Characteristics & outcomes of cancer patients with COVID-19: A multicentre retrospective study from India

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Background & objectives: High mortality has been observed in the cancer population affected with COVID-19 during this pandemic. We undertook this study to determine the characteristics and outcomes of cancer patients with COVID-19 and assessed the factors predicting outcome.

Methods: Patients of all age groups with a proven history of malignancy and a recent diagnosis of SARS-CoV-2 infection based on nasal/nasopharyngeal reverse transcriptase (RT)-PCR tests were included. Demographic, clinical and laboratory variables were compared between survivors and non-survivors groups, with respect to observed mortality.

Results: Between May 11 and August 10, 2020, 134 patients were included from the three centres and observed mortality was 17.1 per cent. The median age was 53 yr (interquartile range 39-61 yr) and thirty four patients (25%) were asymptomatic. Solid tumours accounted for 69.1 per cent and breast cancer was the most common tumour type (20%). One hundred and five patients (70.5%) had received chemotherapy within the past four weeks and 25 patients (19.3%) had neutropenia at presentation. On multivariate analysis, age [odds ratio (OR) 7.99 (95% confidence interval [CI] 1.18-54.00); *P*=0.033], haemoglobin [OR 6.28 (95% CI 1.07-37.04); *P*=0.042] neutrophil–lymphocyte ratio [OR 12.02 (95% CI 2.08-69.51); *P*=0.005] and baseline serum albumin [OR 18.52 (95% CI 2.80-122.27); *P*=0.002], were associated with higher mortality. Recent chemotherapy, haematological tumours type and baseline neutropenia did not affect the outcome.

Interpretation & conclusions: Higher mortality in moderate and severe infections was associated with baseline organ dysfunction and elderly age. Significant proportion of patients were asymptomatic and might remain undetected.

Key words Cancer - COVID-19 - infection - mortality - outcome

The first few cases of COVID-19 were reported from Wuhan, China, and initial studies suspected a zoonotic origin[1]. As of May 1, 2022 the disease had affected 510 million people and almost six million people died, worldwide[2]. One of the vulnerable populations affected during this pandemic comprises patients with cancer. Not only this group has been at risk of higher morbidity and mortality but also the pandemic has led to significant disruption of cancer-directed services in the country[3]. Some large studies have reported their observations in this patient population, but more data are needed[4,5]. Moreover, as various studies suggest infectivity and fatality rates of COVID-19 is affected by regional variations, information sharing between different regions becomes pivotal[6,7]. This study was aimed to demonstrate the experience with COVID-19 in cancer patients in cancer care facilities in India and to identify the factors predicting outcome.

Material & Methods

Study design & participants: This was a retrospective study involving patients from three centres in New Delhi, India, namely All India Institute of Medical Sciences (AIIMS), B.L.K Superspeciality Hospital, New Delhi and Asian Institute of Medical Sciences, Faridabad, Haryana. All these hospitals were designated COVID-19 care centres and all had separate oncology units. Patients with cancer, who were infected with COVID-19 were managed by designated COVID-19 specialty teams in continuous consultation with oncologists. The study period was from May 11 to August 10, 2020. All cases with biopsy-proven malignancy who were admitted or advised home isolation, at any of the participating centres on the diagnosis of COVID-19 by the reverse transcriptase-polymerase chain reaction (RT-PCR) on nasopharyngeal swab were included. Cases diagnosed based on rapid antigen tests only were excluded. Patients of all age groups were allowed to participate.

As a uniform policy among the three centres, all cancer patients with suspected symptoms were tested. Asymptomatic patients were tested only before a planned invasive procedure or as a part of screening if they had a high risk of infection after contact exposure to a known case of COVID-19.

All the hospitalized cases were followed up till discharge or death during COVID-19 illness. The primary criteria for discharge in hospitalized cases were the resolution of symptoms and a minimum stay of two weeks, in the absence of follow up PCR negativity. Those who became asymptomatic and were PCR negative on repeat swab tests were discharged earlier. All asymptomatic patients and a few of mildly symptomatic cases were kept on home isolation after initial evaluation. All these patients were monitored daily telephonically and followed up till they became asymptomatic for a minimum period of two weeks, since the diagnosis of SARS-CoV-2 infection.

