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Previous immune checkpoint inhibitor therapy is associated with decreased COVID-19-related hospitalizations and complications in patients with cancer: Results of a propensity-matched analysis of the OnCovid registry

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ABSTRACT

Objectives: To date, studies have not provided definitive answers regarding whether previous immune checkpoint inhibitor (ICI) treatment alters outcomes for cancer patients with COVID-19.
Methods: The OnCovid registry (NCT04393974) was searched from February 27, 2020, to January 31, 2022, for patients who received systemic anti-cancer therapy in the 4 weeks before laboratory-confirmed COVID-19 diagnosis. Propensity-score matching using country, vaccination status, primary tumor type, sex, age, comorbidity burden, tumor stage, and remission status investigated differences in predefined clinical outcomes comparing those who had or had not received ICIs.
Results: Of 3523 patients screened, 137 ICI-only and 1378 non-ICI met inclusion criteria. Before matching, ICI patients were older, male, enrolled at centers in Italy, and had histories of smoking, thoracic cancers, advanced cancer stages, and active malignancies ($P \leq 0.02$). After matching, there were 120 ICI and 322 non-ICI patients. ICI patients had no differences (odds ratio: 95% CI) in presenting COVID-19 symptoms (0.69: 0.37-1.28), receipt of COVID-specific therapy (0.88: 0.54-1.41), 14-day (0.95: 0.56-1.61), or 28-day (0.79: 0.48-1.29) mortalities. However, ICI patients required less COVID-19-related hospitalization (0.37: 0.21-0.67) and oxygen therapy (0.51: 0.31-0.83) and developed fewer complications (0.57: 0.36-0.92).
Conclusion: In this propensity-score matched analysis, previous ICI therapy did not worsen and potentially improved COVID-19 outcomes in patients with cancer.
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Introduction

Immune checkpoint inhibitor (ICI) use steadily increased since early reports describing marked efficacy [1]. They are now a mainstay treatment for several cancer types. Since the start of the SARS-CoV-2 pandemic, questions persisted about whether and how immune-enhancing properties of ICIs impact outcomes in cancer patients with COVID-19 [2–4]. In particular, considering the cytokine-release syndrome as the major event driving the deranged immune response underlying severe COVID-19, the major concerns were related to the possible exacerbating effect of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-1/programmed death ligand-1 (PD-1/PD-L1) checkpoint inhibitors [5]. In addition, ICIs are known to produce immune-related adverse events, including interstitial pneumonitis, with potential implications of synergistic lung injury. On the one hand, animal studies suggest checkpoint pathways are protective in certain systemic viral infections [6], while initial clinical evidence indicates potential synergistic antiviral effects of PD-L1 inhibition and antiretroviral therapy in HIV-1-positive patients [7].

Determining how ICIs impact outcomes in cancer patients with COVID-19 is difficult for several reasons. While used for several cancer types, fewer cancer patients receive ICIs compared to other systemic anticancer therapies (SACT). Also, many variables confound this assessment, including comorbidities, cancer type, COVID-19 infection, and ICI regimen. In a systematic review and meta-analysis we conducted of 42 reports published before May 2021, only nine provided data to assess adjusted outcomes [8]. Of these, considerable heterogeneity of ICI effect on survival and severe events existed ($I^2 = 42\%$, $P = 0.10$ and $I^2 = 52\%$, $P = 0.08$ respectively). Only one study investigated more than 100 ICI patients while more than half studied fewer than 10 patients. Studies with adjusted analyses included fewer than 44 patients each. Although no association with clinical outcomes was found, certainty of evidence was very low due to limited ICI patient numbers and few adjusted analyses. Recent reports published in 2022 continue to be at odds regarding whether ICIs have a harmful, beneficial, or no effect in this patient group [9–11].

Recognizing the importance of understanding SARS-CoV-2 infection in patients with cancer, registries were initiated early in the pandemic that systematically compiled data from cancer patients. These registries provide increasingly informative tools for examining ICI treatment in patients with SARS-CoV-2 infection. OnCovid is one such registry including 37 centers from UK, Italy, Spain, France, Belgium, and Germany. It prospectively collected data from patients with cancer presenting with laboratory-confirmed COVID-19 and reports from this registry were previously published [12–19]. We employed this registry in combination with propensity-matched analysis to compare ICI therapy alone vs non-ICI SACT received within 4 weeks of COVID-19 diagnosis on outcomes in patients with cancer.

Methods

In this retrospective analysis we utilized the OnCovid registry (NCT04393974) database to explore the potential association between previous exposures to chemotherapy-free ICI regimens and COVID-19 severity. Some methods employed to explore the OnCovid registry described in this study were published previously [12–20]. A full description of the OnCovid study design and procedures is provided in Supplementary Methods. For details on data collection, refer to Supplementary Methods and Supplementary Table 1.

Study approval

Development and use of the OnCovid registry (NCT04393974) was approved by United Kingdom Health Research Authority (20/HRA/1608) and corresponding research ethics committees at each participating institution. Further approval was provided by National Institutes of Health's Office of Technology Transfer.

Patient selection and study design

The OnCovid registry prospectively collected consecutive patients meeting inclusion criteria: (i) age ≥18 years; (ii) COVID-19 diagnosis confirmed by nasopharyngeal swab reverse transcription-polymerase chain reaction; (iii) any history of malignancy. Non-invasive/premalignant lesions or those with low malignant potential (i.e. skin basal cell carcinoma, cervical non-invasive carcinoma in situ, ductal carcinoma in situ) were excluded. For hematologic malignancies, only diseases with defined malignant behavior (lymphoma, leukemia, multiple myeloma) were included.

