Clinical impact of COVID-19 on patients with cancer treated with immune checkpoint inhibition

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ABSTRACT

Background Patients with cancer who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are more likely to develop severe illness and die compared with those without cancer. The impact of immune checkpoint inhibition (ICI) on the severity of COVID-19 illness is unknown. The aim of this study was to investigate whether ICI confers an additional risk for severe COVID-19 in patients with cancer.

Methods We analyzed data from 110 patients with laboratory-confirmed SARS-CoV-2 while on treatment with ICI without chemotherapy in 19 hospitals in North America, Europe and Australia. The primary objective was to describe the clinical course and to identify factors associated with hospital and intensive care (ICU) admission and mortality.

Findings Thirty-five (32%) patients were admitted to hospital and 18 (16%) died. All patients who died had advanced cancer, and only four were admitted to ICU. COVID-19 was the primary cause of death in 8 (7%) patients. Factors independently associated with an increased risk for hospital admission were ECOG ≥2 (OR 39.25, 95% CI 4.17 to 369.2, p=0.0013), treatment with combination ICI (OR 5.68, 95% CI 1.58 to 20.36, p=0.0273) and presence of COVID-19 symptoms (OR 5.30, 95% CI 1.57 to 17.89, p=0.0073). Seventy-six (73%) patients interrupted ICI due to SARS-CoV-2 infection, 43 (57%) of whom had resumed at data cut-off.

Interpretation COVID-19–related mortality in the ICI-treated population does not appear to be higher than previously published mortality rates for patients with cancer. Inpatient mortality of patients with cancer treated with ICI was high in comparison with previously reported rates for hospitalized patients with cancer and was due to COVID-19 in almost half of the cases. We identified factors associated with adverse outcomes in ICI-treated patients with COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] As of October 2020, more than 35,000,000 people have been infected with SARS-CoV-2 worldwide with more than 1,000,000 deaths.[2] The clinical spectrum of COVID-19 varies enormously from asymptomatic individuals to critical illness and death.[3] Risk factors for severe disease include older age, male sex and comorbidities such as cardiovascular and pulmonary diseases, diabetes and cancer.[4 5] Mortality rates of COVID-19 infection in the cancer population range from 7.6% to 33%[5–9] compared with 1.4%–2.3%[3 10] in an unselected population.

One key question specific for the cancer population pertains to the potential impact of immune checkpoint inhibition (ICI) on the clinical course of COVID-19. Programmed cell death 1 (PD-1)–based immunotherapy releases the brakes of immune tolerance mechanisms leading to effective anti-tumor responses.[11] Adaptive immune cells involved in this process, in particular CD8$^+$ and CD4$^+$ T cells, are also essential to control and establish immunity against viruses, and ICI may enhance immunologic control of viral

infections.[12 13] It is therefore theoretically possible that ICI offers protection against the development of severe COVID-19 illness. Nevertheless, these immune cells—either through direct cytotoxicity or cytokine release—can also contribute to inflammation and may aggravate the clinical course of COVID-19. An example of an immune-mediated consequence of SARS-CoV-2 is acute respiratory distress syndrome which is the leading cause of mortality in COVID-19.[14 15]

ICI has been associated with severe disease in some[9 16 17] but not all[18] studies, and the numbers of ICI-treated patients in these studies were small. Although vigilance is certainly warranted in the ICI-treated patient population, unnecessary treatment delays may compromise cancer-related outcomes and some patients may not be offered ICI therapy in areas of high COVID-19 prevalence due to concerns of infection and severe illness. With the pandemic continuing, recommendations are needed to inform ICI-related treatment decisions. In this multicentric study, we describe the clinical course, treatment and outcomes of COVID-19 infection in patients treated with ICI across different tumor types and across different geographic regions.

