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Immune checkpoint inhibitor therapy and outcomes from SARS-CoV-2 infection in patients with cancer: A joint analysis of OnCovid and ESMO-CoCARE registries

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Immune checkpoint inhibitor therapy and outcomes from SARS-CoV-2 infection in patients with cancer: a joint analysis of OnCovid and ESMO-CoCARE registries

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ABSTRACT

Background As management and prevention strategies against COVID-19 evolve, it is still uncertain whether prior exposure to immune checkpoint inhibitors (ICIs) affects COVID-19 severity in patients with cancer.

Methods In a joint analysis of ICI recipients from OnCovid (NCT04393974) and European Society for Medical Oncology (ESMO) CoCARE registries, we assessed severity and mortality from SARS-CoV-2 in vaccinated and unvaccinated patients with cancer and explored whether prior immune-related adverse events (irAEs) influenced outcome from COVID-19.

Findings The study population consisted of 240 patients diagnosed with COVID-19 between January 2020 and February 2022 exposed to ICI within 3 months prior to COVID-19 diagnosis, with a 30-day case fatality rate (CFR_{30}) of 23.6% (95% CI 17.8 to 30.7%). Overall, 42 (17.5%) were fully vaccinated prior to COVID-19 and experienced decreased CFR_{30} (4.8% vs 28.1%, p=0.0009), hospitalization rate (27.5% vs 63.2%, p<0.0001), requirement of oxygen therapy (15.8% vs 41.5%, p=0.0030), COVID-19 complication rate (11.9% vs 34.6%, p=0.0040), with a reduced need for COVID-19-specific therapy (26.3% vs 57.9%, p=0.0004) compared with unvaccinated patients. Inverse probability of treatment weighting (IPTW)-fitted multivariable analysis, following a clustered-robust correction for the data source (OnCovid vs ESMO CoCARE), confirmed that vaccinated patients experienced a decreased risk of death at 30 days (adjusted OR, aOR 0.08, 95% CI 0.01 to 0.69).

Overall, 38 patients (15.8%) experienced at least one irAE of any grade at any time prior to COVID-19, at a median time of 3.2 months (range 0.13–48.7) from COVID-19 diagnosis. IrAEs occurred independently of baseline characteristics except for primary tumor (p=0.0373) and were associated with a significantly decreased CFR_{30} (10.8% vs 26.0%, p=0.0462) additionally confirmed by the IPTW-fitted multivariable analysis (aOR 0.47, 95% CI 0.33 to 0.67). Patients who experienced irAEs also presented

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ SARS-CoV-2 vaccines significantly improve COVID-19 morbidity and mortality in patients with cancer. Efficacy data from large registry studies in patients receiving immune checkpoint inhibitors (ICIs) are still lacking.

WHAT THIS STUDY ADDS

⇒ This joint analysis of patients recently exposed to ICI from OnCovid and European Society for Medical Oncology-CoCARE registries confirms clinical efficacy of SARS-CoV-2 vaccination in reducing COVID-19 morbidity and mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Considering the continuously expanding indication for ICI therapy, these findings are of the utmost importance to ensure effective utilization of this therapy during and beyond the SARS-CoV-2 global pandemic.

a higher median absolute lymphocyte count at COVID-19 (1.4 vs 0.8 10^9 cells/L, p=0.0098).

Conclusion Anti-SARS-CoV-2 vaccination reduces morbidity and mortality from COVID-19 in ICI recipients. History of irAEs might identify patients with pre-existing protection from COVID-19, warranting further investigation of adaptive immune determinants of protection from SARS-CoV-2.

INTRODUCTION

The efficacy of immune checkpoint inhibitors (ICIs) strongly relies on their capacity of inducing T-cell immune reconstitution.[1] T-cell exhaustion is a contributory mechanism underlying the severity of SARS-CoV-2 infection,[2] leading on one hand to the investigation of programmed-cell death-1 inhibitors as a therapeutic strategy in severe COVID-19.[3] On the other hand, given the pathological immune-mediated mechanisms underlying COVID-19 and the risk of immune-pathology stemming from ICI use, there has been growing concern around the use of ICI in patients with COVID-19 and cancer.[4 5]

Clinical data in support of a protective, as opposed to detrimental, effect of ICI in the prognosis of COVID-19 in patients with cancer have been inevitably biased by patient selection and underlying clinical characteristics. Initial reports revealed inconsistent results ranging from worse outcomes,[6 7] to no difference in COVID-19 severity[8 9] in ICI-exposed patients compared with ICI-unexposed patients.

Large metanalyses have suggested no differential impact of ICIs on COVID-19 morbidity and mortality in comparison to other systemic anticancer therapies.[10 11]

However, COVID-19 outcomes in patients with cancer have substantially evolved over time. Improved management of COVID-19,[12] immunization campaigns,[13 14] changes in community transmission and the emergence of new SARS-CoV-2 variants[15] have considerably changed the clinical impact of SARS-CoV-2 infection on patients with cancer since March 2020.

To date, a significant gap in knowledge remains as to whether the positive effect of SARS-CoV-2 vaccination observed in the general population extends to patients with cancer treated with ICI. Recent evidence suggesting that ICI may precipitate subclinical cytokine release following SARS-CoV-2 vaccination[16] strengthens the need to understand the relationship between COVID-19 vaccination and clinical outcomes.

With the aim of providing a contemporary description of COVID-19 morbidity and mortality in patients with cancer who were receiving ICIs at COVID-19 diagnosis and to assess the protective role of SARS-CoV-2 vaccination in this population, we developed this joint analysis of the OnCovid and European Society for Medical Oncology (ESMO) CoCARE registries.

METHODS

Study design

OnCovid (NCT04393974) is a European registry study approved by the UK Health Research Authority (20/HRA/1608) collecting data from consecutive patients fulfilling the following inclusion criteria: (1) age ≥18 years; (2) Reverse transcription polymerase chain reaction (RT-PCR) confirmed diagnosis of SARS-CoV-2 infection; (3) history of solid or haematological malignancy either active or in remission at the time of COVID-19 diagnosis.

The ESMO-CoCARE is an observational prospective study, based on a longitudinal multicenter survey of patients with cancer with any solid or hematological malignancy who were diagnosed with COVID-19.

For both registries, data from consecutive, all-comer patients were collected using electronic case report forms designed with the Research Electronic Data Capture software (Vanderbilt University, Nashville, Tennessee, USA). Study details and procedures, patients' eligibility, and clinical endpoints for both studies have already been extensively presented.[12–14 17–24] A list of participating centers with eligible patients for the present analysis is provided as online supplemental table 1.

Objectives and endpoints

The main objective of this analysis was to assess the protective role of SARS-CoV-2 vaccination in patients with cancer treated with a unique immunotherapy strategy, by comparing COVID-19 morbidity and mortality between unvaccinated and vaccinated patients.

In addition, we aimed to describe differences in COVID-19 severity and mortality depending on prior history of immune-related adverse events (irAEs) captured from ICI initiation until COVID-19 diagnosis.

Data of patients who received ICI within 3 months prior to COVID-19 diagnosis were merged from the OnCovid and ESMO CoCARE registries. Patients on chemotherapy-ICI and targeted therapy-ICI combinations were excluded from the analysis.

To reflect the temporal evolution of the pandemic, we first categorized patients according to date of COVID-19 diagnosis into prevaccination (from February 2020 to November 2020), alpha–delta (B.1.1.7–B.1.617.2) variants (from December 2020 to December 14, 2021), and omicron (B.1.1.529) variant (from December 15, 2021 to February 2022) pandemic phases as previously reported,[13] and described COVID-19 mortality over time.

