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ORIGINAL ARTICLE

Comparable outcomes but higher risks of prolonged viral RNA shedding duration and secondary infection in cancer survivors with COVID-19: A multi-center, matched retrospective cohort study*

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Abstract

Objective To identify the differences in clinical features and outcomes between cancer survivors and non-cancer patients with coronavirus disease 2019 (COVID-19).

Methods In this multicenter, retrospective, and observational cohort study from February 10, 2020 to March 31, 2020 in Wuhan, China, all cancer survivors infected with COVID-19 were screened, and statistically matched with non-cancer patients with COVID-19 using propensity score matching. Demographic, clinical, treatment, and laboratory data were extracted from a standardized medical recording system and underwent review and assessment.

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Abstract

Results Sixty-one cancer survivors and 183 matched non-cancer patients were screened from 2,828 COVID-19 infected patients admitted to 4 hospitals in Wuhan, China. The median ages of the cancer survivor cohort and non-cancer patient cohort were 64.0 (55.0–73.0) and 64.0 (54.0–73.5), respectively (P = 0.909). Cancer survivors reported a higher incidence of symptom onset than non-cancer patients. Fever (80.3% *vs.* 65.0%; P = 0.026) was the most prevalent symptom, followed by cough (65.6% *vs.* 37.7%; P < 0.001), myalgia, and fatigue (45.9% *vs.* 13.6%; P < 0.001). The risks of the development of severe events (adjusted hazard ratio [AHR] = 1.25; 95% confidence interval [CI]: 0.76–2.06; P = 0.378) and mortality (relative risk [RR] = 0.90, 95% CI: 0.79–1.04; P = 0.416) in the cancer survivor cohort were comparable to those of the matched non-cancer patient cohort. However, the cancer survivor cohort showed a higher incidence of secondary infection (52.5% *vs.* 30.1%; RR = 1.47, 95% CI: 1.11–1.95; P = 0.002) and a prolonged viral RNA shedding duration (32 days [IQR 26.0–46.0] *vs.*24.0 days [IQR 18.0–33.0]; AHR = 0.54; 95% CI: 0.38–0.80; P < 0.05).

Conclusion Compared to non-cancer patients, cancer survivors with COVID-19 exhibited a higher incidence of secondary infection, a prolonged period of viral shedding, but comparable risks of the development of severe events and mortality. It is helpful for clinicians to take tailored measures to treat cancer survivors with COVID-19.

Key words: COVID-19; SARS-CoV-2; cancer survivor; prognosis; viral shedding; mortality

Since the beginning of the coronavirus disease 2019 (COVID-19) outbreak in late December 2019, the epidemic has swept the world at an alarming rate. Due to its highly contagious nature and global spread, the World Health Organization (WHO) has declared the coronavirus outbreak a pandemic. Globally, as of 11 November, 2020, there have been 51,251,715 confirmed cases of COVID-19, including 1,270,930 deaths according to the WHO report [1].

According to a report by the GLOBOCAN 2018, it was estimated that there would be 18.1 million newly diagnosed cancer patients worldwide in 2018 [2]. Given the global spread of COVID-19, the infected population may contain a large number of cancer patients. Currently, patients with cancer are considered to be more susceptible to COVID-19 and at a higher risk for a severe disease course [3–6]. Studies have suggested that cancer patients have a worse prognosis than individuals without cancer owing to the immunocompromised status caused by malignancy and anti-cancer treatments, including surgery, chemotherapy, radiotherapy, and immunotherapy [5, 7]. A retrospective analysis of patients in Wuhan showed that cancer patients were 2.3 times more likely to be infected with COVID-19 than the community population8. The case-fatality rate among patients with preexisting cancer reached 5.6% compared to 2.3% in general patients [6]. The small sample size of these studies may have limited the representativeness of the results.

With advances in early diagnosis, improved treatment options, and increased life expectancy, an increasing number of cancer patients are cured and survive [9–10]. Cancer survivors are a huge population that cannot be ignored in this COVID-19 outbreak. Due to distinctions in nutritional and immune status, it is assumed that cancer survivors and patients may have different outcomes after COVID-19. A study on COVID-19 patients with cancer showed that non-metastatic cancer patients experienced similar frequencies of severe conditions to those observed in patients without cancer [11]. However, non-metastatic cancer patients are the same as cancer survivors; nearly half of the patients in the study had received anti-cancer treatment within 40 days, and the interference in outcome could not be ruled out.

Thus, we collected the clinical data of 61 cancer survivors from 4 designated hospitals in Wuhan and compared them with the data of 183 matched non-cancer patients. Our study aimed to determine the clinical characteristics and outcomes of cancer survivors with COVID-19 and identified the difference with non-cancer patients.

Materials and methods

Study design and patients

This retrospective cohort study included two cohorts of adult patients and was conducted in four designated hospitals for COVID-19 patients in Wuhan, including the Optical Valley Branch of Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology, Sino-French New Town Branch of Tongji Hospital, Wuhan Pulmonary Hospital, and Wuhan No.1 Hospital. The cancer survivor cohort consisted of cancer survivors who were confirmed to have COVID-19 infection by RNA testing of swab samples, and the non-cancer patient cohort consisted of matched COVID-19 patients without a history of cancer, all of whom were discharged or died between February 10 and March 31, 2020. Each cancer survivor was matched to 3 patients using a propensity score with a caliper value equal to 0.03. This study was approved by the ethics committee

of Tongji Hospital of Huazhong University of Science and Technology (No. TJ-IRB20200409) and was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2000031327). The requirement for informed consent was waived by the ethics committee.

