Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study

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Summary

Background Data on patients with COVID-19 who have cancer are lacking. Here we characterise the outcomes of a cohort of patients with cancer and COVID-19 and identify potential prognostic factors for mortality and severe illness.

Methods In this cohort study, we collected de-identified data on patients with active or previous malignancy, aged 18 years and older, with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from the USA, Canada, and Spain from the COVID-19 and Cancer Consortium (CCC19) database for whom baseline data were added between March 17 and April 16, 2020. We collected data on baseline clinical conditions, medications, cancer diagnosis and treatment, and COVID-19 disease course. The primary endpoint was all-cause mortality within 30 days of diagnosis of COVID-19. We assessed the association between the outcome and potential prognostic variables using logistic regression analyses, partially adjusted for age, sex, smoking status, and obesity. This study is registered with ClinicalTrials.gov, NCT04354701, and is ongoing.

Findings Of 1035 records entered into the CCC19 database during the study period, 928 patients met inclusion criteria for our analysis. Median age was 66 years (IQR 57–76), 279 (30%) were aged 75 years or older, and 468 (50%) patients were male. The most prevalent malignancies were breast (191 [21%]) and prostate (152 [16%]). 366 (39%) patients were on active anticancer treatment, and 396 (43%) had active (measurable) cancer. At analysis (May 7, 2020), 121 (13%) patients had died. In logistic regression analysis, independent factors associated with increased 30-day mortality, after partial adjustment, were: increased age (per 10 years; partially adjusted odds ratio 1·84, 95% CI 1·53–2·21), male sex (1·63, 1·07–2·48), smoking status (former smoker *vs* never smoked: 1·60, 1·03–2·47), number of comorbidities (two *vs* none: 4·50, 1·33–15·28), Eastern Cooperative Oncology Group performance status of 2 or higher (status of 2 *vs* 0 or 1: 3·89, 2·11–7·18), active cancer (progressing *vs* remission: 5·20, 2·77–9·77), and receipt of azithromycin plus hydroxychloroquine (*vs* treatment with neither: 2·93, 1·79–4·79; confounding by indication cannot be excluded). Compared with residence in the US-Northeast, residence in Canada (0·24, 0·07–0·84) or the US-Midwest (0·50, 0·28–0·90) were associated with decreased 30-day all-cause mortality. Race and ethnicity, obesity status, cancer type, type of anticancer therapy, and recent surgery were not associated with mortality.

Interpretation Among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general risk factors and risk factors unique to patients with cancer. Longer follow-up is needed to better understand the effect of COVID-19 on outcomes in patients with cancer, including the ability to continue specific cancer treatments.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting illness, COVID-19, have emerged as a global pandemic.[1] Initial reports suggested that patients with a history of or active malignancy might be at increased risk of contracting the virus and developing COVID-19-related complications.[2–4] Yet, initial reports are restricted by sample size, geographical region, and a lack of generalisability of findings to the overall population of patients with cancer.

Patients with cancer might be immunocompromised by the effects of antineoplastic therapy, supportive

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Research in context

Evidence before this study

Very little evidence exists describing the natural history of patients with cancer who have COVID-19, the disease associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of May 7, 2020, the peer-reviewed literature was limited to small or single-institution case series; the largest series that we are aware of had 334 cases at a single institution. These case series are of insufficient size or breadth to draw statistical and generalisable conclusions about the factors that might be associated with better or worse outcomes for patients with cancer.

Added value of this study

To our knowledge, we report the largest series of patients with cancer and COVID-19 to date, including over 900 patients with a broad geographical distribution. The population is diverse in terms of age distribution, race and ethnicity, cancer status, and whether they are on active anticancer treatment. We found significant associations with increased 30-day all-cause mortality and the general factors of increasing age, male sex, former smoking, number of comorbidities, and receipt of azithromycin plus hydroxychloroquine; and the cancer-specific factors of moderate or poor Eastern Cooperative Oncology Group performance status and active (measurable) cancer. However, we cannot formally ascertain if the combination of hydroxychloroquine and azithromycin gives any clinical benefit or overall harm to patients, given the non-randomised nature of the study, and the possibility of other potential clinical imbalances.

