Immune checkpoint inhibitors use and effects on prognosis of COVID-19 infection: A systematic review and meta-analysis

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Systematic Review

Keywords: Immune checkpoint inhibitor, COVID-19, Prognosis, Meta-analysis

Posted Date: September 23rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-82103/v1>

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Version of Record: A version of this preprint was published at Immunotherapy on August 25th, 2021. See the published version at <https://doi.org/10.2217/imt-2021-0007>.

Abstract

Background: The influence of prior exposure to immune checkpoint inhibitors (ICIs) on the coronavirus disease 2019 (COVID-19) infection remains unknown.

Methods: We searched the PubMed, Embase, and Web of Science databases from the inception of each database through August 8, 2020. We included studies that reported ICI use in cancer patients and their prognosis in the context of COVID-19. Raw data from the included studies were pooled to determine effect estimates. Chi-squared and I^2 tests were used to calculate heterogeneity among the included studies.

Results: Eighteen studies were included for the systematic review, and 8 of those were included in the meta-analysis. Patients with prior ICI treatment exhibited a higher rate of hospitalization (OR [odds ratio] 2.6, 95% CI 1.45-4.68, $p=0.001$; $I^2=0\%$) and severe disease (OR 1.98, 95% CI 1.14-3.43, $p=0.015$). However, the OR of mortality in ICI-exposed cases was similar to non-ICI exposed patients (OR 0.90, 95% CI 0.60-1.34, $p=0.60$; $I^2=49\%$). No statistically significant difference in mortality was observed between patients exposed to ICI and other antitumor treatments.

Conclusions: Although a higher rate of hospitalization and severe disease was observed, prior exposure to ICI did not significantly increase the rate of death in the context of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) has already quickly spread on a global scale, evolving into a pandemic and threatening global health (1, 2). The rapid rise of the disease, and the resultant hospitalizations and deaths have strained public health systems (3). In addition to lung injury, COVID-19 is associated with hepatitis, gastrointestinal symptoms, such as diarrhea, and damage to other organs (4). However, there currently are no effective therapies for its treatment. Cancer patients are more vulnerable due to the tumor itself and anticancer treatment (5, 6). It remains to be seen whether the application of anticancer drugs results in differential prognoses for patients infected with COVID-19. It is critically important for clinicians to identify risk factors associated with severity and mortality and take appropriate interventions.

Currently, immunotherapy has raised major concerns amid different therapeutic strategies in cancer treatment, due to its intrinsic and extensive influence on the immune system (7). Immunotherapy primarily consists of several immune checkpoint inhibitors (ICIs), including inhibitors targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). Anti-CTLA-4 and anti-PD-1/PD-L1 antibodies reactivate cytotoxic CD8⁺ T cells for antitumor activity through targeting T-cell exhaustion pathways (8). In patients with malignancy, ICI sometimes induces adverse events, including liver injury, pneumonia, and colitis (9). Given the convergence of the downstream effects on innate immunity and organ damage caused by both ICI and COVID-19 infections, we investigated whether patients present worse prognosis due to prior exposure to ICIs.

Given that ICI therapy represents an important treatment choice for some patients, whether ICI has an impact on the prognosis of COVID-19 infection in cancer patients should be elucidated. However, whether COVID-19 patients receiving ICI are prone to poorer prognosis remains unknown. This systematic review and meta-analysis aimed to assess the safety of ICI application in COVID-19 patients and to make reasonable recommendations by reviewing available publications.

2. Methods

2.1 Search strategy

We searched the PubMed, Embase, and Web of Science databases, limiting our search to papers written in English from the inception of each database until August 8, 2020. Key words used for the search were “severe acute respiratory syndrome coronavirus 2”, “SARS-CoV-2”, “2019-nCoV”, “COVID-19”, “Cancer”, “Melanoma”, “Malignancy”, “Tumor”, “Immune checkpoint inhibitors”, “PD-1”, “CTLA-4”, and “Immunotherapy”. Articles were also retrieved by screening the reference lists of included studies and from related review papers. One reviewer (Y.T.) with experience in database searches designed the search, and 2 reviewers (W.Q., Y.T.) independently screened the titles, abstracts, and full text according to these eligibility criteria, assessing the eligibility of publications.

