A Single Center Retrospective Study of the Impact of COVID-19 Infection on Immune-related Adverse Events in Cancer Patients Receiving Immune Checkpoint Inhibitors

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Summary: Immune checkpoint inhibitors (ICIs) can cause a variety of immune-related adverse events (irAEs). The coronavirus disease 2019 (COVID-19) is associated with increased amounts of pro-inflammatory cytokines, which may affect the outcome of irAEs. Data are limited regarding the impact of COVID-19 on irAEs in ICI-treated cancer patients. Hence, in this study, we retrospectively analyzed ICI-treated adult patients with malignant solid tumors at a single institution between August 2020 and August 2021. Patients who had the most recent ICI treatment over 1-month before or after the positive COVID-19 test were excluded from the study. For the COVID-19 positive group, only the irAEs that developed after COVID-19 infection were considered as events. A total of 579 patients were included in our study, with 46 (7.9%) in the COVID-19 positive group and 533 (92.1%) in the COVID-19 negative group. The baseline characteristics of patients in the 2 groups were similar. With a median follow-up of 331 days (range: 21–2226), we noticed a nonsignificant higher incidence of all-grade irAEs in the COVID-19 positive group (30.4% vs. 19.9%, $P = 0.18$). The incidence of grade 3 and 4 irAEs was significantly higher in the COVID-19 positive group (10.9% vs. 3.2%, $P = 0.02$). Multivariate analysis confirmed the association between COVID-19 infection and increased risk of severe irAE development (odds ratio: 1.08, 95% confidence interval: 1.02–1.14, $P = 0.01$). Our study suggested that COVID-19 may pose a risk of severe irAEs in cancer patients receiving ICIs. Close monitoring and possibly delaying ICI administration could be considered when cancer patients are infected with COVID-19.

Key Words: COVID-19, immune checkpoint inhibitor, immune-related adverse events, cancer, immunosuppressant

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The coronavirus disease 2019 (COVID-19) has rapidly spread worldwide and brought about a significant burden on the global economy and health, posing challenges in all aspects of healthcare. A higher risk of developing severe symptoms and worse outcomes from COVID-19 infection is seen in the older population and those with comorbidities, including chronic lung disease, cardiovascular conditions, obesity, and cancers.

Immune checkpoint inhibitors (ICIs) are a type of cancer immunotherapy that target several immune checkpoint proteins, promoting T cells to fight against cancer cells. The ICIs have demonstrated robust anti-tumor activity and revolutionized the management of various types of cancers. Despite their favorable oncological outcomes, ICIs have been associated with multiple inflammation-induced autoimmune tissue damages, referred to as immune-related adverse events (irAEs). The irAEs can involve almost every organ system with different frequencies and timing of onset. Varying in severity, they are often mild to moderate; however, they can sometimes be severe and even fatal.

Data regarding the impact of COVID-19 on cancer patients receiving ICIs are limited and conflicting. The ICIs may enhance anti-viral immune response, positively affecting the trajectory of COVID-19 infection in cancer patients.[1,2] On the other hand, COVID-19 infection is associated with increased amounts of pro-inflammatory cytokines. Cytokine release syndrome (CRS) is characterized by increased levels of interferon (IFN)-γ, interleukin-6 (IL-6), and other cytokines, leading to immune hyperactivation. The CRS has been reported in patients receiving ICIs and in COVID-19 infections.[3–7] The anti-IL-6 receptor (anti-IL-6R) agent tocilizumab can be used to treat the CRS induced by either ICIs or COVID-19. On theoretical grounds, ICIs and COVID-19 infection could simultaneously promote adverse immune hyperactivation, potentially resulting in an increase in irAEs. Conversely, ICI-induced irAEs often require immunosuppressive therapies, which may hamper the immune response against the virus, in turn leading to an increased risk and a severe course of COVID-19 infection.

To date, few data are available regarding irAEs in cancer patients who were infected with COVID-19 while being treated with ICIs. The association between COVID-19 infection and outcomes of cancer patients receiving ICIs has yet to be further evaluated. This retrospective study aimed

to investigate the impact of COVID-19 on irAEs in ICI-treated cancer patients.

