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ORIGINAL RESEARCH **CORONA EXPERIENCE**

Clinical spectrum and outcomes of cancer patients affected with COVID-19 in Indian population: A single-center retrospective study

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ABSTRACT

Introduction: Cancer patients affected with COVID-19 are at high risk of severe infection and death which depends upon their functional status, cancer type and treatment modality. In this study, we measured outcome by mortality and length of stay in hospital and intensive care unit, need of oxygen and respiratory assist devices and performance status after discharge.

Methodology: This retrospective observational study was carried out in active cancer patients with confirmed positive RT-PCR for SARS-CoV-2 between April 2021 and August 2021. Patients with cancer treated more than 6 months back, those in remission and home isolation were excluded. Demographic profile, cancer type, staging and treatment, severity of COVID, treatment, oxygen supplementation, as well as ICU and hospital stay were analyzed. Statistical analysis was done using descriptive and inferential analysis. Significance was assessed at 5% level of significance. Chi-square/ Fisher Exact test was used to find the significance of the study parameters on categorical scale between two or more groups, non-parametric setting for qualitative data analysis. Fisher Exact test was used when cell samples were very small. $P \leq 0.01$ was considered as strongly significant.

Results: Out of 92 patients, there were 17 deaths (mortality 18.4%). Mortality was associated with cancer stage, comorbidities, severity of COVID symptoms, use of oxygen, high flow nasal cannula, non-invasive ventilation and decreased Eastern Cooperative Oncology Group score on discharge ($P = 0.001$). Age, raised C-reactive protein and D dimer levels were associated with increased severity of COVID-19.

Conclusion: Cancer patients with COVID-19 have increased morbidity and mortality affected by various factors related either to pre-existent cancer or the newly acquired COVID-19.

Abbreviations: CRP - C-reactive protein; ECOG - Eastern Cooperative Oncology Group score; RT-PCR - Reverse Transcriptase Polymerase Chain Reaction; HFNC - High Flow Nasal Cannula

Key words: COVID-19; Critical Illness; Neoplasms; Death; Oxygen

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1. INTRODUCTION

Corona virus disease-19 (COVID-19) caused by SARS-CoV-2 virus has affected the whole world and caused havoc to millions of people. Old age and comorbidities like diabetes, hypertension, cardiac disease, chronic obstructive pulmonary disease and cancer have been found to adversely affect the disease severity and mortality.[1] Cancer patients have diminished immunity due to the disease itself and the side effects of chemotherapy, radiotherapy and anticancer drugs. In addition, they carry a very high risk of perioperative pulmonary complications after surgery.[2] The risk varies with functional status of the patient, cancer type, and/or treatment modalities.

Mortality and morbidity of COVID-19 is higher in cancer patients than in non-cancer population.[3] Emerging data has suggested variability in susceptibility to the infection and ultimately outcome. Among different types of cancer, an overall COVID-19 related mortality of as high as 32 to 40% was noted in hematological cancer patients.[4] In these immunocompromised patients, morbidity and mortality is very high and the respiratory virus sheds for a long time causing severe pneumonia.[5]

Studies related to COVID-19 in cancer-affected population are very few, especially from developing nations like India. Keeping this in mind, we evaluated the clinical characteristics and outcome of COVID-19 in cancer patients and to assess the risk factors associated with poor outcome. Primary outcome was measured by all-cause mortality within 30 days of diagnosis of COVID-19 and secondary outcome by length of stay in hospital and intensive care unit (ICU), need of oxygen and use of respiratory assist devices.

This study is expected to help in better decision making and identify risk factors, if any, that could be modified for future management in COVID affected cancer patients.

2. METHODOLOGY

This retrospective observational study was carried out in cancer patients affected with COVID-19 between April 2021 to August 2021 at a tertiary care cancer institute. Patients with active cancer with Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) confirmed SARS-CoV-2 infection after hospital admission were included. Patients were tested for SARS-CoV-2 if they were symptomatic or needed hospitalization or if they were scheduled to undergo a cancer-related treatment. Those diagnosed with cancer in the past who received chemotherapy/radiotherapy or surgery more than six months back, those in remission and those in home isolation were excluded to avoid selection bias.

