrated increased mortality rate among cancer patients who get infected with severe acute respiratory syndrome CoV-2. To identify the prognostic factors are very crucial to tailor the treatment strategy and to reduce the severity of COVID-19 related illness among cancer patients. Patients with haematological malignancies and lung carcinoma remain at the greatest risk of mortality whereas advanced age, presence of co-morbidities, smoking, increased inflammatory markers are observed as established prognostic factors for poor outcome by many studies. We have reviewed the published available data on the impact of COVID-19 in cancer patients and have highlighted several such prognostic factors which may exert adverse effect on general population and on the 'vulnerable' cohort of cancer patients as well.

KEYWORDS :

INTRODUCTION

Novel corona virus disease 2019 (COVID-19) outbreak was identified first as a 'Public Health Emergency of International Concern' (PHEIC) on 30th January 2020 by World Health Organization (WHO) and gradually the infection spread across the globe to an unprecedented scale of 'pandemic'.¹ However; the dynamics of COVID-19 is heterogeneous across the different sub regions of the world. The risk of the infection spread is found different in the different subpopulation of age and ethnic groups.^[2, 3, 4] Clinical manifestations of the infection caused by the severe acute respiratory syndrome CoV-2 (SARS-CoV-2) virus is similarly heterogeneous.

The respiratory symptoms may range from mild cough and upper respiratory symptoms to extreme hypoxia associated with acute respiratory distress syndrome (ARDS). Apart from the respiratory symptoms, SARS-CoV-2 virus may develop major neurological and gastrointestinal dysfunction and response to the standard treatment is also found to be markedly varied. This heterogeneous landscape of COVID-19 infection strongly suggests that certain genetic, ethnic, and immunological factors play crucial role in determining the disease severity and response to the treatment.

Identification of such factors for patients with malignancy is extremely crucial because of their already deregulated immunological background. As per the recent GLOBOCAN database, nearly 19.3 million new cancer cases have been reported in 2020 globally and a considerable number of those patients also contracted SARS-CoV-2 infection.⁵ It posed a significant challenge to health care providers to treat such 'vulnerable' cancer patients with COVID-19 and to identify the prognostic and determining factors for disease severity and treatment response for this particular cohort of the population.

Vulnerability of cancer patients to respiratory infection before COVID era:

The susceptibility of immune-compromised patients to get contracted with influenza virus was well known before the emergence of SARS-CoV-2.^[6,7] Influenza virus increases the risk of hospital admission with severe respiratory symptoms by four folds, and the risk of death in the intensive critical unit by 10 folds when compared with patients without malignancy. Hence the added risk of getting more severe respiratory symptoms was well established before the COVID-19 era of 2020.

Immunological challenges for cancer patients with COVID-19, disease severity and response to treatment

A) Immunological background of COVID-19

Secondary haemophagocytic lymphohistiocytosis is a less recognized hyper inflammatory condition in viral infection, which may result into fulminant

'cytokine storm' with multiorgan dysfunction. A deranged acute phase reactants profile with elevated interleukin (IL) IL-2, IL-6, IL-7, granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein 1- α , interferon- γ inducible protein 10, monocyte chemo-attractant protein 1, and tumour necrosis factor- α are found to be associated with worse outcome in infection by SARS-CoV-2 as well. Macrophages M1 and the danger-associated molecular patterns (DAMPs) trigger the release of those pro-inflammatory cytokines and subsequent activation of inflammasome. Whereas an imbalance between the proinflammatory and anti-inflammatory macrophages M2 is observed which is possibly the root cause of lung damage in the COVID 19 pneumonia.⁸

Inter-linked immunological factors in cancer patients and COVID-19 infection

There is a complex, inter-connected cascade of immunological events by which malignancy, anti-cancer therapies, and various immunomodulators act and create impact on each other.

Hematological malignancies such as acute phase leukemia may harbour specific defects in lymphoid and myeloid lineages. Similarly, patients with solid malignancies on chronic course of the disease can have persistent hyper inflammatory state with elevated cytokines.

Cytotoxic chemotherapy and surgery may further add on lymphopenia in the landscape of generalised immunosuppression of such patients. The extent to which these events impact immune responses in COVID-19 (innate or adaptive) is still not clearly established. However; it is observed by many investigators that, cancer patients are more prone to develop features of severe COVID-19 infection because of their already deregulated immunological landscape.

