

# Haematological cancers and the risk of severe COVID-19: Exploration and critical evaluation of the evidence to date

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## Summary

From the outset of the COVID-19 pandemic, patients and healthcare professionals have been concerned that a history of haematological malignancy will lead to an increased risk of severe COVID-19. This led to the UK government advising patients with blood cancers to shield, massive re-organisation of NHS haematology and cancer services, and changes in treatment plans for thousands of patients. Given the unknown effects that relaxation of social-distancing measures will have on the infection rate, we review the evidence to date to see whether a history of haematological malignancy is associated with increased risk of COVID-19. Multivariable analysis of large population studies, taking other known risk factors into account, do indicate that patients with haematological malignancy, especially those diagnosed recently, are at increased risk of death from COVID-19 compared to the general population. The evidence that this risk is higher than for those with solid malignancies is conflicting. There is suggestive evidence from smaller cohort studies that those with myeloid malignancy may be at increased risk within the blood cancer population, but this needs to be confirmed on larger studies. Ongoing large collaborative efforts are required to gain further evidence regarding specific risk factors for severe complications of COVID-19.

**Keywords:** COVID-19, SARS-CoV-2, cancer, haematological malignancies.

On 23 March 2020, people in the UK with ‘cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment’ were included in the list of clinically extremely vulnerable people, and were advised to shield (to minimise interaction with other people, and not to leave their house except for healthcare appointments, although this advice has since been relaxed to some extent) due to the risk of severe illness from COVID-19.

Whilst based on best evidence at the time, it is important to re-evaluate the evidence as extended periods of shielding can have a significant adverse impact on cancer patients and their families and on delivery of cancer care services.

There are numerous theoretical reasons why patients with cancers in general and haematological cancers in specific may have a different risk of contracting SARS-CoV-2 infection or developing severe complications compared to the general population (Box 1). Firstly, the altered and lowered immune function either from the haematological cancer itself or treatment is hypothesised to lead to a more severe course, as is seen with other respiratory viruses.<sup>1</sup> Lymphopenia, often seen in this patient group, has been associated with a worse overall survival (OS) in patients with COVID-19 (although this could be a biomarker for disease severity rather than pre-existing lymphopenia being a risk factor).<sup>2</sup> It has also been hypothesised that increase of angiotensin-converting enzyme 2 (ACE2) expression in some tumour types may theoretically lead to increased susceptibility of patients to infections with SARS-CoV-2 due to this being an entry point for the virus.<sup>3</sup> Likelihood of exposure may be higher in cancer patients compared to non-cancer patients, even in those who are strictly shielding, as they may still require hospital visits for monitoring and treatment of their cancer. There are also several confounding factors to consider such as shared risk factors for cancer and severe COVID-19, for example, increasing age, obesity and smoking or the known higher rate of co-morbidities in patients with cancer.<sup>4</sup>

A literature review was undertaken to evaluate whether the evidence published to date is supportive of the hypothesis that patients with cancer and haematological cancers are at ‘increased risk of COVID-19’.

## Methods

Pubmed was searched on 17 May 2020 and the search was updated on 3 June 2020 using the terms ‘COVID-19’ and ‘Cancer’. Of the 1 285 articles found, only articles relevant to risk of COVID-19 based on title and abstract were further analysed. Further reports were then found through relevant references from these articles. Large population-wide datasets that reported on co-morbidities were also included. Papers

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**BOX 1.** Potential factors that may lead to a difference in published outcomes to COVID-19 for patients with haematological malignancy compared to the rest of the population.

#### Patient behaviour

- Are cancer patients more likely to shield, even before advice was given by government?
- Are cancer patients more likely to be exposed if requiring hospital visits?
- Are cancer patients more likely to inform secondary care of symptoms due to direct access e.g. via specialist nurses?

#### Healthcare professional behaviour

- Are healthcare professionals more likely to test patients with a history of cancer for COVID-19?
- Are cancer patients more likely to be admitted due to concern regarding cancer/ COVID-19?
- Are patients with a limited prognosis for their cancer less likely to be treated aggressively or given organ support?

