Changes in hospital mortality in patients with cancer during the COVID-19 pandemic (ISARIC-CCP-UK)

Changes in hospital mortality in patients with cancer during the COVID-19 pandemic (ISARIC-CCP-UK): a prospective, multicentre cohort study

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Summary

Background Patients with cancer are at greater risk of dying from COVID-19 than many other patient groups. However, how this risk evolved during the pandemic remains unclear. We aimed to determine, on the basis of the UK national pandemic protocol, how factors influencing hospital mortality from COVID-19 could differentially affect patients undergoing cancer treatment. We also examined changes in hospital mortality and escalation of care in patients on cancer treatment during the first 2 years of the COVID-19 pandemic in the UK.

Methods We conducted a prospective cohort study of patients aged older than 19 years and admitted to 306 health-care facilities in the UK with confirmed SARS-CoV-2 infection, who were enrolled in the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol (CCP) across the UK from April 23, 2020, to Feb 28, 2022; this analysis included all patients in the complete dataset when the study closed. The primary outcome was 30-day in-hospital mortality, comparing patients on cancer treatment and those without cancer. The study was approved by the South Central–Oxford C Research Ethics Committee in England (Ref: 13/SC/0149) and the Scotland A Research Ethics Committee (Ref 20/SS/0028), and is registered on the ISRCTN Registry (ISRCTN66726260).

Findings 177 871 eligible adult patients either with no history of cancer (n=171 303) or on cancer treatment (n=6568) were enrolled; 93 205 (52·4%) were male, 84 418 (47·5%) were female, and in 248 (13·9%) sex or gender details were not specified or data were missing. Patients were followed up for a median of 13 (IQR 6–21) days. Of the 6568 patients receiving cancer treatment, 2080 (31·7%) died at 30 days, compared with 30 901 (18·0%) of 171 303 patients without cancer. Patients aged younger than 50 years on cancer treatment had the highest age-adjusted relative risk (hazard ratio [HR] 5·2 [95% CI 4·0–6·6], p<0·0001; *vs* 50–69 years 2·4 [2·2–2·6], p<0·0001; 70–79 years 1·8 [1·6–2·0], p<0·0001; and >80 years 1·5 [1·3–1·6], p<0·0001) but a lower absolute risk (51 [6·7%] of 763 patients <50 years died compared with 459 [30·2%] of 1522 patients aged >80 years). In-hospital mortality decreased for all patients during the pandemic but was higher for patients on cancer treatment than for those without cancer throughout the study period.

Interpretation People with cancer have a higher risk of mortality from COVID-19 than those without cancer. Patients younger than 50 years with cancer treatment have the highest relative risk of death. Continued action is needed to mitigate the poor outcomes in patients with cancer, such as through optimising vaccination, long-acting passive immunisation, and early access to therapeutics. These findings underscore the importance of the ISARIC-WHO pandemic preparedness initiative.

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Introduction

Patients with cancer were identified as being at higher risk of poor outcomes if they developed SARS-CoV-2 infection early on in the COVID-19 pandemic. In the UK, 10% of patients admitted to hospital with COVID-19 had a history of malignancy, and these patients had increased in-hospital mortality (hazard ratio [HR] 1·13 [95% CI 1·02–1·24]; p=0·017).[1] Subsequently, many studies have reported outcomes of patients with cancer and COVID-19. These studies were mostly retrospective and have also reported worse outcomes in patients with cancer. Older patients and those with haematological malignancies are particularly at risk.[2–6] However, a key issue common to many studies published has been the absence of a contemporaneous non-cancer population matched for age and sex, admitted to hospital during the same time period of the pandemic. Furthermore, previous studies have not provided a continuum across the pandemic.

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Research in context

Evidence before this study

We searched PubMed using the search terms "coronavirus", "COVID-19", "cancer", "pandemic", and "time course" for studies published between Jan 1, 2020, and Oct 29, 2023, related to outcomes of patients with cancer versus those without cancer across the time course of the COVID-19 pandemic. Although several studies have assessed the risks associated with SARS-CoV-2 infection in patients with cancer, we found no study that prospectively collected data on patients with cancer and those without cancer on a national protocol, from all hospitals across a specific geographical region, over an equivalent period, thus minimising bias and controlling for age, sex, and comorbidity.

Added value of this study

To the best of our knowledge, this is the first study to compare outcomes between patients receiving cancer treatment and patients with no history of cancer recruited at the same time during the first 2 years of the COVID-19 pandemic based on prospective data from a pre-planned pandemic response protocol. Additionally, this study represents the largest cohort of patients with cancer admitted to hospital with COVID-19. We make several key novel observations. We found that younger patients having cancer treatment have the highest relative risk of death compared with age-matched non-cancer patients for any age group, which had not been reported previously. The number of comorbidities had little influence on the outcome from COVID-19 in patients undergoing cancer treatment. The effect of frailty was increased in patients who were having cancer treatment at the time of hospital admission with COVID-19. Despite having a similar severity of illness and physiological impairment at presentation to hospital, patients on cancer treatment had worse outcomes than those without a history of cancer. Across the course of the pandemic from April, 2020, to February, 2022, differences were seen in the mortality rate between patients having cancer treatment and non-cancer patients, with mortality in patients on cancer treatment increasing during the alpha and delta waves of the pandemic.

Implications of all the available evidence

This study shows that patients being treated for cancer and admitted to hospital with SARS-CoV-2 infection are at increased risk of death compared with non-cancer patients, even if they are asymptomatic. Further work is needed to understand the differences seen between patients receiving cancer treatment and patients without cancer, and how age, cancer type, and treatment might have affected mortality or escalation of care, as well as the possible influence of COVID-19 vaccination and socioeconomic factors. These data are important for future pandemic planning for patients on cancer treatment and reinforce the importance of the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol.

The substantial heterogeneity and variability of data collection and reporting, exemplified by the use of 14 different definitions of severe events across various studies of COVID-19 and cancer, further limits the generalisability of these studies.[2] Vaccination has reduced the severity of and mortality associated with COVID-19,[7] including in patients with cancer.[8,9] However, population-level data[10] indicate that vaccine effectiveness is reduced in patients with cancer.

Previously, we reported outcomes of immunocompromised patients from one of the largest and most temporally continuous datasets of patients admitted to hospital with COVID-19, the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol (CCP) UK cohort.[11] Patients undergoing treatment for cancer were at greatest risk of dying from COVID-19 compared with other patients who were immunocompromised due to non-malignant conditions. This cohort was recruited on a national protocol at centres across the UK, not just cancer centres, and enrolled patients with and without cancer. This approach minimises the potential ascertainment bias inherent in running studies from major cancer centres—the source of many earlier reports on this topic.