Data collection and definition

The demographic data, past medical history, onset symptoms, laboratory testing, treatments, and outcome parameters were collected via a standardized electronic medical record. All data were verified by two researchers and reviewed by a third researcher.

The European Organization for Research and Treatment of Cancer (EORTC) Cancer Survivorship Task Force definition of cancer survivors have been adopted in this study, namely, patients who have completed their primary treatment [12]. Restrictions were added on the basis of the EORTC Cancer Survivorship Task Force definition to distinguish between cancer patients and cancer survivors in this study. The included cancer survivors were all diagnosed with malignant tumors, had a treatment-free interval of more than six months, and showed no evidence of disease, while adjuvant endocrine therapy was acceptable.

We defined survival time as the interval between hospital admission and the final events, discharge, or death. Severe events included severe and critical illness, and the time to severe events was defined as the interval between symptom onset and the diagnosis of severe or critical illness by the physician according to the diagnosis standard [13]. Viral RNA shedding duration was defined as the interval between symptom onset and the date of the last severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA-positive result for naso- or oropharyngeal swabs.

Severe illness was defined as meeting at least one of the following criteria: 1. Shortness of breath, respiratory rate ≥ 30/min; 2. pulse oxygen saturation (SpO2) ≤ 93% at rest; 3. partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) ≤ 300 mmHg (1 mmHg = 0.133kPa). Critical illness was defined as meeting at least one of the following criteria: 1. respiratory failure occurred and mechanical ventilation was required; 2. shock; 3. combined with failure of other organs and intensive care unit treatment was required [13].

Acute respiratory distress syndrome (ARDS) was defined according to the Berlin Definition [14], acute kidney injury according to the KDIGO Clinical Practice Guidelines [15], and shock according to the 2016 Third International Consensus Definition [16]. Secondary infection was diagnosed when patients exhibited clinical symptoms of pneumonia or bacteremia, or a new laboratory-confirmed pathogen after admission [16].

Statistical analysis

Descriptive statistical methods were used to analyze the variables. Categorical variables were described as *n* (%) and the characteristics between cancer and non-cancer were compared using the Chi-square test or Fisher's exact test. Continuous variables are shown as medians with interquartile ranges (IQRs), and the Mann-Whitney *U* test was conducted to compare the variables between groups. The Kaplan-Meier method was adopted for time-to-event data to estimate the proportion of events. Propensity score matching was used to make the two groups comparable in clinical and demographic characteristics. Cox proportional hazards models were used to estimate the HRs and 95% CIs for cancer survivors and the main outcomes. Model 1 included age (continuous). Model 2 included age and sex (male, female). Model 3, the final multivariate model, was adjusted for age, sex, hypertension (yes or no), D-dimer (continuous), lactate dehydrogenase (LDH) (continuous), high-sensitivity C-reactive protein (hs-CRP) (continuous), and lymphocyte count (continuous). Previous studies have shown that these factors are related to adverse clinical outcomes [2, 17–19]. Therefore, we chose age, sex, hypertension, D-dimer, LDH, hs-CRP, and lymphocyte count to enter the multivariate-adjusted models.

All *P* values were two-tailed, and *P* values less than 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS version 23.0 and R version 3.5.2.

Results

Demographic data and Baseline characteristics

Of the 2,828 COVID-19 patients admitted to the 4 hospitals between February 10 and March 31, 2020, in Wuhan, China, 61 cancer survivors and 183 matched non-cancer patients were included in this study. The median age of cancer survivors was 64 years (IQR 55.0–73.0), and 37 (60.7%) cancer survivors were women. Hypertension was the highest in both cohorts. Cancer survivors reported a higher incidence of symptom onset than non-cancer patients. Fever (80.3% vs. 65.0%, $P = 0.026$) was the most prevalent symptom in both cohorts, followed by cough (65.6% vs. 37.7%; $P < 0.001$), myalgia, and fatigue (45.9% vs. 13.6%; $P < 0.001$) (Table 1). Cancer survivors had histories of 15 different types of cancer: 14 (23.0%) with thyroid cancer, 12 (19.7%) with breast cancer, 12 (19.7%) in the urinary system, 8 (13.1%) in the intestinal tract, 7 (11.4%) had lung cancer, 3 (4.9%) had lymphoma, and 6 (9.8%) had other cancers (Fig. 1a). Moreover, 51 patients (83.6%) had stage I or stage II disease among all cancer survivors. The previous anti-cancer treatments in the cancer cohort consisted of surgery for 37 (60.7%) patients, chemotherapy and/or radiotherapy for 8 (13.1%)

patients, endocrine therapy for 5 (8.2%), targeted therapy for 1 (1.6%), and conservative therapy for 1 (1.6%).

