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COVID-19 incidence and mortality and effect of primary tumour subtype and patient demographics: a prospective cancer cohort study (UKCCMP)

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

Keywords: cancer, coronavirus, COVID-19, SARS-CoV-2, United Kingdom, Public Health, subtype, age, demographics

48 Abstract

49

50 *Background*

51 Patients with a diagnosis of cancer are purported to have poor outcomes from COVID-19. However, cancer is a
52 heterogeneous group of diseases encompassing a spectrum of tumour subtypes. The aim of this study is to
53 evaluate COVID-19 risk according to tumour subtype and patient demographics in the cancer population.

54

55 *Methods*

56 A comparison of adult cancer patients enrolled in the *UK Coronavirus Cancer Monitoring Project (UKCCMP)* from
57 18th March to 8th May and a parallel non-COVID-19 UK cancer control population cohort was performed, analysing
58 effect of tumour subtype and patient demographics (age and sex) on the incidence and mortality from COVID-19
59 using univariate and multivariable models.

60

61 *Findings*

62 In 1,044 patients with COVID-19, an overall case fatality rate of 0.31 was observed, of which 92.5% (295/319) of
63 deaths due to COVID-19. Age is a risk factor for COVID-19 with a case fatality rate (CFR) in the 40-49, 50-59, 60-
64 69, 70-79 and over 80 groups being 0.10, 0.17, 0.28, 0.35 and 0.48 respectively. Patients with haematological
65 malignancies (leukaemia/lymphoma/myeloma) run a more severe COVID-19 trajectory (OR 1.57, 95% CI 1.15-
66 2.15; p<0.01) compared to patients with solid organ tumours. CFR following COVID-19 in patients with leukaemia
67 is increased compared to other cancer types, even considering other risk factors (OR 2.25, 95% CI [1.13 to 4.57];
68 p=0.02). Recent chemotherapy use in haematological patients is associated with additional risk of death on
69 multivariate analyses (OR 2.09 95% CI [1.09 to 4.08]; p=0.03).

70

71 *Interpretation*

72 Cancer patients with different tumours have differing SARS-CoV-2 susceptibility and COVID-19 phenotypes. We
73 have generated individualised risk tables for cancer patients taking into account age/sex and tumour subtype. This
74 will be useful for physicians to have an informed risk-benefit discussion to explain COVID-19 risk and to enable an
75 evidenced approach to national social isolation policies.

76

77 *Funding*

78 University of Birmingham, University of Oxford

79 **Introduction**

80

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

88

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

97

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

105

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

111 **Methods**

112 **Study Design and Participants**

113 The UK Coronavirus Cancer Monitoring Project (UKCCMP) database of United Kingdom (UK) cancer patients has
114 been designed as a Public Health Surveillance registry for the COVID-19 pandemic and a prospective
115 observational cohort study¹⁰. The database was designed as a public health surveillance registry to support rapid
116 clinical decision making, in accordance with the UK Policy Framework for Health and Social Care Research, the
117 UK National Research Ethics Service, and the UK Governance Arrangement for Research Ethic Committees.
118 Ethical approval was not specifically required, as confirmed following consultation with the Health Research
119 Authority (HRA). The study involved the collection of clinical and outcome data as routinely recommended for good
120 practice. Each participating centre was required to obtain local approvals and follow local information governance
121 processes. Written consent was not required for inclusion in this study. Eligibility criteria were (1) adult patients
122 (18 and older), (2) with active cancer, (3) who presented to the UKCCMP network from March 18th 2020 to 8th May
123 2020, (4) with a positive SARS-CoV-2 PCR test were eligible for enrolment on the registry. Patients with active
124 cancer were defined as those with metastatic cancer or those undergoing anti-cancer treatment in any setting
125 (curative/radical/adjuvant/neoadjuvant) or those treated within the past 12 months with surgery/systemic anti-
126 cancer therapy/radiotherapy. All patients attended secondary care to be reviewed for potential hospitalization and
127 were not part of a proactive surveillance program. Management of cancer patients with COVID-19 was directed by
128 the patient's clinician team without input from the UKCCMP and were based on local policies and standard UK
129 clinical practice at the time of this study. Decisions on ITU admission and ventilation were guided by the UK National
130 Health Service, National Institute of Health and Care Excellence COVID-19 rapid guidelines.¹¹ This study was
131 conducted in accordance with the Strengthening the Reporting of Observational studies in Epidemiology
132 (STROBE) statement.
133

134 **Data Collection and analysis**

135 Data collection was performed as previously outlined¹⁰. Tumour subtype and demographics analysis utilised the
136 latest release of the "Cancer Registration Statistics, England, 2017"¹². This is the latest cancer registration
137 database in England and involves registrations of patients up to 2017. Cancer registrations in England take years
138 after a given calendar year to reach nationally validated quality control measures for robustness of analyses due
139 to continuing accrual of registrations.
140

141 **Outcomes**

142 The main outcome of interest was the effect of primary tumour subtype, age and gender, and likelihood of
143 contracting SARS-CoV-2 infection and subsequent COVID-19 clinical course. A comparison of adult cancer
144 patients enrolled in the UK Coronavirus Cancer Monitoring Project (UKCCMP) and a parallel non-COVID-19 UK
145 cancer control population cohort was performed (the UK Office for National Statistics (ONS) cancer control
146 dataset), analysing effect of tumour subtype and patient demographics (age and sex) on the incidence and mortality
147 from COVID-19 using univariate fisher exact tests and multivariable logistic regression. The primary outcome of
148 interest was all-cause inpatient case fatality rate (during the COVID-19 episode). This included death designated
149 as a direct result of COVID-19 as well as death from any other cause such as cancer progression and treatment
150 toxicity. Skin cancers were not included in these analyses as the majority are not managed in oncological setting
151 so they are not representative as a comparison group.
152

153 **Statistical analysis & Data visualisation**

154 This analysis was a pre-planned analysis milestone. Analyses were performed without an *a priori* power calculation,
155 as this were not possible due to the lack of information about the effect size/interactions and the nature and rapid
156 evolution of the pandemic. Patients that had missing data points required for a particular analysis were excluded.
157 A two-sided Fisher's exact test was used to compare categorical data from different categories. Multivariable
158 logistic regression¹³ was used to estimate odds ratios and 95% confidence intervals of each defined factor after
159 adjustment for potential confounders of patient age and gender. Analyses were performed in R version 3.6.3.
160

161 **Role of the funding source**

162 The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of
163 the report. LL, JBC, TS, RA, VB, NAC, HMC, AS, SH, CPM, CP, ASO, CDT, CV had access to the raw data. LL,
164 JBC, TS, GM, RK had the final responsibility for the decision to submit for publication
165
166
167

Results

We are reporting on 1,044 patients with active cancer and a documented SARS-CoV-2 infection/COVID-19 registered in the UKCCMP database from the 18th of March with outcomes censored at 8th May 2020. 87 patients were excluded from the analysis as they had an unspecified tumour site or malignant neoplasia of the skin. Of this cohort, 595/1044 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. Median follow up was 6 days (IQR 2-11).

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 (57.1% (592/1037) in UKCCMP vs 51.3% (145034/282878) in ONS, OR 1.26 95% CI [1.12 to 1.43]; $p < 0.01$), 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) (appendix page 2).

We found that certain tumour subtypes were overrepresented in the UKCCMP COVID-19+ patient cohort compared with the ONS control population. 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]; $p < 0.01$), myeloma (OR 2.03 95% CI [1.42 to 2.83]; $p < 0.01$) and lymphomas (OR 1.63 95% CI [1.28 to 2.06]; $p < 0.01$) (Table 1). In contrast, patients with lung cancer and prostate cancer were relatively underrepresented in the COVID-19+ UKCCMP series compared to the control ONS series of cancers. Lung cancer made up 10.7% (111/1041) of the UKCCMP series compared to 13.7% (38878/282878) of ONS cases (OR 0.75 95%CI [0.61-0.91]; $p < 0.01$). Similarly, prostate cancer comprised 11.0% (114/1041) of the UKCCMP series compared to 14.6% (41200/282878) of the ONS cohort (OR 0.72 95%CI [0.59-0.88]; $p < 0.01$).