In the present study, we aimed to investigate how factors influencing outcomes from COVID-19, such as age, comorbidities, and frailty, could differentially affect patients undergoing cancer treatment. We also report on how outcomes have changed for patients with cancer during the first 2 years of the COVID-19 pandemic in the UK—a period covering the emergence of the alpha (B.1.1.7), delta (B.1.617.2), and omicron (B.1.1.529) variants—as well as both the pre-vaccination and post-vaccination periods of the pandemic. Finally, we investigated whether there were any differences in the escalation of care between patients with cancer and those without cancer.

Methods

Study design and participants

The WHO ISARIC CCP-UK study is a prospective cohort study that collected clinical data on patients with COVID-19 admitted to 306 health-care facilities in the UK. The study closed to recruitment of patients with COVID-19 on Feb 28, 2022. Outcomes were recorded on March 30, and data extracted on April 30, 2022. For patients who provided only routine clinical data, because of the important public health nature of the study, consent was not required.

This analysis, based on the final dataset, is limited to adults (aged ≥19 years on admission); data on children have been reported separately.[12,13] Confirmation of SARS-CoV-2 infection was done with PCR. Patients admitted to hospital for another reason, but who tested positive for SARS-CoV-2 in hospital, were also included in this analysis. We analysed data collected from April 23, 2020, onwards—the date the case record form was amended to identify patients undergoing active treatment for cancer. Active treatment was defined as: undergoing chemotherapy, immunotherapy, antibody treatment, or targeted therapy; bone marrow or stem-cell transplant within the preceding 6 months; radical radiotherapy for lung cancer; or haematological malignancies at any stage of treatment. Disease severity was measured with the 4C Mortality Score[14] (where a higher score indicates a higher risk of in-hospital mortality) and the 4C Deterioration Model (where a higher score indicates a higher risk of deterioration);[15] the inflammatory severity component (excluding age and comorbidity) of the 4C Mortality Score alone is also reported (C-reactive protein [CRP], respiratory rate, oxygen saturation, urea, and Glasgow Coma Scale).

The CCP-UK CRF identified patients with cancer in two fields: one for a history of cancer, with no information on timing or treatment; and another that identified patients having current treatment (appendix p 39). We sought to inform cancer treatment decisions by ascertaining the effect of influencing factors on outcomes of patients with COVID-19 who are being treated for cancer. Therefore, we compared patients undergoing treatment for cancer (any patient in whom current treatment was recorded) with patients who had no history of cancer recorded (both case record form variables negative). We excluded patients with a history of cancer, but for whom recent treatment was not recorded (recent treatment variable negative or not recorded).

The study was approved by the South Central – Oxford C Research Ethics Committee in England (Ref: 13/SC/0149) and by the Scotland A Research Ethics Committee (Ref: 20/SS/0028). Full details of the study protocol and materials are available online and have previously been reported.[1] This study is registered on the ISRCTN Registry (ISRCTN66726260).

Procedures

During the first wave of the pandemic, every patient admitted to hospital was eligible for inclusion; in subsequent waves sites enrolled every tenth laboratory-positive case, irrespective of comorbidities. Patients were followed up until discharge, death, or 90 days if they were still admitted to hospital. Sex and gender were defined as per patients' medical records, which are self-defined.

Wave 1 of the pandemic in the UK started before April 23, 2020, the date the cancer treatment variable was introduced, and continued until Aug 31, 2020, the nadir of hospital admissions between the first and second waves. Wave 2 was defined as occurring between Sept 1, 2020, and March 31, 2021, during which the alpha variant became dominant. The third wave was defined as occurring between April 1, 2021 and Dec 12, 2021, caused by the delta variant. From Dec 13, 2021, onwards, omicron became the dominant circulating variant in the UK.[16] We refer to this period as the fourth wave, and in the period of data collection SARS-CoV-2 infection was either with BA.1 or BA.2 lineages.

Outcomes

The primary outcome was 30 day in-hospital mortality, compared between patients undergoing cancer treatment and patients who did not have cancer. Secondary outcomes were deterioration (defined as the requirement for intensive care, ventilation, or in-hospital mortality), intensive care admission, and invasive mechanical ventilation, non-invasive ventilation, and oxygen treatment.

Statistical analysis

Categorical data were summarised as counts and percentages. Differences in categorical data were tested with the χ^2 test or exact tests where expected cell counts were less than 5. Parametric continuous data were summarised as means (SDs). Continuous data that did not follow a normal distribution were summarised as medians (IQRs). Differences in continuous variables were tested with the Kruskal-Wallis test. p values less than 0·05 were considered significant.

See Online for appendix

For survival outcomes, we used risk multivariable logistic regression models and Cox proportional hazards models to describe the impact of cancer on in-hospital mortality, and the effects of age, symptoms, frailty, and comorbidity on outcomes. Models were adjusted for age, sex, deprivation, ethnicity, comorbidities, and vaccination status. Interactions between patient cancer status and age, symptoms, frailty, and comorbidity were tested. The reported date of symptom onset was taken as day 0; for asymptomatic patients, day 0 was the date of admission. Survival analysis was performed with a Fine and Gray competing risk approach[17] (discharged patients remained in the at-risk population) and was visualised with Kaplan–Meier plots. The assumption of proportional hazards were inspected visually (appendix p 2). In each case, centre-level effects were accounted for with random effects. Visualisation of trends over time used unadjusted rolling averages and 95% CIs with a 4-week window for each group.

For the **study protocol and materials** see https://isaric4c.net

All statistical analyses were done with R (version 3.6.3) using the tidyverse,[18] finalfit,[19] mcgv, zoo, survival, stringdist, janitor, patchwork, Mice, and Hmisc packages. Data are presented in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

The data were examined to determine patterns of missingness. Multiple imputation with chained equations

was performed (ten iterations and ten datasets). Analysis results were combined with Rubin's Rules.[20] Sensitivity analyses were also performed with complete case data.

Role of the funding source

The funders (the UK National Institute for Health Research and UK Medical Research Council) and the sponsor (University of Oxford, Oxford, UK) had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication.

Results

Between April 23, 2020, and Feb 28, 2022, 192 426 eligible adult patients with outcome and cancer data available were recruited. 14 555 patients only had a past history of cancer, with no information on cancer treatment, and were thus excluded. Of the remaining 177 871 patients, 171 303 had no history of cancer and 6568 were receiving cancer treatment, according to the definition given in the case record form (figure 1). Median follow-up was 13 days (IQR 6–21).