Implications of all the available evidence

We identified several cancer-specific factors that are associated with increased 30-day all-cause mortality in patients with cancer and COVID-19, in addition to previously reported factors of age and sex in the general population. These findings have implications for patients and health-care providers who will be confronted with difficult decisions during the SARS-CoV-2 pandemic, such as whether to withhold or continue anticancer treatments, and whether to accelerate end-of-life planning under some circumstances.

medications such as steroids, and the immunosuppressive properties of cancer itself; they might also have an augmented immune response to infection secondary to immunomodulatory drugs, such as programmed cell death 1 or programmed cell death ligand 1 inhibitors.[5] Additionally, patients with cancer are often older (ie, aged ≥60 years) with one or more major comorbidities, putting them at increased risk for COVID-19-related morbidity and mortality.[6] Furthermore, they often have high levels of contact with the health-care system through provider visits for anticancer therapy, monitoring, and preventive and supportive care.

Given the worldwide prevalence of cancer and the high transmissibility of SARS-CoV-2, an understanding of the disease course of COVID-19 and factors influencing clinical outcomes in patients with cancer is urgently needed. In this cohort study, we hypothesised that demographic, clinical, underlying cancer, and COVID-19 treatment-related variables are associated with 30-day all-cause mortality in this population.

Methods

Study design and participants

In this cohort study, we report data from the COVID-19 and Cancer Consortium (CCC19) registry database. The CCC19 was formed on March 15, 2020, to study the clinical characteristics and course of illness among patients with COVID-19 who have a current or past diagnosis of cancer; accrual to the registry started on March 17, 2020.[7] The registry is built and maintained as an electronic REDCap database housed at Vanderbilt University Medical Center (VUMC).[8]

The CCC19 registry is accruing de-identified data on adult patients (aged 18 years or older) with a current or past history of haematological malignancy or invasive solid tumour who have either a laboratory-confirmed SARS-CoV-2 infection or a presumptive diagnosis of COVID-19. Contributing institutions in the consortium (appendix pp 2–5) independently identify consecutive patients and report data through the online REDCap data collection survey instruments developed by CCC19 (appendix pp 14–18). Participating institutions were restricted to the USA and Canada. Participation by anonymous individual health-care practitioners located in Argentina, Canada, the EU, the UK, and the USA is also allowed. The mechanism of data collection can be retrospective (after the course of COVID-19) or concurrent, at the discretion of the respondent. Collection of follow-up data is strongly encouraged.

For this initial analysis, we collected data for patients who had baseline data entered onto the database between March 17 and April 16, 2020, and had follow-up data entered up until May 7, 2020. Patients eligible for inclusion were adults (aged 18 years or older), with a diagnosed invasive or haematological malignancy at any time, and a resident of the USA, Canada, or Spain. Due to possible confounding by other infections, patients with presumptive COVID-19 who did not have a laboratory-confirmed SARS-CoV-2 infection were excluded. Patients with non-invasive cancers including non-melanomatous skin cancer, in-situ carcinoma, or precursor haematological neoplasms were excluded from this analysis.

This study was considered exempt from institutional review board (IRB) review (VUMC IRB 200467) and was approved by local IRBs at participating sites per institutional policy, according to the principles of the Declaration of Helsinki. This study is registered on ClinicalTrials.gov, NCT04354701, and is ongoing.

Procedures

The CCC19 survey collects de-identified data across approximately 300 structured and free-text variables in five forms: patient demographics, COVID-19 initial course of illness, cancer details, respondent details (ie, health-care provider details), and follow-up. Potential prognostic variables were included: age, sex, race and ethnicity, geographical location of patient residence, smoking status, obesity, number of comorbidities requiring active treatment, recent surgery (including, but not limited to cancer surgeries, within 4 weeks of COVID-19 diagnosis), type of malignancy, cancer status (remission *vs* active [measurable] disease, with active further defined as stable or responding to treatment *vs* progressing), Eastern Cooperative Oncology Group (ECOG) performance status, anticancer therapy, and COVID-19 treatment with azithromycin, hydroxychloroquine, or both in combination. Active anticancer therapy was defined as either cytotoxic chemotherapy or all other therapies except surgery (targeted drugs, endocrine therapy, immunotherapy, radiotherapy) given within 4 weeks of COVID-19 diagnosis (appendix pp 14–18).

Outcomes

The primary endpoint was all-cause mortality within 30 days of diagnosis of COVID-19. Secondary outcomes were: a composite of severe illness (death, severe illness requiring admission to hospital, admission to an intensive care unit [ICU], mechanical ventilation, or a combination of these); admission to hospital; admission to an ICU; mechanical ventilation; and need for supplemental oxygen during the course of COVID-19.

