Outcomes of COVID-19 and risk factors in patients with cancer - a cohort study

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Article

Abstract

Background

Patients with cancer who develop COVID-19 are at higher risk for severe disease and death. We aimed to study the outcomes of patients with cancer who were infected with SARS CoV2, and identify risk factors for adverse outcomes after COVID-19.

Methods

We included patients with cancer, who were diagnosed with SARS CoV2 between 11th April 2020 and February 2021 at a tertiary referral cancer centre in India. We collected data on age, sex, coexisting medical conditions, type of cancer, intent of cancer management, cancer treatment details, and severity and outcome of COVID-19. The primary outcome was a composite of severe COVID (defined as grade 6 or more on the WHO ordinal scale) or death within 30 days. We performed multivariable logistic regression analysis to identify risk factors for severe COVID or death.

Results

We obtained data on 1253 patients with cancer and SARS CoV2 infection, of whom 293 (23.6%) had hematological malignancies. The severity of COVID was mild (grade 1 to 3 on WHO ordinal scale) in 1014 (81%) patients, moderate (WHO grade 4 or 5) in 167 (13%) patients and severe (WHO grade 6 or 7) in 72 (6%) patients. The primary outcome was seen in 160 patients (12.8%) and the all-cause 30-day mortality was 10.9% (138 deaths). Advanced age [adjusted OR 1.84 (0.86; 3.94)], history of smoking [aOR 1.78 (1.10; 2.91)], palliative intent of treatment [aOR 3.57 (2.48 to 5.12)] and presence of more than 2 comorbidities [aOR 1.66 (1.03 to 2.67)] were significant risk factors for severe COVID or death. Advanced age and palliative intent of treatment remained significant risk factors for 30-day mortality. Recent systemic anti-cancer therapy, sex or cancer type did not influence outcomes.

Conclusion

Most patients with cancer who developed COVID-19 in our setting had mild disease; the elderly and those treated with palliative intent were at higher risk of severe COVID-19 or death. Recent cancer therapy did not impact COVID-19 severity or outcomes suggesting that in most patients with cancer, the management of cancer should continue uninterrupted during the pandemic.

Background And Introduction

The current COVID-19 pandemic has infected more than 239 million people globally, causing nearly 5 million deaths.[1] Global data suggest that increasing age, presence of concurrent illnesses and

immunosuppression are some of the risk factors associated with poor outcomes after COVID-19.[2,3] Patients with cancer are often immunosuppressed by the disease, as well as its treatment, and are at higher risk; in addition, some of the important predisposing factors for cancer like smoking and obesity are also contributory factors for adverse outcomes after COVID-19. Overall, patients with cancer have been found to have higher rates of severe disease and fatality after COVID-19 than the general population.[4] The presence of additional comorbidities, poor performance status, specific cancer types and recent systemic anti-cancer therapy have been variably identified as adverse prognostic factors in patients with cancer and COVID-19; [4–7] however, the actual risk associated with some of these factors remains unclear.

India has seen 34 million individuals infected with COVID-19, resulting in 450,000 deaths.[1] Case fatality rates in general have been lower in India compared to other countries, especially Western Europe and the United States.[1] While this has been attributed to under-reporting of cases (and deaths), the difference cannot be explained on this basis alone.[8] It is likely that there are other factors, possibly acquired immunity due to the population being infected by other coronaviruses in the past, and other less known factors, which may contribute to the low fatality rate.[9] There is very little data from India on the outcomes of COVID-19 in patients with cancer.[10–12] Given that cancer treatment should be considered a priority, reliable data on outcomes of COVID-19 in patients with cancer are necessary to guide management during future surges of the pandemic. The aim of this study was to assess the short-term outcomes of COVID-19 in patients with cancer at a tertiary-referral cancer centre in Western India, and to identify risk factors for adverse outcomes.

