Characteristics and outcomes of coronavirus disease 2019 (COVID-19) patients with cancer: A single-center retrospective observational study in Tokyo, Japan

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Abstract

Background

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an international outbreak of coronavirus disease 2019 (COVID-19), data on the clinical characteristics of COVID-19 patients with cancer are limited. This study aimed to evaluate the clinical characteristics and outcomes including mortality and viral shedding period in COVID-19 patients with cancer in Japan.

Methods

We retrospectively analyzed 32 patients with a history of cancer who were referred to our hospital between January 31, 2020 and May 25, 2020. We evaluated the association between clinical outcomes and potential prognostic factors using univariate analyses.

Results

The median age was 74.5 (range, 24–90) years and 22 patients (69%) were men. A total of 11 patients (34%) died. Our analyses demonstrated that the mortality was significantly associated with lymphocyte count, albumin, lactate dehydrogenase, serum ferritin, and C-reactive protein on admission. The median period between illness onset and the first effective negative SARS-CoV-2 PCR result was 22 days (interquartile range, 18–25) in survivors. Of four patients with hematological malignancy who developed COVID-19 within the rest period of chemotherapy, three died and the other patient, who received bendamustine plus rituximab therapy, had the longest duration of viral shedding (56 days).

Conclusion

Our study suggested that the risk factors for mortality previously reported in general COVID-19 patients, including lymphocytopenia, were also effective in cancer patients. Patients who received cytotoxic chemotherapy recently or were treated with chemotherapy, which can lead to lymphocyte reduction, had poor prognosis and prolonged periods of viral shedding.

Introduction

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally since December 2019 [1,2]. In Japan, the first patient with COVID-19 was reported on January 15, 2020 [3], and the number of patients increased rapidly from March to May. In this context, COVID-19 has been a great concern for patients who have a history of cancer. Previous reports have shown that patients with cancer had a higher risk of developing severe events [4-12]. The World Health Organization-China Joint Mission reported that the overall mortality was 3.8%, while the mortality of cancer patients was 7.6% in China [2].

Several studies reported the risk factors associated with development of severe events caused by CODIV-19 in general people. A previous systematic review of 10 prognostic models for predicting poor prognosis in patients with COVID-19 showed that the most frequently reported predictors included age, sex, features derived from computed tomography (CT) scans, C-reactive protein (CRP), lactic dehydrogenase (LDH), and lymphocyte count [13]. Although some studies suggested the risk factors for mortality in cancer patients [5,9], there are still insufficient data regarding the clinical characteristics and the risk factors for mortality in cancer patients. In particular, details of the viral shedding period and its association with chemotherapy have not been well described.

In this retrospective study, we evaluated the clinical characteristics and outcomes including the mortality and viral shedding period in COVID-19 patients with a history of cancer using the database in our hospital in Japan.

Patients And Methods

Study design and patients

This was a retrospective, single-center, observational study. We reviewed the records of 32 patients with a history of cancer out of 235 COVID-19 patients who were referred to our hospital between January 31, 2020 and May 25, 2020. Clinical data were retrieved from electronic medical records, including demographic and clinical features, laboratory findings, radiological data, and the results of reverse transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2.

This study was approved by the institutional ethics review boards of our hospital, and the requirement to obtain a written informed consent was waived.

Definitions

All patients were diagnosed with COVID-19 by RT-PCR assay for SARS-CoV-2. The discharge criteria included symptom improvement and two consecutive negative results of RT-PCR test of nasopharyngeal swab taken at least 24 hours apart. The first effective negative PCR test was defined as the first test of the two negative PCR tests. The following comorbidities were also risk factors for COVID-19: diabetes, hypertension, coronary heart disease, chronic obstructive pulmonary disease (COPD), and asthma. Patients with active cancer were defined as those who received treatment for cancer such as chemotherapy, immunotherapy, or hormone therapy within 30 days of COVID-19 onset, those scheduled to undergo cancer treatment, and/or those with metastasis to other organs. The illness onset was defined as the day when symptoms appeared.

