COVID-19 in cancer patients on systemic anti-cancer therapies: outcomes from the CAPITOL (COVID-19 Cancer PatIenT Outcomes in North London) cohort study

Valerie E. Crolley* [ID], **Daire Hanna*, Nalinie Joharatnam-Hogan, Neha Chopra, Ekin Bamac, Meera Desai, Yuk-Chun Lam, Sabiq Dipro, Ruhi Kanani, Jack Benson, William Wilson, Thomas A. Fox, Kai-Keen Shiu, Martin Forster, John Bridgewater, Daniel Hochhauser and Khurum Khan**

Abstract

Background: Patients with cancer are hypothesised to be at increased risk of contracting COVID-19, leading to changes in treatment pathways in those treated with systemic anti-cancer treatments (SACT). This study investigated the outcomes of patients receiving SACT to assess whether they were at greater risk of contracting COVID-19 or having more severe outcomes.

Methods: Data was collected from all patients receiving SACT in two cancer centres as part of CAPITOL (COVID-19 Cancer PatIenT Outcomes in North London). The primary outcome was the effect of clinical characteristics on the incidence and severity of COVID-19 infection in patients on SACT. We used univariable and multivariable models to analyse outcomes, adjusting for age, gender and comorbidities.

Results: A total of 2871 patients receiving SACT from 2 March to 31 May 2020 were analysed; 68 (2.4%) were diagnosed with COVID-19. Cancer patients receiving SACT were more likely to die if they contracted COVID-19 than those who did not [adjusted (adj.) odds ratio (OR) 9.84; 95% confidence interval (CI) 5.73–16.9]. Receiving chemotherapy increased the risk of developing COVID-19 (adj. OR 2.99; 95% CI = 1.72–5.21), with high dose chemotherapy significantly increasing risk (adj. OR 2.36, 95% CI 1.35–6.48), as did the presence of comorbidities (adj. OR 2.29; 95% CI 1.19–4.38), and having a respiratory or intrathoracic neoplasm (adj. OR 2.12; 95% CI 1.04–4.36). Receiving targeted treatment had a protective effect (adj. OR 0.53; 95% CI 0.30–0.95). Treatment intent (curative *versus* palliative), hormonal- or immunotherapy and solid *versus* haematological cancers had no significant effect on risk.

Conclusion: Patients on SACT are more likely to die if they contract COVID-19. Those on chemotherapy, particularly high dose chemotherapy, are more likely to contract COVID-19, while targeted treatment appears to be protective.

Keywords: cancer, chemotherapy, COVID-19, coronavirus, hormone therapy, immunotherapy, novel coronavirus, oncology, SACT, SARS-CoV-2, systemic anti-cancer treatment, tumour, targeted treatment

Correspondence to:
Khurum Khan
Gastrointestinal Oncology Service and Cancer of Unknown Primary Service, University College London Hospital, UCL Cancer Institute and North Middlesex University Hospital, GI Cancer Lead North London Cancer Research Network and Oncology Research Lead North Middlesex University Hospital, 250 Euston Rd, London NW1 2PG, UK
North Middlesex University Hospital, London, UK
UCL Cancer Institute, 72 Huntley St, Bloomsbury, London WC1E 6DD, UK
khurum.khan1@nhs.net; khurum.khan@ucl.ac.uk

**Daire Hanna
Neha Chopra
Ekin Bamac
Meera Desai
Thomas A. Fox
Kai-Keen Shiu
Yuk-Chun Lam**
University College NHS Foundation Trust, London, UK

**Valerie E. Crolley
Sabiq Dipro
Ruhi Kanani
Jack Benson**
North Middlesex University Hospital, London, UK

William Wilson
Cancer Research UK, Oxford, UK

UCL Cancer Trials Centre, Bloomsbury, London, UK

**Martin Forster
John Bridgewater
Daniel Hochhauser
Nalinie Joharatnam-Hogan**
University College NHS Foundation Trust, London, UK

University College London, London, UK

*Joint first authors

Summary box

What is already known on this topic
- One of the major challenges with COVID-19 has been the changes to cancer services, including changes to the type of systemic anti-cancer treatment being delivered to patients.
- There needs to be a better understanding of which cancer patients are at the greatest amount of risk to make informed decisions on how cancer treatment can be altered to protect patients from COVID-19 infection.
- To the best of our knowledge, this is one of the first investigations into the risk of contracting COVID-19 in a cohort of all cancer patients on systemic anti-cancer therapy.

What this study adds
- Patients on systemic anti-cancer therapy are more likely to die if they contract COVID-19.
- The type of anti-systemic cancer treatment received by cancer patients can affect their likelihood of contacting COVID-19, with chemotherapy increasing risk, targeted therapy decreasing risk and a potential protective effect for hormonal and immunotherapy.

Introduction

COVID-19, the disease caused by the SARS-CoV-2 virus, has caused a global pandemic.[1] As of 31 August 2020, the United Kingdom (UK) has seen 334,471 cases and 41,499 deaths due to COVID-19.[2] During the course of this pandemic, heterogeneity in the rate of infection and mortality from COVID-19 throughout the population has become increasingly apparent. Distinct patient subgroups including the elderly, male gender and patients with comorbidities including hypertension, ischaemic heart disease, diabetes, chronic lung disease and cancer appear to be at significantly increased risk.[3]

It has been widely hypothesised that patients on systemic anti-cancer therapies are at higher risk of contracting COVID-19, and are subsequently at higher risk of developing severe complications owing to being immunocompromised by the effects of systemic anticancer therapy, the use of supportive medications such as steroids or due to the immunosuppressive properties of cancer itself.[4] Moreover, patients receiving immunomodulatory drugs such as checkpoint inhibitors may be susceptible to severe COVID-19 illness due to an enhanced immune response to infections.

Several studies from across the world have therefore investigated the outcomes of cancer patients who contracted COVID-19.[4-11] The majority of these have indicated that outcomes for patients with cancer diagnosed with COVID-19 are poor, with a high mortality rate.[4,6-11] Even before these results were available, measures were being taken in order to protect cancer patients as much as possible from increased risks of COVID-19 based on initial data from China demonstrated that patients with cancer were at increased risk of COVID-19 infection.[12,13] Changes to the types of anti-systemic cancer therapy delivered by increasing the usage of targeted therapies, hormonal therapy and immunotherapy and reducing the dose of cytotoxic chemotherapy have been applied.[14] There has already been large scale disruption to cancer diagnostics and surgery due to the pandemic, which will likely lead to a backlog of accumulated cancer cases and a potential increase in mortality.[15,16] Before decisions are made in the longer term to continue with the changes made to the delivery of systemic anti-cancer therapy (SACT), it is important to understand which cancer patients are at highest risk of developing COVID-19 and its complications, to personalise cancer treatment and to ensure that measures are put in place to protect cancer patients on SACT.