METHODS
Study design and participants
We conducted a multicenter, retrospective, cohort study in 19 centers across 9 countries (Australia, Canada, France, Germany, Italy, Switzerland, The Netherlands, UK and USA). Between March 5 and May 15, 2020, we included 110 adult (aged ≥18 years) patients with any type of solid malignancy who had undergone treatment with ICI and had laboratory-confirmed positive SARS-CoV-2. The test could either be nucleic acid detection based (nasopharyngeal swabs) or serological. Asymptomatic patients found positive for SARS-CoV-2 were included in this study. These patients were tested according to local policies after exposure to a person with confirmed SARS-CoV-2 (transmission tracking and contact tracing). All patients must have received at least one cycle of ICI within 12 months prior to testing positive for SARS-CoV-2. Patients who received chemotherapy within 12 weeks prior to COVID-19 diagnosis were excluded as chemotherapy-induced immunosuppression may have confounded analyses. Combinations of ICI with anti-VEGF agents were allowed. Clinical and laboratory data were obtained from the medical records from each of the centers. Local Institutional Review Board approval was required for each center. All study procedures were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki.

Procedures
Clinical data were extracted from medical records and de-identified for analysis. Data were divided into the following categories: demographics and patient characteristics (age, sex, geographic region, Eastern Cooperative Oncology Group (ECOG) performance status), cancer characteristics (cancer type, American Joint Committee on Cancer stage, treatment setting), comorbidities (cardiovascular, pulmonary, renal disease or diabetes mellitus), ICI treatment (anti-PD-1/anti-PD-L1, combination anti-PD-1 plus anti-CTLA-4 or other), COVID-19 symptoms (fever, cough, dyspnea), laboratory tests (leukocytes, lymphocytes, C reactive protein (CRP) and creatinine), management (oxygen therapy, mechanical ventilation, use of vasopressors, renal replacement therapy, antivirals, antibiotics, glucocorticoids, anti-IL-6 agents and intravenous immunoglobulins) and clinical outcomes (hospital admission, intensive care unit admission and mortality).

Statistical analysis
Patient demographics and clinical characteristics are summarized by their frequency and proportion. Primary outcomes were hospital admission (coded yes/no) and overall survival (time to event). Measures for association between demographic and clinical characteristics on one hand and hospital admission on the other hand were assessed using univariate and multivariate logistic regression. ORs and associated 95% CIs are reported. Overall survival was assessed using univariate Cox proportional hazard regression; given the low number of deaths observed, multivariate Cox was not considered. HRs and associated 95% CIs are reported. For associations between demographic and clinical characteristics and intensive care unit admission, only frequencies are reported given the low absolute number of events. The selection of symptoms and laboratory findings was based on previous reports.[19]

RESULTS
Patient characteristics
Between March 5 and May 15, 2020, 110 patients with cancer on ICI only who tested positive for SARS-CoV-2 were included in this study. The median follow-up since COVID-19 diagnosis was 82 days (range 1–119 days). The median age was 63 years (range 27–86) and most patients were male (65%). Seventy (64%) patients were treated in Europe (48 in Italy) and 36 (33%) in North America. Eighty-three (75%) patients had advanced cancer, including 64 (58%) with melanoma, 17 (16%) with non-small cell lung cancer (NSCLC) and 10 (9%) with renal cell carcinoma (RCC) (table 1). Most patients did not have an underlying comorbidity (55%); the most common comorbidities were cardiovascular disease (27%), diabetes mellitus (15%), pulmonary disease (12%) and/or renal disease (5%). Overall, for cancer, 90 (82%) patients were treated with anti-PD-(L)1 monotherapy (nivolumab, pembrolizumab, spartalizumab, atezolizumab or durvalumab) and 16 (15%) with combination anti-PD-(L)1 and anti-CTLA-4 (nivolumab–ipilimumab, durvalumab–tremelimumab or pembrolizumab–MK1308). Twenty-five (23%) patients had chemotherapy prior to ICI. The median time between last chemotherapy and COVID-19 diagnosis was 40 weeks