Data recording: The study protocol was reviewed and approved by the Institutional Ethics Committees at all the participating centres. Consent waiver was granted given retrospective nature of the analysis. Confidentiality was maintained by the de-identification of data. All the data were analyzed at the cut-off date of August 24, 2020.

The majority of the data was retrieved from prospectively maintained medical records. The missing data were collected telephonically during the time of analysis. The severity of the disease was defined according to the WHO definition[8].

All the demographic data, clinical information, laboratory parameters and complications during the hospital stay were recorded. The staging of the solid tumours was recorded as per TNM (tumour, nodes and metastases) staging[9]. Haematological tumours were not staged. Among laboratory parameters, neutropenia was defined as an absolute neutrophil count less than or equal to 1500 cells/µl.

Statistical analysis: The differences between the demographic factors, cancer history, clinical findings and laboratory parameters between the survivors and non-survivors groups were analyzed. Descriptive statistics were used to analyze the baseline clinical and treatment characteristics of the overall population. A comparison of baseline and treatment characteristics was performed using t tests and Wilcoxon rank-sum tests for the continuous variables and Chi-squared tests and Fisher's exact tests for categorical variables, among the two groups.

For continuous parameters, receiver operating characteristic analysis was done to arrive at optimal cut-off values. Thereafter, univariate logistic regression analyses were performed for clinically significant baseline factors to determine the associations with death, while multivariate logistic regression analysis was performed for relevant factors with a significance

of *P*<0.05. All statistical tests were two-sided and the significance level was defined *a priori* at the conventional level as <0.05. The analyses were conducted using Stata statistical software (StataCorp. 2013. Release 13. College Station, TX).

Analysis of numerical and categorical data from moderate and severe cases was done using standard built-in packages of the R statistical software (v4.1.2; R Core Team 2021). Welch's two-sided t test was performed for comparing numerical data using the t test function followed by a multiple testing correction using the Benjamini-Hochberg method[10]. Fisher's exact test was performed using fisher.test function using default parameter for a two-sided test on 2×2 contingency tables constructed from the categorical parameters or treatment with rows representing patient outcome (survival or death) while columns representing the presence or absence of the treatment.

The Uniform Manifold Approximation and Projection (U-MAP) dimensionality reduction and embedding were calculated using the 'umap' package from the CRAN R package repository [arXiv:1802.03426 (stat.ML)] and the U-MAP plot were generated using ggplot2 package in R.

Results

A total of 7297 (including non-cancer patients) SARS-CoV-2-infected individuals were screened during the study period for inclusion and 134 were selected based on confirmed RT-PCR test positivity for SARS-CoV-2 and history of malignancy (Fig. 1). Overall, 23 (17.1%) patients died during the study.

The median age was 53 yr (interquartile range 39-61 yr) in the overall population, with non-survivor subset being significantly older than the survivor's subset, *i.e.* 59 *vs.* 53 yr (*P*=0.03). Eleven patients (8.0%) belonged to the paediatric age group (0-18 yr). The median follow up of all patients was 14 days (range=1-48 days). Gender distribution favoured females in the overall population (53.0%); however, mortality was significantly higher among males (73.9%) (*P*=0.01). Solid tumours accounted for more than two-thirds (69.4%) of all patients and breast cancer was the most common cancer overall (20.1%) with SARS-CoV-2 positivity. Among 41 patients with haematological cancer, leukaemia was the most common (51.0%) diagnosis.

History of fever, cough, headache and myalgia, among symptoms, were more common in non-survivors' group. Overall, 41 (30.6%) patients were classified as with moderate or severe symptoms, as per the WHO classification and 34 (25%) patients were asymptomatic. Three fourths (n=99) of all cases had an Eastern Co-operative Oncology Group performance status of 2-4 and this proportion was significantly more in non-survivors' group (*P*=0.008).

One hundred and four patients (77.6%) had evidence of active disease in the body at the time of inclusion. This set included active disease on treatment, treatment naïve patients as well as patients with refractory and progressive disease. History of treatment within the last four weeks revealed that around 105 (78.5%) received chemotherapy and 21 (15.7%) patients were treatment naïve. Ninety four (70.1%) received cytotoxic chemotherapy. History of chemotherapy, as well as the nature of agents used was not significantly different between the two groups.