METHODS

This retrospective, single-center study was approved by the Institutional Review Board at AdventHealth Orlando. We reviewed all adult cancer patients who received at least 1 cycle of ICI [programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1)/cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibitors] either as monotherapy or as multi-agent therapy at our infusion center between August 1, 2020 and August 31, 2021. Patients were tested for COVID-19 periodically per our institutional policy. Eligible patients were divided into 2 groups, those who were tested positive for COVID-19 (COVID-19 positive group) and those who were tested negative (COVID-19 negative group). For the COVID-19 positive group, only patients who had ICI treatment within 1 month before or after the positive COVID-19 tests were included, and only the irAEs that happened after COVID-19 infection were considered as events. For the COVID-19 negative group, all irAEs documented were considered as events. If a patient has multiple irAEs, only the highest grade of irAEs was considered an event. Patients without oncology follow-up visit notes after the initiation of ICI therapy were excluded. All COVID-19 infections were confirmed by reverse transcription polymerase chain reaction (RT-PCR) test.

We collected data regarding patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status score at the time of ICI initiation, cancer histology, ICI therapy-related data, irAE-related data, and survival outcomes related to COVID-19 infection and irAEs. The Common Terminology Criteria of Adverse Events (version 5.0) was used to grade irAE at its peak severity. The time to irAE was defined as the time between the start of ICI therapy to the onset of the initial irAE. The time to COVID-19 infection was defined as the time between the start of ICI therapy to the day of the positive COVID-19 test. The censor date was set as December 31, 2021.

Statistical Analyses

Differences between the COVID-19 positive and COVID-19 negative groups were analyzed using Student t test for continuous variables and Fisher exact test, or χ^2 test for categorical variables, as applicable. Univariate and multivariate logistic regression models were used to identify the risk factors associated with irAEs. The P-values in univariate analysis were adjusted using the Benjamini-Hochberg method. Akaike information criterion selection method was used for variable selection in multivariate analysis. Odds ratio (OR) and associated 95% confidence interval (CI) were reported. All P-values were 2-tailed, and $P < 0.05$ was considered statistically significant. All analyses were done using GraphPad Prism and R version 4.0 software.

RESULTS

Patients' Basic Characteristics

After excluding 17 patients with no follow-up notes, 590 patients were further investigated. In total, 57 patients were tested positive for COVID-19 between April 2020 and November 2021, of which 11 patients were excluded because of longer than 1-month duration between the most recent ICI cycle and COVID-19 test. Finally, a total of 579 patients were included in our study, with 46 patients (7.9%) in the COVID-19 positive group and 533 patients (92.1%) in the COVID-19 negative group (Fig. 1).

Patient demographics are shown in Table 1. For the entire cohort, the median patient age was 67 years (range: 24–98), and 49.2% were male. The most common cancer type was non–small cell lung cancer (31.4%), followed by renal cell carcinoma (8.1%), melanoma (7.3%), and urothelial cancer (5.7%). Most patients received PD-1 inhibitors including pembrolizumab (61.3%) and nivolumab (13.6%), followed by PD-L1 inhibitor atezolizumab (14.2%). The baseline characteristic of patients in the 2 groups were similar in terms of age, ethnicity, ECOG performance status, cancer histology, and type of ICI. We found a higher proportion of female patients in the COVID-positive group (67.4% vs. 49.3%, $P = 0.03$).