More patients on cancer treatment were male compared with those without cancer (3775 [57·5%] of 6568 *vs* 89 430 [52·2%] of 171 303; p<0·0001; table 1)

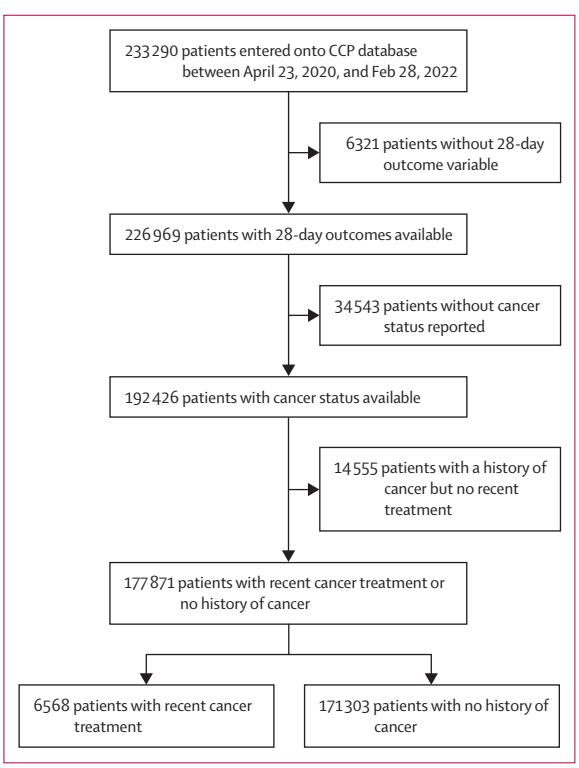

Figure 1: **Flow diagram of patients in the study**
The total number of patients in the ISARIC CCP-UK database, reasons for exclusion, and numbers of patients with known cancer status, and the number of patients with recent cancer treatment and with no history of cancer are shown. ISARIC=International Severe Acute Respiratory and emerging Infections Consortium. CCP=WHO Clinical Characterisation Protocol.

	Patients not on cancer treatment (n=171 303)	Patients on cancer treatment (n=6568)	p value
Median age, years	70·9 (54·5–82·6)	71·8 (61·3–79·6)	<0·0001
Age on admission, years	..	..	<0·0001
<50	37 043 (21·6%)	763 (11·6%)	..
50–69	48 134 (28·1%)	2280 (34·7%)	..
70–79	34 546 (20·2%)	2001 (30·5%)	..
≥80	51 510 (30·1%)	1522 (23·2%)	..
Data missing	70 (<0·1%)	2 (<0·1%)	..
Sex	..	..	<0·0001
Male	89 430 (52·2%)	3775 (57·5%)	..
Female	81 637 (47·7%)	2781 (42·3%)	..
Not specified	188 (0·1%)	12 (0·2%)	..
Data missing	48 (<0·1%)	0	..
Ethnicity	..	..	<0·0001
Black	5570 (3·3%)	159 (2·4%)	..
Asian	12 588 (7·3%)	265 (4·0%)	..
Minority ethnic	9919 (5·8%)	309 (4·7%)	..
White	121 032 (70·7%)	5124 (78·0%)	..
Data missing	22 194 (13·0%)	711 (10·8%)	..
IMD quintile			<0·0001
1	47 294 (27·6%)	1477 (22·5%)	..
2	32 861 (19·2%)	1184 (18·0%)	..
3	27 117 (15·8%)	1126 (17·1%)	..
4	25 695 (15·0%)	1165 (17·7%)	..
5	22 962 (13·4%)	1227 (18·7%)	..
Data missing	15 374 (9·0%)	389 (5·9%)	..
Median 4C score	9·0 (5·0–11·0)	9·0 (7·0–12·0)	<0·0001
Median 4C score–inflammatory	2·0 (1·0–4·0)	3·0 (1·0–4·0)	<0·0001
Number of comorbidities	..	..	<0·0001
0	33 303 (19·4%)	1447 (22·0%)	..
1	44 848 (26·2%)	1751 (26·7%)	..
≥2	93 152 (54·4%)	3370 (51·3%)	..
Hypertension			<0·0001
No	89 514 (52·3%)	3736 (56·9%)	..
Yes	73 582 (43·0%)	2563 (39·0%)	..
Data missing	8207 (4·8%)	269 (4·1%)	..
Chronic pulmonary disease	..	..	0·0031
No	138 542 (80·9%)	5184 (78·9%)	..
Yes	26 202 (15·3%)	1085 (16·5%)	..
Data missing	6559 (3·8%)	299 (4·6%)	..
Asthma (physician diagnosed)			<0·0001
No	139 603 (81·5%)	5621 (85·6%)	..
Yes	25 026 (14·6%)	643 (9·8%)	..
Data missing	6674 (3·9%)	304 (4·6%)	..

(Table 1 continues in next column)

	Patients not on cancer treatment (n=171 303)	Patients on cancer treatment (n=6568)	p value
(Continued from previous column)			
Chronic renal disease	..	..	0·0133
No	137 812 (80·4%)	5167 (78·7%)	..
Yes	26 584 (15·5%)	1085 (16·5%)	..
Data missing	6907 (4·0%)	316 (4·8%)	..
Chronic neurological disorder	..	..	<0·0001
No	143 873 (84·0%)	5686 (86·6%)	..
Yes	19 989 (11·7%)	528 (8·0%)	..
Data missing	7441 (4·3%)	354 (5·4%)	..
Chronic haematological disease	..	..	<0·0001
No	157 834 (92·1%)	4758 (72·4%)	..
Yes	5765 (3·4%)	1493 (22·7%)	..
Data missing	7704 (4·5%)	317 (4·8%)	..
HIV/AIDS	..	..	0·6807
No	159 709 (93·2%)	6052 (92·1%)	..
Yes	594 (0·3%)	20 (0·3%)	..
Data missing	11 000 (6·4%)	496 (7·6%)	..
Obesity (as defined by clinical staff)	..	..	<0·0001
No	124 537 (72·7%)	4945 (75·3%)	..
Yes	22 960 (13·4%)	584 (8·9%)	..
Data missing	23 806 (13·9%)	1039 (15·8%)	..
Diabetes	..	..	<0·0001
No	118 302 (69·1%)	4882 (74·3%)	
Type 1	4191 (2·4%)	143 (2·2%)	..
Type 2	39 017 (22·8%)	1266 (19·3%)	..
Data missing	9793 (5·7%)	277 (4·2%)	
Diabetes with complications	..	..	<0·0001
No	141 636 (82·7%)	5580 (85·0%)	..
Yes	10 060 (5·9%)	310 (4·7%)	..
Data missing	19 607 (11·4%)	678 (10·3%)	..
Diabetes (any)	..	..	0·0012
No	133 735 (78·1%)	5268 (80·2%)	..
Yes	17 817 (10·4%)	609 (9·3%)	..
Data missing	19 751 (11·5%)	691 (10·5%)	..
Rheumatological disorder	..	..	0·0419
No	142 303 (83·1%)	5498 (83·7%)	..
Yes	20 949 (12·2%)	746 (11·4%)	..
Data missing	8051 (4·7%)	324 (4·9%)	..
Dementia	..	..	<0·0001
No	143 959 (84·0%)	5917 (90·1%)	..
Yes	19 427 (11·3%)	310 (4·7%)	..
Data missing	7917 (4·6%)	341 (5·2%)	..
Malnutrition	..	..	<0·0001
No	149 830 (87·5%)	5557 (84·6%)	..
Yes	3205 (1·9%)	204 (3·1%)	..
Data missing	18 268 (10·7%)	807 (12·3%)	..
Moderate or severe liver disease	..	..	<0·0001
No	159 867 (93·3%)	5983 (91·1%)	..
Yes	3161 (1·8%)	218 (3·3%)	..
Data missing	8275 (4·8%)	367 (5·6%)	..
Mild liver disease	..	..	0·1160
No	159 554 (93·1%)	6056 (92·2%)	..
Yes	2958 (1·7%)	130 (2·0%)	..
Data missing	8791 (5·1%)	382 (5·8%)	..
Chronic cardiac disease	..	..	<0·0001
No	116 157 (67·8%)	4579 (69·7%)	..
Yes	48 560 (28·3%)	1666 (25·4%)	..
Data missing	6586 (3·8%)	323 (4·9%)	..
COVID-19 vaccination >28 days before admission	..	..	<0·0001
No	135 054 (78·8%)	4693 (71·5%)	..
Yes	36 249 (21·2%)	1875 (28·5%)	..