Laboratory findings

Major laboratory results on admission were recorded, and patients in the non-cancer cohort had more prominent laboratory abnormalities than those in the cancer survivor cohort. Lymphocytopenia and anemia were present in 49.2% and 82.0% of the cancer survivors, compared with 68.3% and 56.3% of the non-cancer cohort, respectively, indicating significant differences ($P < 0.05$; Table 2). Compared to the cancer cohort, non-cancer patients showed significantly higher levels of D-dimer (median [IQR], 0.73 [0.39–3.51] *vs.* 0.58 [0.22–1.68]; $P = 0.002$), LDH (319.0 [241.5–399.0] *vs.* 218.0 [170.5–373.0]; $P < 0.001$), and hs-CRP (51.7 [14.8–98.0] *vs.* 25.2 [1.8–59.2]; $P < 0.001$; Table 2). Among patients with available data, non-cancer patients had significantly higher levels of interleukin (IL) 6, IL-10, and IL-1β than cancer survivors, while the level of ferritin was much lower.

Therapeutic methods

In both cohorts, the majority of patients received antiviral treatment and antibiotics. The application of both treatments was based on empirical experience, except for the secondary infection of the identified pathogen. Among cancer survivors, 16 (26.2%) were prescribed lopinavir/ritonavir (400 mg/day) and 9 (14.9%) arbidol (200 mg/day). In comparison to non-cancer patients, significantly fewer cancer survivors received corticosteroids (22 [36.1%] *vs.* 132 [72.1%]; $P < 0.001$) and interferon atmotherapy (12 [19.7] *vs.* 82 [44.8%]; $P < 0.001$; Table 1). It is notable that fewer patients received oxygen therapy in the cancer survivor cohort, which tended to receive simpler respiratory support.

Clinical outcomes and complications

The risks of the development of severe events (HR = 0.73, 95% CI: 0.48–1.11; $P = 0.141$) and survival (HR = 0.62, 95% CI: 0.31–1.23; $P = 0.169$) of cancer survivors were comparable to those of 183 matched non-cancer patients (Fig. 1b, 1d; Table 3). Both cohorts had a comparable mortality rate (15.6% *vs.* 24.6%; RR = 0.90, 95% CI: 0.79–1.04; $P = 0.416$). During hospitalization, the rates of development of severe and critical illness in the course of disease were comparable between the two cohorts. However, the median duration of viral RNA shedding was longer in the cancer cohort than in the non-cancer cohort (32.0 days [IQR, 26.0–46.0] *vs.* 24.0 days [IQR, 18.0–33.0]; HR = 0.49, 95% CI: 0.35–0.68; $P < 0.001$; Fig. 1c). The timelines of viral RNA shedding of 61 cancer survivors and 61 randomly selected non-cancer patients are displayed in Fig. 2. During the follow-up after discharge, 4.9% of the cancer survivors retested positive in the SARS-CoV-2 RNA testing, which was slightly higher than that of the non-cancer cohort without a statistical difference (Table 3).

In terms of complications, 32 (52.5%) cancer survivors had secondary infection, which was significantly higher than that of the non-cancer patients (33 [52.5%] *vs.* 55 [30.1%]; RR = 1.47, 95% CI:MM 1.11–1.95; $P = 0.002$). Other complications, including ARDS and acute cardiac injury, showed no difference between both cohorts (Table 2).

The univariate-adjusted and multivariate-adjusted relationships between cancer survivor status and the main outcomes, including survival time, time to severe events, and viral RNA shedding duration, are presented in Table 4. No significant association was found between cancer survivors and the increasing survival time in the fully adjusted model (AHR = 0.36; 95% CI: 0.11–1.20; $P = 0.096$) between cancer survivors and time to severe events (AHR = 1.25; 95% CI: 0.76–2.06; $P = 0.378$). However, compared to the non-cancer patients, cancer survivors were positively associated with the prolonged duration of virus RNA shedding in the age-adjusted model (HR = 0.49; 95% CI: 0.35–0.68; $P < 0.05$). Adjusting the additional factors including sex, hypertension, and other

Table 1 Baseline characteristics between cancer survivor and non-cancer cohorts

Characteristics	Overall	Cancer survivor	Non-cancer	*P* value
Number of patients	244	61	183	
Age (years)	64.0 (55.0–72.4)	64.0 (55.0–73.0)	64.0 (54.0–73.5)	0.909
Gender				1.000
Male	96 (39.3)	24 (39.3)	72 (39.3)	–
Female	148 (60.7)	37 (60.7)	111 (60.7)	–
Body-mass-index	23.8 (21.0–25.2)	24.0 (20.5–25.5)	23.6 (21.3–25.1)	0.899
Smoking	14 (5.7)	3 (4.9)	11 (6.0)	1.000
Comorbidities	144 (59.0)	39 (63.9)	105 (57.4)	0.103
Hypertension	83 (34.0)	21 (34.4)	62 (33.9)	1.000
Cardiovascular diseases	24 (9.8)	6 (9.8)	18 (9.8)	1.000
Diabetics	37 (15.2)	12 (19.7)	25 (13.6)	0.431

