Vaccination against SARS-CoV-2 protects from morbidity, mortality and sequelae from COVID19 in patients with cancer

18 April 2025

European Journal of Cancer

Vaccination against SARS-CoV-2 protects from morbidity, mortality, and sequelae from COVID19 in patients with cancer

--Manuscript Draft--

Manuscript Number:	EJC-D-22-00628R1
Article Type:	COVID-19
Keywords:	COVID-19, SARS-CoV-2, vaccines, prevention, cancer, clinical efficacy.
Corresponding Author:	Alessio Cortellini, M.D. Imperial College London London, UNITED KINGDOM
First Author:	David Pinato
Order of Authors:	David Pinato
	Daniela Ferrante
	Juan Aguilar-Company
	Mark Bower
	Ramon Salazar
	Oriol Mirallas
	Anna Sureda
	Alexia Bertuzzi
	Joan Brunet
	Matteo Lambertini
	Clara Maluquer
	Paolo Pedrazzoli
	Federica Biello
	Alvin JX Lee
	Christopher CT Sng
	Raquel Linan
	Sabrina Rossi
	MCarmen Carmona Garcia
	Rachel Sharkey
	Simeon Eremiev
	Gianpiero Rizzo
	Hamish DC Bain
	Tamara Yu
	Claudia Andrea Cruz
	Marta Perachino
	Nadia Saoudi-Gonzalez
	Roser Fort-Culillas
	Kris Doonga
	Laura Fox

	Elisa Roldán
	Federica Zoratto
	Gianluca Gaidano
	Isabel Ruiz-Camps
	Riccardo Bruna
	Andrea Patriarca
	Marianne Shawe-Taylor
	Vittorio Fusco
	Clara Martinez-Vila
	Rossana Berardi
	Marco Filetti
	Francesca Mazzoni
	Armando Santoro
	Sara Delfanti
	Alessandro Parisi
	Paola Queirolo
	Avinash Aujayeb
	Lorenza Rimassa
	Aleix Prat
	Josep Tabernero
	Alessandra Gennari
	Alessio Cortellini, M.D.
Abstract:	Background: Although SARS-CoV-2 vaccines immunogenicity in patients with cancer has been investigated, whether they can significantly improve the severity of COVID-19 in this specific population is undefined. Methods: Capitalizing on OnCovid (NCT04393974) registry data we reported COVID-19 mortality and proxies of COVID-19 morbidity, including post COVID-19 outcomes, according to the vaccination status of the included patients. Results: 2090 eligible patients diagnosed with COVID-19 between 02/2020 and 11/2021 were included, of whom 1930 (92.3%) unvaccinated, 91 (4.4%) fully vaccinated and 69 (3.3%) partially vaccinated. With the exception of a higher prevalence of patients from the UK (p=0.0003) and receiving systemic anticancer therapy at COVID-19 diagnosis (p=0.0082) among fully vaccinated patients, no demographics/oncological features were associated with vaccination status. The 14-days case fatality rate (CFR) (5.5% vs 20.7%, p=0.0004) and the 28-days CFR (13.2% vs 27.4%, p=0.0028) demonstrated a significant improvement for fully vaccinated patients in comparison with unvaccinated patients. The receipt of prior full vaccination was also associated with reduced symptomatic COVID-19 (79.1% vs 88.5%, p=0.0070), need of COVID-19 oriented therapy (34.9% vs 63.2%, p<0.0001), complications from COVID-19 (28.6% vs 39.4%, p=0.0379), hospitalizations due to COVID-19 (42.2% vs 52.5%, p=0.0007), and oxygen therapy requirement (35.7% vs 52%, p=0.0036). Following Inverse Probability Treatment Weighting (IPTW) procedure no statistically significant difference according to the vaccination status was confirmed; however, all COVID-19 related outcomes were concordantly in favour of full vaccination. Among the 1228 (58.8%) patients who underwent a formal reassessment at participating centers after COVID-19 resolution, fully vaccinated patients experienced less sequelae than unvaccinated patients (6.7% vs 17.2%, p=0.0320). Conclusions: This analysis provides initial evidence in support of the beneficial effect of SARS-CoV-2 vaccines against morbidity and mortality from COVID-19 in patients with cancer.

Running title: COVID-19 vaccines in patients with cancer.

Vaccination against SARS-CoV-2 protects from morbidity, mortality, and sequelae from COVID19 in patients with cancer.

David J. Pinato[1,2] MD PhD, Daniela Ferrante[3] PhD, Juan Aguilar-Company[4,5] MD, Mark Bower[6] MD PhD, Ramon Salazar[7] MD PhD, Oriol Mirallas[4] MD, Anna Sureda[8] MD PhD, Alexia Bertuzzi[9] MD, Joan Brunet[10] MD PhD, Matteo Lambertini[11,12] MD PhD, Clara Maluquer[8] MD, Paolo Pedrazzoli[13,14] MD, Federica Biello[2] MD, Alvin JX Lee[15] MD, Christopher CT Sng[15] MD, Raquel Liñan[10] MD, Sabrina Rossi[9] MD, M. Carmen Carmona-García[10] MD, Rachel Sharkey[6] RN, Simeon Eremiev[4] MD, Gianpiero Rizzo[13] MD, Hamish DC Bain[15] MD, Tamara Yu[15] MD, Claudia Andrea Cruz[16] MD, Marta Perachino[11,12] MD, Nadia Saoudi-Gonzalez[4] MD, Roser Fort-Culillas[10] MD, Kris Doonga[6] MD, Laura Fox[17] MD, Elisa Roldán[4] MD, Federica Zoratto[18] MD, Gianluca Gaidano[19] MD, Isabel Ruiz-Camps[5] MD PhD, Riccardo Bruna[19] MD, Andrea Patriarca[19] MD, Marianne Shawe-Taylor[15] MD, Vittorio Fusco[20] MD, Clara Martinez-Vila[21] MD, Rossana Berardi[22] MD PhD, Marco Filetti[23] MD, Francesca Mazzoni[24] MD, Armando Santoro[9,25] MD, Sara Delfanti[26] MD, Alessandro Parisi[27] MD, Paola Queirolo[28] MD, Avinash Aujayeb[29] MD, Lorenza Rimassa[9,25] MD, Aleix Prat[16,30] MD PhD, Josep Tabernero[31] MD PhD, Alessandra Gennari[2] MD PhD, Alessio Cortellini[1] MD.
On behalf of the OnCovid study group (investigators list is provided as supplementary material).