Methods

We performed an ambi-directional (predominantly prospective) cohort study of patients with cancer diagnosed with SARS-CoV2 infection between 11th April 2020 and 28th February 2021. The study was approved by the Institutional Ethics Committee, registered with the Clinical Trials Registry of India (CTRI/2020/07/026339) and carried out in accordance with the principles of good clinical research practice.

We included all patients (adult and paediatric) with a proven diagnosis of cancer at any stage of management [under evaluation, on active treatment (curative or palliative intent) or on follow-up (short or long-term)], with SARS CoV2 infection confirmed by a positive RT-PCR test during the study period; those patients with a clinical or radiological suspicion of COVID-19, who tested negative on an RT-PCR test were not included. During the study period, the institutional policy on COVID-19 testing included testing all patients who had symptoms suggestive of COVID and those planned for surgery or other aerosol-generating procedures.

We collected data from electronic medical records for the following variables: age, sex, co-morbidities needing active treatment, smoking status (ever vs never-smoker), date of diagnosis of cancer, type of cancer (solid vs hematological), intent of management (curative versus palliative), status of management

(evaluation, active treatment, follow-up), type of management (chemotherapy, radiation therapy, surgery, palliative care, combination or other), date of completion of last systemic anti-cancer treatment (SACT) (defined as chemotherapy, immunotherapy, targeted therapy or a combination of these), date of COVID diagnosis, severity of COVID-19 (classified as per the WHO ordinal scale)[13] and COVID-19 outcome (dead or alive). The WHO ordinal scale uses the intervention used to treat COVID-19 as a measure of severity, and not the symptoms, and hence would underestimate the severity in situations where care was not escalated due to the terminal nature of the comorbid disease like cancer or an overwhelmed health system. Therefore, we used a composite outcome of severe COVID (WHO grade 6 or more) or death within 30 days from the date of COVID diagnosis as our primary outcome. We used a multivariable logistic regression model to look at association between independent predictors – age, sex, smoking status, presence of comorbidities, type of cancer (solid versus hematological), intent of management (curative versus palliative), duration from last systemic anti-cancer treatment to COVID diagnosis (less than versus more than 30 days) and the primary outcome. We also conducted a similar multivariable analysis to identify risk factors for 30-day mortality. Patients were censored at the last date of follow-up and statistical tests were interpreted at a two-tailed 5% level of significance.

Results

We collected data from 1253 patients with a confirmed diagnosis of cancer and SARS CoV2 diagnosed between 11th April 2020 and 28th February 2021. There were 730 male (58%) and 523 female (42%) patients; the mean age was 44 (+/- 18) years (range 1 to 84 years). The baseline characteristics of the patients are described in Table 1. At a median follow-up of 76 days, 160 patients (12.8%) met the composite end-point of severe COVID or death within 30 days of COVID diagnosis. The 30-day all-cause mortality was 10.9% (138 deaths).

Table-1: Baseline characteristics

Age in years	Less than 18	161 (12.8)
	18 to 64	933 (74.5)
	65 and above	159 (12.7)
Gender	Male	730 (58.3)
	Female	523 (41.7)
Smoking (n= 1227)	Yes	186 (15.2)
	No	1041 (84.8)
Hypertension (n=1240)	Yes	209 (16.9)
	No	1031 (83.1)
Diabetes (n=1241)	Yes	185 (14.9)
	No	1056 (85.1)
More than 2 comorbidities (n=1241)	Yes	148 (11.9)
	No	1093 (88.1)
Polypharmacy (5 or more medications) (n=1243)	Yes	73 (5.9)
	No	1170 (94.1)
Cancer diagnosis	Hematolymphoid	293 (23.4)
	Solid	960 (76.6)
Cancer details	Oral / oropharyngeal	135 (10.8)
	Breast	114 (9.1)
	ALL	107

