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Impact of SARS-CoV-2 vaccines and recent chemotherapy on COVID-19 morbidity and mortality in patients with soft tissue sarcoma: an analysis from the OnCovid registry

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Abstract

Background: To date, limited evidence exists on the impact of COVID-19 in patients with soft tissue sarcoma (STS), nor about the impact of SARS-CoV-2 vaccines and recent chemotherapy on COVID-19 morbidity and mortality in this specific population.

Methods: We described COVID-19 morbidity and mortality among patients with STS across 'Omicron' (15 December 2021–31 January 2022), 'Pre-vaccination' (27 February 2020–30 November 2020), and 'Alpha-Delta' phase (01 December 2020–14 December 2021) using OnCovid registry participants (NCT04393974). Case fatality rate at 28 days (CFR_{28}) and COVID-19 severity were also described according to the SARS-CoV-2 vaccination status, while the impact of the receipt of cytotoxic chemotherapy within 4 weeks prior to COVID-19 on clinical outcomes was assessed with Inverse Probability of Treatment Weighting (IPTW) models adjusted for possible confounders.

Results: Out of 3820 patients, 97 patients with STS were included. The median age at COVID-19 diagnosis was 56 years (range: 18–92), with 65 patients (67%) aged <65 years and most patients had a low comorbidity burden (65, 67.0%). The most frequent primary tumor sites were the abdomen (56.7%) and the gynecological tract (12.4%). In total, 36 (37.1%) patients were on cytotoxic chemotherapy within 4 weeks prior to COVID-19. The overall CFR_{28} was 25.8%, with 38% oxygen therapy requirement, 34% rate of complications, and 32.3% of hospitalizations due to COVID-19. CFR_{28} (29.5%, 21.4%, and 12.5%) and all indicators of COVID-19 severity demonstrated a trend toward a numerical improvement across the pandemic phases. Similarly, vaccinated patients demonstrated numerically improved CFR_{28} (16.7% *versus* 27.7%) and COVID-19 morbidity compared with unvaccinated patients. Patients who were on chemotherapy experienced comparable CFR_{28} (19.4% *versus* 26.0%, $p=0.4803$), hospitalizations (50.0% *versus* 44.4%, $p=0.6883$), complication rates (30.6% *versus* 34.0%, $p=0.7381$), and oxygen therapy requirement (28.1% *versus* 40.0%, $p=0.2755$) compared to those who were not on anticancer therapy at COVID-19, findings further confirmed by the IPTW-fitted multivariable analysis.

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Conclusion: In this study, we demonstrate an improvement in COVID-19 outcomes in patients with STS over time. Recent exposure to chemotherapy does not impact COVID-19 morbidity and mortality and SARS-CoV-2 vaccination confers protection against adverse outcomes from COVID-19 in this patient population.

Plain language summary

An analysis from the OnCovid registry on the impact of chemotherapy and SARS-CoV-2 vaccines on clinical outcomes of patients with soft tissue sarcoma and COVID-19

Soft tissue sarcomas (STS) are a group of rare and aggressive tumours, usually treated with high dose cytotoxic chemotherapy. To date no clear evidence exists on the impact of COVID-19 in patients with STS, nor on the potential impact of recent chemotherapy and prior SARS-CoV-2 vaccination in this specific patient population. This is the 1st study to show COVID-19 outcomes in patients with STS, highlighting a substantial vaccine efficacy with no negative impact of recent chemotherapy on COVID-19 outcomes.

Keywords: chemotherapy, COVID-19, pandemic, sarcoma, SARS-CoV-2, soft tissue sarcoma, vaccines

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Introduction

The SARS-CoV-2 pandemic represented a global health threat which significantly impacted oncology care.[1] Large cohort studies from the pre-vaccination period clearly showed a high risk of complications and increased mortality to coronavirus disease 2019 (COVID-19) in patients with cancer.[2] Although the significant improvements in healthcare systems capacity, immunization campaigns, and the development of specific SARS-CoV-2 therapies are allowing a progressive return to pre-pandemic oncological care,[3,4] several lines of evidence indicate reduced natural immunity and SARS-CoV-2 vaccine immunogenicity for immunocompromised patients such as those with cancer.[5–7]

