COVID-19 in cancer patients: Effect of primary tumour subtype and patient demographics

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Running Title: A detailed analysis of risk to cancer patients with COVID-19

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Abstract

Background

Patients with a diagnosis of cancer are purported to have poor outcomes from COVID-19. However, cancer is a heterogeneous group of diseases encompassing a wide spectrum of primary tumour subtypes and there have been no studies evaluating risk from COVID-19 according to cancer subtype and general demographics in the cancer patient population

Methods

A comparison of cancer patients enrolled in the *UK Coronavirus Cancer Monitoring Project (UKCCMP)* and a parallel non-COVID-19 UK cancer control population cohort was performed, analysing the effect of tumour subtype and patient demographics (age and sex) on the risk and the trajectory of COVID-19.

Findings

In 1,044 patients with COVID-19 enrolled into the UKCCMP we observe that tumour features as well as patient demographics impact on viral susceptibility and COVID-19 phenotype. SARS-CoV-2 susceptibility is increased in patients with haematological malignancies (leukaemia/lymphoma/myeloma), and these patients run a more severe COVID-19 trajectory (OR 1.57, 95% CI 1.15-2.15; p=0.004) and require more intensive clinical support. Case fatality rate following COVID-19 in patients with leukaemia is increased compared to other cancer types, even considering other risk factors (OR 2.25, 95% CI [1.13 to 4.57]; p=0.023). Gender and age are the overriding risk factors for SARS-CoV-2 infection and severity of COVID-19 for most cancer patients, as they are for the general population.

Interpretation

Cancer patients with different tumours have differing SARS-CoV-2 susceptibility and COVID-19 phenotypes. We have generated individualised risk tables for cancer patients taking into account age/sex and tumour subtype. This will be useful for physicians to have a more informed risk-benefit discussion to explain COVID-19 risk to their cancer patients.

Introduction

The disease course of individuals contracting SARS-CoV-2 infection is phenotypically diverse. Many patients suffer only mild symptoms and it is becoming increasingly apparent from antibody data, that others suffer no symptoms at all but can actively carry and transmit the infection. However, at the other end of the spectrum, some individuals develop very severe symptoms and can follow an extreme phenotype with the development of respiratory failure, cytokine release syndrome and multi-organ failure. Subgroups of COVID-19 patients have been identified who appear to be at increased risk of extreme morbidity and mortality, including patients of advancing age, male gender (versus female) and those with co-morbidities such as hypertension, chronic lung disease, diabetes and cancer (1).

Since COVID-19 started to spread across the globe in early 2020, patients with a diagnosis of cancer were designated as a particularly vulnerable subgroup of the population. Cancer patients have been reported to be not only at increased risk of contracting SARS-CoV-2 infections, but also of running a more severe disease course, with a higher proportion requiring higher levels of intensive care, having a more rapidly evolving disease, and with increased risk of death. (2) (3) (4) However, as every subspecialised oncologist knows, the term 'cancer' encompasses a myriad of disease, with a diverse array of primary tumour subtype and stages, affecting a heterogeneous group of patients of all ages, and which result in very different cancer prognoses and outcomes. Therefore, labelling all cancer patients as 'COVID-19 vulnerable' is probably neither reasonable nor informative.

As a consequence of generic advice given to 'COVID-19 vulnerable' members of the population, cancer patients (of any age, gender, tumour subtype and stage) have been labelled as high risk from COVID-19 and this has led to sweeping changes in cancer management for all cancer types over the last few months, including abbreviation of radiotherapy, switching from IV to oral chemotherapy regimens, and the avoidance of immunotherapy. (5) (6) (7) (8) These changes, perhaps reasonably in an acute pandemic situation, were instigated with very little evidence to support them. And due to lack of evolving evidence, there has been little attempt to define the individualised risk for a given patient, taking into account their primary tumour subtype, age and gender.

We report here, from the UK Coronavirus Cancer Monitoring Project (9), the first analysis of the complex interaction between patient demographics and tumour subtype, to more accurately estimate the risk of SARS-CoV-2 infection / COVID-19 in patients with cancer. We describe the clinical outcomes of COVID-19+ cancer patients entered on the UKCCMP registry, and compare primary cancer subtype prevalence/case fatality rate to the United Kingdom's (UK) Office for National Statistics (ONS) cancer incidence data.

Methods

Study Design and Participants

The UKCCMP database of United Kingdom (UK) cancer patients was set up on the 18th of March and has been designed as a Public Health Surveillance registry for the COVID-19 pandemic. At an institutional level, the entry of patients on to the registry was approved according to local information governance processes. All patients with active cancer and who presented to a cancer centre within the UKCCMP network from March 18th 2020 with a positive SARS-CoV-2 test, were eligible for enrolment on the registry. The patients presented for secondary care review for potential hospitalization and were not part of a proactive surveillance program. Patients with active cancer were defined as those with metastatic cancer, or those undergoing anti-cancer treatment in any setting (curative/radical/adjuvant/neoadjuvant) or those treated within the past 12 months with surgery/cytotoxic chemotherapy/radiotherapy. Data collection is ongoing within the registry but for all patients presented here, outcomes were monitored up to May 8th 2020. This study was conducted in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

Data Collection

Prospective data collection was performed by a pan-UK cancer centre emergency response network set up by the UKCCMP. All registry patient entries were de-identified at source to ensure that all data is anonymous to researchers. Data was entered into a Research Electronic Data Capture (REDCap) browser-based metadata driven electronic data capture (EDC) software system. (10) The secure EDC platform was hosted by the Institute of Translational Medicine at the University of Birmingham. Patient demographics and cancer features were obtained from the direct assessment of the Emergency Response Reporting Individual or Local Emergency Response Reporting Group (ERRI/LERRG) and/or through hospital medical records. In keeping with international practice, patients were deemed to have SARS-CoV-2 infection if there was a positive Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay test from a throat/nose swab. Patients with a radiological, clinical diagnosis of SARS-CoV-2, without a positive RT-PCR test were not included in this analysis. Bronchoalveolar lavage is not recommended in the UK (27). Primary cancer subtype was defined according to ICD-10 diagnostic codes.

Clinical management

Management of cancer patients with COVID-19 was directed by the patient's clinician team without input from the UK CCMP. They were based on local policies and standard UK clinical practice at the time of this study. Decisions on ITU admission and ventilation were guided by the UK National Health Service, National Institute of Health and Care Excellence COVID-19 rapid guidelines (11).

UKCCMP data processing and analysis

The data through the REDCap platform was transferred securely through to the Compute and Storage for Life Science (CaStLeS) infrastructure as part of the Birmingham Environment for Academic Research local Cloud (BEARCloud) (12) via the Centre for Computational Biology, University of Birmingham. Within CaStLeS, the data is curated to avoid duplications and errors, then annotated with further information such as geolocation before it can be analysed and disseminated.

Comparator data sources

A historical control dataset was obtained from the UK Office for National Statistics (ONS). Tumour subtype and demographics analysis utilised the latest release of the "Cancer Registration Statistics, England, 2017" which is publicly available. (13). This is the latest cancer registration database in England and involves registrations of patients up to 2017. Cancer registrations in England take years after a given calendar year to reach nationally validated quality control measures for robustness of analyses due to continuing accrual of registrations.