Statistical analysis

A predefined statistical analysis plan was finalised before accrual lock (April 16, 2020) and was revised once before data analysis (April 18, 2020; appendix pp 6–8). Because of the possibility of a small number of events (deaths), we prespecified the potential prognostic variables for the primary outcome using clinical knowledge and allowable complexity of the model (ie, the number of covariates and degrees of freedom) on the basis of an effective sample size. We provided an unknown category for every variable in the survey. Because some of the survey questions were optional, we anticipated a non-zero level of missingness for some variables (ie, the answer box for the question could be left blank). We used multiple imputation using additive regression, bootstrapping, and predictive mean matching with ten iterations for variables with a 10% or lower missingness rate; variables with a missingness rate of more than 10% were not included in our analyses.

We used descriptive statistics to show the baseline demographic information of the participants included in our analyses.

Due to privacy restrictions, we collected dates of COVID-19 diagnosis as intervals (eg, diagnosed 2–4 weeks ago). As a result, we planned an interval-censored Cox proportional hazards analysis; however, wide diagnosis intervals and insufficient primary outcome events restricted our ability to do this analysis. Therefore, we examined the correlations between the study variables and primary endpoint using a logistic regression model for bivariable and predetermined multivariable data analysis. In the multivariable model we partially adjusted the odds ratios: age was adjusted for sex, smoking status, and obesity; sex was adjusted for age, smoking status, and obesity; smoking status was adjusted for age, sex, and obesity; obesity was adjusted for age, sex, and smoking status; and the other covariates were adjusted for age, sex, smoking status, and obesity. Age was treated as a continuous variable with age 90 years and older transformed into 90 years for modelling. We did not adjust our results for multiple comparisons. We assessed goodness of fit using Harrell's C-statistic with 95% CIs determined using DeLong and colleagues' method.[9,10] We calculated variance inflation factors for every potential prognostic variable in each adjusted model.

In an exploratory subanalysis, we also applied an elastic net regularised logistic regression analysis to examine the shrinkage of the coefficients in the predetermined set of covariates.[11] Given the high rate of clinically important secondary outcomes, we did a post-hoc, fully adjusted, logistic regression analysis of the secondary composite endpoint of severe illness. We also did post-hoc power analyses for the recent surgery and anticancer treatment variables to examine the study effect sizes.

We did all data analyses using base R (version 3.6.3) and the R packages rms 5.1-4 and Hmisc 4.4-0.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 1035 records with completed baseline forms added to the database during our study period, 928 patients met criteria for inclusion in the analyses (appendix p 10). Of these records, 73 (8%) reports originated from community practices and 851 (92%) from academic medical centres. 826 (89%) reports were from participating institutions and the remaining 102 (11%) were anonymous. Median follow-up for the cohort was 21 days (IQR 11–41 days). 570 (61%) records were initialised during the course of COVID-19; of these, 255 (45%) had at least one follow-up report.

Demographic, clinical, and tumour characteristics for the analysable population are in table 1 (data for 84 non-laboratory-confirmed cases are in the appendix [pp 22–23]). Median patient age was 66 years (IQR 57–76), 279 (30%) were aged 75 years or older, and 468 (50%) patients were

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For the **COVID-19 and Cancer Consortium website** see https://ccc19.org/

See **Online** for appendix

	Analysable population (n=928)
Age, years*	
Median	66 (57–76)
Range	18 to >90
<65	412 (44%)
65–74	237 (26%)
≥75	279 (30%)
Sex	
Female	459 (49%)
Male	468 (50%)
Not specified	1 (<1%)
Race and ethnicity†	
Non-Hispanic white	460 (50%)
Non-Hispanic black	148 (16%)
Hispanic	150 (16%)
Other or unknown	128 (14%)
Data missing	42 (5%)
Region of patient residence‡	
US-Northeast	375 (40%)
US-Midwest	203 (22%)
US-South	117 (13%)
US-West	116 (13%)
Canada	49 (5%)
Spain	68 (7%)
Smoking status†	
Never smoked	469 (51%)
Former smoker	326 (35%)
Current smoker	43 (5%)
Unknown	57 (6%)
Data missing	33 (4%)
Obesity status†	
Not specified	720 (78%)
Obese	172 (19%)
Data missing	36 (4%)
Number of comorbidities†	
0	132 (14%)
1	202 (22%)
2	231 (25%)
3	117 (13%)
≥4	192 (21%)
Unknown	23 (2%)
Data missing	31 (3%)
Type of malignancy§	
Solid tumours	758 (82%)
Breast	191 (21%)
Prostate	152 (16%)
Gastrointestinal	108 (12%)
Thoracic	91 (10%)
Gynaecological	49 (5%)
Renal cell carcinoma	45 (5%)
Endocrine	39 (4%)
Melanoma	38 (4%)

