CLINICAL FEATURES AND DISEASE COURSE OF CANCER PATIENTS INFECTED WITH SARS-COV-2 DURING ANTICANCER TREATMENTS

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ABSTRACT

Cancer patients infected with SARS-CoV-2 during their active anticancer treatment represent a highly vulnerable population. We aimed this investigation to show clinical features and outcomes of the patients who had mild to moderate COVID-19 symptoms or were asymptomatic at the admission to the COVID Center. The retrospective study included 25 cancer patients confirmed with SARS-CoV-2 within seven days of their last anticancer treatment. Clinical data were collected from medical records and processed by methods of descriptive and inferential statistics. Patients' mean age was 68.1±10.4 years. More than 2/3 of the patients were with ECOG PS 0 and 1, and about 4/5 of patients were in III or IV cancer stage. The most frequently applied types of therapy were radiotherapy and combined radio/chemotherapy. Eleven (44.0%) patients had bilateral while 4 (16%) had unilateral pneumonia. The most frequent symptoms were fever (72%), fatigue (72%), dyspnea (32%), and cough (32%). 1/5 of the patients needed oxygen support. Mean neutrophil (2.6±1.2), lymphocyte (0.9±0.6) and platelets (200.1±88.1) number significantly increased from admission to discharge ($p=0.004$, $p=0.005$, $p<0.001$). Median CRP significantly decreased from 40.4 (6.2-96.2) at admission to 11.35 (3.75-27.65) at discharge ($p=0.008$). Twenty-four patients were cured, and one patient died. Naso-pharyngeal SARS-CoV-2 clearance time was 19.4±6.9 days; the minimum was seven, and the maximum was 39 days. Cancer patients infected with SARS-CoV-2 during active anticancer treatment can successfully overcome COVID-19 without developing further respiratory or other complications during hospitalization. An increase in lymphocyte and neutrophil counts, with a decrease in CRP, may be markers of a favorable prognosis.

Keywords: *SARS-CoV-2, COVID-19, cancer, chemotherapy, radiotherapy.*

INTRODUCTION

In December 2019. China was experiencing an outbreak of a novel beta coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). On January 30, 2020, the WHO declared the coronavirus disease 2019 (COVID-19) outbreak a public health emergency of international concern and, in March 2020, began to characterize it as a pandemic (2).

Cancer patients are regarded as a highly vulnerable group in the COVID-19 pandemic due to immunosuppression caused by malignancy and systemic anticancer therapies. The potential to cause harm by SARS-CoV-2 is at least three-fold larger in oncology patients (3). Delivering cancer care during this crisis is challenging, given the competing risks of death from cancer versus death or serious complications from COVID-19 (4).

Cancer patients with “active disease” who are receiving chemotherapy or extensive radiotherapy or who have received chemotherapy in the last three months are at higher risk of infection. The specific risk groups are those with an impaired immune system such as leukocytopenia, low immunoglobulin levels, and long-lasting immunosuppression (steroids, antibodies) (5).

In general, all adults with COVID-19 can be grouped into the several severities of illness categories from asymptomatic infection to critical illness, although the criteria in each category may overlap or vary across guidelines and clinical trials (6). The most common symptoms are fever, cough, sore throat, malaise, fatigue, headache, and muscle pain. The symptoms of lower respiratory tract infectious disease are diagnosed in patients with tracheitis and bronchitis, whereby dyspnea and/or declining oxygen saturation at ambient air often predict bi-lateral ground-glass infiltrates seen earliest on computed tomography (CT) scans, hence identifying viral pneumonia (7).

The first investigations of cancer patients infected with SARS-CoV-2 showed the fatality rate in this population was 5,6% compared with 2,3% in the general population (8). Zhang at al. (9) showed that cancer patients develop deteriorating conditions and poor outcomes with high mortality. They also found that within 14 days, anti-tumor therapies were significantly associated with the occurrence of severe clinical events in SARS-CoV-2 infection. On the other hand, Lee at al. analyzed 800 patients with a diagnosis of cancer and symptomatic for COVID-19 and could not identify evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatment were at an increased risk of mortality from COVID-19 compared with those not on active treatment (10).

Due to contradictory and insufficient data related to cancer patients infected with SARS-CoV-2 during the period of their cancer treatment, we aimed this investigation to show our clinical experience related to this vulnerable population and to gather new information on their clinical and laboratory features, and disease course.