Statistical analysis & Data visualisation

In this study, we report on the cancer patient demographics (primary tumour subtype, age and gender) of those who contract the SARS-CoV-2 infection and describe their COVID-19 clinical course. We compare these demographic characteristics with those gleaned for the whole cancer population from the UK Office for National Statistics (ONS) cancer control dataset. The primary outcome of interest was all-cause inpatient case fatality rate (during the COVID-19 episode) and this was used for all regression analyses and analyses by tumour subtype. This included death designated as a direct result of COVID-19 as well as death from any other cause such as cancer progression and treatment toxicity. Skin cancers were not included in these analyses as they are excluded

from the ONS dataset. Patients with an unspecified tumour subtype were also excluded from this analysis. A two-sided Fisher's exact test was used to compare categorical data from different categories. Multivariable logistic regression (14) was used to estimate odd ratios and 95% confidence intervals of each defined factor after adjustment for potential confounders of patient age and gender.

Results

Susceptibility to SARS-CoV-2 Infection

We are reporting on 1,044 patients with active cancer and a documented SARS-CoV-2 infection/COVID-19 registered in the UKCCMP database with outcomes censored at 8th May, 2020. Of this cohort, 595 were men (57.0%) and the median age was 70 years, IQR 60-77. Patients were followed up from the point of COVID-19 diagnosis to either discharge from hospital or death. Mean follow up was 7.8 days (standard deviation 8.2 days).

The demographics and cancer subtype of the COVID-19+ cancer population from the UKCCMP registry were compared with those from the population of cancer patients represented in the ONS cancer census which was used as a historical control group. Compared to the ONS control population of cancer patients, we found that COVID-19+ cancer patients were significantly more likely to be male (57.0% in UKCCMP vs 51.3% in ONS, OR 1.26 95% CI [1.12 to 1.43]; p=0.0002) but the age distribution of cancer patients who contracted COVID-19 was not significantly different to the ONS cancer control population (median age group 70-79 for both series) (Supp. Figure 1).

We found that certain tumour subtypes were overrepresented in the UKCCMP COVID-19+ patient cohort. Patients with haematological malignancies appeared to be at significantly increased risk, and these included those with leukaemia (OR 2.82 95% CI [2.21 to 3.55]; p<0.001), myeloma (OR 2.03 95% CI [1.42 to 2.83]; p<0.001) and lymphomas (OR 1.63 95% CI [1.28 to 2.06]; p<0.001) (Table 1). In contrast, patients with lung cancer and prostate cancer were relatively underrepresented in the COVID19+ UKCCMP series compared to the control ONS series of cancers. Lung cancer made up 10.7% of the UKCCMP series compared to 13.7% of ONS cases (OR 0.75 95%CI [0.61-0.91]; p=0.003). Similarly, prostate cancer comprised 11.0% of the UKCCMP series compared to 14.6% of the ONS cohort (OR 0.72 95%CI [0.59-0.88]; p<0.001).

Case fatality rate from COVID-19

337 of the 1044 COVID-19+ UKCCMP cancer patients died (29.7%), of which the cause of death was recorded as due to COVID-19 in 92.3% (n=311). The all-cause case fatality rate in cancer patients following COVID-19 was significantly linked to increasing age, with the case fatality rate in the 40-49, 50-59, 60-69, 70-79 and over 80 groups being 0.10, 0.17, 0.28, 0.35 and 0.48 respectively, and no deaths recorded in the under 40 group (Figure 1, Supp. Figure 2). In addition, the all-cause case fatality rate in cancer patients once they had contracted COVID-19 also appeared to be associated with gender, in males being 0.34 and that in females being 0.23, (OR 1.92 95% CI [1.51 to 2.45], p<0.001). We confirmed that advancing age was a significant risk factor for death following COVID-19, with the population of over 70-year olds being over-represented (Supp. Figure 3).

We compared the case fatality rate for each primary tumour subtype in the UK CCMP to a reference, the C15-C26 subtype (digestive organs) as it was the tumour subtype with the central case fatality rate. On univariate analysis we observed a significantly higher risk in patients with prostate cancer (OR 2.14, 95% CI [1.17 to 3.96]; p=0.014), and leukaemia (OR 2.03, 95% CI [1.04 to 3.97]; p=0.038) and a significantly lower risk for patients with breast cancer (OR 0.53, 95% CI [0.28 to 1.00]; p=0.049) and female genital organ cancer (OR 0.36, 95% CI [0.13-0.87]; p=0.031) (Figure 2, Supp. Figure 4). We then performed a multivariate correction for clinically relevant confounders, age and gender. Compared to the rest of the UKCCMP cohort, patients with leukaemia remained at significantly increased case fatality rate (OR 2.25, 95% CI [1.13 to 4.57]; p=0.023), (Table 2, Supp. Figure 5). However, after multivariate correction, prostate cancer was no longer significantly associated with increased case fatality rate, and breast and female genital cancers were no longer associated with reduced case fatality rate, highlighting the striking effect of patient age and gender on case fatality rate. Also, on multivariate analysis, we did not find a significantly increased case fatality rate from COVID19 in the lung cancer population (OR 1.41 95%CI [0.75-2.67]; p=0.285) compared to the rest of the UKCCMP population.

We then undertook a specific detailed analysis of the 227 patients with haematological malignancies who were diagnosed with COVID-19. Compared to the remainder of the UKCCMP cohort (with non-haematological cancers), we found that these patients presented with similar symptoms. (Supp Table 2). However, adjusting for potential confounding variables of age and gender, patients with haematological malignancies were significantly more likely to require high flow oxygen (OR 1.82 95% CI [1.11 to 2.94]; p =0.015)], non-invasive ventilation (OR 2.10 95% CI [1.14-3.76; p=0.014]), ITU admission for ventilation (OR 2.73 % CI [1.43 to 5.11]; p=0.002) and have a severe/critical disease course (OR 1.57 95% CI [1.15 to 2.15]; p=0.004) (Supp. Table 1). 47.6% of patients with haematological malignancies had received recent chemotherapy within 4 weeks of COVID-19 presentation compared to 29.5% of those with non-haematological cancers (OR 2.15 95% CI [1.57-2.95]; p<0.0001) (Supp. Table 1). On univariate analysis, recent use of chemotherapy in these patients, was not associated with significantly

increased risk compared to those who had no recent chemotherapy use. However, following correction for age and gender, patients with haematological malignancies who had recent chemotherapy were at increased risk of death during the COVID-19 associated admission (OR 2.09 95% CI [1.09 to 4.08]; p=0.028).