All-cause case fatality rate at 30 days (CFR_{30}) was chosen as the main clinical endpoint, to differentiate early COVID-19-related mortality, from late, likely cancer-related deaths. As measures of COVID-19 morbidity, we evaluated the all-cause hospitalization and intensive care unit (ICU) admission rates, the rate of COVID-19 complications (at least one among acute respiratory failure, ARDS, kidney injury, secondary infections, sepsis, septic shock, acute cardiac injury, acute liver injury and others including thrombo-embolic events and other

coagulopathies, autoimmune diseases, gastrointestinal reactions), the receipt of at least one COVID-19-oriented therapy (including antivirals, chloroquine-based treatment, antibiotics, corticosteroids, interleukin-6 inhibitors and others) (yes vs no), and supplemental oxygen therapy requirement (yes vs no).

Patients who received two doses of the BNT162b2, mRNA-1273, ChAdOx1-S, and CoronaVac vaccines prior to COVID-19, or in case of infection diagnosed at least 28 days after a single dose of the Ad.26.COV2.S vaccine, were defined as fully vaccinated. Patients who received one vaccination, without meeting the above-mentioned time criteria, were considered partially vaccinated, while patients who received a third dose of either the BNT162b2 or mRNA-1273 vaccine (or a second dose after the Ad.26.COV2.S vaccine) were considered boosted. Considering the limited sample size of vaccinated patients with breakthrough infections in the study population, and that the electronic case report form of the ESMO-CoCARE registry was not designed to collect information on booster doses, patients were grouped as unvaccinated (including partially vaccinated) and fully vaccinated (either double-dosed or boosted patients) for all the comparative analyses, while patients with unknown vaccination status were excluded.

For the irAEs analysis, we evaluated COVID-19 outcomes according to the experience of any grade (National Cancer Institute Common Toxicity Criteria for Adverse Events, V.5.0) treatment-related side effects with a putative immune-mediated mechanisms at any time prior to COVID-19. These were previously evaluated by clinicians at participating sites during routine consultations as clinically indicated, without predefined time points, and collected retrospectively by investigators.

Considering the recognized role of lymphopenia as prognostic biomarker in patients with COVID-19,[25] we explored the association between the absolute lymphocyte count at COVID-19 (within 1 week of diagnosis) and the experience of prior irAEs in the subset of patients from the OnCovid registry. A detailed description of statistical analysis is provided as online supplemental methods.

RESULTS

Study population

By the respective data lock dates of February 4, 2022 and May 17, 2022, the OnCovid and ESMO CoCARE included 3820 and 2310 patients. After the exclusion of ineligible patients, data from 178 (74.2%—OnCovid) and 62 (25.8%—ESMO CoCARE) patients diagnosed with COVID-19 between January 2020 and February 2022, who were receiving ICIs within 3 months prior to SARS-CoV-2 infection diagnosis, were merged.

Figure 1 reports a detailed study flow diagram. The final study population consisted of 240 patients, of whom 130 (54.2%) were diagnosed with COVID-19 during the prevaccination phase, 79 (32.9%) during the alpha–delta phase, and 31 (12.9%) during the omicron phase, with reducing CFR_{30} over time: 25.8% (24/93 patients, 95% CI 16.5 to 38.4), 31.5% (17/54 patients, 95% CI 18.3 to 50.4), 3.6% (1/28 patients, 95% CI 0.09 to 19.8).

The most frequent primary tumor was lung cancer (47.1%), the majority of patients were male (67.5%), aged ≥65 years (62.1%), with at least one comorbidity (77.1%) and presented an active (76.7%), and advanced-stage (80.2%) tumor (table 1).

The received ICI-based regimens were: 136 (56.7%) PD-1 inhibitors monotherapy, 54 (22.5%) PD-L1 inhibitors monotherapy, 20 (8.3%) others/experimental

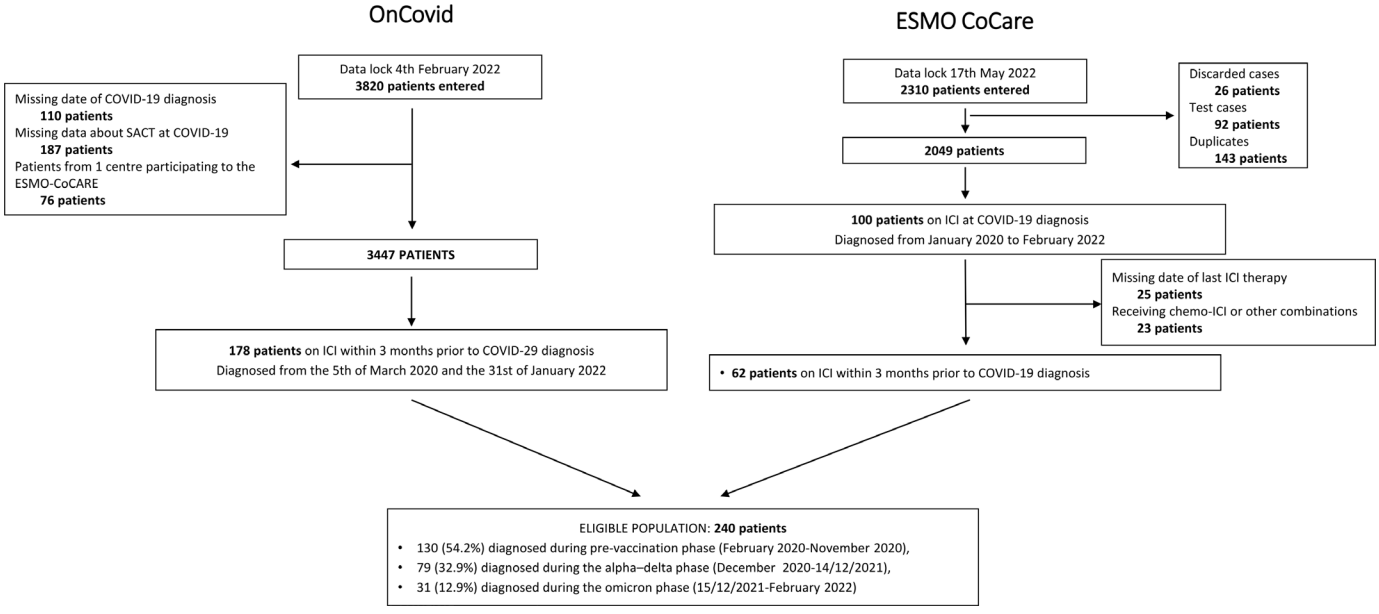

Figure 1 Study flow diagram. ESMO, European Society for Medical Oncology; ICI, immune checkpoint inhibitor; SACT, systemic anti-cancer therapies.

Table 1 Baseline patient characteristic and COVID-19 outcomes of the study population

	ICI population
	N=240 (%)
Country	
UK	47 (19.6)
Spain	77 (32.1)
Italy	90 (37.5)
Others	26 (10.8)
Sex	
Female	78 (32.5)
Male	162 (67.5)
Age	
<65 years	90 (37.5)
≥65 years	149 (62.1)
Missing	1 (0.4)
Comorbidities	
No	55 (22.9)
Yes	185 (77.1)
Primary tumor	
Lung	113 (47.1)
Melanoma	51 (21.2)
Others	76 (31.7)
Tumor stage	
Non-advanced	37 (15.6)
Advanced	190 (80.2)
Missing	10 (4.2)
Tumor status at COVID-19 diagnosis	
Remission/in-response	52 (21.7)
Active malignancy	184 (76.7)
Missing	4 (1.7)
SARS-CoV-2 vaccination status	
Unvaccinated	182 (75.8)
Fully vaccinated	42 (17.5)
Partially vaccinated	3 (1.3)
Unkown	13 (5.4)
COVID-19 outcomes	
	N (rate, 95% CI)
Oxygen therapy Missing	81 (**37.6**, 29.9 to 46.8) 25
COVID-19-specific therapy Missing	114 (**51.6**, 42.5 to 61.9) 19
Complications from COVID-19	73 (**30.4**, 23.8 to 38.2)
Hospitalization Missing	131 (**56.2**, 47.0 to 66.7) 7
ICU admission Missing	22 (**9.4**, 5.9 to 14.3) 7
30-days case fatality rate Missing	55 (**23.6**, 17.8 to 30.7) 7

COVID-19 outcomes' rates are provided in bold.
ICI, immune checkpoint inhibitor; ICU, intensive care unit.