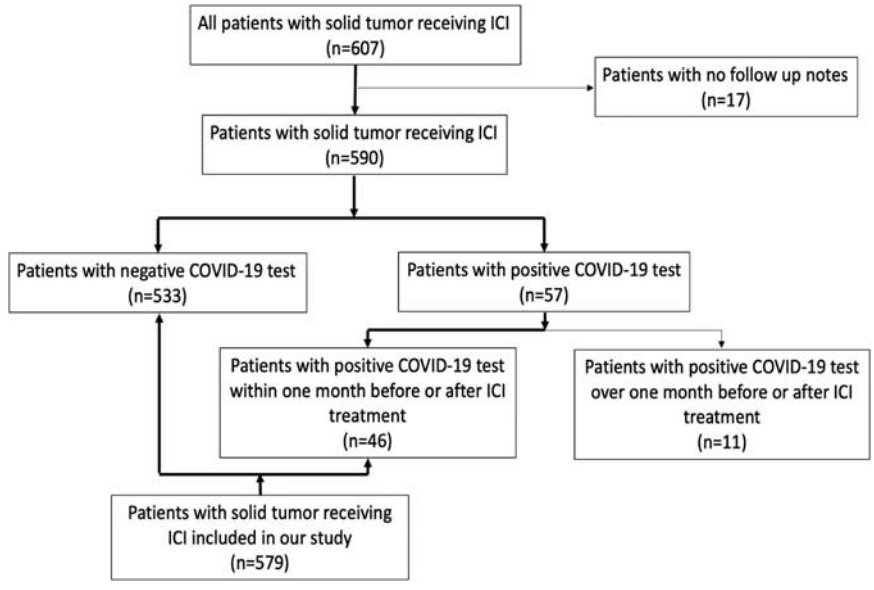

FIGURE 1. Flow diagram of the patient cohort. COVID-19 indicates coronavirus disease 2019; ICI, immune checkpoint inhibitor.

TABLE 1. Basic Characteristics of Patients for the Entire Study Cohort

Variable	COVID-19 Positive (n = 46)	COVID-19 Negative (n = 533)	*P*
Age, median (range), y	67.5 (41–91)	66 (18–98)	0.18
Sex, n (%)	—	—	0.03
Male	15 (32.6)	270 (50.7)	
Female	31 (67.4)	263 (49.3)	
Ethnicity, n (%)	—	—	0.80
White	35 (76.1)	390 (73.2)	
African American	3 (6.5)	62 (11.6)	
Other	8 (17.4)	81 (15.2)	
ECOG score, n (%)			0.35
0–1	45 (97.8)	495 (92.9)	
2 and beyond	1 (2.2)	38 (7.1)	
Cancer type, n (%)			0.62
NSCLC	16 (34.8)	166 (31.1)	
Renal cell carcinoma	3 (6.5)	44 (8.2)	
Melanoma	2 (4.3)	40 (7.5)	
Urothelial cancer	3 (6.5)	30 (5.6)	
Head and neck cancer	0 (0.0)	27 (5.1)	
Hepatocellular carcinoma	4 (8.7)	27 (5.1)	
Small cell lung cancer	1 (2.2)	27 (5.1)	
Endometrial cancer	5 (10.9)	25 (4.7)	
Cervical cancer	2 (4.3)	20 (3.7)	
Breast cancer	2 (4.3)	17 (3.2)	
Uterine carcinoma	3 (6.5)	11 (2.1)	
Colorectal cancer	1 (2.2)	11 (2.1)	
Ovarian cancer	1 (2.2)	11 (2.1)	
Gastric cancer	2 (4.3)	10 (1.9)	
Esophageal cancer	0 (0.0)	10 (1.9)	
Lymphoma	0 (0.0)	8 (1.5)	
Prostate cancer	0 (0.0)	8 (1.5)	
Anal cancer	0 (0.0)	5 (0.9)	
Cholangiocarcinoma	0 (0.0)	4 (0.7)	
Others	1* (2.2)	32† (6.0)	
Type of ICI, n (%)			0.42
Pembrolizumab	29 (63.0)	326 (61.2)	
Atezolizumab	5 (10.9)	77 (14.4)	
Nivolumab	6 (13.0)	73 (13.7)	
Durvalumab	3 (6.5)	37 (6.9)	
Ipilimumab + Nivolumab	3 (6.5)	20 (3.8)	

*Includes small cell carcinoma of the bladder.

†Includes ampullary adenocarcinoma, carcinosarcoma, duodenal carcinoma, esophageal cancer, fallopian tube cancer, gallbladder cancer, glioblastoma multiforme, neuroendocrine carcinoma, metastatic cancer with unknown primary, mesothelioma, sarcoma, small cell carcinoma, thymic carcinoma, and vulvar squamous cell carcinoma.

ECOG indicates Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; NSCLC, non–small cell lung cancer.