The CAPITOL (COVID-19 CAncer PatIenT Outcomes in North London) study has therefore been designed to investigate the outcomes of patients on any form of SACT; to further understand the incidence of COVID-19 in this patient group as well as to understand factors that increase risk and alter outcomes of COVID-19 infection.

Methods

Patient selection

This retrospective study includes all consecutive patients with any active malignancies who received

systemic anti-cancer therapy at two North London teaching hospitals (University College London Hospital and North Middlesex University Hospital) between 2 March and 31 May 2020. We defined systemic anti-cancer therapy as any medication prescribed to treat a malignancy. Figure 1 illustrates how patients were diagnosed with COVID-19 using reverse transcription-polymerase chain reaction (RT-PCR). Patients who were infected with COVID-19 before commencing SACT were excluded from the study ($n=16$). Outcomes were monitored until 24 July 2020.

Data collection

Patient records were reviewed using the hospital electronic medical records (EMR) for clinical characteristics including age, gender, ethnicity and comorbidities [the presence of hypertension, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and diabetes]. Primary tumour types were classified according to International Classification of Disease, 10th revision (ICD-10) codes.[17] Data was collected on medications including systemic anti-cancer treatment [defined as immunotherapy, chemotherapy, targeted or hormonal (including endocrine) treatments], long-term anti-coagulation and steroid therapy. Patients were considered to be on long-term steroid therapy if taking equivalent to 5 mg prednisolone daily for a minimum of 28 days during the selected data collection period. Data collected for patients with COVID-19 included laboratory values, symptoms at presentation, presence of radiological findings in keeping with COVID-19 and severe outcomes [defined as a composite of death, intensive care unit (ICU) admission, NIV (non-invasive ventilation) and/or intubation].

Outcomes

The primary outcome of this study was to evaluate the association between a diagnosis of COVID-19 and mortality in oncology patients on active systemic anti-cancer treatment. Secondary outcomes were the association between systemic anti-cancer treatment type and primary tumour subtype with the risk of contracting COVID-19.

Statistical methodology

Patient demographics and clinical characteristics were explored descriptively using STATA v15.1, 2017 (StataCorp, College Station, TX, USA).

Logistic regression was used to determine the odds ratio (OR) for mortality in those with a diagnosis of COVID-19 *versus* those without. Baseline factors were compared between COVID-19 positive and negative patients using chi-squared tests and their prognostic value was assessed using logistic regression; p values <0.05 were considered significant. All logistic regression models were adjusted for age, gender and comorbidities (the presence of hypertension, cardiovascular disease, diabetes, and COPD). Forest plots were created using GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA).

Patient and public involvement

This study was conducted using electronic patient records, so patients were not directly involved in the design of this study.

Results

Patient characteristics

A total of 2871 patients were recorded as receiving SACT during the recorded time period; 80 patients were excluded from further analysis, either because they were treated for basal cell carcinoma or a non-malignant haematological condition (such as TTP, MAHA or HUS). A final total of 2791 patients were analysed (Figure 2).

Out of a total of 2791 patients analysed, 2.4% ($n=68$) were diagnosed with COVID-19; 57 patients had confirmation of COVID-19 by RT-PCR test and 11 patients had a radiological and clinical diagnosis of COVID-19. Regarding gender, 48.1% ($n=1345$) of patients were male and 51.8% ($n=1446$) were female. The median age of all patients was 64 years (interquartile range 52–73), and the median number of comorbidities per patient was one. Regarding their cancer, 55.3% ($n=1544$) had a solid tumour and 44.6% ($n=1247$) a haematological malignancy. Following adjustment for age, gender, comorbidities, $n=2764$ were analysed (Table 1).

