



# Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study

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## Summary

**Background** COVID-19 has spread globally. Epidemiological susceptibility to COVID-19 has been reported in patients with cancer. We aimed to systematically characterise clinical features and determine risk factors of COVID-19 disease severity for patients with cancer and COVID-19.

**Methods** In this multicentre, retrospective, cohort study, we included all adult patients (aged  $\geq 18$  years) with any type of malignant solid tumours and haematological malignancy who were admitted to nine hospitals in Wuhan, China, with laboratory-confirmed COVID-19 between Jan 13 and March 18, 2020. Enrolled patients were statistically matched (2:1) with patients admitted with COVID-19 who did not have cancer with propensity score on the basis of age, sex, and comorbidities. Demographic characteristics, laboratory examinations, illness severity, and clinical interventions were compared between patients with COVID-19 with or without cancer as well as between patients with cancer with non-severe or severe COVID-19. COVID-19 disease severity was defined on admission on the basis of the WHO guidelines. Univariable and multivariable logistic regression, adjusted for age, sex, comorbidities, cancer type, tumour stage, and antitumour treatments, were used to explore risk factors associated with COVID-19 disease severity. This study was registered in the Chinese Clinical Trial Register, ChiCTR2000030807.

**Findings** Between Jan 13 and March 18, 2020, 13 077 patients with COVID-19 were admitted to the nine hospitals in Wuhan and 232 patients with cancer and 519 statistically matched patients without cancer were enrolled. Median follow-up was 29 days (IQR 22–38) in patients with cancer and 27 days (20–35) in patients without cancer. Patients with cancer were more likely to have severe COVID-19 than patients without cancer (148 [64%] of 232 vs 166 [32%] of 519; odds ratio [OR] 3·61 [95% CI 2·59–5·04];  $p < 0\cdot0001$ ). Risk factors previously reported in patients without cancer, such as older age; elevated interleukin 6, procalcitonin, and D-dimer; and reduced lymphocytes were validated in patients with cancer. We also identified advanced tumour stage (OR 2·60, 95% CI 1·05–6·43;  $p = 0\cdot039$ ), elevated tumour necrosis factor  $\alpha$  (1·22, 1·01–1·47;  $p = 0\cdot037$ ), elevated N-terminal pro-B-type natriuretic peptide (1·65, 1·03–2·78;  $p = 0\cdot032$ ), reduced CD4+ T cells (0·84, 0·71–0·98;  $p = 0\cdot031$ ), and reduced albumin–globulin ratio (0·12, 0·02–0·77;  $p = 0\cdot024$ ) as risk factors of COVID-19 severity in patients with cancer.

**Interpretation** Patients with cancer and COVID-19 were more likely to deteriorate into severe illness than those without cancer. The risk factors identified here could be helpful for early clinical surveillance of disease progression in patients with cancer who present with COVID-19.

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## Introduction

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally. As of May 27, 2020, there were 5 491 678 confirmed cases and 349 190 deaths, with the numbers still surging across 217 countries worldwide.<sup>1</sup> With the continued increase in cases and affected regions, extra preparations to protect high-risk populations should be made, especially for older patients and those with existing conditions.

Notably, initial analyses of patient characteristics from China have shown that diabetes, hypertension, and

cardiovascular diseases are highly prevalent among patients with COVID-19, and patients with these comorbidities are predisposed to a poor clinical outcome.<sup>2–4</sup> COVID-19 might act as a precipitating factor to worsen existing conditions, potentially leading to death.<sup>4</sup> Cancer, which affects tens of millions of people each year worldwide, has been found to be a major risk factor in patients with COVID-19.<sup>5</sup> Evidence suggests that patients with cancer might be more susceptible to COVID-19 than those without cancer.<sup>6</sup> However, because of the small sample sizes in most of the reports, there are insufficient

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## Research in context

### Evidence before this study

We searched PubMed and Preprint websites (medRxiv and bioRxiv) on Mar 18, 2020, for articles that documented the risk factors of COVID-19 illness severity of patients with cancer and COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using the search terms (“novel coronavirus” OR “SARS-CoV-2” OR “COVID-19”) AND (“cancer” OR “carcinoma” OR “tumor”) with no language or date restrictions. Epidemiological features and susceptibility of patients with cancer and COVID-19 have been reported. Among these studies, one study described baseline demographic data, such as age, sex, smoking status, and underlying comorbidities in 18 patients with cancer and COVID-19. The small sample sizes in most reports make it difficult to accurately describe or even to explore a possible association between cancer and COVID-19. Detailed clinical symptoms, radiological characteristics, biochemical markers, and progression of patients with cancer and COVID-19 are scarce at this stage, especially regarding risk factors influencing their progression or disease severity. Thus, a systematic understanding of the clinical features of patients with cancer and COVID-19 is urgently needed to protect susceptible patients with cancer from SARS-CoV-2 infection, monitor reliable markers for disease course, and administer effective treatment for this particular population.

### Added value of this study

To our knowledge, this study is the largest multicentre cohort study published so far on the clinical features of patients with cancer and COVID-19. We found that the odds of COVID-19 progressing into severe illness was 3.611 times higher for patients with cancer than for those without cancer. Furthermore, we identified several novel risk factors for severity of COVID-19 in patients with cancer, such as advanced tumour stage and elevated tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), as well as decreased CD4+ T cells and albumin-globulin ratio. These indices are helpful for assessing disease severity and should be extensively monitored during COVID-19 treatment in case of adverse status.

### Implications of all the available evidence

Greater attention should be given to patients with COVID-19 who have cancer, as our findings suggest they are more likely to deteriorate into severe illness. The potential risk factors of elevated TNF- $\alpha$  and NT-proBNP and decreased CD4+ T cells or albumin-globulin ratio can be helpful for clinicians in terms of early surveillance of COVID-19 progression, alongside older age; elevated interleukin-6, procalcitonin, and D-dimer; and decreased lymphocytes.

data to accurately describe or even to explore a possible association between cancer and COVID-19. Notably, detailed clinical symptoms, radiological findings, biochemical markers, clinical characteristics, and progression of patients with cancer and COVID-19 are scarce at this stage, especially for the risk factors affecting their COVID-19 progression or disease severity, such as inflammatory cytokines or immune cell changes. Therefore, a systemic understanding of the clinical features of patients with cancer and COVID-19 is urgently needed to protect these susceptible patients from SARS-CoV-2 infection, monitor reliable markers for disease course, and administer effective treatments for this particular population.

Here, we report results from a cohort study from nine hospitals that were designated to treat patients with COVID-19 in Wuhan, China, the initial epicentre of the COVID-19 outbreak. We aimed to systematically characterise the clinical features and determine the risk factors of disease severity for patients with cancer and COVID-19.