2.2 Inclusion criteria

We included randomized controlled trials (RCTs), observational studies, case series, and case reports that reported ICI use in cancer patients and their prognosis in the context of COVID-19. Exclusion criteria were as follows: (1) the same patients enrolled in different studies and (2) studies such as clinical reviews, editorials, letters, or erratum that did not report original data. When data was inadequate in some studies, attempts were made to contact the investigators for the missing data.

2.3 Data extraction and definitions

Two researchers (W.Q., Y.T.) independently extracted data from the included studies in a double-blinded manner. Any disagreements were resolved by a third investigator (L.Z.) or by consensus. The following variables were extracted: name of first author, country, date of COVID-19 diagnosis, study type, age, gender, number of total patients, number of patients receiving ICI, treatment interval before diagnosis of COVID-19, treatment and cancer type, and outcome of infection, such as hospitalization and/or severity and/or mortality (Table 1). Severe disease was defined according to the original studies, primarily based on the symptoms present during treatment—e.g., admission to the intensive care unit (ICU), development of severe or critical symptoms, and utilization of

invasive mechanical ventilation (5). To ensure high-quality evidence, this study was performed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) statement.

2.4 Quality assessment

The Newcastle-Ottawa Scale (NOS) was used for observational studies to evaluate the methodological quality of the original study (**Table 1**). The risk of bias was independently assessed by two authors (W.Q., Y.T.). The NOS consists of eight criteria and produces scores ranging from 0 to 9. Studies with NOS scores of ≥ 7 were regarded as high quality.

2.5 Data synthesis and statistical analysis

All statistical analyses in this study were performed using R (version 4.0.2). Odds ratios (OR) were used to describe the ratio of the probability of events occurring in cancer patients treated with different therapies. The Chi-squared and I^2 tests were used to calculate heterogeneity among the included studies. $P < 0.05$ or $I^2 > 50\%$ indicated substantial heterogeneity across the articles (10), and a random-effects model was used (11). Otherwise, the fixed-effects model was used. Publication bias was examined by funnel plots and evaluated by Egger's regression test (12) if applicable. A $p < 0.05$ was considered statistically significant.

3. Results

3.1 Search results

The search strategy identified 1619 articles. Among these studies, 890 were duplicates. After screening the title and abstract, 1556 were excluded, and the full text of the remaining 63 articles was reviewed. Among these, 18 studies reported ICI use in cancer patients and prognosis of COVID-19 infection (5, 13-29). The 18 articles consisted of 9 cohort studies, 5 case series and 4 case reports. These 18 studies were included for review. Finally, 8 of these studies were eligible for the meta-analysis, excluding studies containing less than four ICI patients.

3.2 Patient characteristics

Patient characteristics of the included studies are shown in **Table 1**. The studies were from eight countries, including Belgium ($n=1$), China ($n=2$), Germany ($n=2$), Italy ($n=6$), Spain ($n=2$), the United Kingdom ($n=3$), the United States ($n=5$), and Turkey ($n=1$). Eight of these studies included more than three ICI users, and the median age of study participants was 64 to 69 years old. Of these 8 studies, clinical outcomes were defined as hospitalization in four studies, severity in six studies, and mortality in seven studies (**Table 1**). However, there was nonuniformity in the criterion of the time interval from last dose to COVID-19 diagnosis (13-19) (**Table 1**). Results of the quality assessment of the included studies assessed by NOS scores are presented in **Table 1**.

