Factors Associated with Severity of COVID-19 Illness in Cancer Patients

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ABSTRACT

Objective: To identify the various risk factors associated with severe COVID-19 complications in cancer patients.

Study design: Cross-sectional study.

Place and duration of study: Combined Military Hospital, Rawalpindi Pakistan, from Jun to Nov 2022.

Methodology: Seventy-one cancer patients with COVID-19 infection confirmed by PCR test on nasopharyngeal swab were included in the study. They were assessed for their, ECOG status, smoking habit, comorbidity, vaccination status, cancer type, lung involvement and chemotherapy after written informed consent. COVID-19 symptoms were categorized.

Results: Out of 71 patients included in the study, 16(22.5%) cancer patients had asymptomatic COVID-19 infection, 34(47.9 %) patients had mild symptoms, 13(18.3%) had moderate disease, and 7(9.9%) had severe COVID-19 illness. A significant association was found between severity of COVID-19 illness with age, gender, ECOG status, presence or absence of comorbid, vaccination status and type of malignancy (*p*-value<0.05).

Conclusions: Old, male, frail and unvaccinated patients with comorbidity more frequently developed serious COVID-19 disease. Patients with hematologic or lung malignancies had worse outcomes, while vaccinated ones were protected against severe disease. Chemotherapy or smoking had no significant impact on the severity of COVID-19 illness.

Keywords: Cancer, COVID-19, Complications, Eastern cooperative oncology group (ECOG) performance status.

INTRODUCTION

Patients with cancer have an increased risk of being affected by the COVID-19 pandemic as compared to those without cancer. In New York, Patients with malignancy comprised 8.4% of deceased individuals. Similarly, the rate of complications is high, leading to a mortality rate of 25%.[1,2] Furthermore, the oncological treatment of patients with malignancy has been compromised due to the COVID-19 pandemic, which has caused uncertainty about the benefit versus risk ratio of cancer-directed therapy.[3,4] For this reason, many researchers have tried to find different possible ways to reduce the high mortality associated with COVID-19 infection in cancer patients.[5,6]

Generally, two kinds of studies were done, i.e., either cancer-type specific or general studies on characteristics of oncological patients.[7,8] However, there is still a paucity of data about which aspects of cancer and its treatment confer a risk of severe COVID-19 complications. This information is critical to ensure reducing SARS-CoV-2 mortality while continuing cancer treatment. Hence, there is an intense need to find these risk factors to guide oncological decisions

and reassure patients if the risk is low. Hence, the study was aimed to evaluate the impact of possible patient and cancer-related factors on the severity of COVID-19 illness in cancer patients.

METHODOLOGY

The cross-sectional study was conducted at Combined Military Hospital, Rawalpindi Pakistan, from June to November 2022, after approval from the Hospital Ethical Committee (Letter number 313). The consecutive sampling technique was used, and the sample size was calculated via the WHO sample size calculator taking local incidence of SARS-COVID-19 infection among cancer patients was taken as 3.23%.[6]

Inclusion Criteria: Patients of either gender, aged more than 18 years with proven malignancy for at least three months and having a diagnosis of SARS-CoV-2 infection confirmed by a positive PCR on nasopharyngeal swab were included.

Exclusion Criteria: Pediatric patients, those with undiagnosed or suspected malignancy or those who were already oxygen-dependent or hospitalized for other reasons were excluded.

Included patients were followed throughout the illness for the severity of the disease. Data was collected after informed consent. Patients were asked about their age, number of COVID-19-specific vaccines

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administered in the last six months, smoking history and comorbidities, including diabetes, hypertension, cardiac or renal diseases or chronic lung diseases other than cancer. They were evaluated for performance status, type of cancer, lung involvement and chemotherapy given in the last 30 days before SARS-CoV-2 infection. They were followed till they clinically recovered or died. Severity was classified in terms of asymptomatic, mild, moderate, severe, critical disease or death.[9,10] The mild disease was defined as minimal symptoms of transient fever, diarrhoea, myalgias, etc., managed at home. Moderate disease was defined as

symptoms severe enough to require hospital admission based on local criteria. Severe disease was defined by oxygen dependency, but ventilatory support was not required. Those with critical illness were given ventilatory support and eventually recovered.