ICIs, 19 (7.9%) CTLA-4/PD-1 inhibitors combinations and 11 (4.6%) not specified chemotherapy-free ICI regimens.

Most patients were unvaccinated prior to COVID-19 (75.8%), 17.5% were fully vaccinated, 1.3% partially vaccinated, while vaccination status was unknown for 13 patients (5.4%). Among fully vaccinated patients, 17 from the OnCovid registry received a booster dose. Vaccination details for both the registries are summarized in online supplemental table 2.

The median observation period for the whole cohort was 91 days (IQR: 15.8–319.0) and the CFR_{30} was 23.6% (95% CI 17.8% to 30.7%). All COVID-19 outcomes for the whole cohort are summarized in table 1

SARS-CoV-2 vaccination is associated with improvement in COVID-19 outcomes in ICI recipients

After the exclusion of 13 patients with unknown vaccination status, 227 patients were included in the SARS-CoV-2 vaccine analysis.

None of the baseline demographics and oncological characteristics were associated with SARS-CoV-2 vaccination status, with the exception of a higher proportion of patients with at least one comorbidity among unvaccinated patients (80.5% vs 64.3%, p=0.0230) (online supplemental table 3).

Univariable analysis revealed that fully vaccinated patients experienced decreased rates of death at 30 days (4.8% vs 28.1%, p=0.0009), hospitalization (27.5% vs 63.2%, p<0.0001), COVID-19 complications (11.9% vs 34.6%, p=0.0040), reduced need for COVID-19-specific therapy (26.3% vs 57.9%, p=0.0004) and oxygen therapy (15.8% vs 41.5%, p=0.0030) in comparison to unvaccinated/partially vaccinated patients. We found no significant difference in terms of ICU admission rates, despite arithmetically fewer vaccinated patients being admitted to ICU (4.8% vs 28.1%, p=0.14) (figure 2, online supplemental table 4).

Distribution of baseline patient characteristics prior to and after inverse probability of treatment weighting (IPTW) is reported in online supplemental table 5. Given the suboptimal balancing ability, country, comorbidities, tumor status and tumor stage were included in all IPTW-fitted multivariable logistic regression models for each COVID-19 outcome, which are reported in full as online supplemental table 6 and are summarized in the forest plot graph provided in figure 3. Compared with unvaccinated patients, full vaccination was associated with a decreased risk of death at 30 days (adjusted OR, aOR 0.08, 95% CI 0.03 to 0.26), of hospitalization (aOR 0.15, 95% CI 0.07 to 0.36), of COVID-19 complications (aOR 0.24, 95% CI 0.12 to 0.49) and of need for COVID-19-specific therapy (aOR 0.25, 95% CI 0.13 to 0.46). However, after clustered-robust correction for data source, the upper limit CI crosses one for all COVID-19 outcomes except for CFR_{30} (aOR 0.08, 95% CI 0.01 to 0.69).

History of irAEs prior to COVID-19 is associated with decreased COVID-19 mortality in patients receiving ICI

Overall, 38 patients (15.8%) experienced any grade irAEs at any time prior to COVID-19, which are summarized in online supplemental table 7. The median time from occurrence of irAEs and COVID-19 diagnosis was 3.2 months (range 0.13–48.7, computed on data of 27 patients from the OnCovid registry).

The occurrence of irAEs was not associated with any of the baseline demographics and oncological characteristics, including the disease status (active vs remissive/in response) at COVID-19 (p=0.5339), with the exception of the primary tumor (p=0.0373) (online supplemental table 8).

Univariable analysis showed similar rates of hospitalization (51.3% vs 57.1%, p=0.5158), ICU admission (16.2% vs 8.1%, p=0.1252), COVID-19 complications (23.7% vs 31.7%, p=0.3265), COVID-19-specific therapy (45.7% vs 52.6%, p=0.4498) and oxygen requirement (39.3% vs 37.4%, p=0.8251) between patients who experienced and those who did not experience irAEs prior to COVID-19 (online supplemental table 9). However, the occurrence of irAEs was associated with a significantly decreased CFR_{30} (10.8% vs 26.0%, p=0.0462) (figure 4A).

Distribution of baseline characteristics distribution prior to and after the IPTW is reported in online supplemental table 10. Given the suboptimal balancing ability, country, tumor stage, primary tumor and vaccination status were included in the IPTW-fitted multivariable logistic regression model for COVID-19 mortality, which confirmed that patients who experienced any grade irAEs prior to COVID-19 had a decreased risk of death at 30 days (aOR 0.47, 95% CI 0.23 to 0.99). Clustered-robust correction for data source further strengthened this finding (aOR 0.47, 95% CI 0.33 to 0.67) (online supplemental table 11).

Lastly, in a subset of patients from the OnCovid cohort, we revealed that the median absolute lymphocyte count within 1 week of COVID-19 diagnosis was significantly higher among patients who experienced any grade irAEs prior to COVID-19 than in those who did not experience irAEs (1.4 vs 0.8 10^9 cells/L, p=0.0098) (figure 4B).

DISCUSSION

Our study is the largest analysis on patients with cancer on ICIs diagnosed with COVID-19 to date. With the inclusion of patients diagnosed up until February 2022, it provides a more contemporary picture of COVID-19 outcomes in this specific population. Although merely descriptive due to the limited sample size of subgroups, the reducing CFR_{30} across the pandemic phases suggests a time-dependent improvement of COVID-19 mortality, especially during the more recent Omicron outbreak, as already reported for the OnCovid population.[13]

Even considering the time requirements for the delivery of immunization campaigns since the first SARS-CoV-2 vaccine approval,[26] and that most of the included