(Table 1 continues in next column)

male. 460 (50%) patients were non-Hispanic white, 148 (16%) were non-Hispanic black, and 150 (16%) were Hispanic. The most common geographical region of residence was the US-Northeast (375 [40%]). The most prevalent malignancies were breast (191 [21%]) and prostate (152 [16%]). 422 (45%) patients were reported to be in remission and 396 (43%) to have active cancer. Of those

	Analysable population (n=928)
(Continued from previous column)	
Head and neck	30 (3%)
Sarcoma	24 (3%)
Nervous system	12 (1%)
Solid tumour, not otherwise specified	43 (5%)
Haematological malignancies	204 (22%)
Lymphoid neoplasms	102 (11%)
Low-grade non-Hodgkin lymphoma	54 (6%)
High-grade non-Hodgkin lymphoma	27 (3%)
Acute lymphoblastic leukaemia	6 (1%)
Multiple myeloma	55 (6%)
Myeloid neoplasms	42 (5%)
Acute myeloid leukaemia	13 (1%)
Haematological malignancy, not otherwise specified	6 (1%)
Cancer status†	
Remission or no evidence of disease	422 (45%)
Present, stable, or responding to treatment	294 (32%)
Present, progressive disease	102 (11%)
Unknown	59 (6%)
Data missing	51 (5%)
ECOG performance status†	
0 or 1	614 (66%)
2	72 (8%)
3 or 4	46 (5%)
Unknown	167 (18%)
Data missing	29 (3%)
Type of anticancer therapy§	
None in the 4 weeks before COVID-19 diagnosis	553 (60%)
Non-cytotoxic therapy	206 (22%)
Targeted therapy	75 (8%)
Endocrine	85 (9%)
Immunotherapy¶	38 (4%)
Radiotherapy	12 (1%)
Surgery‖	2 (<1%)
Cytotoxic systemic therapy	160 (17%)
Unknown	9 (1%)
Recent surgery†	
None in the 4 weeks before COVID-19 diagnosis	811 (87%)
Yes‖	32 (3%)
Unknown	42 (5%)
Data missing	43 (5%)

(Table 1 continues on next page)

with active cancer, 294 (74%) had stable or responding disease, and 102 (26%) had progressive disease at the time of COVID-19 diagnosis. 366 (39%) patients had received anticancer therapy within 4 weeks of COVID-19 diagnosis, of whom, 160 (44%) were receiving cytotoxic therapy and 206 (56%) were receiving other anticancer therapies. The four most common presenting symptoms of COVID-19 were fever (590 [64%]), cough (563 [61%]), fatigue or malaise (396 [43%]), and dyspnoea (382 [41%]; appendix p 11). 40 (4%) patients were reported as asymptomatic. 89 (10%) patients were given hydroxychloroquine alone, 93 (10%) were given azithromycin alone, and 181 (20%) were given a combination of these drugs. Notably, only two (<1%) patients were reported to have been given these drugs within the context of a clinical trial.

As of May 7, 2020, 121 (13%) patients had died, all within 30 days of COVID-19 diagnosis (table 2). None of the potential prognostic variables had a missingness rate of more than 10% and all were therefore included in the multivariable models. Associations between prognostic variables and 30-day all-cause mortality are shown in table 3. Goodness of fit was similar across the fitted models, with an average C-statistic value of 0·75 (95% CI 0·71–0·80; appendix p 25). None of the variance inflation factors except for comorbidity was greater than five (appendix p 25), indicating that significant multicollinearity was not present in the models, with this exception. Multiple clinically relevant prognostic variables associated with increased 30-day all-cause mortality were identified, after partial adjustment in our multivariable model: increasing age, male sex, smoking status (former smoker *vs* never smoked), cancer status (present, stable, or responding, and present, progressive disease *vs* remission or no evidence of disease), ECOG performance status (2 *vs* 0 or 1; 3 or 4 *vs* 0 or 1); and treatment with hydroxychloroquine plus azithromycin versus treatment with neither (table 3). Two, three, and four or more comorbidities requiring treatment were also associated with increased mortality, although the 95% CIs were