## Methods

### Study design and participants

This multicentre, retrospective, cohort study was done in nine hospitals in Wuhan, China, that were designated centres for COVID-19 treatment: Tongji Hospital, Wuhan Union Hospital, Wuhan First Hospital, the Central Hospital of Wuhan, Wuhan Fourth Hospital and Puai

Hospital, Fifth Hospital of Wuhan, Wuhan Pulmonary Hospital, Wuhan Jinyintan Hospital, and Wuhan Hankou Hospital. These hospitals are located across Wuhan and have admitted most of the patients with COVID-19 in Wuhan. We included all adult patients (aged  $\geq 18$  years) admitted between Jan 13 and March 18, 2020, with laboratory-confirmed SARS-CoV-2 infection by RT-PCR who had any type of malignant solid tumour and haematological malignancies. Enrolled patients were statistically matched with patients admitted with COVID-19 who did not have cancer by propensity score matching<sup>7</sup> at an approximate ratio of 2:1 based on age, sex, and comorbidities. Hypertension, diabetes, coronary heart disease, chronic kidney damage, cerebrovascular disease, hepatitis, and chronic obstructive pulmonary disease (COPD) were used as matching factors in this study; these conditions have been reported to be risk factors for disease severity or death from COVID-19.<sup>2,3</sup>

Because public health interventions in Wuhan changed over the enrolment period,<sup>8</sup> we grouped patients into two groups according to time of admission: early stage (Jan 13 to Feb 16, 2020) or late stage (Feb 17 to March 18, 2020).

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20200335) and granted a waiver of informed consent from study participants. Recruitment sites, principal investigators responsible for the sites, and the number of patients recruited are listed in the appendix (p 2).

See Online for appendix

## Definitions

All enrolled patients were classified as having non-severe or severe COVID-19 on admission; disease classification was checked and revised if necessary during hospitalisation. We defined disease severity according to WHO guidelines,<sup>9</sup> complemented by the Seventh Revised Trial Version of the COVID-19 Diagnosis and Treatment Guidance (2020) of China.<sup>10</sup> Patients had severe disease if they had any of the following criteria: respiratory rate of at least 30 breaths per min, oxygen saturation of 93% or lower in a resting state, ratio of arterial partial pressure of oxygen and oxygen concentration no greater than 300 mm Hg, or more than 50% lesion progression in lung imaging within 24–48 h.

Time of follow-up was defined as the duration from hospital admission to outcomes (survivor or non-survivor) of patients; survivors were defined as patients who were discharged from hospital or still hospitalised at the end of the study.

## Data collection

Epidemiological, clinical, laboratory, and radiological data of all patients with laboratory-confirmed SARS-CoV-2 were obtained with data collection forms from the electronic medical records of each designated hospital. Data were reviewed and verified by a team of physicians (XY, QZ, ZY, and BL). Any missing or uncertain records were collated and clarified through communication with involved health-care providers or patients and their families. Detailed demographics information, comorbidities, symptoms, and disease severity of all patients were recorded or diagnosed on admission. Laboratory examinations including routine blood tests; lymphocyte subsets; inflammatory or infection-related biomarkers; cardiac, renal, liver, and coagulation function tests; and chest CT scans were obtained at initial diagnosis. Clinical treatment details were also included. There were no cases lost to follow-up in this study.

## Laboratory procedures

Concentrations of interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-2 receptor (IL-2R), IL-6, IL-8, IL-10, and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) were assessed in serum samples and detected in most patients on admission and during hospitalisation, using a fully automated analyser (Cobas e602; Roche Diagnostics, Indianapolis, IN, USA) by chemiluminescence immunoassay method.<sup>11</sup> Kits for IL-1 $\beta$ , IL-2R, IL-8, IL-10, and TNF- $\alpha$  were purchased from DiaSorin (Vercelli, Italy) and the IL-6 kit was purchased from Roche Diagnostics.

## Statistical analysis

Continuous variables with a skewed distribution were described as median (IQR) using the empirical distribution function with averaging method. Categorical variables were expressed as frequencies. The Mann-Whitney *U* test was used to compare continuous

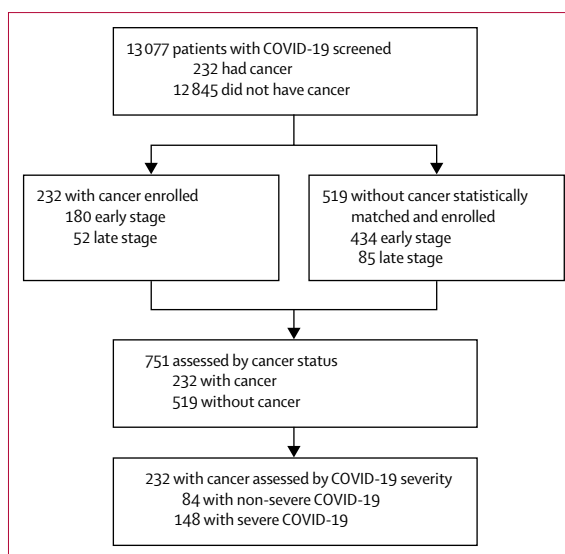


Figure: Study profile

variables. The  $\chi^2$  test with Yates' correction was used for  $2 \times 2$  contingency data,<sup>12</sup> and Pearson's  $\chi^2$  test was used for contingency data for variables with more than two categories. To explore risk factors, or their interactions, associated with severity of COVID-19 in patients with cancer, univariable and multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% CIs, adjusting for age, sex, comorbidities, cancer type, tumour stage, and antitumour treatments. Cox proportional-hazards models were applied to determine hazard ratios (HRs) and 95% CIs for disease outcome, adjusted for the aforementioned confounders. Sensitivity analyses were done for all adjustment variables, comparing the results between univariable analysis without adjusting confounders and multivariable analysis with adjusting confounders for disease severity in patients with cancer and COVID-19. We did a power analysis for severity of COVID-19 in patients with or without cancer using the Pearson  $\chi^2$  test for two proportions method, and the power was more than 0.95. A two-sided  $p < 0.05$  was considered statistically significant. All statistical analyses were done using SAS (version 9.4) and SPSS (version 22.0). This study was registered in the Chinese Clinical Trial Register, ChiCTR2000030807.

## Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Jan 13 and March 18, 2020, 13 077 patients with confirmed SARS-CoV-2 infection were admitted to the

	All patients (n=751)	Patients without cancer (n=519)	Patients with cancer (n=232)	p value
<b>Demographics</b>				
Age, years	64.0 (57.0-69.0)	64.0 (56.0-70.0)	64.0 (58.0-69.0)	0.42
Sex	..			0.57
Female	379 (50%)	266 (51%)	113 (49%)	..
Male	372 (50%)	253 (49%)	119 (51%)	..
<b>Clinical characteristics and outcomes</b>				
Current smoker	45 (6%)	31 (6%)	14 (6%)	0.89
<b>Comorbidities</b>				
Hypertension	292 (39%)	196 (38%)	96 (41%)	0.39
Diabetes	198 (26%)	143 (28%)	55 (24%)	0.31
Coronary heart disease	74 (10%)	52 (10%)	22 (9%)	0.92
Chronic kidney disease	23 (3%)	21 (4%)	6 (3%)	0.44
Cerebrovascular disease	23 (3%)	14 (3%)	9 (4%)	0.52
Hepatitis	10 (1%)	4 (1%)	6 (3%)	0.097
COPD	4 (1%)	1 (<1%)	3 (1%)	0.17
<b>Symptoms at admission</b>				
Fever	514 (68%)	364 (70%)	150 (65%)	0.16
Dry cough	368 (49%)	249 (48%)	119 (51%)	0.45
Fatigue	153 (20%)	101 (19%)	52 (22%)	0.41
Dyspnoea	152 (20%)	89 (17%)	63 (27%)	0.0022
Expectoration	135 (18%)	83 (16%)	52 (22%)	0.044
Chest tightness	97 (13%)	68 (13%)	29 (13%)	0.91
Diarrhoea	89 (12%)	63 (12%)	26 (11%)	0.81
Sore throat	46 (6%)	43 (8%)	3 (1%)	0.00042
Aversion to cold	42 (6%)	33 (6%)	9 (4%)	0.23
Coryza	45 (6%)	41 (8%)	4 (2%)	0.0018
Vomiting	34 (5%)	25 (5%)	9 (4%)	0.70
Headache	37 (5%)	29 (6%)	8 (3%)	0.29
COVID-19 severity	..	..	..	<0.0001
Non-severe	437 (58%)	353 (68%)	84 (36%)	..
Severe	314 (42%)	166 (32%)	148 (64%)	..
Follow-up, days	28 (20-36)	27 (20-35)	29 (22-38)	0.0076
<b>Clinical outcomes</b>				
Survivor	649 (86%)	463 (89%)	186 (80%)	..
Non-survivor	102 (14%)	56 (11%)	46 (20%)	..
<b>CT findings</b>				
Ground-glass opacity	331/496 (67%)	183/301 (61%)	148/195 (76%)	0.00070
Patchy shadows	278/496 (56%)	152/301 (50%)	126/195 (65%)	0.0027
Fibrous stripes	179/496 (36%)	102/301 (34%)	77/195 (39%)	0.24
Pleural thickening	145/496 (29%)	85/301 (28%)	60/195 (31%)	0.61
Nodules	74/496 (15%)	46/301 (15%)	28/195 (14%)	0.88
Lymphadenopathy	86/496 (17%)	51/301 (17%)	35/195 (18%)	0.87
Bilateral pulmonary	351/496 (71%)	201/301 (67%)	150/195 (77%)	0.020
Right lung	36/496 (7%)	27/301 (9%)	9/195 (5%)	0.099
Left lung	31/496 (6%)	23/301 (8%)	8/195 (4%)	0.16

(Table 1 continues on next page)

nine hospitals in our study. Among these patients, 232 patients with cancer and 519 matched patients without cancer were enrolled in this study (figure). Patients were followed up until March 26, 2020. 614 patients were included in the early stage group

(ie, hospital admission between Jan 13 and Feb 16, 2020) and 137 in the late stage group (hospital admission between Feb 17 and March 18, 2020).

The patients with cancer had 24 different types of cancer; detailed distribution and baseline characteristics

	All patients (n=751)	Patients without cancer (n=519)	Patients with cancer (n=232)	p value
(Continued from previous page)				
<b>Laboratory examinations</b>				
<b>Cytokines and inflammatory factors</b>				
TNF- $\alpha$ , pg/mL (n=425)	7.1 (5.0-9.5)	6.9 (4.8-9.3); n=336	8.7 (5.6-10.9); n=89	0.0040
IL-6, pg/mL (n=488)	6.2 (2.2-21.8)	4.9 (1.9-18.3); n=350	12.8 (3.7-32.5); n=138	<0.0001
IL-10, pg/mL (n=426)	5.0 (5.0-5.9)	5.0 (5.0-5.5); n=338	5.0 (5.0-7.0); n=88	0.15
IL-2R, U/mL (n=419)	555.0 (364.0-861.0)	535.0 (348.5-839.0); n=340	615.0 (428.0-1028.0); n=79	0.012
Procalcitonin, ng/mL (n=412)	0.1 (0.0-0.2)	0.1 (0.0-0.1); n=251	0.1 (0.0-0.3); n=161	0.0041
C-reactive protein, mg/L (n=337)	42.7 (18.5-70.2)	40.7 (17.3-64.9); n=246	46.4 (21.8-94.9); n=91	0.047
<b>Lymphocytes</b>				
Lymphocytes (n=718)	16.6% (8.5-24.9)	16.8% (9.2-25.3); n=515	15.9% (7.2-23.5); n=203	0.099
Lymphocyte count per $\mu$ L (n=746)	0.9 (0.5-1.3)	0.9 (0.6-1.3); n=515	0.8 (0.5-1.3); n=231	0.039
CD3-CD19+ B-cell count per $\mu$ L (n=111)	156.0 (98.0-213.0)	175.0 (117.0-219.0); n=82	102.0 (66.4-154.0); n=29	0.0039
CD4+ T cells (n=136)	44.3% (38.1-49.7)	47.7% (42.6-53.9); n=82	41.1% (35.6-44.0); n=54	<0.0001
CD4+ T-cell count per $\mu$ L (n=119)	460.0 (343.0-770.0)	652.5 (415.0-899.0); n=82	370.0 (312.0-400.0); n=37	<0.0001
CD8+ T cells (n=136)	22.4% (17.4-26.9)	20.7% (17.1-25.7); n=82	23.1% (18.4-30.3); n=54	0.10
CD8+ T-cell count per $\mu$ L (n=125)	267.0 (145.0-353.0)	305.0 (184.0-386.0); n=82	206.0 (109.0-307.0); n=43	0.0081
CD4+ T cells/CD8+ T cells (n=125)	2.1 (1.5-2.7)	2.2 (1.7-2.9); n=82	1.8 (1.1-2.5); n=43	0.0052
<b>Organ damage indices</b>				
Alanine transaminase, U/L (n=464)	20.0 (14.0-34.0)	18.0 (13.0-30.0); n=283	25.0 (16.0-42.0); n=181	<0.0001
Aspartate transaminase, U/L (n=464)	29.0 (20.0-44.0)	29.0 (20.0-45.0); n=283	27.5 (18.7-43.0); n=181	0.19
Lactate dehydrogenase, U/L (n=458)	208.0 (176.0-342.0)	194.0 (171.0-257.0); n=283	253.0 (194.0-455.0); n=175	<0.0001
Total protein, g/L (n=372)	68.0 (63.9-71.4)	68.3 (64.4-71.6); n=279	66.0 (61.7-70.6); n=93	0.011
Albumin, g/L (n=462)	36.8 (33.1-39.9)	37.2 (34.5-40.0); n=281	34.7 (30.1-39.8); n=181	<0.0001
Globulin, g/L (n=372)	31.8 (28.9-35.3)	32.1 (29.5-35.9); n=279	30.7 (26.8-33.4); n=93	0.00061
Albumin-globulin ratio (n=372)	1.2 (1.0-1.4)	1.1 (1.0-1.3); n=279	1.2 (1.0-1.5); n=93	0.40
NT-proBNP, pg/mL (n=331)	171.0 (59.0-558.0)	171.5 (56.0-519.0); n=214	158.0 (68.0-678.0); n=117	0.28
Myoglobin, ng/mL (n=234)	41.4 (29.7-95.6)	41.4 (28.5-91.8); n=133	41.3 (30.6-105.8); n=101	0.60
hs-cTnI, pg/mL (n=368)	2.7 (1.9-8.1)	2.4 (1.9-4.5); n=229	4.1 (1.9-14.3); n=139	0.0083
Leucocyte count, $\times 10^9/L$ (n=462)	5.6 (4.2-7.8)	5.7 (4.3-8.0); n=281	5.5 (4.2-7.7); n=181	0.58
Neutrophils (n=462)	70.6% (62.2-80.7)	67.8% (61.5-76.4); n=281	73.1% (64.2-86.1); n=181	<0.0001
Neutrophil count, $\times 10^9/L$ (n=462)	4.0 (3.0-5.3)	4.1 (3.4-5.0); n=281	3.9 (2.8-6.5); n=181	0.84
Eosinophils (n=462)	0.7% (0.0-1.6)	0.8% (0.0-1.8); n=281	0.6% (0.0-1.7); n=181	0.72
Eosinophil count, $\times 10^9/L$ (n=462)	0.1 (0.0-0.1)	0.1 (0.0-0.1); n=281	0.0 (0.0-0.1); n=181	0.034
Erythrocyte count, $\times 10^{12}/L$ (n=462)	4.0 (3.6-4.5)	4.1 (3.7-4.5); n=281	3.8 (3.3-4.3); n=181	<0.0001
Haemoglobin, g/L (n=462)	123.0 (108.3-134.0)	126.0 (114.0-137.0); n=281	118.0 (98.0-128.0); n=181	<0.0001
Platelet count, $\times 10^9/L$ (n=461)	196.0 (138.0-264.0)	210.0 (142.0-277.0); n=281	182.0 (131.5-237.0); n=180	0.0061
D-dimer, $\mu$ g/mL (n=447)	0.9 (0.4-2.6)	0.8 (0.4-2.1); n=280	1.2 (0.5-4.7); n=167	0.054
Prothrombin time, s (n=447)	13.3 (12.7-13.9)	13.2 (12.8-13.6); n=278	13.6 (12.4-14.8); n=169	0.036
Activated partial thromboplastin time, s (n=394)	34.6 (30.2-39.9)	34.1 (30.2-38.2); n=239	35.5 (30.2-42.9); n=155	0.046
Prothrombin activity (n=373)	89.0% (79.0-98.0)	89.0% (81.0-98.3); n=280	88.0% (73.0-96.0); n=93	0.092
Data are n (%), n/N (%), or median (IQR), unless specified otherwise. COPD=chronic obstructive pulmonary disease. TNF- $\alpha$ =tumor necrosis factor $\alpha$ . IL=interleukin. IL-2R=IL-2 receptor. CD=cluster of differentiation. NT-proBNP=N-terminal pro-B-type natriuretic peptide. hs-cTnI=high-sensitivity cardiac troponin I.				
<b>Table 1: Demographic, clinical, radiographical, and laboratory findings of patients with COVID-19 with and without cancer</b>				