Discussion

During the COVID-19 pandemic, there has been a dual fold effect on cancer practice. There have been radical changes to the treatment of patients already diagnosed with cancer, including cessation/interruptions of active therapies and delays in surgery. (15) (16) There has also been a concerning dramatic reduction in oncology referrals to secondary care in the United Kingdom. (17) There is likely to have been a number of factors contributing to this observation. However, a perception of excessive vulnerability of all cancer patients or futility of cancer treatments in the context of a pandemic is one proposed cause. Unchallenged, this is likely to lead to decreased/delayed cancer presentations or referrals and expose a significant proportion of the population to considerable harm beyond COVID-19. At the inception of our study, the largest study of cancer patients who developed COVID-19 was a 105 patient cohort study from China and the authors reported high mortality rates from COVID-19 in patients with haematological malignancies, lung cancer and patients with metastatic cancer. (18) However, the small size of that cohort and therefore the very small numbers of patients with each tumour type within it, made it difficult to be conclusive about these findings. For all cancer patients, in any situation, whether we are attempting cure or trying to palliate symptoms and extend life, there is a fine balance between potential benefits and risks of treatment. Therefore, it is critical that we do properly identify the individualised risk of harm from COVID-19 for each cancer patient, rather than treating them as a homogeneous 'vulnerable' population, and that we put that risk into the context of their individual cancer prognosis.

Risk of severe morbidity and eventual mortality from SARS-CoV-2 infection for any individual in the population is driven by two key factors, baseline *viral susceptibility* and the ensuing *COVID-19 phenotype*. *Viral susceptibility* is a dynamic interplay between specific exposure and potential host predisposition/vulnerability to infection. In cancer patients, there may be a particular host predisposition/vulnerability either as a result of having a dysregulated immune response skewing it away from an ability to fight viral infection; or indeed cancer-induced damage to epithelial membranes. The *COVID-19 phenotype* experienced by a cancer patient is likely to be a complex interplay of several factors, including patient demographics, other co-morbidities, cancer phenotype and effects of cancer treatment, as well as the intensity of COVID-19 treatment that the individual patient then receives.

The UKCCMP has collected primary tumour type and demographic data on over 1000 patients with cancer who contracted SARS-CoV-2 and developed COVID-19, and analysed this not only within the UKCCMP population, but also compared it with ONS data from the general cancer population. This has allowed us to segregate the cancer population by risk, considering the already known risk factors for COVID-19 such as gender (males at higher risk than females) and advancing age.

In this study, we have found that both *viral susceptibility* and the *COVID-19 phenotype* are influenced by primary tumour subtype. Patients with haematological malignancies (leukaemias, lymphomas and myelomas) appear to have an *a priori* increased viral susceptibility, and to be at greater risk of having a more severe *COVID-19 clinical phenotype*, to require more intensive supportive interventions, and to suffer an elevated risk of death. Patients with the haematological codes (C86, C88, C96) had the highest viral susceptibility. The reasons for this are unclear and likely reflects the small number of patients involved and stochastic effects (n=29), but it is possible that these haematological subtypes may have a specific immunological susceptibility to COVID-19 infection. On multivariate analysis, patients with leukaemia still had a significantly higher risk of death related to COVID-19, considering age and gender. The increased case fatality rate in haematological malignancies is similar to that observed in a pre-print article from the United Kingdom (19) and Chinese cohorts (20) (21), but in contrast to a recent American cohort study (22) which does not suggest increased mortality in this group.

Recent large COVID-19 cancer cohorts of predominantly solid organ tumours have identified no significant excess mortality risk from recent chemotherapy (16) (22). In this study, we have identified that in haematological malignancies, following multivariable analysis, risk does appear to be heightened by recent (within 4 weeks) or current chemotherapy. It is possible that haematological patients undergoing chemotherapy may be responsible for observations from other cohorts (23).

There are likely to be a number of possible reasons for these observations. The immunological disruption *per se* observed in patients with leukaemia and the use of intensely myelosuppressive regimes may result in a devastating combination of risk, both in terms of the likelihood of initial SARS-CoV-2 infection and its ability to gain a foothold in the host and also in terms of the downstream disease course and likelihood of severe consequences such as cytokine storm and significant multiorgan failure. Further work is necessary in larger haematological cancer cohorts to have the power to discern the relative importance of these factors with more certainty.

Contrary to the findings from the Chinese series and data from a European registry (24), we found that patients with lung cancer were relatively underrepresented in the UKCCMP cohort compared to the ONS data. In addition, once COVID-19 was established in lung cancer patients, we found no significantly increased case fatality rate compared to the general COVID19+ cancer population within UKCCMP, suggesting that lung cancer patients are not a specifically vulnerable group. There are likely to be a number of reasons for this difference in findings. Firstly, there are methodological differences, with this study comparing lung cancer cases to a cancer population rather than a non-cancer population. Secondly, there may now be more effective shielding of lung cancer patients at an early stage in the pandemic when they were designated as vulnerable. Thirdly, lung cancer is the commonest cancer in China, and hence would be overrepresented in their COVID-19+ cancer patient population and finally the European registry does not use a controlled group and this highlights the importance of our intra population-controlled studies.

Prostate cancer patients were relatively underrepresented in the UKCCMP cohort again compared to ONS data, again perhaps due to shielding, or perhaps due to a reluctance to bring this cohort of patients to hospital even if they developed COVID symptoms. In terms of risk of death once COVID-19 was established, initially the prostate cancer group of patients did appear to be an increased case fatality rate, but multivariate analysis that actually their risk was no greater than the rest of the COVID-19+ cancer population in UKCCMP, reflecting again the importance of gender more specifically as factor.

Patients with breast cancers or malignancies of the female genital tract appeared to be at much lower risk, either of contracting or of dying from COVID-19. However multivariate analysis again demonstrated that this protection was by virtue of the patients being female, rather than an inherently lower risk tumour per se. (25) (26)

Overall, in interpreting these data, and putting them into context, our diverse subpopulations of cancer patients are at equally diverse risks of SARS-CoV-2 infection and of suffering a severe COVID-19 phenotype upon infection. This needs to be borne in mind when deciding on the level of shielding cancer patients require, depending on the likely prognosis from their cancer. For example, many patients may take the risk of COVID-19 and see their grandchildren, rather than spend the last two months of their life alone. Exposure to SARS-CoV-2 should be minimised for all cancer patients through judicious and contextualised use of social/clinical isolation measures but also perhaps through measures such as regular SARS-CoV-2 infection screening of their clinical and home contacts whilst continuing treatment with optimal anti-cancer treatment. However, enhanced strategies to prevent viral transmission must be employed in patients with haematological conditions, particularly where the risk of not proceeding with systemic treatment is high. For all cancer types, risk is lower in younger patients and those of female sex, reinforcing the importance of gender and age as determinants of SARS-CoV-2 / COVID-19 risk.

This paper allows oncologists and other healthcare professionals to more effectively risk stratify cancer patients and to counsel them accordingly during this unprecedented time for oncological care. We note some of the limitations of this analysis. Our analyses are based on symptomatic cancer patients who seek help from cancer centres. Therefore, the cohort may not be entirely representative of all patients with cancer, and patients may therefore be more likely to be those under ongoing oncological follow-up, and less likely to be patients on an end of life pathway or from nursing homes/hospices. There may be limitations in our comparison to the ONS control population of cancer patients. In this study, we report on patients with “Active Cancer” whereas the ONS control population is a historical control, consisting of all patients with a diagnosis of cancer up to 2017 and therapies in oncology and the spectrum of disease may have changed. Therefore, more contemporary analyses, in diverse population datasets will need to be performed. In addition, as discussed, there is a low admission rate of cancer patients to ITU, which is likely to impact on COVID-19 outcomes in cancer patients in the United Kingdom (16). Furthermore, we have only performed multivariable correction for age and sex, which appear to be the primary drivers of case fatality. Finally, this analysis has been performed without an a priori power calculation in order to facilitate timely dissemination of results.