(Table 1 continues in next column)

Data are n (%) or median (IQR). p values for χ^2 tests are shown. IMD=Index of Multiple Deprivation.

Table 1: **Patient characteristics**

The most common symptoms of COVID-19 were shortness of breath (3174 [48·3%] in patients on cancer treatment *vs* 87 510 [51·1%] in patients without cancer), cough (2921 [44·5%] *vs* 78 005 [45·5%]), and fever and malaise (2266 [34·5%] *vs* 48 737 [28·5%]; appendix pp 3, 11–13). 5309 (80·8%) of 6568 patients on cancer treatment had at least one symptom, compared with 133 194 (77·8%) of 171 303 patients without cancer (p<0·0001). No clinically significant differences were seen between patients on cancer treatment and patients without cancer (appendix pp 3, 11–12).

Patients on cancer treatment were more likely to die than patients without cancer (table 2). The absolute risk of death was highest in the oldest patients on cancer treatment: 459 (30·2%) of 1522 patients aged older than 80 years , 497 (24·8%) of 2001 patients aged 70–79 years, 404 (17·7%) of 2280 patients aged 50–69 years, and 51 (6·7%) of 763 aged younger than 50 years died (appendix p 13). However, the relative risk of death was higher in younger patients. In patients aged younger than 50 years, mortality was around three times higher in patients on cancer treatment (51 [6·7%] of 763) than in patients without cancer (786 [2·1%] of 37 043 patients; appendix p 13). Among patients aged older than 80 years,

	Patients not on cancer treatment (n=171 303)	Patients on cancer treatment (n=6568)	p value
Death	..	..	<0·0001
No	140 402 (82·0%)	4488 (68·3%)	..
Yes	30 901 (18·0%)	2080 (31·7%)	..
Deterioration	..	..	<0·0001
No	111 533 (65·1%)	3774 (57·5%)	..
Yes	59 770 (34·9%)	2794 (42·5%)	..
Invasive ventilation	..	..	<0·0001
No	159 575 (94·6%)	6216 (96·0%)	..
Yes	9088 (5·4%)	258 (4·0%)	..
Data missing	2640	94	..
Non-invasive ventilation	..	..	0·6131
No	142 664 (84·6%)	5458 (84·4%)	..
Yes	25 922 (15·4%)	1010 (15·6%)	..
Data missing	2717	100	..
Critical care	..	..	<0·0001
No	141 188 (83·0%)	5670 (86·9%)	..
Yes	28 860 (17·0%)	853 (13·1%)	..
Data missing	1255	45	..
Oxygen	..	..	0·6593
No	64 679 (38·1%)	2497 (38·4%)	..
Yes	104 997 (61·9%)	4006 (61·6%)	..
Data missing	1627	65	..

Data are n (%) of patients reporting each primary and secondary outcome. p values for χ^2 tests are shown.

Table 2: **Patient outcomes**

30·2% (459 of 1522) of those on cancer treatment died, compared with 23·3% (11 988 of 51 510) patients without cancer—a smaller relative difference. To investigate the effects of other variables, logistic regression models were constructed, adjusted for variables known to influence the outcome from COVID-19. This analysis showed the same pattern: among patients aged younger than 50 years, patients on cancer treatment had higher odds of dying than patients without cancer (odds ratio [OR] 2·71 [95% CI 2·02–3·65], p=0·010). Among patients aged older than 80 years the corresponding ORs (with patients without cancer <50 years as the reference group) were 21·34 (95% CI 18·68–24·38, p=0·010) for patients on cancer treatment and 14·62 (13·59–15·73, p=0·010) for patients without cancer (figure 2A). For patients aged 50–69 years and 70–79 years, the effects were intermediate (figure 2A). Complete case analysis based on multiple imputation to account for missing data showed similar results (appendix p 4).

Sensitivity analysis based on Cox proportional hazards regression with patients without cancer as the reference group in each age bracket confirmed these findings and showed that, although patients with cancer had a higher risk of death, the timing of death was not appreciably different from that of patients without cancer. Patients on cancer treatment aged younger than 50 years, although having the lowest absolute mortality risk, nevertheless had the greatest increase in risk compared with patients without cancer of the same age (HR 5·2 [95% CI 4·0–6·6], p<0·0001) and had a similar mortality risk to patients without cancer aged 50–69 years (HR 1·5 [95% CI 1·3–1·6], p<0·0001; appendix p 5).

The risk of death in patients on cancer treatment was elevated irrespective of the presence of symptoms of COVID-19 (figure 2C). Frailty, measured by the Dalhousie University Clinical Frailty Score (DUCFS),[21] was also associated with the risk of death (figure 2E).

As expected, patients on cancer treatment without any comorbidities had higher mortality than patients without cancer who had any comorbidities (OR 2·86 [95% CI 2·51–3·27], p=0·010), and a similar risk of death to patients without cancer with two or more comorbidities (OR 2·35 [95% CI 2·24–2·46], p=0·010; figure 2D). The risk of death in patients on cancer treatment (compared with patients without cancer with no comorbidities) increased with an increasing number of comorbidities in addition to cancer, but the relative effect of comorbidities was lower than for non-cancer patients (figure 2G). Univariable ORs for mortality are shown in the appendix (p 14). The variables included in the analyses were also assessed for co-linearity, which was not found to be present (variance inflation factor always <1·2, data not shown).

Across the variables examined (age, symptoms, frailty, and comorbidities), patients on cancer treatment were more likely to deteriorate, defined as a new requirement for non-invasive mechanical ventilation, invasive mechanical ventilation, and admission to an intensive care unit (ICU) as well as death, compared with patients without cancer (figure 2B, D, F, H). Univariable ORs for deterioration are shown in the appendix (p 15).