	Analysable population (n=928)
(Continued from previous page)	
Treatment of COVID-19†**	
Hydroxychloroquine alone	89 (10%)
Azithromycin alone	93 (10%)
Azithromycin plus hydroxychloroquine	181 (20%)
Neither	486 (52%)
Unknown	22 (2%)
Data missing	57 (6%)

Data are n (%), median (IQR), or range. Due to rounding, not all variables might add up to 100%. ECOG=Eastern Cooperative Oncology Group. *Age ≥90 years transformed into exact age of 90 years for reporting purposes. †These questions were optional in the survey, such that a proportion of results are missing. ‡US regions are census-tract defined. §Proportions might add up to more than 100% because some patients had more than one malignancy or received more than one treatment concurrently. ¶Includes checkpoint inhibitors, allogeneic haemopoietic stem-cell transplant, and adaptive cellular therapy. ||Cancer surgeries are separated in the table for descriptive purposes but are combined with any recent surgery in the prognostic modelling. **Some patients were already taking these medications at the time of presentation: hydroxychloroquine (n=12 [1%]), azithromycin (n=26 [3%]), or both (n=23 [2%]).

Table 1: **Patient demographic, clinical, and tumour characteristics**

	Died	Met composite endpoint	Admitted to an ICU	Required mechanical ventilation
Total (n=928)	121 (13%)	242 (26%)	132 (14%)	116 (12%)
Age, years				
<65 (n=412)	25 (6%)	68 (17%)	44 (11%)	38 (9%)
65–74 (n=237)	26 (11%)	60 (25%)	38 (16%)	34 (14%)
≥75 (n=279)	70 (25%)	114 (41%)	50 (18%)	44 (16%)
Sex*				
Female (n=459)	43 (9%)	101 (22%)	52 (11%)	45 (10%)
Male (n=468)	78 (17%)	141 (30%)	80 (17%)	71 (15%)
Race and ethnicity				
Non-Hispanic white (n=460)	71 (15%)	126 (27%)	60 (13%)	53 (12%)
Non-Hispanic black (n=148)	20 (14%)	42 (28%)	28 (19%)	25 (17%)
Hispanic (n=150)	16 (11%)	32 (21%)	18 (12%)	16 (11%)
Other or unknown (n=128)	12 (9%)	37 (29%)	24 (19%)	21 (16%)
Data missing (n=42)	2 (5%)	5 (12%)	2 (5%)	1 (2%)
Region of patient residence†				
US-Northeast (n=375)	55 (15%)	107 (29%)	56 (15%)	54 (14%)
US-Midwest (n=203)	19 (9%)	55 (27%)	38 (19%)	32 (16%)
US-South (n=117)	15 (13%)	30 (26%)	19 (16%)	17 (15%)
US-West (n=116)	19 (16%)	27 (23%)	14 (12%)	9 (8%)
Canada (n=49)	3 (6%)	11 (22%)	5 (10%)	4 (8%)
Spain (n=68)	10 (15%)	12 (18%)	0	0
Smoking status				
Never smoked (n=469)	44 (9%)	99 (21%)	54 (12%)	48 (10%)
Former smoker (n=326)	64 (20%)	116 (36%)	64 (20%)	55 (17%)
Current smoker (n=43)	5 (12%)	8 (19%)	4 (9%)	4 (9%)
Unknown (n=57)	6 (11%)	15 (26%)	9 (16%)	8 (14%)
Data missing (n=33)	2 (6%)	4 (12%)	1 (3%)	1 (3%)
Obesity status				
Not specified (n=720)	98 (14%)	190 (26%)	95 (13%)	83 (12%)
Obese (n=172)	20 (12%)	49 (28%)	36 (21%)	32 (19%)
Data missing (n=36)	3 (8%)	3 (8%)	1 (3%)	1 (3%)
Number of comorbidities				
0 (n=132)	3 (2%)	12 (9%)	6 (5%)	4 (3%)
1 (n=202)	13 (6%)	31 (15%)	18 (9%)	13 (6%)
2 (n=231)	41 (18%)	79 (34%)	42 (18%)	39 (17%)
3 (n=117)	24 (21%)	37 (32%)	20 (17%)	18 (15%)
≥4 (n=192)	31 (16%)	71 (37%)	41 (21%)	35 (18%)
Unknown (n=23)	5 (22%)	8 (35%)	4 (17%)	5 (22%)
Data missing (n=31)	4 (13%)	4 (13%)	1 (3%)	2 (6%)
Type of malignancy				
Solid tumour (n=654)	76 (12%)	151 (23%)	78 (12%)	70 (11%)
Haematological malignancy (n=167)	24 (14%)	58 (35%)	37 (22%)	28 (17%)
Multiple cancers‡ (n=107)	21 (20%)	33 (31%)	17 (16%)	18 (17%)