In the COVID-19 positive group, 4 patients (8.7%) received the first cycle of ICI after the positive COVID-19 test, 31 (67.4%) were tested positive in between 2 cycles of ICI with the most recent cycle within 1 month of the positive test, and 11 (23.9%) had ICI discontinued right after COVID-19 infection with the last cycle of ICI infused before their positive tests. Of the 11 patients who discontinued ICI right after COVID-19 infection, 9 (81.8%) patients had ICI cessation because of COVID-19 infection, while 2 (18.2%) cessations were related to irAEs.

irAEs in the Entire Cohort

For the entire cohort, the median duration of follow-up since the initiation of ICI therapy was 331 days (range: 21–2226). The median duration of ICI treatment was 220 days (range: 14–2267), and 10 cycles (range: 1–103). Among the 579 patients, 120 patients (20.7%) developed irAEs of any grade, with grade 1–2 irAEs observed in 98 patients (16.9%), and grade 3–4 irAEs in 22 patients (3.8%). No irAE-related death was observed, while 9 COVID-19-related death occurred. The median time to the irAE onset was 157.5 days (range: 7–1662), and 6 cycles (range: 1–72). The most common irAEs were dermatitis/rash, which occurred in 37 patients (6.4%), followed by colitis/diarrhea in 20 patients (3.6%), hepatitis in 8 (1.4%), and pneumonitis in 7 (1.2%) patients. Of the 120 patients with irAEs, 61 (50.8%) required systemic corticosteroid treatment for the irAEs, and 4 (3.3%) cases required additional immunosuppressive treatment, including tumor necrosis factor-α inhibitor and intravenous immune globulin.

TABLE 2. Clinical Features of the Immune-related Adverse Events (irAEs) Between the Coronavirus Disease 2019 (COVID-19) Positive and COVID-19 Negative Groups of Patients

Variables	irAE in COVID-19 Positive (n = 14)	irAE in COVID-19 Negative (n = 106)	*P*
Corticosteroid use, n (%)			0.78
Yes	8 (57.1)	60 (56.6)	
No	6 (42.9)	46 (43.4)	
Route of corticosteroid, n (%)			1.00
Intravenous	1 (7.1)	7 (6.6)	
Oral	7 (50.0)	46 (43.4)	
Use of additional immunosuppressant, n (%)			1.00
Yes	0 (0.0)	4* (3.8)	
No	14 (100.0)	102 (96.2)	
Time to irAE, median (range)			
Treatment cycle	6 (2–72)	6 (1–56)	0.54
Days	255.5 (48–1662)	153.5 (7–1415)	0.25
Death related to irAE, n (%)			1.00
Yes	0 (0.0)	0 (0.0)	
No	14 (100.0)	106 (100.0)	

*Two patients with grade 3 colitis required infliximab treatment, 1 patient with grade 3 encephalitis and another patient with grade 3 Guillain-Barré Syndrome required intravenous immune globulin (IVIG) treatment.

Of the 120 irAEs cases among the entire study cohort, 14 occurred in the COVID-19 positive group, while 106 occurred in the COVID-19 negative group. Between the 2 groups, no differences in the types of irAEs, the time to irAE, corticosteroid use, or additional immunosuppressant use for irAEs were observed (Tables 2, 3). We noticed a higher but nonsignificant incidence of all-grade irAEs in the COVID-19 positive group (30.4% vs. 19.9%, $P = 0.18$). The incidence of grade 3 and 4 irAEs was significantly higher in the COVID-19 positive group (10.9% vs. 3.2%, $P = 0.02$). A trend in a higher incidence of all-grade diarrhea/colitis (8.7% vs. 3.0%, $P = 0.07$) and grade 3–4 hepatitis (4.3% vs. 0.8%, $P = 0.08$) was noted in the COVID-19 positive group; however, the difference was not statistically significant. No significant difference in the incidence of pneumonitis (2.2% vs. 1.1%, $P = 0.44$), nephritis (2.2% vs. 0.8%, $P = 0.34$), or dermatitis (6.5% vs. 6.4%, $P = 1.00$) were noted between the COVID-19 positive and negative groups cases (Table 3).

irAEs in the COVID-19 Positive Group

Of the 14 patients (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JIT/A688)