1.Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, London, UK;
2.Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy;
3.Department of Translational Medicine, Unit of Medical Statistics, University of Piemonte Orientale, Novara, Italy;
4.Medical Oncology, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain;
5.Infectious Diseases, Vall d'Hebron University Hospital, Barcelona, Spain;
6. Department of Oncology and National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, UK;
7.Department of Medical Oncology, ICO L'Hospitalet, Oncobell Program (IDIBELL), CIBERONC, Hospitalet de Llobregat, Spain;
8.Haematology Department, ICO Hospitalet, Hospitalet de Llobregat, IDIBELL, Universitat de Barcelona, Barcelona, Spain;
9.Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy;
10.Department of Medical Oncology, Catalan Institute of Oncology, University Hospital Josep Trueta, Girona, Spain;
11.Medical Oncology Department, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy;
12.Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy;
13.Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;
14.Department of Internal Medicine and Medical Therapy, University of Pavia, Pavia Italy;
15.Cancer Division, University College London Hospitals, London, UK;
16.Department of Medical Oncology, Hospital Clinic, Barcelona, Spain;
17.Department of Hematology, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain;
18.Medical Oncology, St Maria Goretti Hospital, Latina, Italy;
19.Division of Haematology, Department of Translational Medicine, University of Piemonte Orientale and Maggiore della Carità Hospital, Novara, Italy;
20.Oncology Unit and Centro Documentazione Osteonecrosi, Azienda Ospedaliera "SS Antonio e Biagio e Cesare Arrigo", Alessandria, Italy;
21. Fundació Althaia Manresa, Manresa, Spain;
22.Medical Oncology, AOU Ospedali Riuniti, Polytechnic University of the Marche Region, Ancona, Italy;
23. Medical Oncology, St. Andrea Hospital, Rome, Italy;
24.Medical Oncology, Careggi University Hospital, Florence, Italy;

25. Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 20090 Pieve Emanuele, Milan, Italy;
26. Mesothelioma Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy;
27.Department of Life, Health & Environmental Sciences, University of L'Aquila, L'Aquila, Italy;
28.Melanoma and Sarcoma Medical Treatment Unit, IEO - Istituto Europeo di Oncologia, Milan, Italy;
29.Respiratory Department, Northumbria Healthcare NHS Foundation Trust, North Shields, UK;
30.Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain;
31.Medical Oncology, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain.

WORD COUNT (excluding headings): 2663

Running Head: SARS-CoV-2 vaccines in patients with cancer

To whom correspondence should be addressed:

Dr Alessio Cortellini MD
Imperial College London Hammersmith Campus,
Tel: +44 020 83833720
E-mail: alessiocortellini@gmail.com, a.cortellini@imperial.ac.uk

Abstract

Background: Although SARS-CoV-2 vaccines immunogenicity in patients with cancer has been investigated, whether they can significantly improve the severity of COVID-19 in this specific population is undefined.

Methods: Capitalizing on OnCovid (NCT04393974) registry data we reported COVID-19 mortality and proxies of COVID-19 morbidity, including post COVID-19 outcomes, according to the vaccination status of the included patients.

Results: 2090 eligible patients diagnosed with COVID-19 between 02/2020 and 11/2021 were included, of whom 1930 (92.3%) unvaccinated, 91 (4.4%) fully vaccinated and 69 (3.3%) partially vaccinated. With the exception of a higher prevalence of patients from the UK (p=0.0003) and receiving systemic anticancer therapy at COVID-19 diagnosis (p=0.0082) among fully vaccinated patients, no demographics/oncological features were associated with vaccination status. The 14-days case fatality rate (CFR) (5.5% vs 20.7%, p=0.0004) and the 28-days CFR (13.2% vs 27.4%, p=0.0028) demonstrated a significant improvement for fully vaccinated patients in comparison with unvaccinated patients. The receipt of prior full vaccination was also associated with reduced symptomatic COVID-19 (79.1% vs 88.5%, p=0.0070), need of COVID-19 oriented therapy (34.9% vs 63.2%, p<0.0001), complications from COVID-19 (28.6% vs 39.4%, p=0.0379), hospitalizations due to COVID-19 (42.2% vs 52.5%, p=0.0007), and oxygen therapy requirement (35.7% vs 52%, p=0.0036). Following Inverse Probability Treatment Weighting (IPTW) procedure no statistically significant difference according to the vaccination status was confirmed; however, all COVID-19 related outcomes were concordantly in favour of full vaccination. Among the 1228 (58.8%) patients who underwent a formal reassessment at participating centers after COVID-19 resolution, fully vaccinated patients experienced less sequelae than unvaccinated patients (6.7% vs 17.2%, p=0.0320).

Conclusions: This analysis provides initial evidence in support of the beneficial effect of SARS-CoV-2 vaccines against morbidity and mortality from COVID-19 in patients with cancer.

Keywords: COVID-19, SARS-CoV-2, vaccines, prevention, cancer, clinical efficacy.

INTRODUCTION.

Patients with cancer are intrinsically more vulnerable to morbidity and mortality from Coronavirus Disease 2019 (COVID-19)[1,2]. All levels of cancer care including screening, diagnosis and treatment have been heavily impacted by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic[3,4]. In addition to the threat imposed by acute morbidity and mortality from COVID-19 in cancer patients, recent evidence highlights that oncological continuity of care can be further disrupted by long term consequences from COVID-19, which affect approximately 15% of patients with cancer who recover from the acute phase[5].

Widespread vaccination against SARS-Cov-2 represents a highly important public health measure to reduce severity and lethality of SARS-Cov-2.

The immunogenicity and safety profile of SARS-Cov-2 vaccines have been ~~widely~~ investigated across several type of cancers and irrespective of exposure to recent anti-cancer therapy[6-8]. Evidence of seroconversion following SARS-Cov-2 vaccination confirmed an antibody response in >90% of patients with solid tumours[9,10], which is comparable to the general population[11]. However, several reports highlight that a proportion of patients with cancer, such as those with haematological malignancies undergoing anti-CD20 treatments, elicit a diminished immune response to vaccines with seroconversion rates of <60%[9,10]

Evidence on the efficacy of SARS-Cov-2 vaccines from randomized clinical trials is limited to patients with stable oncological disease and off immunosuppressive anti-cancer therapy at the time of vaccination[12]. Therefore, unresolved questions exist around whether SARS-CoV-2 vaccination is effective independent of anti-cancer treatment and whether vaccinal immunity protects from long-term consequences from COVID-19.

With these premises in mind, we performed a dedicated update of the OnCovid registry to provide initial evidence regarding the magnitude of clinical benefit of SARS-CoV-2 vaccines in influencing outcome from COVID-19 in a large real-world oncological population.

STUDY DESIGN AND OUTCOMES.

OnCovid (NCT04393974) is a European registry study that collects data from consecutive patients with solid/hematologic malignancy diagnosed with COVID-19.