METHODS

Study design and participants

The retrospective study included 25 cancer patients diagnosed with SARS-CoV-2 infection, referred from the Institute of Oncology and Radiology of Serbia (IORS) to COVID Center Zemun. Patients with different types of solid cancers were tested for SARS-CoV-2 infection on the day of the scheduled continuation of their ongoing anticancer treatment, or during the hospitalization in IORS due to the presence of symptoms or data about risk contacts with persons tested positive for SARS-CoV-2. A confirmed case of SARS-CoV-2 positive patient was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens. Only laboratory-confirmed cases were included in the analysis. The patients were admitted to the COVID Center Zemun between March 07, 2020, and April 18, 2020. on the day of the confirmation of SARS-CoV-2 infection. This study included only cancer patients with mild or moderate COVID-19 severity or were asymptomatic at hospital admission. Disease severity was assessed according to the WHO summary of typical features of COVID-19 severity (11). All patients received the last dose of anticancer therapy within seven days before admission to COVID Center Zemun. We obtained data from the medical records for hospitalized patients. Radiologic assessments included chest radiography, and all laboratory testing was performed at hospital admission and further according to the patients' clinical care needs. The patients were discharged from the hospital after they achieved criteria according to Guidance for discharge and ending the isolation in the context of widespread community transmission of SARS-CoV-2 of the European Centre for Disease Prevention and Control (ECDC) (12). A COVID-19 patient is considered 'fully discharged' if no symptoms are related to acute COVID-19 for ≥48 hours AND two negative tests at 24-hour intervals from nasal and oropharyngeal swabs.

Statistical analysis

Descriptive statistics were calculated for the baseline demographic and clinical features. Categorical variables were presented as number and percentage. Continuous data distribution was tested with mathematical and graphical methods. Continuous variables were presented as mean with standard deviation (SD) or median with 25-75 th percentile, according to data distribution. Differences between admission and discharge were analyzed using Student’s paired t-test (or Wilcoxon signed rank test) for continuous variables. For all statistical calculations, the significance level (α) was 0.05. For statistical processing of the obtained results, we used the SPSS software package (version 23.0, SRSS Inc., Chicago, IL).

RESULTS

This study included 25 cancer patients with confirmed COVID-19 diagnosis or SARS-CoV-2 infection, mean age 68.1±10.4 years. Baseline clinical characteristics are presented in table 1. Male patients were dominant, and the gastrointestinal system was the most affected system, with ECOG PS 0 and 1 in more than 2/3 of the patients. Most of the patients were in III or IV stages of cancer, and radiotherapy or combined radio/chemotherapy were the most frequently applied types of therapy.

In 3/4 of the patients, the main symptoms at the hospital admission were fever and fatigue (table 2**)**. Eleven (44.0%) patients had bilateral pneumonia (figure 1), while 4 (16) had unilateral pneumonia. At admission, 2/3 of the patients had leucopenia and lymphopenia, without leukocytosis and lymphocytosis in any patient. Neutropenia was present in less than half of the SARS-CoV-2 positive cancer patents. A high level of CRP was present in 2/3 of the patients. Thrombocytopenia was present in 1/3 of the patients and anemia in more than 80%. A high level of D-Dimer was present in all, except for 2 patients with referent values. More than half of the patients had low proteins and albumin levels. The level of LDH was increased in one-third of the patents. Sodium levels were low in 5, while potassium level was low in 6 patients. Low calcium level was present in more than half of the SARS-CoV-2 positive patients. The iron level was low in 70%, and ferritin was high in more than half of the patents. Urea and creatinine levels were mostly in reference ranges. Liver enzymes were sporadically increased in some patients (table 3).

Mean neutrophils number was 2.6 ± 1.2 at admission and significantly increased 3.1 ± 1.1 at discharge p=0.004 (figure 2). Mean lymphocytes number also significantly increased from 0.9 ± 0.6 to 1 ± 0.5 at discharge (p=0.005), (figure 2). NLR and PLR increased at discharge, but change was not significant (NLR 2.83 (1.66-6) to 3.7 (1.81-5.35), p=0.346; PLR 195 (131.17-453.33) to 323.9 (175.75-552.5), p=0.607). Median CRP significantly decreased from 40.4 (6.2-96.2) at admission to 11.35 (3.75-27.65) at discharge (p=0.008) (figure 2). Mean number of platelets significantly increased from 200.1 ± 88.1 to 300.3 ± 124.6, p<0.001, while mean hemoglobin remained unchanged (113.4 ± 19.7 to 111.4 ± 17.9, p=0.686).