Table 1 Demographic, disease and treatment findings at COVID-19 diagnosis

	All patients (n=110)		Admitted (n=35)		Died (n=18)	
Median age (range) years	63 (27–86)		65 (35–83)		63 (42–81)	
<65	58	(53%)	17	(49%)	9	(50%)
≥65	52	(47%)	18	(51%)	9	(50%)
Sex						
Female	38	(35%)	11	(32%)	7	(39%)
Male	72	(65%)	24	(68%)	11	(61%)
Region						
Australia	4	(3%)	1	(3%)	0	(0%)
Europe	70	(64%)	16	(46%)	5	(27%)
Italy	48	(45%)	6	(17%)	3	(17%)
UK	8	(7%)	5	(14%)	1	(5%)
The Netherlands	6	(5%)	2	(6%)	0	(0%)
Germany	4	(3%)	1	(3%)	0	(0%)
France	3	(3%)	2	(6%)	1	(5%)
Switzerland	1	(1%)	0	(0%)	0	(0%)
North America	36	(33%)	18	(51%)	13	(73%)
USA	29	(27%)	16	(45%)	11	(62%)
Canada	7	(6%)	2	(6%)	2	(11%)
ICI treatment setting						
(Neo)adjuvant	27	(25%)	4	(11%)	0	(0%)
Advanced	83	(75%)	31	(89%)	18	(100%)
Cancer type						
Melanoma	64	(58%)	17	(49%)	5	(28%)
NSCLC	17	(16%)	5	(14%)	4	(22%)
RCC	10	(9%)	4	(11%)	2	(11%)
Other	19	(17%)	9	(26%)	7	(39%)
Coexisting disorder						
None	60	(55%)	21	(60%)	8	(44%)
Cardiovascular	30	(27%)	5	(14%)	2	(11%)
Diabetes mellitus	16	(15%)	6	(17%)	3	(17%)
Pulmonary	13	(12%)	5	(14%)	4	(22%)
Renal	6	(5%)	3	(9%)	3	(17%)
ICI						
Anti-PD-1/PD-L1	90	(82%)	23	(66%)	13	(72%)
Anti-PD-1 plus anti-CTLA-4	16	(15%)	10	(28%)	4	(22%)
Other*	4	(3%)	2	(6%)	1	(6%)
Previous chemotherapy						
Yes	25	(23%)	8	(23%)	6	(33%)
No	85	(77%)	27	(77%)	12	(67%)
Response to ICI at COVID-19 diagnosis Adjuvant						
NED	4	(4%)	1	(3%)	0	(0%)
Advanced						
PR/CR	29	(26%)	7	(20%)	3	(17%)

Continued

Table 1 Continued

	All patients (n=110)		Admitted (n=35)		Died (n=18)	
SD	20	(18%)	6	(17%)	4	(22%)
PD	17	(16%)	11	(31%)	6	(33%)
Not reported	40	(36%)	10	(29%)	5	(28%)

*Pembrolizumab–bevacizumab, pembrolizumab–anti-TIGIT, avelumab–axitinib, pembrolizumab–vopratelimab.
CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibition; NED, no evidence of disease; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.

(range 12–559). Out of 70 patients with response evaluation available at COVID-19 diagnosis, 33 had a partial or complete response (advanced setting) or no evidence of recurrence (adjuvant setting), 20 stable disease and 17 disease progression. Further demographic, clinical, treatment and laboratory findings are presented in table 1.

Diagnosis and management of COVID-19

Median time between COVID-19 diagnosis and last ICI dose was 26 days (range 0–363). Sixty-seven (62%) patients were symptomatic at COVID-19 diagnosis. The most common COVID-19–related symptoms were fever (67%), cough (58%) and dyspnea (33%), and 10% of patients presented ECOG ≥2 at the time of COVID-19 diagnosis. Lymphocytopenia was the most common laboratory abnormality in 47% of the 79 patients who had laboratory tests available within 3 days of COVID-19 diagnosis, and 15 patients (14%) were on prednisone equivalent dose of ≥10 mg at diagnosis, mostly for ICI toxicity (table 2). Thirty-five (32%) patients were admitted to hospital and 7 (6%) to intensive care (figure 1). For the patients managed in hospital, 20 received oxygen therapy and 3 mechanical ventilation. Antibiotics and antiviral agents were given to 24 and 5 admitted patients, respectively. Only 10 patients were treated with glucocorticoids for COVID-19; anti-IL6 and intravenous immunoglobulin were given to 2 patients and 1 patient, respectively (table 2). Two patients required vasopressor support and one patient renal replacement therapy. Of the 110 patients, ICI was interrupted in 76 (73%) and resumed in 43 (57%).