Main study outcomes

Cancer patients receiving SACT were more likely to die if they contracted COVID-19 than those who did not contract COVID-19 [OR 9.80; 95% confidence interval (CI) 5.76–16.7; $p<0.001$]. This association persisted even after correction for age, gender and comorbidities [cardiovascular
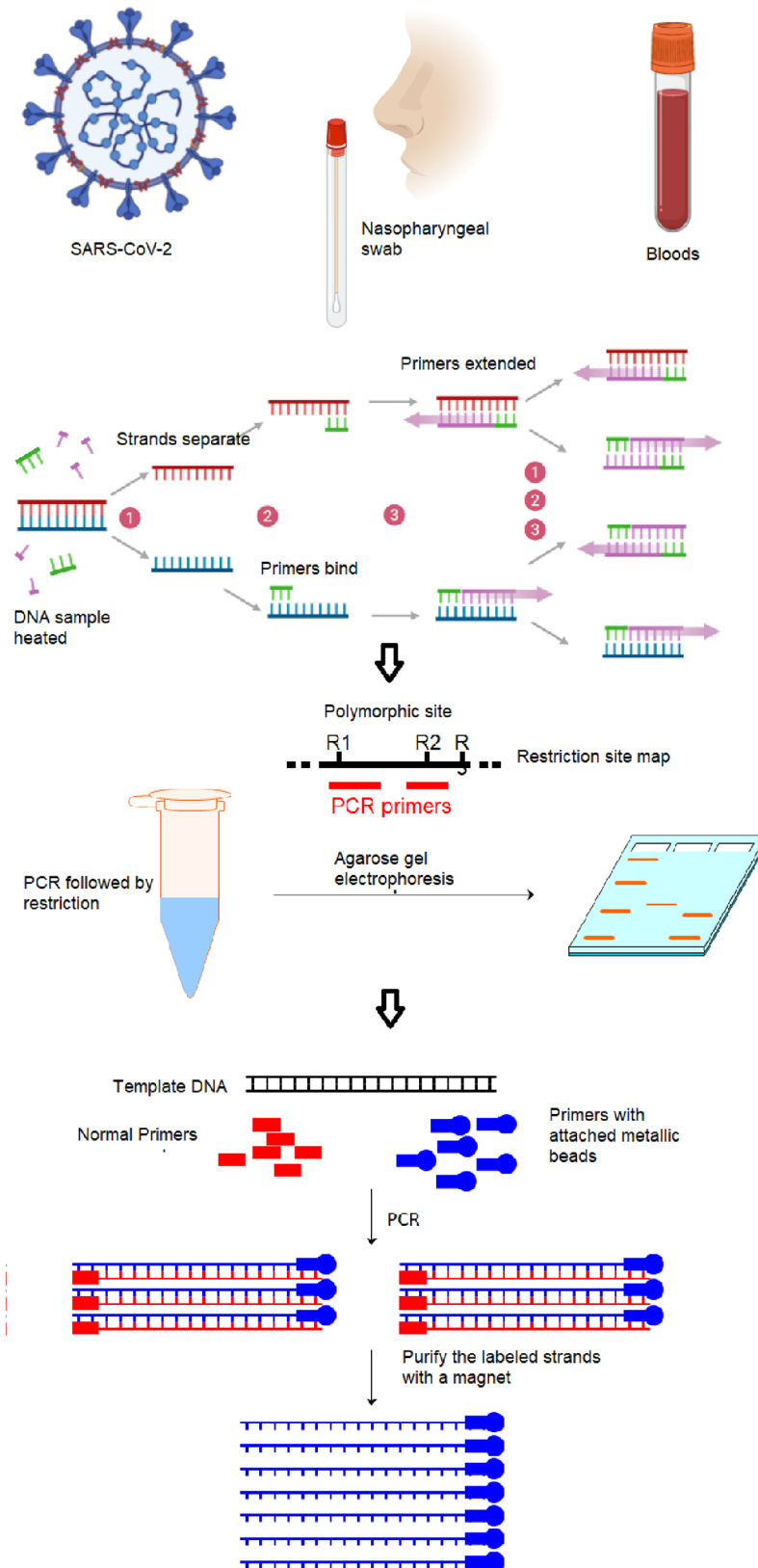
Figure 1. An illustration depicting the current RT-PCR based method of detecting patient infection with SARS-CoV-2 to confirm a diagnosis of COVID-19.
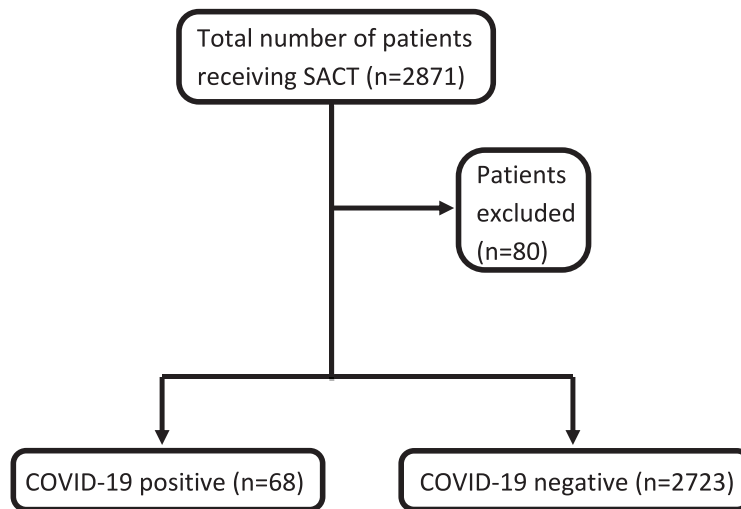RT-PCR, reverse transcription-polymerase chain reaction.

Figure 2. A CONSORT diagram illustrating the study design and the overall patient numbers. SACT, systemic anti-cancer treatments.

disease (CVD), hypertension (HTN), COPD and diabetes] [adjusted (adj. OR 9.84; 95% CI 5.73–16.9; $p < 0.001$].

Univariate analysis demonstrated that receiving chemotherapy increased the risk of contracting COVID-19 (Table 1, Figures 3 and 4), even after correction for age, gender and comorbidities (adj. OR 2.99; 95% CI = 1.72–5.21; $p = 0.001$). In patients receiving chemotherapy, high dose (compared with low or standard dose chemotherapy) was significantly associated with risk of COVID-19 (adj. OR 2.36, 95% CI 1.35–6.48, $p < 0.05$). Receiving hormone therapy (adj. OR 0.18; 95% CI 0.02–1.33; $p = 0.09$) or immunotherapy (adj. OR 0.31 95% CI 0.08–1.28; $p = 0.11$) did not have a significant effect on the likelihood of contracting COVID-19. Conversely, receiving targeted treatment appeared to have a protective effect against contracting COVID-19 (adj. OR 0.53; 95% CI 0.30–0.95). Treatment intent (curative or palliative) did not affect the risk of contracting COVID-19 (adj. OR 0.89; 95% CI = 0.53–1.48; $p = 0.65$).

Patients with a haematological cancer were not found to be at higher risk of contracting COVID-19 than patients with solid tumours (adj. OR 1.22; 95% CI 0.74–2.00; $p = 0.44$). Patients with respiratory and intrathoracic neoplasms (including non-small cell lung cancer, small cell lung cancer and mesothelioma) were at an increased risk of contracting COVID-19 (adj. OR 2.12; 95% CI 1.04–4.36; $p < 0.05$). Cancer of the male reproductive organs (including prostate cancer) trended towards a reduced likelihood of contracting COVID-19, but the association was not statistically significant (adj. OR 0.13; 0.02–1.00; $p = 0.05$). Non-Hodgkin lymphoma appeared to increase the risk of contracting COVID-19, but the significance of this association was lost after adjusting for age, gender and comorbidities (adj. OR 1.77; 0.96–3.27; $p = 0.07$).

The presence of any comorbidities significantly increased the risk of contracting COVID-19 (adj. OR 2.29; 95% CI 1.19–4.38; $p = 0.01$), but no association was seen when analysing for separate comorbidities (cardiovascular disease, hypertension, COPD and diabetes). Patients on long-term steroids were at increased risk of contracting COVID-19 (adj. OR 2.03; 95% CI 1.14–3.62; $p < 0.05$), while patients on long-term anticoagulation had no increased risk of developing COVID-19 (adj. OR 1.64; 95% CI 0.83–3.23; $p = 0.15$).