All patients were treated with hydroxychloroquine. Sixteen (64.0%) patients were treated with Azithromycin. The most often applied antibiotics were Azithromycin and Ceftriaxone. In patients with pneumonia, Ceftazidime, Meropenem, Metronidazole, and Levofloxacin were applied depending on the clinical symptoms, CRP values, and performance status of the patients' (table 4**)**. Twenty-four patients were cured, and one patient had a deadly outcome. Negative results of the PCR test were present after 19.4 ± 6.9 days; the minimum was seven days and maximal after 39 days.

Table 1. Baseline clinical characteristics of SARS-CoV-2 positive cancer patients with mild to moderate SARS-CoV-2 symptoms at the admission to the Covid center

		n (%)
Gender	male	18 (72)
	female	7 (28)
Age*		68.1±10.4
Localization of the primary tumor	Gastrointestinal tract (GIT)	9 (36)
	Urogenital tract (UGT)	5 (20)
	Respiratory tract (RT)	6 (24)
	Other	5 (20)
ECOG PS [a]	0	4 (16)
	1	16 (64)
	2	1 (4)
	3	3 (12)
	4	1 (4)

		n (%)
Cancer stage	II	3 (12)
	IIA	1 (4)
	III	9 (36)
	IIIB	1 (4)
	IV	6 (24)
	IVA	5 (20)
Type of current cancer therapies	HT [b]	2 (8)
	CT [c]	4 (16)
	CT/Biological therapy	1 (4)
	RT [d]	9 (36)
	HT/RT	1 (4)
	CT/RT	5 (20)
	Not started	3 (12)
Comorbidities		16 (64)
Hypertension		13 (52)
Diabetes mellitus		2 (8)
Unilateral pneumonia		11 (44)
Bilateral pneumonia		4 (16)

*data are expressed as mean±sd;
a) ECOG PS - Eastern Cooperative Oncology Group (ECOG) Performance Status
b) HT - hormone therapy;
c) CT- chemotherapy;
d) RT - radiotherapy

Table 2. SARS-CoV-2 symptoms of infected cancer patients on a day of admission to COVID Center

Symptom	Yes	No
Fever	18 (72%)	7 (28%)
Cough	8 (32%)	17 (68%)
Dyspnea	8 (32%)	17 (68%)
Need for oxygen support	5 (20%)	20 (80%)
Fatigue	18 (72%)	7 (28%)

Table 3. Laboratory findings of SARS-CoV-2 positive cancer patients with mild to moderate SARS-CoV-2 symptoms at the admission to the COVID Center

Laboratory findings	Values	N (%)
Leucocytes	Leucopenia	18 (72)
	referent values	7 (28)
Neutrophils	Neutropenia	11 (44)
	reference values	14 (56)

Laboratory findings	Values	N (%)
Lymphocytes	Lymphopenia	17 (68)
	reference values	8 (32)
Platelets	Thrombocytopenia	9 (36)
	reference values	16 (64)
Hemoglobin	low	22 (88)
	reference values	3 (12)
CRP	reference values	7 (28)
	high	18 (72)
D-Dimer	low	0 (0)
	reference values	2 (9.1)
	high	20 (90.9)
Proteins	low	15 (60)
	reference values	10 (40)
	high	0 (0)
Albumins	low	16 (64)
	reference values	9 (36)
	high	0 (0)
LDH	low	0 (0)
	reference values	16 (66.7)
	high	8 (33.3)
Sodium	low	5 (20.8)
	reference values	19 (79.2)
	high	0 (0)
Calcium	low	14 (60.9)
	reference values	9 (39.1)
	high	0 (0)
Potassium	low	6 (25)
	reference values	13 (54.2)
	high	5 (20.8)
Iron	low	14 (70)
	reference values	6 (30)
	high	0 (0)
Ferritin	low	1 (4.8)
	reference values	9 (42.9)
	high	11 (52.4)
Urea	low	0 (0)
	reference values	21 (84)
	high	4 (16)
Creatinine	low	0 (0)
	reference values	23 (92)
	high	2 (8)
AST	low	0 (0)

Laboratory findings	Values	N (%)
	reference values	15 (68.2)
	high	7 (31.8)
ALT	low	0 (0)
	reference values	20 (90.9)
	high	2 (9.1)
GGT	low	0 (0)
	reference values	15 (75)
	high	5 (25)

Table 3. Laboratory findings of SARS-CoV-2 positive cancer patients with mild to moderate SARS-CoV-2 symptoms at the admission to the COVID Center