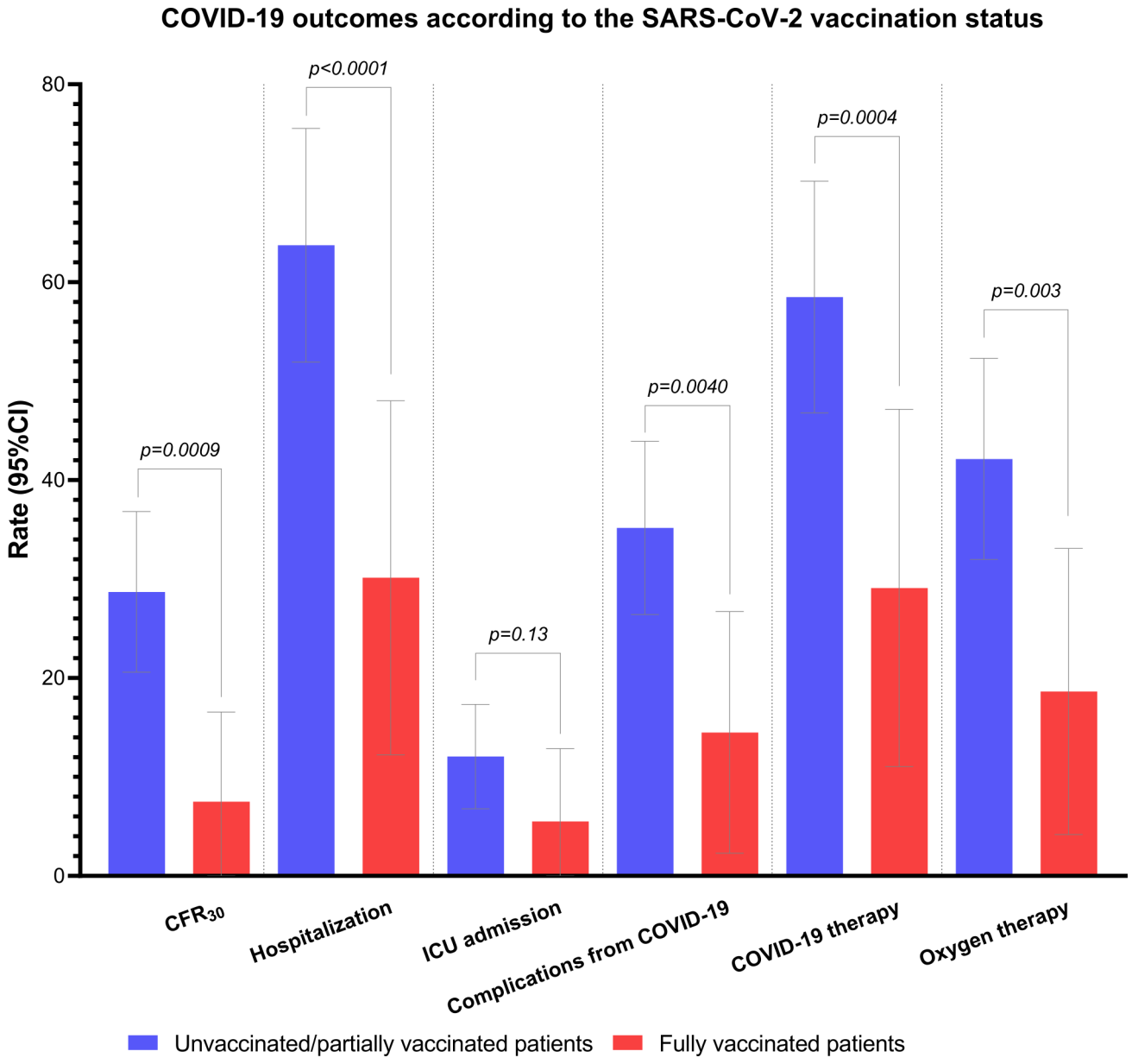

Figure 2 Histogram plot summarizing all COVID-19 outcomes according to the vaccination status. All rates with 95% CIs are available in online supplemental table 4. CFR30, 30-day case fatality rate; ICU, intensive care unit.

patients were diagnosed during the prevaccination phase, we consider 17.5% of full vaccination a relatively low rate, and a possible impact of vaccine hesitancy, as initially reported in early 2021,[27 28] cannot be excluded.

Although preliminary evidence from clinical trials supports the safety and immunogenicity of SARS-CoV-2 vaccines in patients with cancer on active ICI-based treatments,[16 29 30] this study demonstrates the efficacy of anti-COVID-19 vaccination in patients receiving ICI in routine clinical practice. The ~83% reduction in the CFR_{30} in fully vaccinated patients along with COVID-19-related morbidity is confirmed after adjustment for major prognostic confounders in IPTW-fitted models, a process made necessary by the inherent differences existing in study procedures and data collection modalities between the two registries.

The convergence of COVID-19 and ICI-toxicity in eliciting unopposed T-cell activation and downstream cytokine excess has been highlighted suggested as a hypothetical source of clinical risk to patients with cancer ever since the beginning of the pandemic.[5 31] Contrary to initial concerns, we document an association between the occurrence of irAEs and reduced CFR_{30}: a novel finding of potential interest in the development of COVID-19-specific therapeutics.

In our study, the protective role of irAEs of all grades on COVID-19-related mortality was independent of common clinicopathological features relating to cancer and COVID-19 prognosis, including SARS-CoV-2 vaccination status. It has been established that patients experiencing irAEs are those capable of mounting a more vigorous anticancer immune reconstitution, resulting in

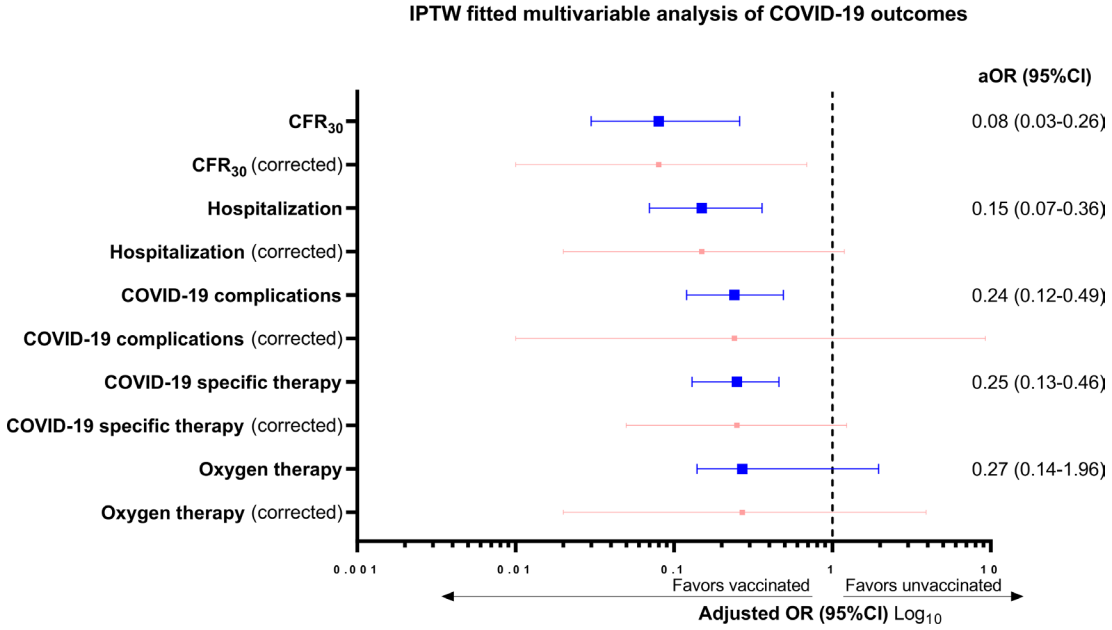

Figure 3 Summary of the inverse probability of treatment weighing (IPTW) fitted multivariable analyses for each COVID-19 outcomes according to the vaccination status prior to (blue) and after (red) the clustered-robust SE and 95% CI adjustments for the data source. Adjusting covariates for each COVID-19 outcome were country of origin, comorbidities, tumor status, and tumor stage at COVID-19. Full multivariable models are available in online supplemental table 6. aOR, adjusted OR; CFR30, 30-day case fatality rate.