SACT is primarily administered in active and/or advanced stage disease. Therefore, to mitigate bias from comparing patients with non-active/early-stage disease, we focused this analysis on patients who received SACT within 4 weeks before COVID-19 diagnosis. The group of interest is patients receiving chemotherapy-free, ICI-based regimens. Patients receiving other SACT modalities (chemotherapy, chemotherapy combinations, tyrosine kinase inhibitors, endocrine therapy, and other monoclonal antibodies) comprised the control group (designated as ICI and non-ICI patients, respectively).

We describe distribution of key baseline characteristics across the overall study population, ICI, and non-ICI groups. We next performed propensity-score matching (PSM) between ICI and non-ICI cohorts to obtain comparable subgroups. Outcomes were compared in unmatched and matched groups.

Clinical data and outcomes

Variables related to key demographics and tumor characteristics were abstracted: country, sex, age, number of comorbidities, smoking status, primary tumor site, tumor stage, tumor status, and SARS-CoV-2 vaccination status (see Supplementary Methods for definition and Supplementary Table 2). Patients were observed from confirmation date of first SARS-CoV-2 infection until death or loss of follow-up. Patients that did not attend planned follow-up appointments scheduled by treating clinicians, for any reason, were considered lost to follow-up.

Acknowledging the competing influence of the underlying malignancy in determining clinical outcomes, we elected the all-cause 14-day and 28-day case fatality rate as the clinical endpoints of interest, in an attempt to differentiate early (COVID-19-related) from late (cancer-related) mortality as consistently done in with our registry [15,16,17,21].

The following were abstracted as a proxy of COVID-19 morbidity: COVID-19-related symptoms, COVID-19 complications, receipt of COVID-19-oriented therapy, hospitalization due to COVID-19, need for oxygen therapy, and mortality. Patients hospitalized at enrollment (designated as pre-existing) were excluded from hospitalization analysis. Mortality was validated by investigators at each center through electronic medical records and death certificates. Predefined COVID-19-related symptoms, complications, and therapies can be found in the Supplemental Methods.

Statistical analysis

Baseline characteristics are reported using descriptive statistics. Categorical variables were analyzed using Fisher exact test and Pearson $\chi 2$ test as appropriate with estimation presented as unadjusted odds ratio and 95% CI. Median follow-up was calculated using reverse Kaplan-Meier method.

PSM with a 1:3 ratio (ICI vs non-ICI) and caliper of 0.2 was performed using MatchIt package in R with “nearest” method, to obtain comparable cohorts of ICI vs non-ICI SACT within 4 weeks before COVID-19 diagnosis, with balancing measured through post-matching standardized mean difference (SMD). Patients receiving ICIs were set as the reference group. Patients enrolled with the diagnosis of breast cancer were excluded from matching as none received ICI therapy. Patients were matched based on key variables: country (United Kingdom, Italy, Spain, others), sex (male vs female), age (≥65 vs <65 years), number of comorbidities (0-2 vs >2 comorbidities), primary tumor (gastrointestinal, gynecological/genitourinary, thoracic, hematologic, and other), tumor stage (advanced vs non-advanced), tumor status (active/progressive vs non-active/in remission), and vaccination status (fully/boosted vs partially/unvaccinated). Patients with missing information for these were excluded from matching.

Each outcome is presented as a crude rate and compared with univariable analysis in the overall study population. To mitigate any residual variability in baseline covariates after matching, a double adjustment approach [22] was used by fitting separate multivariable logistic regression models to compare each outcome between the PSM cohort using sex, age, comorbidities, tumor stage, tumor status, and vaccination status as adjusting covariates. Results are presented as odds ratios (OR) and 95% CI. For all analyses, *P*-value of <0.05 was considered statistically significant. Analyses were performed using R-studio software (R Core Team (2021). R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org) and MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Results

Patient characteristics and outcomes in unmatched groups

Of 3523 patients assessed, 1515 patients received SACT within 4 weeks before COVID-19 diagnosis, including 137 treated with ICIs as their SACT (Figure 1). The administered ICIs included mostly PD-1/PD-L1 checkpoint inhibitor monotherapy (n = 107, 78.1%), followed by PD-1/PD-L1 and CTLA-4 inhibitors combinations (N = 13, 9.5%), experimental monotherapy (N = 13, 9.5%) and experimental combinations (N = 4, 2.9%). A detailed list of types of ICI is available in Supplementary Table 3. Baseline data for these patients are provided in the left-hand columns of Table 1. Compared to non-ICI patients, more ICI patients were enrolled at centers in Italy, were male, and had histories of smoking, thoracic cancers, advanced cancer, and active malignancies ($P \leq 0.02$). Almost 15% of patients lacked documented smoking histories and this planned covariate was excluded from matching. Overall, most patients were unvaccinated (81.8%) with a trend of fewer unvaccinated ICI patients (77.0 vs 82.2%, $P = 0.09$). Most vaccinated patients received an mRNA vaccine (Supplementary Table 2). Proportions of ICI and non-ICI patients with 0 to 1 or ≥2 comorbidities were similar.

Outcomes for unmatched patients are shown on the left side of Table 2. COVID-19-related symptoms and complications were similar between ICI and non-ICI groups. Treatment with oxygen or COVID-19-specific therapies was also similar. While fewer ICI patients required COVID-19-related hospitalization compared to non-ICI (45.9 vs 58.4%, $P = 0.02$), mortality rate in ICI patients was greater at 14 days (22.4 vs 14.3%, $P = 0.01$) and was greater at 28 days in a trend approaching significance (26.9 vs 19.8%, $P = 0.053$).