319 of the 1044 COVID-19+ UKCCMP cancer patients died, a case fatality rate (CFR) 0.31, of which the cause of death was recorded as due to COVID-19 in 92.5% ($n=295$). The all-cause CFR in cancer patients following COVID-19 was significantly linked to increasing age, with the CFR 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, Appendix page 2-3). In addition, the all-cause CFR in cancer patients once they had contracted COVID-19 was significantly associated with gender, in males being 0.36 (212/595) and that in females being 0.24 (105/445), (OR 1.92 95% CI [1.51 to 2.45], $p < 0.01$)

We compared the case fatality rate for each primary tumour subtype in the UKCCMP 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]; $p=0.01$), and leukaemia (OR 2.03, 95% CI [1.04 to 3.97]; $p=0.04$) and a significantly lower risk for patients with breast cancer (OR 0.53, 95% CI [0.28 to 1.00]; $p<0.05$) and female genital cancers (OR 0.36, 95% CI [0.13-0.87]; $p=0.03$) (Figure 2, appendix page 3). 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]; $p=0.02$), (Table 2, appendix page 4). 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 COVID-19 in the lung cancer population (OR 1.41 95%CI [0.75-2.67]; $p=0.29$) 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 (appendix page 5). 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; $p=0.01$]), ITU admission for ventilation (OR 2.73 % CI [1.43 to 5.11]; $p < 0.01$) and have a severe/critical disease course (OR 1.57 95% CI [1.15 to 2.15]; $p < 0.01$) (appendix page 5). 47.6% (108/227) of patients with haematological malignancies had received recent chemotherapy within 4 weeks of COVID-19 presentation (appendix page 5). On univariate analysis, recent use of chemotherapy in haematology patients was not associated with significantly increased risk of death compared to those who had no recent chemotherapy use. However,

227 following correction for age and gender, patients with haematological malignancies who had recent chemotherapy
228 were at increased risk of death during the COVID-19 associated admission (OR 2.09 95% CI [1.09 to 4.08]; p=0.03).

229 **Discussion**

230

231 Our results show that cancer patients with different tumours have differing SARS-CoV-2 susceptibility and COVID-
232 19 disease phenotypes, notably an association of increased SARS-CoV-2 hospital presentations in patients with
233 haematological cancers. We have generated individualised risk tables for cancer patients displaying effect of
234 age/sex and tumour subtype.

235

236 There are variations and challenges in determining if COVID-19 was the direct cause of death for a patient, or if it
237 was a terminal event in a patient who was approaching the end of their cancer care. All-causes case fatality rate
238 was analysed in study and we feel this was a strength, in addition to the comparisons to a general cancer population
239 control group.

240

241 Patients with haematological malignancies (leukaemias, lymphomas and myelomas) are overrepresented, perhaps
242 suggestive of an *a priori* increased viral susceptibility. Patients with extranodal NK/T-cell lymphoma-C86,
243 Waldenström macroglobulinemia-C88, unspecified neoplasm of lymphoid, hematopoietic and related tissue-C96
244 were greatly overrepresented. The reasons for this are unclear and likely reflects the small number of patients
245 involved and stochastic effects (n=29), but it is possible that these haematological subtypes may have a specific
246 immunological susceptibility to COVID-19 infection.

247

248 Case fatality rate was compared relative to the median reference group, in order not to exaggerate the odds ratio
249 and to take the most conservative approach. Patients with haematological malignancies were at greater risk of
250 having a more severe *COVID-19 clinical phenotype*, to require more intensive supportive interventions, and to
251 suffer an elevated risk of death. On multivariate analysis, patients with leukaemia still had a significantly higher risk
252 of death related to COVID-19, considering age and gender. Admittedly, there are challenges in interpretation as
253 this study relied on ICD-10 cancer subtype codes and leukaemia encompass a heterogeneous group of conditions.
254 However, the increased case fatality rate in haematological malignancies is similar to that observed in a pre-print
255 article from the United Kingdom¹⁴ and Chinese cohorts^{15 16}, but in contrast to a recent American cohort study¹⁷
256 which does not suggest increased mortality in this group.

257

258 Recent large COVID-19 cancer cohorts of predominantly solid organ tumours have identified no significant excess
259 mortality risk from recent chemotherapy.^{10 17} In this study, we have identified that in haematological malignancies,
260 following multivariable analysis, risk does appear to be heightened by recent (within 4 weeks) or current
261 chemotherapy, similar to that observed in other cohorts.¹⁸

262

263 There are likely to be a number of possible reasons for these observations. The immunological disruption *per se*
264 observed in patients with leukaemia and the use of intensely myelosuppressive regimes may result in a devastating
265 combination of risk, both in terms of the likelihood of initial SARS-CoV-2 infection, its ability to gain a foothold in
266 the host and also in terms of the downstream disease course and likelihood of severe consequences such as
267 cytokine storm and significant multiorgan failure. Further validation work is therefore important.

268

269 Contrary to the findings from the Chinese series and data from a European registry¹⁹, we found that patients with
270 lung cancer were relatively underrepresented in the UKCCMP cohort compared to the ONS data. In addition, once
271 COVID-19 was established in lung cancer patients, we found no significantly increased case fatality rate compared
272 to the general COVID19+ cancer population within UKCCMP, suggesting that lung cancer patients are not a
273 specifically vulnerable group. There are likely to be a number of reasons for this difference in findings. Firstly, there
274 are methodological differences, with this study comparing lung cancer cases to a cancer population rather than a
275 non-cancer population. Secondly, there may now be more effective shielding of lung cancer patients at an early
276 stage in the pandemic when they were designated as clinically vulnerable. Thirdly, lung cancer is the commonest
277 cancer in China, and hence would be overrepresented in their COVID-19+ cancer patient population and finally the
278 European registry does not use a controlled group and this highlights the importance of our intra population-
279 controlled studies.

280

281 Prostate cancer patients were relatively underrepresented in the UKCCMP cohort again compared to ONS data.
282 In terms of risk of death once COVID-19 was established, initially the prostate cancer group of patients did appear
283 to be an increased case fatality rate, but multivariate analysis showed that actually their risk was no greater than
284 the rest of the COVID-19+ cancer population in UKCCMP, reflecting again the importance of age and gender more
285 specifically as factor.

286

287 Patients with breast cancers or malignancies of the female genital tract appeared to be at much lower risk, either
288 of contracting or of dying from COVID-19. However multivariate analysis again demonstrated that this protection
289 was by virtue of the patients being female, rather than an inherently lower risk tumour per se.
290

291 We accept some the limitations in our report. Our analyses are based on symptomatic cancer patients who seek
292 help from cancer centres. Therefore, the cohort may not be entirely representative of all patients with cancer, and
293 we observe a high proportion of patients with advanced/metastatic disease, patients who are under ongoing active
294 oncological follow-up. It is also unlikely that patients on an end of life pathway or residing in nursing homes/hospices
295 would be reported or included in this registry. There are potential limitations with the use of ONS control population
296 of cancer patients as our comparator. In the presented study, we report on patients with current “active Cancer”
297 whereas the ONS control population is a historical control, consisting of all patients with a diagnosis of cancer in
298 2017 and it is possible that prognoses and therapeutic choices may have changed during this period. Therefore, it
299 would be useful to perform analyses using more contemporaneous controls when these data become available.
300 Other possible limitations include that performance status, patient co-morbidity scale/index and ethnicity were not
301 initially collected as part of the study data entry form and therefore could not be used in multivariable models.
302 However, rates of COVID-19 in cancer patients remain thankfully low overall and the age distribution of patients in
303 the UKCCMP reflects the age distribution in the ONS dataset suggesting that our comparator population is as
304 appropriate as possible at this stage.
305

306 In addition, as discussed, we observed a low admission rate of cancer patients to ITU, which is likely to impact on
307 COVID-19 outcomes in cancer patients in the United Kingdom ¹⁰. Reasons for this low ITU admission rate, perhaps
308 due to perceived futility of intensive support in cancer patients, warrants further exploration.
309

310 Despite these limitations, our study is unique in comparing a large cancer COVID-19 population collected in real
311 time to an accurate geographically appropriate cancer population control dataset. Morbidity and case fatality rate
312 from COVID-19, once established, in UK cancer patients attending hospital is relatively high, particularly in those
313 with haematological malignancies and advancing age, but we have established that not all cancer patients are
314 affected equally, which is a very important finding, and will allow clinicians some ability to risk stratify their cancer
315 populations and make informed decisions on appropriate levels of social isolation/shielding. Future work by the
316 UKCCMP, in collaboration with international consortia will define risk in much greater granularity, including different
317 subtypes of a given tumour.