Demographic details, performance status by Eastern Cooperative Oncology Group (ECOG) score on admission and discharge, type and staging of cancer, surgical intervention and ongoing chemotherapy or radiotherapy, clinical features and severity of COVID-19, need for oxygen requirement, high flow nasal cannula (HFNC), non-invasive (NIV) and invasive ventilation, ICU admission, treatment received for COVID-19 and total duration of stay in hospital and ICU were the factors analyzed. Baseline laboratory investigations were noted on day one. C-reactive protein (CRP), D-dimer levels and CT thorax were done after 3 days based on the severity of symptoms and other logistic issues. The severity of COVID-19 infection was classified according to the World Health Organization (WHO) guideline into mild, moderate, severe and critical.[6] These data were obtained from electronic data base and medical registry from COVID-19 ward.

According to hospital COVID-19 protocol, antibiotics were given by the treating doctor. Awake proning was encouraged for 30 min to 2 h as tolerated with supplemental oxygen via face mask. For moderate symptoms, injection dexamethasone 0.1-0.2 mg/kg/day or injection methylprednisolone 0.5-1 mg/kg in 2 divided doses for 5-10 days were given. Anticoagulation was achieved with low molecular weight heparin 0.5-1 mg/kg/day in two divided doses. Remdesivir, a broad-spectrum antiviral, was used in severe cases. Critically ill cases with ARDS, sepsis, septic shock or thrombosis were admitted in the ICU for ventilation and shock management.

Statistical analysis

Descriptive and inferential statistical analysis was carried out. Results on continuous measurements are presented as mean ± SD (Min-Max) and results on categorical measurements are presented in numbers (%). Significance is assessed at 5% level of significance.

Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for qualitative data analysis. Fisher Exact test was used when cell samples were very small. $P < 0.10$ was of suggestive significance, $P \leq 0.05$ was moderately significant and $P \leq 0.01$ was highly significant.

All analyses were done using the Statistical Package for Social Sciences (SPSS) version 22.0 and R environment ver. 3.2.2. Microsoft Word and Excel were used to generate graphs and tables.

Table 1: Relationship of age (y) and gender to mortality

Variable	No. of patients (n = 92)	Deaths (n = 17)	P value
Age (y)			
1-10	4 (4.3)	0 (0)	0.076
11-20	3 (3.3)	0 (0)	
21-30	5 (5.4)	0 (0)	
31-40	9 (9.8)	1 (5.9)	
41-50	21 (22.8)	3 (17.6)	
51-60	25 (27.2)	3 (17.6)	
61-70	21 (22.8)	7 (41.2)	
>70	4 (4.3)	3 (17.6)	
Gender			
Male	64 (69.6)	13 (76.5)	0.699
Female	28 (30.4)	4 (23.5)	

Data presented as n (%)

The effects of several variables on the outcomes of death, ICU admission, and intubation were assessed using separate multivariable logistic regression models and a multivariable Poisson regression model (for hospital stay) to estimate the relevant adjusted odds ratios and rate ratio. The variables were chosen based on their clinical importance and obtainability. These included level of consciousness, O_2 saturation, systolic blood pressure, temperature, respiratory rate, pulse rate, Hb, white blood cells count, platelet count and creatinine.

3. RESULTS

A total of 92 patients were included in the study based on the inclusion and exclusion criteria. Middle aged males were the most common denomination in the study population (Table 1). Regarding CRP and D-dimer levels, 77 patients had normal levels, whereas 14 had raised levels (15.2%). Abnormal baseline investigations were found in 42 (45.6%) patients; and 17 (18.5%) patients had various comorbidities like hypertension, diabetes, chronic obstructive lung disease, thyroid disorder and liver disease. Patients receiving chemotherapy and radiotherapy respectively were 50 (54.3%) and 30 (32.6%).

Most patients presented with solid tumors out of which carcinoma esophagus was the most common. Hematological malignancies include acute lymphoblastic leukemias, chronic lymphoblastic leukemias and lymphomas (Figure 1).