Patient characteristics and outcomes in matched groups

After matching, there were 322 and 120 patients in non-ICI and ICI groups, respectively, that were well-balanced with an overall SMD of 0.01. Distribution of propensity scores was well-balanced on visual inspection (Supplementary Figure 1) and individual covariate SMDs were ≤0.1 (Supplementary Table 4). Previous differences in baseline characteristics of unmatched groups were no longer evident, as shown in the right-hand columns of Table 1. Results of multivariable analysis are shown on the right side of

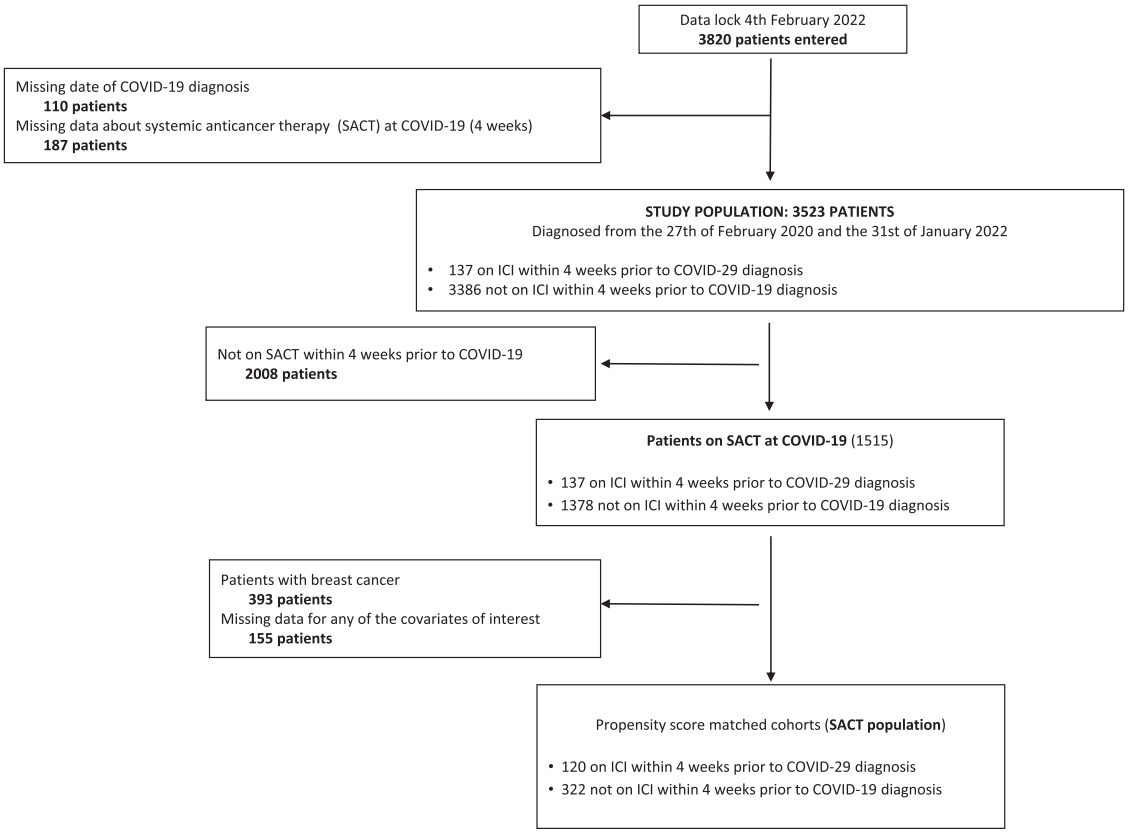

Figure 1. OnCovid database patients included in analysis.

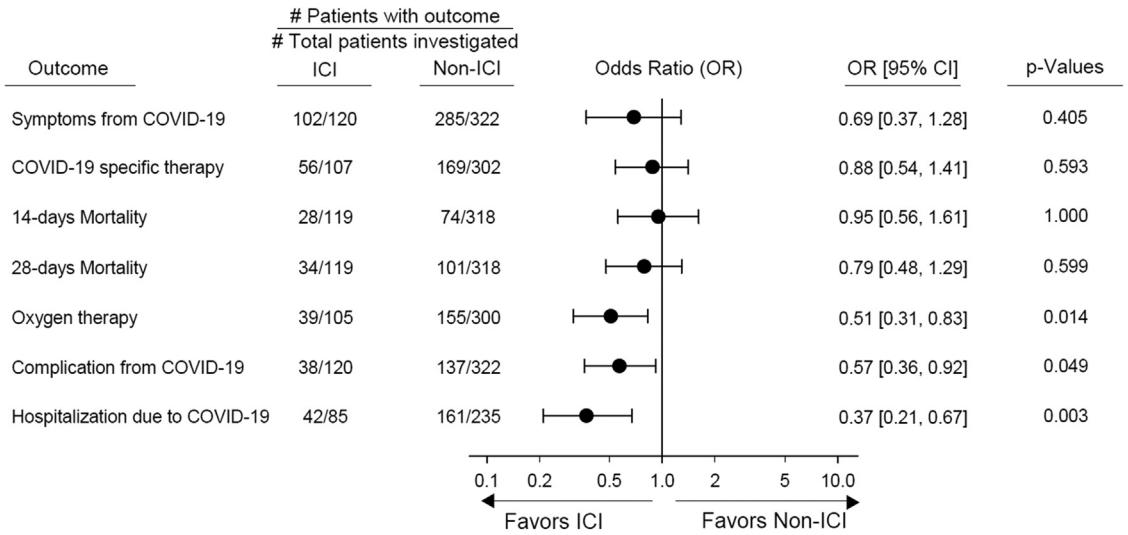

Figure 2. Forest-plot graph reporting the propensity score matching fitted multivariable logistic regression results for each COVID-19 outcome. Numbers in each calculation are provided in Table 2. Full multivariable models are presented in Supplementary Table 4.
CI, confidence intervals; OR, odds ratio.