#### Biological differences

- Are patients with cancer more likely to contract COVID-19 if exposed to SARS-CoV-2 virus?
- Are patients with cancer less likely to be asymptomatic/ have mild symptoms with COVID-19?
- Is detection rate, accuracy of RT-PCR the same in cancer patients to general population?
- Are patients with cancer more likely to develop ARDS once they have COVID-19?
- Are patients with cancer more likely to develop secondary complications e.g. bacterial supra-added infection?
- Is neutropenia, lymphopenia, or immunoparesis a risk factor for severe disease?

#### Treatment

- Does anti-neoplastic treatment lead to increased risk of COVID-19 and its complications

#### Confounding factors

- Are patients with cancer more likely to have co-morbidities that are associated with increased risk of severe complications?
- Increased prevalence of cancer with increasing age.
- Increased prevalence of smoking history.

reporting data on 25 or more cancer patients were examined in more detail, and those with at least nine patients with haematological malignancies (where specified) have been included in a summary table.

## Results

All studies that have included at least nine patients with haematological malignancies (where specified) and COVID-19 are summarised in Table I.

### *Is cancer a risk factor for developing COVID-19?*

The prevalence of cancer in cohorts of patients admitted with COVID-19 has been elucidated and compared to the prevalence of cancer in the general population by several groups. In a cohort of 1 590 COVID-19 patients admitted into hospitals in China, Liang *et al.*<sup>5</sup> found 18 with a history of cancer (including one lymphoma patient) (1%; 95% CI 0.61–1.65) which was reported as higher than the overall incidence of cancer in the Chinese population at 0.29%. Subsequent studies have also reported a slightly higher prevalence of cancer in Chinese populations with COVID-19 of 2.5% in 8 161 patients and 2.7% in 1 380 patients.<sup>6,7</sup> A meta-analysis of 11

published studies reporting prevalence of cancer in patients with COVID-19 (including Liang *et al.*) found the overall prevalence to be 2% (95% CI 2–3%); this was unadjusted for age and co-morbidities.<sup>8</sup> A large UK-wide study is collecting the baseline characteristics of 20 133 patients admitted into 208 hospitals for COVID-19; at time of publication the malignancy history is known for 17 354 patients of whom 10% had a history of cancer, but the initial publication has not detailed the malignancy types.<sup>9</sup> Whilst these studies indicate that the prevalence of cancer in patients with COVID-19 may be higher than in the general population, not all studies have found this to be the case. For example, in 1 307 patients who were admitted to intensive-care units (ICUs) in Russia, only 2.4% had a history of cancer (none of which were haematological) and the authors concluded this was a similar prevalence to that in the general population.<sup>10</sup> Zhou *et al.*<sup>11</sup> showed that in 191 patients who were admitted into one of two hospitals in the Wuhan province only two had a history of carcinoma. Other cohorts ( $n = 41–201$ ) of patients with COVID-19 have also been published with only one patient with malignancy in each of the cohorts.<sup>12–15</sup>

The converse prevalence has also been investigated by many groups, that is, the prevalence of COVID-19 in cancer patients. Yu *et al.*<sup>16</sup> estimated an infection rate of 0.79%

Table 1. Details of cohort and population studies with  $\geq 9$  patients with haematological malignancy (where specified) and COVID-19.

Reference	Location	Type of study	Main relevant outcome measure	Outcome	Risk factors for outcome	Study limitations
Williamson <i>et al.</i> (2020) <sup>37</sup>	UK	Cohort study of 5 683 pts with COVID-19-related hospital death compared to linked electronic health records of 17 million NHS pts (210 patients with haem malignancy)	Comparison of rate of characteristics of pts who died due to COVID-19 compared to rate in general population	HR for in-hospital COVID-19 death: haem pts diagnosed < 1yr 3.52 (CI 2.41–5.14) haem pts diagnosed > 5yr 1.88 (CI 1.55–2.29)	More recent diagnosis, age, male, co-morbidities	
Kuderer <i>et al.</i> (2020) <sup>39</sup>	USA/ Canada/Spain	Multicentre international cohort study of 928 pts with lab-confirmed COVID-19 with history of cancer (167 with haem malignancy)	30-day all-cause mortality from day of diagnosis Partially adjusted OR logistic regression analysis. Risk factors for 30-day mortality	13% (121/928) 14% (24/167) in haem malignants Active disease (stable) OR 1.79 (CI 1.09–2.95) Active disease (progressing) OR 5.2 (2.77–9.77) Haem malignancy OR 1.4 (0.83–2.37)	Age, smoking status, number of co-morbidities, active disease Cancer type and type of cancer therapy were not associated with outcome	
Lee <i>et al.</i> (2020) <sup>38</sup>	UK	Prospective multicentre cohort study of 800 patients with cancer with lab-confirmed COVID-19 (169 with haem malignancy)	Mortality rate Univariate regression analysis and odds of death within cohort	28% (226/800) 36% (60/169) in haem malignancy Lymphoma OR 1.3 (CI 0.71–2.30, $P = 0.373$ ) Other haem malignancy OR 1.57 (CI 1.01–2.42, $P = 0.04$ )	Age, male, co-morbidities	
Tian <i>et al.</i> (2020) <sup>30</sup>	Hubei, China	Multicentre cohort study of 232 cancer pts with COVID-19 and compared to 519 matched controls with COVID-19 but no history of cancer (12 with haem malignancy)	Severe events in cancer pts <i>versus</i> matched cohort Death in cancer pts <i>versus</i> matched cohort Risk factors for severe event within cancer cohort	64% vs. 32% $P < 0.0001$ , OR3.61 (CI 2.59–5.04) 3/12 with haem malignancy died 25% 20% vs. 11%, $P = 0.0012$ Increasing age, time since cancer diagnosis	Age, diagnosis < 1 yr	