Multivariable analysis
Multivariable analysis including age, gender, comorbidities (CVD, HTN, COPD, diabetes), receiving chemotherapy, having a respiratory tract cancer and use of long-term steroids consolidated the previous results showing associations with the risk of developing COVID-19. Multivariable analysis including ethnicity (which significantly reduces the sample size) maintained the results with the exception of respiratory cancers, which were no longer associated with an

increased risk of contracting COVID-19. This is potentially due to the fact that a higher proportion of respiratory cancer patients were white compared with the rest of the population. Receiving chemotherapy still significantly increased the risk of developing COVID-19 (adj. OR 2.67; 95% CI 1.43–4.97; $p < 0.05$, as did White ethnicity ($p = <0.001$) and steroid use ($p = <0.001$), with Mixed/Multiple ethnicities decreasing risk ($p = <0.001$).

COVID-19 positive patient analysis
Of the 68 patients positive for COVID-19 infection, 65% ($n = 44$) were male and the median age was 65 years. The median number of comorbidities was one. By ethnic group, 57% ($n = 39$) were White, 16% ($n = 11$) were Black African, Black Caribbean or Black British, 7% ($n = 5$) were Asian or Asian British, 4% ($n = 3$) were Mixed/Multiple Ethnic Groups, 3% ($n = 2$) were listed as Other and 12% ($n = 8$) as Unknown. Computed
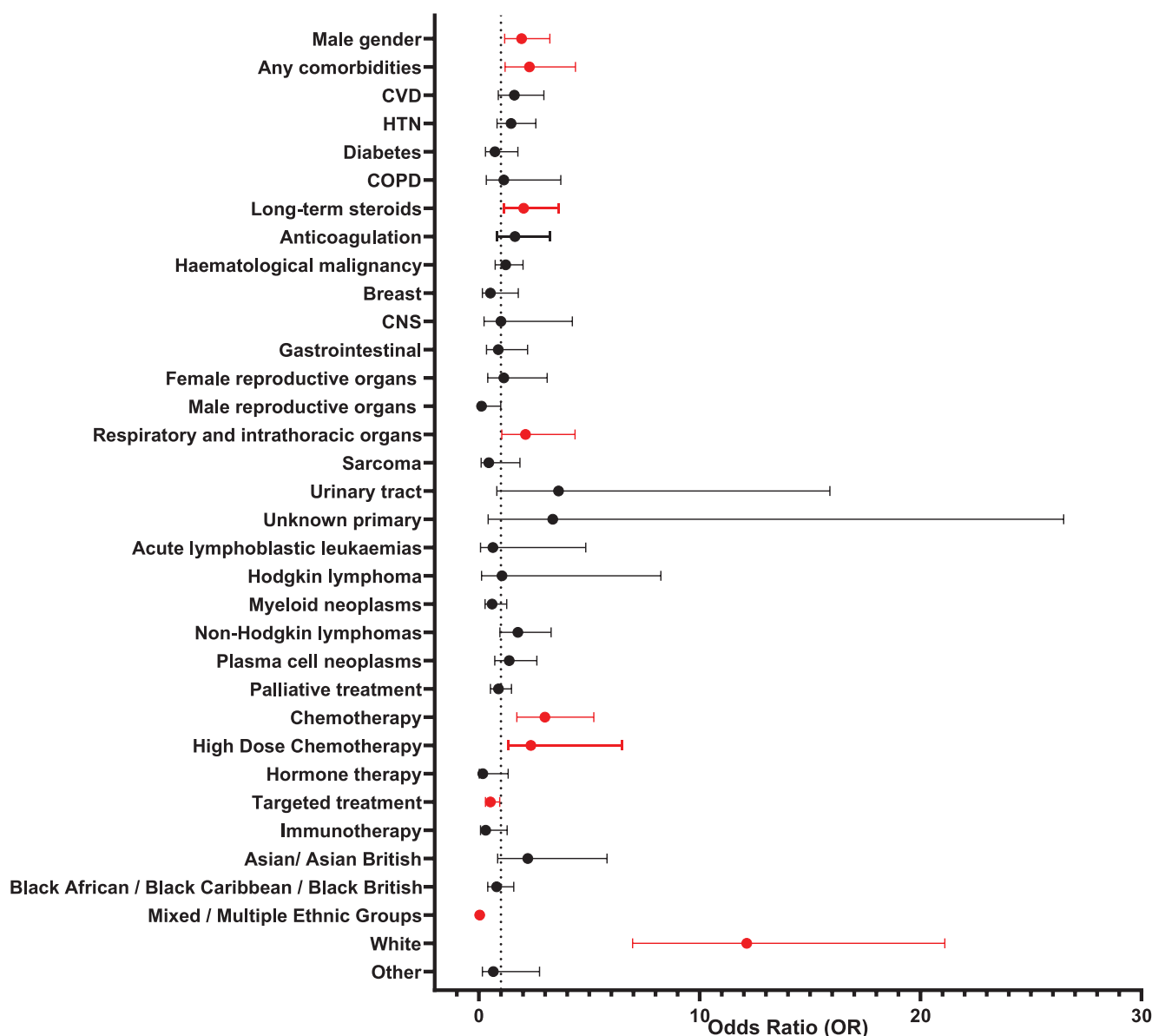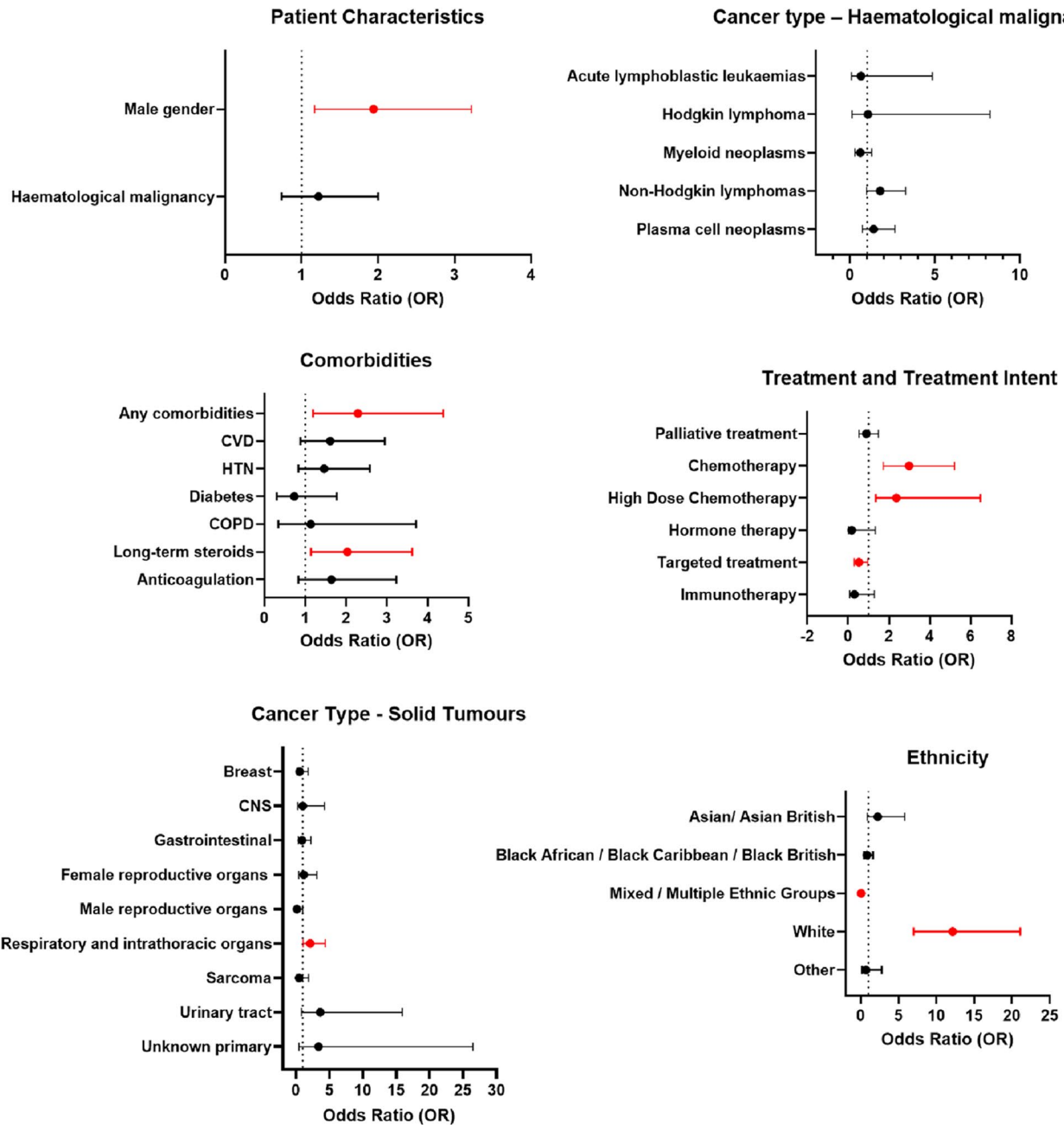