Laboratory findings	Values	N (%)
Leucocytes	Leucopenia	18 (72)
	referent values	7 (28)
Neutrophils	Neutropenia	11 (44)
	reference values	14 (56)
Lymphocytes	Lymphopenia	17 (68)
	reference values	8 (32)
Platelets	Thrombocytopenia	9 (36)
	reference values	16 (64)
Hemoglobin	low	22 (88)
	reference values	3 (12)
CRP	reference values	7 (28)
	high	18 (72)
D-Dimer	low	0 (0)
	reference values	2 (9.1)
	high	20 (90.9)
Proteins	low	15 (60)
	reference values	10 (40)
	high	0 (0)
Albumins	low	16 (64)
	reference values	9 (36)
	high	0 (0)
LDH	low	0 (0)
	reference values	16 (66.7)
	high	8 (33.3)
Sodium	low	5 (20.8)
	reference values	19 (79.2)
	high	0 (0)
Calcium	low	14 (60.9)

Laboratory findings	Values	N (%)
	reference values	9 (39.1)
	high	0 (0)
Potassium	low	6 (25)
	reference values	13 (54.2)
	high	5 (20.8)
Iron	low	14 (70)
	reference values	6 (30)
	high	0 (0)
Ferritin	low	1 (4.8)
	reference values	9 (42.9)
	high	11 (52.4)
Urea	low	0 (0)
	reference values	21 (84)
	high	4 (16)
Creatinine	low	0 (0)
	reference values	23 (92)
	high	2 (8)
AST	low	0 (0)
	reference values	15 (68.2)
	high	7 (31.8)
ALT	low	0 (0)
	reference values	20 (90.9)
	high	2 (9.1)
GGT	low	0 (0)
	reference values	15 (75)
	high	5 (25)

Table 4. The list of applied therapy and the outcome of SARS-CoV-2 positive cancer patients with mild to moderate SARS-CoV-2 symptoms at the admission to the Covid center

Type of therapy	Aplication of therapy	n (%)
Hydroxychloroquine	No	0 (0)
	Yes	25 (100)
Azithromycin	No	9 (36)
	Yes	16 (64)
Ceftriaxone	No	12 (48)
	Yes	13 (52)
Ceftazidime	No	24 (96)
	Yes	1 (4)
Meropenem	No	24 (96)
	Yes	1 (4)
Metronidazole	No	22 (88)

Type of therapy	Aplication of therapy	n (%)
	Yes	3 (12)
Levofloxacin	No	24 (96)
	Yes	1 (4)
Outcome	Death	1 (4)
	Cured	24 (96)

Figure 1. Changes of neutrophil, lymphocyte, and CRP counts from admission to discharge of SARS-CoV-2 positive cancer patients with mild to moderate SARS-CoV-2 symptoms: significantly increase of mean neutrophils and lymphocytes number and decrease of median CRP value at discharge

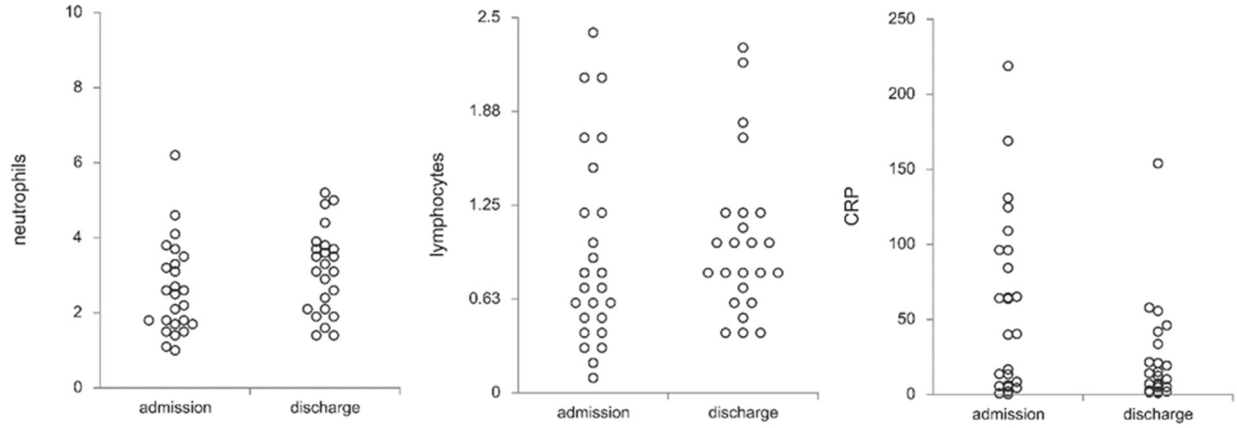
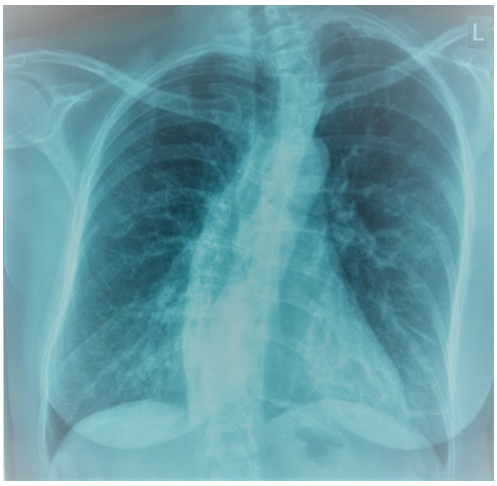