However, rates of COVID-19 in cancer patients remain thankfully low overall and the age distribution of patients in the UKCCMP reflects the age distribution in the ONS dataset suggesting that our comparator population is as appropriate as possible at this stage.

Despite these noted limitations, our study is unique in comparing the dataset to an accurate cancer population control dataset. Morbidity and case fatality rate from COVID-19 (once established) in UK cancer patients attending hospital is relatively high, particularly in those with haematological malignancies and advancing age, but not all

cancer patients are affected equally which is a very important finding. The UKCCMP will continue to monitor risks to patients following the end of the first UK pandemic peak, provide early warning of further pandemic peaks and provide timely and meaningful information to the cancer community to enable the highest quality of cancer care to continue.

	UKCCMP cases (%)	ONS cases (%)	Odds Ratio (95% CI)	p value
Patient Features				
-Male	595 (57.0%)	145034 (51.3%)	1.26 (1.12-1.43)	0.0002
-Female	445 (42.6%)	137844 (48.7%)		
-Other	4 (0.4%)	0 (0.0%)		
-Median age/years	70	NA*		
Cancer Subtype				
-Breast (C50-C50)	143 (13.7%)	46109 (16.3%)	0.82 (0.68-0.98)	0.026
-Colorectal (C18-C21)	124 (11.9%)	36039 (12.7%)	0.93 (0.76-1.12)	0.456
-Prostate (C61)	114 (11.0%)	41200 (14.6%)	0.72 (0.59-0.88)	<0.001
-Lung (C34)	111 (10.7%)	38878 (13.7%)	0.75 (0.61-0.91)	0.003
-Digestive organs (non-colorectal) (C15-C26)	95 (9.1%)	30096 (10.6%)	0.84 (0.68-1.04)	0.118
-Urinary tract (C64-C68)	77 (7.4%)	19333 (6.8%)	1.09 (0.85-1.38)	0.46
-Female genital organs (C51-C58)	56 (5.4%)	17969 (6.4%)	0.84 (0.63-1.10)	0.226
-Lip, oral cavity and pharynx (C00-C14)	33 (3.2%)	7558 (2.7%)	1.19 (0.82-1.69)	0.334
-Central nervous system (C69-C72)	25 (2.4%)	5038 (1.8%)	1.36 (0.87-2.02)	0.127
-Mesothelial and soft tissue (C45-C49)	16 (1.5%)	4682 (1.7%)	0.93 (0.53-1.52)	0.903
-Respiratory and intrathoracic organs (not lung) (C30-C39)	11 (1.1%)	2780 (1.0%)	1.08 (0.53-1.94)	0.752
-Bone and articular cartilage (C40-C41)	4 (0.4%)	376 (0.1%)	2.90 (0.78-7.50)	0.053
-Male genital organs (C60-C63)	4 (0.4%)	2435 (0.9%)	0.44 (0.12-1.14)	0.126
-Endocrine glands (C73-C75)	4 (0.4%)	3374 (1.2%)	0.32 (0.09-0.82)	0.01
-Lymphoma (C81-C85)	*79 (7.6%)*	13537 (4.8%)	1.63 (1.28-2.06)	<0.001
-Leukaemia (C91-C95)	*79 (7.6%)*	8018 (2.8%)	2.82 (2.21-3.55)	<0.001
-Myeloma (C90)	*37 (3.6%)*	5033 (1.8%)	2.03 (1.42-2.83)	<0.001
-Other Haematological (C86, C88, C96)	*29 (2.8%)*	423 (0.1%)	19.14 (12.59-28.05)	<0.001

Table 1: Demographics and tumour subtype representation in the UKCCMP Covid-19 cohort compared to the ONS cancer control population. * Individual ages not available in dataset. Univariate analysis was performed, p values were determined by Fisher exact test and unadjusted for age and gender.

Tumour subtype	No. of Deaths	Case-fatality rate	Univariate odds ratio (95% CI)	p value	Multivariable adjusted odds ratio (95% CI)	p value
Prostate (C61)	49	0.43	2.14 (1.17-3.96)	0.014	1.09 (0.51-2.33)	0.824
Lung (C34)	43	0.387	1.62 (0.89-3.00)	0.118	1.41 (0.75-2.67)	0.285
Mesothelial and soft tissue (C45-C49)	6	0.375	1.18 (0.37-3.51)	0.772	1.52 (0.43-5.30)	0.505
Urinary tract (C64-C68)	23	0.299	1.08 (0.54-2.13)	0.834	0.87 (0.41-1.81)	0.715
Colorectal (C18-C21)	35	0.282	1.03 (0.56-1.90)	0.934	0.85 (0.44-1.64)	0.627
Central nervous system (C69-C72)	7	0.28	1.15 (0.39-3.18)	0.797	1.87 (0.57-6.05)	0.292
Respiratory organs (C30-C39)	3	0.273	0.84 (0.17-3.29)	0.813	0.96 (0.18-4.10)	0.954
Lip, oral cavity and pharynx (C00-C14)	8	0.242	0.75 (0.28-1.85)	0.542	0.77 (0.25-2.27)	0.644
Breast (C50)	26	0.182	0.53 (0.28-1.00)	0.049	0.97 (0.40-2.52)	0.942
Female genital organs (C51-C58)	7	0.125	0.36 (0.13-0.87)	0.031	0.79 (0.24-2.63)	0.704
Myeloma (C90)	16	0.432	1.85 (0.81-4.22)	0.142	1.65 (0.71-3.85)	0.241
Leukaemia (C91-C95)	33	0.418	2.03 (1.04-3.97)	0.038	2.25 (1.13-4.57)	0.023
Lymphoma (C81-C85)	25	0.316	1.60 (0.80-3.19)	0.184	1.72 (0.81-3.68)	0.156
Other Haematological (C86, C88, C96)	7	0.241	0.81 (0.28-2.12)	0.675	0.81 (0.26-2.33)	0.702
Digestive organs (C15-C17, C22-C26)	28	0.295	Reference	Reference	Reference	Reference

Table 2: All-cause case fatality rate following COVID-19 by tumour subtype, before and after age and sex correction. Odds ratio was performed relative to Digestive organs (non-colorectal) (C15-C26). Multivariable corrections were performed correcting for patient age and gender.

