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Original Research

Persistence of long-term COVID-19 sequelae in patients with cancer: An analysis from the OnCovid registry



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Abstract Introduction: A significant proportion of patients with cancer who recover from Coronavirus Disease 2019 (COVID-19) may experience COVID-19 sequelae in the early post-infection phase, which negatively affect their continuity of care and oncological outcome. The long-term prevalence and clinical impact of the post-COVID-19 syndrome in patients with cancer are largely unknown.

Methods: In this study, we describe the time course of COVID-19 sequelae in patients with non-advanced cancers enrolled in the OnCovid registry.

Results: Overall, 186 patients were included, with a median observation period of 9.9 months (95%CI:8.8–11.3) post-COVID-19 resolution. After a median interval of 2.3 months post-COVID-19 (interquartile range: 1.4–3.7), 31 patients (16.6%) reported ≥ 1 sequelae, including respiratory complications (14, 7.6%), fatigue (13, 7.1%), neuro-cognitive sequelae (7, 3.8%). The vast majority of the patients were not vaccinated prior to COVID-19. COVID-19-related sequelae persisted in 9.8% and 8% of patients 6 and 12 months after COVID-19 resolution. Persistence of sequelae at first oncological follow-up was associated with history of complicated COVID-19 (45.2% vs 24.8%, $p = 0.0223$), irrespective of oncological features at COVID-19 diagnosis.

Conclusion: This study confirms for the first time that, in a largely unvaccinated population, post-COVID-19 syndrome can affect a significant proportion of patients with non-advanced cancer who recovered from the acute illness. COVID-19 sequelae may persist up to 12 months in some patients, highlighting the need for dedicated prevention and supportive strategies.

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1. Introduction

A significant proportion of Coronavirus Disease 2019 (COVID-19) survivors are at risk of developing the post-COVID-19 syndrome [1], a complex manifestation of likely immune-inflammatory pathogenesis that is characterized by a wide variety of symptoms including persistent fatigue, neuro-cognitive sequelae and varying degrees of respiratory impairment. Evidence in non-cancer populations suggests chronic consequences from COVID-19 to persist beyond 6 months post-infection [2,3].

Patients with cancer are especially vulnerable to COVID-19 [4–6], and recent evidence from the OnCovid study highlights that at least 15% of those who outlive the acute phase of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection can experience COVID-19 sequelae, which significantly affect the continuity of their oncological care and survival outcome, independent of oncological prognostic factors [7].

There is no evidence to suggest whether the post-COVID-19 syndrome can lead to long-term consequences in patients with cancer. In this study, we evaluated OnCovid registry participants with non-

advanced cancer, to estimate prevalence, duration and clinical significance of long-term sequelae from COVID-19.

2. Patients and methods

OnCovid (NCT04393974) is an active European registry study that, since the beginning of the pandemic, has collected consecutive patients fulfilling the following inclusion criteria: 1) age ≥ 18 years; 2) diagnosis of SARS-CoV-2 infection confirmed by RT-PCR of a nasopharyngeal swab; 3) history of solid or hematologic malignancy, at any time during the patients' past medical history, either active or in remission at the time of COVID-19 diagnosis.

By the data-lock of 22nd of December 2021, the registry included 3237 consecutive patients from 37 institutions across 6 countries (UK, Italy, Spain, France, Belgium and Germany), and included patients diagnosed with COVID-19 between the 27th of February 2020 and the 30th of November 2021. A list of the participating centres with eligible patients for this analysis is provided in [Supplementary Table 1](#).

We evaluated long-term outcomes in patients with non-advanced cancer who had survived COVID-19 by describing the prevalence and natural history of COVID-19 sequelae over time. For this purpose, we included only patients who underwent a clinical reassessment 6 months after COVID-19 diagnosis at each participating institution.

Acknowledging the competing influence of the underlying malignancy in affecting symptomatic burden and survival post-COVID-19, patients with advanced/metastatic malignancy were excluded from the analysis, to avoid bias in the attribution of causality of long-term sequelae.