Figure 3. (Continued)

Figure 3. Univariate regression analysis and OR of developing COVID-19, with 95% CIs. Red bars indicate criteria for statistical significance were met (*p* < 0.05).
All models include variables age (continuous), gender (male/female), CVD (yes/no), HTN (yes/no), COPD (yes/no) and diabetes (yes/no) by default.
CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HTN, hypertension; OR, odds ratio.

tomography (CT) images from one of the cases are shown in Figure 5.

In all, 61% (*n* = 41) of patients positive for COVID-19 presented with symptoms of fever, 54% (*n* = 36) with cough, 34% (*n* = 23) with short-ness of breath, 18% (*n* = 12) with gastrointestinal

symptoms, 13% (*n* = 9) were asymptomatic and no patients presented with anosmia or ageusia. Presenting symptoms were not recorded for one patient.

Of the 67% (*n* = 41) of patients who had imaging (chest X-ray or CT chest, *n* = 61) had evidence of
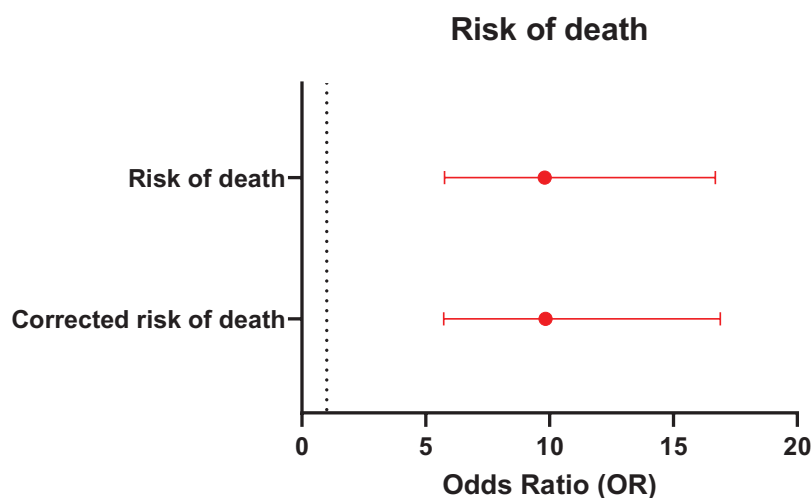
Risk of death

Figure 4. Univariate regression analysis and OR of death from COVID-19, with 95% CIs. Red bars indicate criteria for statistical significance were met ($p < 0.05$). The corrected risk of death included include variables age (continuous), gender (male/female), CVD (yes/no), HTN (yes/no), COPD (yes/no) and diabetes (yes/no). CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HTN, hypertension; OR, odds ratio.

changes suggestive of a diagnosis of COVID-19. 53% ($n = 31$) had bilateral changes, while 10% ($n = 6$) had incidental changes associated with or diagnostic of COVID-19. Of note, 5% ($n = 3$) of patients received a diagnosis of venothromboembolism while diagnosed with COVID-19.

A total of 34% ($n = 23$) of patients diagnosed with COVID-19 died during the follow-up period of this study. There was no difference in the likelihood of death if the last administered dose of systemic anti-cancer therapy was within 28 days of the diagnosis of COVID-19 (OR 1.56; 95% CI = 0.27–9.12; $p = 0.62$, corrected for age, gender and comorbidities), but only four patients had treatment more than 28 days before being diagnosed with COVID-19. Treatment within 28 days of diagnosis did not increase the likelihood of ICU admission (adj. OR 1.11; 95% CI 0.10–12.84; $p = 0.94$) or of a severe outcome (death, ICU admission, invasive or non-invasive ventilation) (adj. OR 1.10; 95% CI 0.19–6.24). Reducing the interval to 14 days between the most recent treatment and diagnosis of COVID-19 also did not demonstrate any association ($p = 0.26$ for the likelihood of death and $p = 0.34$ for the likelihood of a severe outcome).