according to cancer type are presented in the appendix (pp 3–10, 17). Because medical care within different hospitals was done according to the Seventh Revised Trial Version of COVID-19 diagnosis and treatment guidance, the clinical outcomes (survivor and non-survivor) among different hospitals were not significantly different ( $p=0.30$ ; appendix p 2). 92 (15%) of

614 patients admitted in the early stage died compared with ten (7%) of 137 patients admitted in the late stage.

When comparing symptoms at admission, patients with cancer were more likely to have dyspnoea and expectoration than patients without cancer, but less likely to have sore throat and coryza (table 1). Moreover, CT scans showed that ground-glass opacity and patchy

shadows were more frequent in patients with cancer (table 1). Differences in some symptoms and CT findings were found also when comparing patients with cancer with severe and non-severe COVID-19 (table 2).

When comparing biochemical indexes of COVID-19 between patients with and without cancer, we found that pro-inflammatory cytokines including TNF- $\alpha$ , IL-6, and IL-2R were higher in patients with cancer than in those without cancer. Infection-related biomarkers procalcitonin and C-reactive protein were also higher in patients with cancer. In terms of immune cells, the decline of lymphocytes, CD4+ T cells, CD8+ T-cell counts, and the ratio of CD4+ T cells to CD8+ T cells were more pronounced in patients with cancer (table 1). Additionally, there was greater evidence of multiple-organ damage in patients with cancer compared with those without cancer, since patients with cancer presented with higher levels of neutrophils, alanine transaminase, lactate dehydrogenase, and hs-cTnI, whereas eosinophils, albumin, globulin, and total protein were decreased (table 1). Furthermore, coagulation-related indicators, such as falling platelet counts and prolonged prothrombin time and activated partial thromboplastin time were also pronounced in patients with cancer (table 1). Notably, aggravated inflammatory responses, lymphopenia, and multiple-organ damage, especially decreased albumin–globulin ratio and elevated NT-proBNP, were more pronounced in patients with cancer who had severe COVID-19 compared with those with non-severe disease (table 2). Other laboratory indices or organ damage biomarkers in both patients with and without cancer, as well as patients with cancer and severe or non-severe COVID-19, are presented in the appendix (pp 11–12).

166 (32%) of 519 patients without cancer and 148 (64%) of 232 patients with cancer had severe COVID-19 at hospital admission (table 1); the risk of having severe illness was higher for patients with cancer (OR 3.61; 95% CI 2.59–5.04;  $p < 0.0001$ ) for patients with cancer. Patients with cancer had a longer follow-up than those without cancer, indicating that they spent more time in hospital, and were also more likely to die during follow-up (table 1). Additionally, the time for viral clearance was longer in patients with cancer (24 [IQR 17–29] days) than in those without cancer (21 days [IQR 15–24];  $p = 0.045$ ).

When comparing the cancer characteristics between patients with severe and non-severe COVID-19, we found that patients with severe COVID-19 were older, had higher Eastern Cooperative Oncology Group (ECOG) performance status scores, and more advanced stage cancer than those with non-severe COVID-19 (table 2). Patients with severe COVID-19 were more likely to have received chemotherapy, radiotherapy, targeted therapy, or immunotherapy than those with non-severe disease, who were more likely to have had surgical antitumour treatment (table 2). The time interval between last chemotherapy treatment and hospital admission, and time since cancer diagnosis also differed between

patients with severe and non-severe COVID-19 (appendix p 13).