TABLE 3. Type and Grade of the Immune-related Adverse Events (irAEs) in Patients With or Without COVID-19 Infection

Variables	Entire Cohort (n = 579)	COVID-19 Positive Group (n = 46)	COVID-19 Negative Group (n = 533)	*P*
Total irAEs, n (%)				
All grades	120 (20.7)	14 (30.4)	106 (19.9)	0.18
Grade 3/4	22 (3.8)	5 (10.9)	17 (3.2)	0.02
Type of irAE All grades, n (%) [grade 3/4, n (%)]				
Colitis/diarrhea	20 (3.6)/4 (0.7)	4 (8.7)/1 (2.2)	16 (3.0)/3 (0.6)	0.07/0.28
Dermatitis/rash	37 (6.4)/1 (0.2)	3 (6.5)/0 (0.0)	34 (6.4)/1 (0.2)	1.00/1.00
Hepatitis	8 (1.4)/6 (1.0)	2 (4.3)/2 (4.3)	6 (1.1)/4 (0.8)	0.13/0.08
Pneumonitis	7 (1.2)/2 (0.3)	1 (2.2)/1 (2.2)	6 (1.1)/1 (0.2)	0.44/0.15
Nephritis	5 (0.9)/3 (0.5)	1 (2.2)/1 (2.2)	4 (0.8)/2 (0.4)	0.34/0.22
Hypothyroidism	17 (2.9)/0 (0.0)	1 (2.2)/0 (0.0)	16 (3.0)/0 (0.0)	1.00/1.00
Adrenal insufficiency	4 (0.7)/0 (0.0)	1 (2.2)/0 (0.0)	3 (0.6)/0 (0.0)	0.28/1.00
Ocular toxicity	1 (0.2)/0 (0.0)	1 (2.2)/0 (0.0)	0 (0.0)/0 (0.0)	0.08/1.00
Arthritis/arthralgia	7 (1.2)/0 (0.0)	0 (0.0)/0 (0.0)	7 (1.3)/0 (0.0)	1.00/1.00
Myositis/myalgia	3 (0.5)/1 (0.2)	0 (0.0)/0 (0.0)	3 (0.6)/1 (0.2)	1.00/1.00
Encephalitis	3 (0.5)/2 (0.3)	0 (0.0)/0 (0.0)	3 (0.6)/2 (0.4)	1.00/1.00
Pancreatitis	1 (0.2)/0 (0.0)	0 (0.0)/0 (0.0)	1 (0.2)/0 (0.0)	1.00/1.00
Hematologic disorder	1 (0.2)/1 (0.2)	0 (0.0)/0 (0.0)	1 (0.2)/1 (0.2)	1.00/1.00
Hyperthyroidism	2 (0.3)/0 (0.0)	0 (0.0)/0 (0.0)	2 (0.4)/0 (0.0)	1.00/1.00
Hypophysitis	1 (0.2)/0 (0.0)	0 (0.0)/0 (0.0)	1 (0.2)/0 (0.0)	1.00/1.00
Peripheral neuropathy	1 (0.2)/0 (0.0)	0 (0.0)/0 (0.0)	1 (0.2)/0 (0.0)	1.00/1.00
GBS	1 (0.2)/1 (0.2)	0 (0.0)/0 (0.0)	1 (0.2)/1 (0.2)	1.00/1.00
Pericarditis	1 (0.2)/1 (0.2)	0 (0.0)/0 (0.0)	1 (0.2)/1 (0.2)	1.00/1.00

COVID-19 indicates coronavirus disease 2019; GBS, Guillain-Barré syndrome.

who developed irAEs after COVID-19 infection, the median time from COVID-19 diagnosis to irAE onset was 123.5 days (range: 8–314). The median time from last ICI treatment to COVID-19 diagnosis was 0 days (range: −30–28), with 8 patients receiving ICI treatment on the same day of COVID-19 diagnosis. Two patients had a history of grade 1 dermatitis/rash before their COVID-19 infection, then developed de-novo grade 1 colitis/diarrhea and grade 2 hypothyroidism after COVID-19 infection, respectively. One patient developed concomitant grade 2 colitis and grade 2 hepatitis after COVID-19 infection. There was 1 grade 2 ocular toxicity manifesting as diplopia which was improved after intravenous steroid treatment.