Table I. (Continued)

Reference	Location	Type of study	Main relevant outcome measure	Outcome	Risk factors for outcome	Study limitations
Mehra <i>et al.</i> (2020) <sup>19</sup>	USA	Single-centre cohort study of 218 patients with cancer and COVID-19 (54 with haem malignancy)	Mortality rate Comparison of risk of death in the cancer cohort compared to age- and sex-matched control cohort	28% (37% in haem pts) OR 2.45 $P < 0.0001$	Myeloid malignancies trend for higher mortality; older age, co-morbidities	
Yang <i>et al.</i> (2020) <sup>21</sup>	Hubei, China	Retrospective multicentre cohort study of 205 pts admitted with lab-confirmed COVID-19 who also have a history of cancer (22 with haem malignancy)	Proportion of patients admitted with COVID-19 who have cancer Case fatality rate	2-5% (205/8 139)  20% (40/205) overall 41% (9/22) in haem malignancy and 17% in solid malignancy, HR 3.28 (CI 1.56-6.91, $P = 0.0009$ ) Chemo within 4 weeks OR 3.51 (CI 1.16-10.59, $P = 0.026$ ) male sex OR 3.86 (CI 1.57-9.5, $P = 0.0033$ ) 10% vs. 7.1%	Male, haem malignancy, time since diagnosis, chemotherapy or targeted therapy within 4 weeks, admission before 13 Feb associated with death in univariate analysis Age and co-morbidities were not associated with outcome	Patients with radiological diagnosis only were not included more patients with haem malignancy had treatment within 4 weeks compared to solid malignancy (55% vs. 12%)
He <i>et al.</i> (2020) <sup>18</sup>	Hubei, China	Cohort study at two centres of 128 inpatients with haematological cancer	Multivariate regression analysis Risk factors for death  Rate of COVID-19 in cohort compared to 226 HCP Mortality rate in pts with COVID-19 compared to HCP	62% vs. 0%		Pts who developed COVID-19 after lung CT may have been missed if mild 8 pts were in ICU and 8 HCP were working in ICU prior to developing COVID-19
Dai <i>et al.</i> (2020) <sup>29</sup>	Hubei, China	Multicentre cohort study of 105 pts with cancer and COVID-19 and compared to 536 age-matched pts without cancer (9 pts with haem malignancy)	Death rate in cancer pts Multivariate logistic regression, risk of death	11.4% in cancer cohort 33% in haem pts (3/9) OR 2.17, $P = 0.06$ Pairwise comparison of haem malignancy versus no cancer OR 9.07 (CI 2.16-48.18, $P = 0.01$ )	Haem malignancy, higher stage of disease, recent surgery for cancer	

Table I. (Continued)