184 (79%) of 232 patients with cancer and COVID-19 received antiviral treatment, 204 (88%) patients received antibiotics, and 85 (37%) received immunomodulators. These treatments did not differ significantly between patients with cancer and severe or non-severe COVID-19 (appendix p 14). Ventilation treatment was the conventional non-drug therapy, and, compared with patients without cancer, patients with cancer were more likely to receive high-flow nasal cannula oxygen therapy (77 [33%] of 232 patients with cancer vs 121 [23%] of 519 patients without cancer), non-invasive mechanical ventilation (62 [27%] vs 99 [19%]), or invasive mechanical ventilation (21 [9%] vs 23 [4%]; appendix p 14). Of note, the disease severity statuses of some patients with cancer changed during hospitalisation (appendix p 18): 22 (26%) of 84 patients developed severe disease during hospitalisation, whereas 107 (72%) of 148 patients changed from severe to non-severe disease. Eight (10%) patients with cancer who were admitted with non-severe COVID-19 and 38 (26%) patients with cancer who were admitted with severe COVID-19 died during follow-up (table 2). Treatment processes, dynamic changes of haematological parameters, and clinical outcomes of six typical patients with different types of cancer are shown in the appendix (p 19).

When exploring risk factors of COVID-19 severity in patients with cancer, sensitivity analyses showed no significant difference for most factors between univariable and multivariable analysis (table 3). We found that patients with older age, higher ECOG scores, and advanced tumour stage had increased odds of severe COVID-19. Moreover, compared with those who only received surgical treatment for cancer, patients who received targeted or immunotherapy had higher odds of severe illness (table 3). The effects of time interval since last chemotherapy treatment to hospital admission and time since cancer diagnosis on COVID-19 severity and death are shown in the appendix (pp 15–16). Risk of COVID-19 severity and death was highest for patients with last chemotherapy treatment within 2 weeks of admission, and decreased as the time interval since last chemotherapy increased, with significantly reduced risk when last treatment was at least 3 weeks before hospital admission (appendix pp 15–16). Moreover, patients with longer time since cancer diagnosis (1–5 years or >5 years) had lower risk of COVID-19 severity and death compared with patients with less than 1 year of tumour history (appendix pp 15–16).

After adjusting for age, sex, comorbidities, cancer type, tumour stage, and antitumour treatments in multivariable analyses, we found that pro-inflammatory and infection-related biomarkers, including TNF- $\alpha$ , IL-6, procalcitonin, and C-reactive protein, as well as organ damage indices (leucocytes, neutrophils, and lactate dehydrogenase), coagulation-related indicators (D-dimer, prothrombin

	All patients with COVID-19 and cancer (n=232)	Patients with cancer and non-severe COVID-19 (n=84)	Patients with cancer and severe COVID-19 (n=148)	p value
<b>Demographics</b>				
Age, years	64.0 (58.0–69.0)	63.0 (57.0–67.0)	64.0 (58.0–69.0)	0.024
Sex	..	..	..	0.21
Female	113 (49%)	46 (55%)	67 (45%)	..
Male	119 (51%)	38 (45%)	81 (55%)	..
<b>Clinical characteristics and outcomes</b>				
ECOG performance status	..	..	..	<0.0001
0–2	141 (61%)	81 (96%)	60 (41%)	..
3–4	91 (39%)	3 (4%)	88 (59%)	..
Tumour stage*	..	..	..	0.048
I, II, or III	192/226 (85%)	77/84 (92%)	115/142 (81%)	..
IV	34/226 (15%)	7/84 (8%)	27/142 (19%)	..
Clinical cancer grade	..	..	..	0.43
High differentiation	189 (81%)	72 (86%)	117 (79%)	..
Moderate differentiation	16 (7%)	5 (6%)	11 (7%)	..
Low differentiation	27 (12%)	7 (8%)	20 (14%)	..
Antitumour treatments				
Surgery	197 (85%)	78 (93%)	119 (80%)	0.018
Chemotherapy or radiotherapy	214 (92%)	73 (87%)	141 (95%)	0.042
Targeted therapy or immunotherapy	32 (14%)	6 (7%)	26 (18%)	0.044
Comorbidities				
Hypertension	96 (41%)	28 (33%)	68 (46%)	0.083
Diabetes	55 (24%)	22 (26%)	33 (22%)	0.61
Coronary heart disease	22 (9%)	5 (6%)	17 (11%)	0.25
Chronic kidney disease	6 (3%)	2 (2%)	4 (3%)	1.0
Cardiovascular disease	9 (4%)	3 (4%)	6 (4%)	1.0
Hepatitis	6 (3%)	2 (2%)	4 (3%)	1.0
COPD	3 (1%)	1 (1%)	2 (1%)	1.0
Symptoms at admission				
Fever	150 (65%)	51 (61%)	99 (67%)	0.42
Dry cough	119 (51%)	33 (39%)	86 (58%)	0.0088
Fatigue	52 (22%)	13 (15%)	39 (26%)	0.081
Dyspnoea	63 (27%)	11 (13%)	52 (35%)	0.00051
Expectoration	52 (22%)	5 (6%)	47 (32%)	<0.0001
Chest tightness	29 (13%)	6 (7%)	23 (16%)	0.098
Diarrhoea	26 (11%)	8 (10%)	18 (12%)	0.69
Sore throat	3 (1%)	0	3 (2%)	0.48
Aversion to cold	9 (4%)	1 (1%)	8 (5%)	0.21
Coryza	4 (2%)	0	4 (3%)	0.32
Vomiting	9 (4%)	2 (2%)	7 (5%)	0.59
Headache	8 (3%)	2 (2%)	6 (4%)	0.77
Follow-up, days	29 (22–38)	27 (19–36)	30 (23–40)	0.029
Clinical outcomes	..	..	..	0.0052
Survivor	186 (80%)	76 (90%)	110 (74%)	..
Non-survivor	46 (20%)	8 (10%)	38 (26%)	..
<b>CT findings</b>				
Ground-glass opacity	148/195 (76%)	45/79 (57%)	103/116 (89%)	<0.0001
Patchy shadows	126/195 (65%)	34/79 (43%)	92/116 (79%)	<0.0001
Fibrous stripes	77/195 (39%)	20/79 (25%)	57/116 (49%)	0.0014
Pleural thickening	60/195 (31%)	16/79 (20%)	44/116 (38%)	0.014
Nodules	28/195 (14%)	9/79 (11%)	19/116 (16%)	0.44

(Table 2 continues on next page)