3.3 ICI use and risk of hospitalization in COVID-19 patients

We combined 4 studies (13, 15, 17, 18) reporting the hospitalization of COVID-19 infection in patients on ICI treatment, and the pooled estimate of the rate of hospitalization was 0.67 (95% CI 0.54-0.77), and no heterogeneity was observed among these studies ($I^2 = 0\%$, $p = 0.75$; **Figure 2**). Three (13, 15, 17) of the 4 studies contained hospitalization information of patients without ICI exposure. The proportion of hospitalization was markedly increased in patients treated with ICI therapy compared to those without ICI treatment (OR 2.60 [95% CI 1.45-4.68], $p = 0.001$; $I^2 = 0\%$; **Figure 3**). Publication bias was not evaluated due to the small number of included studies.

3.4 ICI use and influence on COVID-19 severity

Six studies (5, 13, 15, 17-19) that included 79 COVID-19 cases with ICI exposure reported on COVID-19 severity in relation to ICI exposure. The combined proportion of severe disease was 0.4 (95% CI 0.30-0.51, $I^2 = 0\%$; **Figure 2**). Out of these 6 studies, four studies (5, 13, 15, 17) included 64 COVID-19 cases with ICI exposure and 650 COVID-19 cases unexposed to ICI. The pooled OR of COVID-19 severity was 1.98 (95% CI, 1.14-3.43, $p = 0.02$; **Figure 3**). Moderate heterogeneity was observed among the studies ($I^2 = 35\%$; $p = 0.20$). Publication bias was not evaluated due to the small number of included studies.

3.5 ICI use and risk of mortality in COVID-19 patients

The overall analysis included 7 studies (5, 13-16, 18, 19). Together, 148 COVID-19 cases with ICI exposure and 1850 COVID-19 cases without ICI exposure were included. The pooled proportion of mortality in COVID-19 patients with ICI exposure was 0.26 (95% CI, 0.20-0.34; $I^2 = 0\%$; **Figure 2**). Next, the risk associated with ICI use and mortality was assessed. Overall, the OR of mortality in ICI-exposed cases was similar to non-ICI exposed COVID-19 patients (OR 0.90, 95% CI 0.60-

1.34, $p=0.60$; **Figure 3**). Moderate heterogeneity was observed among the studies ($I^2=49\%$; $p=0.10$). Publication bias was not observed by funnel plot (**Figure S1**) or Egger test ($p=0.14$) for mortality.

We further examined the mortality between exposure to ICI and other treatments in cancer patients in the context of COVID-19. However, we did not identify significant differences between ICI and chemotherapy (OR 1.06, 95% CI 0.67-1.67, $p=0.80$; $I^2=3\%$; **Figure 4A**), hormone therapy (OR 1.26, 95% CI 0.44-3.59, $p=0.67$; $I^2=59\%$; **Figure 4B**), radiotherapy (OR 1.44, 95% CI 0.67-3.07, $p=0.35$; $I^2=46\%$; **Figure 4C**), surgery (OR 1.21, 95% CI 0.50-2.98, $p=0.67$; $I^2=0\%$; **Figure 4D**), or targeted therapy (OR 1.53, 95% CI 0.89-2.63, $p=0.13$; $I^2=0\%$; **Figure 4E**).

3.6 Temporal relationship between prior ICI receipt and diagnosis of COVID-19

Given that the receptor can be occupied for months (30) and the initial start of ICI therapy results in a distinct proliferative burst (31-34), different intervals from the last dose of ICI to the diagnosis of COVID-19 may theoretically influence the prognosis of COVID-19 infection. Luo et al (15) defined five categories of prior PD-1 blockade, including no prior PD-1, ever received PD-1 blockade, last receipt within 6 months, last receipt within 6 weeks, and first receipt within 3 months, detecting the outcomes of interest. Overall, there was no significant difference in prognosis regardless of PD-1 blockade exposure. We extracted data from this study and regrouped patients according to intervals from last dose of ICI to the diagnosis of COVID-19: no prior PD-1, interval > 6 months, interval between 6 months and 6 weeks, interval < 6 weeks and initial dose within 3 months (**Figure 5**). However, we did not capture any statistically significant differences between no prior PD-1 group and the other four groups tested by Chi-square test or Fisher's exact test in terms of prognosis, including hospitalization, severe disease and mortality (**Figure 5**). Consistent with the above outcomes, Wu et al (19) observed a similar risk of severity in different intervals from the last ICI administration to COVID-19 diagnosis (interval ≥ 28 days vs. interval < 28 days, $p=1.00$).