Reference	Location	Type of study	Main relevant outcome measure	Outcome	Risk factors for outcome	Study limitations
Cook <i>et al.</i> (2020) <sup>27</sup>	UK	Multicentre cohort study of 75 pts with myeloma with lab-confirmed COVID-19	Case fatality rate	54.6% (41/75)	age	
Aries <i>et al.</i> (2020) <sup>26</sup>	UK	Single-centre cohort study of 35 pts with haem malignancy and lab-confirmed COVID-19	Mortality rate	40% (14/35)	Age, number of co-morbidities Active treatment was not a risk factor	
Martín-Moro <i>et al.</i> (2020) <sup>24</sup>	Spain	Single-centre cohort study of 34 patients with haematological malignancies and COVID-19	Mortality rate	32%	Age, active disease, MPN, MDS	
Malard <i>et al.</i> (2020) <sup>25</sup>	France	Single-centre cohort study of 25 pts with haem malignancy admitted with lab-confirmed COVID-19	Descriptive analysis of cohort	10/24 had myeloma enriched compared to hospital practice 36% (9/25)		
Li <i>et al.</i> (2020) <sup>17</sup>	Hubei, China	Survey of 530 pts in community with CML	Mortality rate/ rate of severe ARDS Prevalence of COVID-19 in pts with CML Number with proven COVID-19 Exposure history	0.9% 5 4 confirmed contact (1 developed COVID-19)	Not in CHR (2/5 ifor pts with COVID compared to 8/525, $P = 0.003$ ) Advanced phase CML $P = 0.004$ Co-morbidities (4/5 compared to 136/525, $P = 0.024$ )	Online study Self-selected cohort of patients (more likely to want to be tested) Not every participant was tested for COVID-19, i.e. asymptomatic patients would not be captured.

Abbreviations: ARDS, acute respiratory distress syndrome; CHR, complete haematological remission; CI, 95% confidence intervals; CML, chronic myeloid leukaemia; haem, haematological; CT, computed tomography; HCP, healthcare professional; HR, hazard ratio; MDS, myelodysplastic syndromes; MPN; myeloproliferative neoplasms; NHS, National Health Service; OR, odds ratio; pts, patients.

( $n = 12$ ) of 1 524 patients who were admitted into a single Chinese centre and compared this to the infection rate in the general population of 0.37% (odds ratio, 2.31; 95%CI, 1.89–3.02); all 12 had solid cancers. Two studies focussed on the prevalence of COVID-19 in patients with haematological cancer. Li *et al.*<sup>17</sup> attempted to capture the prevalence of COVID-19 in 530 patients with chronic myeloid leukaemia (CML) in the community through patient-completed surveys and found that five had a history of COVID-19 and that this rate of 0.9% was higher than 0.1% in the general population during the same period. However, another group compared the rate of COVID-19 development in inpatients at a single centre to the rate in healthcare professionals working at the same site and found it to be similar (10% vs. 7%).<sup>18</sup>

### *Is going to hospital for the treatment or monitoring of malignancy a risk factor for developing COVID-19?*

Several groups stated that many of the cancer patients that developed COVID-19 had either been inpatients or visited the hospital in the 14 days prior to the diagnosis of COVID-19 suggesting this may have been an exposure risk. For example He *et al.*<sup>18</sup> noted that a cluster of 16 cases of both patients and healthcare professionals who subsequently developed COVID-19 were all based in the ICU. Of the 61 patients who died due to COVID-19 in a New York centre, 37 were either residents in nursing homes or had been in hospitals in the 30 days prior to diagnosis.<sup>19</sup> A single centre examined the outcomes of all their stem cell patients who developed COVID-19, all seven were either inpatients or requiring weekly visits to hospital.<sup>20</sup>

### *In patients hospitalised with COVID-19, is there a higher risk of severe end-points in patients with cancer?*

The first paper to suggest that those with cancer may have a worse outcome was the cohort study by Liang *et al.*<sup>5</sup> The 18 patients with cancer in this cohort had a higher risk of severe events (composite end-point of being admitted to ICU, requiring invasive ventilation, death) compared to patients without cancer, 7/18 vs. 124/1 572 ( $P = 0.0003$ ); however, the patients with cancer were older (63 years vs. 48.7 years) and more likely to have a smoking history.

Since then, numerous small-cohort studies of patients with COVID-19 and cancer have also been published and the outcomes compared to the published outcomes for the general population. Three papers retrospectively examined the characteristics of 28–67 patients with known cancer who were admitted with COVID-19 within a total of eight centres all located in Wuhan, China.<sup>21–23</sup> Only three patients with haematological cancers were identified in the series reported by Zhang *et al.* and one lymphoma patient by Yang *et al.*, none of these patients were on active treatment. The mortality rate in these small cohorts was 21–29%. In the study by Yang *et al.*, all patients who died had co-morbidities.