Statistical Package for Social Sciences (SPSS) version 22.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

Table: Association of Various Risk Factors in Cancer Patients with Severity of COVID -19 Infection (n=71)

Baseline Characteristics	Study Groups						*p*-value
	Group A (n=16	Group B (n=34)	Group C (n=13)	Group D (n=6)	Group E (n=1	Group F (n=1)	
Age Groups							
<30 years	9(56.2%)	7(20.6%)	2(15.4%)	0(0.0%)	0(0.0%)	0(0.0%)	0.013
30-59 years	7(43.8%)	17(50%)	4(30.8%)	2(33.3%)	0(0.0%)	1(100%)	
>59 years	0(0.0%)	10(29.4%)	7(53.8%)	4(66.7%)	1(100%)	0(0.0%)	
Gender							
Male	5(31.2%)	15(44.1%)	12(92.3%)	5(83.3%)	1(100%)	1(100%)	0.006
Female	11(68.8%)	19(55.9%)	1(7.7%)	1(16.7%)	0(0.0%)	0(0.0%)	
Eastern Cooperative Oncology Group (ECOG) Performance Status							
I/II	12(75%)	25(73.5%)	4(30.8%)	1(16.7%)	1(100%)	0(0.0%)	0.008
III/IV	4(25%)	9(26.5%)	9(69.2%)	5(83.3%)	0(0.0%)	1(100%)	
Smoking Status							
Smoker/Ex-Smoker	3(18.8%)	8(23.5%)	3(23.1%)	4(66.7%)	1(100%)	1(100%)	0.057
Non-Smoker	13(81.2%)	26(76.5%)	10(76.9%)	2(33.3%)	0(0.0%)	0(0.0%)	
Diabetes Mellitus							
Yes	2(12.5%)	10(29.4%)	9(69.2%)	4(66.7%)	1(100%)	1(100%)	0.006
No	14(87.5%)	24(70.6%)	4(30.8%)	2(33.3%)	0(0.0%)	0(0.0%)	
Hypertension							
Hypertensive	1(6.2%)	7(20.6%)	4(30.8%)	5(83.3%)	1(100%)	0(0.0%)	0.003
Non-hypertensive	15(93.8%)	27(79.4%)	9(69.2%)	1(16.7%)	0(0.0%)	1(100%)	
Ischemic Heart Disease							
IHD history	1(6.2%)	2(5.9%)	4(30.8%)	3(50.0%)	0(0.0%)	1(100%)	0.005
No history of IHD	15(93.8%)	32(94.1%)	9(69.2%)	3(50.0%)	1(100.0%)	0(0.0%)	
Chronic Obstructive Pulmonary Disease (COPD)							
Present	0(0.0%)	7(20.6%)	6(46.2%)	4(66.7%)	0(0.0%)	1(100%)	0.004
Absent	16(100%)	27(79.4%)	7(53.8%)	2(33.3%)	1(100%)	0(0.0%)	
Vaccination							
Not vaccinated	1(6.2%)	12(35.3%)	5(38.5%)	3(50.0%)	1(100%)	1(100%)	0.019
1 dose received in last six months	4(25.0%)	(29.4%)	(53.8%)	3(50.0%)	0(0.0%)	0(0.0%)	
At least 2 doses in last 6 months	11(68.8%)	(35.3%)	1(7.7%)	0(0.0%)	0(0.0%)	0(0.0%)	
Lung Involvement							
Lung involved	1(6.2%)	3(8.8%)	5(38.5%)	3(50.0%)	0(0.0%)	1(100%)	0.007
Lung not involved	15(93.8%)	31(91.2%)	8(61.5%)	3(50.0%)	1(100%)	0(0.0%)	
Hematological versus Solid Cancers							
hematological	2(12.5%)	16(47.1%)	10(76.9%)	2(33.3%)	1(100%)	1(100%)	0.010
Solid	14(87.5%)	18(52.9%)	3(23.1%)	4(66.7%)	0(0.0%)	0(0.0%)	
Chemotherapy in last 30 Days							
Received	10(62.5%)	17(50.0%)	3(23.1%)	1(16.7%)	0(0.0%)	1(100%)	0.116
Not received	6(37.5%)	17(50.0%)	10(76.9%)	5(83.3%)	1(100%)	0(0.0%)	

RESULTS

Of the total 71 patients, 16(22.5%) cancer patients had asymptomatic COVID-19 infection, 34(47.9%) patients had mild symptoms, 13(18.3%) had moderate disease (admitted to the hospital but no oxygen dependency), and 7(9.9%) had severe COVID-19 illness (oxygen dependent with or without ventilator requirement) (Figure).
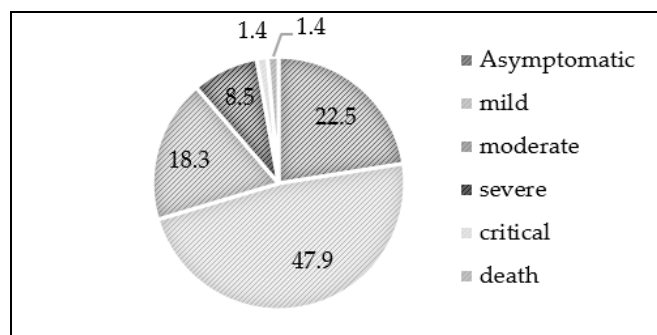

Figure: COVID-19 Severity in Cancer Patients (n=71)

Thirty-two (45%) patients had hematological malignancy while others had solid organ malignancy. 32(45%) had received chemotherapy within previous 30 days before COVID diagnosis. 23(32%) were unvaccinated. 43(60%) patients had ECOG status of I/II. 13(18%) patients had lung malignancy or metastasis. The association of these risk factors with COVID severity is described in the Table.