To ensure we considered differences in management decisions due only to COVID-19, escalation to ICU was analysed only for patients who were symptomatic upon admission. There were modest differences in the proportion of patients on cancer treatment admitted to ICU or receiving invasive ventilation compared with patients without cancer. 258 (4·0%) of 6474 patients on cancer treatment were ventilated, compared with 9088 (5·4%) of 168 663 patients without cancer (p<0·0001; table 2). In logistic regression models, this difference was significant in patients older than 50 years (figure 3A; appendix p 6). Therefore, although patients on cancer treatment younger than 50 years were escalated to ICU at the same rate as patients without cancer of the same age, they still had increased mortality. Univariable ORs for escalation to ICU are shown in the appendix (p 16).

With non-frail patients without cancer as the reference group, patients on cancer treatment with low frailty (DUCFS 1–3) were admitted to ICU less frequently than patients without cancer. With increasing frailty this difference disappeared (figure 3B).

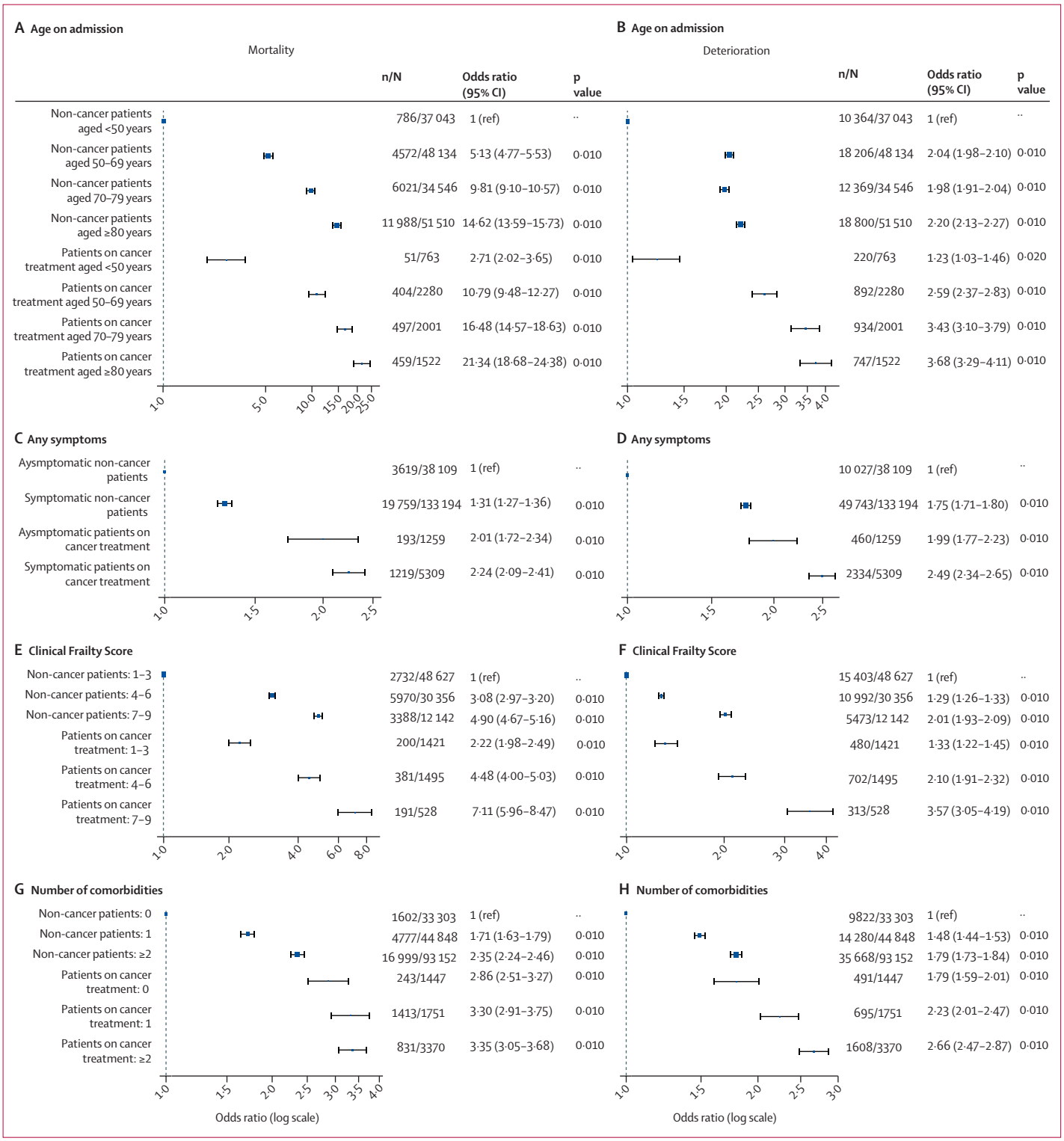

Figure 2: **Association of key variables with in-hospital mortality and deterioration**

Odds ratios (ORs) and 95% CIs from multivariable logistic regression models for death (A, C, E, G) and deterioration (B, D, F, H), presenting the effects of age, symptoms, frailty, and multimorbidity in patients with cancer and those without cancer on death in hospital are shown. Analyses are adjusted for age (except for panel A), sex, ethnicity, deprivation, and the presence of chronic cardiac, pulmonary, and renal disease, and dementia (except for panel D), and vaccination status. Multiple imputation was used to deal with missing data. The interaction effects for the variable of interest and cancer status are shown in the appendix (pp 38–39).

Additional comorbidities increased the chance of ICU admission in patients without cancer but had no such effect in patients on cancer treatment (although the confidence intervals were wide; figure 3C). After admission to ICU, mortality of patients on cancer treatment remained higher than that of patients without cancer (figure 3D). Univariable ORs according to location of care are shown in the appendix (p 17). Sensitivity analysis based on complete cases (appendix p 6), or invasive mechanical ventilation as an alternative outcome variable (appendix p 8), yielded nearly identical findings.

Patients with cancer were significantly less likely than patients without cancer to receive tocilizumab in wave 2 only, although this difference was small overall (appendix p 10). There were no significant differences in the numbers of patients receiving steroids in each group (appendix p 10). In patients without hypoxia, tocilizumab was very rarely used, but steroids were used in some patients, following a similar pattern to their use in hypoxic patients (appendix p 10).

The proportion of patients admitted to hospital having cancer treatment rose between waves 1 and 2, and between waves 2 and 3 (figure 4A). This corresponded with an increase in asymptomatic SARS-CoV-2 infections in these inter-wave periods (figure 4B). More patients were entered into the database during the second wave compared with other waves (appendix p 17).