Table 2 Clinical characteristics, laboratory findings and complications

	Overall	Cancer survivor	Non-cancer	*P* value
Clinical characteristics				
Number of patients	244	61	183	
Initial common symptom	220 (90.2)	54 (88.5)	166 (90.7)	0.681
Fever	179 (73.4)	49 (80.3)	119 (65.0)	0.026
Cough	109 (44.7)	40 (65.6)	69 (37.7)	< 0.001
Myalgia or fatigue	53 (21.7)	28 (45.9)	25 (13.6)	< 0.001
Dyspnea	58 (23.8)	22 (36.1)	36 (19.7)	0.015
Admission body temperature (°C)	36.9 (36.5–37.9)	38.3 (38.0–39.0)	37.6 (36.5–38.3)	0.032
Systolic pressure (mm Hg)	128.0 (120.0–143.0)	131.0 (123.0–145.0)	126.0 (118.0–141.2)	0.164
Respiratory rate (breaths per min)	20.0 (20.0–24.0)	20.0 (20.0–25.0)	20.0 (20.0–24.0)	0.984
Pulse rate (beats per min)	88.0 (80.0–97.0)	84.0 (79.0–96.0)	88.0 (80.0–98.0)	0.302
Laboratory findings				
WBC count (× 10^9/L)	6.28 (4.41–8.91)	6.66 (5.28–8.29)	6.11 (4.13–9.14)	0.175
< 3.5	31 (12.7)	4 (6.6)	27 (14.8)	0.018*
3.5–9.5	160 (65.6)	48 (78.7)	112 (61.2)	–
> 9.5	53 (21.7)	9 (14.8)	44 (24.0)	–
Neutrophil count (× 10^9/L)	4.36 (2.84–7.64)	4.60 (3.33–6.51)	4.34 (2.57–7.91)	0.637
< 1.8	18 (7.4)	1 (1.6)	17 (9.3)	0.024*
1.8–6.3	148 (60.7)	44 (72.1)	104 (56.8)	–
> 6.3	78 (32.0)	16 (26.2)	62 (33.9)	–
Lymphocyte count (× 10^9/L)	0.88 (0.64–1.28)	1.12 (0.77–1.75)	0.83 (0.60–1.18)	0.077
< 1.1	155 (63.5)	30 (49.2)	125 (68.3)	< 0.001*
1.1–3.2	86 (35.2)	29 (47.5)	57 (31.1)	–
> 3.2	3 (1.3)	2 (3.3)	1 (0.6)	–
IL-1b (pg/mL)	6.01 (4.21–8.12)	5.67 (2.52–6.31)	6.87 (4.01–9.11)	0.011
< 5.0	118 (48.4)	45 (73.8)	73 (39.9)	< 0.001*
≥ 5.0	126 (51.6)	16 (26.2)	110 (60.1)	–
IL-2R (U/mL)	524.5 (386.2–721.2)	456.0 (397.0–562.0)	562.0 (338.0–730.5)	0.814
< 223	18 (7.4)	5 (8.2)	13 (7.1)	0.304*
223–710	120 (49.2)	34 (55.7)	86 (47.0)	–
> 710	106 (43.4)	22 (36.1)	84 (45.9)	–
IL-6 (pg/mL)	8.2 (4.6–28.6)	4.9 (2.8–28.9)	11.0 (6.8–28.2)	0.008
< 7	112/233 (48.1)	83 (45.4)	29/50 (58.0)	< 0.001*
≥ 7	121/233 (51.9)	100 (54.6)	21/50 (42.0)	–
IL-8 (pg/mL)	11.8 (8.6–17.8)	11.7 (7.7–15.8)	11.8 (9.8–30.5)	0.129
< 62	157 (64.3)	106 (57.9)	51 (83.6)	< 0.001*
≥ 62	87 (35.7)	77 (42.1)	10 (16.4)	–
IL-10 (pg/mL)	7.5 (6.5–10.9)	6.6 (6.3–13.1)	9.1 (7.5–11.7)	0.022
< 9.1	132/239 (55.2)	95 (51.9)	37/56 (66.1)	< 0.001*
≥ 9.1	107/239 (44.8)	88 (48.1)	19/56 (33.9)	–
TNF-α (pg/mL)	8.3 (7.0–12.6)	9.6 (7.3–13.1)	7.5 (6.2–8.5)	0.026
< 8.1	145/241 (60.2)	111 (60.7)	34/58 (58.6)	0.572*
≥ 8.1	94/241 (39.0)	72 (39.3)	24/58 (41.4)	–
Ferritin (μg/L)	715.9 (237.5–960.4)	945.0 (818.0–1079.6)	425.1 (114.7–671.7)	0.011
Hemoglobin (g/L)	125.0 (114.0–135.0)	120.0 (112.0–128.0)	128.0 (114.5–135)	0.023
< 130	153 (62.7)	50 (82.0)	103 (56.3)	< 0.001*
130–175	91 (37.3)	11 (18.0)	80 (43.7)	–
Myoglobin (ng/mL)	62.4 (42.5–81.3)	66.1 (45.2–87.2)	60.3 (41.1–79.1)	0.331
≤ 154.9	195 (79.9)	46 (75.4)	149 (81.4)	0.229*
> 154.9	49 (20.1)	15 (24.6)	34 (18.6)	–
PT (s)	13.5 (12.6–14.8)	13.6 (12.9–14.3)	13.5 (12.6–14.9)	0.897
≤ 16	216 (88.5)	57 (93.4)	159 (86.9)	0.130*
> 16	28 (11.4)	4 (6.6)	24 (13.1)	–