	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)	0.46
-Prostate (C61)	114 (11.0%)	41200 (14.6%)	0.72 (0.59-0.88)	0.0008
-Lung (C34)	111 (10.7%)	38878 (13.7%)	0.75 (0.61-0.91)	0.0033
-Digestive organs (non-colorectal) (C15-C26)	95 (9.1%)	30096 (10.6%)	0.84 (0.68-1.04)	0.12
-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)	0.23
-Lip, oral cavity and pharynx (C00-C14)	33 (3.2%)	7558 (2.7%)	1.19 (0.82-1.69)	0.33
-Central nervous system (C69-C72)	25 (2.4%)	5038 (1.8%)	1.36 (0.87-2.02)	0.13
-Mesothelial and soft tissue (C45-C49)	16 (1.5%)	4682 (1.7%)	0.93 (0.53-1.52)	0.90
-Respiratory and intrathoracic organs (not lung) (C30-C39)	11 (1.1%)	2780 (1.0%)	1.08 (0.53-1.94)	0.75
-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)	0.13
-Endocrine glands (C73-C75)	4 (0.4%)	3374 (1.2%)	0.32 (0.09-0.82)	0.0096
-Lymphoma (C81-C85)	79 (7.6%)	13537 (4.8%)	1.63 (1.28-2.06)	<0.0001
-Leukaemia (C91-C95)	79 (7.6%)	8018 (2.8%)	2.82 (2.21-3.55)	<0.0001
-Myeloma (C90)	37 (3.6%)	5033 (1.8%)	2.03 (1.42-2.83)	0.0001
-Other Haematological (C86, C88, C96)	29 (2.8%)	423 (0.1%)	19.14 (12.59-28.05)	<0.0001

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.

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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)	0.82
Lung (C34)	43	0.387	1.62 (0.89-3.00)	0.118	1.41 (0.75-2.67)	0.29
Mesothelial and soft tissue (C45-C49)	6	0.375	1.18 (0.37-3.51)	0.772	1.52 (0.43-5.30)	0.51
Urinary tract (C64-C68)	23	0.299	1.08 (0.54-2.13)	0.834	0.87 (0.41-1.81)	0.72
Colorectal (C18-C21)	35	0.282	1.03 (0.56-1.90)	0.934	0.85 (0.44-1.64)	0.63
Central nervous system (C69-C72)	7	0.28	1.15 (0.39-3.18)	0.797	1.87 (0.57-6.05)	0.29
Respiratory organs (C30-C39)	3	0.273	0.84 (0.17-3.29)	0.813	0.96 (0.18-4.10)	0.95
Lip, oral cavity and pharynx (C00-C14)	8	0.242	0.75 (0.28-1.85)	0.542	0.77 (0.25-2.27)	0.64
Breast (C50)	26	0.182	0.53 (0.28-1.00)	0.049	0.97 (0.40-2.52)	0.94
Female genital organs (C51-C58)	7	0.125	0.36 (0.13-0.87)	0.031	0.79 (0.24-2.63)	0.70
<i>Myeloma (C90)</i>	16	0.432	1.85 (0.81-4.22)	0.142	1.65 (0.71-3.85)	0.24
<i>Leukaemia (C91-C95)</i>	33	0.418	2.03 (1.04-3.97)	0.038	2.25 (1.13-4.57)	0.02
<i>Lymphoma (C81-C85)</i>	25	0.316	1.60 (0.80-3.19)	0.184	1.72 (0.81-3.68)	0.16
<i>Other Haematological (C86, C88, C96)</i>	7	0.241	0.81 (0.28-2.12)	0.675	0.81 (0.26-2.33)	0.70
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.

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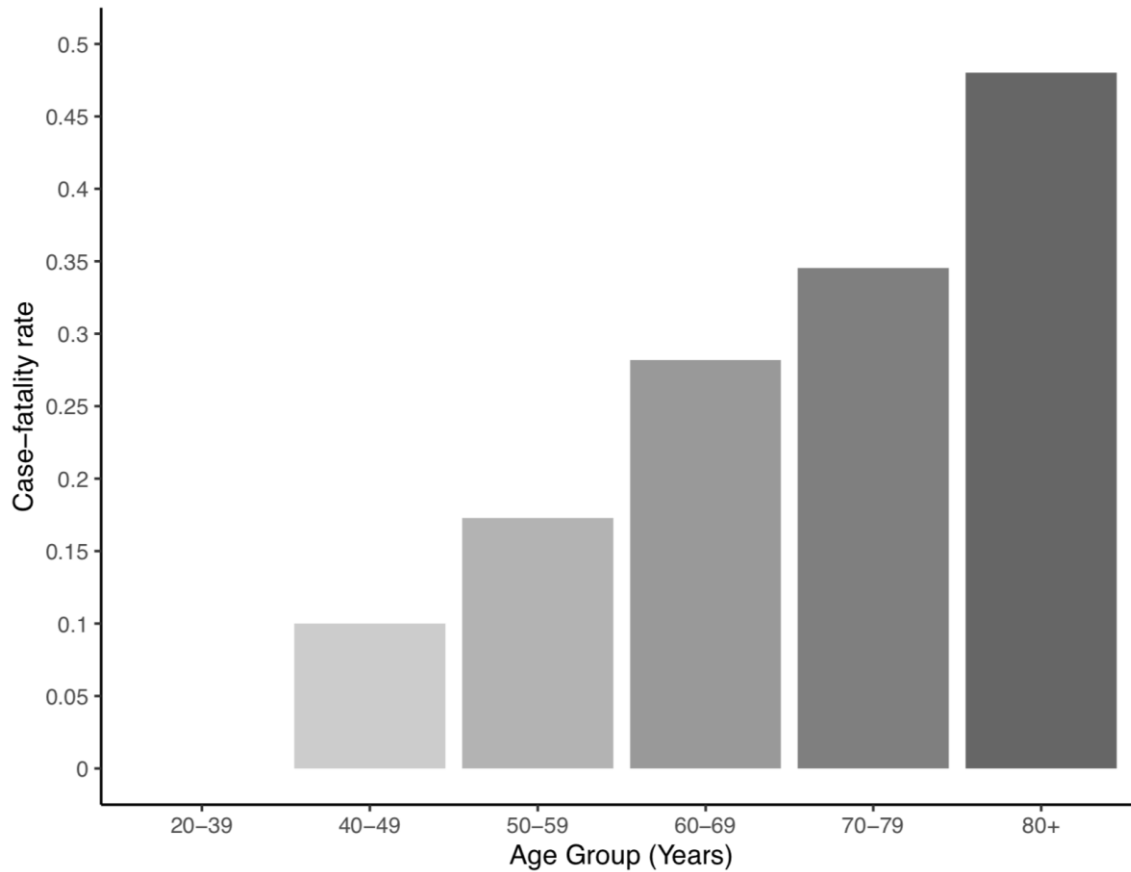


Figure 1: Age and risk of all-cause case fatality rate of patients following a presenting with COVID-19 in the UKCCMP cohort.