There was an increased risk of death among patients contracting COVID-19 if they were treated for a haematological malignancy *versus* patients treated for a solid tumour, even after correction for age, gender and comorbidities (OR 6.92; 95% CI

1.47–32.61; $p < 0.05$). Treatment intent (curative or palliative) did not affect the likelihood of death (adj. OR 0.83; 95% CI = 0.25–2.78; $p = 0.76$). There was no significant difference in the risk of death in COVID-19 positive patients by treatment type received; chemotherapy ($n = 46$, adj. OR 0.59; 95% CI 0.18–1.94; $p = 0.38$), targeted treatment ($n = 18$, adj. OR 2.91, 95% CI 0.83–10.21, $p = 0.096$), and there were no deaths among patients receiving hormone therapy ($n = 1$) or immunotherapy ($n = 2$). The targeted treatments received by COVID-19 positive patients included lenalidomide/dexamethasone ($n = 3$), afatinib ($n = 2$), rituximab ($n = 2$), azacytidine ($n = 2$), rituximab and bendamustine and polatuzumab ($n = 2$), ixazomib/lenalidomide, ruxolitinib, imatinib, eribulin, temozolamide, acalabrutinib, bortezomib/thalidomide/dexamethasone, bortezomib/panobinostat/dexamethasone, and ralitrexed (all $n = 1$). The two patients on immunotherapy received durvalumab and guadecitabine/pembrolizumab, and the patient on hormone therapy received abiraterone. COVID-19 patients who had received chemotherapy were not more likely to be admitted to ICU (adj. OR 1.38; 95% CI 0.26–7.43; $p = 0.71$) and the use of long-term steroids had no impact on the risk of death ($p = 0.495$).

A total of 88% ($n = 60$) of patients diagnosed with COVID-19 were either admitted to hospital or were already an inpatient at diagnosis. The length of admission was 0–135 days (median 6 days) in COVID-19 positive patients. Treatment with
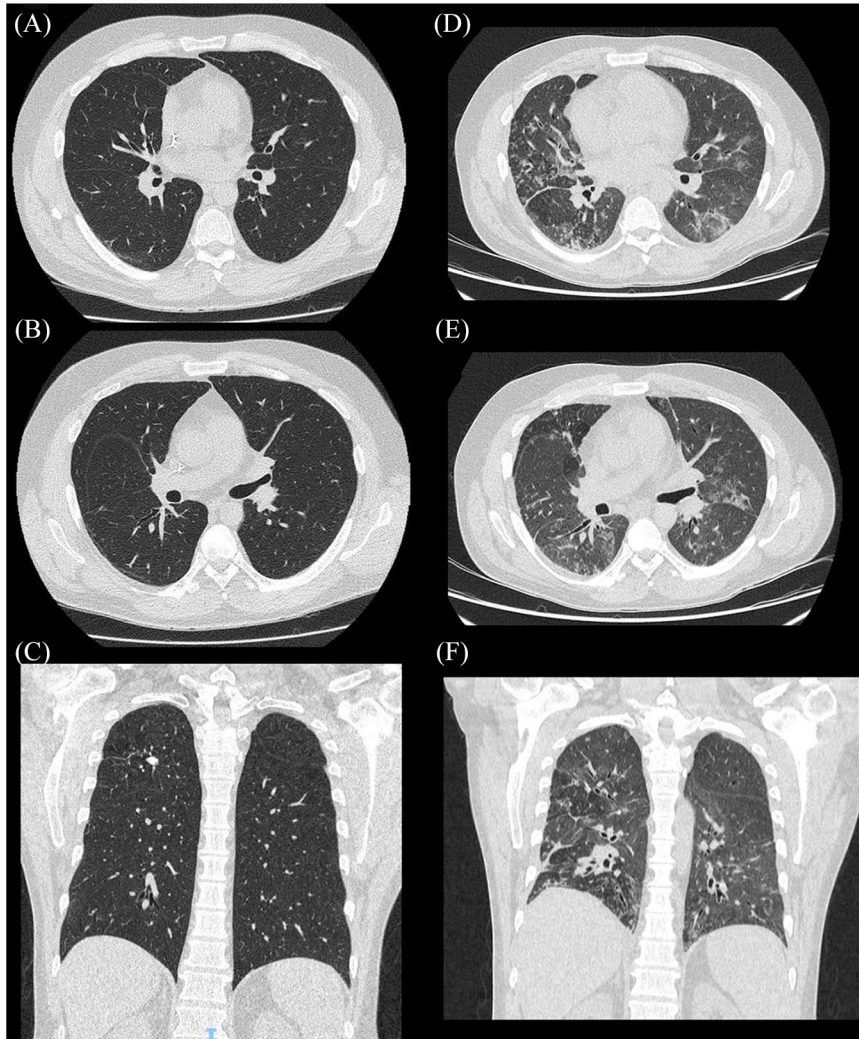
Figure 5. (A–C) HR-CT chest of a 48-year-old man with (DLBCL), prior to infection with COVID-19. (D–F) HR-CT of the same DLBCL patient at the time of diagnosis with COVID-19. Images show bilateral multiple patchy areas of ground-glass changes involving all the lobes, mainly peripheral. Systemic anti-cancer treatment at time of infection was with rituximab and polatuzumab (bendamustine had been held in light of the COVID-19 pandemic). DLBCL, diffuse large B-cell lymphoma; HR-CT, High resolution computed tomography.

dexamethasone had no impact on the likelihood of death (adj. OR 1.07; 95% CI = 0.26–4.46; $p = 0.925$); however, patients who had been receiving long-term anticoagulation when diagnosed with COVID-19 (either LMWH or DOAC) appeared to have an increased risk of death (adj. OR = 13.03; 95% CI = 2.85–59.50; $p = 0.001$).