		(8.5)
	NHL	92 (7.3)
	Colorectal	92 (7.3)
	Other hematolymphoid	89 (7.1)
	Bone	57 (4.5)
	Cervix	53 (4.2)
	Lung	51 (4.1)
	Stomach	43 (3.4)
	Gall bladder and bile duct	41 (3.3)
	Ovary	40 (3.2)
	Oesophagus	36 (2.9)
	Pancreas	36 (2.9)
	CNS	31 (2.5)
	Liver	29 (2.3)
	Bladder	29 (2.3)
	Prostate	23 (1.8)
	Thyroid	20 (1.6)
	Others*	135 (10.8)
Intent of management	Under evaluation	9 (0.7)
	Curative intent	900 (71.8)

	Palliative intent	344 (27.4)
Current treatment	Awaiting treatment	302 (24.1)
	On active treatment	863 (68.9)
	Chemotherapy	*398*
	Targeted therapy	*60*
	Immunotherapy	*3*
	Multimodality	*216*
	Radiation	*31*
	Surgery	*78*
	Combination(chemo+targeted therapy)	*51*
	Others (hormonal therapy, steroids, interventional procedures, trans-arterial chemotherapy)	*26*
	Follow-up	88 (7.0)
whether on systemic anti-cancer treatment within 30 days prior to COVID	Yes	439 (35.0)
	Chemotherapy	*337*
	Targeted therapy	*54*
	Immunotherapy	*2*
	Combination	*46*
	No	814 (65.0)

Data represents actual numbers with percentages in parentheses

* Other cancers include skin, soft tissue, kidney, larynx, uterus, hypopharynx, nasopharynx, testis, penis, vulva, mediastinum, melanoma, appendix, adrenal.

The severity of COVID was mild (grade 1 to 3 on WHO ordinal scale) in 1014 (81%) patients, moderate (WHO grade 4 or 5) in 167 (13%) patients and severe (WHO grade 6 or 7) in 72 (6%) patients. In patients with limited life expectancy due to advanced cancer, who were considered unsuitable for escalation of therapy, the severity of COVID was graded as per the treatment provided and therefore, may have under-

estimated the actual severity. All-cause 30-day mortality was 2.4% (24/1014), 38.3% (64/167) and 69.4% (50/72) respectively in patients with mild, moderate and severe COVID.

Table – 2: Risk factors for Composite outcome

		Composite outcome	Unadjusted analysis		Adjusted analysis	
			OR with 95% CI	P value	OR with 95% CI	P value
Age (years)	Less than 18	9/161 (6%)	reference		reference	
	18 to 65	116/933 (13%)	2.40 (1.19 to 4.83)	0.01	1.84 (0.86; 3.94)	0.12
	More than 65	35/159 (22%)	4.77 (2.21 to 10.30)	<0.01	3.21 (1.36 to 7.56)	0.01
Gender	Female	69/523 (13%)	ref		ref	
	Male	91/730 (13%)	0.94 (0.67 to 1.31)	0.70	0.76 (0.51 to 1.14)	0.18
Smoking	No	120/1041 (12%)	ref		ref	
	Yes	36/186 (19%)	1.84 (1.22 to 2.78)	0.004	1.78 (1.10; 2.91)	0.01
More than 2 comorbidities	No	125/1093 (12%)	ref		ref	
	Yes	32/148 (22%)	2.14 (1.39 to 3.30)	0.01	1.66 (1.03 to 2.67)	0.04
Cancer type	Solid	122/960 (13%)	ref		ref	
	HL	38/293 (13%)	1.02 (0.69 to 1.51)	0.91	1.54 (0.96 to 2.48)	0.08
Treatment intent	Curative	70/900 (8%)	ref		ref	
	Palliative	88/344 (26%)	4.08 (2.89 to 5.75)	<0.01	3.57 (2.48 to 5.12)	<0.01
On active SACT within 30 days prior to COVID diagnosis	No	99/812 (12%)	ref		ref	
	Yes	61/439 (14%)	1.16 (0.83 to 1.64)	0.39	1.09 (0.72 to 1.63)	0.70

In a separate multivariable logistic regression analysis with 30-day mortality as the primary outcome, we identified advanced age (OR 4.30; 95% CI 1.59 to 11.64) and palliative intent of treatment (OR 4.20; 95% CI 2.84 to 6.20) as independent risk factors. Among patients treated with palliative intent, those who received SACT within 30 days prior to COVID, 25% (36/145) had an event, compared to 26% (52/199) in those who did not. In patients older than 65 years who received SACT within 30 days prior to COVID, 10/34 (29%) experienced the composite end-point compared to 20% (25/125) in those who had not received SACT.