Definitions of symptoms, clinical syndromes and complications from COVID-19 followed standardized criteria published by the World Health Organization [8]. However, these were assessed by treating physicians as per local practice and when clinically indicated, for instance during clinical consultation, symptoms review, physical examination, imaging and/or laboratory findings review. Timing of follow-up was not standardized, but dictated by the treating physicians as per standard of care.

COVID-19 sequelae were categorized according to the system/organ involved into: respiratory symptoms (including dyspnoea and chronic cough), residual fatigue, neuro-cognitive sequelae (including cognitive, visual impairment, anosmia/dysosmia - age/dyseusia, headache, confusion, lethargy) and others (including other organs dysfunctions, weight loss, residual fever, muscle cramps, arthralgia, skin conditions etc).

Additionally, sequelae were also differentiated as single-site and multiple-sites, in case of patients experiencing multiple sequelae.

First, we documented the prevalence and type of COVID-19 sequelae at the time of the first oncological assessment post-COVID-19 and their distribution according to key demographics, oncological and COVID-19-related characteristics, including the receipt of SARS-CoV-2 vaccines prior to the infection. We also evaluated patterns of resumption of systemic anti-cancer therapy (SACT) at the first reassessment among patients who were on SACT within 4 weeks of COVID-19 diagnosis. Lastly, we described the prevalence and type of COVID-19 sequelae at 6 and 12-months following recovery from SARS-Cov-2 infection (\pm 28 days). Detailed methodology is provided in [Supplementary Methods](#).

3. Results

The eligible study population consisted of 3108 patients. After the exclusion of patients with advanced/metastatic disease and those who had not undergone a 6-months reassessment and those who experienced SARS-CoV-2 re-infection during follow-up, 186 patients were included in this analysis ([Fig. 1](#)).

The first reassessment was performed as per local practice, with a median interval of 2.3 months (interquartile range: 1.4–3.7) from COVID-19 diagnosis. This coincided with the 6-months follow-up assessment for 40 patients. Overall, 31 patients (16.6%) experienced at least one COVID-19 complication, including respiratory sequelae (14, 7.6%), post-COVID-19 fatigue (13, 7.1%), neuro-cognitive sequelae (7, 3.8%) and others (7, 3.8%) ([Fig. 2A](#)); 7 patients (3.7%) experienced >1 sequelae. The median post-COVID-19 follow-up was 9.9 months (95%CI: 8.8–11.3) and with only 12 events, the median post-COVID-19 survival was not reached.

Patients suffering from sequelae at the first post-COVID-19 reassessment were more likely smokers (68% vs 38.5%, $p = 0.007$) and had history of complicated COVID-19 (45.2% vs 24.8%, $p = 0.0223$) ([Fig. 2B](#)). No associations between sequelae and oncological features, including the receipt of SACT within 4 weeks of COVID-19, were reported. The proportion of patients experiencing oncological disease progression at the first reassessment was comparable in patients with and without sequelae ($p = 0.2335$). The vast majority of the patients were not vaccinated prior to COVID-19 ([Table 1](#)). Among the 75 patients (40.8%) who were on SACT at COVID-19, 15 (20%) permanently discontinued treatment, 8 (10.7%) resumed treatment following dose/regimen adjustments.