Table 2. Compared to non-ICI, those on ICI regimens maintained no significant differences in presence of COVID-19-related symptoms (OR 0.69, 95% CI: 0.37-1.28) or receipt of COVID-19-oriented therapy (OR 0.88, 95% CI: 0.54-1.41) (Figure 2). ICI recipients no longer had differences in 14-day (OR 0.95, 95% CI: 0.56-1.61) and 28-day mortality (OR 0.79, 95% CI: 0.48-1.29). However, receipt of ICI was associated with reduced need for oxygen therapy (OR 0.51, 95% CI: 0.31-0.83), hospitalization due to COVID-19 (OR 0.37, 95% CI: 0.21-0.67), and COVID-19 related complications (OR 0.57, 95% CI: 0.36-0.92). Full PSM-fitted multivariable regression models are reported in Supplementary Table 5.

Discussion

ICIs amplify the host cellular immune response, thus augmenting anti-tumor and, in some instances, anti-pathogen responses [1,7]. However, COVID-19 pathology and mortality are in part related to an exuberant host immune response, leading to

Table 1
Baseline characteristics of all patients who were on systemic anticancer therapy in the 4 weeks before COVID-19 diagnosis.

Baseline characteristics	All patients	All patients			Matched patients		
	(N = 1515)	Non-ICI patients (N = 1378)	ICI patients (N = 137)	*P*-value	Non-ICI patients (N = 322)	ICI patients (N = 120)	*P*-value
Country							
United Kingdom	324 (21.4)	304 (22.1)	20 (14.6)	0.0192	49 (15.2)	18 (15.0)	0.648
Spain	502 (33.1)	459 (33.3)	43 (31.4)		127 (39.4)	42 (35.0)	
Italy	570 (37.6)	503 (36.5)	67 (48.9)		122 (37.9)	53 (44.2)	
Others	119 (7.9)	112 (8.1)	7 (5.1)		24 (7.5)	7 (5.8)	
Sex							
Female	815 (53.9)	770 (56.0)	45 (32.8)	<0.0001	107 (33.2)	39 (32.5)	0.975
Male	697 (46.1)	605 (44.0)	92 (67.2)		215 (66.8)	81 (67.5)	
Missing	3	3	-				
Age							
<65 years	728 (48.3)	681 (49.7)	47 (34.6)	0.0007	133 (41.3)	44 (36.7)	0.438
≥65 years	778 (51.7)	689 (50.3)	89 (65.4)		189 (58.7)	76 (63.3)	
Missing	9	8	1		-	-	
Comorbidities							
0-1	941 (62.1)	860 (62.4)	81 (58.1)	0.4498	209 (64.9)	70 (58.3)	0.245
≥2	574 (37.9)	518 (37.6)	56 (40.9)		113 (35.1)	50 (41.7)	
Smoking history							
Never smokers	710 (46.7)	671 (57.4)	39 (31.5)	<0.0001	123 (38.2)	35 (29.2)	0.083
Former/current smokers	584 (38.5)	449 (42.6)	85 (68.5)		163 (50.6)	75 (62.5)	
Missing	221	208	13		36 (11.2)	10 (8.3)	
Primary tumor							
Breast	393 (26.1)	393 (28.7)	-	<0.0001	-	-	0.620
Gastrointestinal	351 (23.3)	311 (22.7)	40 (29.4)		111 (34.5)	36 (30.0)	
Gynecological/Genito-Urinary	241 (15.9)	216 (15.8)	25 (18.4)		74 (23.0)	25 (20.8)	
Thoracic	230 (15.3)	168 (12.3)	62 (45.6)		113 (35.1)	52 (43.3)	
Others	85 (5.6)	79 (5.8)	6 (4.4)		21 (6.5)	6 (5.0)	
Hematological	207 (13.7)	204 (14.9)	3 (2.2)		3 (0.9)	1 (0.8)	
Missing	8	7	1		-	-	
Tumor stage							
Non-advanced	447 (33.4)	459 (35.4)	18 (13.4)	<0.0001	39 (12.1)	15 (12.5)	1.000
Advanced	952 (66.6)	836 (64.6)	116 (86.6)		283 (87.9)	105 (87.5)	
Missing	86	83	3		-	-	
Status at COVID-19 diagnosis							
Remission/non-measurable	509 (33.4)	484 (35.3)	25 (18.4)	0.0001	62 (19.3)	23 (19.2)	1.000
Active malignancy	1002 (66.3)	891 (64.7)	111 (81.6)		260 (80.7)	97 (80.8)	
Missing	4	3	1		-	-	
SARS-CoV-2 vaccination status							
Unvaccinated	1171 (81.8)	1074 (82.2)	97 (77.0)	0.0924	Unvaccinated:		0.490
Partially vaccinated	37 (2.6)	36 (2.8)	1 (0.8)		271 (84.2)	97 (80.8)	
Fully vaccinated	124 (8.7)	110 (8.4)	14 (11.1)		Vaccinated:		
Boosted	100 (7.0)	86 (6.6)	14 (11.1)		51 (15.8)	23 (19.2)	
Unknown	83	72	11		-	-	