3.7 ICI-induced lung injury and COVID-19 infection

ICI-induced pneumonitis presents similar clinical and radiological features to COVID-19, challenging the early diagnosis of COVID-19 (20). Guerini et al (23) and Lovly et al (24) reported two cases that experienced misdiagnosis caused by ICI-induced pneumonitis who died due to uncontrolled COVID-19 infection. Clinicians should always consider COVID-19 as a differential diagnosis, as few places were spared during the pandemic. In another report (35), 2 patients were initially highly suspected of COVID-19 infection based on clinical manifestations, imaging findings, and epidemiology. Steroids were withheld in one of them, and the disease became worse until a third CT scan was obtained and a second negative RT-PCR test was released after admission. Both patients were eventually diagnosed with ICI-induced pneumonitis, and a mean delay of 3 days in steroid initiation was attributed to the COVID-19 pandemic.

Except for missed window of optimal treatment caused by delayed diagnosis, ICI-induced pneumonitis itself reduces patient resistance and exacerbates COVID-19 infection. Here, we were curious about the influence of ICI in lung cancer patients infected with COVID-19. Data showed that ICI application did not significantly influence the severity of COVID-19 in lung cancer patients (ICI application [7/12] vs. no ICI application [8/23], $p=0.181$) (17). Consistently, ICI exposure in lung cancer patients did not exhibit a higher risk for developing severity than in patients with other solid cancers (lung cancer [7/12] vs. other solid cancers [5/19], $p=0.13$) (17).

4. Discussion

This review included 18 articles that encompassed 220 ICI users infected with COVID-19. Findings suggest that ICI application does not increase mortality among cancer patients infected with COVID-19; however, it did result in increased hospitalizations and severe infections. In addition, different intervals from the last dose of ICI to diagnosis of COVID-19 might not influence the prognosis of COVID-19 infection. Finally, given the unpredictable duration of the pandemic, we should always keep in mind a differential diagnosis of COVID-19 and rational adjustment of ICI use.

Patients with cancer are theoretically more vulnerable to infection due to poor health status and immunosuppressive conditions provoked by both the cancer and antitumor therapies (36-39). Poorer prognosis in COVID-19 infection has been associated with several factors, including older age, gender, and comorbidities such as pulmonary disease, cardiac disease, hypertension, and cancer (16, 40). Liang et al collected and analyzed 1590 cases from 575 hospitals (41). In their study, 18 of 1590 (1%; 95% CI 0.61-1.65) COVID-19 cases had a history of cancer, which was higher than the overall incidence of cancer in the population (285.83 [0.29%] per 100 000 people). Importantly, patients with cancer exhibited a higher rate of severe disease than patients without cancer (7/18 (39%) vs. 124/1572 (8%), $p=0.0003$). In a study from America (17), 423 patients with cancer were diagnosed with COVID-19. Among them, 40% were hospitalized for COVID-19, 20% developed severe respiratory illness and 12% died. While in Europe, Pinato et al reported a high mortality (33.6%) in a multicenter study, reflecting serious strains to the public health system (16). We here pooled the prognostic data from COVID-19-infected cases with prior exposure to ICI. The rate of hospitalization was 67%, 42% developed severe disease and 26% died.

Physicians worry about the influence of ICI administration on COVID-19 infection for two main reasons (42). The first is the potential overlap between the two lung injuries: possible pneumological toxicity from ICI use and COVID-19 pneumonia. The incidence of ICI-related pneumonitis was reported to be 2.5-5% with anti-PD-1/PD-L1 monotherapy and 7-10% with anti-CTLA-4/anti-PD-1 combination therapy (43). This fatal immune-related adverse events (irAEs) accounted for 35% of treatment-related deaths (44). The second concern is the potential synergy between ICI mechanisms and COVID-19 pathogenesis, both of which are involved in immune hyperactivation (45-47). Elizabeth V. Robilotti et al (17) identified prior ICI exposure as an independent risk factor for hospitalization (OR 2.84, 95% CI 1.24-6.72, $p=0.013$) and severe disease (HR 2.74, 95% CI 1.37-5.46, $p=0.004$). Some studies reported negative effects of ICI on mortality (13).