Among laboratory parameters, median haemoglobin was significantly lower in non-survivors (8.6 *vs.* 10.5 g/dl, *P*=0.001). In response to chemotherapy, 25 (19.3%) patients had neutropenia (ANC ≤1500/µl) at presentation, whereas, the median neutrophil-lymphocyte ratio (NLR), more than 4 (median), was higher among non-survivors (*P*=0.02). On further analysis, we could not find any significant difference if a cut-off of ANC=500 was taken. Metabolic parameters such as serum creatinine was significantly higher (*P*=0.001), whereas serum albumin was significantly lower in the non-survivors' group (*P*=0.001).

For treatment, steroids were the most common drug used in the overall population (58.0%). Among drugs with potential antiviral activities, azithromycin and hydroxychloroquine were the two most common drugs (39.5 and 31.3 per cent, respectively; Table I). During the hospital stay, 41 (30.6%) patients required oxygen administration and among these, 21 (51.2%) patients died. Intensive care unit (ICU) admission was required in 32 (23.9%), of whom 21 (65.6%) died. Twenty eight patients (n=28) developed acute respiratory distress syndrome (ARDS) and required mechanical ventilation; however, majority of these (n=21) succumbed (Table II).

On univariate regression analysis, it was found that age more than 60 yr, gender, type of tumour, symptom duration, the severity of disease, haemoglobin <8.9 g/dl, NLR >4.6, albumin ≤3.3 mg/dl and serum creatinine
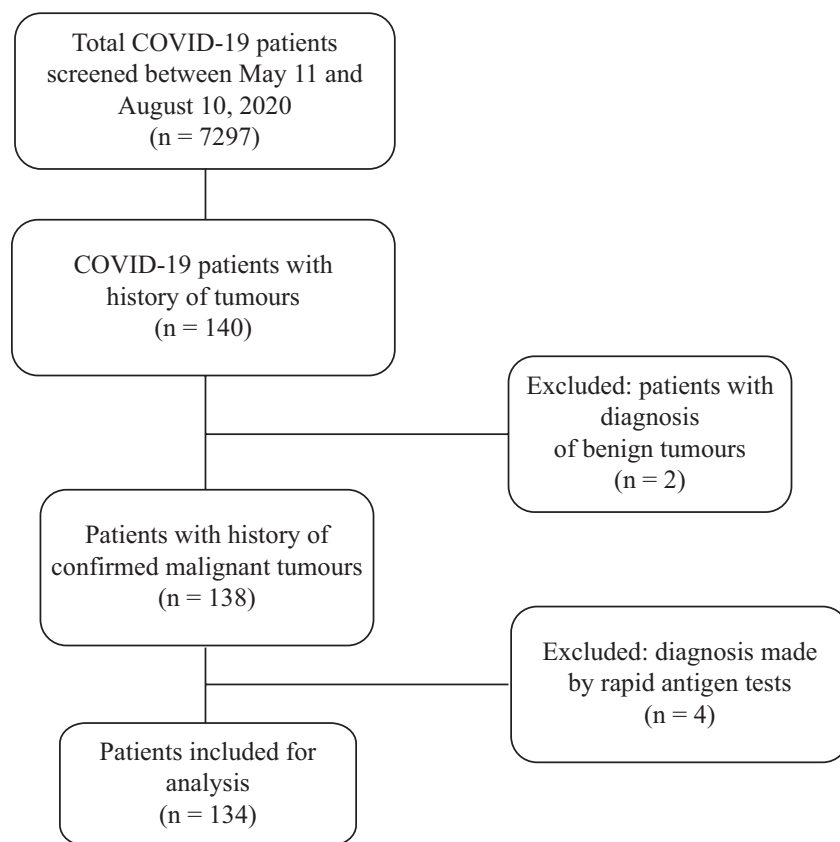
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┌─────────────────────────┐
│   Total COVID-19 patients │
│  screened between May 11 and │
│      August 10, 2020      │
│       (n = 7297)          │
└─────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│   COVID-19 patients with  │
│    history of tumours     │
│       (n = 140)           │
└─────────────────────────┘         ┌──────────────────────┐
            │───────────────────────│ Excluded: patients with│
            │                        │      diagnosis        │
            │                        │   of benign tumours   │
            │                        │       (n = 2)         │
            ▼                        └──────────────────────┘
┌─────────────────────────┐
│  Patients with history of │
│ confirmed malignant tumours│
│       (n = 138)           │
└─────────────────────────┘         ┌──────────────────────┐
            │───────────────────────│ Excluded: diagnosis made│
            │                        │  by rapid antigen tests│
            │                        │       (n = 4)         │
            ▼                        └──────────────────────┘
┌─────────────────────────┐
│   Patients included for   │
│        analysis           │
│       (n = 134)           │
└─────────────────────────┘
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Fig. 1. Flowchart showing patient profile and screening.