Statistical analysis

We used the Mann-Whitney U test or Fisher’s exact test to compare the characteristics between survivors and non-survivors. We used a receiver operating characteristic curve in order to determine the best cut off value of laboratory data. Overall survival (OS) was defined as the period from illness onset to the date of

last follow-up or death from any cause. OS was estimated using the Kaplan-Meier method. Differences between survival curves were tested for significance using the log-rank test. Two-sided *P* values of 0.05 or less were considered significant. Hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards models. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [14].

Results

Patient characteristics

A total of 235 patients were referred to our hospital with COVID-19 between January 31, 2020 and May 25, 2020. We retrospectively enrolled 32 patients with a history of cancer. They were all Asians except for one Australian. A total of 11 patients (34%) eventually died, and all deaths were due to COVID-19. Twenty-one patients (66%) were discharged or transferred with negative RT-PCR results.

Table 1 shows the clinical characteristics of these patients. The median age was 74.5 (range, 24–90) years and 22 patients (69%) were men. A total of 25 patients (78%) had solid tumors, while 7 (22%) had hematologic malignancies. In addition to cancer, 19 (59%) had at least one comorbidity, with hypertension being the most common (13 patients, 41%). Thirteen patients (41%) received cancer treatment within 30 days.

CT or X-ray on admission showed radiological features of pneumonia in 27 patients (84%). Lymphocytopenia (lymphocyte count $<0.8\times10^9$ /L) occurred in 13 patients (41%) and was predominant among the non-survivors (73% vs. 24%). Twenty-two patients (69%) received favipiravir, while ten patients (31%) were treated with systematic glucocorticoids.

The median time from illness onset to admission was 7 days (interquartile range [IQR], 4–8). The median time from illness onset to death was 24 days (IQR, 15–26). The median period between illness onset and the first effective negative SARS-CoV-2 RT-PCR result was 22 days (IQR, 18–25) in survivors.

Risk factors for mortality

The results of univariate analysis for OS are shown in Table 2. The following risk factors were significantly associated with mortality: lymphocyte count, albumin, LDH, serum ferritin, and CRP on admission. In our study, age, comorbidities, D-dimer, and cancer status were not associated with OS. The Kaplan-Meier survival curve stratified by high and low lymphocyte count is shown in Figure 1A (30-day OS: 90% and 46%, *P*=0.004). We further stratified patients with high and low lymphocyte count by comorbidities (30-day OS: 100%, 82%, 80%, and 25%, *P*=0.003, for high lymphocyte count and no comorbidities, high lymphocyte count and some comorbidities, low lymphocyte count and no comorbidities, and low lymphocyte count and some comorbidities) (Figure 1B).

We suspected that the reduction in lymphocyte count was possibly caused by a certain factor, such as hematological toxicity of recent cytotoxic chemotherapy. Hence, we stratified patients with low lymphocyte count by whether they developed COVID-19 within the rest periods of cytotoxic chemotherapy or not. There was no significant difference between patients within the rest periods and other patients (30-day OS: 44% and 50%, *P*=0.75) (Figure 1C).

Outcomes in patients with active cancer

The clinical characteristics of 17 patients with active cancer are summarized in Supplementary Table 1. Seven patients received chemotherapy, while two patients received ICIs (nivolumab and pembrolizumab + ipilimumab) within 30 days before the onset of COVID-19. Four patients received continuous hormone therapy. Pembrolizumab treatment was discontinued in one patient with metastatic lung cancer more than 200 days before the onset of COVID-19. One patient experienced a relapse with liver metastases after remission induced by repeated chemotherapy and surgery for rectal cancer. Two patients had not been treated yet as they developed COVID-19 before cancer treatment.