Discussion

There have been conflicting data on the outcomes of oncology patients who contracted COVID-19 illness and required hospital admission. This, however, is one of the first studies exploring the risk of contracting COVID-19 infection in patients receiving active SACT.[18]

This study demonstrated that patients on active SACT were significantly more likely to die if infected with COVID-19 when compared with patients on SACT who did not develop COVID-19. One-third (34%, $n = 23$) of those infected subsequently died from COVID-19, which is in keeping with current literature on oncology patients.[9,11]

The prevalence of COVID-19 in our cohort of patients was 2.5%, a figure eight-fold greater than that reported for the general population matched by location and timeframe.[19] During the same period, the prevalence of COVID-19 was 0.3% in Camden and Enfield (the two north London boroughs in which the hospitals in our study are

Table 1. Univariate regression analysis and OR of developing COVID-19, with 95% CIs. Red bars indicate criteria for statistical significance were met ($p < 0.05$).

Predictor		n = 2764	OR* (95% CI)	p-value*
Sex, n (%)	Male	1332 (48.2%)	1.94 (1.17–3.22)	0.01
	Female (ref)	1432 (51.8%)		
Age, median (IQR)		64 years (52–73)	1.00 (0.98–1.02)	0.93
Comorbidities, n (%)				
CVD		382 (13.8%)	1.61 (0.88–2.95)	0.12
HTN		664 (24.0)	1.46 (0.83–2.58)	0.19
Diabetes		256 (9.3%)	0.73 (0.30–1.77)	0.49
COPD		90 (3.3%)	1.13 (0.34–3.71)	0.85
Long-term steroids		347 (12.6%)	2.03 (1.14–3.62)	<0.05
Anticoagulation		332 (12.0%)	1.64 (0.83–3.23)	0.15
Any comorbidities, n (%)		1448 (52.4%)	2.29 (1.19–4.38)	0.01
Type of malignancy, n (%)	Haematological	1245 (45.3%)	1.22 (0.74–2.00)	0.44
	Solid (ref)	1519 (55.0%)		
Cancer type – Solid malignancies, n (%)				
Breast		316 (11.4%)	0.53 (0.16–1.79)	0.31
CNS		88 (3.2%)	1.00 (0.24–4.24)	>0.99
Gastrointestinal		223 (8.1%)	0.88 (0.35–2.21)	0.78
Female reproductive organs (n = 1432)		246 (17.2%)	1.13 (0.41–3.10)	0.81
Male reproductive organs (n = 1332)		178 (13.4%)	0.13 (0.02–0.997)	0.05
Respiratory and intrathoracic organs		205 (7.4%)	2.12 (1.04–4.36)	0.04
Sarcoma		180 (6.5%)	0.45 (0.11–1.86)	0.27
Urinary tract		23 (0.8%)	3.61 (0.82–15.90)	0.09
Unknown primary		14 (0.5%)	3.35 (0.42–26.48)	0.25
Cancer type – Haematological malignancies, n (%)				
Acute lymphoblastic leukaemias		57 (2.1%)	0.64 (0.08–4.84)	0.67
Hodgkin lymphoma		41 (1.5%)	1.05 (0.13–8.24)	0.96
Myeloid neoplasms		478 (17.3%)	0.60 (0.28–1.27)	0.18
Non-Hodgkin lymphomas		324 (11.7%)	1.77 (0.96–3.27)	0.07
Plasma cell neoplasms		345 (12.5%)	1.38 (0.72–2.63)	0.33
Treatment intent, n (%)	Palliative	1782 (64.5%)	0.89 (0.53–1.48)	0.65
	Curative (ref)	982 (35.5%)		

(Continued)

Table 1. (Continued)

Predictor	n = 2764	OR* (95% CI)	p-value*
Cancer treatment, n (%)			
Chemotherapy	1421 (51.4%)	2.99 (1.72–5.21)	<0.001
High dose	130 (9.1%)	2.36 (1.35–6.48)	0.007
Standard dose (ref)	1291 (90.9%)		
Hormone therapy	144 (5.2%)	0.18 (0.02–1.33)	0.09
Targeted treatment	964 (34.9%)	0.53 (0.30–0.95)	0.03
Immunotherapy	229 (8.3%)	0.31 (0.08–1.28)	0.11
Ethnicity, n (%)	**n = 1808**		
Asian/Asian British	76 (4.2%)	2.22 (0.85–5.81)	0.10
Black/African/Caribbean/Black British	408 (22.6%)	0.81 (0.41–1.58)	0.53
Mixed/Multiple Ethnic Groups	957 (52.9%)	0.04 (0.01–0.13)	<0.001
White	278 (15.4%)	12.13 (6.96–21.1)	<0.001
Other	89 (4.9%)	0.66 (0.16–2.75)	0.56

*All models include variables age (continuous), gender (male/female), CVD (yes/no), HTN (yes/no), COPD (yes/no) and diabetes (yes/no) by default. CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HTN, hypertension; IQR, interquartile range; OR, odds ratio.

located). However, the utility of this figure is clearly limited by the lack of other matched variables and the rate of testing in the general public compared with the population of cancer patients on active treatment.

A UK-based prospective study evaluated 1044 COVID-19 positive patients using data from the UK Coronavirus Cancer Monitoring Project (UKCCMP) to assess the association between cancer type (in all cancer patients) and the likelihood of COVID-19 infection. Control data was a non-COVID-19 UK cancer population from the UK Office for National Statistics from 2017, adjusted for age and sex.[10] Here, we concentrate solely on cancer patients receiving systemic anti-cancer therapy and have taken into account various other confounding factors including co-morbidities and type of cancer treatment, a real-world comparator to determine which characteristics can impact cancer patient vulnerability to COVID-19 infection.

The proportions of haematological to solid organ cancer patients were relatively evenly split (55% *versus* 45%). Haematological malignancy did not impact the risk of COVID-19 infection, but

patients had a significantly worse risk of mortality if infected. This is reflected in work elsewhere, including a European study of 890 patients which reported worse outcomes in haematological cancer patients infected with COVID-19,[9,20] as well as data from Hubei, China.[21] There are several reasons why haematological cancer patients could be more susceptible to severe outcomes, namely the negative impact of the cancer itself or its treatment on the immune system.[22] There is utility in making this comparison in a study such as ours where all individuals are on active treatment, as it removes the potential confounding of patients off-treatment shielding at home more strictly. The most recent UKCCMP study by Lee *et al.* found a higher prevalence of COVID-19 in haematological patients[10]; a reason for the discrepancy in our data could be due to the heterogeneous group that leukaemia encompassed and the over-representation of myelodysplastic syndromes in our cohort.