(Table 2 continues on next page)

	Died	Met composite endpoint	Admitted to an ICU	Required mechanical ventilation
(Continued from previous page)				
Cancer status				
Remission or no evidence of disease (n=422)	39 (9%)	95 (23%)	63 (15%)	55 (13%)
Present, stable, or responding to treatment (n=294)	41 (14%)	80 (27%)	40 (14%)	38 (13%)
Present, progressive disease (n=102)	25 (25%)	36 (35%)	12 (12%)	11 (11%)
Unknown (n=59)	11 (19%)	23 (39%)	14 (24%)	11 (19%)
Data missing (n=51)	5 (10%)	8 (16%)	3 (6%)	1 (2%)
ECOG performance status				
0 or 1 (n=614)	54 (9%)	135 (22%)	81 (13%)	81 (13%)
2 (n=72)	23 (32%)	31 (43%)	16 (22%)	8 (11%)
3 or 4 (n=46)	19 (41%)	22 (48%)	6 (13%)	5 (11%)
Unknown (n=167)	22 (13%)	51 (31%)	28 (17%)	21 (13%)
Data missing (n=29)	3 (10%)	3 (10%)	1 (3%)	1 (3%)
Type of anticancer therapy				
None in the 4 weeks before COVID-19 diagnosis (n=553)	75 (14%)	156 (28%)	91 (16%)	79 (14%)
Non-cytotoxic therapy (n=206)	23 (11%)	50 (24%)	24 (12%)	24 (12%)
Cytotoxic systemic therapy (n=160)	22 (14%)	35 (22%)	17 (11%)	12 (8%)
Unknown (n=9)	1 (11%)	1 (11%)	0	1 (11%)
Recent surgery				
None in the 4 weeks before COVID-19 diagnosis (n=811)	108 (13%)	212 (26%)	118 (15%)	104 (13%)
Yes (n=32)	6 (19%)	12 (38%)	6 (19%)	7 (22%)
Unknown (n=42)	4 (10%)	14 (33%)	6 (14%)	3 (7%)
Data missing (n=43)	3 (7%)	4 (9%)	2 (5%)	2 (5%)
Treatment of COVID-19				
Hydroxychloroquine alone (n=89)	11 (12%)	32 (36%)	18 (20%)	14 (16%)
Azithromycin alone (n=93)	12 (13%)	26 (28%)	15 (16%)	14 (15%)
Azithromycin plus hydroxychloroquine (n=181)	45 (25%)	86 (48%)	53 (29%)	51 (28%)
Neither (n=486)	41 (8%)	80 (16%)	39 (8%)	29 (6%)
Unknown (n=22)	7 (32%)	8 (36%)	2 (9%)	4 (18%)
Data missing (n=57)	5 (9%)	10 (18%)	5 (9%)	4 (7%)

Data are n (%). Due to rounding, not all variables might add up to 100%. The composite endpoint was a combination of death, severe illness requiring admission to hospital, admission to an ICU, or mechanical ventilation. ECOG=Eastern Cooperative Oncology Group. ICU=intensive care unit. *Data not shown for one patient, with sex not specified. †US regions are census-tract defined. ‡Any patient with two or more cancers reported, which could be solid, haematological, or both.

Table 2: **Primary and secondary outcomes by potential prognostic variables**

very wide due to a small number of events in the reference group (no comorbidities). Residence in Canada or the US-Midwest was associated with decreased mortality compared with residence in the US-Northeast. Race and ethnicity, obesity, type of malignancy, type and recency of anticancer therapy, and recent surgery were not associated with 30-day all-cause mortality in the partially adjusted analysis. A forest plot of the potential prognostic variables is shown in figure 1. Results of the elastic net regularised logistic regression analysis are similar to those of the primary analysis; however, the association between present and stable or responding disease and mortality was no longer significant (appendix p 26).