Depending on whether immunosuppressant was used for the management of COVID-19 infection, we further divided the 46 patients in the COVID-19 positive group into immunosuppressant-treated group (n = 13, 28.3%) and non–immunosuppressant-treated group (n = 33, 71.7%). The basic patient characteristics were similar between the 2 subgroups in terms of age, sex, ethnicity, ECOG score, and ICI type (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/JIT/A689). The time to COVID-19 infection was also comparable between the 2 subgroups. We found a nonsignificantly lower incidence of all-grade irAEs (15.4% vs. 36.4%, $P = 0.29$) but a significantly higher incidence of COVID-19-related death (46.1% vs. 9.1%, $P = 0.01$) among patients who received immunosuppressive treatment for COVID-19 infection.

Risk Factors Associated With irAEs

As reported in Table 4, in univariate analysis, male gender (OR: 1.63, 95% CI: 1.08–2.45, $P = 0.02$) and combination therapy with ipilimumab and nivolumab (OR: 12.10, 95% CI: 4.16–35.20, $P < 0.0001$) were associated with increased risk of developing irAEs of any grade. However, no significant association between COVID-19 infection and all-grade irAEs was found (OR: 1.58, 95% CI: 0.81–3.12, $P = 0.18$). Multivariate analysis confirmed that combination therapy was an independent risk factor associated with all-grade irAEs (OR: 1.67, 95% CI: 1.39–2.01, $P < 0.0001$). In univariate analysis, COVID-19 infection (OR: 3.70, 95% CI: 1.30–10.54, $P = 0.01$) and melanoma (OR: 4.54, 95% CI: 1.41–14.63, $P = 0.03$) were all associated with the development of severe irAEs. The effect of COVID-19 infection on severe irAEs remained significant in multivariate analysis (OR: 1.08, 95% CI: 1.02–1.14, $P = 0.01$).

DISCUSSION

In the past decade, ICIs have revolutionized cancer treatment. With an increasing rise in the use of ICIs across the cancer spectrum, a corresponding rise in irAEs follows. IrAEs are diverse and driven by several components of the immune system. Immune dysregulation is the basis of irAEs. irAEs occurred because of ICI-induced immune system activation against not only tumor cells but also self-antigens, which results in normal tissue injury.[8] By blocking the inhibitory immune checkpoints that inhibit anti-tumor immune responses and simultaneously limit autoimmunity, ICIs disrupt immune homeostasis, potentially leading to varied autoimmune events.[9] Possible mechanisms of irAEs include increased pro-inflammatory cytokine levels, T-cell infiltration into normal tissues, B-cell mediated autoantibodies, direct molecular mimicry, and influence of environmental factors such as microbiome on the immune system.[8–10] Meanwhile, the severity of COVID-19 infection is attributable to both direct viral damage and immune dysregulation. This immune dysregulation can result in excessive inflammatory response, leading to high levels of pro-inflammatory cytokines, which can result in the development of CRS in severe uncontrolled situations.[1] The CRS has also been described as a rare irAE. Thus, the coexistence of COVID-19 infection and irAE may pose a potential mutual and dangerous interaction to cancer patients. Consequently, when facing cancer patients infected

TABLE 4. Univariate and Multivariate Analyses for Risk Factors Associated With irAEs