DISCUSSION

The results of our study showed that advanced age was significantly related to the poor outcomes of COVID-19 infection in cancer patients, just as in the case of non-cancer patients. Those with ECOG III/IV had worse outcomes in terms of severity of COVID-19 illness in our study. This is by the results of an Irish study, which showed that 80% of those with performance status III or more died.[9] Overall, males were found to have more complications than females in our study. Similarly, Jin *et al.* showed that the number of men who died from COVID-19 was 2.4 times that of women.[10]

It is thought that the Structural and immunologic damage caused by tobacco increases susceptibility to infections. Thus, Smokers were at 2.4 times higher risk of COVID-19 severe events such as (ICU admission, MV or death compared with non-smokers.[11,12] Although our study also showed a significant association between COVID-19 severity and COPD, contrary to the hypothesis, it suggested no significant relationship with smoking. Rossato *et al.* supports that on severely

affected COVID-19 patients; 84.8% had never smoked, while only 15.2% were former smokers, and there was no difference in the disease severity between the two groups.[13]

In our study, Patients with primary lung cancer or those with pulmonary metastasis were found to have more severe respiratory complications and oxygen dependency as compared to those suffering from other types of cancer. This is due to damaged lungs by malignant cells. Previously, in China, it was found that 78% of patients with lung involvement showed severe symptoms with a mortality rate of 39%.[14] Another study done in Italy,[15] showed that COVID-19-related mortality rate among cancer patients in general was 14.7%, while among those with lung cancer was about 23.8. A US-based CCC-19 cohort study of lung cancer demonstrated an overall mortality rate of 13%, a hospitalization rate of 50%, including 14% of ICU admissions, and a 12% rate of mechanical ventilation.[16] Contrary to the above, the UK Coronavirus Cancer Monitoring Project (UKCCMP),[17] did not observe an increased case–fatality rate for patients with lung cancer compared with other cancers. However, the relatively small sample size may have affected these results.

Our study results also showed the efficacy of vaccination against COVID-19. 21% of those without vaccination developed oxygen dependency compared to 0% of those who had completed their vaccination (at least two doses). With only one dose of vaccination done, 12% developed severe disease. This was because less than a third of individuals with cancer (29%) developed antibodies after receiving the first dose, compared to 84% in the control group. On the other hand, 86% of patients developed antibodies after administering the second dose.[18] Those who had received chemotherapy in the last 30 days were not found to develop severe disease as compared to those who had not received parenteral chemotherapy in our study. This follows the results of a study by Robilotti *et al.*[19] on 423 patients, which proved that systemic parenteral chemotherapy was not related to increased risk of COVID-19 severity.

Contrary to the above, in TERAVOLT study,[20] which included data from 26 countries, the researchers found that patients receiving chemotherapy within the last three months had a 64% higher risk of dying from COVID-19 than those who did not have chemotherapy. Among 79.4% of deaths from COVID-19, 46.8% had chemotherapy in the last three months. Thus, this

factor has a controversial role. In our study, 12% of patients with haematological cancers developed oxygen dependency after COVID-19 infection as compared to 10% of solid cancer patients excluding lung cancer, and the association was found significant. Previous research, such as Jee *et al*. proved that diagnosis of hematologic malignancy was associated with severe COVID-19 disease with a hazard ratio of 1.90. Among those with acute myeloid leukaemia, 87.5% developed a critical illness.[21]

LIMITATION OF STUDY

There was a lack of objective evidence from radiological and biochemical data to define the severity of COVID-19 illness accurately. In addition, we did not subclassify different cancers and chemotherapy based on myelosuppressive risk to further define the role of different chemotherapy drugs/regimens in the severity of COVID-19 illness.

CONCLUSION

We concluded that the severity of COVID-19 infection was directly related to advanced age, male gender, poor performance status, comorbidities (including diabetes, hypertension, IHD and COPD), haematological cancers, lung involvement by malignancy and unvaccinated status. In contrast, it was found not to be related to smoking status or recent chemotherapy.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MN & MN: Conception, study design, drafting the manuscript, approval of the final version to be published.

A & U: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

FM: Data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Nisar MI, Ansari N, Khalid F, Amin M, Shahbaz H, Hotwani A, et al. Serial population-based serosurveys for COVID-19 in two neighbourhoods of Karachi, Pakistan. Int J Infect Dis 2021; 106: 176-182. https://doi.org/10.1016/j.ijid.2021.03.040

2. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55(5): 2000547. https://doi.org/10.1183/13993003.00547-2020.