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	Overall	Cancer survivor	Non-cancer	*P* value
D-D dimer (μg/mL FEU)	0.72 (0.30–2.85)	0.58 (0.22–1.68)	0.73 (0.39–3.51)	0.002
≤ 0.5	100/243 (41.2)	28/60 (46.7)	72 (39.3)	0.243*
> 0.5	143/243 (58.8)	32/60 (53.3)	111 (60.7)	–
ALT (U/L)	22.0 (14.0–37.0)	21.0 (15.0–32.0)	22.0 (14.0–40.0)	0.312
≤ 50	209 (85.7)	57 (93.4)	152 (83.1)	0.031*
> 50	35 (14.3)	4 (6.6)	31 (16.9)	–
AST (U/L)	29.0 (19.0–45.0)	22.0 (17.8–31.0)	33.0 (20.0–49.0)	0.004
≤ 40	169/243 (69.5)	52/60 (86.7)	117 (63.9)	< 0.001*
> 40	74/243 (30.5)	8/60 (13.3)	66 (36.1)	–
LDH (U/L)	298.0 (205.0–399.0)	218.0 (170.5–373.0)	319.0 (241.5–399.0)	< 0.001
≤ 245	93 (38.1)	55 (30.1)	38 (62.3)	< 0.001*
> 245	151 (61.9)	128 (69.9)	23 (37.7)	–
Albumin (g/L)	35.1 (31.3–38.8)	36.6 (32.0–41.0)	34.5 (30.5–38.3)	0.022
< 35	120 (49.2)	26 (42.6)	94 (51.4)	0.170*
≥ 35	124 (50.8)	35 (57.4)	89 (48.6)	–
Total bilirubin (μmol/L)	10.1 (6.58–13.51)	8.34 (6.27–12.6)	10.6 (6.90–13.9)	0.061
≤ 21	226 (92.6)	59 (96.7)	167 (91.3)	0.133*
> 21	18 (7.4)	2 (3.3)	16 (8.7)	-
PTH (mg/L)	0.04 (0.04–0.08)	0.05 (0.04–0.11)	0.04 (0.04–0.06)	0.311
High sensitive (CRP, mg/L)	45.0 (10.8–94.0)	25.2 (1.80–59.2)	51.7 (14.8–98.0)	< 0.001
≤ 5.0	46 (18.9)	22 (36.1)	24 (13.1)	< 0.001*
> 5.0	194 (79.5)	35 (57.4)	159 (86.9)	–
Complications				
Coagulopathy	28 (11.4)	4 (6.6)	24 (13.1)	0.245
Acute cardic injury	84 (34.4)	27 (44.3)	57 (31.1)	0.086
Acute kidney injury	13 (5.3)	5 (8.2)	8 (4.4)	0.321
Acute liver injury	24 (9.8)	7 (11.5)	17 (9.3)	0.623
Secondary infection	87 (35.7)	32 (52.5)	55 (30.1)	0.002

Data are median [IQR], *n* (%), or n/N (%), where N is the total number of patients with available data. ICU, Intensive care unit; ARDS, Acute respiratory distress syndrome; UOC, Usual oxygen care, including standard nasal catheter and facemask inhalation; HFNC, High-flow nasal cannula oxygen; (N)IMV, (Non-) Invasive mechanical ventilation; ECMO, Extracorporeal membrane oxygenation; WBC, White blood cell; PLT, Blood platelet count; APTT, Activated partial thromboplastin time; PT, Prothrombin time; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; ALP, Alkaline phosphatase; γ-GT, gamma-Glutamyl transpeptidase; hs-CRP, high-sensitivity C-reactive protein. * χ^2 test comparing all subcategories

factors in model 3 did not alter the positive association between cancer survivors and the prolonged duration of viral RNA shedding (AHR = 0.54; 95% CI: 0.38–0.80; $P < 0.05$; Table 4).

Discussion

The results of this study suggest that although the prognosis of cancer survivors with COVID-19 was similar to that of non-cancer patients, cancer survivors had prolonged duration of SARS-CoV-2 RNA shedding and a higher incidence of secondary infection.

Cancer survivors, with history of either hematologic or solid tumors, were reported to have an increased risk of infection and mortality due to immunocompromised status compared to the general population, especially from respiratory infections [20–23]. However, our study of COVID-19 infection in cancer survivors did not support this view. Our study found that the mortality rate in the cancer survivor group was 15%, which was comparable to the matched non-cancer cohort. In a study involving 106 cancer patients, the mortality rate of cancer patients was 11% [11], and the incidence of comorbidities such as hypertension and diabetes was lower than that in our study, suggesting that chronic comorbidities may be one of the most important risk factors for survival outcomes, which was consistent with previous studies.