ICI, immune checkpoint inhibitor.

immunosuppressive therapies as the mainstay of COVID-19 treatment [5]. Therefore, the interplay between previous ICI therapy and COVID-19 disease progression and outcomes in cancer patients is complex. In this study, we specifically focused on whether and how previous ICI therapy impacts virus-related outcomes in cancer patients presenting with COVID-19. This question can only be addressed with observational studies. SARS-CoV-2-infected cancer patients are complex, and investigation related to COVID-19 requires adjustment for multiple confounding variables. In our previous systematic review of reports published up to May 2021, no study provided adjusted analysis on more than 44 ICI-treated patients, and most included 10 or fewer [8]. We concluded larger cohorts are needed to address this question. A recent informal literature search suggests this investigation is now one of three studies utilizing adjusted analysis in greater than 100 ICI patients [10,23].

Examination of unmatched patients demonstrates a need to adjust for confounding variables of ICI treatment in cancer patients with COVID-19. Compared to non-ICI patients, significantly more ICI patients were male, older than 65 years, and had histories of smoking, thoracic cancers, advanced cancer, and active disease. These are also characteristics consistent with type and stage of tumor that ICIs are employed for. Possibly related to these imbalances, ICI patients had similar COVID-19-related symptoms, complications, and COVID-19-specific therapeutic needs, but greater 14-day and 28-day mortality in unmatched analysis. However, basis for their reduced hospitalization rates in unmatched analysis is unclear, and one could only postulate that ICIs may have an effect on accelerated immune response and viral clearance. It does not appear to reflect a protective effect of ICIs since mortality rates with ICIs were increased. In an earlier report from this registry in 890 patients, 456 of whom were on SACT, ICI therapy was not associated with worse unadjusted outcomes, including mortality [8,19].

After matching, ICI and non-ICI patient groups were well-balanced based on SMDs, distribution of propensity scores, and absence of previous significant baseline differences in unmatched groups. Possibly because age, cancer stage, and level of activity were similar, ICI patients no longer had trends of increased mortality rates in matched analysis. While presence of COVID-19 symp-

Table 2
Outcomes in patients who were on systemic anticancer therapy in the 4 weeks before COVID-19 diagnosis.

Outcomes	All Patients	All Patients			Matched Patients		
	(N = 1515)	Non-ICI Patients (N = 1378)	ICI Patients (N = 137)	OR (95% CI)	Non-ICI Patients (N = 322)	ICI Patients (N = 120)	OR (95% CI)
COVID-19 specific therapy							
No	632 (44.8)	573 (44.5)	59 (48.0)	0.87(0.60-1.26)	133 (41.6)	51 (42.5)	0.88(0.54 – 1.41)
Yes	780 (55.5)	716 (52.0)	64 (52.0)		169 (56.0)	56 (52.3)	
Missing	103	89	14		20	13	
Symptoms from COVID-19							
No	204 (13.5)	181 (13.1)	23 (16.8)	0.75(0.47-1.23)	37 (11.5)	18 (15.0)	0.69(0.37 – 1.28)
Yes	1311 (86.5)	1197 (86.9)	114 (83.2)		285 (88.5)	102 (85.0)	
Oxygen therapy requirement							
No	831 (58.9)	755 (58.5)	76 (63.3)	0.82(0.55-1.20)	145 (45.0)	66 (55.0)	0.51(0.31 – 0.83)
Yes	580 (41.1)	536 (41.5)	44 (36.7)		155 (51.7)	39 (37.1)	
Missing	104	87	17		22	15	
Complications from COVID-19							
No	1026 (67.7)	931 (67.6)	95 (69.3)	0.92(0.62-1.34)	185 (57.5)	82 (68.3)	0.57(0.36 – 0.92)
Yes	489 (32.3)	447 (32.4)	42 (30.7)		137 (42.5)	38 (31.7)	
Hospitalization							
Not required	520 (42.6)	467 (41.6)	53 (54.1)	0.61(0.40-0.92)	74 (23.0)	43 (35.8)	0.37(0.21 – 0.67)
Due to COVID-19	700 (57.4)	655 (58.4)	45 (45.9)		161 (68.4)	42 (49.4)	
Pre-existing	279	244	35		87	35	
Missing	16	12	4				
14-day mortality rate							
No	1264 (84.9)	1160 (85.7)	104 (77.6)	1.71(1.09-2.61)	244 (75.8)	91 (75.8)	0.95(0.56 – 1.61)
Yes	224 (15.1)	194 (14.3)	30 (22.4)		74 (23.3)	28 (23.5)	
Missing	27	24	3		4	1	
28-day mortality rate							
No	1184 (79.6)	1086 (80.2)	98 (73.1)	1.49(0.98-2.22)	217 (67.4)	85 (70.8)	0.79(0.48 – 1.29)
Yes	304 (20.4)	268 (19.8)	36 (26.9)		101 (31.8)	34 (28.6)	
Missing	27	24	3		4	1	

CI, confidence interval; ICI, immune checkpoint inhibitor; OR, odds ratio.

toms at presentation and receipt of COVID-19-specific therapy was similar, significantly fewer ICI patients required oxygen therapy or developed COVID-19-related complications. These differences provide a basis for why ICIs were associated with reduced hospitalizations and suggest in balanced populations, net effects of ICI therapy may be protective.