3. Zhang JT, Zhong WZ, Wu YL. Cancer treatment in the coronavirus disease pandemic. Lung Cancer 2021; 152(10): 98-103. https://doi.org/10.1016/j.lungcan.2020.12.012.

4. Saini KS, Tagliamento M, Lambertini M, McNally R, Romano M, Leone M, et al. Mortality in patients with cancer and coronavirus disease 2019: A systematic review and pooled analysis of 52 studies. Eur J Cancer 2020; 139:43-50.

5. Fillmore NR, La J, Szalat RE, Tuck DP, Nguyen V, Yildirim C, et al. Prevalence and Outcome of COVID-19 Infection in Cancer Patients: A National Veterans Affairs Study. J Natl Cancer Inst 2021; 113(6): 691-698. https://doi.org/10.1093/jnci/djaa159.

6. Yusuf A. Cancer care in the time of COVID-19-a perspective from Pakistan. Ecancermedicalscience 2020; 14: 1026.

7. Wu JT, Leung K, Bushman M, Kishore N, Niehus R, de Salazar PM, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nat Med 2020; 26(4): 506-510. https://doi.org/10.1038/s41591-020-0822-7.

8. Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V. UK Coronavirus Monitoring Project Team; Kerr R, Middleton G. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020; 395(10241): 1919-1926. https://doi.org/10.1016/s0140-6736(20)31173-9.

9. Linehan A, Fitzpatrick O, Cowzer D, Hennessy MA, Coyne ZL, Nolan A, et al. COVID-19-related mortality in cancer patients in an Irish setting. Ir J Med Sci 2022; 191(5): 2013-2018. https://doi.org/10.1007%2Fs11845-021-02815-9.

10. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health 2020; 8(1): 152. https://doi.org/10.3389%2Ffpubh.2020.00152.

11. Luo J, Rizvi H, Preeshagul IR, Egger JV, Hoyos D, Bandlamudi C, et al. COVID-19 in patients with lung cancer. Ann Oncol 2020; 31(10): 1386-1396. https://doi.org/10.1016/j.annonc.2020.06.007.

12. Ismail N, Hassan N, Abd Hamid MHN, Yusoff UN, Khamal NR, Omar MA, et al. Association of Smoking And Severity of Covid-19 Infection Among 5,889 Patients In Malaysia: A Multi-Center Observational Study. Int J Infect Dis 2022; 116: 189-196. https://doi.org/10.1016/j.ijid.2022.01.011.

13. Rossato M, Russo L, Mazzocut S, Di Vincenzo A, Fioretto P, Vettor R, et al. Current smoking is not associated with COVID-19. Eur Respir J 2020; 55(6): 2001290. https://doi.org/10.1183/13993003.01290-2020.

14. . Hu Y, Zhan C, Chen C, Ai T, Xia L. Chest CT findings related to mortality of patients with COVID-19: A retrospective case-series study. PLoS One 2020; 15(8): e0237302. https://doi.org/10.1371/journal.pone.0237302.

15. Rugge M, Zorzi M, Guzzinati S. SARS-CoV-2 infection in the Italian Veneto region: adverse outcomes in patients with cancer. Nat Cancer 2020; 1(8): 784-788. https://doi.org/10.1038/s43018-020-0104-9.

16. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020; 395(10241): 1907-1918. https://doi.org/10.1016/s0140-6736(20)31187-9.

17. Passaro A, Bestvina C, Velez Velez M, Garassino MC, Garon E, Peters S, et al. Severity of COVID-19 in patients with lung cancer: evidence and challenges. J Immunother Cancer 2021; 9(3): e002266. https://doi.org/10.1136%2Fjitc-2020-002266.

18. Ben-Aharon I, Waldhorn I, Holland R, Peer A, Halberthal M, Goshen - Lago TG, et al. 1559O Efficacy and toxicity of BNT162b2 vaccine in cancer patients. Ann Oncol 2021; 32: S1130. https://doi.org/10.1016%2Fj.annonc.2021.08.1552.

19. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020; 26(8): 1218-1223. https://doi.org/10.1038/s41591-020-0979-0.

20. Garassino MC, Whisenant JG, Huang LC, Trama A, Torri V, Agustoni F, et al. TERAVOLT investigators. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol 2020; 21(7): 914-922. https://doi.org/10.1016%2FS1470-2045(20)30314-4.

21. Jee J, Foote MB, Lumish M, Stonestrom AJ, Wills B. Chemotherapy and COVID-19 Outcomes in Patients With Cancer. J Clin Oncol 2020; 38(30): 3538-3546. https://doi.org/10.1200/jco.20.01307.

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