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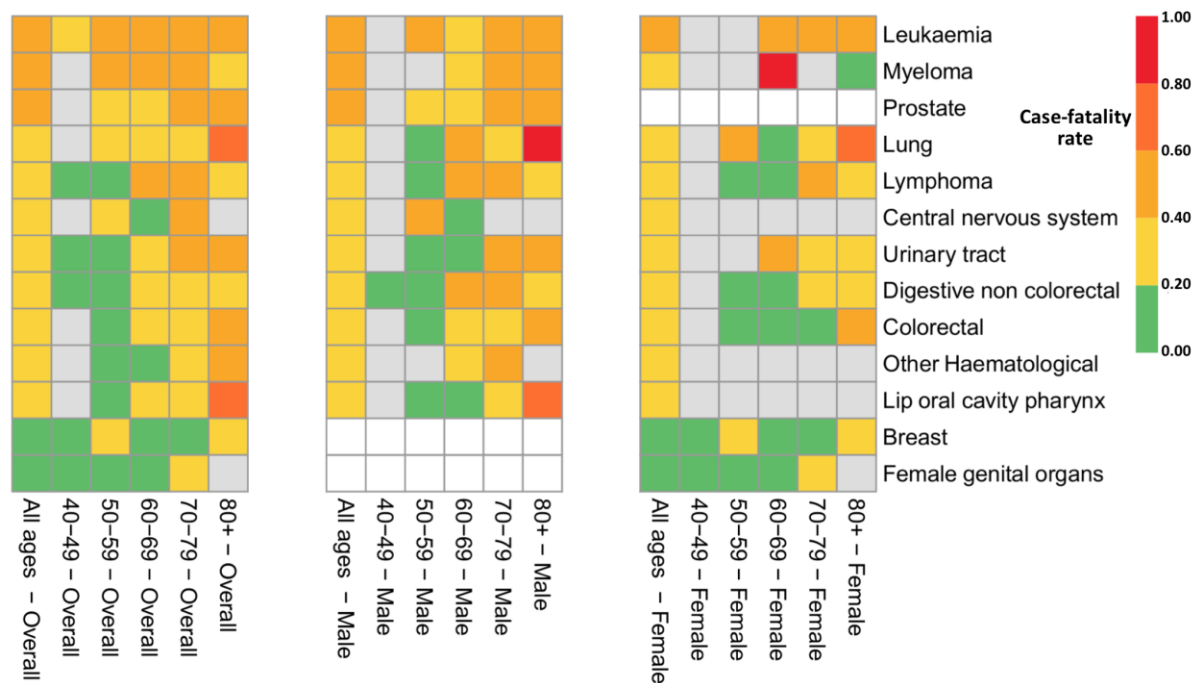


Figure 2: Heatmap demonstrating case fatality rate following a COVID-19 presentation, broken down by tumour subtype, age and gender. Grey bars represent where number of cases were less than 4.

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344

345
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349 were involved in the data collection; LYWL, JBC, TS, RA, VB, NAC, VC, HMC, PE, AG, SH, DJH, AJXL, HM,
350 CPM, ACOB, CP, EP, KP, ASP, AS, CV, VW, GM and RK were involved in data acquisition and management;
351 LYWL, JBC, SB, TS, CDT, AB, GM, and RK were involved in data analysis and interpretation; LYWL, JBC, KP,
352 TS, SB, AB, GM, and RK were involved in manuscript writing; and RK made the decision to submit.

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354
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360
361 **Declaration of interest**

362
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411 international, registry-based, cohort study. *Lancet Oncol.* **0**, (2020).
- 412

413 **Research in Context**

414

415 **Evidence before the study:**

416 A literature review was performed using PubMed for all studies from 1st December 2019 to 1st July 2020 related to
417 SARS-CoV-2 infection susceptibility and clinical course of coronavirus disease (COVID-19) in cancer patients. This
418 used the search terms, COVID-19, SARS-CoV-2, cancer and was not limited to English language publications.
419 Several studies describe the correlations of patient demographics, namely age and gender and increased COVID-
420 19 morbidity and mortality including Docherty et al (2020), Robilotti et al (2020), Miyashita et al (2020). Two pivotal
421 cancer cohorts have identified no significant effect of chemotherapy on mortality, Lee et al (2020), Kuderer et al
422 (2020) and this was also noted by Vaugnat et al (2020). However, a small study had identified a small risk, Yang
423 et al (2020). The effect of cancer subtype is unclear. Dai et al (2020) identified that patients with haematological or
424 lung malignancies have a poorer disease course. The elevated risk in haematological malignancies was also noted
425 by Yang et al (2020) and in lung cancer by Garassino et al (2020), but Kuderer et al (2020) did not identify increased
426 mortality by cancer subtype.

427

428 **Added value of the study**

429 This UK Coronavirus Cancer Monitoring Project (UKCCMP) study is a national monitoring project of cancer patients
430 who contract COVID-19 disease, consisting of 1044 patients to date. We have compared cancer patients enrolled
431 in the UKCCMP and a parallel non-COVID-19 UK cancer control population cohort, analysing the effect of tumour
432 features (primary subtype and stage) and patient demographics (age and sex) on the risk and the trajectory of
433 COVID-19 disease. Tumour features (primary subtype and stage) as well as patient demographics impact on viral
434 susceptibility and COVID-19 disease phenotype. There is increased SARS-CoV-2 susceptibility in patients with
435 haematological cancers (leukaemia/lymphoma/myeloma). Haematology patients run a more severe COVID-19
436 disease trajectory and require more intensive clinical support with additional risk conferred by recent chemotherapy
437 use. As observed in the general population, age and gender are predominant risk factors for SARS-CoV-2 infection
438 and severity of COVID-19 disease for most cancer patients.

439

440 **Implications of all the available evidence**

441 Our data indicates that cancer patients with different tumours have differing SARS-CoV-2 susceptibility and COVID-
442 19 disease phenotypes, notably association of increased SARS-CoV-2 susceptibility in patients with
443 haematological cancers. We have generated individualised risk tables for cancer patients taking into account
444 age/sex and tumour subtype. This will be useful for physicians to have a more informed risk-benefit discussion to
445 explain COVID-19 risk to their cancer patients.

COVID-19 incidence and mortality and effect of primary tumour subtype and patient demographics: a prospective cancer cohort study (UKCCMP)

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

Keywords: cancer, coronavirus, COVID-19, SARS-CoV-2, United Kingdom, Public Health, subtype, age, demographics

48 Abstract

49

50 *Background*

51 Patients with a diagnosis of cancer are purported to have poor outcomes from COVID-19. However, cancer is a
52 heterogeneous group of diseases encompassing a spectrum of tumour subtypes. The aim of this study is to
53 evaluate COVID-19 risk according to tumour subtype and patient demographics in the cancer population.

54

55 *Methods*

56 A comparison of adult cancer patients enrolled in the *UK Coronavirus Cancer Monitoring Project (UKCCMP)* from
57 18th March to 8th May and a parallel non-COVID-19 UK cancer control population cohort was performed, analysing
58 effect of tumour subtype and patient demographics (age and sex) on the incidence and mortality from COVID-19
59 using univariate and multivariable models.

60

61 *Findings*

62 In 1,044 patients with COVID-19, an overall case fatality rate of 0.31 was observed, of which 92.5% (295/319) of
63 deaths due to COVID-19. Age is a risk factor for COVID-19 with a case fatality rate (CFR) in the 40-49, 50-59, 60-
64 69, 70-79 and over 80 groups being 0.10, 0.17, 0.28, 0.35 and 0.48 respectively. Patients with haematological
65 malignancies (leukaemia/lymphoma/myeloma) run a more severe COVID-19 trajectory (OR 1.57, 95% CI 1.15-
66 2.15; p<0.01) compared to patients with solid organ tumours. CFR following COVID-19 in patients with leukaemia
67 is increased compared to other cancer types, even considering other risk factors (OR 2.25, 95% CI [1.13 to 4.57];
68 p=0.02). Recent chemotherapy use in haematological patients is associated with additional risk of death on
69 multivariate analyses (OR 2.09 95% CI [1.09 to 4.08]; p=0.03).

70

71 *Interpretation*

72 Cancer patients with different tumours have differing SARS-CoV-2 susceptibility and COVID-19 phenotypes. We
73 have generated individualised risk tables for cancer patients taking into account age/sex and tumour subtype. This
74 will be useful for physicians to have an informed risk-benefit discussion to explain COVID-19 risk and to enable an
75 evidenced approach to national social isolation policies.