The impact of COVID-19 across cancer subtypes remains a heavily debated question. Available evidence reports significant heterogeneity in its protective role against morbidity and mortality across different tumor types, with worst outcomes observed in patients with hematological malignancy and lung cancer[8,9] and better outcomes reported among patients with breast cancer.[10]

Soft tissue sarcomas (STS) are a group of rare and heterogeneous tumors, classified into over 80 subtypes by the World Health Organization (WHO) classification, based on a combination of distinctive morphological, immunohistochemical, and molecular features.[11] In particular, the estimated incidence of adult-type soft tissue and visceral sarcomas (excluding GIST) averages 4–5 cases/100.000/year in Europe, with the most common types represented by liposarcomas and leiomyosarcomas.[12]

Management of STS is uniquely different from that of other solid tumors. Multimodal utilization of surgical, radiation, and cytotoxic chemotherapy is key for optimal patient outcomes. The cornerstone of systemic treatments in both localized and advanced STS is anthracycline-based chemotherapy, historically linked to an increased risk of neutropenia and infection.[13,14] Cytotoxic chemotherapy is linked to increased morbidity and mortality to COVID-19 and to decreased immunogenicity of SARS-CoV-2 vaccines.[5,8,15,16]

Considering the rarity of STS and the high proportion of patients requiring cytotoxic chemotherapy within this heterogeneous patient group, it is of the utmost importance to produce evidence about the impact of COVID-19 on this specific patient population, to inform clinical practice and help ensure safe oncological continuity of care.

In this sub-analysis of the OnCovid study, we aimed to describe COVID-19 outcomes in a large

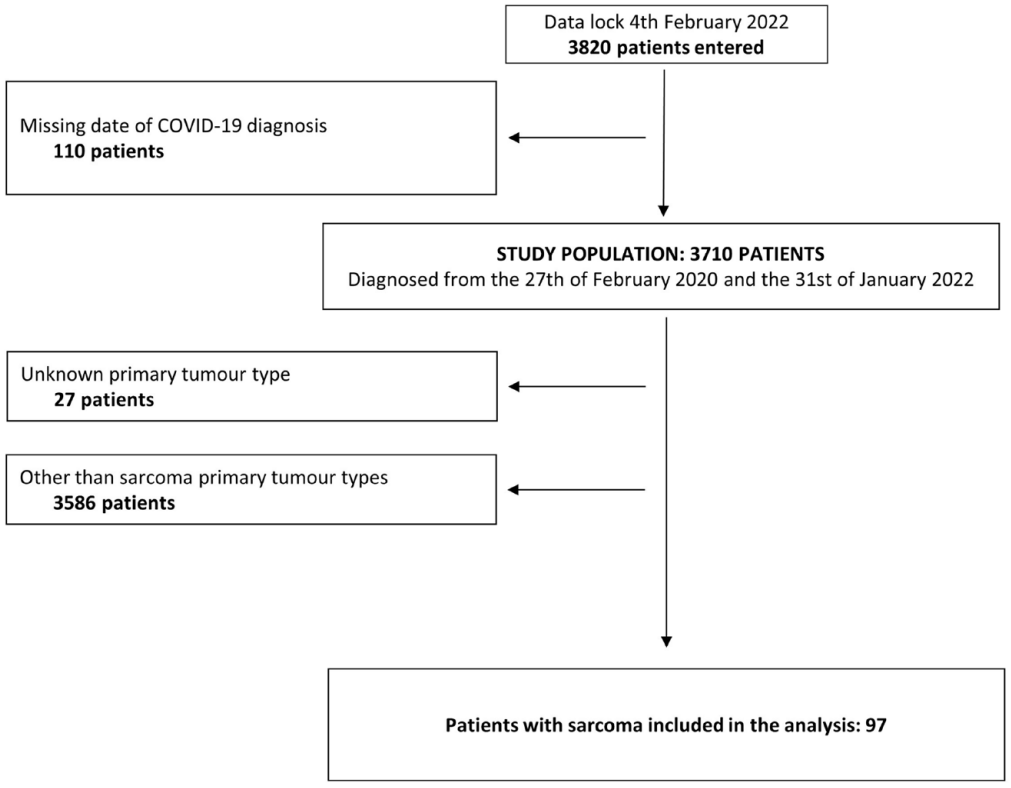

Figure 1. Study flow graph.

multicenter cohort of patients with STS. We evaluated the impact of recent chemotherapy exposure and the efficacy of the SARS-CoV-2 vaccines in patients with STS entered in the registry.