We found that the median duration of SARS-CoV-2 RNA shedding in cancer survivors was 32 days, which was much longer than the 17–20 days reported in the general patients [17, 24] and 24 days in the non-cancer cohort in this study. In our study, even after balancing or weighting these factors, viral RNA shedding in the cancer survivor cohort was still significantly longer than that in

Table 3 Treatments and outcomes

	Overall	Cancer survivor	Non-cancer	*P* value
Treatments				
Antibiotics	202 (82.8)	49 (80.3)	153 (83.6)	0.561
Antiviral treatment	239 (98.0)	58 (95.1)	181 (98.9)	0.101
Corticosteroids	154 (63.1)	22 (36.1)	132 (72.1)	< 0.001
Interferon atmotherapy	94 (35.8)	12 (19.7)	82 (44.8)	< 0.001
Intravenous immunoglobin	73 (29.9	12 (19.7)	61 (33.3)	0.053
Oxygen therapy	221 (86.3)	49 (76.6)	172 (89.6)	0.004
Standard nasal catheter and facemask inhalation	196 (80.3)	34 (53.1)	162 (88.5)	<.001
High-flow nasal cannula oxygen therapy	31 (12.7)	6 (9.8)	25 (13.7)	0.512
Non-invasive mechanic ventilation	72 (29.5)	8 (13.1)	64 (35.0)	0.001
Invasive mechanic ventilation	15 (6.1)	1 (1.6)	14 (7.7)	0.125
Outcomes				
Disease severity status				0.125
Mild-moderate	121 (49.6)	36 (59.0)	85 (46.4)	–
Severe	73 (29.9)	16 (26.2)	57 (31.2)	–
Critical	50 (20.5)	9 (14.8)	41 (22.4)	–
ARDS	88 (36.1)	15 (24.6)	68 (37.2)	0.086
ICU admission	3 (1.2)	3 (4.9)	5 (2.7)	0.416
Deceased	87 (35.7)	10 (15.6)	45 (24.6)	0.218
Duration of viral sheddling after COVID-19 onset, days	27.0 (20.0–34.0)	32.0 (26.0-46.0)	24.0 (18.0–33.0)	< 0.001
Re-positive of COVID-19 diagnosis	11 (4.5)	3 (4.9)	7 (3.8)	0.716

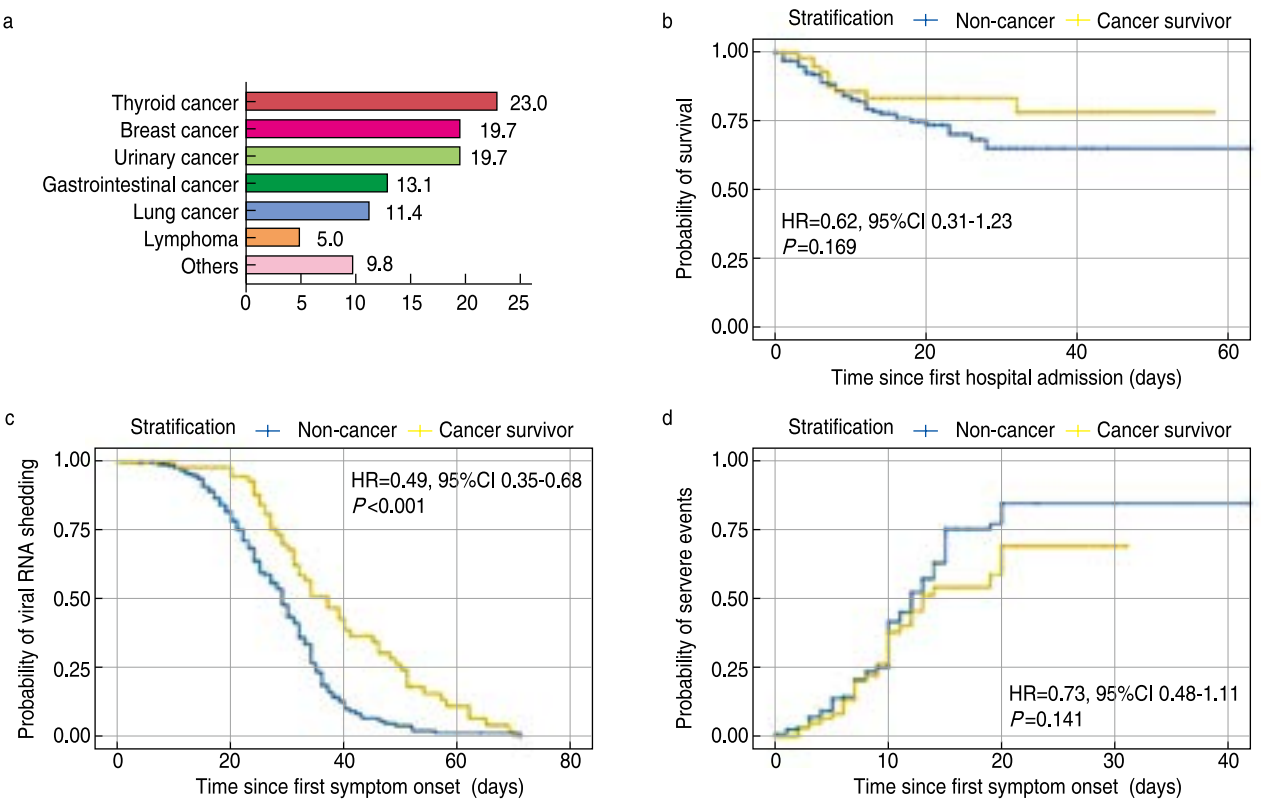

Fig. 1 Tumor categories of cancer survivors (a). The probabilities of survival (b), viral RNA shedding (c) and severe events (d) of the cancer survivors were compared to the non-cancer patients