76

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78 University of Birmingham, University of Oxford

79 **Introduction**

80

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

88

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

97

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

105

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

111 **Methods**

112 **Study Design and Participants**

113 The UK Coronavirus Cancer Monitoring Project (UKCCMP) database of United Kingdom (UK) cancer patients has
114 been designed as a Public Health Surveillance registry for the COVID-19 pandemic and a prospective
115 observational cohort study¹⁰. The database was designed as a public health surveillance registry to support rapid
116 clinical decision making, in accordance with the UK Policy Framework for Health and Social Care Research, the
117 UK National Research Ethics Service, and the UK Governance Arrangement for Research Ethic Committees.
118 Ethical approval was not specifically required, as confirmed following consultation with the Health Research
119 Authority (HRA). The study involved the collection of clinical and outcome data as routinely recommended for good
120 practice. Each participating centre was required to obtain local approvals and follow local information governance
121 processes. Written consent was not required for inclusion in this study. Eligibility criteria were (1) adult patients
122 (18 and older), (2) with active cancer, (3) who presented to the UKCCMP network from March 18th 2020 to 8th May
123 2020, (4) with a positive SARS-CoV-2 PCR test were eligible for enrolment on the registry. Patients with active
124 cancer were defined as those with metastatic cancer or those undergoing anti-cancer treatment in any setting
125 (curative/radical/adjuvant/neoadjuvant) or those treated within the past 12 months with surgery/systemic anti-
126 cancer therapy/radiotherapy. All patients attended secondary care to be reviewed for potential hospitalization and
127 were not part of a proactive surveillance program. Management of cancer patients with COVID-19 was directed by
128 the patient's clinician team without input from the UKCCMP and were based on local policies and standard UK
129 clinical practice at the time of this study. Decisions on ITU admission and ventilation were guided by the UK National
130 Health Service, National Institute of Health and Care Excellence COVID-19 rapid guidelines.¹¹ This study was
131 conducted in accordance with the Strengthening the Reporting of Observational studies in Epidemiology
132 (STROBE) statement.
133

134 **Data Collection and analysis**

135 Data collection was performed as previously outlined¹⁰. Tumour subtype and demographics analysis utilised the
136 latest release of the "Cancer Registration Statistics, England, 2017"¹². This is the latest cancer registration
137 database in England and involves registrations of patients up to 2017. Cancer registrations in England take years
138 after a given calendar year to reach nationally validated quality control measures for robustness of analyses due
139 to continuing accrual of registrations.
140

141 **Outcomes**

142 The main outcome of interest was the effect of primary tumour subtype, age and gender, and likelihood of
143 contracting SARS-CoV-2 infection and subsequent COVID-19 clinical course. A comparison of adult cancer
144 patients enrolled in the UK Coronavirus Cancer Monitoring Project (UKCCMP) and a parallel non-COVID-19 UK
145 cancer control population cohort was performed (the UK Office for National Statistics (ONS) cancer control
146 dataset), analysing effect of tumour subtype and patient demographics (age and sex) on the incidence and mortality
147 from COVID-19 using univariate fisher exact tests and multivariable logistic regression. The primary outcome of
148 interest was all-cause inpatient case fatality rate (during the COVID-19 episode). This included death designated
149 as a direct result of COVID-19 as well as death from any other cause such as cancer progression and treatment
150 toxicity. Skin cancers were not included in these analyses as the majority are not managed in oncological setting
151 so they are not representative as a comparison group.
152

153 **Statistical analysis & Data visualisation**

154 This analysis was a pre-planned analysis milestone. Analyses were performed without an *a priori* power calculation,
155 as this were not possible due to the lack of information about the effect size/interactions and the nature and rapid
156 evolution of the pandemic. Patients that had missing data points required for a particular analysis were excluded.
157 A two-sided Fisher's exact test was used to compare categorical data from different categories. Multivariable
158 logistic regression¹³ was used to estimate odds ratios and 95% confidence intervals of each defined factor after
159 adjustment for potential confounders of patient age and gender. Analyses were performed in R version 3.6.3.
160

161 **Role of the funding source**

162 The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of
163 the report. LL, JBC, TS, RA, VB, NAC, HMC, AS, SH, CPM, CP, ASO, CDT, CV had access to the raw data. LL,
164 JBC, TS, GM, RK had the final responsibility for the decision to submit for publication
165
166
167

Results

We are reporting on 1,044 patients with active cancer and a documented SARS-CoV-2 infection/COVID-19 registered in the UKCCMP database from the 18th of March with outcomes censored at 8th May 2020. 87 patients were excluded from the analysis as they had an unspecified tumour site or malignant neoplasia of the skin. Of this cohort, 595/1044 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. Median follow up was 6 days (IQR 2-11).

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 (57.1% (592/1037) in UKCCMP vs 51.3% (145034/282878) in ONS, OR 1.26 95% CI [1.12 to 1.43]; $p < 0.01$), 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) (appendix page 2).

We found that certain tumour subtypes were overrepresented in the UKCCMP COVID-19+ patient cohort compared with the ONS control population. 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]; $p < 0.01$), myeloma (OR 2.03 95% CI [1.42 to 2.83]; $p < 0.01$) and lymphomas (OR 1.63 95% CI [1.28 to 2.06]; $p < 0.01$) (Table 1). In contrast, patients with lung cancer and prostate cancer were relatively underrepresented in the COVID-19+ UKCCMP series compared to the control ONS series of cancers. Lung cancer made up 10.7% (111/1041) of the UKCCMP series compared to 13.7% (38878/282878) of ONS cases (OR 0.75 95%CI [0.61-0.91]; $p < 0.01$). Similarly, prostate cancer comprised 11.0% (114/1041) of the UKCCMP series compared to 14.6% (41200/282878) of the ONS cohort (OR 0.72 95%CI [0.59-0.88]; $p < 0.01$).

319 of the 1044 COVID-19+ UKCCMP cancer patients died, a case fatality rate (CFR) 0.31, of which the cause of death was recorded as due to COVID-19 in 92.5% ($n=295$). The all-cause CFR in cancer patients following COVID-19 was significantly linked to increasing age, with the CFR 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, Appendix page 2-3). In addition, the all-cause CFR in cancer patients once they had contracted COVID-19 was significantly associated with gender, in males being 0.36 (212/595) and that in females being 0.24 (105/445), (OR 1.92 95% CI [1.51 to 2.45], $p < 0.01$)

We compared the case fatality rate for each primary tumour subtype in the UKCCMP 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]; $p=0.01$), and leukaemia (OR 2.03, 95% CI [1.04 to 3.97]; $p=0.04$) and a significantly lower risk for patients with breast cancer (OR 0.53, 95% CI [0.28 to 1.00]; $p<0.05$) and female genital cancers (OR 0.36, 95% CI [0.13-0.87]; $p=0.03$) (Figure 2, appendix page 3). 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]; $p=0.02$), (Table 2, appendix page 4). 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 COVID-19 in the lung cancer population (OR 1.41 95%CI [0.75-2.67]; $p=0.29$) 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 (appendix page 5). 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; $p=0.01$]), ITU admission for ventilation (OR 2.73 % CI [1.43 to 5.11]; $p < 0.01$) and have a severe/critical disease course (OR 1.57 95% CI [1.15 to 2.15]; $p < 0.01$) (appendix page 5). 47.6% (108/227) of patients with haematological malignancies had received recent chemotherapy within 4 weeks of COVID-19 presentation (appendix page 5). On univariate analysis, recent use of chemotherapy in haematology patients was not associated with significantly increased risk of death compared to those who had no recent chemotherapy use. However,

227 following correction for age and gender, patients with haematological malignancies who had recent chemotherapy
228 were at increased risk of death during the COVID-19 associated admission (OR 2.09 95% CI [1.09 to 4.08]; p=0.03).

229 **Discussion**

230

231 Our results show that cancer patients with different tumours have differing SARS-CoV-2 susceptibility and COVID-
232 19 disease phenotypes, notably an association of increased SARS-CoV-2 hospital presentations in patients with
233 haematological cancers. We have generated individualised risk tables for cancer patients displaying effect of
234 age/sex and tumour subtype.

235

236 There are variations and challenges in determining if COVID-19 was the direct cause of death for a patient, or if it
237 was a terminal event in a patient who was approaching the end of their cancer care. All-causes case fatality rate
238 was analysed in study and we feel this was a strength, in addition to the comparisons to a general cancer population
239 control group.

240

241 Patients with haematological malignancies (leukaemias, lymphomas and myelomas) are overrepresented, perhaps
242 suggestive of an *a priori* increased viral susceptibility. Patients with extranodal NK/T-cell lymphoma-C86,
243 Waldenström macroglobulinemia-C88, unspecified neoplasm of lymphoid, hematopoietic and related tissue-C96
244 were greatly overrepresented. The reasons for this are unclear and likely reflects the small number of patients
245 involved and stochastic effects (n=29), but it is possible that these haematological subtypes may have a specific
246 immunological susceptibility to COVID-19 infection.