	All-grade irAEs			
	Univariate		Multivariate	
Variate (Comparator)	**OR (95% CI)**	***P****	**OR (95% CI)**	***P***
Age ≥65 y	0.94 (0.62–1.40)	0.75	—	—
Male sex	1.63 (1.08–2.45)	0.02	1.06 (0.99–1.13)	0.11
Cancer type (vs. breast cancer)				
Lung cancer	2.34 (0.52–10.50)	0.54	—	—
Melanoma	5.78 (1.18–28.33)	0.20	—	—
Renal cell carcinoma	4.82 (0.99–23.42)	0.20	—	—
Gastrointestinal cancer	1.01 (0.18–5.73)	0.99	—	—
Genitourinary cancer	0.59 (0.11–3.31)	0.63	—	—
Hepatic cell carcinoma	2.04 (0.37–11.33)	0.63	—	—
Head and neck cancer	1.84 (0.32–10.69)	0.63	—	—
Other	2.53 (0.50–12.67)	0.54	—	—
ECOG score ≥2	0.69 (0.28–1.68)	0.41	—	—
ICI type (vs. atezolizumab)				
Pembrolizumab	1.5 (0.75–2.99)	0.33	1.08 (0.98–1.19)	0.12
Nivolumab	1.90 (0.84–4.34)	0.26	1.09 (0.97–1.24)	0.16
Durvalumab	1.61 (0.59–4.39)	0.35	1.07 (0.92–1.25)	0.40
Ipilimumab + Nivolumab	12.10 (4.16–35.20)	<0.0001	1.67 (1.39–2.01)	<0.0001
COVID–19 infection	1.58 (0.81–3.12)	0.18	—	—
Severe irAEs				
Age ≥65 y	0.97 (0.94–1.00)	0.08	0.98 (0.95–1.01)	0.22
Male sex	1.03 (0.44–2.42)	0.94	—	—
Cancer type (vs. other types)				
Lung cancer	1.14 (0.41–3.20)	0.80	—	—
Melanoma	4.54 (1.41–14.63)	0.03	—	—
Renal cell carcinoma	1.50 (0.31–7.27)	0.80	—	—
ECOG score ≥2	0.65 (0.09–4.07)	0.68	—	—
ICI type (vs. atezolizumab)				
Pembrolizumab	0.84 (0.23–3.09)	0.80	0.99 (0.95–1.04)	0.75
Nivolumab	0.68 (0.11–4.21)	0.80	0.99 (0.93–1.05)	0.68
Durvalumab	1.39 (0.22–8.64)	0.80	1.01 (0.94–1.09)	0.69
Ipilimumab + Nivolumab	5.54 (1.14–26.87)	0.12	1.14 (1.04–1.24)	0.005
COVID–19 infection	3.70 (1.30–10.54)	0.01	1.08 (1.02–1.14)	0.01

*A Benjamini-Hochberg *P*–value adjustment was done.

CI indicates confidence interval; COVID–19, Coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; irAEs, immune–related adverse events; OR, odds ratio.

with COVID-19, clinicians are confronted with a dilemma of whether to continue or postpone ICI treatment.

On theoretical grounds, the potential overlapping immunologic enhancement of COVID-19 infection and ICI therapy could result in an increase in irAEs. In our study, the incidence of all-grade irAEs in the COVID-19 positive group was higher compared with the COVID-19 negative group (30.4% vs. 19.9%), but this was not statistically significant ($P = 0.13$). This finding could be partially explained by the fact that we only considered irAEs that occurred after COVID-19 infection as events in the COVID-19 positive group, as the goal of the study was to evaluate events potentially triggered by COVID-19 infection, while all the irAEs that ever occurred were included in the COVID-19 negative group, which could underestimate the total incidence of irAEs in the COVID-19 positive group.

In our study, 13 of the 46 COVID-19 infected patients had severe symptoms requiring immunosuppressant treatment. Compared with those who did not require treatment for COVID-19 infection, the patients who received immunosuppressants had a nonsignificantly lower incidence of all-grades irAEs (15.4% vs. 36.4%, $P = 0.29$). As immunosuppressant is usually used in severe COVID-19 cases, it is not surprising to see a high mortality rate in this subgroup, with 6 of 13 (46.2%) patients dying from COVID-19 infection. This COVID-19-related mortality may also lower the incidence of irAEs in the COVID-19 positive group since some patients may have died too soon to allow any irAE to occur. Mandala et al[11] conducted a prospective study evaluating the impact of COVID-19 infection on the outcomes of 293 consecutive asymptomatic and paucisymptomatic cancer patients receiving either ICI, chemotherapy, or targeted therapies. Of the 159 patients treated with ICIs, 52 patients (32.7%) were infected with COVID-19. In their study, all types of adverse events (AEs), including hypertension, bacterial infection, and COVID-19 pneumonitis, were investigated. Compared with patients without COVID-19 infection, the authors found the incidence of AEs was not increased in the COVID-19 positive group treated with either ICIs, chemotherapy, or targeted therapy ($P = 0.22$), and there was no apparent increased risk of irAEs in the COVID-19 infected patients.