>0.74 mg/dl were associated with higher odds of death (Table III). On multivariate analysis older age, serum albumin, haemoglobin and NLR were found to be associated with significantly high odds of death.

Most of the deaths were observed in the group with moderate and severe symptoms at presentation. Hence, the data of 41 patients were analyzed separately who presented with moderate to severe symptoms. A significant association was found in a two-sided t test of patient mortality with higher levels of creatinine ($P<0.007$) and lower levels of serum albumin ($P<0.0051$) (Fig. 2A-E). In terms of categorical data (Fig. 2F-J), a marginally significant association of mortality was found with patient gender ($P=0.062$).

Finally, we used unsupervised learning using U-MAP for dimensionality reduction to visualize the correlated structure of our multi-parameter dataset. It was found that the patients data points were distributed in three clusters recapitulating the observations based on the severity of infection and outcome. The first cluster was dominated by asymptomatic patients with no mortality, the second cluster had a majority of mild and a few moderate severity patients with 3.0 per cent mortality, while the third cluster had a majority of severe and a few moderate patients with 68.0 per cent mortality. Moderate patients were split across two clusters, with 12 patients in cluster two and six patients in cluster three.

Discussion

The observed mortality (17.1%) due to COVID-19 in this subset of cancer patients was alarming, but was similar to that reported in two other studies from this region[11,12]. Increased death risk in cancer patients has also been observed in studies reported from China and US[13,14]. Site-specific variation in mortality has been observed in larger studies where patients of lung cancer infected with COVID-19 have experienced higher mortality[15]. However, due to the small sample size, we could not get similar observations.

It was found that baseline serum albumin could predict higher mortality in the overall population. Low serum albumin, although is a known predictor of poor outcomes in cancer, it may also be a result of the acute-phase response[16]. It has been recognized as

Table I. Treatment details in patients during hospitalization			
Therapy	Total cases (n=134), n (%)	Asymptomatic + mild (n=93), n (%)	Moderate + severe (n=41), n (%)
Steroids	58 (43.3)	20 (21.5)	38 (92.7)
Hydroxychloroquine	42 (31.3)	22 (23.6)	20 (48.8)
Azithromycin	53 (39.5)	32 (34.4)	21 (51.2)
Remdesivir	14 (10.4)	2 (2.1)	12 (29.3)
Doxycycline	12 (9)	5 (5.4)	7 (17.1)
Favipiravir	7 (5.2)	6 (6.4)	1 (2.4)
Ivermectin	8 (6)	4 (4.3)	4 (9.7)
Interleukin-6 inhibitors	3 (2.2)	0	3 (7.3)
Plasma	3 (2.2)	0	3 (7.3)

Table II. Disease course and complications		
Complications	Intervention (n=134), n (%)	Death, n (%)
Oxygen administration	41 (30.6)	21/41 (51.2)
ICU	32 (23.9)	21/32 (65.6)
ARDS	28 (20.9)	21/28 (75)
Mechanical ventilation	25 (18.7)	19/25 (76)
Sepsis	22 (16.4)	15/22 (68.2)
MODS	9 (6.7)	9/9 (100)
ARF	8 (6)	7/8 (87.5)
Cardiac dysfunction	5 (3.7)	4/5 (80)
CNS event	4 (3)	3/4 (75)

ICU, intensive care unit; ARDS, acute respiratory distress syndrome; MODS, multi organ dysfunction syndrome; ARF, acute renal failure; CNS, central nervous system

a poor prognostic factor in the non-cancer COVID-19 population[17-19]. It may have a therapeutic role, that requires further investigations[20]. High NLR was found to be associated with poor outcomes in our study. Being a known marker of immune activation, observed poor prognostic role is similar to other reported studies[21,22]. Lower haemoglobin (≤8.9) was another factor observed to be associated with poor outcomes as reported in past studies[23].

Among patients with age more than 60 yr, high mortality was observed. This finding was in concordance with already reported observations[4].

Some previous studies suggested lower fatality rates in paediatric cancer patients[24,25]. Our study had 11 paediatric patients and around two-thirds had a diagnosis of haematological tumours (data not shown). There was only one mortality among them, but the sample size was too small to derive any discrete conclusion.