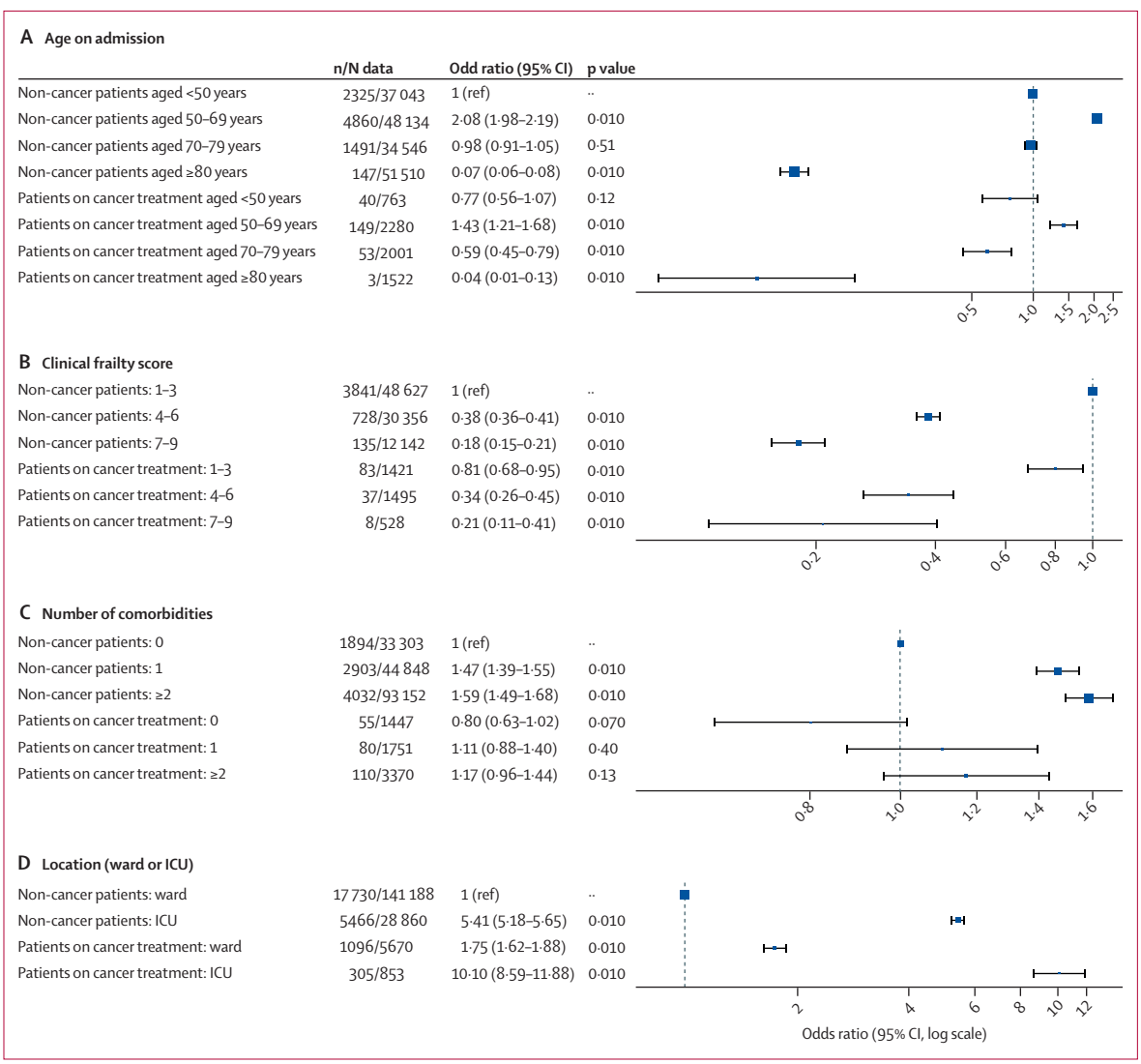

Figure 3: **Escalation of care in symptomatic patients with COVID-19**

Odds ratios (ORs) and 95% CIs from multivariable logistic regression models for intensive care unit (ICU) admission (A–C) and location of death (D) as the outcome variables are shown. The association of age (A), frailty (B), and multimorbidity (C) with critical care unit admission in patients with cancer and those without cancer is shown. Models were adjusted for age (except for panel A), sex, ethnicity, deprivation and the presence of chronic cardiac, pulmonary, and renal disease, and diabetes (except for panel C), and vaccination status. ORs for the death of patients without cancer and patients on cancer treatment on the ward and in the ICU are shown. Missing data were handled by imputation. The interaction effects for the variable of interest and cancer status are shown in the appendix (pp 38–39).