Table 2: Characteristics of other variables and their relation to mortality

Variables	No. of patients (n = 92)	Deaths (n = 17)	P value
Stage of cancer			
I	0	0 (0)	
II	33 (35.9)	4 (23.5)	0.040*
III	30 (32.6)	3 (17.6)	
IV	29 (31.5)	10 (58.8)	
Oxygen supplementation	27 (29.3)	16 (94.1)	< 0.001**
HFNC/NIV	7 (7.6)	5 (29.4)	< 0.001**
Invasive ventilation	4 (4.3)	2 (11.8)	0.154
Comorbidities	17 (18.5)	5 (27.5)	0.016
Surgery	36 (39.1)	11 (31.4)	0.026
Severity of COVID symptoms			
Mild	59 (64.1)	2 (3.4)	
Moderate	26 (28.3)	9 (34.6)	0.001**
Severe	7 (7.6)	6 (85.7)	
ECOG score			
2	53 (57.6)	1 (5.9)	
3	23 (25)	1 (4.3)	< 0.001**
5	16 (17.4)	15 (94.1)	

*Data presented as n (%); * Significant; ** Highly significant*

Table 3: Length of stay in COVID ward, ICU and overall hospital stay and their relation with mortality

Stay in COVID ward (days)	No. of patients (n = 92)	Deaths (n = 17)	P value
1-5	14 (15.2)	12 (70.6)	
6-12	42 (45.7)	5 (29.4)	0.459
13-21	33 (35.9)		
> 21	3 (3.3)	0	
Stay in hospital (days)			
1-5	9 (9.8)	4 (23.5)	
6-12	26 (28.3)	10 (58.8)	0.173
13-21	36 (39.1)		
> 21	21 (22.8)	3 (17.6)	
Stay in ICU (days)			
No	89 (96.7)	14 (82.4)	0.005**
Yes	3 (3.3)	3 (17.6)	

*Data presented as n (%); ** strongly significant*

Table 4: Age, CRP and D dimer levels with COVID severity

Variable	COVID-19 Severity			Total (n=92)	P value
	Mild (n = 60)	Moderate (n = 27)	Severe (n = 5)		
Age (y)					
1-10	2 (3.4)	2 (7.7)	0 (0)	4 (4.3)	0.033**
11-20	2 (3.4)	1 (3.8)	0 (0)	3 (3.3)	
21-30	2 (3.4)	3 (11.5)	0 (0)	5 (5.4)	
31-40	7 (11.9)	2 (7.7)	0 (0)	9 (9.8)	
41-50	14 (23.7)	6 (23.1)	1 (14.3)	21 (22.8)	
51-60	21 (35.6)	4 (15.4)	0 (0)	25 (27.2)	
61-70	10 (16.9)	7 (26.9)	4 (57.1)	21 (22.8)	
>70	2 (3.4)	2 (7.7)	0 (0)	4 (4.3)	
CRP, D dimer					
Normal	56 (93.2)	21 (76.9)	1 (28.6)	78 (83.7)	0.001**
High	4 (6.8)	6 (23.1)	4 (71.4)	14 (15.2)	

*Data presented as n (%); ** strongly significant*

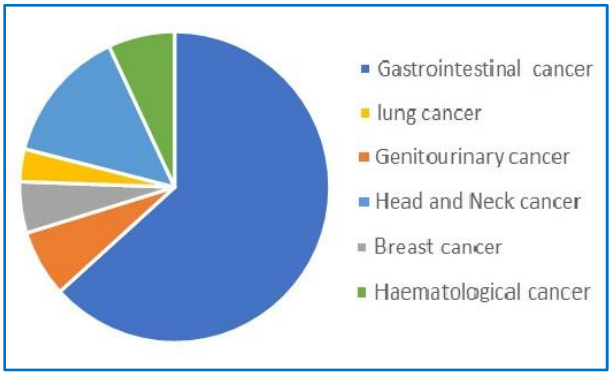

Figure 1: Distribution of various types of cancer. Gastrointestinal malignancy was the most common. Hematological malignancies include ALL, CLL, and lymphomas.

Overall, there were 17 deaths bringing the mortality rate to 18.4%.

Cancer stage (P = 0.040) and presence of comorbidities (P = 0.016) was associated with increased mortality and morbidity. Additional need of oxygen supplementation (P < 0.001) and the use of HFNC or NIV (p <0.001) were also positively associated with mortality. However, no co-relation was observed with the use of invasive ventilation with mortality (Table 2).

Majority of the patients had mild COVID symptoms. Patients with moderate and severe COVID-19 symptoms had significantly higher mortality (P = 0.001) (Table 2).

About half of the patients stayed in COVID-19 ward for 6-12 days. 21 patients stayed in the hospital for more than 21 days and 3 patients stayed in the ICU all of whom died during the study period (P = 0.005) (Table 3).