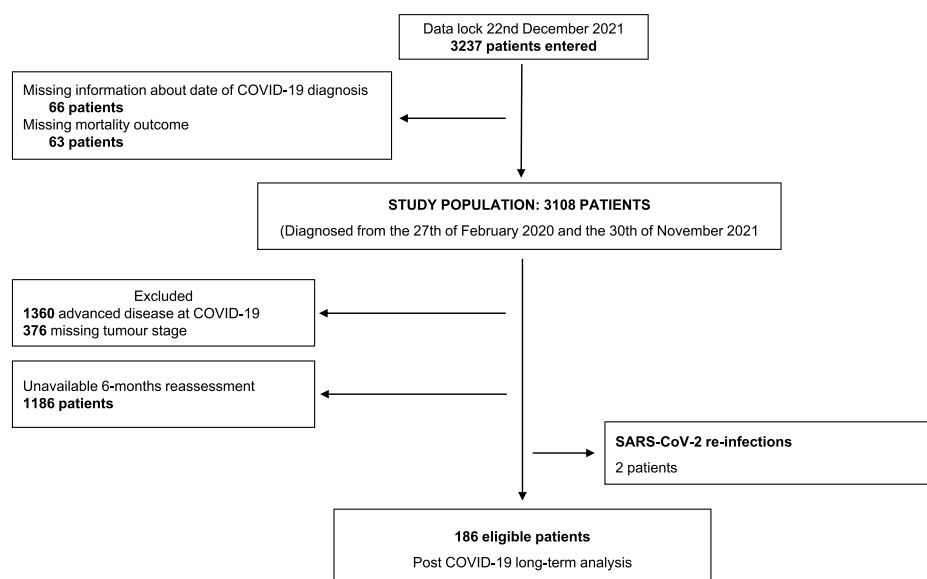


Fig. 1. Study flow diagram.

At the 6-months follow-up, COVID-19 sequelae were reported for 18 patients (9.8%), of whom 5 (2.7%) had multiple symptoms. In detail, 9 patients (4.9%) experienced respiratory sequelae, 6 patients (3.2%) experienced post-COVID-19 fatigue, 4 patients (2.2%) neuro-cognitive sequelae and 5 patients (2.7%) had sequelae of other kinds (Fig. 2A). Disease progression at 6 months

was reported for 9 patients among those experiencing sequelae (50%) and for 54 (32.5%) among those who did not experienced sequelae ($p = 0.1390$).

Data on oncological follow-up at 12-months was available for 100 patients; among them 8 (8%) experienced COVID-19 sequelae and 2 patients (2%), multiple-sites sequelae. In detail, 3 patients (3%)