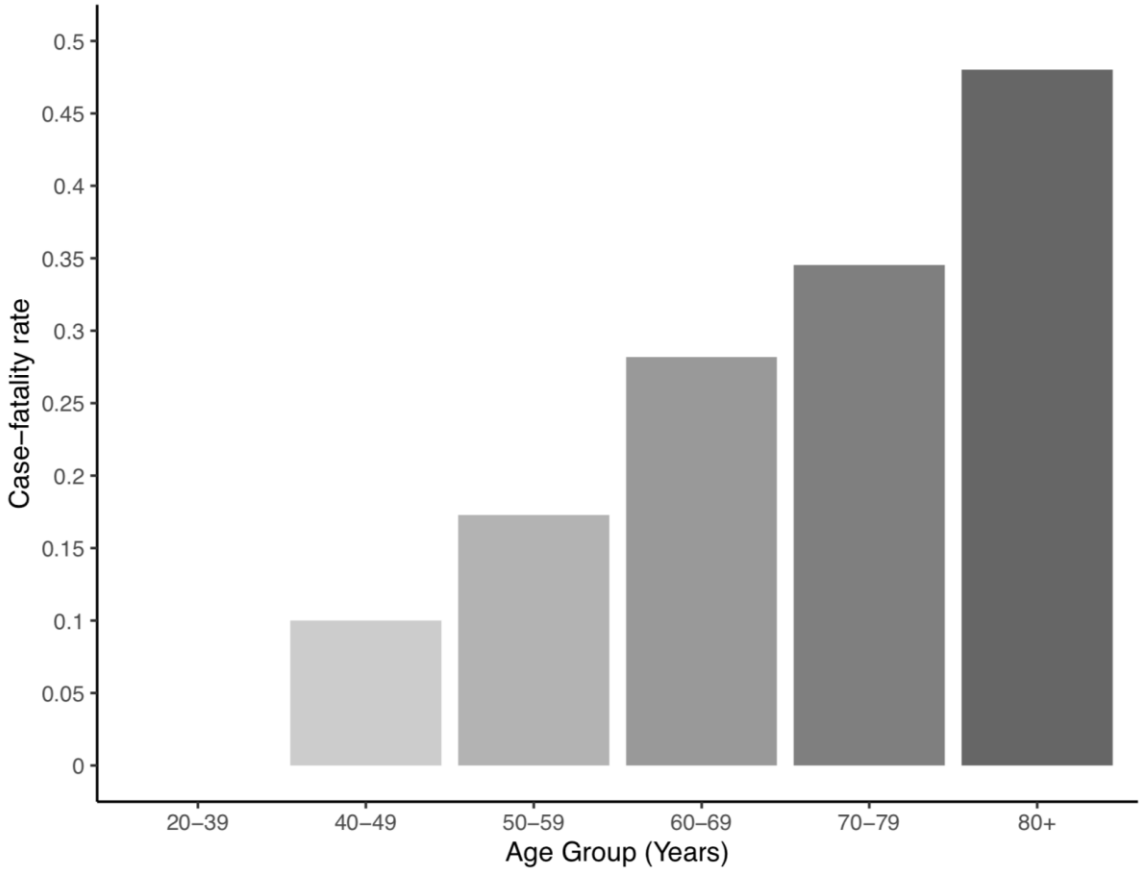


Figure 1: Age and risk of all-cause case fatality rate of patients following a presenting with COVID-19 in the UKCCMP cohort.

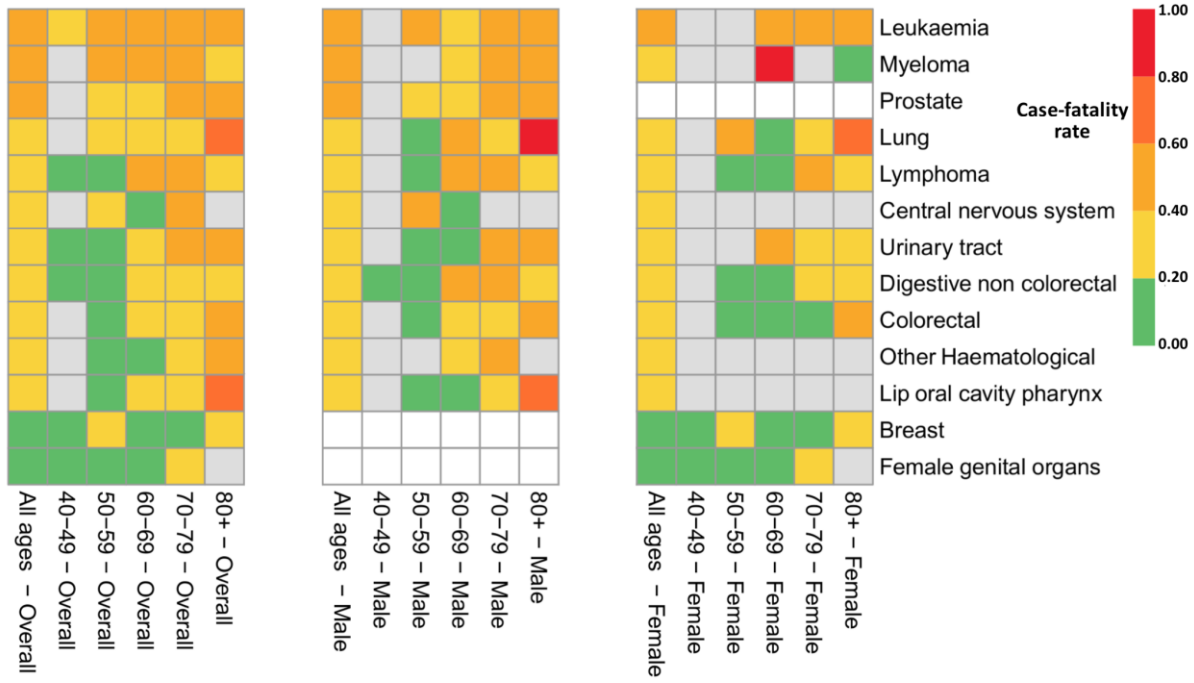


Figure 2: Heatmap demonstrating case fatality rate following a COVID-19 presentation, broken down by tumour subtype, age and gender. Grey bars represent where number of cases were less than 4.