247

248 Case fatality rate was compared relative to the median reference group, in order not to exaggerate the odds ratio
249 and to take the most conservative approach. Patients with haematological malignancies were at greater risk of
250 having a more severe *COVID-19 clinical phenotype*, to require more intensive supportive interventions, and to
251 suffer an elevated risk of death. On multivariate analysis, patients with leukaemia still had a significantly higher risk
252 of death related to COVID-19, considering age and gender. Admittedly, there are challenges in interpretation as
253 this study relied on ICD-10 cancer subtype codes and leukaemia encompass a heterogeneous group of conditions.
254 However, the increased case fatality rate in haematological malignancies is similar to that observed in a pre-print
255 article from the United Kingdom¹⁴ and Chinese cohorts^{15 16}, but in contrast to a recent American cohort study¹⁷
256 which does not suggest increased mortality in this group.

257

258 Recent large COVID-19 cancer cohorts of predominantly solid organ tumours have identified no significant excess
259 mortality risk from recent chemotherapy.^{10 17} In this study, we have identified that in haematological malignancies,
260 following multivariable analysis, risk does appear to be heightened by recent (within 4 weeks) or current
261 chemotherapy, similar to that observed in other cohorts.¹⁸

262

263 There are likely to be a number of possible reasons for these observations. The immunological disruption *per se*
264 observed in patients with leukaemia and the use of intensely myelosuppressive regimes may result in a devastating
265 combination of risk, both in terms of the likelihood of initial SARS-CoV-2 infection, its ability to gain a foothold in
266 the host and also in terms of the downstream disease course and likelihood of severe consequences such as
267 cytokine storm and significant multiorgan failure. Further validation work is therefore important.

268

269 Contrary to the findings from the Chinese series and data from a European registry¹⁹, we found that patients with
270 lung cancer were relatively underrepresented in the UKCCMP cohort compared to the ONS data. In addition, once
271 COVID-19 was established in lung cancer patients, we found no significantly increased case fatality rate compared
272 to the general COVID19+ cancer population within UKCCMP, suggesting that lung cancer patients are not a
273 specifically vulnerable group. There are likely to be a number of reasons for this difference in findings. Firstly, there
274 are methodological differences, with this study comparing lung cancer cases to a cancer population rather than a
275 non-cancer population. Secondly, there may now be more effective shielding of lung cancer patients at an early
276 stage in the pandemic when they were designated as clinically vulnerable. Thirdly, lung cancer is the commonest
277 cancer in China, and hence would be overrepresented in their COVID-19+ cancer patient population and finally the
278 European registry does not use a controlled group and this highlights the importance of our intra population-
279 controlled studies.

280

281 Prostate cancer patients were relatively underrepresented in the UKCCMP cohort again compared to ONS data.
282 In terms of risk of death once COVID-19 was established, initially the prostate cancer group of patients did appear
283 to be an increased case fatality rate, but multivariate analysis showed that actually their risk was no greater than
284 the rest of the COVID-19+ cancer population in UKCCMP, reflecting again the importance of age and gender more
285 specifically as factor.

286

287 Patients with breast cancers or malignancies of the female genital tract appeared to be at much lower risk, either
288 of contracting or of dying from COVID-19. However multivariate analysis again demonstrated that this protection
289 was by virtue of the patients being female, rather than an inherently lower risk tumour per se.
290

291 We accept some the limitations in our report. Our analyses are based on symptomatic cancer patients who seek
292 help from cancer centres. Therefore, the cohort may not be entirely representative of all patients with cancer, and
293 we observe a high proportion of patients with advanced/metastatic disease, patients who are under ongoing active
294 oncological follow-up. It is also unlikely that patients on an end of life pathway or residing in nursing homes/hospices
295 would be reported or included in this registry. There are potential limitations with the use of ONS control population
296 of cancer patients as our comparator. In the presented study, we report on patients with current “active Cancer”
297 whereas the ONS control population is a historical control, consisting of all patients with a diagnosis of cancer in
298 2017 and it is possible that prognoses and therapeutic choices may have changed during this period. Therefore, it
299 would be useful to perform analyses using more contemporaneous controls when these data become available.
300 Other possible limitations include that performance status, patient co-morbidity scale/index and ethnicity were not
301 initially collected as part of the study data entry form and therefore could not be used in multivariable models.
302 However, rates of COVID-19 in cancer patients remain thankfully low overall and the age distribution of patients in
303 the UKCCMP reflects the age distribution in the ONS dataset suggesting that our comparator population is as
304 appropriate as possible at this stage.
305

306 In addition, as discussed, we observed a low admission rate of cancer patients to ITU, which is likely to impact on
307 COVID-19 outcomes in cancer patients in the United Kingdom ¹⁰. Reasons for this low ITU admission rate, perhaps
308 due to perceived futility of intensive support in cancer patients, warrants further exploration.
309

310 Despite these limitations, our study is unique in comparing a large cancer COVID-19 population collected in real
311 time to an accurate geographically appropriate cancer population control dataset. Morbidity and case fatality rate
312 from COVID-19, once established, in UK cancer patients attending hospital is relatively high, particularly in those
313 with haematological malignancies and advancing age, but we have established that not all cancer patients are
314 affected equally, which is a very important finding, and will allow clinicians some ability to risk stratify their cancer
315 populations and make informed decisions on appropriate levels of social isolation/shielding. Future work by the
316 UKCCMP, in collaboration with international consortia will define risk in much greater granularity, including different
317 subtypes of a given tumour.

	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)	0.46
-Prostate (C61)	114 (11.0%)	41200 (14.6%)	0.72 (0.59-0.88)	0.0008
-Lung (C34)	111 (10.7%)	38878 (13.7%)	0.75 (0.61-0.91)	0.0033
-Digestive organs (non-colorectal) (C15-C26)	95 (9.1%)	30096 (10.6%)	0.84 (0.68-1.04)	0.12
-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)	0.23
-Lip, oral cavity and pharynx (C00-C14)	33 (3.2%)	7558 (2.7%)	1.19 (0.82-1.69)	0.33
-Central nervous system (C69-C72)	25 (2.4%)	5038 (1.8%)	1.36 (0.87-2.02)	0.13
-Mesothelial and soft tissue (C45-C49)	16 (1.5%)	4682 (1.7%)	0.93 (0.53-1.52)	0.90
-Respiratory and intrathoracic organs (not lung) (C30-C39)	11 (1.1%)	2780 (1.0%)	1.08 (0.53-1.94)	0.75
-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)	0.13
-Endocrine glands (C73-C75)	4 (0.4%)	3374 (1.2%)	0.32 (0.09-0.82)	0.0096
-Lymphoma (C81-C85)	79 (7.6%)	13537 (4.8%)	1.63 (1.28-2.06)	<0.0001
-Leukaemia (C91-C95)	79 (7.6%)	8018 (2.8%)	2.82 (2.21-3.55)	<0.0001
-Myeloma (C90)	37 (3.6%)	5033 (1.8%)	2.03 (1.42-2.83)	0.0001
-Other Haematological (C86, C88, C96)	29 (2.8%)	423 (0.1%)	19.14 (12.59-28.05)	<0.0001

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.

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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)	0.82
Lung (C34)	43	0.387	1.62 (0.89-3.00)	0.118	1.41 (0.75-2.67)	0.29
Mesothelial and soft tissue (C45-C49)	6	0.375	1.18 (0.37-3.51)	0.772	1.52 (0.43-5.30)	0.51
Urinary tract (C64-C68)	23	0.299	1.08 (0.54-2.13)	0.834	0.87 (0.41-1.81)	0.72
Colorectal (C18-C21)	35	0.282	1.03 (0.56-1.90)	0.934	0.85 (0.44-1.64)	0.63
Central nervous system (C69-C72)	7	0.28	1.15 (0.39-3.18)	0.797	1.87 (0.57-6.05)	0.29
Respiratory organs (C30-C39)	3	0.273	0.84 (0.17-3.29)	0.813	0.96 (0.18-4.10)	0.95
Lip, oral cavity and pharynx (C00-C14)	8	0.242	0.75 (0.28-1.85)	0.542	0.77 (0.25-2.27)	0.64
Breast (C50)	26	0.182	0.53 (0.28-1.00)	0.049	0.97 (0.40-2.52)	0.94
Female genital organs (C51-C58)	7	0.125	0.36 (0.13-0.87)	0.031	0.79 (0.24-2.63)	0.70
<i>Myeloma (C90)</i>	16	0.432	1.85 (0.81-4.22)	0.142	1.65 (0.71-3.85)	0.24
<i>Leukaemia (C91-C95)</i>	33	0.418	2.03 (1.04-3.97)	0.038	2.25 (1.13-4.57)	0.02
<i>Lymphoma (C81-C85)</i>	25	0.316	1.60 (0.80-3.19)	0.184	1.72 (0.81-3.68)	0.16
<i>Other Haematological (C86, C88, C96)</i>	7	0.241	0.81 (0.28-2.12)	0.675	0.81 (0.26-2.33)	0.70
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.