By the data lock of 22/12/2021, the registry included 3237 patients diagnosed with COVID-19 between the 27/02/2020 and the 30/11/2021. Patients with unknown

vaccination status were excluded. Similarly, to maintain consecutive accrual, we excluded centres that did not actively enroll subjects during the March-December accrual timeframe. A list of participating centers with eligible patients for this analysis is provided in **Supplementary Table 1.**

The primary objective of this study was to describe COVID-19 mortality in patients with cancer according to SARS-CoV-2 vaccination status. As secondary objectives we estimated the impact of COVID-19 vaccines on COVID-19 symptoms and morbidity. In addition, we evaluated whether receipt of SARS-CoV-2 vaccination was associated with the occurrence of COVID-19 sequelae among patients who underwent a clinical reassessment at the participating centers.

Patients were categorized as fully vaccinated at the time of COVID-19 diagnosis if they had received two doses for the BNT162b2, mRNA-1273, and ChAdOx1-S vaccines or in case of infection diagnosed at least 28 days after a single dose of the Ad.26.COV2.S vaccine[13]. Patients who received at least one vaccination, without meeting the above-mentioned criteria, were considered partially vaccinated.

Acknowledging the competing influence of the underlying malignancy in determining clinical outcomes, we elected the all-cause 14-days case fatality rate (CFR) as the clinical endpoints of interest, in an attempt of differentiating early (COVID-19 related) from late (cancer-related) mortality as already done in with our registry[14]. Considering the limited number of 14-days events recorded among fully vaccinated patients, which prevented the planned Inverse Probability of Treatment Weighting (IPTW) procedure, we also evaluated the 28-days CFR.

First, we reported the distribution of key demographics and oncological characteristics consistently associated with clinical outcome in the study population[5,14-18] across the vaccination categories, subsequently, we analyzed COVID-19 related outcomes according to the vaccination status, with a formal comparison between fully vaccinated and unvaccinated patients.

We then reported prevalence and distribution of COVID-19 associated symptoms, and as proxy of COVID-19 morbidity, we analyzed other COVID-19 related outcomes reproducibly described in the registry[5,14-17], including the need of COVID-19 oriented therapy, the incidence of COVID-19 complications, the hospitalization rate and the need of oxygen therapy.

Although recognizing that the unbalanced sample size of the vaccination subgroups did not allow a powered and formal weighted comparison, we performed as exploratory analysis an IPTW procedure including key baseline demographics and oncological characteristics, to provide a preliminary adjusted estimation of the CFR and COVID-19 related outcomes.

Considering the evidence of a mild decrease over time of the antibody response to SARS-CoV-2 vaccination[19,20], we also provided a descriptive analysis of COVID-19 outcome according to vaccination timing, including only patients with available date of vaccination. For this purpose, fully vaccinated patients were considered those who had received two doses of the BNT162b2, mRNA-1273, and ChAdOx1-S vaccines at least 7 days before the infection and those who received one dose of the Ad.26.COV2.S vaccine at least 28 days before the breakthrough infection[13,21-23]. Patients who received at least one vaccination, without meeting the above-mentioned criteria, were considered partially vaccinated, while those patients diagnosed with COVID-19 more than 6-months following the complete vaccination were considered separately.

Lastly, in order to describe the potential role of SARS-CoV-2 vaccines in reducing the occurrence of COVID-19 sequelae in patients with cancer, we focused on those patients who underwent a formal clinical assessment at the participating centers after COVID-19 recovery as previously done[5], and reported the incidence of COVID-19 sequelae according to their vaccination status. Sequelae were assessed by treating physicians as per local practice, and categorized according to the system/organ involved into: respiratory symptoms (including dyspnoea and chronic chough), residual fatigue, weight loss, neuro-cognitive sequelae (including cognitive, visual impairment, ano/dysosmia - age/dysgeusia, headache, confusion, lethargy), and others (including other organs disfunctions, residual fever, muscle cramps, arthralgia, skin conditions, etc). For the purpose of the analysis, COVID-19 sequelae were further clustered as: respiratory (either alone or combined with other complications) and post COVID-19 fatigue.

A detailed description of study methodology and statistical analysis is provided in **Supplementary eMethods.**

RESULTS.

Vaccination and patients' characteristics

At the time of database lock, the registry included 3237 patients. A total of 129 patients were excluded due to unconfirmed date of COVID-19 diagnosis and missing mortality outcome, another 133 patients were excluded because of unknown vaccination status. A further group of 885 patients previously entered from centers which did not enroll patients for the present update were further excluded to maintain consecutive accrual and minimize selection bias (**Figure 1**).

In total, 2090 eligible patients (67.2%) were included in this analysis, including 1930 (92.3%) unvaccinated, 91 (4.4%) fully vaccinated and 69 (3.3%) partially vaccinated

patients. Among fully vaccinated patients 54 (59.3%) received the BNT162b2 vaccine, 18 (19.8%) received the mRNA-1273 vaccine, 16 (17.6%) received the ChAdOx1-S vaccine and 3 (3.3%) received the Ad.26.COV2.S vaccine. Among partially vaccinated patients 32 (46.4%) received the BNT162b2 vaccine, 27 (39.1%) received the mRNA-1273 vaccine and 10 (14.5%) received the ChAdOx1-S vaccine.

Table 1 reports the detailed distribution of demographics and oncological characteristics across the vaccination subgroups. As compared to unvaccinated patients, there was a higher prevalence of patients from the United Kingdom (49.5% vs 31.5%, p=0.0003) and receiving systemic anticancer therapy at COVID-19 diagnosis (54.5% vs 40.3%, p=0.0082) among fully vaccinated patients, while no other characteristics including sex, age, comorbidities burden and tumour features were significantly associated with vaccination status. Of note, primary tumour types were well balanced across vaccination subgroups. Importantly, the great majority of patients diagnosed after the approval of the first SARS-CoV-2 vaccine in UK were still unvaccinated at COVID-19 diagnosis (560 vs 91/69 fully and partially vaccinated patients respectively).

Full vaccination is associated with improvement in COVID-19 morbidity and mortality.

The 14-days CFR were significantly lower in fully vaccinated patients (5.5%) in comparison with unvaccinated patients (20.7%, p=0.0004). Similarly, the 28-days CFR was significantly lower among fully vaccinated patients compared with unvaccinated patients (13.2% vs 27.4%, p=0.0028). Compared to unvaccinated patients, the receipt of a full vaccination course was associated with improved morbidity from COVID-19, as showed by the significant reduction in the rates of symptomatic COVID-19 (79.1% vs 88.5%, p=0.0070), provision of COVID-19-specific therapy (34.9% vs 63.2%, p<0.0001), acute complications from COVID-19 (28.6% vs 39.4%, p=0.0379), hospitalizations due to COVID-19 (42.2% vs 52.5%, p=0.0007) and requirement for oxygen therapy (35.7% vs 52%, p=0.0036). **Table 2** provides a summary of COVID-19 related outcomes according to the vaccination status, also visualized in **Figure 2A** and reported as unadjusted OR in **Figure 3A**.