Figure 2. Chest X-ray findings in cancer patients infected with COVID-19 during the cancer treatment: four examples of bilateral pneumonia show patchy or diffuse ground-glass opacity with small fields of consolidation and reticular areas of increased opacity. Patients had no diagnosed lung metastases.

A)



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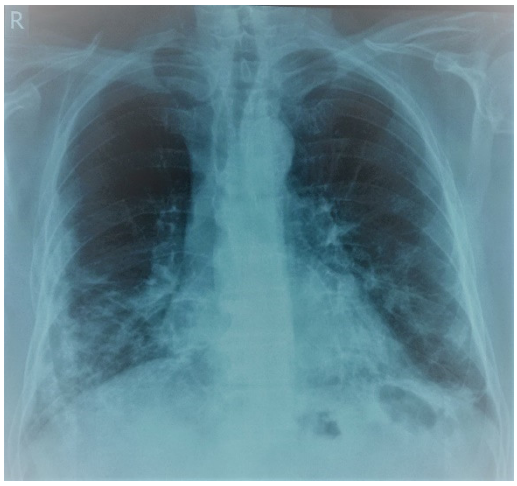
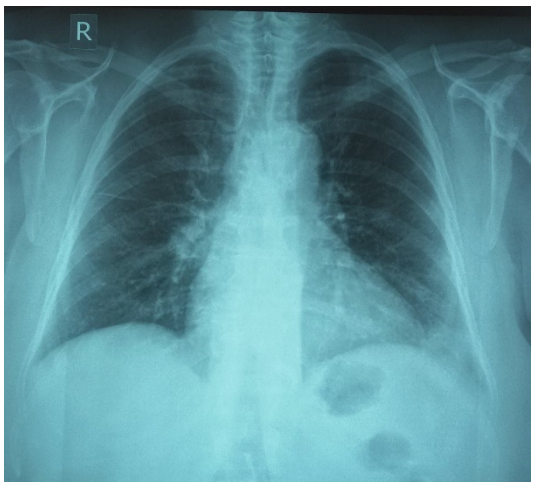
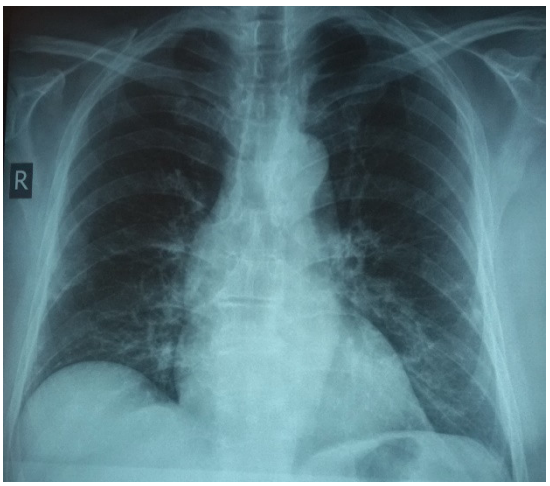


C)



D)



DISCUSSION

We present the clinical course and laboratory characteristics of 25 cancer patients infected with SARS-CoV-2 during their active anticancer treatment. At presentation, all patients had mild or moderate symptoms or were asymptomatic, and most of them successfully overcame SARS-CoV-2 infection and were discharged from the hospital able to continue their further oncology treatment.