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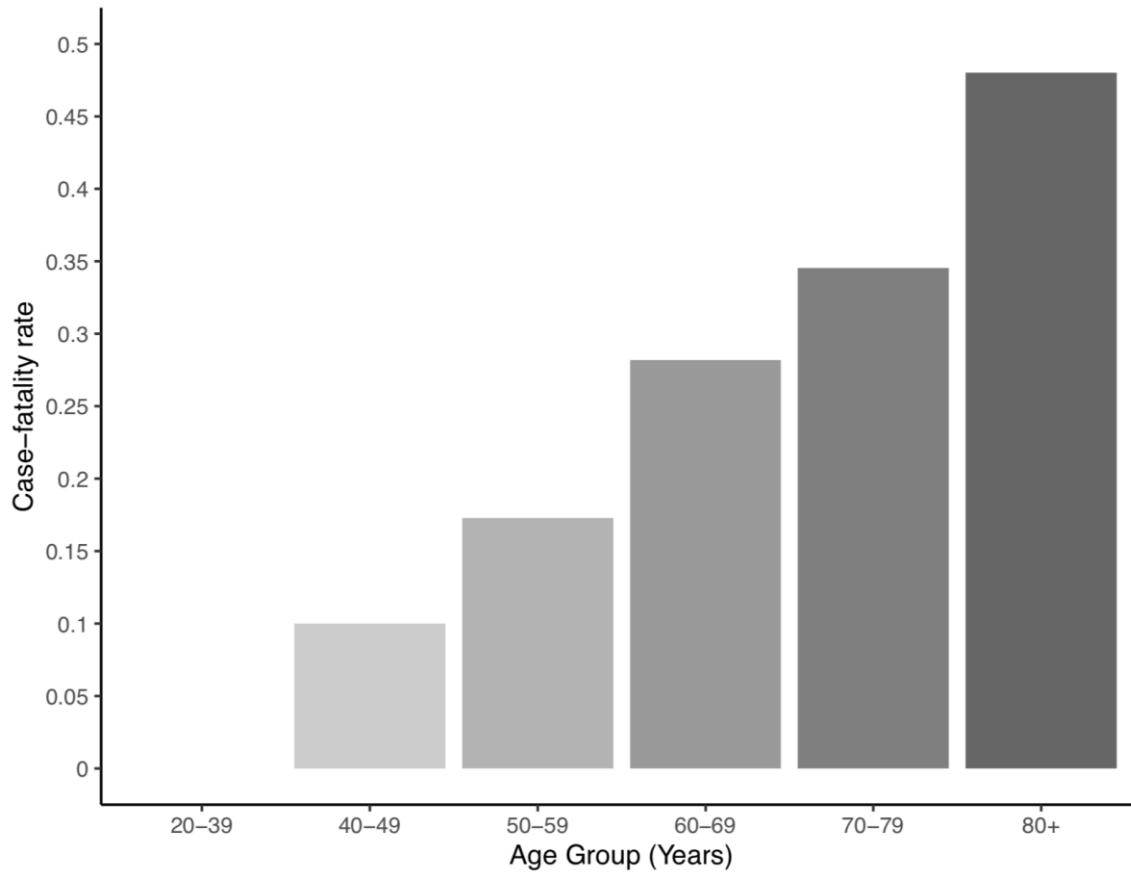


Figure 1: Age and risk of all-cause case fatality rate of patients following a presenting with COVID-19 in the UKCCMP cohort.

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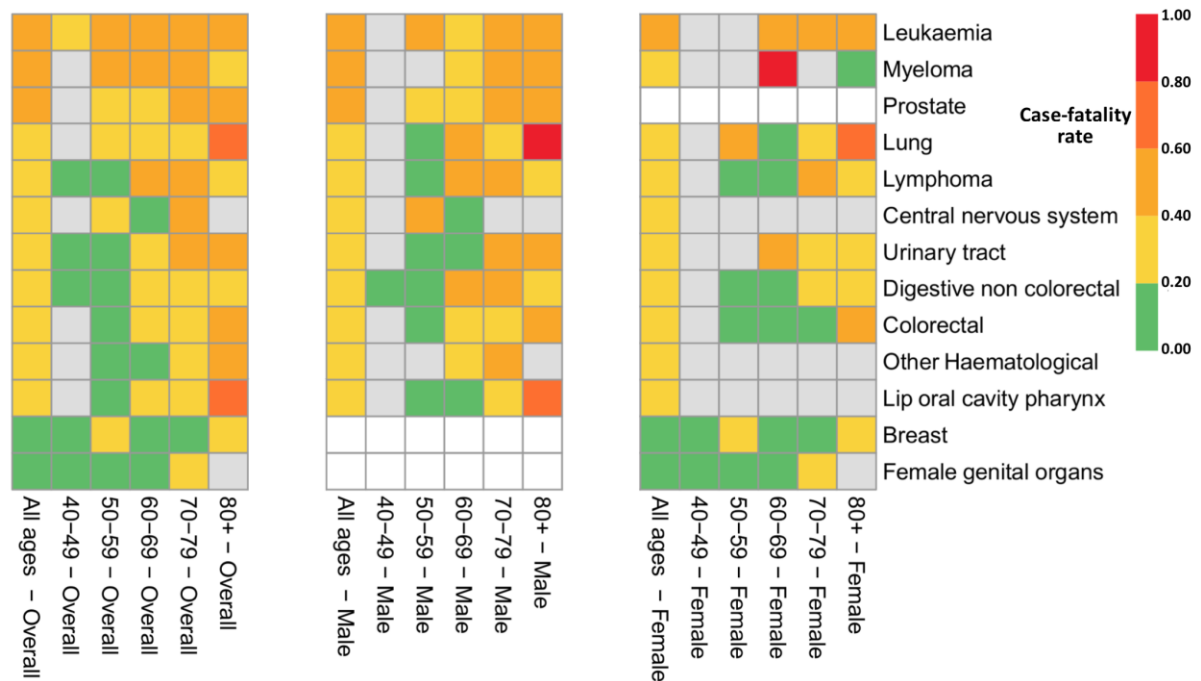


Figure 2: Heatmap demonstrating case fatality rate following a COVID-19 presentation, broken down by tumour subtype, age and gender. Grey bars represent where number of cases were less than 4.

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338 healthcare staff working tirelessly on the frontlines of the COVID-19 pandemic.

339
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341 contributing data at a challenging time as listed in the web appendix (appendix page 1)

342
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344

345
346 **Author Contributions**

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

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359
360
361 **Declaration of interest**

362
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- 412

413 **Research in Context**

414

415 **Evidence before the study:**

416 A literature review was performed using PubMed for all studies from 1st December 2019 to 1st July 2020 related to
417 SARS-CoV-2 infection susceptibility and clinical course of coronavirus disease (COVID-19) in cancer patients. This
418 used the search terms, COVID-19, SARS-CoV-2, cancer and was not limited to English language publications.
419 Several studies describe the correlations of patient demographics, namely age and gender and increased COVID-
420 19 morbidity and mortality including Docherty et al (2020), Robilotti et al (2020), Miyashita et al (2020). Two pivotal
421 cancer cohorts have identified no significant effect of chemotherapy on mortality, Lee et al (2020), Kuderer et al
422 (2020) and this was also noted by Vaugnat et al (2020). However, a small study had identified a small risk, Yang
423 et al (2020). The effect of cancer subtype is unclear. Dai et al (2020) identified that patients with haematological or
424 lung malignancies have a poorer disease course. The elevated risk in haematological malignancies was also noted
425 by Yang et al (2020) and in lung cancer by Garassino et al (2020), but Kuderer et al (2020) did not identify increased
426 mortality by cancer subtype.