However, most of these studies did not observe statistically significant differences with respect to ICI on the prognosis of COVID-19 infection (5, 14-16). Integrating multiple studies into the present study, we found that prior receipt of ICI significantly increased the rate of hospitalization and severe disease. In contrast, there was no significant difference in mortality among patients with or without prior ICI exposure (OR 0.90, 95% CI 0.60-1.34, $p=0.60$) (Figure 3).

Most of the included studies focused on the impact of ICI use or not on the prognosis of COVID-19 (5, 13, 14, 16-18), but they did not take other important factors into consideration, including courses of ICI use, intervals from the last dose to the diagnosis of COVID-19, and the effect of the first dose. Wu et al (19) found that patients who received 3 or more cycles of ICI were more likely to develop severe COVID-19, albeit this difference was not statistically significant (6/7 [85.7%] vs. 1/4 [25%], $p=0.09$). Additionally, they divided patients into 2 groups according to the most recent dose before diagnosis of COVID-19: >28 days and <28 days, though no association was found between that time interval and disease severity (4/6 [66.7%] vs. 3/5 [60%], $p=1.00$). Another study (15) included 69 patients and defined 5 groups according to the interval from last ICI receipt to COVID-19 diagnosis: no prior PD-1, ever received PD-1, last receipt within 6 months, last receipt within 6 weeks, and first receipt within 3 months. Overall, there was no statistically significant difference in different groups in terms of the rate of hospitalization, severe disease or death.

As the influence of ICI on cancer patients infected with COVID-19 is not clear, there are no authoritative guidelines for ICI modifications in the context of COVID-19. Modifications of drug application are often empirical and based on the mechanism of drug action, taking tumor treatment and epidemic prevention into account (48). Wang (49) et al suggested that administration of anticancer drugs should be changed from infusion to oral administration if available. For maintenance therapy, we could appropriately prolong the infusion intervals according to patient condition. Aeppli et al performed an online survey among physicians involved in the treatment of renal cell carcinoma (50). Compared to that outside the pandemic, the use of ipilimumab/nivolumab fell by half in intermediate/poor-risk patients during the pandemic (80% vs. 41%). In favorable risk patients, ICI-containing regimens were consistently chosen less often, and instead, more TKI monotherapies were prescribed. In patients responding to established ICI-containing therapies, most participants modified treatment regimen by extending cycle length. Another survey focused on patient perspective on oncological care (51). In patients with adjusted treatment, immunotherapy (32%) was most frequently adjusted. Consistently, in patients with delay and discontinuation of treatment, immunotherapy (39% and 33%) was the most frequently included modality.

This study has important implications for clinical practice. Given that the pandemic may last for another several months or even years, physicians should balance cancer treatment and COVID-19 infection. Our results indicate that ICI administration increases the rate of severe disease, though it did not significantly increase the rate of death in COVID-19-infected patients. This suggests that we should not easily postpone, suspend, or alter our established treatment decisions in clinical practice, especially for patients who are undergoing ICI-containing regimens, because ICI has irreplaceable performance in certain antitumor treatments (8). Delay or modification of therapy should be considered on a case-by-case basis (52).