242 (26%) patients met the composite severe illness endpoint; 132 (14%) patients were admitted to the ICU; and 116 (12%) required mechanical ventilation (table 2). 52 (39%) of 132 patients who were in the ICU at baseline had 30-day follow-up data available. During follow-up, 16 (31%) of 52 died, 13 (25%) were still in the ICU, and 19 (37%) had recovered. Notably, 71 (59%) of 121 patients who died were never admitted to the ICU; a comparison between patients who died with and without ICU admission is in the appendix (p 27). A numerically higher rate of death outside the ICU was seen in patients with present cancer, with the reverse pattern seen for those in remission. Furthermore, we saw a numerically higher rate of death outside the ICU for patients receiving palliative care, and the reverse pattern for these receiving care with a curative intent. 43 (61%) of 70 patients who died aged 75 and older died without ICU admission, compared with 27 (39%) who died with ICU admission. 466 (50%) required admission to hospital, of whom 175 (38%) were actively receiving anticancer therapy. Admissions to hospital differed by geographical region, from 37 (32%) of 116 patients in the US-West region to 34 (69%) of 49 patients in Canada. 405 (44%) patients required supplemental oxygen (appendix pp 28–29).

The crude mortality for patients who met the secondary outcomes was 106 (23%) of 466 for any admission to hospital, 110 (27%) of 405 for any supplemental oxygen needed, 50 (38%) of 132 for admission to ICU, 50 (43%) of 116 for requiring mechanical ventilation, and 121 (50%) of 242 for the composite secondary endpoint. Incidence of secondary outcomes by cancer type, cancer status, and anticancer therapy type-defined subgroups are shown in figure 2 and in the appendix (p 12). ICU admission rates were highest in former smokers and in those with obesity, four or more comorbidities, haematological malignancies, unknown cancer status, and an ECOG performance status of 2. Rates of mechanical ventilation were highest in those with unknown comorbidity status and in those with recent surgery.

From our post-hoc analysis of the severe illness composite outcome we found that increasing age, other or unknown race or ethnicity, number of comorbidities (two and four or more), haematological malignancy, progressing cancer or unknown cancer status, ECOG performance status of 2 or higher, or treatment with azithromycin, hydroxychloroquine, and both in combination were associated with an increased rate of the composite outcome (appendix pp 13, 30–31). Based on the post-hoc power analysis of the recent surgery and anticancer treatment variables, the effect sizes are reasonable and clinically meaningful (appendix p 9).