Figure 2 shows the timeline of cancer treatment, illness onset, SARS-CoV-2 RNA detection, and death in this subgroup of patients. The longest period between illness onset and the first effective negative SARS-CoV-2 RT PCR result was 56 days in a patient who received bendamustine plus rituximab (BR) for Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma. Moreover, another patient who received BR for mantle cell lymphoma 17 days before the illness onset tested positive for the virus at 42 days after the onset and eventually died. One patient who received azacytidine for acute myeloid leukemia (AML) 10 days before the onset and showed severe pancytopenia at the onset progressed rapidly and died in one week. One patient with ALK-negative anaplastic large cell lymphoma (ALCL) who received brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisolone (A+CHP) 7 days prior to the onset of COVID-19 also died within 26 days. Among the four COVID-19 patients with hematological malignancy who developed COVID-19 within the rest periods of chemotherapy, three died and the other one had the longest duration of viral shedding among survivors. The two patients with AML and acute lymphocytic leukemia (ALL) had received induction and consolidation therapy, respectively. They both recovered from pancytopenia, remained in remission at the onset of COVID-19, and were eventually cured.

Two patients receiving ICIs within 30 days eventually improved and were discharged, although one of them had elevated CRP and ferritin levels on admission and was treated with high-flow nasal cannula oxygen therapy without glucocorticoid therapy.

Discussion

To our knowledge, this is the first study to report on COVID-19 patients with a history of cancer in Japan. The factors associated with mortality were similar to those reported in previous studies conducted on general patients with COVID-19, including lymphocytopenia on admission. Patients who received myelosuppressive chemotherapy recently or received lymphocyte-reducing chemotherapy, such as BR, were found to have a greater risk of mortality and prolonged viral shedding periods.

Lymphocytopenia is one of the frequently mentioned features of COVID-19 and correlates with clinical severity [15-17]. In the same way, T-cell count in peripheral blood is also significantly reduced and associated with high mortality rate [18-21]. Moreover, T-cells from COVID-19 patients have significantly higher expression levels of PD-1 and Tim-3, which suggests the surviving T-cell appear functionally exhausted [19]. These results imply that cellular immune response necessary for effective viral elimination is attenuated in COVID-19 patients. In our study, the detectable SARS-CoV-2 RNA persisted for a median of 22 days from the illness onset in survivors, which is almost the same as that reported in previous studies in general patients [22,23]. Interestingly, the virus was detectable for especially long duration in two patients who received BR, one of whom eventually died. This treatment is known to suppress cellular immunity and reduce lymphocyte count strongly compared with rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) [24,25]. Thus, BR makes cellular immune response much weaker, thus leading to the prolongation of viral shedding and poor outcomes. Likewise, highly myelosuppressive chemotherapy for hematological malignancy causes pancytopenia, and also lymphocytopenia as a matter of course, and can lead to severe COVID-19. Our finding showed that patients with low lymphocyte count had poor OS regardless of the presence or absence of recent cytotoxic agent administration (Figure 1C). However, recent cytotoxic chemotherapy may be an important adverse factor in COVID-19 patients as a cause of lymphocytopenia.

Some retrospective study did not show any significant association between recent cancer treatment and mortality, as with our study [9-12]. However, one retrospective study in China reported a higher likelihood of experiencing severe events in patients who received antitumor treatment within 14 days of COVID-19 diagnosis [5]. In this study, two patients who received cytotoxic chemotherapy within the rest periods (azacytidine for AML and A+CHP for ALK-negative ALCL) developed severe COVID-19 and eventually died. On the contrary, patients with AML and ALL, who recovered from pancytopenia and remained in remission at the onset of COVID-19 after intensive treatment, were cured. Therefore, the risk of developing severe COVID-19 must be considered in patients who received myelosuppressive chemotherapy recently.

One of the important aggravating mechanisms of COVID-19 is cytokine release syndrome [26,27]. Meanwhile, immune checkpoint inhibitors may also activate the immune system and cause cytokine release syndrome [28]. One retrospective study reported that immunotherapy within 90 days was an independent risk factor for hospitalization and severe disease in cancer patients [10]. In our study, two patients received immunotherapy within 30 days. One patient had elevated CRP and ferritin levels on admission and required high-flow nasal cannula oxygen therapy. However, they eventually recovered even without receiving glucocorticoids. Further study is needed to confirm the association between immunotherapy and mortality of COVID-19.