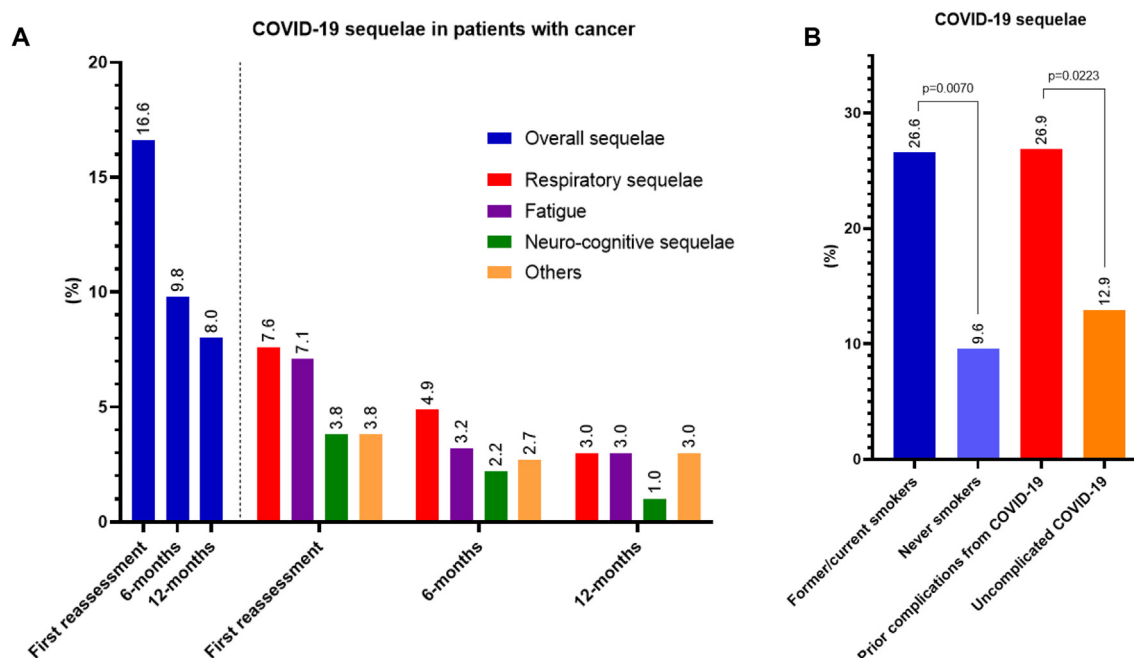


Fig. 2. Prevalence of COVID-19 sequelae. **A**) Prevalence at the first clinical reassessment (31/184: 16%), at 6 months (18/184: 9.8%) and at 12 months (8/100: 8%). Type of sequelae at the first reassessment: respiratory sequelae (14: 7.6%), fatigue (13: 7.1%), neuro-cognitive sequelae (7: 3.8%), others (7: 3.8%). Type of sequelae at the 6-months reassessment: respiratory sequelae (9: 4.9%), fatigue (6: 3.2%), neuro-cognitive sequelae (4: 2.2%), others (5: 2.7%). Type of sequelae at the 12-months reassessment: respiratory sequelae (3: 3%), fatigue (3: 3%), neuro-cognitive sequelae (1: 1%), others (3: 3%). **B**) Prevalence of COVID-19 sequelae at the first reassessment among never smokers (8/83: 9.6%), current/former smokers (17/64: 26.6%), among patients who did not experience prior complications from COVID-19 (17/132: 12.9%) and those who experienced complicated COVID-19 (14/52: 26.9%).

Table 1

Distribution of baseline demographics, tumour and COVID-19 characteristics at the first re-assessment according to COVID-19 sequelae experiencing.

| | Without COVID-19 Sequelae N = 153 (%) | With COVID-19 Sequelae N = 31 (%) | P value |
|---|--|--|---------|
| Contry | | | |
| United Kingdom | 54 (35.3) | 8 (25.8) | 0.5927 |
| Spain | 55 (35.9) | 13 (41.9) | |
| Italy | 44 (28.8) | 10 (32.3) | |
| Sex | | | |
| Male | 77 (50.3) | 15 (48.4) | 0.8443 |
| Females | 76 (49.7) | 16 (51.6) | |
| Age | | | |
| <65 years | 67 (43.8) | 14 (45.2) | 0.8888 |
| ≥65 years | 86 (56.2) | 7 (54.8) | |
| Comorbidities | | | |
| 0–1 | 85 (55.6) | 14 (45.2) | 0.2911 |
| ≥2 | 68 (44.4) | 17 (54.8) | |
| Smoking history | | | |
| Never smokers | 75 (61.5) | 8 (32) | 0.0070 |
| Former/current smokers | 47 (38.5) | 17 (68) | |
| Missing | 31 | 6 | |
| Primary Tumour | | | |
| Breast | 44 (28.8) | 6 (20) | 0.8850 |
| Gastrointestinal | 29 (19) | 6 (20) | |
| Gynaecological/ Genito-Urinary | 32 (20.9) | 7 (23.3) | |
| Thoracic | 13 (8.5) | 4 (13.3) | |
| Others | 19 (12.4) | 3 (10.0) | |
| Haematological | 16 (10.5) | 4 (13.3) | |
| Missing | 0 | 1 | |
| SACT at COVID-19 diagnosis^a | | | |
| No | 94 (62.7) | 19 (63.3) | 0.9452 |
| Yes | 56 (37.3) | 11 (36.7) | |
| Missing | 3 | 1 | |
| COVID-19 therapy | | | |
| No | 59 (40.4) | 9 (31) | 0.3454 |
| Yes | 87 (59.6) | 20 (69) | |
| Missing | 7 | 2 | |
| Complicated COVID-19 | | | |
| No | 115 (75.2) | 17 (54.8) | 0.0223 |
| Yes | 38 (24.8) | 14 (45.2) | |
| Hospitalization | | | |
| Not required | 48 (31.8) | 8 (25.8) | 0.7847 |
| Required | 83 (55.0) | 19 (61.3) | |
| Pre-existing | 20 (13.2) | 4 (12.9) | |
| Missing | 2 | – | |
| Vaccination status prior to COVID-19 | | | |
| Unvaccinated | 138 (93.9) | 31 (100) | 0.3681 |
| Fully vaccinated | 3 (2) | – | |
| Partially vaccinated | 6 (4.1) | – | |
| Missing | 6 | – | |
| Disease progression at 1st assessment | | | |
| No | 119 (77.8) | 21 (67.7) | 0.2335 |
| Yes | 34 (22.2) | 10 (32.3) | |