Discussion

In this study of patients with cancer who developed COVID-19, we identified advanced age, history of smoking, palliative intent of treatment and presence of more than 2 comorbidities to be risk factors for severe COVID or death within 30 days. Advanced age and palliative intent of treatment remained independently associated with 30-day mortality. Recent systemic anti-cancer therapy, gender and cancer type were not significantly associated with adverse outcomes.

Since the onset of the COVID-19 pandemic, there have been concerns about the outcomes of COVID-19 in patients with cancer. A meta-analysis of 26 studies including 23736 patients with cancer found a pooled all-cause in-hospital mortality rate of 19%, with nearly three times higher odds of dying than those without cancer.[4] Early data from China suggested that patients with cancer and COVID had a considerably poorer survival than the general population with mortality estimates between 20 and 29%.[14–17] These studies were limited by their small sample sizes and largely retrospective nature. Subsequent studies from other parts of the world reported short-term mortality rates between 10% and 29% in patients with cancer and COVID, with the UK and some countries in Europe reporting much higher fatality rates than other parts of the world.[5–7,18–21] The results from our study are at the lower end of the published range of fatality data on COVID-19 outcomes in patients with cancer.

The dissimilarity in results between these quoted studies need to be interpreted keeping in mind that they were done at various time periods corresponding to different phases of the pandemic. Studies at the beginning of the pandemic typically reported higher case fatality rates as very little was known about the disease and its management. Also, differences in testing strategies between countries may imply that in some studies, patients with cancer who were symptomatic with mild disease and potentially favourable outcomes may not have been identified as opposed to those with moderate and severe disease, resulting in higher estimated fatality rates. Another factor which needs to be considered is the indication for hospital admission. Our study and other studies from India[10,11] reported only 4 to 11% of severe COVID cases among those admitted, compared to 20 to 45% in other studies.[5,6,18,21] Inadequate facilities for home isolation, possibly led to a number of hospital admissions for social reasons in patients with mild disease, leading to a reduction in the proportion of those with severe disease and a decrease in hospital mortality. In addition, the outcomes of patients with cancer and COVID-19 need to be compared to the outcomes in the general population for that same country. Countries such as Italy and the UK have

reported population case fatality rates of 3 to 5% compared to 1.1% in India .[1] These differences could be partly related to population characteristics, with developed countries having a high proportion of elderly individuals with comorbidities.[22] For example, many African countries where the life expectancy is low and the population is predominantly young have reported very low COVID fatality rates.[23] Other associated factors include time trends in the spread of the pandemic, capacity and strategy for testing, and the accuracy of reporting deaths.[22] The low COVID fatality rate in India could also be because of the decreased severity of infection, possibly due to cross-immunity from exposure to other coronaviruses which are endemic in the population.[9]

The focus of research on COVID outcomes in patients with cancer has been to identify prognostic factors to aid risk stratification and early recognition of patients likely to have adverse outcomes. In keeping with the published literature, we found that advanced age was an independent risk factor for poor outcomes after COVID, and within this group, elderly patients who had received recent systemic anti-cancer therapy had worse outcomes than those who did not.[6,17,18] Similar to other studies, we found that the presence of comorbidities and smoking adversely affected COVID severity and outcomes.[6,21] Our study also showed no impact of gender, type of cancer or recent SACT on COVID-19 outcomes. These findings strongly support the continuation of cancer care in most patients during future surges of the pandemic.