427

428 **Added value of the study**

429 This UK Coronavirus Cancer Monitoring Project (UKCCMP) study is a national monitoring project of cancer patients
430 who contract COVID-19 disease, consisting of 1044 patients to date. We have compared cancer patients enrolled
431 in the UKCCMP and a parallel non-COVID-19 UK cancer control population cohort, analysing the effect of tumour
432 features (primary subtype and stage) and patient demographics (age and sex) on the risk and the trajectory of
433 COVID-19 disease. Tumour features (primary subtype and stage) as well as patient demographics impact on viral
434 susceptibility and COVID-19 disease phenotype. There is increased SARS-CoV-2 susceptibility in patients with
435 haematological cancers (leukaemia/lymphoma/myeloma). Haematology patients run a more severe COVID-19
436 disease trajectory and require more intensive clinical support with additional risk conferred by recent chemotherapy
437 use. As observed in the general population, age and gender are predominant risk factors for SARS-CoV-2 infection
438 and severity of COVID-19 disease for most cancer patients.

439

440 **Implications of all the available evidence**

441 Our data indicates that cancer patients with different tumours have differing SARS-CoV-2 susceptibility and COVID-
442 19 disease phenotypes, notably association of increased SARS-CoV-2 susceptibility in patients with
443 haematological cancers. We have generated individualised risk tables for cancer patients taking into account
444 age/sex and tumour subtype. This will be useful for physicians to have a more informed risk-benefit discussion to
445 explain COVID-19 risk to their cancer patients.

Figure 1 | Editable

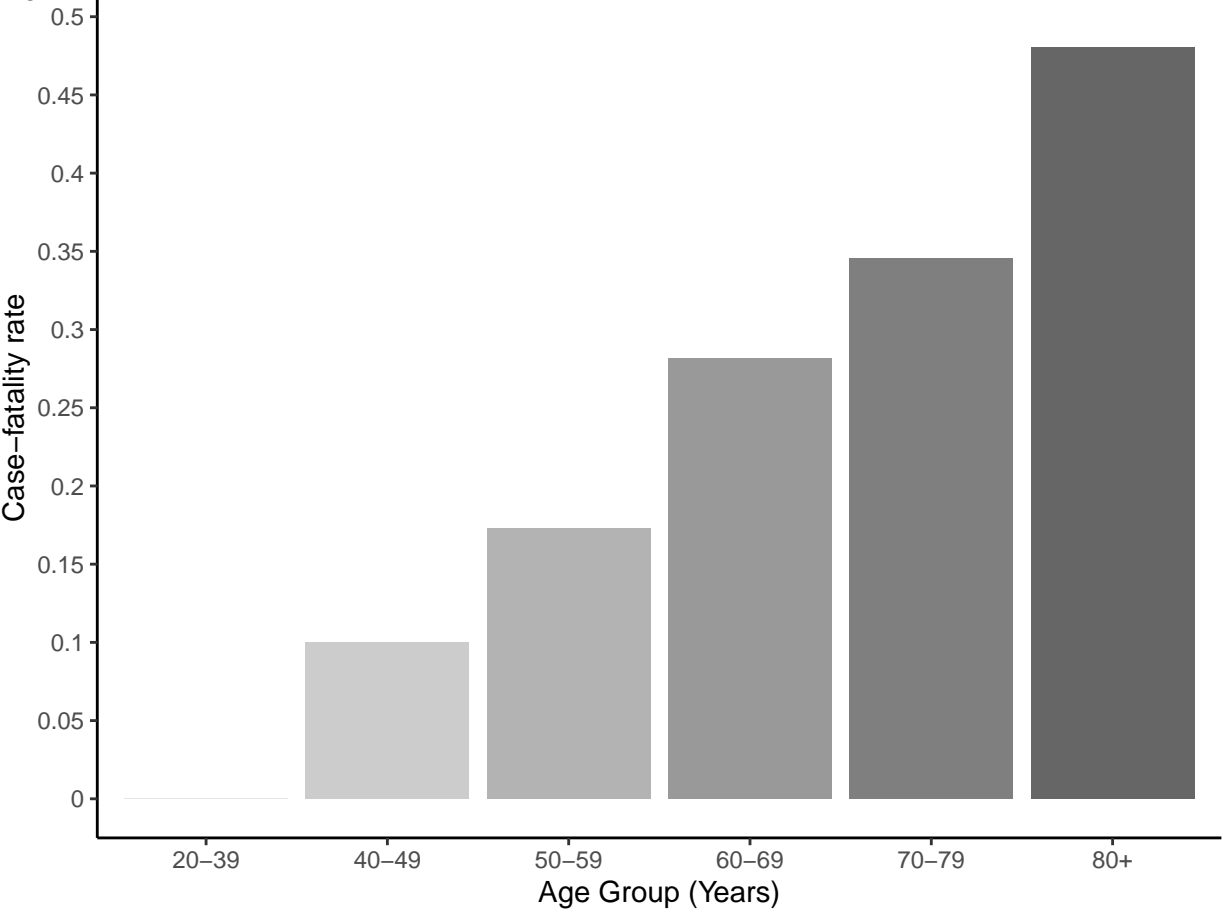
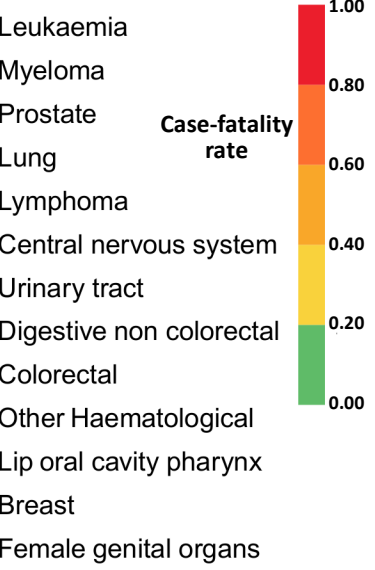
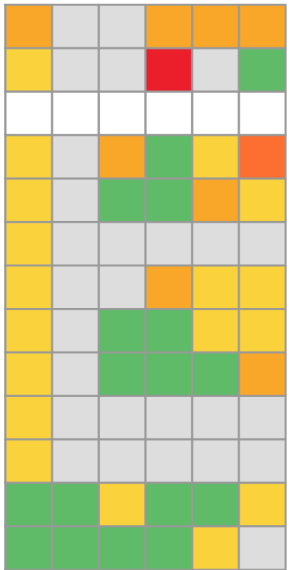
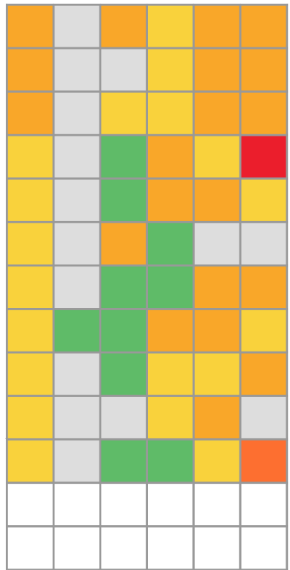
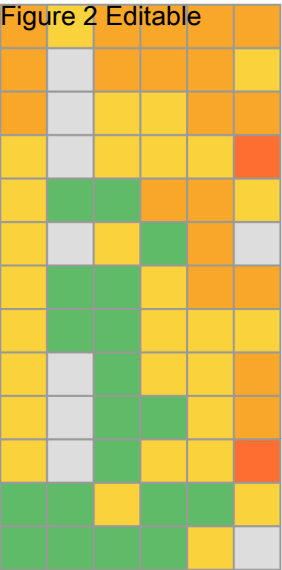


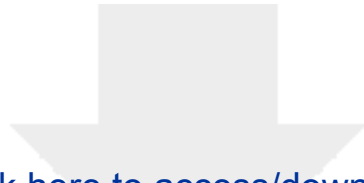
Figure 2 Editable



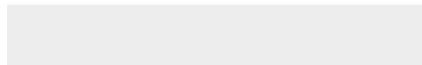


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