Methods

Study endpoints and definitions

This is a sub-analysis of the OnCovid registry (NCT04393974) focusing on patients with STS, with the overarching aim of describing the impact of COVID-19 on this patient population. OnCovid (NCT04393974) is an active European registry study that, since the beginning of the pandemic, has collected consecutive patients who met the following inclusion criteria: (1) age 18 years or older, (2) diagnosis of SARS-CoV-2 infection confirmed by reverse transcription–polymerase chain reaction of a nasopharyngeal swab, and (3) history of solid or hematologic cancer at any time during the patient's past medical history, either active or in remission at the time of COVID-19 diagnosis.

We screened the histological category of all patients entered in the registry and included those defined as 'sarcoma'. Although the electronic case report form (eCRF) was not originally designed to capture specific STS subtypes, we further classified patients according to the STS site of origin into abdominal, gynecological tract, bone-cartilage, Kaposi's sarcoma, chest, urinary tract, breast, central nervous system, lymphosarcoma/reticulosarcoma, and unknown.

The registry included 3820 patients aged 18 years or older diagnosed with COVID-19 between 27 February 2020 and 31 January 2022, with a follow-up data lock period of 30 June 2022. The consort flow diagram with patients' selection for the present analysis is shown in Figure 1.

Acknowledging the competing influence of the underlying malignancy in determining clinical outcomes, we elected the all-cause 28-day case fatality rate (CFR_{28}) as the clinical endpoint of interest, in an attempt to differentiate early (COVID-19 related) from late (cancer related) mortality as consistently done in with our registry. As proxies of COVID-19 morbidity, we utilized the rate of hospitalization due to COVID-19, the rate of complications from COVID-19, and the

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requirement for supplemental oxygen therapy as surrogates of COVID-19 morbidity. Considering the limited number of subgroups, we descriptively reported the CFR_{28} across the STS subtypes.

Patients were initially grouped by date of COVID-19 diagnosis into 'pre-vaccination' phase (from 27 February 2020 to 30 November 2020), 'Alpha-Delta' phase (from 1 December 2020 to 14 December 2021) (21), and 'Omicron' phase (from 15 December 2021 to 31 January 2022) (22) to describe time-dependent changes in clinical characteristics and outcomes as previously done (23). Subsequently, we described COVID-19 morbidity and mortality according to the SARS-CoV-2 vaccination status by grouping patients into unvaccinated (including partially vaccinated patients who were incompletely immunized prior to COVID-19 given the limited sample size of subgroups) and vaccinated patients (including patients who received two vaccinal doses and those who received a booster dose). In detail, patients who received two doses of the BNT162b2, mRNA-1273, and ChAdOx1-S 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 at least one vaccination, without meeting the above-mentioned 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.

Lastly, we described COVID-19 outcomes according to the receipt of systemic anticancer therapy (SACT), more specifically systemic chemotherapy, within 4 weeks prior to COVID-19 diagnosis and assessed with multivariable analysis the possible impact of recent chemotherapy on COVID-19 mortality (CFR_{28}).

Variables related to key demographics and tumor characteristics were abstracted: country, sex, age, number of comorbidities, smoking status, tumor stage, and tumor status. A detailed description of the study methodology, baseline variables, oncological features and SACT categories, vaccination categories, and statistical methodology is reported in the Supplementary Material.

The reporting of this study conforms to the Equator network guidelines. The completed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist is available in the Supplemental Material.

Results

Out of 3820 patients, the registry included 97 (2.5%) eligible patients with STS (Figure 1). The distribution of patients across participating centers is provided in Supplemental Table 1.