The most common symptoms were typical for COVID-19 patients and most frequently included fever, fatigue, cough, and dyspnea. Oxygen support was needed by 1/5 of the patients. The most frequent initial laboratory findings were leukopenia, lymphopenia, neutropenia, and thrombocytopenia. Wang at al. (13) shown that COVID-19 patients had significantly lower total number of lymphocytes and NK cells. They also documented that in responsive patients, total lymphocytes, CD8+ T cells, and B cells increased significantly after treatment, and no significant change was detected in CD4+T cells, CD4+/CD8+ ratio. In nonresponsive patients, no significant change was detected. Our study showed that the levels of lymphocytes, neutrophils, and thrombocytes significantly increased at discharge, which could have a positive effect on the outcome of the disease.

At the hospital admission, about 2/5 of patients had bilateral and less than 1/5 unilateral pneumonia. The diagnosis of pneumonia was established by clinical and laboratory examination and confirmed by chest X-ray (CXR) of the lungs. The fact was that some incipient pneumonia might have been remained unrecognized because CXR is insensitive in the detection of early disease (14), but, on the other hand, it was useful for establishing a baseline and as follow-up imaging for disease progression (15). Compared to chest CT, CXR appears to have lower sensitivity and might have higher specificity (16).

Anemia was present in 4/5 of patients, and 1/5 of them needed a blood transfusion, mean hemoglobin remained unchanged. The levels of CRP significantly decreased at discharge. The other laboratory findings showed high D-Dimer, hypoproteinemia, and hypoalbuminemia and were in line with the experiences of other authors (9).

Most of our cancer patients infected with SARS-CoV-2 continued to be respiratory stable during the hospitalization and successfully defeated infection. Our experience was completely different from Zhang et al. (9) reported that 53% of the 28 cancer patients developed severe events, 21,4% were admitted to intensive care units (ICU), 35,7% had life-threatening complications, and 28,6% of the patients died. Yang et al. (17) also showed that receiving chemotherapy within 4 weeks before symptom onset and male sex were risk factors for death during admission to hospital. According to our research, one patient developed a severe respiratory event and was admitted to the intensive care unit (ICU) for non-invasive mechanical ventilation, and one patient died in the terminal stage of metastatic colorectal cancer with mild respiratory symptoms. Of course, the fact that 80% of the patients were in good performance status (ECOG 0 or 1) could positively contribute to this outcome. Also, large COVID-19 cancer cohorts of predominantly solid organ tumors have shown no significant excess mortality risk from recent chemotherapy (18,19).

Despite the large use of antiviral and/or anti-inflammatory drugs, until now, no proven treatment is available for the current COVID-19 pandemic (18,20). Our patients were treated with hydroxychloroquine and one or more antibiotics, depending on the severity of their symptoms and the presence of pneumonia. They also received multivitamin therapy, adequate rehydration, and all needed symptomatic and supportive therapy. No antiviral agents were used. It remains unclear

whether the use of any applied treatment was crucial for the clinical course of the disease and the patients' recovery.

The patients could be discharged from the hospital after two consecutively negative test results plus the absence of respiratory symptoms for at least two consecutive days before testing after prescribed therapy was finished. The therapy was prescribed on the day of confirmation of SARS-CoV-2 infection. Two consecutive negative RT-PCR results were presented after 7 to 39 days (19.4 ± 6.9) after the confirmation of infection. Most patients (76%) took more than 14 days to meet the discharge criteria. Xu at al. (21) observed that time to nasopharyngeal SARS-CoV-2 RNA clearance in their oncology patients was substantially longer than the approximately 17-20 days previously reported in the general population. In their retrospective cohort study, the median time to SARS-CoV-2 clearance was 50 days using the ASCO/CDC criteria of 2 negative RT-PCR assays >24 hours apart, and the virus clearance times differed substantially depending on criteria.

The study's limitation is reflected in patients' small sample size and heterogeneity of cancer types. The study is retrospective and non-randomized, which could not have been avoided given the patients' admission circumstances to our center. However, the study's value is reflected in the fact that clinical features and disease courses were monitored in patients infected with SARS-CoV-2 during their active anticancer treatment when their vulnerability to infections is greatest due to the possible toxicity of oncology therapies.

CONCLUSION

Cancer patients with mild or moderate COVID-19 symptoms or asymptomatic for SARS-CoV-2 infection at presentation can successfully overcome disease without developing any further respiratory or other complications even though the infection occurred during their active anticancer treatment. An increase in neutrophil and lymphocyte counts and a decrease in CRP may be markers of a favorable prognosis.

CONFLICTS OF INTEREST

The authors declare no financial or commercial conflicts of interest.

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None.

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