Table 4 Hazard ratios of survival, viral RNA shedding and severe events for cancer survivor

Survival probability				Model 1			Model 2			Model 3		
	Crude HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Cancer survivor Yes *vs.* No	0.62	0.31–1.23	0.169	0.52	0.26–1.04	0.064	0.53	0.27–1.06	0.074	0.36	0.11–1.20	0.096
Viral RNA Shedding Probability				Model 1			Model 2			Model 3		
	Crude HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Cancer survivor Yes *vs.* No	0.49	0.35–0.68	< 0.001	0.49	0.35–0.68	< 0.001	0.49	0.35–0.68	< 0.001	0.54	0.38–0.80	0.002
Severe events probability				Model 1			Model 2			Model 3		
	Crude HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Cancer survivor Yes *vs.* No	0.73	0.48–1.11	0.141	0.73	0.49–1.11	0.144	0.72	0.47–1.08	0.118	1.25	0.76–2.06	0.378

Model 1 adjusted for age; Model 2 adjusted for age and gender; Model 3 adjusted for age, gender, hypertension, D-dimer, LDH, high sensitive CRP, and lymphocyte count. *P* value was calculated using cox proportional hazard model.

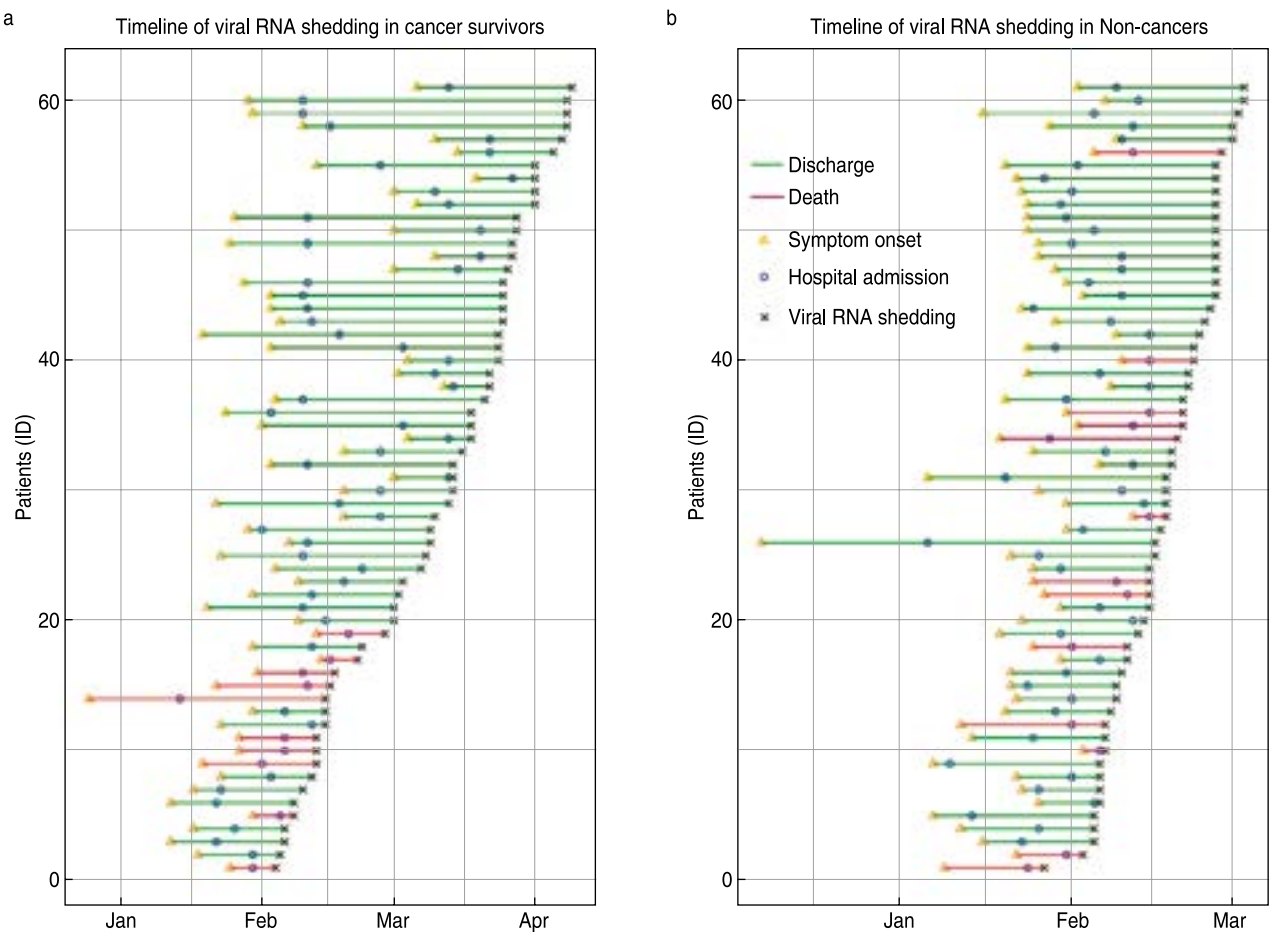

Fig. 2 Timelines of viral RNA shedding of the cancer survivors (a) and the non-cancer patients (b)

the non-cancer patients. In addition, it was found that the incidence of secondary infection was significantly higher in the cancer survivor cohort. These results were consistent with those of previous studies on respiratory viral infections [25–26], suggesting that immunosuppressive status may interfere with viral clearance and increase the risk of secondary infection.