A significantly higher incidence of severe irAEs was noted in the COVID-19 group (10.9% vs. 3.2%, $P = 0.02$), and the effect of COVID-19 infection remained significant

after multivariate adjustment, which supports the hypothesis that COVID-19 infection and ICI use may have a synergistic effect, leading to severe irAEs. The association of COVID-19 infection with the development of severe irAEs was further confirmed in univariate and multivariate logistic regression analyses. Also, our study showed a higher but not statistically significant trend of all-grade immune-related diarrhea/colitis and grade 3–4 immune-related hepatitis in the COVID-19 positive group, which suggested that ICI-treated cancer patients may be more prone to develop irAEs involving the gastrointestinal system after COVID-19 infection.

Immune-related pneumonitis represents a potentially life-threatening irAE. The reported incidence ranges from 2.7% to 19%, and it occurs more commonly in lung cancer patients.[12–18] Clinically, cough and dyspnea often appear in both immune-related pneumonitis and COVID-19 pneumonia. Radiologic features of immune-related pneumonitis are not pathognomonic. Imaging findings can be stratified into 5 distinct groups, among which the commonly reported pattern is peripheral or peribronchial ground-glass or consolidative opacities.[19] Meanwhile, ground-glass opacities are also the typical image finding of COVID-19 pneumonia.[20] Thus, differentiating between immune-related pneumonitis and COVID-19 pneumonia could be challenging. Even though COVID-19 infection can be ascertained by RT-PCR and serological tests, concomitant immune-related pneumonitis cannot be excluded. COVID-19 infection may mask the symptoms of immune-related pneumonitis. In our study, no difference was noted in the incidence of all-grade or grade 3–4 immune-related pneumonitis between the COVID-19 positive and negative groups ($P = 0.44$ and 0.15, respectively). In theory, concomitant COVID-19 infection and ICI therapy may have a synergy in lung injury. This hypothesis is consistent with our study finding that out of the 46 patients infected with COVID-19, 9 (19.6%) COVID-19 pneumonia-related death occurred. This is in accordance with the study carried out by Mandala et al,[11] in which severe adverse events were more frequent in the COVID-19 positive group receiving ICI and chemotherapy ($P = 0.001$), and the increase in severe adverse events was because of pneumonitis. On the other hand, COVID-19 infection may augment the risk of immune-related pneumonitis. However, we only noted 1 immune-related pneumonitis in the COVID-19 positive group. Because of the overlapping clinical and radiologic characteristics, we could not rule out the possibility of concomitant immune-related pneumonitis in these patients.

This study has several limitations. First, as it was a single-center retrospective study, some low-grade irAEs with no intervention required may be under-reported. Second, the sample size of the COVID-19 infected population was relatively small. Third, our study included various types of solid tumor treated with different types of ICIs. This heterogeneity may affect the incidence patterns of irAEs as it is well-known that the incidence of irAEs may vary significantly by ICI type,[8] with colitis and hepatitis more commonly seen in CTLA4 inhibitor and pneumonitis and thyroid dysfunction more common in PD-1/PD-L1 inhibitors. Moreover, COVID-19 patients may have false negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR results,[21–23] especially in asymptomatic patients, which may underestimate the true sample size of COVID-19 infected patients in our study. Finally, our study did not answer the question of whether patients with a past history of irAE are more prone to have a de-novo or recurrent irAE post-COVID-19 infection. Larger prospective studies with a longer follow-up period are needed to further evaluate the interaction of COVID-19 infection with ICIs.

CONCLUSIONS

In summary, our study is the first attempt to solely evaluate the impact of COVID-19 infection on the incidence and severity of irAEs in cancer patients receiving ICI therapy. Our result suggests that COVID-19 infection may pose a risk of severe irAEs in ICI-treated cancer patients. It is important to increase the vigilance of COVID-19 infection among this patient population. Close monitoring and possibly delaying ICI administration could be considered when cancer patients are infected with COVID-19.

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

None reported. All authors have declared there are no financial conflicts of interest with regard to this work.

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