IPTW analysis showed trends towards improvement in COVID-19 outcomes for fully vaccinated patients, however no statistically significant difference according to vaccination status can be confirmed for the 28-days CFR (adjusted odds ration - AOR 0.32, 95% Confidence Intervals - CI: 0.01-13.34), COVID-19 symptoms (AOR 0.46, 95%CI: 0.02-8.19), need of COVID-19 oriented therapy (AOR 0.29, 95%CI: 0.02-3.65), oxygen therapy (AOR 0.43, 95%CI: 0.03-6.18), complications from COVID-19 (AOR

0.48, 95%CI: 0.03-7.90), and hospitalization due to COVID-19 (AOR 0.27, 95%CI: 0.02-4.71) (**Figure 3B**). Multivariable logistic models for each outcome are reported in **Supplementary Table 2.**

Time-dependent characteristics of the relationship between SARS-Cov-2 vaccination and outcomes from COVID-19 infection.

In view of the time-dependent efficacy of SARS-Cov-2 vaccines[20], we postulated whether the improvement in COVID-19 outcomes seen in fully vaccinated patients could change as a function of time. The exact dates of all vaccination doses were available for 147 patients. For this analysis 70 patients (47.6%) were considered partially vaccinated, 64 patients (43.5%) fully vaccinated ≥6 months from the infection, and 13 patients (8.9%) fully vaccinated more than 6 months prior to the date of infection. Among partially vaccinated patients 33 (47.1%) received the BNT162b2 vaccine, 27 (38.6%) received mRNA-1273 and 10 (14.3%) received ChAdOx1-S. Among fully vaccinated patients, 31 (48.4%) received the BNT162b2 vaccine, 17 (26.6%) received mRNA-1273, 13 (20.3%) ChAdOx1-S and 3 (4.7%) Ad.26.COV2.S. Among the patients vaccinated ≥6 months from the infection, 11 (84.6%) received BNT162b2, 1 (7.7%) mRNA-1273, and 1 (7.7%) ChAdOx1-S. As summarized in **Supplementary Table 3** and **Supplementary Figure 1**, we observed a trend towards incremental improvement in all COVID-19-related outcomes across unvaccinated/partially vaccinated to fully vaccinated patients, followed by an increasing trend among patients vaccinated ≥6 months from the infection.

Vaccination against SARS-CoV-2 is associated with lower prevalence of COVID-19 sequelae in patients with cancer.

By the data lock, 1228 (58.8%) of the eligible patients underwent a formal clinical reassessment at participating centers after a median time of 40 days from COVID-19 diagnosis (Inter quartile range: 25-68). Baseline demographics and oncological characteristics stratified by vaccination status are summarized in **Supplementary Table 4**. Similar to what reported for the overall population, fully vaccinated patients were more likely from the United Kingdom (46.7% vs 21.9%, p=0.0003) and were receiving systemic anticancer therapy (SACT) at COVID-19 diagnosis (62.7% vs 47.6%, p=0.0235). No other feature was associated with vaccination status.

Overall, 199 patients (16.2%) reported at least one COVID-19 sequela. As showed in **Figure 2B**, the proportion of patients reporting at least 1 sequela from COVID-19 was significantly lower in fully vaccinated patients compared to unvaccinated controls

(6.7% vs 17.2%, p=0.0320), with no difference in the distribution of individual type of sequelae across groups (**Supplementary Table 5**).

DISCUSSION.

Vaccinal immunity to SARS-CoV-2 has radically changed the natural history of COVID-19. Whilst only partially effective in controlling viral transmission, especially after the emergence of novel variants of concern, vaccines remain widely effective in reducing the severity of COVID-19[23-26]. However, their remarkable clinical efficacy has been only partially demonstrated in patients with cancer[12].

Recently, data from the COVID-19 and Cancer Consortium (CCC19) on 54 fully vaccinated patients reported comparable rates of mortality and risk of adverse outcome from COVID-19 irrespective of vaccination status, highlighting that vaccine protection vaccination may be incomplete in patients with cancer, and supporting the need for further investigation in independent cohorts[27].

In this analysis of the OnCovid registry, we documented for the first time that patients who contracted SARS-Cov-2 after full vaccination were characterised by a lower probability of severe COVID-19 and mortality compared to unvaccinated controls.

Univariable analyses demonstrate a reduction in CFR 14- and 28-days post infection for fully vaccinated patients compared to unvaccinated patients. All indices of COVID-19 morbidity showed a protective effect for fully vaccinated patients, including COVID-19 symptoms, requirement for COVID-19-oriented therapy and oxygen therapy, complications and hospitalization rates due to COVID-19.

The retrospective design of our study and the relatively low proportion of fully vaccinated subjects by data cut-off underscores the preliminary nature of our findings. Baseline characteristics were comparable across exposed and unexposed groups, lending credence to the view that the improvement in outcomes observed in vaccinated patients may be truly due to SARS-Cov-2 immunity. While primary analyses confirmed our hypothesis, IPTW models yielded non statistically significant trends towards improvement of outcomes, as a likely result of largely unbalanced sample size of patients' subgrouping.

In a clinical setting that is deprived from solid level I evidence and within the limitation of a registry study, our findings provide a meaningful contribution to the growing body of knowledge demonstrating the ability of SARS-CoV-2 vaccines as a measure to reduce adverse outcome from the disease. Compelling evidence suggests how SARS-CoV-2 vaccination induces effective immune responses across different tumour types and irrespective of recent exposure to diverse anti-cancer therapies[6-8]. However, protective immunity is not universal in patients with cancer, where evidence of an at diminished immunogenicity has been shown in patients with haematological

malignancies and after treatment with CD20 inhibitors[7,9,10]: a finding that may explain the heterogeneity of results reported by the CCC19, which included 35% of patients with haematological malignancies among those fully vaccinated[27], compared to 12% of our cohort.

Whilst the retrospective nature of our study does not allow us to conclude that the association between full vaccination and improved outcome is truly causal, documentation of CFRs of 5.5% in this subgroup is highly important as it provides an important new benchmark in a more contemporary and clinically relevant estimate of lethality from COVID-19 in the post-vaccinal era[14], as it impressively diverges from the >30% estimates reported during the initial phase of the pandemic across different registries[17,28,29].