A higher mortality was observed in haematological malignancies as compared with solid cancers (24.4 *vs.* 13.9 %, respectively). A few other studies from this region have also suggested a higher mortality risk among infected individuals with haematological malignancies[26,27]. Similar findings have been reported in other countries[28,29]. Tumour type is another factor that may affect prognosis variably, as shown in a few studies[30,31], however, we could not find any differences in outcomes.

Around 30.0 per cent of patients were admitted to the hospital with moderate or severe symptoms and among these, 78.0 per cent of patients required ICU admission. The worrisome trend observed was among sick cases, who developed ARDS. Around three-fourths of such cases could not be salvaged. High fatality rates were also observed in severe cases who developed complications such as sepsis, MODS and ARF. The inability to salvage such cases indicates that the prevention of infection may be the most important strategy. Our study included 19.0 per cent of patients with neutropenia, likely due to recent chemotherapy. The observed mortality in this subset was no different from the non-neutropenic subset.

Distinct clustering of our patients predicting outcome suggested that there could be a potential reclassification of patient severity specifically moderately symptomatic patients, into either critical or non-critical categories, an observation which can further be validated in a larger data set in future. This could help towards optimal utilization of health

| Table III. Bivariate logistic regression analysis of factors associated with death during the hospital stay				
Parameters	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Age (yr)				
≤60	1 (reference)		Reference	
>60	3.32 (1.3-8.46)	0.012	7.99 (1.18-54.00)	0.033
Sex				
Male	1 (reference)		Reference	
Females	0.25 (0.09-0.68)	0.004	0.56 (0.13-2.39)	0.438
Severity				
Asymptomatic + mild	1 (reference)			
Moderate + severe	3.21 (1.91-5.38)	0.001	-	
PS				
0-1	1 (reference)			
2-4	9.71 (1.25-75.02)	0.29	-	
Symptom duration (days)				
≤3	1 (reference)			
>3	1.7 (1.07-2.71)	0.022	2.17 (0.62-11.89)	0.186
Comorbidity				
0	1 (reference)		Reference	
1	0.83 (0.99-8.61)	0.793	0.23 (0.01-2.89)	0.254
≥2	2.92 (0.09-0.31)	0.052	2.61 (0.31-21.91)	0.376