Review of literature on cancer patients with COVID-19 infection

Many studies on the impact of COVID-19 have been published since the pandemic had hit the entire world and subsequent jeopardization of the healthcare system including the cancer care. Several international forums concerning the cancer care have promptly developed guidelines to facilitate the cancer care in this situation and to identify the clinicopathological and immunological aspects of COVID-19 infection which have profound prognostic impact on cancer patients.⁹

Data from the hospitals in China:

14 different hospitals in Hubei province, China (the epicenter of COVID-19 outbreak) revealed nearly 3-fold higher death rate among cancer patients than that of COVID-19 patients without cancer.¹⁰ Patients with hematologic malignancy, lung cancer, and malignancy

with metastasis are found to manifest the most severe COVID-19 disease.

In another case study spanning across the three hospitals in Wuhan, twenty-eight cancer patients were observed who were infected with SARS-CoV-2.¹¹ Lung carcinoma was the most frequent cancer type in this study and eight patients were suspected to have hospital-associated transmission of the virus. If the anti-cancer treatment was given within two weeks of COVID-19 related symptoms, severe respiratory events were observed to develop more in frequency. 53.6% of patients in this study were found to have severe events leading to ICU admission and the mortality rate was calculated as 28.6%. Several cancer centres globally drastically reduced their services after this preliminary report from China came out.

UK Corona virus Cancer Monitoring Project (UKCCMP)

UKCCMP is the European database and the first COVID-19 clinical registry that analysed 800 patients with cancer and COVID-19 co-infection.¹² 35% patients received chemotherapy within 4 weeks before COVID-19 positivity. Mortality rate is reported as twenty eight per cent and the risk of death was significantly associated with general factors such as increasing age, male gender, presence of comorbidities like hypertension and cardiovascular diseases. However, no significant effect of the administration of immune checkpoint inhibitor (ICI), hormonal therapy, targeted therapy and radiotherapy within the past 4 weeks was noted on mortality for patients.

COVID19 and Cancer Consortium (CCC19)

CCC19 registry is prospectively collecting data on the factors which are associated with short- and long-term outcomes of COVID-19, its severity and fatality in patients with cancer from the USA, Canada, and Spain.¹³ Analysis of 928 patients from this database demonstrated that the patients with cancer are at increased risk of severe illness and mortality.¹⁴ Till date, this is the largest cohort of cancer patients with COVID-19 and has observed moderate or poor Eastern Cooperative Oncology Group performance status (PS) and active or measurable cancer to be significantly associated with increased 30-day all-cause mortality. Among general factors advanced age, male gender, history of smoking, presence of comorbidities and receipt of azithromycin plus hydroxychloroquine have been found to be associated with increased mortality rate.

Thoracic Cancers International COVID-19 Collaboration (TERAVOLT)

Patients with thoracic malignancies are found to be more susceptible to severe degree of illness with COVID-19 because of their comparatively older age, habits of smoking, poor PS and pre-existing cardiac and pulmonary comorbidities. TERAVOLT registry from eight different countries including Italy, Spain, France, Switzerland, Netherlands, USA, UK, and China has noted mortality rate as high as 33 % among the patients with thoracic malignancy.¹⁵ The findings have reiterated the prognostic role of certain factors in the malignancy if patients are co-infected with COVID-19 and underlined the need the extra precautions while treating such patients.

Haematopoietic stem-cell transplantation (HSCT)

HSCT recipients are more vulnerable to develop severe disease with COVID-19.¹⁶ Sharma A et al. has demonstrated that 14% of such patients required mechanical ventilation and at 30 days after detection of SARS-CoV2, OS was reported as 68% for recipients of allogeneic HSCT and 67% for autologous HSCT. Age more than 50 years, male gender, and development of COVID-19 within 12 months of transplantation were associated with a higher risk of mortality.

Lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma HSCT recipients.

A systematic review and meta-analysis by Vijenthira *et al.* analysed 3377 patients with haematological malignancies with COVID-19 infection from Asia, Europe, North America and observed that patients aged ≥ 60 years had a significantly higher risk of mortality.¹⁷ Patients with paediatric malignancy was found to be relatively spared. This review did not find any sort of active treatment to influence the risk of the death.