Baseline demographics and oncological characteristics, all well balanced across groups, are an unlikely source of bias. The uneven distribution in country of origin and SACT exposure can be easily explained by country-specific differences in the delivery of immunization campaigns, where vaccines were often offered alongside SACT in some centres.

The evidence that vaccine response may decrease over time[19,20] mirrors our descriptive analysis of vaccination timing, which suggests that the protection provided by SARS-CoV-2 vaccines declines beyond the 6-months landmark. These findings may also be related with the emergence of new variants of concern, such as the B.1.617.2 (delta), which has a higher transmissibility than previous strains and proved to cause a higher rate of breakthrough infections[30,31]. Taken together, these results support the need of prioritizing frail patients for booster doses, to sustain vaccines immunogenicity over time[32].

Another important question that has not been addressed in any previous study in oncological patients is whether vaccinal immunity may affect the risk of developing COVID-19 sequelae. In a recent analysis of the OnCovid registry, we demonstrated that COVID-19 is detrimental to patients' outcome even beyond the acute phase of the disease. COVID-19 sequalae can affect ~15% of patients, with long term consequences for their continuity of care and survival[5]. From this perspective, the additional analysis performed among COVID-19 survivors who underwent a clinical reassessment at participating centres suggests that the protection provided by vaccines extends beyond the acute phase, as supported by the reduced incidence of sequelae in fully vaccinated patients.

Our data collection relies on unplanned time intervals to capture vaccine administration, which could lead to determination bias. Moreover, breakthrough infections could have been asymptomatic with an associated risk of diminished

reporting and underestimation of the effect. However, hard endpoints like mortality/severe disease were unlikely affected.

Notably, we did not discuss booster/third doses, as by the data lock only a small minority of breakthrough infections among patients who received it had been reported. However, considering the recently emerged B.1.1.529 (omicron) variant, its different immunogenic profile, and the wave of infections recorded in Europe during December 2021 and January 2022[33,34], a dedicated update is currently ongoing, to produce reliable dedicated evidence.

Although preliminary, this study provides novel evidence supporting the clinical efficacy against COVID-19 morbidity, mortality and sequelae of SARS-CoV-2 vaccines in a large real-world population of patients with cancer. Universal SARS-CoV-2 vaccination should remain a goal in the management of patients with cancer during and beyond the COVID-19 pandemic.

Role of the funding source

OnCovid is sponsored by Imperial College London and received direct project funding and infrastructural support by the NIHR Imperial Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Neither sponsor nor the funders of the study had any role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to all the data reported in the study.

Ethical approval and consent to participate

OnCovid was granted central approval by the United Kingdom Health Research Authority (20/HRA/1608) and by the corresponding research ethics committees at each participating institution. Full waiver of consent due to the retrospective nature of the study was granted by the UK HRA in accordance with UK law.

Authors' Contributions

All authors contributed to the publication according to the ICMJE guidelines for the 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). Each author has agreed both 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.

Acknowledgements

OnCovid received direct project funding and infrastructural support by the NIHR Imperial Biomedical Research Centre (BRC).

Alessio Cortellini is supported by the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC).
David J Pinato is supported by grant funding from the Wellcome Trust Strategic Fund (PS3416) and from the Associazione Italiana per la Ricerca sul Cancro (AIRC MFAG Grant ID 25697) and acknowledges support by the NIHR Imperial Biomedical Research Centre (BRC), the Imperial Experimental Cancer Medicine Centre (ECMC) and the Imperial College Tissue Bank.
G. Gaidano is supported by the AIRC 5 × 1000 Grant, No. 21198, Associazione Italiana per la Ricerca sul Cancro Foundation, Milan, Italy. A. Gennari is supported by the AIRC IG Grant, No. 14230, Associazione Italiana per la Ricerca sul Cancro Foundation, Milan, Italy. A. Gennari and G. Gaidano from the University of Piemonte Orientale (Novara, Italy) acknowledge support from the UPO Aging Project.

Consent for Publication

Informed consent was waived by competent authorities due to anonymized nature of patient data and retrospective design of the study.

Availability of Data and Material

Study data made available upon reasonable request.

References.

1. Giannakoulis VG, Papoutsi E, Siempos, II. Effect of Cancer on Clinical Outcomes of Patients With COVID-19: A Meta-Analysis of Patient Data. *JCO Glob Oncol* 2020; **6**: 799-808.
2. Tagliamento M, Agostinetto E, Bruzzone M, et al. Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2021; **163**: 103365.
3. Greenwood E, Swanton C. Consequences of COVID-19 for cancer care - a CRUK perspective. *Nat Rev Clin Oncol* 2021; **18**(1): 3-4.
4. Jones D, Neal RD, Duffy SRG, Scott SE, Whitaker KL, Brain K. Impact of the COVID-19 pandemic on the symptomatic diagnosis of cancer: the view from primary care. *Lancet Oncol* 2020; **21**(6): 748-50.
5. Pinato DJ, Tabernero J, Bower M, 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**(12): 1669-80.
6. Oosting SF, van der Veldt AAM, GeurtsvanKessel CH, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. *Lancet Oncol* 2021; **22**(12): 1681-91.
7. Fendler A, Shepherd STC, Au L, et al. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study. *Nature Cancer* 2021; **2**(12): 1305-20.
8. Fendler A, Au L, Shepherd STC, et al. Functional antibody and T cell immunity following SARS-CoV-2 infection, including by variants of concern, in patients with cancer: the CAPTURE study. *Nature Cancer* 2021; **2**(12): 1321-37.
9. Becerril-Gaitan A, Vaca-Cartagena BF, Ferrigno AS, et al. Immunogenicity and risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection after Coronavirus Disease 2019 (COVID-19) vaccination in patients with cancer: a systematic review and meta-analysis. *Eur J Cancer* 2022; **160**: 243-60.
10. Addeo A, Shah PK, Bordry N, et al. Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer. *Cancer Cell* 2021; **39**(8): 1091-8 e2.
11. Wei J, Stoesser N, Matthews PC, et al. Antibody responses to SARS-CoV-2 vaccines in 45,965 adults from the general population of the United Kingdom. *Nature Microbiology* 2021; **6**(9): 1140-9.
12. Thomas SJ, Perez JL, Lockhart SP, et al. 1558O COVID-19 vaccine in participants (ptcpts) with cancer: Subgroup analysis of efficacy/safety from a global phase III randomized trial of the BNT162b2 (tozinameran) mRNA vaccine. *Annals of Oncology* 2021; **32**: S1129.
13. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *New England Journal of Medicine* 2021; **384**(23): 2187-201.