Type of tumour				
Solid	1 (reference)		Reference	
Haematological	0.44 (0.30-0.64)	0.001	1.66 (0.33-8.27)	0.537
Cancer stage (solid tumours)				
1-3	1 (reference)		-	
4	1.88 (0.88-4.01)	0.10		
Cytotoxic chemotherapy				
No	1 (reference)		-	
Yes	0.76 (0.29-1.97)	0.57		
Haemoglobin (g/dl)				
>8.9	1 (reference)			
≤8.9	1.80 (1.12-2.89)	0.015	6.28 (1.07-37.04)	0.042
NLR				
≤4.6	1 (reference)			
>4.6	4.22 (1.62-10.99)	0003	12.02 (2.08-69.51)	0.005
Platelets (lacs)				
>1.39	1 (reference)			
≤1.39	1.43 (0.90-2.28)	0.126		
Albumin (mg/dl)				
>3.3	1 (reference)			
≤3.3	3.16 (1.74-5.73)	<0.001	18.52 (2.80-122.27)	0.002
Creatinine (mg/dl)				
≤0.74	1 (reference)			
>0.74	3.40 (1.31-8.86)	0.012	4.88 (1.01-23.81)	0.050
P<0.05 was considered significant. OR, odds ratio; NLR, neutrophil-lymphocyte ratio; CI, confidence interval; PS, performance status				
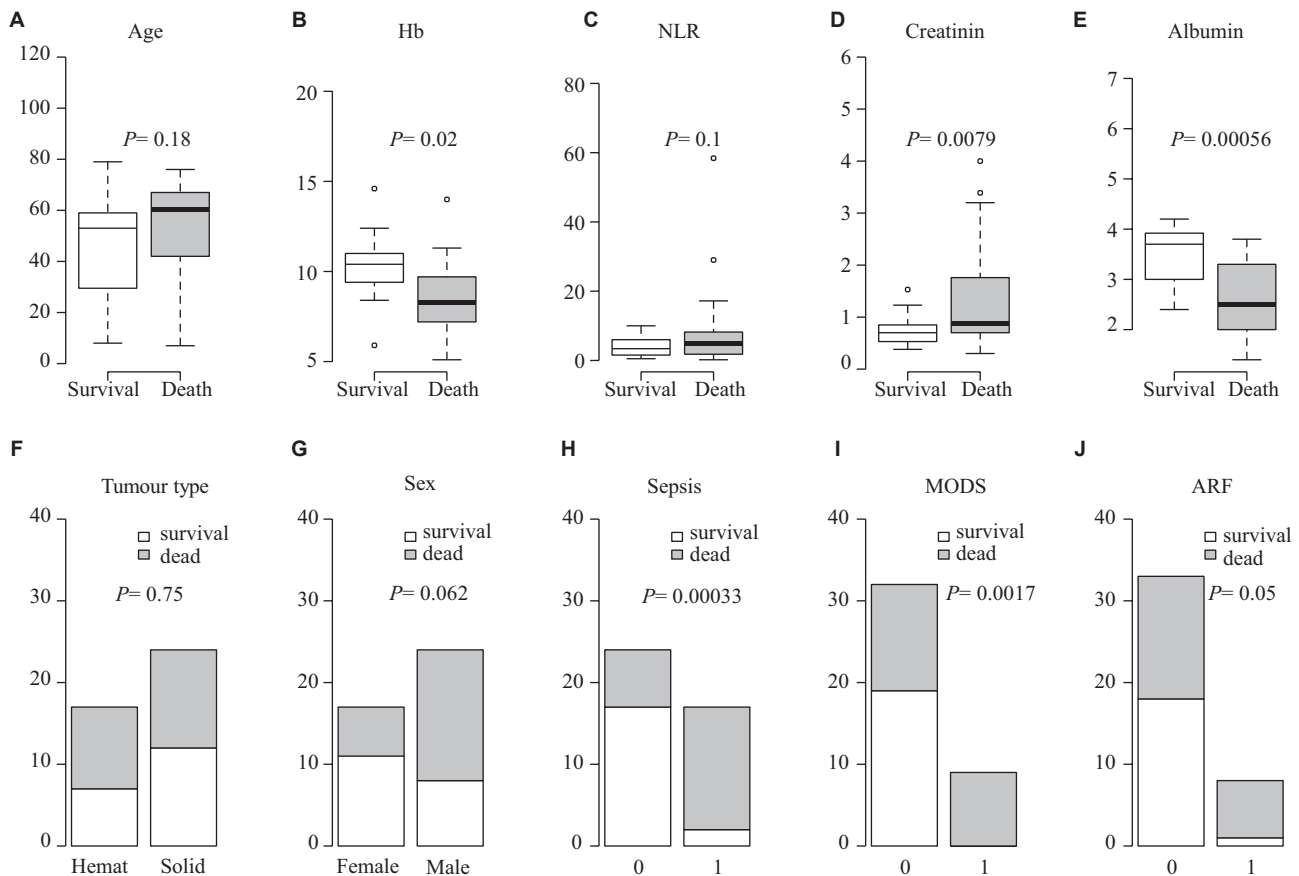
Fig. 2. Factors determining mortality in moderate/severe disease, (**A**) age; (**B**) haemoglobin (Hb); (**C**) neutrophil-lymphocyte ratio (NLR); (**D**) creatinin; (**E**) albumin; (**F**) tumour type; (**G**) Sex; (**H**) sepsis; (**I**) multiorgan dysfunction syndrome (MODS); (**J**) acute renal failure (ARF).

resources and building a system to triage cancer patients suffering from COVID-19 more effectively.

There were certain limitations in our study. A relatively small sample size and limitation of information available for analysis, were most important. We also could not retrieve data on smoking history and comorbidities like obesity, which may have a bearing on the overall outcome, as reported earlier[32,33]. The characteristics of the non-cancer population infected with COVID-19 could not be evaluated during this period; hence, a comparative analysis between the two groups could not be performed.

In conclusion, our study data add to the existing knowledge of cancer patients with COVID-19. It was observed that baseline organ dysfunction and older age might affect outcomes in such patients. Recent chemotherapy may not affect prognosis adversely. There were a large number of asymptomatic individuals who did well on observation. Hence, chemotherapy in asymptomatic COVID-19 infected cancer patients may be a safe option.

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