This systematic review and meta-analysis has several limitations. The most important limitation is that we could not rule out unknown confounders. Previous studies reported that age, sex, smoking and comorbidities, including pulmonary disease, cardiac disease, and hypertension, significantly affect the prognosis of COVID-19 infection. However, these potential confounders were not considered in most of the included studies. Second, due to the relatively small number of studies, we were unable to evaluate the effects of ICI subclasses or their role in individual tumors. Additionally, the benefit of longer duration of ICI on the overall survival (OS) has been determined, and frequent or early interruption of ICI has been proved to be associated with worse OS (8). It will be worthwhile to comment on the cancer outcome in this population. However, limited by a short follow-up period, we failed to assess the cancer outcome in patients who had delayed or interrupted ICI treatment through published studies. Further, studies on the association between irAEs and COVID-19 risk and outcome are needed. Lastly, included studies defined several intervals from the last dose to the diagnosis of COVID-19 infection, which may have influenced the findings.

In conclusion, the results of this meta-analysis suggest that, although a higher rate of hospitalization and severe disease was observed among patients who were undergoing ICI-containing regimens, prior exposure to ICI does not significantly increase the risk of COVID-19 mortality. Additionally, different intervals from last dose of ICI to the diagnosis of COVID-19 may not influence the prognosis of COVID-19 infection.

5. Declarations

Funding: This study was supported by Natural Science Foundation of Shanghai (Grant 19ZR1447100) and Foundation of Shanghai Dermatology Hospital (Grants 17HBDS08 and 2018KYQD02).

Contribution statements: Conception and design: Yun Tian, Wenwei Qian, and Ying Ye. Acquisition of data: Yun Tian, Wenwei Qian, Ying Ye, Lugen Zuo, and Ting Song. Analysis and interpretation of data: Wenwei Qian, Ying Ye, Lugen Zuo, and Yun Tian. Writing, review, and revision of the manuscript: Wenwei Qian, Yun Tian, Lugen Zuo, Qing Xu, and Yinghong Wang. Final approval of manuscript: All authors.

Acknowledgements: This study was supported by Natural Science Foundation of Shanghai (Grant 19ZR1447100) and Foundation of Shanghai Dermatology Hospital (Grants 17HBDS08 and 2018KYQD02).

Conflicts of interest: The authors declare no conflicts of interest

6. Abbreviations

CI: confidence interval; COVID-19: coronavirus disease 2019; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; HR: hazard ratio; ICIs: immune checkpoint inhibitors; ICU: intensive care unit; IQR: interquartile range; NOS: Newcastle-Ottawa Scale; OR: odds ratio; OS: overall survival; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PRISMA: Preferred Reporting Items of Systematic Reviews and Meta-analysis; RCTs: randomized controlled trials.

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8. Table

Table 1 is also available as a PDF in the Supplementary Files.

Table1.Characteristics of the Included Studies.	Quality	8	5	8	6	6
	Included in the meta-analysis	Yes	Yes	Yes	Yes ^a	Yes
	Outcome	Mortality and severity	Hospitalization, severity and mortality	Mortality	Hospitalization, severity and mortality	Mortality
	Cancer stage	Metastatic cancer(17)	I/II(41) III/IV(69)"	Primary tumour localised(149) Primary tumour locally advanced(78) Metastatic(347) Remission(21) No information(205)"	Metastatic or active lung cancer(55)	Non-advanced(539) Advanced(351) "
	Cancer type	Breast cancer(11) Blood cancer(9) Cervix cancer(6) Esophagus cancer(6) Gastrointestinal cancer(13) Lung cancer(22) Thyroid cancer(11)	Gynecologic Cancer(121)	Breast(102) Lip, oral cavity, and pharynx(27) Central nervous system(15) Digestive organs(150) Female genital organs(45) Lymphoma(60) Melanoma (skin) (27) Male genital organs(78) Respiratory and Intrathoracic organs(90) Urinary tract(50) Other haematological(109) Other or unspecified(47)	Lung cancers(69)	Breast(162) Genito-Urinary(132) Gastrointestinal(105) Gynaecological(41) Gastro-esophageal(40) Hepatobiliary(45) Head and Neck(29) Lung(119) Skin(28) Other(52) Haematological Malignancies(137)
	Anti-tumor Treatment	Chemotherapy(17) Immunotherapy(6) Radiotherapy(13) Surgery(8) Targeted therapy(4)	Surgery(11) Chemotherapy(35) Immunotherapy(8) Targeted therapy(13) Hormone therapy(9) Radiotherapy(9)	Chemotherapy(281) Hormone therapy(64) Immunotherapy(44) Radiotherapy(76) Surgery(29) Targeted treatment(72) Other(60) None(272)	Immunotherapy(20)	Chemotherapy(206) Endocrine therapy(92) Immunotherapy(56) Targeted therapy(93)
	Treatment interval before Diagnosis	Within 40 days	NR	Within 4 weeks	Within 6 weeks (n=20) Within 6 months (n=30) Ever(n=40)	Within 4 weeks
	No. of pts with ICI	6	8	44	40	56
	No. of pts	641	121	800	69	890
	Male	302(47%)	NR	449(56%)	33(48%)	503(56.5%)
	Age	Male median:64 Female median:63.5	64(IQR 51-73)	69(range 59-76)	69(range 31-91)	68(range 21-99)
	Study type	Multi-center prospective cohort	Multi-center retrospective cohort	Multi-center prospective cohort	Single-center retrospective cohort	Multi-center retrospective cohort
	Date of COVID-19 diagnosis	January 1, to February 24, 2020	March 1, to April 22, 2020	March 18, to April 26, 2020	March 12, to April 13, 2020	February 26 and May 7, 2020
	Country	China	The United States	The United Kingdom	The United States	The United Kingdom (n=218) Italy (n=343) Spain (n=323) Germany (n=6)
	First author	Dai et al	Lara et al	Lee et al	Luo et al	Pinato et al