^a Within 4 weeks of COVID-19 diagnosis.

reported respiratory sequelae, 3 (3%) post-COVID-19 fatigue (Fig. 2A). Disease progression at 12-months was reported for 5 patients and 39 patients in the sequelae and non-sequelae subgroups, respectively (62.5% vs 42.4%, $p = 0.2951$).

4. Discussion

In the context of a progressive improvement in terms of disease management, hospital/testing capacity, and vaccinal campaigns [9], post-COVID syndrome continues to pose a threat to the well-being of patients with cancer. Although including only patients with non-advanced tumours, with a likely lower burden of cancer-related symptoms, this study confirms our previous findings in unselected patients with cancer [10]. At least ~15% of COVID-19 survivors can experience sequelae during the early post-infection phase, independent of major demographic and tumour characteristics. Features of COVID-19 severity, such as complications from COVID-19 appear the strongest determinants. Whilst the prevalence of COVID-19 sequelae decreases over time, a significant proportion of patients experience persisting symptoms following up to 12 months from recovery. We confirm respiratory symptoms to be the most prevalent sequelae from COVID-19, although we reported a non-negligible proportion of neuro-cognitive sequelae, providing further credence to the role of neuroinflammation as a pathogenic underlying mechanism [11–13].

Our findings mirror those reported among the general population, where between 13% and 60% of COVID-19 survivors are at risk of developing post-COVID-19 symptoms [3,14–16]. In addition, estimates of symptoms' prevalence during the early post-infection phase for the general population reach >30% [17], and up to 25% of patients may report sequelae beyond the 6-months landmark [15].

Whilst limited by the selection of non-advanced cancer patients and by the non-standardized follow-up, due to patients being re-evaluated according to local practice, this study is the first to provide a comprehensive portrait of the long-term impact of post-COVID-19 syndrome in patients with cancer. Whilst COVID-19 sequelae seem to affect a minority of patients who recovered from the acute infection, 8% of them remain symptomatic up to a year after recovery, highlighting the need for dedicated preventative and supportive strategies. Further evidence is required to evaluate the preventative role of SARS-Cov-2 vaccines in protecting patients with cancer from long-term sequelae from COVID-19.

Role of the funding source

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interpretation, or writing of the report. All authors had access to all the data reported in the study.

Data availability statement

The data underlying this article cannot be shared publicly in accordance with current regulations on data protection. The data will be shared on reasonable request to the corresponding author.

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.

Study concept: Alessio Cortellini, David J. Pinato.

Study design: Alessio Cortellini, David J. Pinato.

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Rossella Bertulli, Nikolaos Diamantis, Uma Mukherjee, Gianpiero Rizzo, Tamara Yu, Federica Zoratto, Riccardo Bruna, Anna Sureda, Clara Martinez-Vila, Luca Cantini, Francesca Mazzoni, Federica Grosso, Alessandro Parisi, Mari-stella Saponara, Aleix Prat, David J. Pinato.

Obtained funding: David J. Pinato.

Study supervision: Alessio Cortellini, David J. Pinato.

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.

Conflict of interest statement

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

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 AstraZeneca; 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.

Thomas Newsom-Davis has declared consulting/advisory role for Amgen, Bayer, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Otsuka, Pfizer, Roche, and Takeda; speakers fees from AstraZeneca, MSD, Roche, Takeda and travel, accommodations and expenses paid by AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Otsuka, Roche, and Takeda.

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

Alessandra Gennari has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, Eisai, and Daiichi Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, AstraZeneca, Celgene, and Daiichi 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 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2022.03.019>.

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