The median age at COVID-19 diagnosis was 56 years (range: 18–92), with 65 patients (67%) aged <65 years. Most patients had $\leqslant 2$ comorbidities (65, 67.0%); however, 24 patients (24.7%) had an ECOG-PS of $\geqslant 2$ at COVID-19 diagnosis. The most frequent primary tumor sites were the abdomen (56.7%) and the gynecological tract (12.4%). Table 1 provides a detailed description of patients' characteristics.

Overall, 61 (62.9%), 28 (28.9%), and 8 (8.2%) patients were diagnosed with SARS-CoV-2 infection during the pre-vaccination, Alpha-Delta, and Omicron phase, respectively, and the majority of patients were unvaccinated (79, 81.4%) or partially vaccinated (4, 4.1%), with only six patients (6.2%) who received a full vaccination course (vaccination details provided in Supplemental Table 2). In total, 42 patients (43.3%) were on SACT within 4 weeks prior to COVID-19, with 36 (37.1%) who were receiving chemotherapy.

The median observation period for the entire population was 258 days (95% CI: 141–354), with a median follow-up for patients in the pre-vaccination, Alpha-Delta, and Omicron groups of 354 (95% CI: 196–424), 246 (95% CI: 87–263), and 25 (95% CI: 1–31) days, respectively. Among the study population, the CFR_{28} was 25.8% (95% CI: 16.6–38.0), the oxygen therapy requirement was 38.0% (95% CI: 26.5–52.9), the rate of complications from COVID-19 was 34.0% (95% CI: 23.4–47.8), and the hospitalization rate was 32.3% (95% CI: 21.9–45.8; Table 1). The CFR_{28} across the different primary tumor sites is summarized in Supplemental Figure 1.

CFR_{28} demonstrated a trend toward a numerical improvement across the pandemic phases (29.5%, 21.4%, and 12.5%) although without reaching statistical significance. A similar trend was reported for all the proxies of COVID-19 severity [Figure 2(a)]. CFR_{28}, hospitalization rate, complications rate, and oxygen therapy requirement

Table 1. Baseline patient characteristics and COVID-19 outcomes.

	Study population
	N **= 97 (%)**
Country	
United Kingdom	26 (26.8)
Spain	20 (20.6)
Italy	45 (46.4)
Others	6 (6.2)
Sex	
Female	45 (46.4)
Male	51 (56.2)
Missing	1 (1.0)
Age	
Median (range)	56 (18–92)
<65 years	65 (67.0)
⩾65 years	31 (32.0)
Missing	1 (1.0)
Comorbidity burden	
<2 comorbidities	65 (67.0)
⩾2 comorbidities	32 (33.0)
Smoking status	
Never smokers	52 (53.6)
Former/current smokers	27 (27.8)
Missing	18 (18.6)
ECOG-PS at COVID-19	
0	29 (29.9)
1	30 (30.9)
⩾2	24 (24.7)
Missing	14 (14.4)
Primary tumor site	
Abdominal	55 (56.7)
Gynecological tract	12 (12.4)
Bone-cartilage	8 (8.2)
Kaposi's sarcoma	4 (4.1)
Lymphosarcoma/ reticulosarcoma	4 (4.1)
Chest	4 (4.1)
Urinary tract	3 (3.1)
Breast	2 (2.1)
Central nervous system	2 (2.1)
Unknown	3 (3.1)
Stage	
Non-advanced	36 (37.1)
Advanced	61 (62.9)
Tumor status at COVID-19 diagnosis	
Remission/in-response	34 (35.1)
Active malignancy	63 (64.9)
SARS-CoV-2 vaccination status	
Unvaccinated	79 (81.4)
Partially vaccinated	4 (4.1)
Fully vaccinated (2 or 3 doses)	6 (6.2)
Unknown	8 (8.2)
Pandemic phase	
Pre-vaccination	61 (62.9)
Alpha-Delta	28 (28.9)
Omicron	8 (8.2)
SACT at COVID-19	
No	50 (51.5)
Yes	42 (43.3)
Chemotherapy (including combinations)	36 (37.1)
Immune checkpoint blockade	1 (1.0)
TKIs, MoAbs, and others	5 (5.1)
Missing	5 (5.1)

Table 1. (Continued)