Table 1 (Continued)	Quality	5	5	5			
	Included in the meta-analysis	Yes	Yes	Yes	No	No	No
	Outcome	Hospitalization and severity	Hospitalization, severity and mortality	Severity and mortality	Hospitalization	Severity and mortality	Hospitalization, severity and mortality
	Cancer stage	Metastatic(238)	IV(4)	NR	Metastatic(1)	NR	"Metastatic(1) Locally advanced(1)"
	Cancer type	Breast(86) Colorectal(37) Hematologic(24) Lung(35) Prostate(26) Other(137)	Renal cell carcinoma(2) Urothelial carcinoma(2)	Cervical squamous cancer(1) Colorectal Adenocarcinoma(1) Endometrial cancer(1) Hepatocellular carcinoma(1) Lung cancers(7)	Renal cell carcinoma(1)	Leukemia(16) Lymphoma(3) Ewing sarcoma(2) Hepatoblastoma(2) Other(6)	Melanoma(2)
	Anti-tumor Treatment	Immunotherapy(31)	Immunotherapy(4)	Immunotherapy(11)	Immunotherapy(1)	Chemotherapy(25) Allogeneic stem cell transplant(3) Immunotherapy(1)	Immunotherapy
	Treatment interval before Diagnosis	Within 90 days	Within 90 days	Within 50 days	4 months before diagnosis	NR	8 days before diagnosis
	No. of pts with ICI	31	4	11	1	1	2
	No. of pts	423	4	11	1	29	2
	Male	212(50%)	4(100%)	8(73%)	1(100%)	8(13%)	1(50%)
	Age	416 pts >18 (98%) 234 pts >60 (56%)	67(range 52-72)	66(range 29-73)	51	7(range 0-16)	51 and 74
	Study type	Single-center retrospective cohort	Single-center prospective case series	Case series	Case report	Multi-center retrospective cohort	Case series
	Data of COVID-19 diagnosis	March 10,to April 7, 2020	February 1 and April 27, 2020	January 9,to March 20, 2020	NR	February 23, to April 24, 2020	March 16 and March 25, 2020
	Country	The United States	The United Kingdom	China	Belgium	Italy	Italy
	First author	Robilotti et al	Szabados et al	Wu et al	Artigas et al	Bisogno et al	Giacomo et al