Clinical factors associated with a higher hospital admission

Factors associated with a higher risk for hospital admission for COVID-19 management included treatment with combination immunotherapy (OR 4.37, 95% CI 1.40 to 13.61, p=0.0287), ECOG ≥2 (OR 30.82, 95% CI 3.75 to 253.2, p=0.0014), treatment with corticosteroids at a prednisone equivalent dose of ≥10 mg (OR 5.04, 95% CI 1.54 to 16.48, p=0.0075), COVID-19 symptoms (OR 5.34, 95% CI 1.86 to 15.33, p=0.0018), in particular dyspnea (OR 4.74, 95% CI 1.58 to 14.21, p=0.0054), leukocyte count ≥10,000/mm^3 (OR 8.70, 95% CI 2.15 to 35.29, p=0.0025) and lymphocyte count <1500/mm^3 (OR 3.76, 95% CI 1.39 to 10.16, p=0.0089) (table 3). Of the 13 patients who had leukocytosis, 4 were in treatment

corticosteroids (prednisone equivalent dose ≥10 mg). Factors independently associated with hospital admission were treatment with combination immunotherapy (OR 5.68, 95% CI 1.58 to 20.36, p=0.0273), ECOG ≥2 (OR 39.25, 95% CI 4.17 to 369.2, p=0.0013) and COVID-19 symptoms (OR 5.30, 95% CI 1.57 to 17.89, p=0.0073) (table 3).

Survival outcome

At the time of data cut-off (July 20, 2020), of the 35 patients admitted to hospital, 19 (54%) were discharged and 16 had died in hospital (46%) (figure 1). Two patients died in a nursing unit. Of all 18 (16%) patients who died, COVID-19 was the primary cause of death in 8 patients (7% total cohort), and 3 had evidence of cytokine release syndrome (table 4). Malignancy was the primary cause of death in eight patients (7% total cohort); two patients died of other causes. All 18 patients who died had advanced cancer, 15 (82%) had COVID-19–related symptoms (table 2). Only four patients were admitted to the intensive care unit; six were not admitted because of the underlying malignancy, two due to a constrained healthcare system (Italy), and no reason was specified for the remaining six patients (table 4). Factors associated with an increased risk of death were residence in North America versus Europe (HR 6.30, 95% CI 2.20 to 18.00, p=0.0006), pre-existing kidney disease (HR 4.09, 95% CI 1.17 to 14.29, p=0.0271), ECOG ≥2 (HR 3.84, 95% CI 1.35 to 10.92, p=0.0115), dyspnea (HR 3.49, 95% CI 1.24 to 9.84, p=0.0182), lymphocyte count <1500/mm^3 (HR 4.38, 95% CI 1.20 to 15.94, p=0.0250) and CRP ≥100 mg/mL (HR 3.70, 95% CI 1.24 to 11.10, p=0.0194). Four (24%) out of 17 patients with lung cancer died in comparison with 5 (8%) out of 64 patients with melanoma (HR 3.81, 95% CI 1.02 to 14.27, p=0.0345).

DISCUSSION

This is the largest study of patients with confirmed COVID-19 infection while on treatment with ICI alone. We show a mortality rate due to COVID-19 (7%) higher than what is reported for an unselected COVID-19 positive population (1.4%–2.3%[3 10]) but on the lower side of the range documented for patients with cancer (7.6%–33%).[6–9] Inpatient mortality of patients with cancer