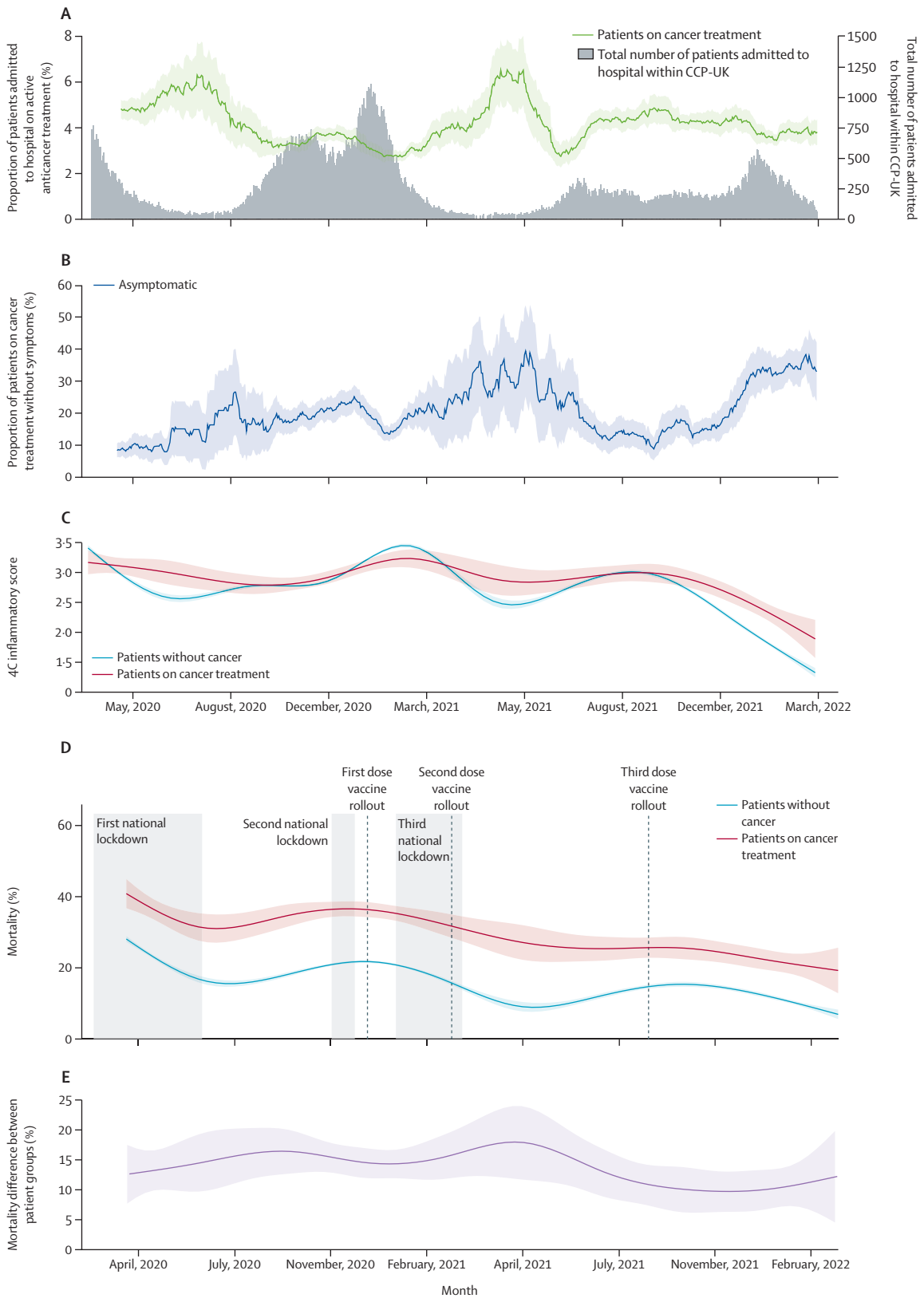

Figure 4: **Admission numbers, symptoms, and illness severity and mortality over time**
(A) Admission numbers over time by cancer minus frequency and total numbers. (B) Proportion of patients on cancer treatment who were symptomatic over time. (C) Illness severity over time, measured by the inflammatory components of the 4C score (C-reactive protein, respiratory rate, oxygen saturation, and urea), fitted with a GAM (line; shaded area represents 95% CI). (D) Mortality rate over time in patients having recent cancer treatment (red line) and patients with no history of cancer (blue line). These data were fitted with a GAM with and without 95% CIs, hence the percentages are slightly different from those reported in the main text. Key events in the first 2 years of the pandemic in the UK are also shown. (E) The percentage difference in mortality between patients on cancer treatment and patients without cancer is shown (GAM with or without 95% CI). CCP=WHO Clinical Characterisation Protocol. GAM=generalised additive model.

Severity of illness on admission, as measured by the inflammatory component of the 4C Mortality Score,[14] was comparable between patients with and without cancer over time (figure 4C). The inflammatory component of the 4C Mortality Score was between 1·9 (95% CI 1·6–2·2) and 3·3 (3·1–3·4) in patients on cancer treatment and between 1·3 (1·2–1·4) and 3·5 (3·4–3·5) in patients without cancer, only falling after the emergence of the omicron variant in the UK in November, 2021.

The mortality rate (4-week rolling average) in patients without cancer steadily decreased over the course of the pandemic, from 26% (95% CI 25–27%) in April, 2020, to 8·1% (95% CI 7·5–8·6%) in February, 2022 (figure 4D). Spikes in the risk of death in hospital for patients on cancer treatment were observed in the inter-wave periods, corresponding with an increase in asymptomatic infections in these periods. 4-week average mortality for patients on cancer treatment was highest in September, 2020 (48%; 95% CI 33–62) and June, 2021 (46%; 30–61). The relative difference in mortality between patients on cancer treatment and patients without cancer peaked in April, 2021, after the beginning of the second vaccine dose roll-out (figure 4E).

Discussion

Many studies have reported that patients with cancer have worse outcomes from COVID-19, but these studies have been limited by various factors including size, the retrospective nature of many, and, crucially, the absence of a contemporaneous control population.[2] Here, we have made four key novel observations. First, over the course of the pandemic, mortality in patients with cancer on treatment was always higher than in patients without cancer, despite the severity of illness being similar between these two groups. Second, while overall mortality reduced for patients with COVID-19 on cancer treatment over the time course of the pandemic, it never reached the lower levels of patients without cancer. Third, there were two periods when relative mortality rose for patients on cancer treatment: the difference in mortality between patients with and without cancer increased between March, 2020, and March, 2021, before decreasing. Last, younger patients had a worse relative outcome when compared with a control population of the same age.

To the best of our knowledge, this is the largest prospective study of COVID-19 outcomes in patients being treated for cancer across the pandemic with a contemporaneously recruited population without cancer. The novelty of our study is that the data are derived from a prespecified national sleeping protocol developed and put in place by the ISARIC in conjunction with WHO. The use of a prespecified protocol, including all patients with a positive SARS-CoV-2 test in all health-care settings continuously, and geographical breadth, reduce bias and strengthen the observations made. By considering patients who had received recent treatment for cancer and were admitted to hospital with COVID-19, we were able to focus on the group in which understanding and modifying the outcome can be expected to have the greatest difference.

Older patients on cancer treatment had the worse absolute outcomes from COVID-19. However, younger patients on cancer treatment were substantially more likely to die than those of the same age without cancer. Several studies have consistently reported that older age is an absolute risk factor for death among patients with cancer and COVID-19 (summarised in the appendix p 18–22).[2–6] These studies have either not made comparisons with contemporaneous control groups without cancer or they have been much smaller in size (appendix pp 18–22, 29–32), reinforcing the importance of suitable controls in observational studies. The reasons for this high relative risk in patients younger than 50 years likely relate to cancer types, treatment intensity, and behavioural factors such as more social mixing in younger patients with cancer. To the best of our knowledge, this the first study to report younger patients with cancer having a higher relative risk of poor outcomes from COVID-19. These data demonstrate the limitations of previous cancer studies, the benefit of prespecified protocols developed as part of pandemic planning, and also indicate the need to examine the comparative effects of age in future outbreaks.

The period of this study spanned from the first wave of the pandemic until the early omicron waves, when the BA.1 and BA.2 variants dominated in the UK. These data indicate that, in the spring of 2021, the gap in the risk of in-hospital mortality from COVID-19 between patients on cancer treatment and patients without cancer actually increased. Previous studies examining changes across the pandemic have not reported this finding. These studies have been limited by smaller sample sizes, the absence of a contemporaneous control population, and comparison of different time periods[22] rather than a continuous period, or they have been population-level studies and not protocolised prospective studies (appendix pp 35–36). In our study, data were updated daily and a population without cancer was available for comparison. Starkey and colleagues[23] reported longitudinal data from a similar period in the UK (November, 2020, to August, 2022). However, this population-level study, conducted over a shorter time period, used routinely collected health-care data, not a prospective case record form. Taken together, this suggests our method of data collection reduced bias as much as possible, explaining why the observation of a widening gap in mortality between patients on cancer treatment and patients without cancer at some points in the pandemic has not been observed by other groups. The reasons for periods of worsening outcomes for patients on cancer treatment are not clear. Increased societal interaction following the lifting of lockdown restrictions before implementation of vaccination might have affected patients with cancer more than patients without cancer, as

this group is more likely to have been shielding than the general population. Other possibilities include changes in the use of systemic anticancer therapy, reduced vaccine efficacy in specific groups of patients with cancer, such as those with haematological malignancies,[9,24] and vaccine waning.[25] An absence of vaccine response might have left patients with cancer more susceptible to the more virulent delta variant[26] in spring 2021—when we observed the greatest difference in mortality between patients on cancer treatment and patients without cancer. Patients with cancer also made up a larger proportion of the total number of patients recruited to CCP-UK during these periods.