Regarding ECOG score, 26.1% of patients had an ECOG score of 2, and 14.1% of patients had a score of 3 on admission whereas the percentage increased to 57.6% and 25% respectively on discharge indicating majority of the patients' performance got affected by it. Moreover, ECOG score on discharge was significantly associated with increased mortality (P < 0.001) (Table 2).

Age (P = 0.033) and high CRP and D dimer (P = 0.001) were associated with increased severity of COVID-19 which was significant. All severe COVID-19 patients had raised CRP and D dimer levels (Table 4).

4. DISCUSSION

Patients with solid and hematological cancers presenting with COVID-19, irrespective of being RT-PCR confirmed or not, are at high-risk of early mortality. COVID-19 is reported as the cause of death in 50% of COVID-19 positive patients with cancer in a 2021 French study.[7] COVID-19 can be considered as an independent risk factor, in addition to old age, male gender, black race, smoking status at present and comorbidities. In another study it was seen that patients affected with hematological malignancies and lung cancer had high mortality.[8] More ICU admissions,

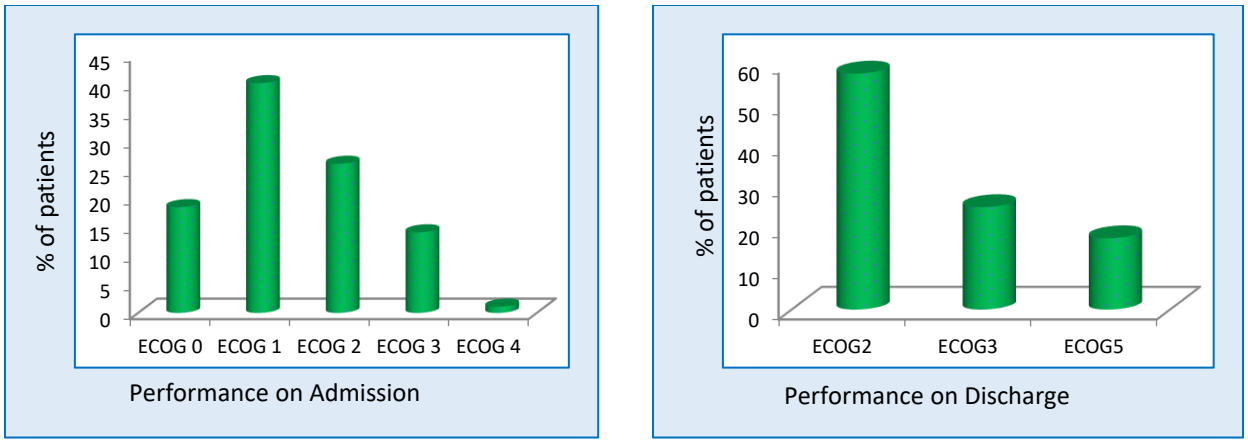

Figure 2: ECOG (Eastern Cooperative Oncology Group) score on admission and on discharge.

mechanical ventilation support and increased mortality rates have been discerned in cancer patients with COVID-19 when compared with patients without malignancies.[9]

Assaad et al. found that among patients with cancer and COVID-19, independent risk factors for death were male gender, Karnofsky performance status < 60, cancer in relapse and respiratory symptoms.[10] Similarly, in the present study, patients with comorbidities, low ECOG performance, those needing oxygen and respiratory assist devices were found to have higher mortality. However, age or sex were found to be unrelated to the mortality rate.

A study conducted on twenty-seven COVID-19 patients with breast cancer showed that the majority (74%) did not require hospitalization and only one male with multiple co-morbidities died. This is of interest, as COVID-19 males have reported worse outcomes than females. While treatment disruptions occurred in most patients (74%), it is unknown whether this represents a deviation from other patients who develop infections on therapy.[11]

Interestingly, majority of the patients in this study contracted COVID-19 after admission to hospital i.e., it is hospital acquired. An incidence of 19.1% was noted in one study and it was found that a high rate of nosocomial transmission of COVID-19 was also associated with increased mortality in the cancer population. Age and advanced cancer were negative predictive factors for COVID-19 severity in patients with cancer. Multivariate analysis demonstrated that hospital-acquired COVID, age, ECOG status and advanced stage of cancer were independently associated with death.[12] In the present study, stages of cancer and ECOG score on discharge did affect the mortality. Age was associated with high grade COVID-19 severity.