Our results showed that treatment with palliative intent was a significant adverse prognostic factor for COVID outcomes, regardless of whether active anti-cancer treatment had been recently administered. This can be attributed to the debilitation caused by the cancer itself, compounded by the effects of COVID. Paradoxically, Di Cosimo showed that patients with metastatic disease receiving anti-cancer therapy had better COVID outcomes than their untreated counterparts;[24] however, this is possibly confounded by selection bias as patients with better general health and performance status are more likely to receive active treatment. Our study suggests that the treatment of patients with advanced, metastatic cancers should be guided by the magnitude of benefit based on the de-novo or progressive nature of cancer, expected toxicities with treatment and potential risks of COVID-19 related complications. This highlights that emphasis should be given to shared-decision making in this scenario. This is particularly true when healthcare systems are overwhelmed by COVID-19, and the resources diverted to palliative chemotherapy would be at the expense of delivery of care to those with other disease conditions, including patients with cancer who are on treatment with curative intent.

Initial data from China suggested that recent SACT was a risk factor for COVID severity and mortality.[14] Based on this, several international organizations issued guidelines for the management of cancer during the pandemic, which included risk minimization by care prioritization, de-intensification of therapies, and postponing therapy where possible.[25] Subsequent studies from other parts of the world have shown differing results – while some studies showed that recent SACT, especially chemotherapy and immunotherapy were risk factors for severity of infection or mortality, other data showed no evidence of an association.[5,6,7,18,19] A systematic review found that chemotherapy within 30 days prior to diagnosis of COVID increased the risk of death but not of severe COVID while other therapies (including radiation

and immunotherapy) had no such effect.[26] While this may be explained on the basis of the intense immunosuppression caused by chemotherapy, it needs to be interpreted cautiously. First, many studies have not been able to capture reliable data on the nature and timing of systemic therapy in relation to COVID and the available data is quite limited. Second, studies may have grouped all forms of anti-cancer therapy which would dilute the effect of individual treatments. Third, changes in practice during the pandemic may have resulted in only fitter patients receiving intense chemotherapy, thus confounding the results.

Our study has several strengths. First, to the best of our knowledge, it is one of the largest single-centre studies examining the outcomes of COVID-19 in patients with cancer, and is possibly the most robust prospective data available from this part of the world. Second, this was a pragmatic study which included all patients regardless of age, cancer type or severity of COVID-19. Finally, being a referral centre in the state for patients with cancer who developed COVID-19, it is likely to be fairly representative of the real-world situation. One possible limitation is that a small proportion of patients who were relatively less symptomatic, but did not have facilities for home isolation were admitted in hospital for social rather than medical reasons, thus potentially skewing the severity scoring of the illness; however, these numbers were few; moreover, since we used categories of disease (mild, moderate and severe) rather than actual scores, this is unlikely to have influenced the results.

The results of our study have important policy-level implications. We have demonstrated that in our setting, most patients with cancer who developed COVID-19 had mild disease and favourable outcomes. Considering that India has a huge burden of COVID cases and has had multiple surges in the number of active infections, this finding is important to assuage fear in patients and treatment-providers. With increasing realization of the adverse outcomes that are likely by deferring active cancer treatment, our results support the continuation of cancer care even during pandemics. Treatment of cancer during the pandemic has been severely hampered due to multiple reasons: inability of patients to access care due to fear of contracting COVID or travel restrictions, reduction in existing cancer care facilities either because of conversion to COVID care centres or due to staffing issues (illness, quarantine or travel restrictions) and recommendations to downscale or delay cancer therapies. A study across 41 cancer centres in India found substantial reductions in volumes of patients treated at these centres during the peak of the pandemic.[27] Even in the pre-pandemic period, several low and middle income countries faced challenges with cancer care related to lack of access, delayed stage presentation and poor outcomes.[28] In such settings, further reductions in cancer care are likely to have disastrous consequences. Many of these countries are now seeing new waves of COVID infections and the findings of this study reinforce that cancer care should not be deprioritized even during a pandemic.

Declarations

We declare that the authors have no competing interests as defined by Nature Research, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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