Our data demonstrate that overall, patients on cancer treatment are less likely to have their care escalated to the ICU than patients without cancer. However, patients on cancer treatment younger than 50 years were not less likely to be admitted to ICU or ventilated than patients without cancer. Nevertheless, they still had higher mortality. We do not have sufficiently detailed data to come to any conclusions about individual-level escalation decisions. However, patients on cancer treatment also had worse outcomes after admission to ICU, suggesting that it is not withholding of treatment that drives mortality in this group. Most patients with cancer who do not get their care escalated are older, frailer, and more comorbid, and so the chance of a positive outcome from ICU is lower, similar to other patient groups. More research is needed into the drivers of the poorer outcomes of patients with cancer escalated to ICU with COVID-19 and whether any specific risk factors or treatments need to be considered.

Our study has some limitations. First, the ISARIC CCP-UK study was not designed to examine outcomes in patients with cancer, although the identification of patients on cancer treatment was performed prospectively and was part of the routine data collected during the study. Crucially, site research teams did not know the cancer status of patients until after selection for data entry. Therefore, selection bias is unlikely. Second, the study is restricted to the UK, which might have had higher mortality rates in patients with cancer compared with other countries.[27] However, these conclusions have been drawn from summative data across several EU countries, which might hide substantial differences between countries. Third, we did not have data on individual cancer types and treatments. The risk across different cancers and cancer treatments is heterogeneous,[2] as is the impact of vaccination.[28] This information is being collected in the follow-up CCP-CANCER UK study. Fourth, some data were missing, addressed by imputation, but there is always a risk of introducing inaccuracy with this approach. Fifth, we did not have detailed data on COVID-19 treatment, although we did have data on steroid use and tocilizumab. Many of our patients were recruited in the first and second waves, before usage of many of these measures was widespread. Sixth, the case record form was modified to collect this variable on April 23, 2020, meaning some data were missing from the first wave. However, at this time in the UK, there was little immunity to SARS-CoV-2 and no vaccines or therapeutics were available. The absence of data from this period does not affect the relevance of our findings going forward. Finally, we did not have data on admissions after Feb 28, 2022. Although mortality was still decreasing at that point, the range of estimates does include scenarios where this could have flattened out. Subsequent reports examining data throughout 2022 suggest that this difference remains and is of a similar magnitude.[29]

For patients receiving treatment for cancer, COVID-19 remains an ongoing risk that must be considered in patients on or commencing cancer treatment and appropriate mitigation strategies should be utilised. These include vaccination, testing of staff in settings of particular risk such as haemato-oncology, and ensuring patients access antivirals or therapeutic antibodies if they are exposed to SARS-CoV-2.[30] These data should inform planning for future pandemics, defining young age and patients on active cancer treatment as specific risk groups compared with the general population as well as ensuring there is a better understanding of the drivers of poorer outcomes for patients with cancer who are escalated to ICU. This study demonstrates the importance of pandemic preparedness and underscores the value of the ISARIC-WHO initiative, which collected data on all patients of all ages and was able to compare different populations prospectively. A key lesson for future pandemics is that, where possible, data for patients with cancer must be prioritised for entry into such prespecified national protocols, given all the advantages this holds compared with stand-alone cancer registries.

Contributors

LT was responsible for conceptualisation of the study, investigation, and writing the original draft. SE was responsible for formal data analysis, and writing (review and editing) of the manuscript. TMD was responsible for conceptualisation of the study, formal data analysis, and writing (review and editing) of the manuscript. MT was responsible for formal data analysis. EGK was responsible for investigation. WG was responsible for resources and investigation. HEH and WO were responsible for collection and curation of data, and project administration. GL and AL were responsible for curation and validation of data. RP and CAS were responsible for formal data analysis, and writing (review and editing) of the manuscript. JKB was responsible for conceptualisation of the study, investigation, funding acquisition, resources, supervision, and writing (review and editing) of the manuscript. PJMO was responsible for conceptualisation of the study, investigation, funding acquisition, and supervision. ABD was responsible for conceptualisation of the study, investigation, and supervision. MGS was responsible for conceptualisation of the study, investigation, funding acquisition, resources, supervision, project administration, and writing (review and editing) of the original draft. EMH was responsible for conceptualisation of the study, investigation, supervision, and writing (review and editing) of the original draft. CP was responsible for conceptualisation of the study, investigation, and writing (review and editing) of the original draft. All authors read and approved the final draft of the manuscript. SE, TMD, MT, AL, RP, CAS, EMH and MGS had access to, and verified, the raw data. All authors had

access to the analyses. No author was prevented from having access to the data using in this study, and all authors accept responsibility for publication.

Declaration of interests

LT has received consulting fees from the Medicines and Healthcare products Regulatory Agency; and from AstraZeneca and Synairgen, paid to the University of Liverpool; speakers' fees from Eisai paid to the University of Liverpool, and support for conference attendance from AstraZeneca. CP reports research grants and support from Pfizer, Daiichi Sankyo, Seagen, and North West Cancer; consulting fees from Pfizer, Roche, Daiichi Sankyo, Novartis, Exact Sciences, Gilead, Seagen, and Eli Lilly; payment for lectures from Pfizer, Novartis, and Eisai; and support for meeting attendance from Roche and Novartis. PJMO declares fees from GSK, Moderna, Seqirus, Sanofi, AstraZeneca, Icosavax, Pfizer, Medscape, and Janessen for consulting, speaking or chairing a symposium, paid to Imperial College London. MGS is chair of the infectious disease advisory board for Integrum Scientific, director of MedEx solutions, a shareholder of Integrum Scientific and MedEx solutions, participated in the data safety monitoring board for Pfizer's COVID-19 vaccine trials, and was donated an investigational medicinal product by Chiesi Farmaceutici. All other authors declare no competing interests.

Data sharing

This work uses data provided by patients and collected by the NHS as part of their care and support #DataSavesLives. The CO-CIN data was collated by ISARIC4C Investigators. ISARIC4C welcomes applications for data and material access through our Independent Data and Material Access Committee (https://isaric4c.net).

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