A Spanish group reported a mortality rate of 32% in 33 patients with haematological malignancies who were admitted with COVID-19.<sup>24</sup> Being male and of older age was associated with worse outcome. Age did not remain significant on multivariate analysis although in this study it was considered a binary variable of below or above 80 years. Similarly, in a single-centre French study, 52% of 25 patients with haematological malignancy and COVID-19 developed acute respiratory distress syndrome (ARDS), and nine subsequently died; however 92% of this population had co-morbidities and seven were not taken to ICU due to age and co-morbidities.<sup>25</sup> A high mortality rate of 40% was also seen in a cohort of 35 patients with haematological malignancy in a single UK centre.<sup>26</sup> The outcome of 75 patients with myeloma who developed polymerase chain reaction (PCR)-confirmed COVID-19 was analysed in a UK-based audit; the mortality rate in this cohort was 54.6%, but the survivors were significantly younger than the non-survivors (66 vs. 78 years,  $P = 0.017$ ).<sup>27</sup>

To try and mitigate for the confounding factor of age when comparing the outcomes of patients with and without cancer, some groups have compared their cancer cohorts with age-matched controls. He *et al.*<sup>18</sup> compared the fatality rate of 62% in 13 cancer patients compared to 0% in 11 healthcare professionals with no significant difference in age, but eight of these patients were already in ICU prior to contracting COVID-19. The characteristics of 25 patients with cancer (two patients with haematological malignancy) and laboratory-confirmed COVID-19 was examined by Stroppa *et al.*<sup>28</sup> and the survival compared to that of a control group of 31 patients who were also hospitalised and matched for age, sex, pneumonia and antiviral treatment. The mortality rate was 36% compared to 16% in the control group ( $P = 0.12$ ) although co-morbidities were not listed in the control group whereas most of the cancer cohort had co-morbidities.

A multicentre study using information from 14 hospitals in the Hubei province in China compared the outcomes of 105 hospitalised patients with cancer to 536 patients without cancer matched for age, hospital and date of admission.<sup>29</sup> Patients with cancer were more likely to have a smoking history but otherwise no statistical difference in co-morbidities, although there was a significantly higher number of patients with cancer who were being treated as inpatients compared to the patients without cancer (19% versus 1.5%,  $P < 0.01$ ). Lung cancer was the most frequent tumour type; 9 of 105 patients had a haematological cancer. The fatality rate within the cancer patient cohort was 11%. Comparing the cancer patient cohort to the control group, higher rates of ICU admission and death were seen in the cancer population and when multivariate logistic regression was performed adjusting for age, sex, smoking and co-morbidities, patients with cancer had an excess odds ratio of 2.17 of death. Another Chinese multicentre matched cohort study has been published more recently comparing the outcomes of 232 patients with



cancer to 519 patients without a history of cancer, matched for age, sex and co-morbidities.<sup>30</sup> The mortality rate was 20% in the cancer cohort compared to 11% in the control group,  $P = 0.0012$ . Patients with cancer were more likely to have severe COVID-19 than patients without cancer, 148/232 vs. 166/519 [overall risk (OR) 3.61, 95% CI 2.59–5.04,  $P < 0.0001$ ].

In New York, the outcome of 218 patients with a history of cancer and COVID-19 treated in a single centre was examined.<sup>19</sup> These included 164 patients with solid tumours and 54 with haematological malignancies. The fatality rate in this cohort was 28% overall with a higher rate of 55% in lung cancer patients and 37% in patients with haematological malignancies. Older age was associated with increased mortality, as were co-morbidities. When age- and sex-matched to 1 090 patients in the same hospital system, case fatality rates were elevated in all age cohorts. The fatality rate was also compared to the official rate published in New York which had a significantly lower fatality rate of 6%.

Most recently, large national and international collaborative groups as well as national surveillance reports have published outcomes of patients with COVID-19 and due to the population size are able to perform multivariable analyses and draw stronger conclusions regarding risk.

The China Medical Treatment Expert group published the outcomes for 1 099 patients and have more recently expanded it to 1 590 patients with COVID-19 from 575 hospitals in China of whom 18 (1%) had a malignancy.<sup>31,32</sup> Analysis was performed according to a composite end-point of admission to ICU, invasive ventilation or death. Overall, 8.3% of the population reached the composite end-point with malignancy being one of the risk factors [hazard ratio (HR) 3.5, 95% CI 1.6–7.64].