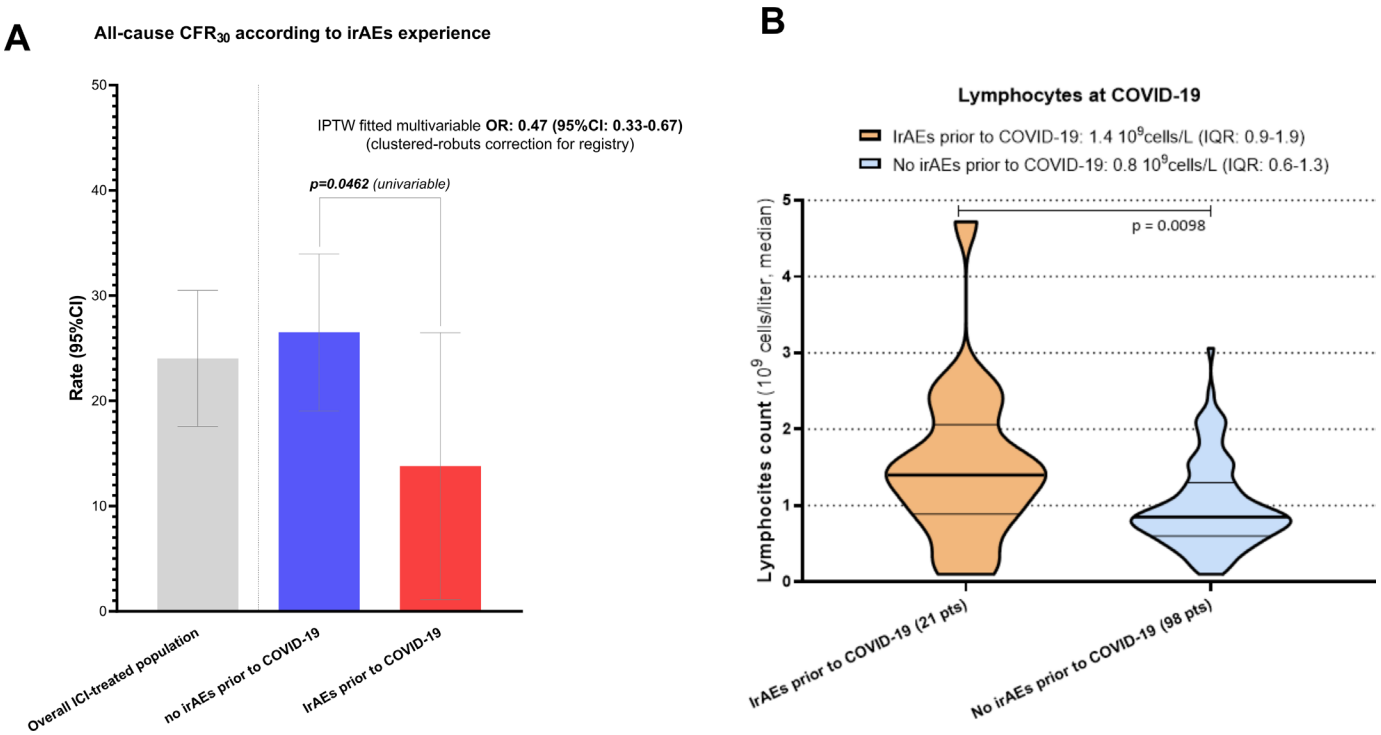

Figure 4 (A) Histogram plot summarizing the all-cause 30-day case fatality rate (CFR30) analysis according to the occurrence of any grade immune-related adverse events prior to COVID-19. Inverse probability of treatment weighing (IPTW) fitted adjusted OR for the risk of death at 30 days with clustered robust 95% CI correction for the data source is presented. All rates with 95% CI are available in online supplemental table 9. Adjusting covariates were country of origin, primary tumor, tumor stage at COVID-19 and vaccination status. Full multivariable model is available in online supplemental table 11. (B) Violin plot reporting the median absolute lymphocyte count at COVID-19 (within 1 week of diagnosis) according to the prior occurrence or any grade irAEs. IrAEs, immune-related adverse events.

longer survival.[32] Because T-cell exhaustion is not solely a hallmark of cancer progression but a mechanism of COVID-19 severity,[25 31] we speculate whether history of prior irAE might be a surrogate of more functional T-cell immunity, leading to improved mortality from COVID-19 irrespective of vaccine status.

In keeping with this view, we found that the absolute lymphocyte count at COVID-19, was significantly higher among patients who experienced prior irAEs. It is well known that patients with severe COVID-19 show reduced counts of peripheral CD4+and CD8+ T cells[31], and that reduced CD4+/CD8+T cells, B cells, NK cells, and absolute lymphocyte cell count levels are significantly associated with COVID-19 mortality in the general population.[25] At the same time, the known mechanisms leading to irAEs involve expansion of intratumoral and peripheral T-cell receptor repertoires along with a mobilization of large numbers of T cells[33 34] and, to a lesser extent, activation and exhaustion of $CD21^{low}$ B cells.[35] On the other hand, a decrease in the absolute lymphocyte count has been reported with severe ICI-associated myocarditis.[36]

While OnCovid and ESMO CoCARE registries lack information on T-cell phenotype at COVID-19 diagnosis, our findings are provocative in suggesting that prior irAE might represent a hallmark of protection from COVID-19 mortality through invigorated T-cell immunity. These findings deserve further mechanistic studies to fully elucidate the immunological links between irAEs and COVID-19 outcomes in patients with cancer.

Our study acknowledges several limitations, including lack of data regarding the smoking status and more detailed information regarding irAEs duration and management. Of note, previous irAEs and their putative immune-mediated mechanism were assessed at participating site in routine practice, without predefined time points. This might have impacted the quality of data with risks of underreporting, as the 16.7% and 3.1% rates of all grade and ≥G3 irAEs, respectively, are lower than those reported in interventional clinical trials with ICI-based regimens,[37] but comparable to reports from clinical practice.[38]

In addition, inherent differences between the two registries significantly impacted the accuracy of the estimates from the vaccination analysis: information about booster doses only recently started to be collected for patients entered in the ESMO CoCARE registry and was not available for our analysis. Furthermore, for ~24% of vaccinated patients, the specific type of vaccine could not be reconstructed. While constituting an important limitation, this is unlikely to have affected our results, given recent evidence suggesting largely comparable efficacy of commonly available SARS-CoV-2 vaccines.[39]

Lastly, despite the inclusion of a significant proportion of more recently diagnosed patients, the lack of availability of viral genomic sequences across the pandemic phases did not allow us to make conclusive considerations about new SARS-CoV-2 variants, while the limited sample size of the 'alpha–delta' and 'omicron' phases subgroups prevented us from running adequately powered time-adjusted analyses.

Despite the mentioned limitations, our results collectively support the notion that ICI recipients are not especially vulnerable to COVID-19, with mortality rates that are in keeping with the general population with COVID-19 and cancer. In these patients, SARS-CoV-2 vaccination leads to significantly improved outcome from COVID-19, comparably with other oncological patient populations.[13 14 40] Considering the continuously expanding indication for ICI therapy,[41] our findings are of utmost importance to ensure effective utilization of this therapy during and beyond the SARS-CoV-2 global epidemic.

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Immune checkpoint inhibitor therapy and outcomes from SARS-CoV-2 infection in patients with cancer: a joint analysis of OnCovid and ESMO-CoCARE registries.

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Supplementary Methods

Statistical plan

Baseline characteristics were summarized as categorical variables and reported using descriptive statistics. We tested associations between categorical variables using the Fisher exact test and the Pearson $\chi 2$ test as appropriate. The Kurkas -Wallis test was used to compare ambsolute lymphocytes counts. COVID-19 outcomes were presented as crude rates with 95% confidence intervals (95%CI).

To optimize the unbalanced sample size of subgroups we performed dedicated Inverse Probability of Treatment Weighting (IPTW) procedures accounting for selected demographics and oncological characteristics for both the vaccination and irAEs analyses. The balancing ability of each IPTW was evaluated through the distribution of the unweighted and weighted selected variables with relevant p-values and standardised mean difference (SMD). Double adjustment for variables with a SMD >0.10 was adopted when exploring clinical outcomes between the weighed cohorts with multivariable analyses(1).

For the multivariable analyses propensity score-weighted logistic regression models were fitted for each COVID-19 outcome of interest, with results presented as adjusted odds ratios (aOR) and 95%CI. To obtain a more powered IPTW we included variables with missing data by grouping them as reference term in case of a <3% of missingness and as an "unknown" category in case of a ≥3% of missingness.