Coagulopathy is also one of the mechanisms that can exacerbate COVID-19. Patients with COVID-19 are at risk of thromboembolism, and an increase in the concentrations of circulating D-dimer indicates pulmonary vascular bed thrombosis with fibrinolysis [29]. Several studies reported that elevated D-dimer on admission predicted mortality [22,30,31]. Meanwhile, cancer patients are originally at high risk of venous thromboembolism [32,33]. Although one retrospective cohort study in New York showed the

association between D-dimer and mortality from COVID-19 in cancer patients [9], our study did not demonstrate a significant correlation between them. Determining the incidence of venous thrombosis in COVID-19 patients with cancer and interpreting the changes in D-dimer concentrations remain challenging.

This study has several limitations. First, this study was a retrospective, single center with a small sample size. Not all laboratory tests related to the prognosis of COVID-19, including albumin, serum ferritin, and D-dimer, were performed in all patients. We did not perform a multivariate analysis due to the lack of data and the small number of the study population. Second, the types of cancer and treatment were very heterogeneous in this study because we included all patients who had a history of cancer. Although it was difficult to draw a conclusive evidence from such a study population, our study provided new insight on the clinical features of COVID-19 patients with cancer. Future studies with a larger sample size are needed to further explore the risk factors for mortality in COVID-19 patients according to cancer or treatment types.

In conclusion, our study suggested that the risk factors for mortality previously reported in general COVID-19 patients, including lymphocytopenia, were also effective in cancer patients. Awareness on the risk of chemotherapy that leads to severe cytopenia or suppresses cellular immunity during the COVID-19 pandemic must be improved.

Declarations

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Competing interests

The authors declare no competing interests.

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Tables

Table 1. Characteristics and outcomes of patients with a history of cancer

	Total (n =32)	Survivors (n = 21)	Non-survivors (n = 11)	P values
al characteristics				
ange), years	74.5 (24–90)	72 (24–87)	76 (53–90)	0.38
> 70	20 (63%)	12 (57%)	8 (73%)	0.47
sex	22 (69%)	12 (57%)	10 (91%)	0.11
ng history (+)	20/29 (69%)	14/19 (74%)	6/10 (60%)	0.67
omorbidities	19 (59%)	10 (48%)	9 (82%)	0.13
betes	7 (22%)	4 (19%)	3 (27%)	0.67
ertension	13 (41%)	7 (33%)	6 (55%)	0.28
onary heart disease	4 (13%)	2 (10%)	2 (18%)	0.59
onic obstructive lung disease	4 (13%)	2 (10%)	2 (18%)	0.59
hma	2 (6%)	1 (5%)	1 (9%)	1
r diagnosis				0.67
natologic	7 (22%)	4 (19%)	3 (27%)	
Acute myeloid leukemia	2 (6%)	1 (5%)	1 (9%)	
Acute lymphocytic leukemia	1 (3%)	1 (5%)	0	
Anaplastic large cell lymphoma	1 (3%)	0	1 (9%)	
Mantle cell lymphoma	1 (3%)	0	1 (9%)	
B-cell lymphoma	1 (3%)	1 (5%)	0	
WM/LPL	1 (3%)	1 (5%)	0	
n-hematologic	25 (78%)	17 (81%)	8 (73%)	
Gastric cancer	5 (16%)	4 (19%)	1 (9%)	
Colorectal cancer	5 (16%)	4 (19%)	1 (9%)	
Prostatic cancer	3 (9%)	0	3 (27%)	
Esophageal cancer	2 (6%)	2 (10%)	0	
Lung cancer	2 (6%)	1 (5%)	1 (9%)	
Breast cancer	2 (6%)	2 (10%)	0	
Kidney cancer	2 (6%)	0	2 (18%)	
Cervical cancer	1 (3%)	1 (5%)	0	
Thymoma	1 (3%)	1 (5%)	0	
Hepatocellular carcinoma	1 (3%)	1 (5%)	0	
Skin cancer	1 (3%)	1 (5%)	0	
r treatment				
ration	13 (41%)	9 (43%)	4 (36%)	1
mone therapy	4 (13%)	2 (10%)	2 (18%)	0.59
motherapy	10 (31%)	7 (33%)	3 (27%)	1
nunotherapy	3 (9%)	2 (10%)	1 (9%)	1
motherapy/immunotherapy (within ≤30 days)	9 (28%)	6 (29%)	3 (27%)	1
treatment (within ≤30 days)	13 (41%)	8 (38%)	5 (46%)	0.72
r status				1
ow-up/Cured	12 (43%)	7 (41%)	5 (46%)	
ive cancer	17 (53%)	11 (52%)	6 (55%)	
s and laboratory findings on admission				
nonia on CT or X-ray	27 (84%)	16 (76%)	11 (100%)	0.14
blood cell count, $\times 10^9$ /L	5.6 (3.6–6.7)	5.4 (3.6–6.3)	5.7 (3.6–12.7)	0.38
ophil count, $\times 10^9$ /L	3.6 (2.4–4.5)	3.5 (2.4–4.1)	4.0 (2.2–11.3)	0.33
5	3 (9%)	1 (5%)	2 (18%)	0.23
hocyte count, $\times 10^9$ /L	1.0 (0.6–1.4)	1.1 (0.8–1.4)	0.6 (0.4–1.1)	0.057
8	13 (41%)	5 (24%)	8 (73%)	0.021
globin, g/dL	12.2 (10.8–13.6)	12.8 (10.9–14.4)	11.3 (10.6–12.9)	0.19
et count, $\times 10^{10}$ /L	20.5 (12.0–24.7)	21.2 (17.5–24.9)	15.3 (8.1–19.3)	0.074
inine, mg/dL	0.7 (0.6–1.0)	0.7 (0.6–0.9)	0.9 (0.7–1.7)	0.15
bilirubin, mg/dL	0.5 (0.4–0.7)	0.5 (0.4–0.6)	0.5 (0.4–0.8)	0.66
in, g/L	3.2 (2.8–3.6)	3.4 (3.1–3.6)	2.5 (2.1–3.3)	0.018
0	8/27 (30%)	2/17 (12%)	6/10 (60%)	0.025
te dehydrogenase, U/L	260.5 (196.3–368.3)	224 (185.0–291.0)	364 (246.0–418.5)	0.068
0	9 (28%)	3 (14%)	6 (55%)	0.035