The outcome of 5 688 patients with COVID-19 in New York was analysed, 334 had a history of cancer (6%); although patients with cancer had a higher rate of intubation, the death rate was not significantly different (37/334 with a history of cancer compared to 518/5 354 without cancer, relative risk 1.15, 95% CI 0.84–1.57).<sup>33</sup> Stratifying according to age, patients under 50 had a higher mortality rate if they had cancer but this difference was not seen in patients over 50 years of age. Co-morbidities were not detailed in this cohort.

The Italian National Institute of Health published and update a report on all patients who die with PCR-proven COVID-19. In the update based on available data by 14 May, co-morbidities were known in 2 848 of the 29 692 patient deaths reported.<sup>34</sup> Of the 2 848 patients, 454 (15.9%) had been diagnosed with active cancer in the past five years. However, the majority of patients who died had at least three co-morbidities, with hypertension, ischaemic heart disease and diabetes being the most frequent. Of the 65 patients under 40 years who died and for whom clinical information was available, 53 had serious pre-existing pathologies, although none listed as cancer, and 12 had no major

pathologies. It should also be noted that all deaths regardless of cause were counted in the rate if a positive COVID-19 swab was detected.<sup>35</sup>

The Chinese Centre for disease control and prevention showed that among 44 672 confirmed cases of COVID-19, the case fatality rate was 2.3%.<sup>36</sup> This rose to 8% in those aged 70–79 and to 14.8% in those aged 80 and over. The case fatality rate (CFR) was also elevated in those with co-morbidities at 5.6% for cancer; however, this is not split according to age.

In the study by Docherty *et al.*,<sup>9</sup> the 1 743 patients with a history of malignancy had a HR for death of 1.13 (95% CI 1.02–1.24,  $P = 0.017$ ). Another large study, OpenSafely Collaborative in the UK, used a platform allowing comparison of the characteristics and co-morbidities of 24 million patients from general-practice records to the rate of these characteristics in those who had died in hospital due to COVID-19.<sup>37</sup> In-hospital death among patients with confirmed COVID-19 showed that patients with cancer had a slightly increased HR of in-hospital death adjusted for sex and age group at 1.83 (1.51–2.21) if diagnosed within a year compared to 1.03 (0.94–1.12) if diagnosed over five years ago. In patients with haematological malignancy this was higher at 4.03 (2.76–5.88) if diagnosed within a year to 2.13 (1.76–2.59) if diagnosed over five years ago. These hazard ratios did not change significantly when fully adjusted for co-morbidities.

#### *In patients with cancer, are there any specific risk factors that are associated with increased risk of severe outcome?*

Two of the smaller cohort studies suggested that those with haematological malignancy were at increased risk of severe outcomes (Table I).<sup>21,29</sup> This has been confirmed in the larger study by the OpenSAFELY collaborative where the HR of death comparing those diagnosed with haematological malignancy within one year to none was higher than those diagnosed with solid cancer within a year, HR 3.52 (95% CI 2.41–5.14) compared to 1.56 (1.29–1.89); however a direct pairwise comparison of the two was not performed.<sup>37</sup> Similarly, in the UK cancer cohort study (CCMP), those with non-lymphoma haematological malignancy had an OR of death of 1.57 (95% CI 1.01–2.42,  $P = 0.04$ ).<sup>38</sup> However, not all large cancer cohorts have found those with haematological malignancy to have a worse outcome, as Kuderer *et al.*<sup>39</sup> found the OR for 30-day mortality to be 1.4 (95% CI 0.83–2.37) in those with haematological malignancy compared to patients with other malignancies.