	All patients with COVID-19 and cancer (n=232)	Patients with cancer and non-severe COVID-19 (n=84)	Patients with cancer and severe COVID-19 (n=148)	p value
(Continued from previous page)				
Lymphadenopathy	35/195 (18%)	8/79 (10%)	27/116 (23%)	0.031
Bilateral pulmonary	150/195 (77%)	43/79 (54%)	107/116 (92%)	<0.0001
Right lung	9/195 (5%)	4/79 (5%)	5/116 (4%)	1.0
Left lung	8/195 (4%)	4/79 (5%)	4/116 (3%)	0.85
<b>Laboratory examinations</b>				
Cytokines and inflammatory factors				
TNF- $\alpha$ , pg/mL (n=89)	8.7 (5.6-10.9)	6.4 (5.0-7.9); n=21	9.4 (6.4-12.6); n=68	0.0050
IL-1 $\beta$ , pg/mL (n=81)	5.0 (5.0-5.0)	5.0 (5.0-5.0); n=20	5.0 (5.0-5.0); n=61	0.87
IL-6, pg/mL (n=138)	12.8 (3.7-32.5)	3.7 (2.4-14.5); n=41	16.1 (6.6-49.9); n=97	<0.0001
IL-8, pg/mL (n=81)	11.6 (6.9-23.4)	9.2 (7.2-12.7); n=20	12.7 (6.8-25.5); n=61	0.13
IL-10, pg/mL (n=88)	5.0 (5.0-7.0)	5.0 (5.0-5.0); n=21	5.0 (5.0-10.4); n=67	0.0029
IL-2R, U/mL (n=79)	615.0 (428.0-1028.0)	445.0 (330.3-557.8); n=20	749.0 (495.0-1145.0); n=59	0.00024
Procalcitonin, ng/mL (n=161)	0.1 (0.0-0.3)	0.1 (0.0-0.1); n=68	0.2 (0.1-0.7); n=93	<0.0001
Ferritin, $\mu$ g/L (n=53)	616.5 (334.3-1613.1)	497.4 (277.1-625.8); n=13	849.7 (347.1-2178.6); n=40	0.17
C-reactive protein, mg/L (n=91)	46.4 (21.8-94.9)	42.5 (4.3-53.4); n=31	49.4 (28.1-99.0); n=60	0.044
Lymphocytes				
Lymphocyte count per $\mu$ L (n=231)	0.8 (0.5-1.3)	1.0 (0.6-1.4); n=83	0.7 (0.4-1.2); n=148	0.0028
CD3+ T-cell count per $\mu$ L (n=43)	605.2 (529.0-643.6)	637.0 (606.5-672.0); n=12	569.0 (455.0-621.0); n=31	0.024
CD3-CD19+ B-cell count per $\mu$ L (n=29)	102.0 (66.4-154.0)	202.0 (147.0-282.0); n=4	92.0 (64.0-145.4); n=25	0.033
CD4+ T-cell count per $\mu$ L (n=37)	370.0 (312.0-400.0)	395.3 (370.0-410.3); n=9	350.5 (296.0-394.5); n=28	0.049
CD3-CD16+CD56+ natural killer-cell count per $\mu$ L (n=29)	105.3 (86.9-123.4)	132.1 (131.0-134.3); n=4	98.0 (86.2-112.0); n=25	0.019
T cell plus B cell plus natural killer-cell count per $\mu$ L (n=29)	794.0 (763.0-869.0)	890.0 (870.0-925.0); n=4	782.0 (763.0-852.0); n=25	0.015
Organ damage indices				
Alanine transaminase, U/L (n=181)	25.0 (16.0-42.0)	23.5 (14.0-36.0); n=70	26.0 (16.0-49.0); n=111	0.11
Aspartate transaminase, U/L (n=181)	27.5 (18.7-43.0)	24.0 (17.9-33.3); n=70	31.0 (19.0-48.0); n=111	0.012
Lactate dehydrogenase, U/L (n=175)	253.0 (194.0-455.0)	209.0 (182.5-281.3); n=68	339.5 (199.5-575.0); n=107	0.00010
Total protein, g/L (n=93)	66.0 (61.7-70.6)	66.1 (61.8-71.7); n=32	66.0 (61.6-70.4); n=61	0.65
Albumin, g/L (n=181)	34.7 (30.1-39.8)	37.6 (32.5-41.6); n=70	33.4 (28.2-38.0); n=111	0.00021
Globulin, g/L (n=93)	30.7 (26.8-33.4)	30.2 (25.2-33.3); n=32	30.7 (27.0-34.4); n=61	0.21
Albumin-globulin ratio (n=93)	1.2 (1.0-1.5)	1.3 (1.0-1.6); n=32	1.1 (0.9-1.3); n=61	0.024
NT-proBNP, pg/mL (n=117)	158.0 (68.0-678.0)	134.3 (68.0-247.0); n=46	321.0 (73.0-501.0); n=71	0.013
Myoglobin, ng/mL (n=101)	41.3 (30.6-105.8)	37.5 (28.1-50.9); n=36	55.0 (33.0-159.3); n=65	0.0043
hs-cTnI, pg/mL (n=139)	4.1 (1.9-14.3)	1.9 (0.1-4.2); n=49	9.6 (2.3-69.0); n=90	<0.0001
Leucocyte count, $\times 10^9$ /L (n=181)	5.5 (4.2-7.7)	5.4 (4.3-6.8); n=70	5.7 (4.0-8.4); n=111	0.17
Neutrophils (n=181)	73.1% (64.2-86.1)	67.5% (61.8-78.7); n=70	79.0% (67.6-88.8); n=111	<0.0001
Neutrophil count, $\times 10^9$ /L (n=181)	3.9 (2.8-6.5)	3.5 (2.6-4.8); n=70	4.11 (2.8-7.4); n=111	0.039
Eosinophils (n=181)	0.6% (0.0-1.8)	1.0% (0.1-2.0); n=70	0.3% (0.0-1.5); n=111	0.0092
Eosinophil count, $\times 10^9$ /L (n=181)	0.0 (0.0-0.1)	0.1 (0.0-0.1); n=70	0.0 (0.0-0.1); n=111	0.018
Erythrocytes count, $\times 10^{12}$ /L (n=181)	3.8 (3.3-4.3)	3.9 (3.5-4.3); n=70	3.7 (3.0-4.3); n=111	0.084
Haemoglobin, g/L (n=181)	118.0 (98.0-128.0)	120.0 (107.0-129.0); n=70	114.0 (94.0-127.0); n=111	0.037
Platelet count, $\times 10^9$ /L (n=180)	182.0 (131.5-237.0)	200.5 (146.5-256.5); n=70	174.0 (122.0-226.0); n=110	0.017
D-dimer, $\mu$ g/mL (n=167)	1.2 (0.5-4.7)	0.7 (0.4-1.7); n=65	1.9 (0.5-8.0); n=102	0.00033
Prothrombin time (n=169), s	13.6 (12.4-14.8)	13.2 (11.8-14.1); n=66	13.9 (12.9-15.4); n=103	0.00054
Activated partial thromboplastin time (n=155), s	35.5 (30.2-42.9)	33.2 (27.8-41.0); n=57	37.7 (32.5-44.1); n=98	0.00060
Prothrombin activity (n=93)	88.0% (73.0-96.0)	90.5% (81.3-99.8); n=32	87.0% (70.0-92.5); n=61	0.044
ECOG=Eastern Cooperative Oncology Group. COPD=chronic obstructive pulmonary disease. TNF- $\alpha$ =tumor necrosis factor $\alpha$ . IL=interleukin. IL-2R=IL-2 receptor. CD=cluster of differentiation. NT-proBNP=N-terminal pro-B-type natriuretic peptide. hs-cTnI=high-sensitivity cardiac troponin I. *Not including leukaemia (n=3) and multiple myeloma (n=3), due to different judgment standard of tumour stage.				
<b>Table 2: Demographic, clinical, radiographical, and laboratory findings of patients with cancer with severe and non-severe COVID-19</b>				