The following covariates were merged from the registries and included in the IPTW procedures: country (United Kingdom vs Spain vs Italy vs others), sex (male vs female), age (≥65 vs <65 years), presence of at least one comorbidity (yes vs no), tumour status at COVID-19 (presence of active/progressive or stable disease vs remissive/in response disease), tumour stage (advanced vs non-advanced vs unknown) and primary tumour (clustered as lung vs melanoma/skin cancers vs others).

Vaccination status was included in the IPTW procedure for the irAEs analysis.

Acknowledging that the data-source consisted of 2 registries with different procedures and data collections modalities, all the results from multivariable analyses were corrected following a clustered-robust standard error and 95%CI correction according to the data source (OnCovid vs ESMO-CoCARE).

All P-values were 2-sided and confidence intervals set at the 95% level, with significance pre-defined to be at <0.05.

Analyses were performed using the R-studio software, R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, and the MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

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Supplementary Table 1: Participating centers list with eligible patients from the OnCovid and ESMO-CoCARE registries.

Centre – OnCovid	Eligible patients	(%)

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Vall d'Hebron University Hospital, Barcelona (Spain)	29	16.3%
ICO Girona (Spain)	12	6.7%
Ospedale Maggiore della Carità, Novara (Italy)	11	6.2%
Institut Gustave Roussy, Villejuif (France)	11	6.2%
Policlinico San Matteo, Pavia (Italy)	10	5.6%
Ospedale Papa Giovanni XXIII, Bergamo (Italy)	10	5.1%
IRCCS AOU San Martino, Genova (Italy)	10	5.1%
Chelsea and Westminster Hospital, London (UK)	9	5.1%
Barts Health NHS Trust, London (UK)	8	4.5%
Careggi University Hospital, Florence (Italy)	8	3.9%
IRCCS Humanitas Research Hospital, Rozzano - Milan (Italy)	8	3.9%
University of Bari 'Aldo Moro', Bari (Italy)	7	3.4%
Hospital Clinic, Barcelona (Spain)	6	3.4%
Imperial College London, London (UK)	5	2.8%
Guy's and St Thomas' NHS Foundation Trust, London (UK)	5	2.8%
ICO L'Hospitalet, L'Hospitalet de Llobregat, Barcelona (Spain)	4	2.2%
Istituto Europeo di Oncologia, Milano (Italy)	4	2.2%
Azienda Ospedaliera Spedali Civili, Brescia (Italy)	4	1.7%
Ospedali Riuniti di Ancona, Universitá Politecnica delle Marche (Italy)	4	1.7%
Università Campus Bio-Medico, Rome (Italy)	3	1.1%
ICO Badalona (Spain)	2	1.1%
Azienda Ospedaliera S Maria, Terni (Italy)	2	1.1%
Institut Jules Bordet, Brussels (Belgium)	1	0.6%
University of L'Aquila, L'Aquila (Italy)	2	0.6%
Santa Maria Goretti Hospital, Latina (Italy)	1	0.6%
Azienda Ospedaliera S. Andrea, Rome (Italy)	2	0.6%
Total	**178**	**100.0%**
Centre – ESMO CoCARE	**Eligible patients**	**(%)**
The Royal Marsden NHS Foundation Trust, London (UK)	20	32.3%
Hospital Universitario Infanta Leonor, Madrid (Spain)	10	16.1%
Hospital Universitario La Paz, Madrid (Spain)	7	11.3%
CHUV Lausanne (Switzerland)	5	8.1%
Hospital Universitario Ramón y Cajal, Madrid (Spain)	4	6.5%
Azienda Ospedaliera "SS Antonio e Biagio e C.Arrigo", Alessandria (Italy)	4	6.5%
H. Universitario Fundación Alcorcón, Madrid (Spain)	3	4.8%
Hospital Prof Doutor Fernando Fonseca, Llisbon (Portugal)	2	3.2%
4th Oncology Dept & Comprehensive Clinical Trials Center, Metropolitan Hospital Athens (Greece)	2	3.2%
401 General Military Hospital of Athens (Greece)	1	1.6%
Sechenov University Hospital, Moscow (Russia)	1	1.6%
Samsung Medical Center, Seul (South Korea)	1	1.6%
Asian Cancer Institute - Asian Hospital and Medical Center, Muntinlupa (Philippines)	1	1.6%
Fundeni Clinical Institute, Department of Medical Oncology, Bucharest (Romania)	1	1.6%
Total	**62**	**100.0%**

Supplementary Table 2: Vaccination details for patients with breakthrough infections from the OnCovid and ESMO CoCARE registries.

	Oncovid		
	Partially vaccinated N (%)	**Double-dosed N (%)**	**Boosted N (%)**
BNT162b2	-	7 (43.7)	10 (58.8)
mRNA-1273	2 (100)	3 (18.7)	5 (29.4)
Ad.26.COV2.S	-	1 (6.2)	-
Not specified	-	5 (31.3)	2 (17.8)

Total	2	16	17
CoCare			
	Partially vaccinated N (%)	**Double dosed N (%)**	
BNT162b2	-	2 (22.2)	
ChAdOx1-S	-	4 (44.4)	
CoronaVac	1 (100)	-	
Not specified	-	3 (33.3)	
Total	1	9	

Supplementary Table 3: Baseline demographics and oncological characteristics according to the SARS-CoV-2 vaccination status. 13 patients with unknown vaccinations status have been excluded.

	Unvaccinated/Partially	**Fully Vaccinated**	**P value**
	N = 185 (%)	**N = 42 (%)**	
Country			
United Kingdom	34 (18.4)	11 (26.2)	0.1764
Spain	66 (35.7)	11 (26.2)	
Italy	61 (33.0)	18 (42.9)	
Others	24 (13.0)	2 (4.8)	
Sex			
Female	57 (30.8)	15 (35.7)	0.5385
Male	128 (69.2)	27 (64.3)	
Age			
<65 years	70 (37.8)	17 (40.5)	0.8548
≥65 years	114 (61.6)	25 (59.5)	
Missing	1 (0.5)	-	
Comorbidities			
No	36 (19.5)	15 (35.7)	0.0230
Yes	149 (80.5)	27 (64.3)	
Primary Tumour			
Lung	84 (45.4)	20 (47.6)	0.9481
Melanoma	39 (21.1)	9 (21.4)	
Others	62 (33.5)	13 (31.0)	
Tumour stage			
Non-advanced	25 (13.5)	8 (19.0)	0.0866
Advanced	152 (82.2)	29 (69.0)	
Missing	8 (4.3)	5 (11.9)	
Status at COVID-19 diagnosis			
Remission/in-response	40 (21.6)	11 (26.2)	0.1962
Active malignancy	143 (77.3)	29 (69.0)	
Missing	2 (1.1)	2 (4.8)	
IrAEs prior to COVID-19			
No	155 (83.8)	34 (81.0)	0.6580
Yes	30 (16.2)	8 (19.0)	

Supplementary Table 4: Summary and univariable analysis of COVID-19 outcomes among vaccinated and unvaccinated patients.

	Unvaccinated/Partially (N=185)	**Fully Vaccinated (N=42)**	**p-value**
	N (Rate, 95%CI)	**N (Rate, 95%CI)**	
Oxygen therapy	69 (**41.5**, 32.3-52.6)	6 (**15.8**, 5.8-34.3)	0.0030
Missing	19	4	
COVID-19 specific therapy	99 (**57.9**, 47.1-70.5)	10 (**26.3**, 12.6-48.4)	0.0004
Missing	14	4	

Complications from COVID-19	64 (**34.6**, 26.7-44.2)	5 (**11.9**, 3.8-27.8)	0.0040
Hospitalization Missing	115 (**63.2**, 52.2-75.8) 3	11 (**27.5**, 13.7-49.2) 2	<0.0001
ICU admission Missing	21 (**11.5**, 7.1-17.6) 3	1 (**2.5,** 0.1-13.9) 2	0.1387
30-days case fatality rate Missing	51 (**28.1**, 20.9-37.1) 4	2 (**4.8**, 0.1-17.6) 1	0.0009

Supplementary Table 5: Distribution of baseline characteristics before and after the IPTW procedure between unvaccinated and vaccinated patients included in the vaccination analysis. Variability of included characteristics is estimated through the standardized mean difference (SMD).