Some of the studies have gone further to suggest that those with myeloid malignancies may have a worse outcome compared to other haematological malignancies.<sup>19,24,38</sup>

The length of time since diagnosis of the cancer has also been shown to be associated with outcome, with those more recently diagnosed more likely to have a worse outcome. For example, patients with a haematological diagnosis within a

year of developing COVID-19 had a HR of 3.52 of death (95% CI 2.41–5.14) in multivariate analysis compared to 1.88 (95% CI 1.55–2.29) in those diagnosed over five years ago.<sup>37</sup> Those with active disease have also been proposed to have a worse outcome compared to those with fully treated disease in large cancer cohorts as well as cohorts with haematological malignancy.<sup>17,24,39</sup> Many groups noted a worse outcome for those patients who had received anti-cancer treatment within the weeks prior to developing COVID-19.<sup>5,6,22,23</sup> For example, the HR for developing a severe event for patients who had treatment within 14 days was 4.079 (95% CI 1.086–15.322,  $P = 0.037$ ) in a cohort of 28 patients.<sup>23</sup> However, this has not been seen in all studies, Lee *et al.*<sup>38</sup> found no difference in mortality between those patients who had treatment within four weeks compared to those who had not, and Aries *et al.*<sup>26</sup> stated that 15 of the patients who were having intensive chemotherapy regimes for haematological malignancy when they developed COVID-19 were still alive.

## Discussion

As the initial peak of cases of severe COVID-19 and its associated death toll begins to fall in the UK, it is important to evaluate the evidence so far regarding the risk of severe complications in patients with haematological malignancies. This will inform the advice we give to patients regarding whether there is an ongoing need to shield, and particularly as their families start to return to work and schools, what extra risk this may bring. Furthermore, this will also have an impact on whether we continue to give treatment both curative and for disease control or defer/abbreviate it due to perceived increased risk for patients with haematological malignancy. The key questions, which cannot be completely answered at present, are whether there is a difference in risk of getting COVID-19, and perhaps more importantly whether there is a risk of developing severe complications in patients with COVID-19 and haematological cancer compared to patients with other cancers and the general population, and furthermore what is the degree of extra risk to this patient group. Understanding of these risks will only come from large population-based analyses of patients. Larger-cohort studies with more uniform characteristics, for example, patients with a particular haematological cancer, will provide us with more granularity, to allow us to understand whether there is a variation in that risk depending on type of malignancy or time or type of treatment.

The increased risk that having a current or previous diagnosis of solid or haematological malignancy has on developing COVID-19 has been investigated by several groups by investigating either the prevalence of cancer in cohort studies of patients with COVID-19 or the COVID-19 infection rate in cohort studies of patients with cancer and comparing them to the rate of cancer or COVID-19 in the general population respectively.

These studies are at best hypothesis-generating as they do not capture the true rates of all patients who contract SARS-CoV-2 and are skewed towards those who develop symptoms related to COVID-19 and therefore get tested. The overall limitation of the majority of these studies is the numerous confounding factors such as known shared risk factors and the high rate of concurrent co-morbidities, compounded by the small numbers in most of these studies. Differing levels of high-risk exposure may also lead to increased vulnerability in the cancer patient cohort, as numerous groups proposed that several of their patients had nosocomial transmission of COVID-19 either through clinic visits or as inpatients. Furthermore, on an international population level, there are marked differences in prevalence of COVID-19 seen in population studies which may be due to differing demographics, testing strategies or possibly different susceptibilities. All these reasons may in part explain the marked variance in prevalence of cancer seen across these studies of 0.5–10%. Li *et al.*<sup>17</sup> tried to account for this by exploring the infection rate in patients with CML in the community via an online survey to attempt to avoid enriching for patients that are requiring multiple hospital visits, and still noted a higher infection rate than that in the general population at 0.9%; however there may be other biases that affect the study in this case, such as likelihood of completing the survey if you have had COVID-19.

Papers published to date that have examined the rate of cancer in cohorts of patients with COVID-19, have compared the prevalence to the prevalence in the general population, and have suggested due to the higher rate of cancer in the COVID-19 cohort, that this could be a risk factor. However, the incidence of cancer increases with age, with a 40% lifetime risk of developing any cancer.<sup>40</sup> To avoid these potential confounding factors, it is necessary to compare the cancer prevalence to an age- and sex-matched population.