	Study population
	N **= 97 (%)**
COVID-19 outcomes	
	N (Rate, 95% CI)
Oxygen therapy	35 (38.0, 26.5–52.9)
Missing	5
Complications from COVID-19	33 (34.0, 23.4–47.8)
Hospitalization	
Due to COVID-19	31 (32.3, 21.9–45.8)
Preexisting	33 (34.4, 23.6–48.3)
Missing	1
28-day case fatality rate	25 (25.8, 16.6–38.0)

95% CI, 95% confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; SACT, systemic anticancer therapy within 4 weeks prior to COVID-19 diagnosis.

were numerically improved among fully vaccinated patients in comparison to unvaccinated patients as well [Figure 2(b)].

After the exclusion of patients with missing information on recent SACT, patients who were on chemotherapy at COVID-19 and those who were not on SACT within 4 weeks prior to COVID-19 experienced comparable CFR_{28} (19.4% *versus* 26.0%, $p = 0.4803$), hospitalization rate (50.0% *versus* 44.4, $p = 0.6883$), complications rate (30.6% *versus* 34.0%, $p = 0.7381$), and oxygen therapy requirement (28.1% *versus* 40.0%, $p = 0.2755$; Figure 3).

Supplemental Table 4 reports the distribution of baseline characteristics before and after the IPTW procedure between patients who were and those who were not on SACT at COVID-19 diagnosis, suggesting an inadequate balancing ability; therefore, all the variables were included in the ITPW-fitted multivariable logistic regression model for the CFR_{28}, which confirmed no significant association between the receipt of chemotherapy and the risk of death within 28 days of COVID-19 diagnosis (aOR 2.02, 95% CI: 0.28–14.26).

Discussion

Sequential and multimodal use of surgery, radiation therapy, and cytotoxic chemotherapy are keys to the optimal management of STS. Unlike epithelial tumors, STS rarely arise in the context of field defects stemming from chronic exposure to carcinogens. As a result, patients with STS do not share the same comorbid burden and demographic features as patients with solid tumors, factors that have been recognized to play a key role in shaping COVID-19 morbidity and mortality. In addition, the heavy and high-dose utilization of cytotoxic regimens makes STS patients potentially more vulnerable to immunosuppression.[13,14]

In this OnCovid analysis, we intended to portray COVID-19 morbidity and mortality in patients with STS and describe the efficacy of SARS-CoV-2 vaccines in this specific population. Overall, our STS population does not seem to be characterized by a unique vulnerability to COVID-19, as the reported 25.8% CFR_{28} is similar to the 25.7% we observed in the entire OnCovid population, while oxygen therapy requirements (38.0% *versus* 47%) and rate of hospitalization due to COVID-19 (32.3% *versus* 48.6%) are numerically lower.[4]

Our descriptive analysis showed a substantial time-dependent improvement of CFR_{28}, hospitalization rate, complications, and oxygen therapy requirements across pandemic phases, along with improved COVID-19 outcomes for fully vaccinated patients. Findings that resemble reports in other cancer subtypes,[10] confirming the general improvement already seen for the overall oncology population and supporting the efficacy of SARS-CoV-2 vaccines even in patients with STS.[4]

We did not find significant interactions between recent chemotherapy and COVID-19 morbidity and mortality in our study population. When compared to patients not receiving SACT, those exposed to chemotherapy within 4 weeks prior to COVID-19 diagnosis experienced comparable CFR_{28}, hospitalization, complication rates, and oxygen therapy requirements, indicating that anticancer therapy can be safely administered to patients with STS.