14. OnCovid Study G, Pinato DJ, Patel M, et al. Time-Dependent COVID-19 Mortality in Patients With Cancer: An Updated Analysis of the OnCovid Registry. *JAMA Oncol* 2021.
15. Pinato DJ, Lee AJX, Biello F, et al. Presenting Features and Early Mortality from SARS-CoV-2 Infection in Cancer Patients during the Initial Stage of the COVID-19 Pandemic in Europe. *Cancers (Basel)* 2020; **12**(7).
16. Pinato DJ, Scotti L, Gennari 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.
17. Pinato DJ, Zambelli A, Aguilar-Company J, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. *Cancer Discov* 2020.
18. Dettorre GM, Dolly S, Loizidou A, 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**(3).
19. Widge AT, Rouphael NG, Jackson LA, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. *New England Journal of Medicine* 2020; **384**(1): 80-2.
20. Naaber P, Tserel L, Kangro K, et al. Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study. *Lancet Reg Health Eur* 2021; **10**: 100208.
21. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine* 2020; **383**(27): 2603-15.
22. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine* 2020; **384**(5): 403-16.
23. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397**(10269): 99-111.
24. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; **384**(5): 403-16.
25. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**(27): 2603-15.
26. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med* 2021.
27. Schmidt AL, Labaki C, Hsu CY, et al. COVID-19 vaccination and breakthrough infections in patients with cancer. *Annals of Oncology* 2021.
28. Garassino MC, Whisenant JG, Huang LC, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol* 2020; **21**(7): 914-22.
29. Lee LY, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet* 2020; **395**(10241): 1919-26.
30. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *New England Journal of Medicine* 2021; **385**(7): 585-94.

31. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature* 2021; **596**(7871): 276-80.
32. Naranbhai V, St. Denis KJ, Lam EC, et al. Neutralization breadth of SARS-CoV-2 viral variants following primary series and booster SARS-CoV-2 vaccines in patients with cancer. *Cancer Cell* 2022; **40**(1): 103-8.e2.
33. Hoffmann M, Krüger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. *Cell* 2021.
34. Araf Y, Akter F, Tang Y-d, et al. Omicron variant of SARS-CoV-2: Genomics, transmissibility, and responses to current COVID-19 vaccines. *Journal of Medical Virology*; **n/a**(n/a).

Figure Legends

Figure 1: study flow diagram.
Figure 2: Summary of COVID-19 outcomes according to vaccination status (**A**). Patients were categorized as fully vaccinated at the time of COVID-19 diagnoses if they had received two doses for the BNT162b2, mRNA-1273, and ChAdOx1-S vaccines or in case of infection diagnosed at least 28 days after a single dose of the Ad.26.COV2.S vaccine. (**B**) Summary COVID-19 sequelae analysis according to the vaccination status.
Figure 3: Forest plot graph reporting the (**A**) unadjusted odds ratio (OR) and the (**B**) adjusted odds ratio (aOR) from the Inverse Probability of Treatment Weighting (IPTW) fitted multivariable logistic regression models for each COVID-19 outcomes. The following covariates were included in each model: country (United Kingdom vs Spain vs Italy), biological sex (male vs female), age (≥65 vs < 65 years), number of co-morbidities (≥2 vs 0-1), tumour status (presence of active vs non-active disease), and the receipt of systemic anticancer therapy (SACT) within 4 weeks of SARS-CoV-2 infection (yes vs no). CFR: case fatality rate. Complete multivariable models for each COVID-19 outcomes are reported in **Supplementary Table 2**.

Table 1: Demographics and oncological characteristics of eligible patients according to the vaccination status. * Within 4 weeks of COVID-19 diagnosis. SACT: systemic anticancer therapy.

	Unvaccinated	Fully vaccinated	P-value	Partially vaccinated
	N = 1930 (%)	N = 91 (%)		N = 69 (%)
Country				
United Kingdom	607 (31.5)	45 (49.5)	0.0003	35 (50.7)
Spain	712 (36.9)	32 (35.2)		26 (37.7)
Italy	611 (31.7)	14 (15.4)		8 (11.6)
Sex				
Male	1043 (54.2)	43 (47.3)	0.1970	35 (50.7)
Females	883 (45.8)	48 (52.7)		34 (49.3)
Missing	4	-		-
Age				
<65 years	753 (39.2)	44 (48.4)	0.0798	26 (38.8)
≥65 years	1170 (60.8)	47 (51.6)		41 (61.2)
Missing	6	-		2
Comorbidities				
0-1	1031 (53.4)	48 (52.7)	0.9000	32 (46.4)
≥2	899 (46.6)	43 (47.3)		37 (53.6)
Smoking history				
Never smokers	818 (50)	34 (41)	0.1095	24 (41.4)
Former/current smokers	819 (50)	49 (59)		34 (58/6)
Missing	293	8		11
Primary Tumour				
Breast	313 (16.4)	16 (17.6)	0.5284	13 (18.8)
Gastrointestinal	385 (20.1)	15 (16.5)		12 (17.4)
Gynaecological/Genito-Urinary	344 (18.0)	21 (23.1)		13 (18.8)
Thoracic	301 (15.7)	15 (16.5)		13 (18.8)
Others	225 (11.8)	13 (14.3)		10 (14.5)
Haematologic	346 (18.1)	11 (12.1)		8 (11.6)
Missing	16	-		-
Tumour stage				
Local/loco-regional	833 (47.2)	34 (40)	0.1959	31 (47)
Advanced	933 (52.8)	51 (60)		35 (53)
Missing	164	6		3
Tumour status at COVID-19 diagnosis				
Remission/non measurable disease	679 (35.5)	30 (33)	0.6249	27 (39.7)
Active malignancy	1235 (64.5)	61 (67)		41 (60.3)
Missing	16	-		1
SACT at COVID-19 diagnosis*				
No	1103 (59.7)	40 (45.5)	0.0082	33 (53.2)
Yes	746 (40.3)	48 (54.5)		29 (46.8)
Missing	81	3		7
Timing of infection				
Post-vaccination phase	560 (29.0)	91 (100)		69 (98.6)
Pre-vaccination phase	1370 (71.0)	-		-

Table 2: Summary of COVID-19 related outcomes according to the vaccination status.