Perhaps the more clinically significant question that several groups have sought to address is whether a history of cancer in patients with COVID-19 is a risk factor for worse outcome, defining this by risk of either 'severe COVID-19', intubation, admission to intensive care or death or a composite of all of these. Some of the smaller studies report case fatality rates from 11% to 62% but again the variation is likely to be due to the heterogeneity of the cohorts and the confounding factors. For example, He *et al.*<sup>18</sup> noted a high mortality rate of 62% in the 13 patients who developed COVID-19; however, eight of them were already in ICU prior to developing COVID-19. Some groups have attempted to address confounding factors by comparing the mortality rate to that in matched controls. The two largest studies to date that used this approach compared the outcomes of 218 and 232 cancer patients to age-, sex- and co-morbidities- (Tian *et al.*) matched control cohorts.<sup>19,30</sup> Mehta *et al.*<sup>19</sup> found an OR of 2.45 for risk of death ( $P < 0.0001$ ) and Tian *et al.*<sup>30</sup> an OR of 3.61 (95% CI 2.59–5.04,  $P < 0.0001$ ) for



risk of severe COVID-19. However, again there will be variability in the groups studied; for example 54 of the patients in the study by Mehta *et al.* had haematological malignancy and only 12 in the study by Tian *et al.* The larger population cohorts that are beginning to be published will provide stronger evidence as to whether there is a difference in outcomes as they can account for age and co-morbidities. Two large studies from UK collaboratives both concluded that a history of malignancy was associated with an increased risk of death due to COVID-19. Docherty *et al.*<sup>9</sup> demonstrated that in the 17 173 patients with known medical history, the cohort with a history of cancer ( $n = 1\ 743$ ) had a HR for death on multivariate analysis of 1.14 (95% CI 1.03–1.25,  $P = 0.008$ ). The OpenSAFELY collaborative also showed a similar hazard ratio for solid malignancies but higher risk in those with haematological malignancies with HR for death 1.88 (95% CI 1.55–2.29) in those diagnosed over five years ago, rising to 3.52 (2.41–5.14) in those diagnosed within a year.<sup>37</sup> One of the strengths of this study is that the analysis was performed on the data from over 17 million patients from general-practice records rather than just an analysis of the cohort who developed COVID-19, giving us perhaps one of the truest indicators of risk. Of course, this does not provide us with details of why patients with haematological malignancy have a higher risk of death, and indeed may be an underestimate of ‘true risk’ if this at-risk population were shielding effectively.

Patients with cancer are a heterogeneous population and so there have been attempts to understand whether patients with certain cancers are more or less likely to have severe outcomes. Similarly, whether time since diagnosis, disease status, treatment status, and type of treatment are risk factors. A number of studies including those examining large populations, do seem to suggest that patients with haematological malignancy have a higher risk of severe complications. Some of the studies focusing on cancer patients have also suggested that possibly patients with myeloid diseases are at higher risk, but this needs to be confirmed in larger studies. There is conflicting evidence in these early datasets regarding whether being on active treatment at time of diagnosis of COVID-19 is associated with worse outcome.<sup>6,26,38</sup>

Type of cancer, disease status and length of time since last treatment are all intimately related particularly within the haematological malignancy cohort. For example, the proposal that patients with acute myeloid leukaemia, myelodysplastic syndromes (MDS) or myeloproliferative disorders are at increased risk compared to those with lymphoid malignancies may be due to biological differences. However, many patients with a history of lymphoid malignancy will have been cured from their cancer and not on active treatment, and so it is difficult to tease apart which is the more significant risk factor. Cohort studies of patients with a single disease entity may provide us more granularity.

## Conclusions

There is suggestive evidence from large population-wide studies in which the age and co-morbidities of patients are known that patients with haematological malignancies are at increased risk of death from severe COVID-19 compared to the general population and possibly compared to patients with solid cancer although not all studies have found this difference. This risk is highest in those that have been diagnosed within the past five years, especially in those diagnosed within the past year. Smaller studies have suggested those with acute leukaemia, MDS or myeloproliferative neoplasms (MPN) are at highest risk, but this needs to be confirmed in larger studies. Ongoing active disease may be a confounding factor for these subgroups. Continued analysis of the data, particularly as testing becomes more widespread within the community, is required to attain further understanding of the risk factors for development of severe COVID-19.

Collaborative national and international efforts, such as CCP-UK and OpenSAFELY collaborative, should continue to capture the characteristics of patients with COVID-19 and correlate this with their outcome. Large cancer cohort studies such as UK Coronavirus Cancer Monitoring Project and COVID-19 and cancer consortium (CCC19) can provide us with more detail regarding risks within the cancer patient population whilst cohorts of single disease groups will allow us to start to understand the reasons for the increased risks.

## Author contributions

DE and SI reviewed the literature, wrote the paper and approved the submitted version of the manuscript.

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