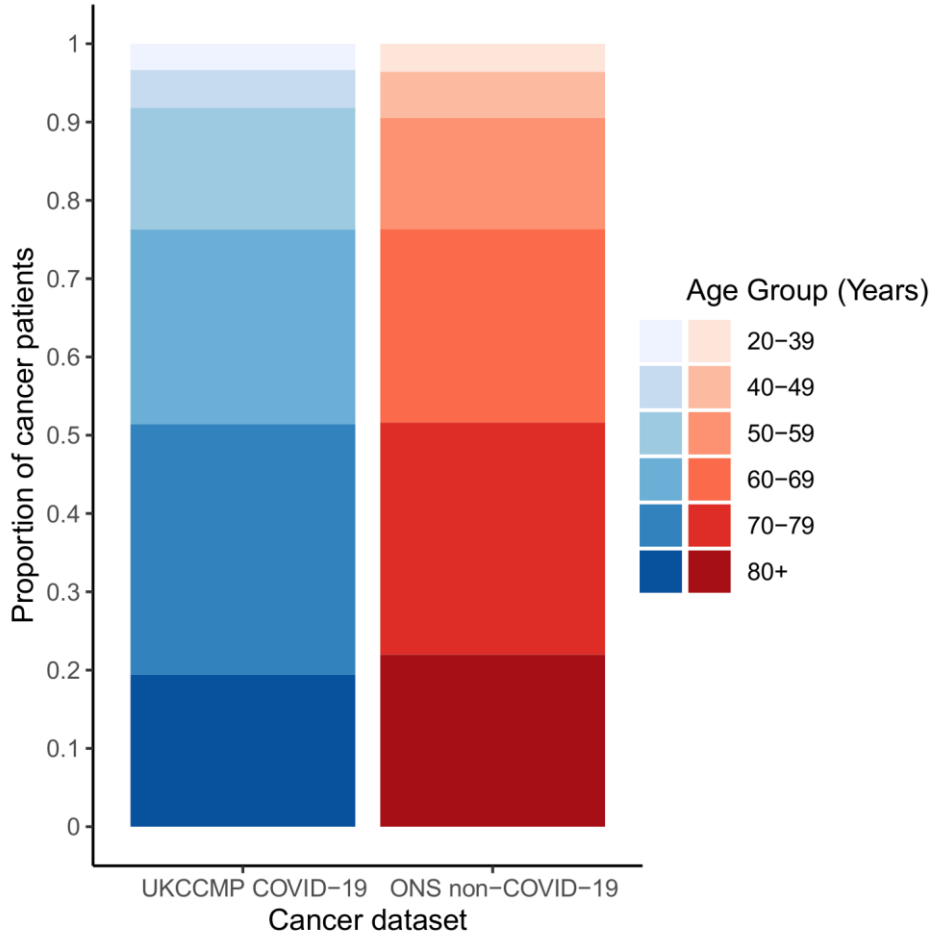
SUPPLEMENTARY METHODS

Statistical analysis & Data visualisation

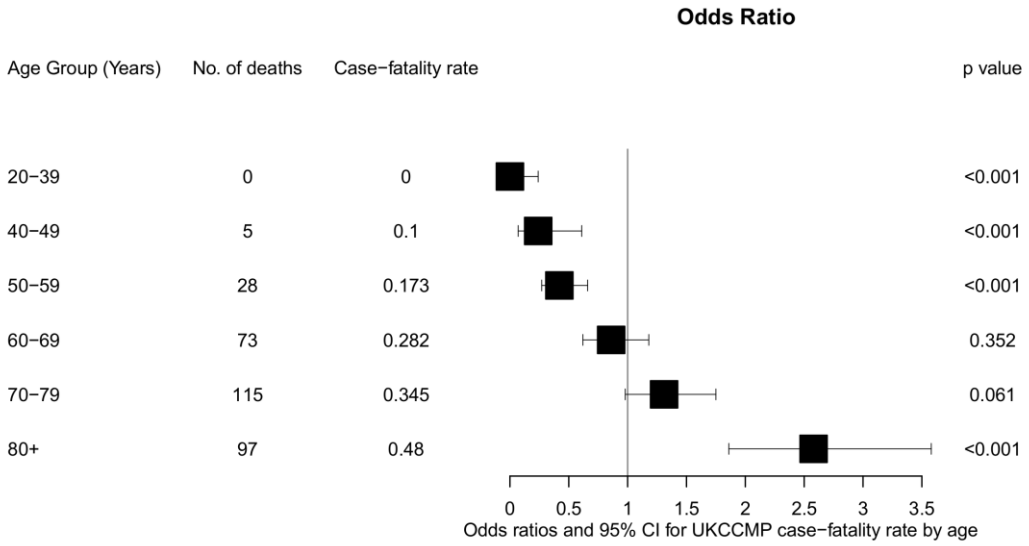
Analyses were performed in R version 3.6.3 utilising the glm() (family = binomial(link = "logit")) and fisher.test() functions, respectively. Data processing and visualisation utilised R (version 3.6.3) packages including broom, dplyr, forestplot, ggplot2, ggsci, pheatmap, RColorBrewer, robustbase and viridis. Data subsetting was performed using the subset() function of 'robustbase' and data reshaping for visualisation involved the use of the tidy() function of 'broom', and group_by() and melt() functions of 'dplyr'. Functions from the ggplot2 R package were used to generate multiple plots including barplots (geom_bar) and lineplots (geom_line). The pheatmap() and forestplot() functions of the 'pheatmap' and 'forestplot' R packages was also used to generate the heatmap and forest plots, respectively.

Data Collection

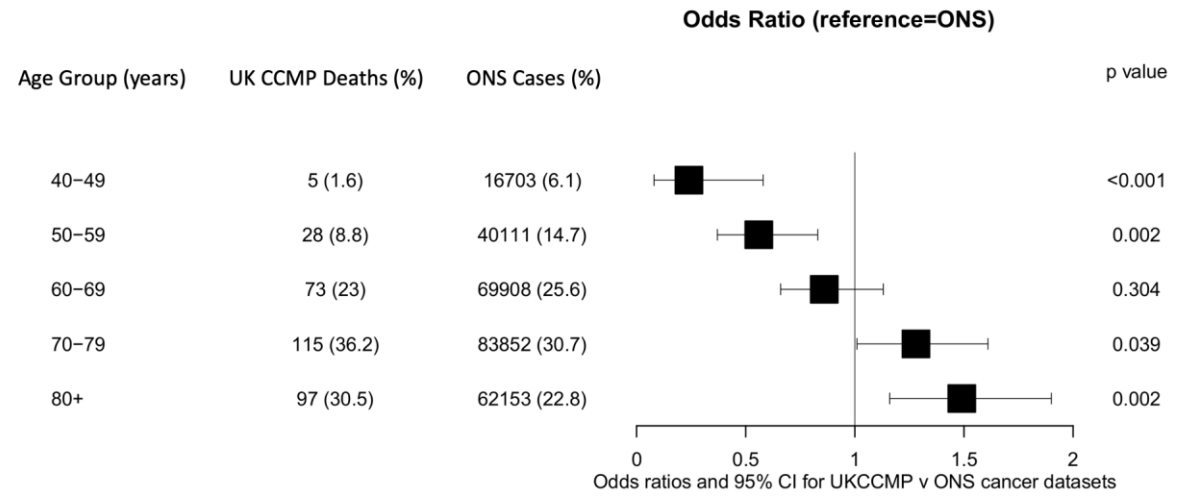
Prospective data collection was performed by the pan-UK cancer centre emergency response network. Case reporting was led by a COVID-19 Emergency Response Reporting Individual (ERRI), supported by a Local Emergency Response Reporting Group (LERRG) at each centre. The UKCCMP encouraged all local reporting sites to enter data in a real time basis, as soon as a positive SARS-CoV-2 test had been identified. The data fields were then re-updated as soon as treatment and outcomes had been identified. The ERRI was a trained/training oncologist who did data review, annotation and entry. In a small number of centres, data entry was performed by data managers but with direct oversight by the ERRI. This secure EDC platform is hosted by the Institute of Translational Medicine at the University of Birmingham.