Among the cancer survivors, 3 patients retested

positive in the RNA testing during the follow-up after discharge. The clinical significance of the nucleic acid re-positivity has not been determined. However, it is inferred that due to the immunocompromised status of cancer survivors, their ability to eliminate the virus has been weakened. Special attention should be paid to persistent viral carriage, recrudescence, and secondary infection.

It was found that, consistent with the data of the general population reported [17], the most prevalent symptom onset in cancer survivors was fever, followed by cough, myalgia, or fatigue; dyspnea was present in more than one-third of cancer survivors. These symptoms were more common in cancer survivors than in non-cancer patients. It is possible that cancer survivors are more concerned about their health conditions and more sensitive to physical changes; hence, they tend to report their symptoms earlier and more frequently and are more likely to seek medical care. Current research suggests that early recognition and medical intervention may improve the prognosis of COVID-19 patients [27]; therefore, early medical attention may contribute to the outcome of cancer survivors infected with COVID-19.

The median age of the cancer survivor cohort was 64 years, while a study of 1,099 patients showed a median age of 47.0 years in COVID-19 patients, suggesting that cancer patients tend to be older, which is consistent with previous studies [10]. Among the cancer survivors, 37 (60.7%) were women and 26 (42.7%) had a history of thyroid and breast cancer. Both types of cancer exhibit a good prognosis, and the patients' nutritional and physical status are less affected. Cancer survivors in the study had a median body mass index of 24 and a median albumin concentration of 36.6 g/L, indicating that most cancer survivors included had recovered from the disease and sequelae of anti-cancer treatments.

In terms of laboratory testing, compared to the cancer survivors, the non-cancer patients had a higher proportion of lymphopenia, higher levels of aspartate transferase, LDH, hs-CRP, and d-dimer, all of which were considered to be associated with adverse outcomes [17, 19, 28]. Among cancer survivors, 21.3% received chemotherapy and radiation, and anemia was more common in this cohort because of the long-lasting toxicity of the bone marrow [29–30]. Although the incidence of anemia was higher in the cancer survivor cohort, the median concentration of hemoglobin was 120 g/L (IQR, 112.0–128.0), and no increase in severe disease or mortality was observed in patients with mild anemia. Thus, mild anemia demonstrated less impact on the development of COVID-19 disease. Accumulated evidence has suggested that the cytokine storm syndrome (CRS) may be an important cause of a critical disease course or death in COVID-19 patients. Such a cytokine storm may destroy the adaptive immunity against SARS-CoV-2 [31], leading to fulminant and fatal multiorgan failure. We found that patients in the cancer survivor cohort had relatively low levels of pro-inflammatory cytokines including IL-6, IL-10, and IL-1b. These trends suggest that cancer survivors had lower or at least similar levels of inflammation compared to non-cancer patients. Impaired cellular immunity in cancer survivors may suppress excessive inflammation, preventing the development of CRS [32]. Therefore, in the case of hyperinflammation, a certain degree of immunosuppression may serve as a protective factor [33]. In summary, the immunosuppressive state may be a double-edged sword for cancer survivors with COVID-19, and which factor dominates the outcome still needs further investigation.

Although the study of Liang et al. revealed a worse outcome in cancer patients infected with COVID-19 [5], there was no distinction between cancer survivors and cancer patients, which may reduce representativeness of the findings. We believe that there are differences between cancer survivors and cancer patients. The immune function and nutritional status of cancer patients were significantly impaired by anti-cancer therapy or disease progression, while most cancer survivors have recovered to varying degrees. Nevertheless, cancer survivors comprise a heterogeneous group, and different tumor types, anti-cancer treatment methods, and durations after diagnosis of cancer would affect the immune status of patients, thus affecting their survival and RNA shedding. To date, little is known about SARS-CoV-2, and more research is needed to determine which factors drive inflammation and which groups are at high risk.

Limitations

Our study has several limitations. First, this study was a retrospective cohort study using propensity score matching methods, which could not represent all cancer survivors. Therefore, prospective controlled studies with larger sample sizes should be carried out to clarify differences among cancer survivors, cancer patients, and non-cancer patients. Second, although this study was a multicenter study, all the centers were located in mainland China. Due to the global spread of COVID 19, international multi-center investigation needs to be considered.

Conclusions

The severe events and mortality risk of cancer survivors with COVID-19 were comparable to those of non-cancer patients, but the viral RNA shedding duration was longer and the incidence of secondary infection was higher. Based on our results, it is helpful for clinicians to take tailored measures to treat cancer survivors with

COVID-19. Although continuous follow-up should be carried out to determine the long-term prognosis of cancer survivors infected with COVID-19, we suggest that the comprehensive care plan of cancer survivors with COVID-19 should take longer viral RNA shedding duration into consideration and pay more attention to such patients than non-cancer patients to prevent development of secondary infections.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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