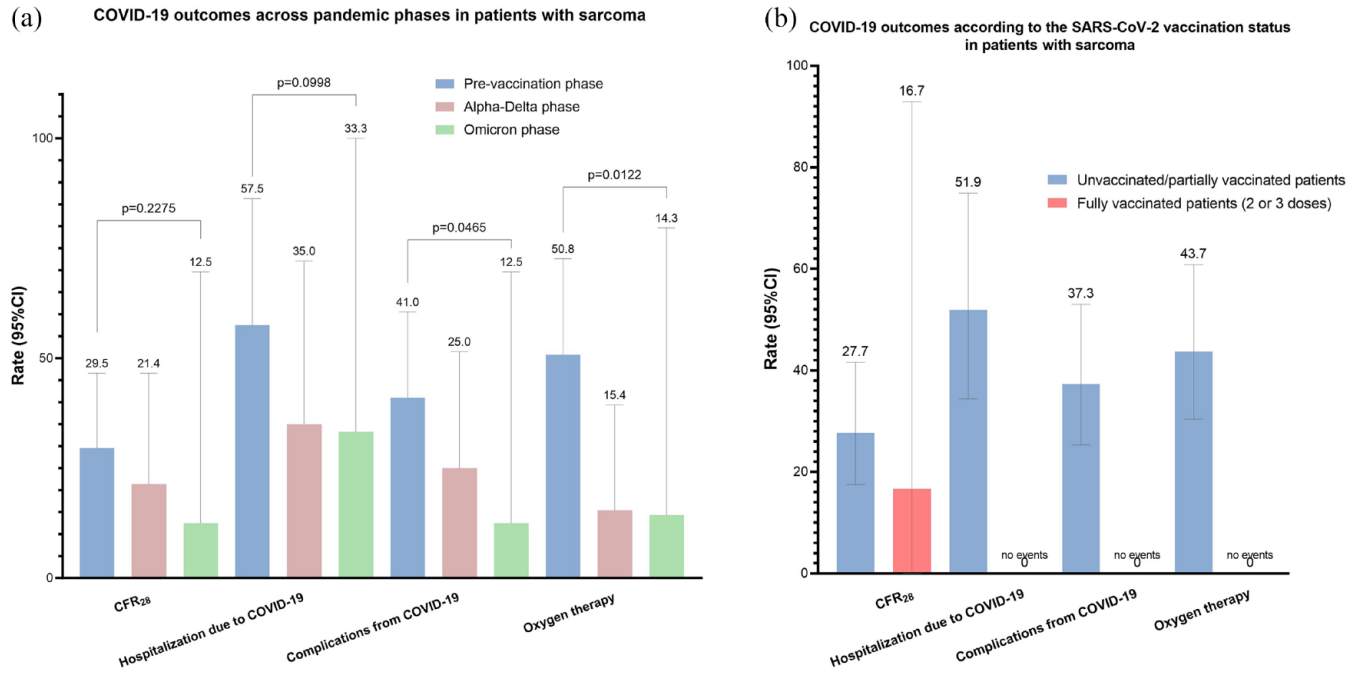

Figure 2. Histogram plots reporting COVID-19-related outcomes with 95% confidence intervals across the three pre-defined pandemic phases (a) and COVID-19 outcomes with 95% CI according to the vaccination status (b). Partially vaccinated patients were included among unvaccinated patients; patients who received two vaccinal and those who received a booster dose were grouped as fully vaccinated patients. COVID-19 outcomes were a 28-day case fatality rate (CFR28), hospitalization due to COVID-19, complications from COVID-19, and need for oxygen therapy. The chi-square test for trend was used for computing *p*-values.

In a similar analysis from the CCC-19 registry,[17] among 281 patients with sarcoma, Wagner *et al.* reported a uniquely low 30-day case fatality rate of 8%, which is aligned with the comparatively mitigated outcomes described in registry studies from the United States in comparison to European studies.[18] However, study authors described a peak in mortality rate among patients with bone sarcoma and highlighted older age, poor performance status, the receipt of recent SACT, and the presence of lung metastases as predictors of increased COVID-19 severity.[17]

When evaluating our results, we need to consider the clinical baseline characteristics of the study cohort, which is enriched in patients aged < 65 years and with low comorbidity burden when compared to the overall OnCovid population, both features related to improved COVID-19 outcomes even among the general population. In fact, STS have a bi-modal distribution among adults, being more common in the third/fourth decades and after the age of 60,[19] making our study population inherently selected for improved outcomes from COVID-19.

This work acknowledges several limitations including the retrospective design and the limited sample size, which limited our ability to make fully powered comparisons between subgroups. Other key issues are the lack of availability of specific histological details of the included STS and viral genomic sequences across the evolving phases of the pandemic, which were defined based on epidemiological criteria. In addition, given the design of our eCRF, we classified advanced-stage sarcomas as tumors with distant metastasis only, including patients with locally advanced disease into the non-advanced group, potentially impairing prognostic stratification, and we were not able to fully reconstruct specific chemotherapy regimens administered in our cohort.