Consistent with present findings, in an analysis of greater than 2500 cancer patients with COVID-19 in the UK adjusting for age, sex, and nine comorbidities, ICI receipt within 30 days of infection in 102 patients was associated with decreased hospital, all-cause, and COVID-19-related mortality compared to other SACT or no anti-cancer therapy [10]. However, in an industry-conducted PSM study using a United States (US) database of more than 17,000 patients with cancer and COVID-19, ICI treatment in 228 patients within 90 days of COVID-19 infection had similar 30-day mortality and COVID-19 severity compared to a group of 456 patients matched on age, sex, region, smoking history, tumor type, and stage, and comorbidities [23]. Another US-based study investigated a registry of more than 12,000 patients with cancer and COVID-19, adjusting for a range of variables [24]. Of 599 registry patients administered some form of immunotherapy within 90 days of infection, 539 received an ICI. This study reported immunotherapy worsened COVID-19 severity or incidence of cytokine storm in patients with baseline immunosuppression. However, because almost 10% of immunotherapy patients received non-ICI therapy, including CAR-T cell therapy, its findings are difficult to interpret with regard to ICI therapy alone.

Considering our study and these other larger ones together, it appears even when adjusted analyses are applied in cohorts more than twice the size of previous reports, overall impact of ICI therapy in cancer patients with COVID-19 remains unclear [8]. Importantly, when considered in context of the nine smaller adjusted analyses in our systematic review, most data suggest recent ICI therapy does not worsen outcomes in cancer patients with COVID-19. Randomized controlled trials (RCTs) examining effects of acute ICI therapy may be informative on safety. In a proof-of-concept RCT, in patients with COVID-19 pneumonia not on mechanical ventilation, ICI plus tocilizumab and standard of care in seven patients reduced time to discharge without increased adverse effects compared to standard of care alone in five relatively well-balanced control patients [25]. However, this study was very small with several investigators reporting potential competing interests. Other RCTs examining effects of early ICI therapy in patients presenting with COVID-19 are registered without results (NCT04413838, NCT04356508, NCT04343144, NCT04268537, EUCTR2020-001373-70-FR, IRCT20150303021315N19).

This study and other large studies described above have limitations. Even with prospectively collected registries, subsequent analysis of registry data is retrospective. Additionally, the number of variables potentially confounding interpretation of effects of ICIs in cancer patients with COVID-19 is growing. ICI regimens are increasingly different with respect to agents, cellular targets, timing, and duration [26,27]. In fact, one of the limitations of our study is missing information on duration of exposure to ICIs before COVID-19 diagnosis. Additionally, the types and stages of cancer ICIs are used for are increasing. ICIs were predominantly used for the treatment of patients with lung cancer and unadjusted analysis showed no effect of ICI therapy on mortality or other severe outcomes in COVID-19 patients with thoracic malignancies [28]. However, the present study finds decreased COVID-19-related hospitalizations and complications in ICI-treated patients, possibly highlighting changing practice patterns. Furthermore, strains of COVID-19 are changing as is vaccination status of cancer patients [29–32]. In a previous analysis of ICI patients from the OnCovid registry, vaccination appeared beneficial [12]. Patients with cancer receiving ICIs are still a small proportion of those receiving SACT. It is

possible no registry or database will provide the granularity and power to definitively assess risks or benefits of previous ICI therapy in this population. While this analysis included country as a variable in matching, this was not a single country-based study.

Patients already hospitalized at time of their COVID-19 diagnosis were excluded from hospitalization analysis. While these patients were hospitalized for non-COVID-19-related reasons and appeared to subsequently develop nosocomial COVID-19, it is possible some had asymptomatic COVID-19 at time of hospitalization. Data related to oxygen therapy were missing for some patients. After assigning all matched ICI patients with missing data a need for oxygen therapy, and all non-ICI patients with missing data a non-need for oxygen therapy, results still favored ICI patients but were no longer significant (OR [95% CI]) (0.88 [0.58-1.34] $P = 0.56$).

Conclusion

In this propensity-matched analysis of cancer patients on SACT who presented with COVID-19, compared to patients who received non-ICI therapy, those who received ICIs had reduced oxygen requirements, COVID-19-related complications, and need for hospitalization due to COVID-19. Further clinical study is necessary to explore these associations.

Declarations of competing interest

Alessio Cortellini received consulting fees from MSD, BMS, AstraZeneca, Roche; and speakers' fees from AstraZeneca, MSD, Novartis, and Eisai. Matteo Lambertini acted as a consultant for Roche, Novartis, Lilly, AstraZeneca, Exact Sciences, MSD, Pfizer, and Seagen and received speaker honoraria from Roche, Novartis, Lilly, Pfizer, Takeda, Ipsen and Sandoz outside the submitted work. Alessandra Gennari has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, Eisai, and Daichii Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, Astra Zeneca, Celgene, and Daichii Sankyo; research funds: Eisai, Eli Lilly, and Roche. CMV has received travel grants and other honoraria from BMS, MSD, Novartis, and Roche. Joan Brunet has declared consulting/advisory role for MSD and Astra Zenec, and support for attending meetings and/or travel for GSK. Josep Tabernero reports personal financial interest in the form of scientific consultancy role for Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Ikena Oncology, Inspirna Inc, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho, Tessa Therapeutics and TheraMyc. Stocks: Oniria Therapeutics and also educational collaboration with Imedex/HMP, Medscape Education, MJH Life Sciences, PeerView Institute for Medical Education, and Physicians Education Resource (PER). Lorenza Rimassa reports receiving consulting fees from AstraZeneca, Basilea, Bayer, BMS, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, Zymeworks; lecture fees from AstraZeneca, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi, Servier; travel expenses from AstraZeneca; and institutional research funding from Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. David J Pinato received lecture fees from ViiV Healthcare, Bayer Healthcare, BMS, Roche, Eisai, Falk Foundation, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, Eisai, Roche, DaVolterra, and Astra Zeneca; research funding (to institution) from MSD and BMS. All remaining authors have declared no conflicts of interest.