Table 2 Symptoms, laboratory findings and treatments for COVID-19

	All patients (n=110)		Admitted (n=35)		Died (n=18)	
Median time between last ICI and COVID-19 diagnosis, days (range)	26 (0–363)		36 (0–363)		17 (0–319)	
Symptomatic at COVID-19 diagnosis						
Yes*	67/108	(62%)	29/35	(83%)	15/18	(82%)
Fever	45/67	(67%)	20/29	(69%)	8/15	(53%)
Cough	39/67	(58%)	15/29	(52%)	8/15	(53%)
Dyspnea	22/67	(33%)	15/29	(52%)	9/15	(60%)
ECOG at COVID-19 diagnosis						
0–1	99	(90%)	25	(72%)	13	(72%)
2–4	11	(10%)	10	(28%)	5	(28%)
Laboratory tests†						
WBC ≥10,000/mm^3	13/79	(16%)	10/29	(34%)	3/15	(20%)
Lymphocytes <1500/mm^3	36/77	(47%)	19/28	(68%)	11/14	(79%)
CRP ≥100 mg/L	11/36	(31%)	11/26	(42%)	8/14	(57%)
Creatinine ≥133 µM	10/78	(13%)	6/28	(21%)	3/14	(21%)
Prednisone ≥10 mg equivalent	15/110	(14%)	10/35	(28%)	4/18	(22%)
Admission to hospital	35/110	(32%)	––	––	16/18	(89%)
Admission to intensive care unit	7/110	(6%)	7/35	(20%)	4/18	(22%)
Oxygen therapy	22/108	(20%)	20/33	(61%)	12/16	(75%)
Mechanical ventilation	3/108	(3%)	3/33	(9%)	2/16	(13%)
Use of antibiotics	28/108	(26%)	24/33	(73%)	13/16	(81%)
Use of antivirals	7/107	(7%)	5/32	(16%)	5/16	(31%)
Use of glucocorticoids	10/107	(9%)	10/32	(31%)	3/16	(19%)
Use of anti-IL6 agents	2/108	(2%)	2/33	(6%)	2/16	(13%)
Use of intravenous immunoglobulins	1/108	(1%)	1/33	(3%)	0/16	(0%)
Use of vasopressor support	2/108	(2%)	2/33	(6%)	2/16	(13%)
Use of renal replacement therapy	1/108	(1%)	1/33	(3%)	0/16	(0%)
ICI interrupted for COVID-19‡						
Yes	76/104 (73%)		24/32 (75%)		13/17 (77%)	
No	28/104 (27%)		8/32 (25%)		4/17 (23%)	
ICI resumed§						
Yes	43/76 (57%)		4/24 (17%)		2/13 (15%)	
No	33/76 (43%)		20/24 (83%)		11/13 (85%)	

*Not known for 2 patients.
†Within 3 days of COVID-19 diagnosis.
‡Information on reason for interrupting ICI was not known for 6 patients.
§Number of patients who resumed ICI after discontinuing because of COVID-19.
CRP, C reactive protein; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibition; WBC, white blood cells.

treated with ICI was high (46%) in comparison with previously reported rates for hospitalized patients with cancer (11%–28%)[17 20 21] and was due to COVID-19 in almost half of the cases. These findings have implications for clinical decision-making for patients who are receiving immunotherapy.

COVID-19 has had, and continues to have, an unprecedented impact on society and healthcare services. The increased risk for severe illness and mortality in patients with cancer has raised safety concerns among patients and clinicians alike.[7 8 17] The notion that a subgroup of patients with severe COVID-19 develop a cytokine storm syndrome,[14] possibly reflecting a high-risk inflammatory phenotype, is of particular concern in a context of ICI.[22] To better understand the impact of ICI on patients with laboratory-confirmed SARS-CoV-2, we integrated and analyzed data from 110 ICI-treated patients with different cancer types.
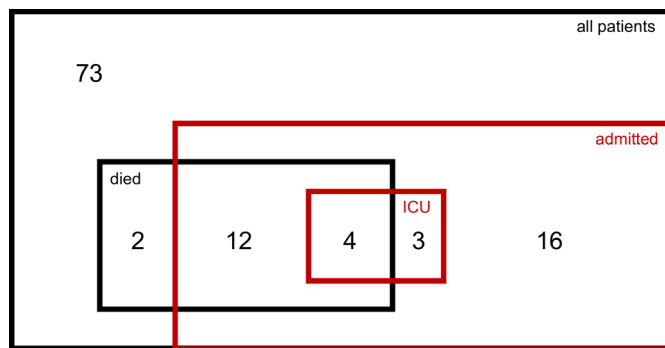
Figure 1 Venn diagram representing all patients (110), patients admitted to hospital (35), admitted to intensive care unit (ICU) (7) and patients who died (18).

Almost 40% of patients had asymptomatic COVID-19 infection, which is well in the range of the reported 30%–75% of individuals with asymptomatic COVID-19 infection in the community.[8 23–25] Although less permissive screening programs in some countries make it challenging to ascertain the true number of asymptomatic COVID-19 cases, patients with cancer are likely to be repeatedly tested. Our findings do not indicate a different symptomatic presentation at diagnosis of COVID-19 in ICI-treated patients. Considering the frequency at which patients on ICI visit healthcare facilities, this finding underscores the importance of transmission tracking and contact tracing in healthcare services to avoid spread of COVID-19 among vulnerable patients.