Despite the mentioned limitations, we provide for the first time reliable evidence on the impact of COVID-19 in patients with STSs. The numerical improvement of all COVID-19 outcomes over time, along with the substantial efficacy of COVID-19 vaccines and the lack of a significant impact of recent chemotherapy on COVID-19 morbidity

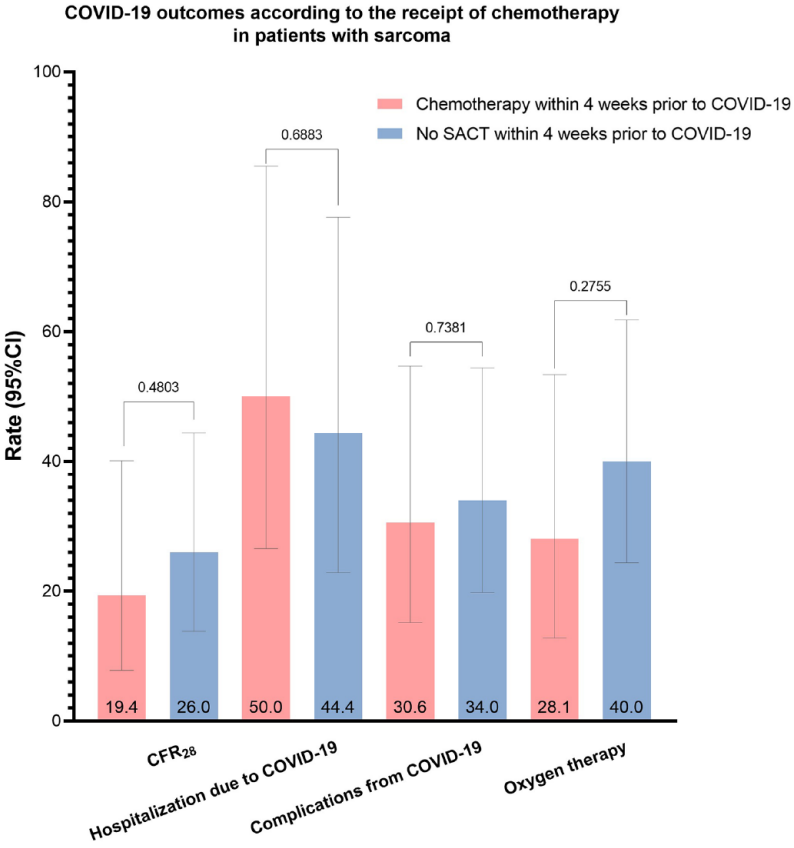

Figure 3. Histogram plot reporting COVID-19-related outcomes with 95% confidence intervals according to the receipt of chemotherapy within 4 weeks prior to COVID-19 diagnosis. COVID-19 outcomes were a 28-day case fatality rate (CFR28), hospitalization due to COVID-19, complications from COVID-19, and need for oxygen therapy.

and mortality, supports the safe resumption of the oncological continuity of care for patients with STS. Despite that, the 12.5% CFR_{28} reported during the Omicron phase is a figure that still deserves attention and indicates the need to continue to promote immunization campaigns in patients with STSs, including vaccine booster doses, along with other prevention strategies.

Declarations

Ethics approval and consent to participate

After central approval Health Research Authority (20/HRA/1608), The OnCovid registry was granted central emergency approval at the participating centers, as commonly used during the first weeks of the pandemic; therefore, individual ethics committee approval information is not available. Informed consent was waived by competent authorities (Health Research Authority – UK) due to the anonymized nature of patient data and retrospective design of the study.

Consent for publication

All authors have approved the submission of this manuscript for publication.

Author contributions

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Alessio Cortellini: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

Individual, de-identified participant data and data dictionary may be made available at the request of investigators whose proposed use of the data has been approved by the OnCovid consortium investigators following a review of a methodologically sound research proposal.

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Supplemental material

Supplemental material for this article is available online.

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