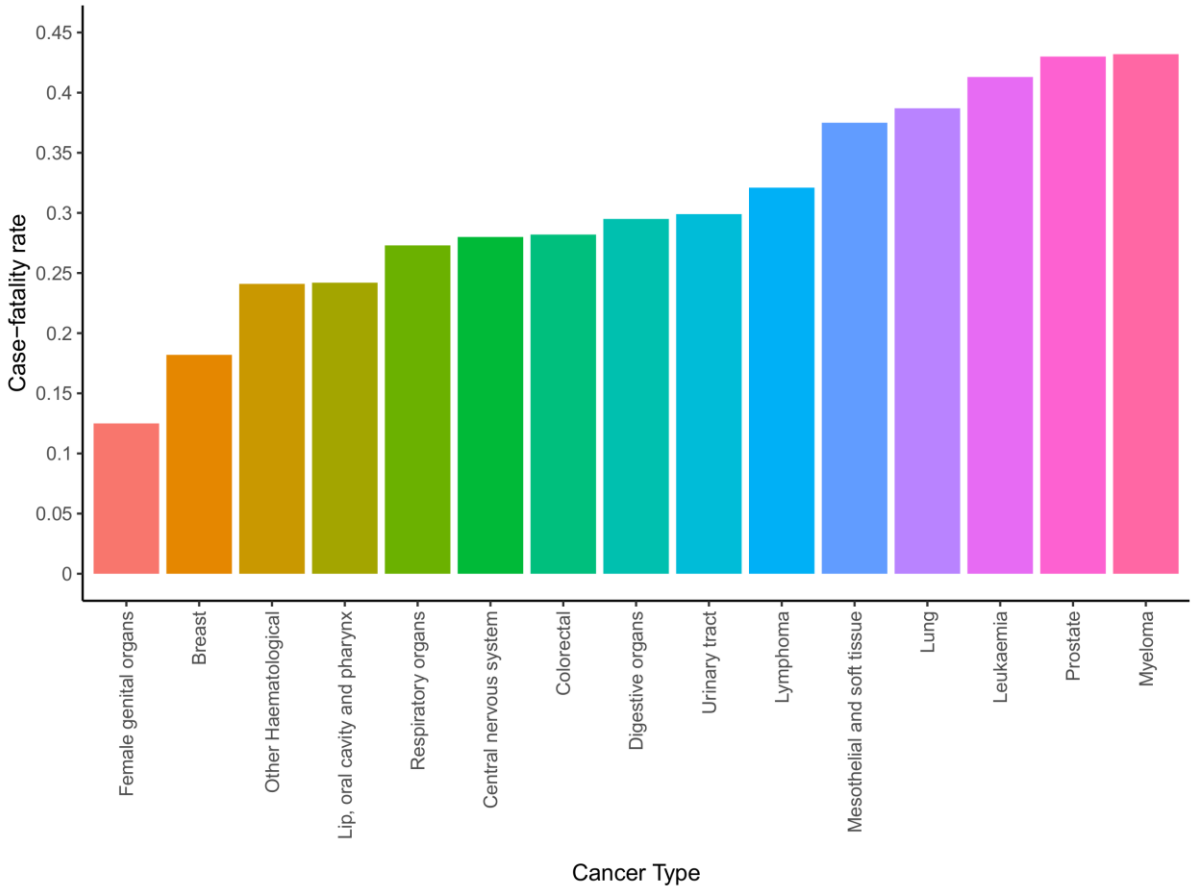
Supplementary Figure 1. Stacked bar chart showing age distribution of cancer patients in the UKCCMP who had contracted SARS-CoV-2 and ONS cancer control population.



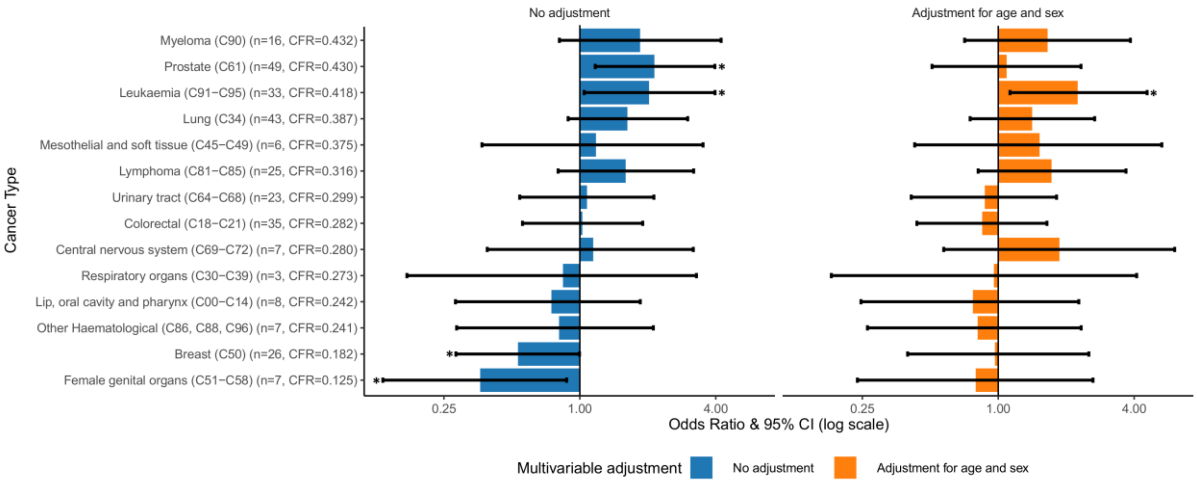
Supplementary Figure 2. Forest plot showing distribution of age groups of cancer patients who died in the UKCCMP and case fatality rates. Odds ratio are relative to the UK CCMP population.



Supplementary Figure 3: Forest plot showing distribution of age groups of patients who died in the UKCCMP relative to the age distribution of the ONS cancer control population.



Supplementary Figure 4: Case fatality rate of patients following a presenting with COVID-19 in the UKCCMP cohort, assessed by tumour subtype.



Supp Figure 5. Waterfall plot showing risk of death for each tumour subtype following COVID-19 compared to other subtypes (reference), before and after age and sex correction multivariable correction. * *denotes statistical significance of p adjusted, where* * p<0.05.