time, and activated partial thromboplastin time), and NT-proBNP were significantly associated with worse severity of COVID-19 in patients with cancer (table 3). Conversely, immune cells (lymphocytes, CD4+ T cells, and natural killer cells) and resistant organ damage indices (albumin and albumin–globulin ratio) were significantly associated with lower severity of COVID-19 in patients with cancer (table 3). We found that TNF- $\alpha$ , NT-proBNP, albumin–globulin ratio, and CD4+ T cells were also associated with the risk of death from COVID-19 (appendix p 16), and the dynamic change of these four indices over follow-up are shown in the appendix (p 20). Levels of TNF- $\alpha$  and NT-proBNP were significantly higher in patients with cancer and severe COVID-19 than in those with non-severe COVID-19 on admission, whereas the levels of CD4+ T cells and albumin–globulin ratio were significantly lower (appendix p 20). These differences increased over 4 weeks of hospitalisation, which was a critical period for COVID-19 progression. For patients with non-severe disease, CD4+ T cells decreased in the first 3 weeks and then gradually increased over the following 2 weeks. By contrast, the decrease of CD4+ T cells among patients with severe COVID-19 was more pronounced and prolonged (appendix p 20).

## Discussion

In face of the COVID-19 pandemic, research is urgently needed to guide the implementation of effective prevention and control measures for susceptible populations. Here, by integrating clinical data from nine hospitals, we found that patients with cancer infected with SARS-CoV-2 have an increased risk of developing severe COVID-19. Furthermore, in addition to previously reported risk factors for this population, such as older age and elevated IL-6, procalcitonin, and D-dimer, we identified novel risk factors including advanced tumour stage, elevated TNF- $\alpha$  and NT-proBNP, and decreased CD4+ T cells and albumin–globulin ratio.

Our enrolled patients without cancer were statistically matched to those with cancer, which helped to minimise the effects of common confounders such as age, sex, and other comorbidities on the severity of COVID-19. The lower prevalence of sore throat and coryza and increased prevalence of dyspnoea and expectoration in patients with cancer compared with those without cancer are in line with the findings of previous studies,<sup>13</sup> and might be due to patients' subjective perception of their disease severity. Moreover, in most situations, CT images of chest lesions in patients with COVID-19 pneumonia is explicitly different from those of lung cancer or metastasis in distribution, density, and size.<sup>14</sup> Notably, all patients in our current study were symptomatic for COVID-19; therefore, a screening or an epidemiological study in the patients with cancer is warranted to understand the rate of asymptomatic infection.

We used unconditional logistic regression methods to explore the factors related with COVID-19 severity in

	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Age, years*	1.04 (1.00–1.07)	0.032	1.04 (1.00–1.07)	0.034
ECOG performance status (per 1-point increase)	2.32 (1.76–3.07)	<0.0001	2.80 (1.96–3.99)	<0.0001
Tumour stage†‡				
I, II, or III	1 (ref)	..	1 (ref)	..
IV	2.58 (1.07–6.23)	0.035	2.60 (1.05–6.43)	0.039
Antitumour treatments§				
Surgery	1 (ref)	..	1 (ref)	..
Chemotherapy or radiotherapy	1.27 (0.85–1.89)	0.25	1.28 (0.85–1.94)	0.24
Targeted therapy or immunotherapy	2.84 (1.12–7.22)	0.028	3.29 (1.26–8.61)	0.015
Cytokines and inflammatory factors				
TNF- $\alpha$ , pg/mL	1.22 (1.04–1.43)	0.015	1.22 (1.01–1.47)	0.037
IL-6, pg/mL	1.03 (1.01–1.06)	0.014	1.03 (1.00–1.05)	0.019
IL-2R, U/mL	1.00 (1.00–1.01)	0.0081	1.00 (1.00–1.01)	0.093
Procalcitonin, ng/mL	2.31 (1.26–3.60)	0.0013	2.76 (1.25–3.93)	0.0015
C-reactive protein, mg/L	1.01 (1.00–1.02)	0.022	1.01 (1.00–1.02)	0.034
Lymphocytes				
Lymphocytes, %	0.96 (0.93–0.99)	0.0042	0.96 (0.93–0.99)	0.020
Lymphocyte count per $\mu$ L	0.52 (0.30–0.89)	0.017	0.56 (0.31–1.00)	0.051
CD3-CD19+ B-cell count per $\mu$ L	0.98 (0.97–1.00)	0.035	0.98 (0.96–1.00)	0.11
CD4+ T cells, %	0.89 (0.79–0.99)	0.040	0.84 (0.71–0.98)	0.031
CD3-CD16+CD56+ natural killer cells, %	0.84 (0.72–0.98)	0.024	0.85 (0.72–0.99)	0.041
Haematological tests				
Leucocyte count, $\times 10^9$ /L	1.12 (1.02–1.22)	0.017	1.11 (1.01–1.22)	0.029
Neutrophils, %	1.06 (1.03–1.08)	<0.0001	1.06 (1.03–1.09)	0.00017
Monocytes, %	0.87 (0.80–0.96)	0.0040	0.88 (0.79–0.98)	0.023
Biochemical factors				
Lactate dehydrogenase, U/L	1.00 (1.00–1.00)	0.0040	1.00 (1.00–1.00)	0.018
Albumin, g/L	0.92 (0.87–0.97)	0.0011	0.92 (0.87–0.98)	0.0091
Albumin–globulin ratio	0.20 (0.05–0.74)	0.016	0.12 (0.02–0.77)	0.024
NT-proBNP, pg/mL	1.64 (1.02–2.61)	0.039	1.65 (1.03–2.78)	0.032
Myoglobin, ng/mL	1.01 (1.00–1.02)	0.044	1.01 (1.00–1.03)	0.050
hs-cTnI, pg/mL	1.01 (1.00–1.02)	0.046	1.01 (1.00–1.02)	0.067
Coagulation function				
Platelet count, $\times 10^9$ /L	1.00 (0.99–1.00)	0.025	1.00 (0.99–1.00)	0.070
Activated partial thromboplastin time, s	1.08 (1.03–1.12)	0.0011	1.12 (1.05–1.18)	0.00016
Prothrombin time, s	1.20 (1.04–1.40)	0.011	1.25 (1.07–1.48)	0.0062
D-dimer, $\mu$ g/mL	1.13 (1.04–1.22)	0.0029	1.12 (1.03–1.21)	0.0074

All analyses were adjusted for age, sex, comorbidities, tumour stage, cancer type, and antitumour treatment unless otherwise specified. OR=odds ratio. ECOG=Eastern Cooperative Oncology Group. TNF- $\alpha$ =tumor necrosis factor  $\alpha$ . IL=interleukin. IL-2R=IL-2 receptor. CD=cluster of differentiation. NT-proBNP=N-terminal pro-B-type natriuretic peptide. hs-cTnI=high-sensitivity cardiac troponin I. \*Adjusted for sex, comorbidities, tumour stage, cancer type, and antitumour treatment. †Not including leukaemia (n=3) and multiple myeloma (n=3), due to different judgment standard of tumour stage. ‡Adjusted for age, sex, comorbidities, cancer type, and antitumour treatment. §Adjusted for age, sex, comorbidities, tumour stage, and cancer type.