n ferritin, μg/L	426.8 (148.8–1104.0)	280.5 (124.1–686.4)	1084.0 (615.8–1894.0)	0.029
0	9/25 (36%)	4/18 (22%)	5/7 (71%)	0.058
ctive protein, mg/dL	3.5 (0.8–8.6)	1.7 (0.2–4.9)	16.1 (4.4–24.0)	0.002
0	13 (41%)	5 (24%)	8 (73%)	0.021
er, μg/L	1.0 (0.7–2.5)	1.0 (0.7–2.3)	1.5 (0.8–4.5)	0.29
0	13/26 (50%)	9/18 (50%)	4/8 (50%)	1
ments for COVID-19				
ravir	22 (69%)	12 (57%)	10 (91%)	0.11
avir/ritonavir	2 (6%)	1 (5%)	1 (9%)	1
onide	5 (16%)	3 (14%)	2 (18%)	1
xychloroquine	3 (9%)	1 (5%)	2 (18%)	0.27
matic glucocorticoids	10 (31%)	3 (14%)	7 (64%)	0.013
mes				
from onset to admission, days	7 (4–8)	7 (4–7)	6 (4–8)	0.76
from onset to death, days			24 (15–26)	
from onset to negative PCR result, days		22 (18–25)		

Data are expressed as n (%), n/N (%), or median (IQR), unless specified otherwise. WM/LPL, Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma

Table 2. Univariable analysis for overall survivals

	Univariate analysis	
	Hazard ratio (95% CI)	*P* values
Age (>70)	1.80 (0.48–6.78)	0.37
Sex (male)	4.82 (0.62–37.73)	0.093
Smoking history (+)	0.55 (0.15–1.96)	0.34
Comorbidities (any)	3.93 (0.84–18.34)	0.057
Diabetes	1.60 (0.42–6.07)	0.48
Hypertension	2.15 (0.65–7.09)	0.19
Coronary heart disease	1.41 (0.30–6.54)	0.65
Chronic obstructive lung disease	1.64 (0.35–7.62)	0.52
Asthma	1.64 (0.21–13.14)	0.63
Cancer diagnosis (hematologic malignancy)	1.36 (0.36–5.13)	0.64
Cancer treatment (any treatment within ≤30 days)	1.31 (0.40–4.33)	0.65
Cancer status (active cancer)	1.16 (0.35–3.83)	0.80
Neutrophil count (<1.5), $\times 10^9$ /L	2.73 (0.59–12.67)	0.18
Lymphocyte count (<0.8), $\times 10^9$ /L	5.74 (1.50–21.92)	0.004
Albumin (<3.0), g/L	5.32 (1.47–19.21)	0.004
Lactate dehydrogenase (>350), U/L	4.40 (1.33–14.63)	0.008
Serum ferritin (>800), μg/L	6.12 (1.18–31.79)	0.014
C-reactive protein (>5.0), mg/dL	5.82 (1.53–22.09)	0.010
D-dimer (>1.0), μg/L	1.10 (0.27–4.38)	0.90

CI, confidential interval

Figures

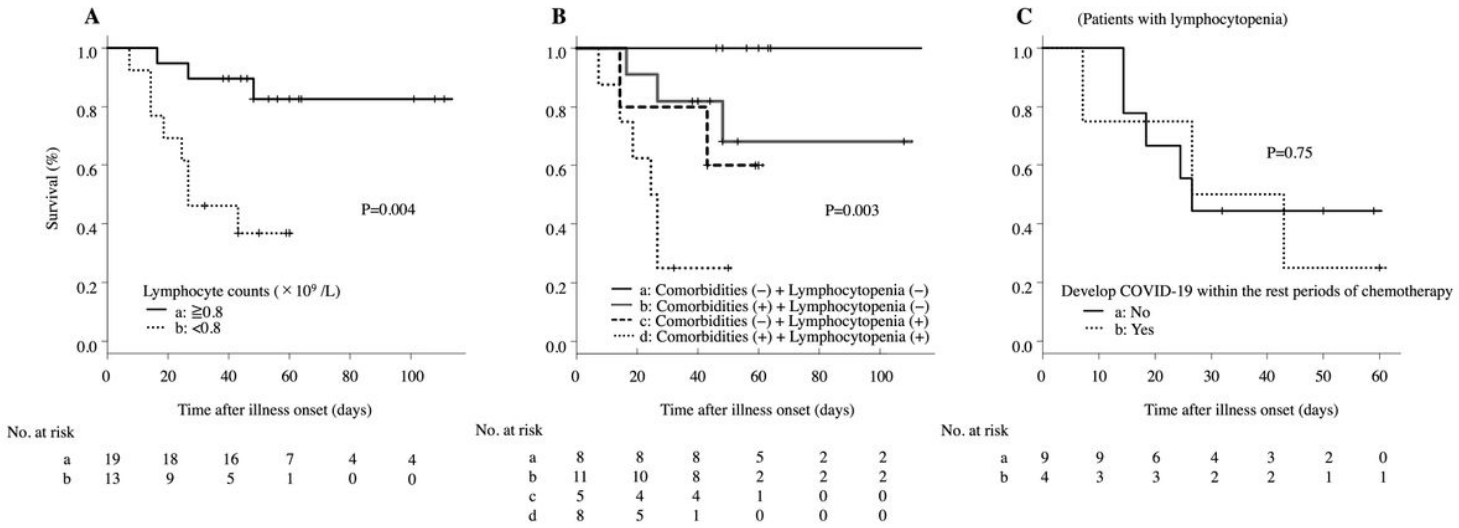

Figure 1

Kaplan-Meier survival curves stratified by lymphocyte count, and lymphocyte count and comorbidities in all patients (A and B) and further stratified patients with low lymphocyte count by whether they developed COVID-19 within the rest periods of chemotherapy or not (C)