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Author contributions

All authors contributed to the publication according to the ICMJE guidelines for authorship. All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Specifically: Study concept and design: AC, SM, PTP. Acquisition of data: AC, DJP, JAC, IRC, JT, LF, CT, JB, MCG, ML, MB, TND, RS, ADP, MR, AP, RS, AS, AP, VM, MVH, ASL, AB, LR, SR, GR, PP, AJL, CM, KB, ND, UM, FP, AS, CMV, RB, GG, GMD, FD, AG. Analysis and interpretation of data: PE, AM, PTP. Drafting of the manuscript: AC, PE, AM, PTP. Statistical analysis: AC, AM. Manuscript review and approval: JA, AC, PE, SM, AM, DJP, PTP, JAC, IRC, JT, LF, CT, JB, MCG, ML, MB, TND, RS, ADP, MR, AP, RS, AS, AP, VM, MVH, ASL, AB, LR, SR, GR, PP, AJL, CM, KB, ND, UM, FP, AS, CMV, RB, GG, GMD, FD, AG. Obtained funding: DJP. Study supervision: AC, DJP, PTP. Each author agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Data sharing statement

Individual, de-identified participant data and data dictionary are available at the request of investigators whose proposed use of the data was approved by the OnCovid consortium. Additional related documents are available at: https://clinicaltrials.gov/ct2/show/NCT04393974. AC and DJP had full access to and verified all the data. Further approval of this study was provided by the National Institutes of Health's Technology Transfer Center.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.11.021.

References

[1] Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell* 2015;**27**:450–61. doi:10.1016/j.ccell.2015.03.001.

[2] Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. *Immunotherapy* 2020;**12**:269–73. doi:10.2217/imt-2020-0067.

[3] Garassino MC, Ribas A. At the crossroads: COVID-19 and immune-checkpoint blockade for cancer. *Cancer Immunol Res* 2021;**9**:261–4. doi:10.1158/2326-6066.CIR-21-0008.

[4] Kattan J, Kattan C, Assi T. Do checkpoint inhibitors compromise the cancer patients' immunity and increase the vulnerability to COVID-19 infection? *Immunotherapy* 2020;**12**:351–4. doi:10.2217/imt-2020-0077.

[5] Gambichler T, Reuther J, Scheel CH, Susok L, Kern P, Becker JC. Cancer and immune checkpoint inhibitor treatment in the era of SARS-CoV-2 infection. *Cancers* 2020;**12**:3383. doi:10.3390/cancers12113383.

[6] Frebel H, Nindl V, Schuepbach RA, Braunschweiler T, Richter K, Vogel J, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. *J Exp Med* 2012;**209**:2485–99. doi:10.1084/jem.20121015.

[7] Gay CL, Bosch RJ, Ritz J, Hataye JM, Aga E, Tressler RL, et al. Clinical trial of the anti-PD-L1 antibody BMS-936559 in HIV-1 infected participants on suppressive antiretroviral therapy. *J Infect Dis* 2017;**215**:1725–33. doi:10.1093/infdis/jix191.

[8] Minkove SJ, Sun J, Li Y, Cui X, Cooper D, Eichacker PQ, et al. Comprehensive adjusted outcome data are needed to assess the impact of immune checkpoint inhibitors in cancer patients with COVID-19: results of a systematic review and meta-analysis. *Rev Med Virol* 2022;**32**:e2352. doi:10.1002/rmv.2352.

[9] Sharafeldin N, Bates B, Song Q, Madhira V, Yan Y, Dong S, et al. Outcomes of COVID-19 in patients with cancer: report from the national COVID cohort collaborative (N3C). *J Clin Oncol* 2021;**39**:2232–46. doi:10.1200/JCO.21.01074.

[10] Várnai C, Palles C, Arnold R, Curley HM, Purshouse K, Cheng VWT, et al. Mortality among adults with cancer undergoing chemotherapy or immunotherapy and infected with COVID-19. *JAMA Netw Open* 2022;**5**:e220130. doi:10.1001/jamanetworkopen.2022.0130.

[11] Wu Q, Luo S, Xie X. The impact of anti-tumor approaches on the outcomes of cancer patients with COVID-19: a meta-analysis based on 52 cohorts incorporating 9231 participants. *BMC Cancer* 2022;**22**:241. doi:10.1186/s12885-022-09320-x.

[12] Cortellini A, Dettorre GM, Dafni U, Aguilar-Company J, Castelo-Branco L, Lambertini M, et al. Immune checkpoint inhibitor therapy and outcomes from SARS-CoV-2 infection in patients with cancer: a joint analysis of OnCovid and ESMO-CoCARE registries. *J Immunother Cancer* 2022;**10**:e005732. doi:10.1136/jitc-2022-005732.