	Unvaccinated (%)	Fully vaccinated (%)	P value	SMD	Unvaccinated Weighted (%)	Fully vaccinated Weighted (%)	P value Weighted	SMD Weighted
Country								
United Kingdom	18.4	26.2	0.17	0.40	19.4	16.1	0.86	0.16
Spain	35.7	26.2			34.5	37.8		
Italy	33.0	42.9			34.4	38.0		
Others	13.0	4.8			11.7	8.1		
Sex								
Male	69.2	64.3	0.66	0.10	69.5	68.4	0.90	0.02
Age								
≥65 years	61.6	59.5	0.93	0.04	62.0	59.3	0.76	0.05
Comorbidities								
Yes	80.5	64.3	0.04	0.37	80.3	66.3	0.08	0.32
Status at COVID-19								
Active malignancy	77.3	69.0	0.35	0.19	77.2	65.6	0.16	0.25
Tumour stage								
Non-advanced	13.5	19.5	0.20	0.29	13.6	21.9	0.31	0.26
Advanced	82.2	70.7			82.2	71.2		
Unknown	4.3	9.8			4.2	6.8		
Primary tumours								
Lung	45.4	47.6	0.94	0.06	45.6	44.1	0.98	0.03
Melanoma	21.1	21.4			20.7	21.8		
Others	33.5	31.0			33.7	34.1		

Supplementary Table 6: Full fitted multivariable logistic regression models after the Inverse Probability of Treatment Weighting (IPTW) procedure for each COVID-19 related outcome comparing all vaccinated patients and unvaccinated patients. Standard errors and adjusted OR with 95%CIs before and after the clustered-robust adjustment for the data source (OnCovid vs ESMO CoCARE) are presented. UK: United Kingdom; Unk: unknown; aOR: adjusted odds ratio; CI: confidence intervals; St. Err: standard error.

30-days Case Fatality Rate	aOR	95%CI	St. Err	95%CI cluster-corrected	St. Err cluster-corrected
Vaccination status: Full vaccination vs unvaccinated	0.08	0.03-0.26	0.55	0.01-0.69	1.06

Country: Spain vs UK	1.11	0.38-3.24	0.54	0.40-3.04	0.51
Country: Italy vs UK	0.81	0.27-2.35	0.54	0.14-4.65	0.89
Country: Others vs UK	0.80	0.16-3.88	0.80	0.28-2.23	0.52
Comorbidities: Yes vs No	1.73	0.62-4.88	0.52	0.90-3.33	0.33
Tumour status: Active malignancy vs Remission/response	4.97	1.34-18.43	0.66	2.89-8.53	0.27
Tumour stage at COVID-19: Advanced vs Non-advanced	1.71	0.43-6.85	0.70	0.99-2.97	0.28
Tumour stage at COVID-19: Unk vs Non-advanced	0.33	0.02-6.08	1.48	0.15-0.72	0.39
Hospitalization (all causes)	**aOR**	**95%CI**	**St. Err**	**95%CI cluster-corrected**	**St. Err cluster-corrected**
Vaccination status: Full vaccination vs unvaccinated	0.15	0.07-0.36	0.42	0.02-1.19	1.02
Country: Spain vs UK	5.19	1.85-14.6	0.52	4.79-5.63	0.04
Country: Italy vs UK	0.25	0.09-0.70	0.52	0.03-1.73	0.98
Country: Others vs UK	0.58	0.12-2.90	0.82	0.24-1.39	0.44
Comorbidities: Yes vs No	2.34	0.89-6.18	0.49	0.92-5.94	0.47
Tumour status: Active malignancy vs Remission/response	6.78	2.33-19.79	0.54	4.02-11.4	0.26
Tumour stage at COVID-19: Advanced vs Non-advanced	1.01	0.33-3.02	0.56	0.92-1.07	0.03
Tumour stage at COVID-19: Unk vs Non-advanced	0.22	0.03-1.31	0.90	0.02-3.80	1.45
COVID-19 complications	**aOR**	**95%CI**	**St. Err**	**95%CI cluster-corrected**	**St. Err cluster-corrected**
Vaccination status: Full vaccination vs unvaccinated	0.24	0.12-0.49	0.35	0.01-9.25	1.85
Country: Spain vs UK	1.23	0.51-2.97	0.44	0.69-2.21	0.29
Country: Italy vs UK	0.28	0.10-0.78	0.51	0.12-0.64	0.42
Country: Others vs UK	1.23	0.35-4.34	0.64	0.28-5.31	0.74
Comorbidities: Yes vs No	0.92	0.41-2.09	0.41	0.19-4.38	0.79
Tumour status: Active malignancy vs Remission/response	1.43	0.62-3.34	0.43	0.85-2.38	0.26
Tumour stage at COVID-19: Advanced vs Non-advanced	1.35	0.48-3.81	0.53	0.35-5.17	0.68
Tumour stage at COVID-19: Unk vs Non-advanced	0.41	0.05-2.93	1.00	0.05-2.87	0.99
COVID-19 specific therapy	**aOR**	**95%CI**	**St. Err**	**95%CI cluster-corrected**	**St. Err cluster-corrected**
Vaccination status: Full vaccination vs unvaccinated	0.25	0.13-0.46	0.31	0.05-1.23	0.81
Country: Spain vs UK	4.24	1.62-11.07	0.49	1.17-15.28	0.65
Country: Italy vs UK	2.38	0.88-6.41	0.50	1.69-3.36	0.17
Country: Others vs UK	3.94	1.02-15.10	0.68	2.23-6.96	0.29
Comorbidities: Yes vs No	1.22	0.55-2.72	0.41	0.36-4.11	0.62
Tumour status: Active malignancy vs Remission/response	0.91	0.43-1.94	0.38	0.87-0.96	0.02
Tumour stage at COVID-19: Advanced vs Non-advanced	1.02	0.40-2.59	0.47	0.74-1.39	0.15
Tumour stage at COVID-19: Unk vs Non-advanced	1.79	0.38-8.40	0.79	0.12-26.36	1.37
Oxygen therapy	**aOR**	**95%CI**	**St. Err**	**95%CI cluster-corrected**	**St. Err cluster-corrected**
Vaccination status: Full vaccination vs unvaccinated	0.27	0.14-1.96	0.34	0.02-3.90	1.34
Country: Spain vs UK	2.54	0.99-6.48	0.47	1.84-3.49	0.16
Country: Italy vs UK	0.63	0.22-1.75	0.52	0.55-0.72	0.06
Country: Others vs UK	1.28	0.33-4.91	0.68	0.20-8.37	0.95
Comorbidities: Yes vs No	1.14	0.48-2.66	0.43	0.11-11.72	1.19
Tumour status: Active malignancy vs Remission/response	1.23	0.55-2.73	0.41	1.12-1.35	0.04
Tumour stage at COVID-19: Advanced vs Non-advanced	0.81	0.31-2.13	0.49	0.31-2.15	0.49
Tumour stage at COVID-19: Unk vs Non-advanced	0.11	0.01-1.34	1.25	0.02-0.78	0.98

Supplementary Table 7: Summary of the irAEs experienced prior to COVID-19 among the OnCovid and ESMO CoCARE cohorts. National Cancer Institute Common Toxicity Criteria for Adverse Events, version 5.0 were used for irAEs grading.