Just under a third of the patients with COVID-19 on immunotherapy were admitted to hospital in our study, most of whom were symptomatic. This is slightly lower than hospital admission rates reported for the cancer population in general.[7] The presence of dyspnea was, as expected, a predictor for both hospital admission and mortality. ICU admission rate in our study was low at only 6%. While this is in line with the notion that 5% of individuals without comorbidities develop severe illness from COVID-19 infection,[3] it is in stark contrast with the high mortality rates in the cancer population. In our study, 18 out of 110 patients died (16%), most not attributed to COVID-19. This fatality rate is clearly higher than the case fatality rate in the community (2.3%)[3] yet within the range of what has been reported for the cancer population (7.6%–33%).[5 6] None of the patients who received adjuvant ICI died. Of the 18 patients who died, 14 were not admitted to ICU. Although underlying malignancy and constrained healthcare systems were reported as factors in decision-making, further exploration of the perceptions of a cancer diagnosis will be essential in an era where increasing numbers of patients with advanced cancer achieve long-term responses to immunotherapy.

Interpreting overall mortality is inherently complicated by the divergent impact ICI may have on COVID-19–related and malignancy-related outcomes. Furthermore, several factors could have influenced mortality rates in our study. First, the effect of tumor type on COVID-19 outcomes has been recognized: higher COVID-19 mortality rates have been reported for hematological[26] and thoracic malignancies.[6] Our cohort included more patients with melanoma than with NSCLC and the mortality rate of patients with melanoma was lower than that of patients with NSCLC. Second, treatment with anti-PD-(L)1 plus anti-CTLA-4 was associated with a significant higher admission but not mortality rate possibly reflecting the higher adverse events rate but better oncological outcomes associated with combination immunotherapy. Third, patients who had chemotherapy in the 12 weeks prior to COVID-19 were excluded from our study. If recent chemotherapy results in worse COVID-19–related outcomes, exclusion of these patients could contribute to a difference in observed outcomes; however, recent administration of chemotherapy has not been invariably associated with worse COVID-19 outcomes.[8 9] Finally, median follow-up in our study was 82 days, which is several times longer than earlier reports.[6 7]

Of particular relevance is the notion, consistent with other reports,[9] that baseline corticosteroid use (at a prednisone equivalent dose of ≥10 mg) is associated with a higher risk for admission. The RECOVERY trial, which had not yet been published when patients in our study were treated, showed that the anti-inflammatory and immunosuppressive effects of dexamethasone were beneficial in patients requiring respiratory support.[22] While the use of corticosteroids may be confounding in an ICI context (immunotherapy-related adverse events), it remains important to note that dampening immune response with corticosteroids in the early stages of COVID-19 infection can be detrimental and may also compromise cancer-related outcomes.[27] In later stages, with an aberrant inflammatory response and less viral activity taking place, corticosteroids could be of benefit. This may be consistent with our finding that prednisone was associated with a higher risk for hospital admission but not with increased mortality. Lymphocytopenia, as reported by Yang et al,[19] and high CRP were predictors for higher mortality but may also impact malignancy-related outcomes.[28] It is, however, somewhat unexpected that a well-established risk factor such as cardiovascular disease was not associated with more severe COVID-19 illness. This is likely the result of a smaller population (ICI-only as opposed to unselected) and cardiovascular disease not being further specified. In our study, older age and male sex were also not associated with a higher mortality (4 out of 18 patients who died were younger than 50 years, 3 of whom were women).

Approximately one fourth of the patients did not interrupt ICI despite COVID-19 infection and most of these patients were asymptomatic. This subset of patients was too small to draw any conclusions regarding adverse outcomes for the patients themselves, yet it is, from a public health perspective, imperative to isolate patients who tested positive for SARS-CoV-2.