	Haematological malignancies (n=227)	Non-haematological malignancies (n=817)	Univariate analysis		Multivariable adjusted analysis	
			Odds Ratio (CI)	p value	Odds Ratio (CI)	p value
Patient features						
- Male	148 (65.2%)	447 (54.7%)	1.53 (1.13-2.09)	0.006	1.58 (1.16-2.16)	0.004
- Female	79 (34.8%)	366 (44.8%)				
- Other	0 (0.0%)	4 (0.5%)				
- Median age/years (std)	69 (14.16)	70 (13.09)		0.034		
Co-morbidities						
- Cardiovascular disease	21 (9.3%)	124 (15.2%)	0.56 (0.34-0.91)	0.023	0.62 (0.36-1.01)	0.065
- COPD	7 (3.1%)	73 (8.9%)	0.32 (0.13-0.66)	0.005	0.35 (0.14-0.72)	0.009
- Diabetes	33 (14.5%)	145 (17.7%)	0.79 (0.51-1.18)	0.262	0.78 (0.50-1.17)	0.243
- Hypertension	60 (26.4%)	283 (34.6%)	0.66 (0.47-0.92)	0.017	0.68 (0.47-0.97)	0.033
- None	52 (22.9%)	153 (18.7%)	1.32 (0.91-1.90)	0.138	1.31 (0.87-1.96)	0.189
- No data	39 (17.2%)	136 (16.6%)				
Smoking status						
- Current smoker	7 (3.1%)	38 (4.7%)	0.99 (0.39-2.17)	0.984	0.77 (0.30-1.74)	0.558
- Ex-smoker	32 (14.1%)	234 (28.6%)	0.59 (0.37-0.94)	0.028	0.63 (0.38-1.03)	0.067
- Never smoker	52 (22.9%)	218 (26.7%)	1.66 (1.06-2.63)	0.027	1.67 (1.04-2.70)	0.035
- No data	136 (59.9%)	327 (40.0%)				
Patient outcome						
- Death (all cause)	82 (36.1%)	237 (29.0%)	1.61 (1.15-2.24)	0.005	1.74 (1.21-2.48)	0.002
- Death (COVID-19)	80 (35.2%)	215 (26.3%)	1.77 (1.27-2.48)	0.001	1.93 (1.35-2.77)	<0.001
- Death (Cancer)	1 (0.4%)	18 (2.2%)	0.21 (0.01-1.02)	0.129	0.22 (0.01-1.06)	0.138
- Death (other)	1 (0.4%)	4 (0.5%)	0.96 (0.05-6.54)	0.972	1.12 (0.06-7.79)	0.923
- Hospitalised	5 (2.2%)	36 (4.4%)	0.52 (0.18-1.23)	0.178	0.53 (0.18-1.26)	0.192
Cancer treatment within 4 weeks						
- Chemotherapy	108 (47.6%)	241 (29.5%)	2.17 (1.60-2.93)	<0.0001	2.15 (1.57-2.95)	<0.0001
- Immunotherapy	0 (0.0%)	39 (4.8%)	0.00 (0.00-2.90E+07)	0.9815	0.00 (0.00-3.17E+07)	0.9813
- Radiotherapy	2 (0.9%)	84 (10.3%)	0.08 (0.01-0.25)	0.0004	0.07 (0.01-0.24)	0.0003
- Surgery	0 (0.0%)	36 (4.4%)	0.00 (0.00-8.99E+07)	0.9816	0.00 (0.00-1.39E+08)	0.9816
- Targeted therapy	26 (11.5%)	65 (8.0%)	1.49 (0.91-2.39)	0.1018	1.45 (0.87-2.33)	0.1397
COVID-19 Symptoms						
- Chills	9 (4.0%)	23 (2.8%)	1.49 (0.64-3.16)	0.324	1.45 (0.62-3.11)	0.357
- Corzyal symptoms	13 (5.7%)	47 (5.8%)	1.04 (0.53-1.90)	0.911	1.03 (0.52-1.90)	0.931
- Cough	93 (41.0%)	381 (46.6%)	0.83 (0.60-1.14)	0.255	0.82 (0.59-1.13)	0.217
- Diarrhoea	26 (11.5%)	63 (7.7%)	1.63 (0.99-2.62)	0.05	1.67 (1.01-2.70)	0.041
- Fatigue	46 (20.3%)	150 (18.4%)	1.19 (0.81-1.73)	0.359	1.22 (0.83-1.77)	0.307
- Fever	133 (58.6%)	450 (55.1%)	1.34 (0.96-1.90)	0.091	1.26 (0.89-1.79)	0.191
- Headache	15 (6.6%)	28 (3.4%)	2.09 (1.07-3.94)	0.026	2.11 (1.07-4.00)	0.026
- Myalgia	18 (7.9%)	60 (7.3%)	1.13 (0.64-1.93)	0.654	1.15 (0.64-1.97)	0.623
- Nausea and/or Vomiting	8 (3.5%)	43 (5.3%)	0.68 (0.29-1.40)	0.332	0.70 (0.30-1.45)	0.372
- Shortness of breath	84 (37.0%)	324 (39.7%)	0.95 (0.69-1.30)	0.734	0.92 (0.66-1.27)	0.61
- Sore throat	9 (4.0%)	32 (3.9%)	1.05 (0.47-2.16)	0.891	0.98 (0.43-2.04)	0.964
- Asymptomatic	5 (2.2%)	39 (4.8%)	0.47 (0.16-1.09)	0.113	0.50 (0.17-1.18)	0.152
- No data	35 (15.4%)	99 (12.1%)				
COVID-19 Severity Score						
- severe/critical	119 (52.4%)	339 (41.5%)	1.53 (1.13-2.06)	0.006	1.57 (1.15-2.15)	0.004
- mild	103 (45.4%)	448 (54.8%)				
- No data	5 (2.2%)	30 (3.7%)				
COVID-19 treatment						
- Antibiotics	145 (63.9%)	495 (60.6%)	1.35 (0.93-2.00)	0.12	1.35 (0.92-2.00)	0.129
- Fluids	86 (37.9%)	247 (30.2%)	1.52 (1.10-2.11)	0.012	1.54 (1.10-2.14)	0.011
- High Flow Oxygen (HFO)	29 (12.8%)	61 (7.5%)	1.89 (1.16-3.01)	0.009	1.82 (1.11-2.94)	0.015
- ITU + Ventilation	19 (8.4%)	25 (3.1%)	3.00 (1.60-5.57)	0.001	2.73 (1.43-5.11)	0.002
- ITU - Ventilation	7 (3.1%)	12 (1.5%)	2.19 (0.81-5.54)	0.104	2.16 (0.78-5.54)	0.118
- Non-invasive Ventilation	19 (8.4%)	35 (4.3%)	2.11 (1.16-3.75)	0.012	2.10 (1.14-3.76)	0.014
- Oxygen	99 (43.6%)	310 (37.9%)	1.38 (1.00-1.90)	0.054	1.41 (1.01-1.96)	0.044
- None	26 (11.5%)	134 (16.4%)	0.67 (0.42-1.04)	0.083	0.65 (0.41-1.02)	0.071
- No data	40 (17.6%)	128 (15.7%)				

Supp. Table 1: Univariate and multivariate analyses of differences in patient demographics/symptoms/cancer treatments and clinical course of haematological vs. non-haematological malignancies. Univariate analysis was conducted with presence compared to absence (reference for each category) in haematological malignancies vs. non-haematological malignancies. Multivariate analyses were conducted corrected for patient age and sex.

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Author Contributions

LYWL, JBC, SB, RA, VC, HMC, DJH, DK, AJXL, ACOB, CP, KP, AB, GM, and RK were involved in the study design; LYWL, JBC, MWF, SG, AJXL, RL, NM, TND, ACOB, TP, KP, OT, GM, RK and UKCCMP were involved in the data collection; LYWL, JBC, TS, RA, VB, NAC, VC, HMC, PE, AG, SH, DJH, AJXL, HM, CPM, ACOB, CP, EP, KP, ASP, AS, CV, VW, GM and RK were involved in data acquisition and management; LYWL, JBC, SB, TS, AB, GM, and RK were involved in data analysis and interpretation; LYWL, JBC, TS, SB, AB, GM, and RK were involved in manuscript writing; and RK made the decision to submit.

Declaration of interest

ACOB has received grant support from Roche, Bristol-Myers-Squibb, Eli Lily, Novartis and UCB Pharma, and personal fees from Roche, Bristol-Myers-Squibb, all outside the submitted work. NM has advisory board roles for Pfizer, Rocher, Boehringer Ingelheim; received speakers' bureau from Merck, Pfizer and Roche, all outside the submitted work. TND has received personal fees from Astra Zeneca, Amgen, Bayer, BMS, Boehringer Ingelheim, MSD, Lily, Novartis, Pfizer, Roche, Takeda and non-financial support from BMS, MSD, Roche and Takeda, all outside the submitted work. The other authors have nothing to disclose.

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