Our results suggest oncology patients are significantly more vulnerable to COVID-19 infection if they were being actively treated with chemotherapy, with a significantly higher risk of COVID-19

associated with high-dose chemotherapy regimens compared with low-dose regimens. There has been much discussion on whether being on anti-cancer treatment, in particular chemotherapy, has an adverse effect on outcomes of COVID-19 positive patients. A study from China with 105 COVID-19 positive patients suggested that chemotherapy is associated with worse mortality in cancer patients.[20] However, this has been disputed by a UK study suggesting that recent anti-cancer treatment regardless of treatment modality is not associated with worse outcomes in COVID-19 positive patients.[11]

Interestingly, our results did not show an increased risk of COVID-19 infection in patients on immunotherapy or hormone therapy, and being on a targeted treatment appeared to have a protective effect. The OR for immunotherapy and hormonal treatments were relatively low, raising the possible hypothesis that these treatments may also have a protective effect against COVID-19. Future studies evaluating the possible beneficial effect of targeted therapy, hormone therapy and immunotherapy on COVID-19 risks with a larger sample size could potentially help direct treatment decisions using an evidence-based approach, should there be a second wave of COVID-19. Consideration could be given to ceasing chemotherapy in preference of checkpoint inhibitor therapy, for example, in those with lung cancer, or commencing further lines of hormonal treatment in preference to chemotherapy in metastatic prostate cancer. This is something we need to approach with caution in light of data suggesting that immunotherapy may be an independent risk factor for severe events in a study of 423 COVID-19 positive patients.[23] Immune checkpoint inhibitors may cause an increase in cytokine release, which is also seen in the cytokine storm that leads to the often-fatal acute respiratory distress syndrome (ARDS) seen in COVID-19 patients. Alternatively, other studies found that treatment with immunotherapy did not impact mortality negatively in COVID-19 positive cancer patients,[11] and it is hypothesised that immunotherapy may reduce the risk of developing the cytokine storm primarily responsible for the development of ARDS in COVID-19.[24] Studies of larger populations looking specifically at different treatment modalities in different tumour groups are needed before we can draw definitive conclusions.

The RECOVERY study concluded a 17% reduction in 28-day mortality in COVID-19 patients requiring respiratory support treated with dexamethasone, but the benefit of dexamethasone was lost in patients who were not unwell enough to require respiratory support.[25] One can hypothesize that dexamethasone is only beneficial in very unwell patients, as it may reduce the effects of the cytokine storm caused by COVID-19, which has the greatest effect in the most unwell patients. Our results suggest that being on long-term steroids enhances the risk of contracting COVID-19, which is not unexpected based on the immunosuppressive effects of long-term steroids.

We found that the presence of any co-morbidity significantly increased a patient's chance of contracting COVID-19. However, when we looked at cardiovascular disease, diabetes, hypertension and COPD individually there was no association found to highlight any of these as specific risk factors. We recognise this is likely due to our small population size, as these four co-morbidities emerged as independent risk factors for COVID-19 related mortality in much larger data sets, including a study on hospitalised patients over 65 in the UK and in a series of 218 patients with cancer in New York, in the United States (US).[26,27] Evidence looking at cancer patient mortality from COVID-19 suggests that the risk of death is driven by age, gender and co-morbidities[11,28]; our evidence suggests that the presence of comorbidities does not increase the chance of contracting COVID-19, but does increase the risk of death if it is contracted.

We recognise several limitations to our study. Firstly, our small sample size of 68 COVID-19 positive patients limits the strength of our results when looking specifically at this cohort. The World Health Organisation (WHO) suggest using chest imaging for diagnostic work-up when initial RT-PCR testing is negative and there is high clinical suspicion of COVID-19,[29] which was the case for 11 patients in our population with a radiological diagnosis of COVID-19. However, we recognise their inclusion is a limitation given the element of subjectivity to diagnosis it introduces as no single radiological feature of COVID-19 is diagnostic or specific. There is perhaps also some strength to be gained from including these patients who are SARS-CoV-2 RT-PCR negative as it may reduce the bias against the exclusion of less severe cases. As the vast majority of the patients who tested positive for COVID-19 had symptoms at presentation, we were not able to identify the true rate of asymptomatic COVID-19

infection, which has been reported to be higher in cancer patients than in their caregivers.[30]

In summary, we found that patients on active systemic anti-cancer treatment are significantly more likely to die if they contract COVID-19. Patients on active cancer treatment are more likely to be infected with COVID-19 if they are being treated with chemotherapy, particularly high-dose chemotherapy; treatment with immunotherapy and hormonal treatments had no significant impact on the chances of contracting COVID-19, while targeted treatment appeared to have a protective effect. Our results also hypothesise a possible protective property against COVID-19 of hormonal treatments and immunotherapy, providing an interesting question for future research.

Author contributions
VEC, KK, NJH NC, KKS, JB, MF and DH were involved in study design. VEC, DH, NJH, NC, EB, MD, YCL, SD, RK, JB and TAF were involved in data collection. VEC, DH, NJH, NC and WW were involved in data analysis and interpretation. VEC, DH, NJH, NC, WW and KK were involved in manuscript writing, VEC, DH and NJH created the figures and all authors approved the final manuscript before submission for publication.

Availability of data and materials
The datasets generated or analysed during the current study are available on request from the corresponding author.

Conflict of interest statement
NJH reports grants from CRUK Clinical Trial Fellowship, outside the submitted work. VEC, WW, TAF, SD, JB, KK, DH, KKS, RK, NC, MD, EB, JB, MF and DH have no conflicts of interest to disclose.

Consent for publication
No patient identifiable information was used in this study.

Data Sharing
Anonymised data will be made available upon reasonable request.

Ethics approval and consent to participate
Research and development approval were sought from University College Hospital, which is where the study was primarily conducted.

Transparency statement
This manuscript is an honest, accurate, and transparent account of our study. No important aspects of the study have been omitted and that discrepancies from the study as originally planned have been explained.

ORCID iD
Valerie E. Crolley (iD) https://orcid.org/0000-0001-7263-4051

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