Our study has some limitations. First, there is no non-ICI control group; this would have been challenging given that treatment choices are inextricably linked to patient and

Table 3 Univariate and multivariate analysis of factors associated with hospital admission and overall survival

	Hospital admission				Overall survival	
	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value	Univariate HR (95% CI)	P value
Age (years)						
≤65	1	0.7662			1	0.5814
>65	1.13 (0.50 to 2.55)				0.76 (0.29 to 2.01)	
Sex						
Male	1	0.5017			1	0.7924
Female	0.74 (0.31 to 1.78)				1.14 (0.42 to 3.10)	
Region						
Europe	1	0.0306			1	0.0006
Australia	0.31 (0.13 to 0.75)				NA*	
North America	0.35 (0.03 to 3.73)				6.30 (2.20 to 18.00)	
Treatment setting						
Advanced	1	0.1080			NA†	
(Neo)adjuvant	0.42 (0.14 to 1.21)				NA	
Cancer type						
Melanoma	1	0.4847			1	0.0345
NSCLC	1.15 (0.35 to 3.75)				3.81 (1.02 to 14.27)	
Other	2.21 (0.75 to 6.53)				5.71 (1.73 to 18.83)	
RCC	1.84 (0.46 to 7.34)				2.65 (0.51 to 13.66)	
Coexisting disorder Cardiovascular						
No	1	0.0498			1	0.1446
Yes	0.34 (0.12 to 1.00)				0.33 (0.08 to 1.46)	
Diabetes						
No	1	0.5566			1	0.6697
Yes	1.39 (0.46 to 4.20)				1.31 (0.38 to 4.57)	
Pulmonary disease						
No	1	0.5482			1	0.1289
Yes	1.44 (0.44 to 4.79)				2.38 (0.78 to 7.31)	
Kidney disease						
No	1	0.3183			1	0.0271
Yes	2.32 (0.44 to 12.15)				4.09 (1.17 to 14.29)	
ICI						
Anti-PD-1/anti-PD-L1	1	0.0287	1	0.0273	1	0.7585
Anti-PD-1+anti-CTLA-4	4.37 (1.40 to 13.61)		5.68 (1.58 to 20.36)		1.43 (0.41 to 5.03)	
Other	2.91 (0.39 to 21.88)		2.13 (0.17 to 26.29)		1.77 (0.23 to 13.62)	
Interval between last ICI dose and COVID-19 diagnosis						
≥28 days	1	0.2021			1	0.6273
<28 days	0.59 (0.26 to 1.33)				1.27 (0.48 to 3.34)	
Previous chemotherapy						
No	1	0.8084			1	0.4246
Yes	0.88 (0.33 to 2.38)				1.53 (0.54 to 4.35)	

Continued

Table 3 Continued

	Hospital admission				Overall survival	
	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value	Univariate HR (95% CI)	P value
ECOG at COVID-19 diagnosis						
0–1	1	0.0014	1	0.0013	1	0.0115
2–4	30.82 (3.75 to 253.2)		39.25 (4.17 to 369.2)		3.84 (1.35 to 10.92)	
Prednisone ≥10 mg/day						
No	1	0.0075			1	0.5099
Yes	5.04 (1.54 to 16.48)				1.52 (0.44 to 5.30)	
Symptoms						
No	1	0.0018	1	0.0073	1	0.0526
Yes	5.34 (1.86 to 15.33)		5.30 (1.57 to 17.89)		4.31 (0.98 to 18.85)	
Fever						
No	1	0.7839			1	0.1786
Yes	1.16 (0.41 to 3.25)				0.50 (0.18 to 1.38)	
Cough						
No	1	0.3484			1	0.5760
Yes	0.63 (0.23 to 1.67)				0.75 (0.27 to 2.07)	
Dyspnea						
No	1	0.0054			1	0.0182
Yes	4.74 (1.58 to 14.21)				3.49 (1.24 to 9.84)	
Laboratory tests‡ WBC ≥10,000/mm^3						
No	1	0.0025			1	0.4181
Yes	8.70 (2.15 to 35.29)				1.70 (0.47 to 6.12)	
Lymphocytes <1500/mm^3						
No	1	0.0089			1	0.0250
Yes	3.76 (1.39 to 10.16)				4.38 (1.20 to 15.94)	
CRP ≥100 mg/L						
No	NA§				1	0.0194
Yes	NA				3.70 (1.24 to 11.10)	
Creatinine ≥133 μM						
No	1	0.0879			1	0.1012
Yes	3.29 (0.84 to 12.88)				2.98 (0.81 to 11.03)	
RECIST response						
SD/PD	1	0.0928			1	0.1422
PR/CR	0.40 (0.14 to 1.17)				0.38 (0.10 to 1.39)	

*No patients in Australia died.
†All patients who died had advanced disease.
‡Within 3 days of COVID-19 diagnosis.
§All patients with CRP ≥100 mg/L were admitted to hospital.
CR, complete response; CRP, C reactive protein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibition; NA, not available; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; WBC, white blood cells.