Table 1 (Continued)	Quality				
	Included in the meta-analysis	No	No	No	No ^b
	Outcome	Hospitalization, severity and mortality	Hospitalization, severity and mortality	Hospitalization, severity and mortality	Severity and mortality
	Cancer stage	NR	IV(2)	Metastatic(5)	Metastatic(11)
	Cancer type	Bladder(12) Breast(27) Colorectal(25) Kidney(4) Lung(9) Prostate(30) Stomach(4) Thyroid(4) Uterus(3) Mesothelioma(1) Other(19)	Lung cancer (2)	Breast(1) Gastric(1) Head and neck(1) Leukaemia(1) Lung(1) Melanoma(1) Urothelial(2) NET(1)	Central nervous system(1) Kidney(1) Lung(17) Colorectal(10) Upper GI cancer(6) Bladder(3) Breast(10) Gynaecologic(2) Prostate(5) Thyroid(3) Head and Neck(4) Sarcoma(1) Cancer of unknown(3)
	Anti-tumor Treatment	Antiangiogenic therapy(1) Chemotherapy(12) Immunotherapy(1) Hormone therapy(1)	Stereotactic radiosurgery+immunotherapy(1) Chemotherapy+immunotherapy(1)	Chemotherapy(3) Immunotherapy(2) Targeted treatment(2)	Chemotherapy(36) Endocrine(10) Immunotherapy(8) Target therapy(7)
	Treatment interval before Diagnosis	Within 60 days	NR	Within 14 days	Within 4 weeks
	No. of pts with ICI	1	2	2	8
	No. of pts	1226	2	9	63
	Male	733(60%)	1(50%)	7(78%)	34(54%)
	Age	73(range 23-100)	58 and 62	68(range 42-79)	66(95%CI 63.4-68.8)
	Study type	Single-center retrospective cohort	Case series	Single-center retrospective case series	Single-center retrospective cohort
	Data of COVID-19 diagnosis	February 1, to April 3, 2020	March 20 and March 24, 2020	February 1, to April 2, 2020	March 9, to April 19, 2020
	Country	Italy	The United States	Italy	Spain
	First author	Pinto et al	Rolfo et al	Trapani et al	Yarza et al
					Yekeduz et al

Figures

Figure 1

Flow chart for study selection.

Figure 2

Pooled prognosis of COVID-19-infected patients with prior exposure to ICI. ICI: immune checkpoint inhibitors; OR: odds ratio; CI: confidence interval.

Figure 3

Pooled prognosis of COVID-19 infection compared between patients with prior ICI treatment and those without. ICI: immune checkpoint inhibitors; OR: odds ratio; CI: confidence interval.

Figure 4

Pooled mortality of COVID-19 infection compared between patients with prior ICI treatment and those with chemotherapy (A, $p = 0.80$), hormone therapy (B, $p = 0.67$), radiotherapy (C, $p = 0.35$), surgery (D, $p = 0.67$), or targeted therapy (E, $p = 0.13$). ICI: immune checkpoint inhibitors; OR: odds ratio; CI: confidence interval.

Figure 5

Impact of prior PD-1 exposure on the prognosis of COVID-19 in patients with lung cancer. Data were extracted from a previous study (15), and patients were redistributed into five groups: no prior PD-1, interval > 6 months (> 6 mo), interval between 6 months and 6 weeks (6 mo-6 w), interval < 6 weeks (< 6 w), and initial dose within 3 months (start < 3 mo). (A) Rate of hospitalization compared between no prior PD-1 and > 6 mo ($p = 0.48$), 6 mo-6 w ($p = 0.26$), < 6 w ($p = 0.17$), and start < 3 mo ($p = 0.30$). (B) Rate of severe disease compared between no prior PD-1 and > 6 mo ($p = 1.00$), 6 mo-6 w ($p = 0.26$), < 6 w ($p = 0.38$), and start < 3 mo ($p = 0.48$). (C) Rate of death compared between no prior PD-1 and > 6 mo ($p = 0.24$), 6 mo-6 w ($p = 0.24$), < 6 w ($p = 1.00$), and start < 3 mo ($p = 0.68$).

Supplementary Files

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