	Unvaccinated	Fully vaccinated	P-value	Partially vaccinated
	N = 1930 (%)	**N = 91 (%)**		**N = 69 (%)**
14-Days case fatality rate				
Alive	1530 (79.3)	86 (94.5)	0.0004	59 (85.5)
Death events	400 (20.7)	5 (5.5)		10 (14.5)
28-Days case fatality rate				
Alive	1401 (72.6)	79 (86.8)	0.0028	55 (79.7)
Death events	529(27.4)	12 (13.2)		14 (20.3)
COVID-19 symptoms				
No	222 (11.5)	19 (20.9)	0.0070	10 (14.5)
Yes	1708 (88.5)	72 (79.1)		59 (85.5)
Need of COVID-19 oriented therapy				
No	676 (36.8)	56 (65.1)	<0.0001	37 (55.2)
Yes	1162 (63.2)	30 (34.9)		30 (44.8)
Missing	92	5		2
Complications from COVID-19				
No	1169 (60.6)	65 (71.4)	0.0379	43 (62.3)
Yes	761 (39.4)	26 (28.6)		26 (37.7)
Hospitalization				
Not required	431 (22.5)	36 (40.0)	0.0007	15 (22.1)
Required due to COVID-19	1006 (52.5)	38 (42.2)		31 (45.6)
Pre-existing	479 (25.0)	16 (17.8)	-	22 (32.4)
Missing	14	1		1
Oxygen therapy				
No	884 (48.0)	54 (64.3)	0.0036	40 (60.6)
Yes	956 (52.0)	30 (35.7)		26 (39.4)
Missing	90	7		3

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-6 4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	4-6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	6-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Figure 1