Table 4 Demographic and treatment findings for patients who died

Age	Sex	Country	Cancer type	ICI type	Symptoms	Admitted to hospital	ICU	Reason not to admit to ICU	Primary cause of death	Cytokine release syndrome
80	F	USA	NSCLC	Anti-PD-1/L1	No	Yes	Yes	–	Other	–
73	F	USA	NSCLC	Anti-PD-1/L1	Yes	Yes	Yes	–	COVID-19	No
54	M	USA	Melanoma	Anti-PD-1/L1	Yes	Yes	No	Underlying malignancy	Malignancy	–
51	M	USA	RCC	Anti-PD-1/L1	Yes	Yes	No	Not stated	Malignancy	–
71	F	USA	Urothelial	Anti-PD-1/L1	Yes	No	No	Underlying malignancy	Malignancy	–
61	M	USA	H&NSCC	Anti-PD-1/L1	Yes	Yes	No	Not stated	Other	–
74	M	USA	Gastric	Anti-PD-1/L1	Yes	Yes	No	Not stated	COVID-19	Yes
81	M	USA	Esophageal	Anti-PD-1/L1	Yes	Yes	Yes	–	COVID-19	No
65	M	USA	Esophageal	Anti-PD-1/L1	Yes	Yes	No	Not stated	COVID-19	Yes
45	F	USA	HCC	Anti-PD-1/L1	Yes	Yes	No	Not stated	Malignancy	–
49	F	USA	Sarcoma	Anti-PD-1 plus anti-CTLA-4	No	Yes	Yes	–	COVID-19	Yes
60	M	Canada	NSCLC	Anti-PD-1/L1	Yes	No	No	Not stated	Malignancy	–
56	M	Canada	RCC	Anti-PD-1 plus anti-CTLA-4	Yes	Yes	No	Underlying malignancy	Malignancy	–
65	M	Italy	NSCLC	Anti-PD-1/L1	Yes	Yes	No	Constrained healthcare system	COVID-19	No
73	F	Italy	Melanoma	Anti-PD-1/L1	Yes	Yes	No	Underlying malignancy	COVID-19	No
72	M	Italy	Melanoma	Anti-PD-1/L1	Yes	Yes	No	Constrained healthcare system	COVID-19	No
35	F	UK	Melanoma	Anti-PD-1 plus anti-CTLA-4	No	Yes	No	Underlying malignancy	Malignancy	–
42	M	France	Melanoma	Anti-PD-1 plus anti-CTLA-4	Yes	Yes	No	Underlying malignancy	Malignancy	–

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; F, female; HCC, hepatocellular carcinoma; H&NSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibition; ICU, intensive care unit; M, male; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; RCC, renal cell carcinoma.

disease characteristics making a retrospective comparison of treatment modalities in a matched patient population elusive. Second, patients contracted COVID-19 relatively early in the pandemic and there was no universal screening for COVID-19 among all ICI-treated patients. This may have resulted in an underestimation of the true number of COVID-19–infected patients on ICI (in particular asymptomatic patients) with possible bias toward symptomatic patients who required hospital admission. Lastly, the low ICU admission rate because of underlying malignancy (and the possible role of advance care directives) complicates case fatality rate interpretation.

In conclusion, this is, to our knowledge, the largest multicenter study to investigate the impact of COVID-19 specifically in ICI-treated patients with cancer. It is well established that patients with cancer are at a higher risk of severe COVID-19 infection in comparison with individuals without comorbidities. Based on our findings, treatment with ICI does not appear to be an additional risk factor for severe COVID-19 infection in patients with cancer. We could identify several factors predictive of a higher risk for hospital admission and/or mortality. This general observation does not exclude the possibility that individual patients at the extremes of the COVID-19 clinical spectrum experience exacerbating or mitigating effects from ICI treatment. A better understanding of high-risk inflammatory phenotypes prone to develop severe COVID-19 illness remains essential, particularly in an ICI context.

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