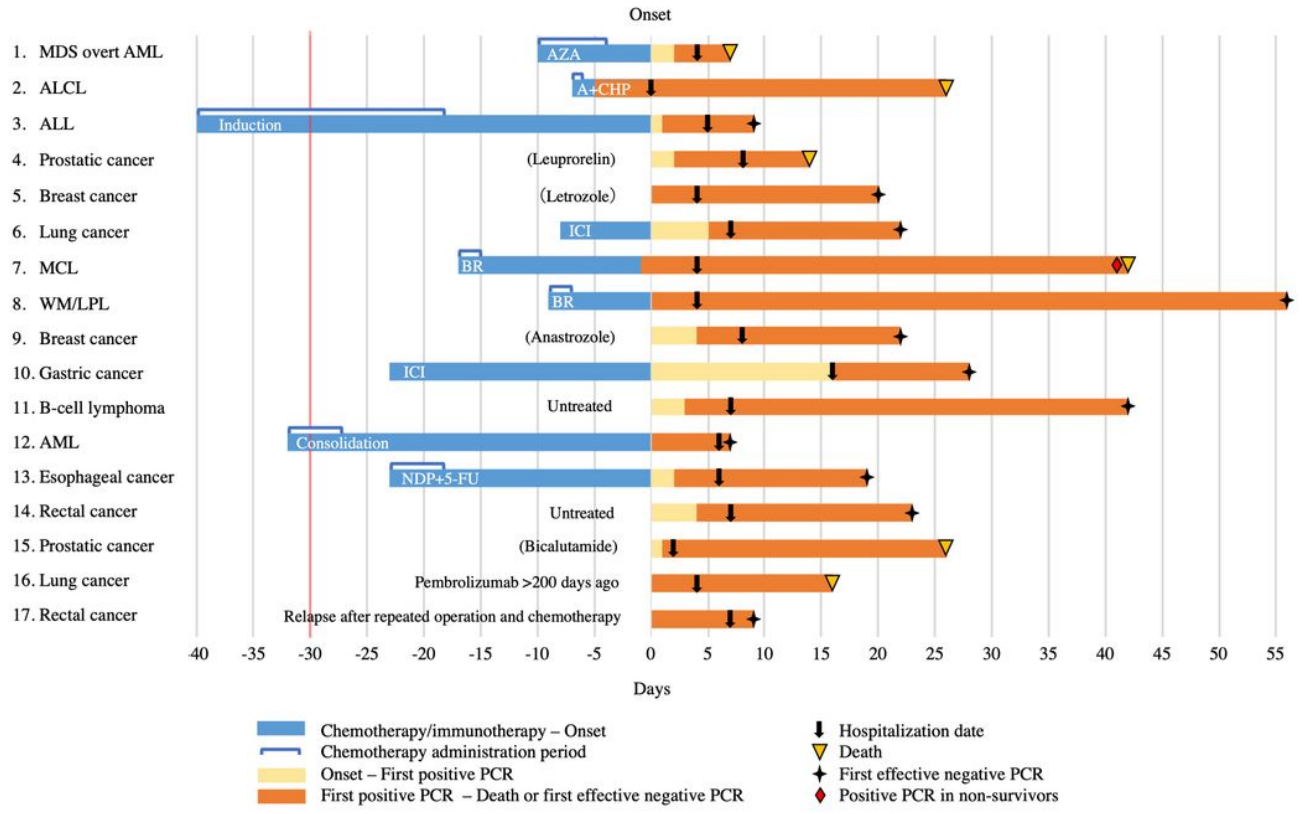

Figure 2

Timeline of treatment for cancer, illness onset, SARS-CoV-2 RNA detection, and death in patients with active cancer. MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; ALCL, anaplastic large cell lymphoma; ALL, acute lymphocytic leukemia; MCL, mantle cell lymphoma; WM/LPL, Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma; AZA, azacytidine; A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisolone; ICI, immune checkpoint inhibitors, BR, bendamustine plus rituximab, NDP + 5-FU, nedaplatin and 5-fluorouracil

Supplementary Files

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- supplementarytable1.docx