Treatment factors:

Entry of SARS-CoV-2 inside the human host cells depends on the binding of the virus spike protein, with angiotensin-converting enzyme 2 receptor on the surface and the priming by transmembrane serine protease 2 (TMPRSS2).¹⁸ Aberrant expression of TMPRSS2 is a

hallmark characteristic of several malignancies and respiratory viruses could also exploit this enzyme to promote their spread inside the human cells.¹⁹ Thus, it is implicated in both cancer cells and the spread of viral infections. TMPRSS2 is an androgen-regulated gene and is found up-regulated in prostate cancer. Androgen deprivation therapy (ADT) strikingly decrease the levels of TMPRSS2.²⁰ In a population based study in Italy, Montopoli M et al. has demonstrated significantly lower risk of SARS-CoV-2 infection with prostate cancer patients who received ADT.²¹

Administration of ICI may trigger immune dysregulation by T cell hyperactivation, and exacerbate the process of lung injury.²² Robilotti *et al.* at Memorial Sloan Kettering Cancer Center found the use of ICI as one of the predictors for hospitalization and severe degree of COVID-19 related illness.²³ Similarly, the use of ICI is demonstrated as an established risk factor for severe outcomes in COVID-19, ICU admission, Mechanical ventilation support independent of age, diagnosis of malignancy, and other comorbid conditions by several studies.

DISCUSSION

The clinical manifestations and response to the standard treatment is greatly heterogeneous for COVID-19 in general population and this is similarly true for patients with cancer as well. Hence to determine the prognostic factors associated with COVID-19 and cancer is difficult and multi-faceted. The treatment protocol for COVID-19 infection is mostly similar for cancer patients and other subgroups of immunocompromised patients, however patients with cancer are more vulnerable and higher mortality rate is observed by most of the published studies. Concerns about the unfavorable outcomes arise because of the complex and poorly understood immunological relation between COVID-19, malignancy and different anticancer treatments. On the review of available published data, the following prognostic factors can be highlighted for the adverse outcome of COVID-19 in cancer patients, though the factors greatly vary on demographic, ethnic and several clinical parameters:

1. Patient factors:

- A) **Age:** Cancer patients older than 60 are more vulnerable; Paediatrics population are relatively less affected
- B) **Gender:** Male patients are prone to severe disease
- C) **Co-morbidities:** Cardiac and renal impairment impact adversely. Presence of diabetes is related to the more chance of ICU admission. Dementia, dyslipidaemia, cerebrovascular disease and many more chronic debilitating co morbidities are found to impact negatively on cancer patients infected with SARS-CoV-2
- D) Smoking habit
- E) Obesity
- F) Low blood pressure

2. Cancer related factors:

- A) **Types of malignancy:** Haematological malignancies and lung cancer are on greater risk of developing severe disease. HSCT recipients similarly are more vulnerable.
- B) **PS:** Poor PS is associated with worse outcome
- C) **Stage:** Patients with metastatic disease are more vulnerable for severe outcome. Uncontrolled or progressive cancer may also lead to worse outcome when infected with COVID-19.
- D) **Recent anti-cancer treatment:** Administration of cytotoxic chemotherapy within 14 days is found to produce worse outcome. However, radiotherapy and hormonal therapy do not effect similarly.
- E) **ADT:** Might be protective
- F) **ICI:** Associated with severe disease

3. General factors:

- A) **Raised acute phase reactants:** Raised LDH, CRP, Ferritin are associated with worse prognosis, similar to general population.
- B) Lymphopenia, increased D-Dimer
- C) High sequential organ failure assessment (SOFA) score
- D) **Distance from the care giving hospital:** Availability of the high quality intensive care, distance from the care giving hospital and logistics are important factors particularly during 'lock-down' or social restriction.^[24,25]

Identifying the prognostic factors can help oncologists and the health care policy makers in tailoring the management strategies for cancer patients during any successive peak of the pandemic. Although multiple prognostic factors have been proposed by several studies and systematic review, the predictive value of most of these factors has not

been firmly established and remains largely uncertain.

CONCLUSION

Delivering cancer care during the COVID-19 pandemic has become a major challenge for the health care providers. The rate of severe disease and ICU admission for COVID-19 in cancer patients is substantial. Vaccination against COVID-19 is certainly a great tool, which can be safely administered to the cancer patients except few contraindications.²⁶ However, the cancer patients given to their already immunocompromised state, always remain 'vulnerable' and it underscores the need of large, prospective, multi centric studies to determine the clinical, biochemical and general prognostic factors on the background of complex, interconnected immunological cascades in malignancy, COVID-19 and anti-cancer treatment.

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