**Table 3: Factors associated with COVID-19 illness severity in patients with cancer**

patients with cancer. Risk factors reported previously in patients without cancer, such as older age; elevated IL-6, procalcitonin, D-dimer, and C-reactive protein; and decreased lymphocytes were validated in patients with

cancer. Additionally, we identified several risk factors for COVID-19 severity in patients with cancer, including advanced tumour stage, elevated TNF- $\alpha$  and NT-proBNP, and decreased CD4+ T cells and albumin–globulin ratio. Older age has previously been reported as an important independent predictor of mortality in severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, and COVID-19.<sup>15–17</sup> Moreover, we observed that advanced tumour stage aggravates COVID-19 progression, which might be due to the tumour burden. Among the measured cytokines, elevation of IL-6 was most pronounced, consistent with recent published studies.<sup>18,19</sup> It is known that IL-6 plays multifaceted roles in regulation of vascular leakage, complement activation, and coagulation pathways, which ultimately causes poor outcomes for acute respiratory distress syndrome, multiple organ dysfunction syndrome, and SARS.<sup>20–22</sup> TNF- $\alpha$ , a potential novel biomarker for COVID-19 identified here, has been reported to facilitate the apoptosis of both lung epithelial cells and endothelial cells, ultimately resulting in vascular leakage, alveolar oedema, and hypoxia.<sup>23</sup> TNF- $\alpha$  has also been reported to mediate airway hyper-responsiveness and pathogenesis in influenza and SARS-CoV infection.<sup>24</sup> Additionally, TNF- $\alpha$  was originally identified as an effective mediator inducing haemorrhagic necrosis in tumours.<sup>25</sup> Collectively, these findings help to explain our results showing that TNF- $\alpha$ , compared with indicators such as C-reactive protein and D-dimer, might be more predictive for COVID-19 severity, especially in patients with cancer.

Reduced CD4+ T cells in patients with COVID-19 has been confirmed by Qin and colleagues, revealing that an immunosuppression feature is pronounced in severe COVID-19 cases.<sup>19</sup> A rapid and well coordinated innate immune response is the first line of defence against viral infections. CD4+ T cells can enhance the ability of cytotoxic T cells to clear pathogens.<sup>26</sup> However, persistent stimulation by the virus might induce T-cell exhaustion and facilitate host immune response disorders, causing excessive inflammation and even death.<sup>23,27</sup> Notably, in addition to dysregulated inflammatory and immune responses, organ damage biomarkers such as elevated NT-proBNP and decreased albumin–globulin ratio, were also associated with COVID-19 severity, as has been confirmed by other studies.<sup>28</sup> Collectively, these findings suggest that aggravated inflammatory storm, dysregulated immune responses, and multiple-organ damage appear to be possible mechanisms in patients with cancer with severe COVID-19.

Successful standardised treatment protocols for patients with COVID-19, especially with severe disease, must be recommended globally to curb poor outcomes. Here, we found that clinical interventions, especially ventilation treatments (high-flow nasal cannula oxygen or mechanical ventilation), were more intensive in patients with cancer than in patients without cancer. In particular, more than 75% of patients with cancer and

COVID-19 received antiviral treatment and antibiotics, and approximately a third of patients received immunomodulators. Several clinical trials are underway to define potential roles for antiviral agents (remdesivir, lopinavir, or ritonavir)<sup>29</sup> and specific immunomodulators such as IL-6 receptor blockade (tocilizumab; ChiCTR2000029765) in COVID-19. Interactions between several chemotherapy agents and antiviral drugs need to be considered when treating patients with cancer and COVID-19;<sup>30</sup> the sample size in our study was too small to permit this analysis. In view of the uncontrolled inflammatory responses, impaired adaptive immune responses, and multiple-organ dysfunction in patients with cancer and COVID-19—especially those with severe COVID-19—the current management of COVID-19 should be focused on inflammatory reaction and immune dysfunction, supportive care including ventilatory support, and treatment of complications.

Based on our findings, three major strategies for the management of patients with cancer during this COVID-19 crisis are warranted. First, robust personal protection provisions should be made for medical staff, patients with cancer, and cancer survivors to avoid cross-infection. Second, intentional postponement of adjuvant chemotherapy or elective surgery for stable cancer should be considered in endemic areas, but oral medications should continue to be administered. Third, more intensive surveillance should be considered for patients admitted with COVID-19 who have cancer, especially older patients or those with other comorbidities.

Our study has several limitations. First, owing to its retrospective design, it lacks dynamic clinical and laboratory data. Second, the potential mechanisms of dysregulated inflammatory cytokines and immune responses were not fully explored and need to be further investigated. Third, our study recruited all available patients with any type of malignant solid tumours and haematological malignancy, but included two patients with basal cell carcinoma and three cancer survivors who had disease-free survival for more than 5 years. Finally, the enrolled patients with cancer represent a mixed sample of multiple cancer types; further studies by cancer type are still needed.

To our knowledge, this study is the largest multicentre cohort study so far among patients with cancer and COVID-19, providing detailed clinical and laboratory information. This study highlights that risk factors including elevated TNF- $\alpha$  and NT-proBNP and decreased CD4+ T cells or albumin–globulin ratio would be helpful for early surveillance of disease progression, in addition to previously reported risk factors of older age; elevated IL-6, procalcitonin, and D-dimer; and decreased lymphocytes.

#### Contributors

XM, XY, and ZW were the overall principal investigators who conceived the study and obtained financial support, were responsible for the study design, and supervised the entire study. CY, BL, JingW, YW, SL, BC, JinW, ZY, XD, FZ, WW, QL, XC, WC, JF, and BS recruited participants. JT, JX, CY, BL, YC, and ZL drafted the paper. JT, YC, ZL, MZ, LW, and

SN did the statistical analyses. JX, CY, BL, QY, SWu, and WL did the data analysis and interpreted the results. XY, QZ, ZH, SWa, X-PY, XM, and ZW reviewed the manuscript. All authors contributed to data interpretation, manuscript writing, and review of the manuscript. All authors agreed 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.

#### Declaration of interests

We declare no competing interests.

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