Cancer patients affected with COVID-19 have an increased risk of severe infection, need of mechanical ventilation, ICU admission and mortality compared with patients without cancer. Patients who received chemotherapy or undergone surgery in the 30 days before presenting with COVID-19 were also found to have a higher risk of severe events than patients who had not undergone chemotherapy or surgery. It was also found that cancer history conferred the highest risk for severe complications and was correlated with poorer outcomes from COVID-19.[13] In this study, use of non-invasive ventilation, high flow nasal cannula and use of invasive ventilation was not associated with increased mortality.

The stay in ICU and decreased ECOG score on discharge was also found to be associated with increased mortality in cancer patients affected with COVID. Although patients receiving chemotherapy and radiotherapy did not affect the mortality in this study, patients undergoing surgery had high mortality.

As shown in other studies too, cancer treatment within 14 days of COVID-19 diagnosis was a high-risk factor for developing severe complications such as acute respiratory distress syndrome (28.6%), septic shock (3.6%), and acute myocardial infarction (3.6%). Hence cancer patients currently on cancer treatments should undergo thorough screening for COVID-19 infection and avoid immunosuppressive therapy in case of the same.[14]

In one study where most patients (77%) were on active systemic therapy or radiotherapy for advanced or metastatic disease, the mortality rate was 16.7% which was similar to that in this study i.e., 18.4%. Around 32.6% and 39% of patients underwent radiotherapy and surgery during hospital admission and almost 54.3% of patients received chemotherapy; 27.5% of patients had more than one comorbidity. Factors contributing towards

mortality after COVID-19 diagnosis included elderly age, smoking, comorbidities, respiratory tract malignancy and management in a setting unequipped for COVID-19 care.[15]

Factors affecting prognosis of COVID-19 affected patients with cancer also influence outcomes in general population. Patients who are frail and who smoked require active preventive measures to reduce the risk of COVID-19 infection and close monitoring in case of exposure. Patients who are otherwise healthy with curable malignancies have COVID-related mortality rates similar to general population. In such patients, cancer treatment should not be delayed. Strict measures to guarantee rigorous follow-up of poor prognosis patients with SARS-CoV-2 must be implemented.

Mortality rates among patients admitted to the ICU were three times higher than patients in the ward as seen in one 2021 study. COVID-19 death was mostly attributed to acute respiratory distress syndrome (ARDS). Obesity, active smoking, diabetes and high qSOFA and CURB-65 scores were associated with an increased risk of mortality. However, there was no significant difference in ICU admission and rate of complications between cancer and noncancer patients. No difference was observed in mortality between cancer and noncancer groups or between active and nonactive patients.[16]

In yet another study on cancer patients, those with hematologic cancer had 63% mortality while patients with solid tumors had 37%. History of cancer, impaired consciousness level, tachypnoea, tachycardia, leukocytosis and thrombocytopenia were associated with an increased risk of death.[17]

Death rates, ICU admission, intubation and length of hospital stay were significantly higher among COVID-19 patients with cancer. Older age, male sex, hypertension or ischemic heart disease have also increased the risk of death. These different results may be due to differences in the gender distribution of cancers such as breast or prostate, or in leukemia which are more common at certain ages.[18,19]

Meng Y et al. observed that abnormal CBC, increased liver enzymes, and high CRP occur more commonly in cancer patients.[20] In this study too, high CRP and D dimer levels contributed towards a high morbidity. The presence of lung cancer and stage IV cancer did not result in significantly increased Relative Risk of severe outcome. Among the available IPD, only age and gender were associated with severe outcomes.[21]

5. CONCLUSION

Cancer with COVID-19 has been proven to be a deadly combination with many infected patients showing signs of moderate to severe infection. Solid tumors and hematological cancers show the worst outcome among all cancers. Mortality rate, length of ICU stay and hospital stay is also high in this category of patients. Factors like age, sex, stage of tumor, severity of COVID-19 symptoms and need of oxygen supplementation/ artificial ventilation are associated with a bad prognosis.

6. Recommendations

There is a need for proper precautions to avoid infection in the first place and proper management after exposure to COVID-19. Studies such as this will help guide clinicians caring for cancer patients on what to expect when COVID-19 hits. A multicentric clinical prospective trial in the future can help create guidelines and protocols of management of COVID-19 affected cancer patients in our country.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

SDK: Concept, Conduct of study, literature search, manuscript preparation

AD, MN: Concept, Conduct of study, manuscript editing

BK: Concept, Manuscript editing

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