30 patients from the OnCovid registry	**8 patients from the CoCare registry**

• Grade 3 colitis, n=1 • Grade 2 colitis, n=1 • Grade 2 pneumonitis, n=4 • Grade 2 skin reactions, n=3 • Grade 1 skin reactions, n= 2 • Grade 1 fatigue, n=1 • Grade 3 hepatitis, n=2 • Grade 2 hepatitis, n=2 • Grade 3 thyroiditis, n=1 • Grade 2 thyroiditis, n=5 • Grade 1 thyroiditis, n=2 • Grade 1 arthritis, n=1 • Grade 1 neuro-muscular reactions, n=2 • Grade 1 other reactions, n=3	• Grade 3 pneumonitis, n=1 • Grade 3 myocarditis, n=1 • Grade 3 hypothyroidism, n=1 • Grade 3 colitis, pneumonitis, hepatitis, thyroiditis, n=1 • Grade 2 myocarditis, hypothyroidism, n=1 • Grade 2 psoriasis, n=1 • Grade 1 thyroiditis, n=1

Supplementary Table 8: Baseline demographics and oncological characteristics according to the experience of immune-related adverse events (irAEs) prior to COVID-19 diagnosis.

	No irAE	**irAEs**	**P value**
	N = 202 (%)	**N = 38 (%)**	
Country			
United Kingdom	41 (20.3)	6 (15.8)	0.8947
Spain	65 (32.2)	12 (31.6)	
Italy	75 (37.1)	15 (39.5)	
Others	21 (10.4)	5 (13.2)	
Sex			
Female	66 (32.7)	12 (31.6)	0.8951
Male	136 (67.3)	26 (68.4)	
Age			
<65 years	76 (37.6)	14 (36.8)	0.9041
≥65 years	125 (61.9)	24 (63.2)	
Missing	1 (0.5)	-	
Comorbidities			
No	46 (22.8)	9 (23.7)	0.9025
Yes	156 (77.2)	29 (76.3)	
Primary Tumour			
Lung	99 (49.0)	14 (36.8)	0.0373
Melanoma	37 (18.3)	14 (36.8)	
Others	66 (32.7)	10 (26.3)	
Tumour stage			
Non-advanced	31 (15.6)	6 (15.8)	0.4645
Advanced	161 (80.9)	29 (76.3)	
Missing	7 (3.5)	3 (7.9)	
Status at COVID-19 diagnosis			
Remission/in-response	42 (20.8)	10 (26.3)	0.5339
Active malignancy	156 (77.2)	28 (73.7)	
Missing	4 (2.0)	-	
SARS-CoV-2 vaccination status			
Unvaccinated	153 (75.7)	29 (76.3)	0.6736
Fully vaccinated	34 (16.8)	8 (21.1)	
Partially vaccinated	3 (1.5)	-	
Unkown	12 (5.9)	1 (2.6)	

Supplementary Table 9: Summary and univariable analysis of COVID-19 outcomes according to the experience of any grade irAEs prior to COVID-19 diagnosis. irAEs: immune-related adverse events.

	No IrAEs	**IrAEs**	**p-value**

	(N=202)	(N=38)	
	N (Rate, 95%CI)	**N (Rate, 95%CI)**	
Oxygen therapy Missing	68 (**37.4**, 29.0.6-43.4) 20	13 (**39.3**, 20.9-67.3) 5	0.8251
COVID-19 specific therapy Missing	98 (**52.6**, 42.7-64.2) 16	16 (**45.7**, 26.1-74.2) 3	0.4498
Complications from COVID-19	64 (**31.7**, 24.4-40.5)	9 (**23.7**, 10.8-44.9)	0.3265
Hospitalization Missing	112 (**57.1**, 47.1-68.7) 6	19 (**51.3**, 30.9-80.2) 1	0.5158
ICU admission Missing	16 (**8.1**, 4.6-13.2) 6	6 (**16.2,** 5.9-35.3) 1	0.1252
30-days case fatality rate Missing	51 (**26.0**, 19.3-34.2) 6	4 (**10.8**, 2.9-27.7) 1	0.0462

Supplementary Table 10: Distribution of baseline characteristics before and after the IPTW procedure between patients who experience and did not experience any grade irAEs prior to COVID-19 diagnosis. Variability of included characteristics is estimated through the standardized mean difference (SMD). irAEs: immune-related adverse events.

	No irAEs (%)	IrAEs (%)	P value	SMD	No irAEs Weighted (%)	IrAEs Weighted (%)	P value Weighted	SMD Weighted
Country								
United Kingdom	20.3	15.8	0.89	0.15	19.8	21.7	0.94	0.11
Spain	32.6	31.6			32.1	34.0		
Italy	37.1	39.5			37.3	32.0		
Others	10.4	13.2			10.8	12.3		
Sex								
Male	67.3	68.4	1.0	0.03	67.4	69.6	0.79	0.04
Age								
≥65 years	61.9	63.2	1.0	0.03	61.8	60.0	0.84	0.03
Comorbidities								
Yes	77.2	76.3	1.0	0.02	76.9	78.8	0.80	0.04
Status at COVID-19								
Active malignancy	77.2	73.7	0.79	0.08	76.6	73.8	0.72	0.06
Tumour stage								
Non-advanced	15.4	15.8	0.67	0.14	15.9	14.4	0.58	0.18
Advanced	80.1	76.3			79.5	76.2		
Unknown	4.5	7.9			4.6	9.4		
Primary tumours								
Lung	49.0	36.8	0.03	0.42	48.4	39.5	0.34	0.27
Melanoma	18.3	36.8			19.0	30.5		
Others	32.7	26.3			32.6	30.0		
Vaccination status								
Unvaccinated	77.2	76.3	0.61	0.19	76.8	77.7	0.71	0.15
Fully vaccinated	16.8	21.1			17.6	19.7		
Unknown	5.9	2.6			5.6	2.5		

Supplementary Table 11: Full fitted multivariable logistic regression model after the Inverse Probability of Treatment Weighting (IPTW) procedure for COVID-19 mortality comparing all patients who experienced and those who did not experience any grade irAEs prior to COVID-19. Standard errors and adjusted OR with 95%CIs before and after the clustered-robust adjustment for the data source (OnCovid vs ESMO CoCARE) are

presented. UK: United Kingdom; Unk: unknown; aOR: adjusted odds ratio; CI: confidence intervals; St. Err: standard error; irAEs: immune-related adverse events.

30-days Case Fatality Rate	aOR	95%CI	St. Err	95%CI cluster-corrected	St. Err cluster-corrected
IrAEs prior to COVID-19: Yes vs No	0.47	0.23-0.99	0.37	0.33-0.67	0.17
Country: Spain vs UK	0.77	0.26-2.26	0.54	0.30-1.97	0.47
Country: Italy vs UK	0.87	0.29-2.58	0.55	0.78-0.96	0.05
Country: Others vs UK	0.36	0.07-1.78	0.81	0.22-0.60	0.25
Primary tumour: Melanoma vs Lung	0.51	0.20-1.32	0.48	0.21-1.22	0.43
Primary tumour: Others vs Lung	0.36	0.15-0.88	0.44	0.16-0.82	0.41
Tumour stage at COVID-19: Advanced vs Non-advanced	3.97	0.94-16.6	0.73	0.81-19.2	0.80
Tumour stage at COVID-19: Unk vs Non-advanced	7.59	1.09-52.5	0.98	1.52-37.8	0.81
Vaccination status: Fully vaccinated vs unvaccinated/partially	0.07	0.01-0.45	0.95	0.03-0.17	0.44
Vaccination status: Unknown vs unvaccinated/partially	0.42	0.04-4.01	1.15	0.24-0.73	0.42