[13] Cortellini A, Salazar R, Gennari A, Aguilar-Company J, Bower M, Bertuzzi A, et al. Persistence of long-term COVID-19 sequelae in patients with cancer: an analysis from the OnCovid registry. *Eur J Cancer* 2022;**170**:10–16. doi:10.1016/j.ejca.2022.03.019.

[14] Dettorre GM, Dolly S, Loizidou A, Chester J, Jackson A, Mukherjee U, et al. Systemic pro-inflammatory response identifies patients with cancer with adverse outcomes from SARS-CoV-2 infection: the OnCovid inflammatory Score. *J Immunother Cancer* 2021;**9**:e002277. doi:10.1136/jitc-2020-002277.

[15] Pinato DJ, Patel M, Scotti L, Colomba E, Dolly S, et al., OnCovid Study Group Time-dependent COVID-19 mortality in patients with cancer: an updated analysis of the OnCovid Registry. *JAMA Oncol* 2022;**8**:114–22. doi:10.1001/jamaoncol.2021.6199.

[16] Pinato DJ, Aguilar-Company J, Ferrante D, Hanbury G, Bower M, Salazar R, et al. Outcomes of the SARS-CoV-2 omicron (B.1.1.529) variant outbreak among vaccinated and unvaccinated patients with cancer in Europe: results from the retrospective, multicentre, OnCovid registry study. *Lancet Oncol* 2022;**23**:865–75. doi:10.1016/S1470-2045(22)00273-X.

[17] Pinato DJ, Ferrante D, Aguilar-Company J, Bower M, Salazar R, Mirallas O, et al. Vaccination against SARS-CoV-2 protects from morbidity, mortality and sequelae from COVID-19 in patients with cancer. *Eur J Cancer* 2022;**171**:64–74. doi:10.1016/j.ejca.2022.04.036.

[18] Pinato DJ, Tabernero J, Bower M, Scotti L, Patel M, Colomba E, et al. Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. *Lancet Oncol* 2021;**22**:1669–80. doi:10.1016/S1470-2045(21)00573-8.

[19] Pinato DJ, Zambelli A, Aguilar-Company J, Bower M, Sng C, Salazar R, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. *Cancer Discov* 2020;**10**:1465–74. doi:10.1158/2159-8290.CD-20-0773.

[20] Garrigós L, Saura C, Martinez-Vila C, Zambelli A, Bower M, Pistilli B, et al. COVID-19 in breast cancer patients: a subanalysis of the OnCovid registry. *Ther Adv Med Oncol* 2021;**13** 17588359211053416. doi:10.1177/17588359211053416.

[21] Pinato DJ, Scotti L, Gennari A, Colomba-Blameble E, Dolly S, Loizidou A, et al. Determinants of enhanced vulnerability to coronavirus disease 2019 in UK patients with cancer: a European study. *Eur J Cancer* 2021;**150**:190–202. doi:10.1016/j.ejca.2021.03.035.

[22] Nguyen TL, Collins GS, Spence J, Daurès JP, Devereaux PJ, Landais P, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Med Res Methodol* 2017;**17**:78. doi:10.1186/s12874-017-0338-0.

[23] Tan R, Yun C, Seetasith A, Sheinson D, Walls R, Ngwa I, et al. Impact of immune checkpoint inhibitors on COVID-19 severity in patients with cancer. *Oncologist* 2022;**27**:236–43. doi:10.1093/oncolo/oyab083.

[24] Bakouny Z, Labaki C, Grover P, Awosika J, Gulati S, Hsu CY, et al. Interplay of immunosuppression and immunotherapy among patients with cancer and COVID-19. *JAMA Oncol* 2023;**9**:128–34. doi:10.1001/jamaoncol.2022.5357.

[25] Sánchez-Conde M, Vizcarra P, Pérez-García JM, Gion M, Martialay MP, Taboada J, et al. Pembrolizumab in combination with tocilizumab in high-risk hospitalized patients with COVID-19 (COPERNICO): a randomized proof-of-concept phase II study. *Int J Infect Dis* 2022;**123**:97–103. doi:10.1016/j.ijid.2022.08.007.

[26] Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. *Annu Rev Pathol* 2021;**16**:223–49. doi:10.1146/annurev-pathol-042020-042741.

[27] Kraehenbuehl L, Weng CH, Eghbali S, Wolchok JD, Merghoub T. Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways. *Nat Rev Clin Oncol* 2022;**19**:37–50. doi:10.1038/s41571-021-00552-7.

[28] Garassino MC, Whisenant JG, Huang LC, Trama A, Torri V, Agustoni F, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol* 2020;**21**:914–22. doi:10.1016/S1470-2045(20)30314-4.

[29] Aleem A, Akbar Samad AB, Slenker AK. Emerging variants of SARS-CoV-2 and novel therapeutics against coronavirus (COVID-19). *Treasure Island: Stat*Pearls; 2022.

[30] Ghosh N, Nandi S, Saha I. A review on evolution of emerging SARS-CoV-2 variants based on spike glycoprotein. *Int Immunopharmacol* 2022;**105**:108565. doi:10.1016/j.intimp.2022.108565.

[31] Mei Q, Hu G, Yang Y, Liu B, Yin J, Li M, et al. Impact of COVID-19 vaccination on the use of PD-1 inhibitor in treating patients with cancer: a real-world study. *J Immunother Cancer* 2022;**10**:e004157. doi:10.1136/jitc-2021-004157.

[32] Wilson SL, Wiysonge C. Social media and vaccine hesitancy. *BMJ Glob Health* 2020;**5**:e004206. doi:10.1136/bmjgh-2020-004206.