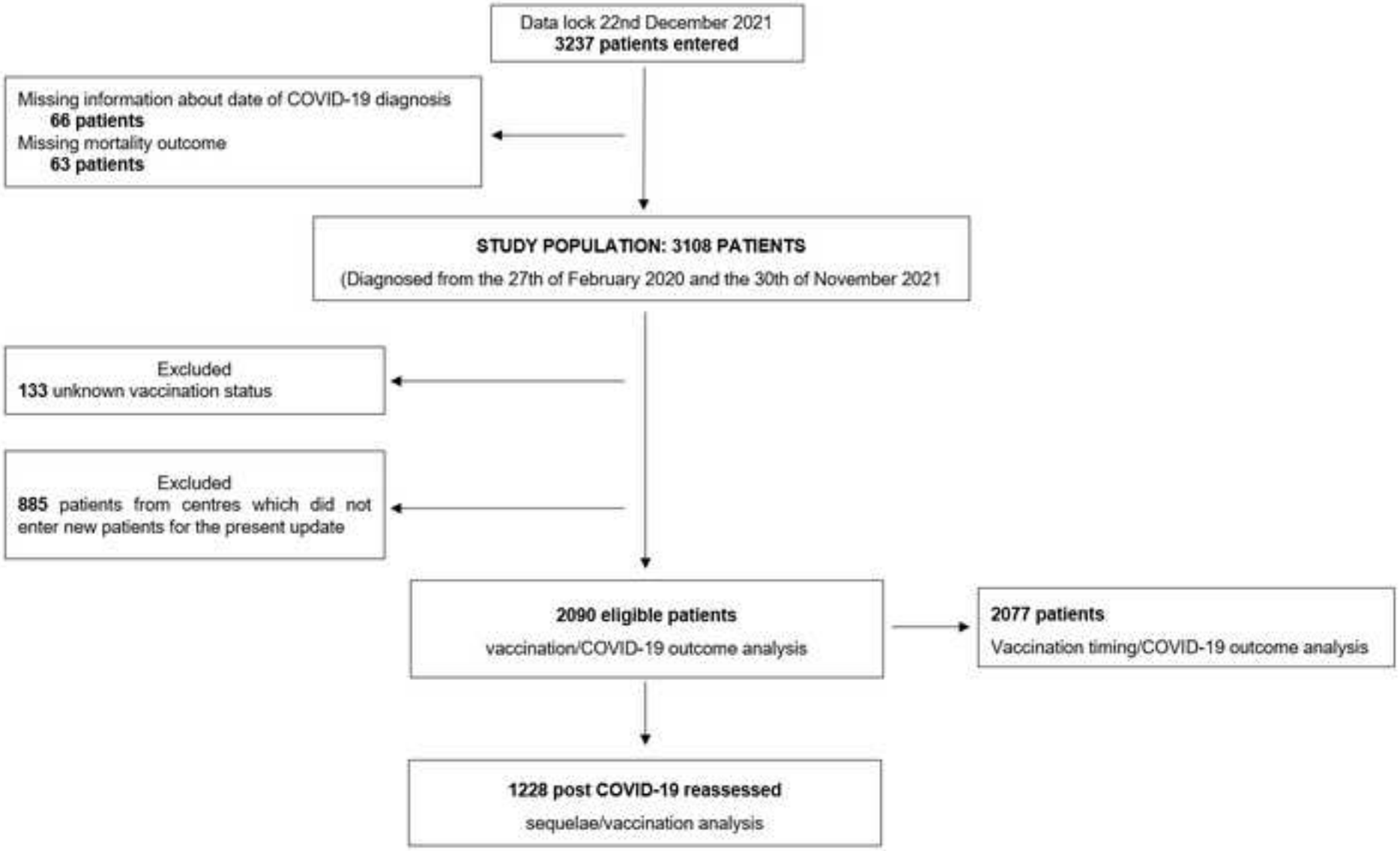


Figure 2

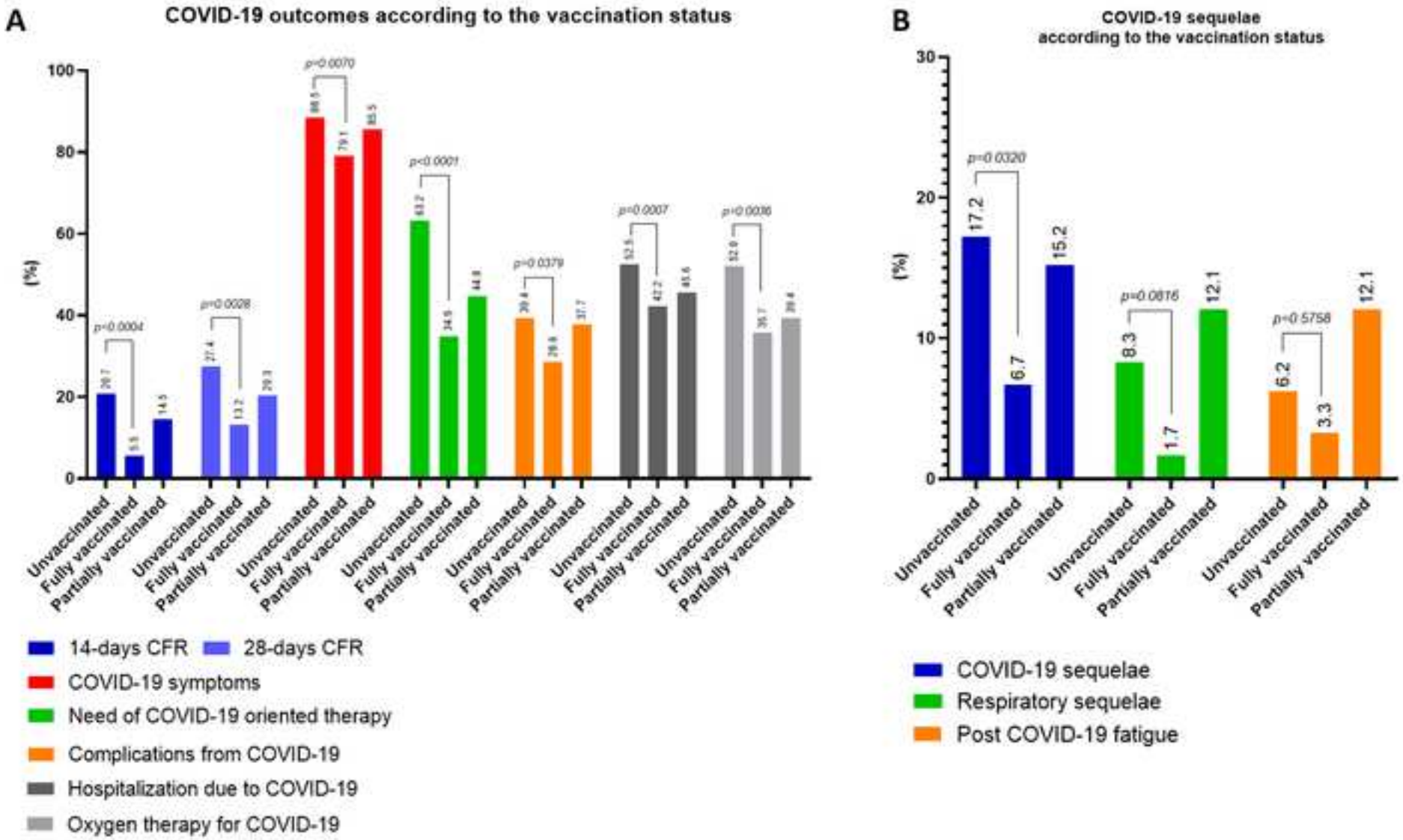
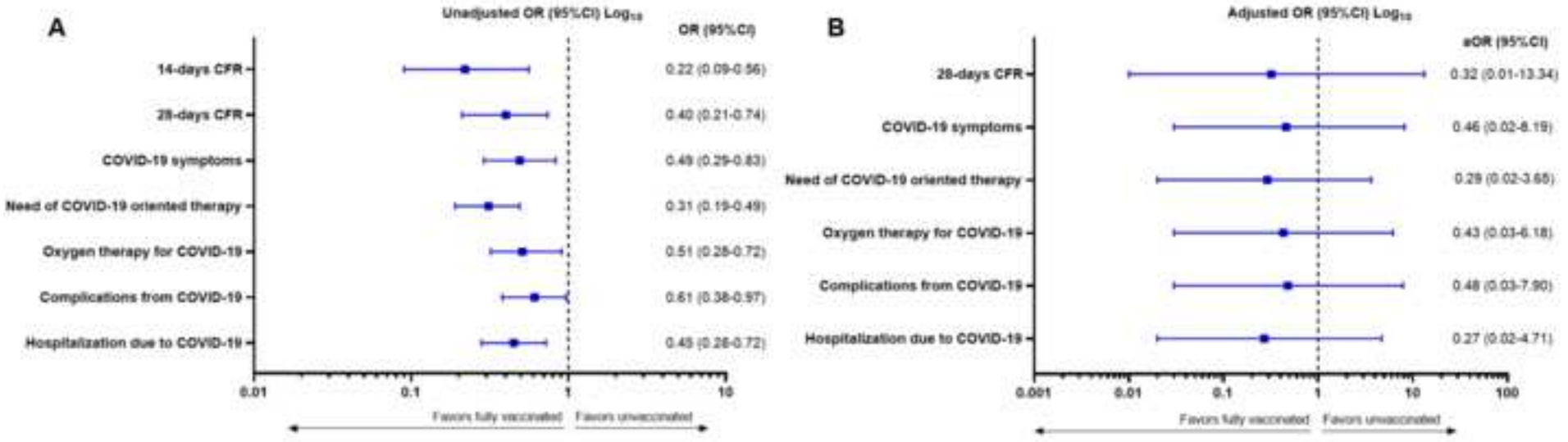


Figure 3

Click here to access/download;Figure;Figure 3.tif



Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Vaccination against SARS-CoV-2 protects from morbidity, mortality, and sequelae from COVID19 in patients with cancer.

As corresponding author of the abovementioned manuscript, I declare on behalf of my co-authors the following conflict of interests:

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.

Aleix Prat has declared personal honoraria from Pfizer, Roche, MSD Oncology, Eli Lilly, and Daiichi Sankyo; travel, accommodations, and expenses paid by Daiichi Sankyo; research funding from Roche and Novartis; and consulting/advisory role for NanoString Technologies, Amgen, Roche, Novartis, Pfizer and Bristol-Myers Squibb.

Matteo Lambertini acted as consultant for Roche, Novartis, Lilly, AstraZeneca, Exact Sciences, MSD, Pfizer, Seagen and received speaker honoraria from Roche, Novartis, Lilly, Pfizer, Takeda, Ipsen and Sandoz outside the submitted work.

Joan Brunet has declared consulting/advisory role for MSD and Astra Zeneca.

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.

Gianluca Gaidano has declared consulting/advisory role for Janssen, Abbvie, Astra-Zeneca and BeiGene, and speaker fees from Janssen and Abbvie.

Lorenza Rimassa received consulting fees from Taiho Oncology, Servier, Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi; travel expenses from Ipsen; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks.

Joseph Tabernero reported consulting fees from Array Biopharma, AstraZeneca, Avvinity, 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, Seattle Genetics, Scandion Oncology, Servier, Sotio Biotech, Taiho, Tessa Therapeutics and TheraMyc. He also reported speaker's fees from Imedex, Medscape Education, MJH Life Sciences, PeerView Institute for Medical Education and Physicians Education Resource (PER). He also declared institutional research support from Amgen Inc, Array Biopharma Inc, AstraZeneca Pharmaceuticals LP, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Debiopharm International SA, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Janssen-Cilag SA , MedImmune, Menarini, Merck Health KGAA, Merck Sharp & Dohme, Merus NV, Mirati, Novartis Farmacéutica SA, Pfizer, Pharma Mar, Sanofi Aventis Recherche & Développement, Servier, Taiho Pharma USA Inc, Spanish Association Against Cancer Scientific Foundation and Cancer Research UK.

Alessio Cortellini received consulting fees from MSD, BMS, AstraZeneca, Roche; speakers' fee from AstraZeneca, MSD, Novartis and Eisai.

All remaining authors have declared no conflicts of interest.

London, April 18th, 2022