	Bivariable odds ratio	Multivariable partially adjusted odds ratio*
Age, per 10 years†	1·88 (1·58–2·24)	1·84 (1·53–2·21)
Sex		
Female	1 (ref)	1 (ref)
Male	1·94 (1·30–2·88)	1·63 (1·07–2·48)
Race and ethnicity		
Non-Hispanic white	1 (ref)	1 (ref)
Non-Hispanic black	0·85 (0·50–1·45)	1·11 (0·63–1·97)
Hispanic	0·65 (0·36–1·17)	1·00 (0·54–1·86)
Other or unknown	0·57 (0·30–1·09)	0·55 (0·28–1·08)
Region of patient residence‡		
US-Northeast	1 (ref)	1 (ref)
US-Midwest	0·60 (0·35–1·04)	0·50 (0·28–0·90)
US-South	0·86 (0·46–1·58)	1·18 (0·61–2·26)
US-West	1·14 (0·65–2·01)	1·21 (0·66–2·23)
Canada	0·38 (0·11–1·26)	0·24 (0·07–0·84)
Spain	1·00 (0·48–2·08)	1·17 (0·54–2·55)
Smoking status		
Never smoked	1 (ref)	1 (ref)
Former smoker	2·35 (1·55–3·55)	1·60 (1·03–2·47)
Current smoker	1·27 (0·47–3·39)	1·34 (0·49–3·67)
Unknown	1·14 (0·46–2·79)	0·89 (0·34–2·27)
Obesity status		
Not specified	1 (ref)	1 (ref)
Obese	0·84 (0·50–1·41)	0·99 (0·58–1·71)
Number of comorbidities		
0	1 (ref)§	1 (ref)§
1	3·12 (0·87–11·19)	1·87 (0·51–6·85)
2	9·52 (2·89–31·40)	4·50 (1·33–15·28)
3	11·54 (3·37–39·53)	5·04 (1·42–17·93)
≥4	8·77 (2·62–29·29)	3·55 (1·03–12·30)
Unknown	12·33 (2·71–56·01)	6·77 (1·42–32·33)
Type of malignancy		
Solid tumour	1 (ref)	1 (ref)
Haematological malignancy	1·28 (0·78–2·09)	1·40 (0·83–2·37)
Multiple cancers	1·86 (1·09–3·17)	1·34 (0·77–2·34)
Cancer status		
Remission or no evidence of disease	1 (ref)	1 (ref)
Present, stable, or responding to treatment	1·57 (0·98–2·49)	1·79 (1·09–2·95)
Present, progressive disease	3·07 (1·77–5·33)	5·20 (2·77–9·77)
Other or unknown	2·24 (1·06–4·71)	2·71 (1·21–6·09)
ECOG performance status		
0 or 1	1 (ref)	1 (ref)
2	4·84 (2·75–8·52)	3·89 (2·11–7·18)
3 or 4	7·33 (3·83–14·01)	5·66 (2·79–11·47)
Unknown	1·59 (0·93–2·73)	1·43 (0·81–2·50)
Type of anticancer therapy		
None in the 4 weeks before COVID-19 diagnosis	1 (ref)	1 (ref)
Non-cytotoxic therapy	0·80 (0·49–1·32)	1·04 (0·62–1·76)
Cytotoxic systemic therapy	1·02 (0·61–1·69)	1·47 (0·84–2·56)
Unknown	0·80 (0·10–6·46)	1·60 (0·18–14·14)
Recent surgery¶		
None in the 4 weeks before COVID-19 diagnosis	1 (ref)	1 (ref)
Yes	1·50 (0·60–3·74)	1·52 (0·58–3·96)
Unknown	0·66 (0·23–1·89)	0·78 (0·26–2·33)
Treatment of COVID-19		
Hydroxychloroquine alone	1·43 (0·71–2·90)	1·06 (0·51–2·20)
Azithromycin alone	1·56 (0·79–3·06)	1·30 (0·65–2·64)
Azithromycin plus hydroxychloroquine	3·42 (2·14–5·45)	2·93 (1·79–4·79)
Neither	1 (ref)	1 (ref)
Unknown	4·82 (1·84–12·60)	3·97 (1·41–11·19)

(Table 3 continues in next column)

(Continued from previous column)

Data are odds ratio with 95% CI in parentheses. ECOG=Eastern Cooperative Oncology Group. *Age is adjusted for sex, smoking status, and obesity; sex is adjusted for age, smoking status, and obesity; smoking status is adjusted for age, sex, and obesity; obesity is adjusted for age, sex, and smoking status; and all other variables are adjusted for age, sex, smoking status, and obesity. †Age ≥90 years transformed into exact age of 90 years for modelling purposes; odds ratios are per 10-year age increment. ‡US regions are census-tract defined. §Precision of estimation for this category is poor due to small number of events in the reference group. ¶Includes any surgery, including cancer-specific surgeries, done within 4 weeks of COVID-19 diagnosis.

Table 3: **Bivariable and multivariable regression models of potential prognostic variables associated with 30-day all-cause mortality**

Discussion

The CCC19 began as a grassroots effort to fill an unmet need generated by the SARS-CoV-2 pandemic. Through social media and other communication networks, over 100 institutions have been mobilised to capture widely needed data regarding outcomes of COVID-19 in patients with cancer. The initial mission of the consortium is data capture to better understand strategies to mitigate risk for patients with cancer. This first analysis of the CCC19 database focuses on important and previously recognised cancer and COVID-19 prognostic factors to provide urgently needed information on the scope, clinical management, and outcomes of patients with cancer and a diagnosis of COVID-19.

Several important hypotheses have emerged from this initial analysis. First, patients with cancer appear to be at increased risk of mortality and severe illness due to SARS-CoV-2 infection, regardless of whether they have active cancer, are on anticancer treatment, or both. Most members of our cohort had symptoms compatible with COVID-19, and the overall rate of complications was high. For example, a report on a cohort of similar size from China in an unselected patient population reported a death rate of 1·4% (*vs* our observed 13%) and a similar composite endpoint with a rate of 6·1% (*vs* our observed 26%).[12] Two publications from single institutions in the

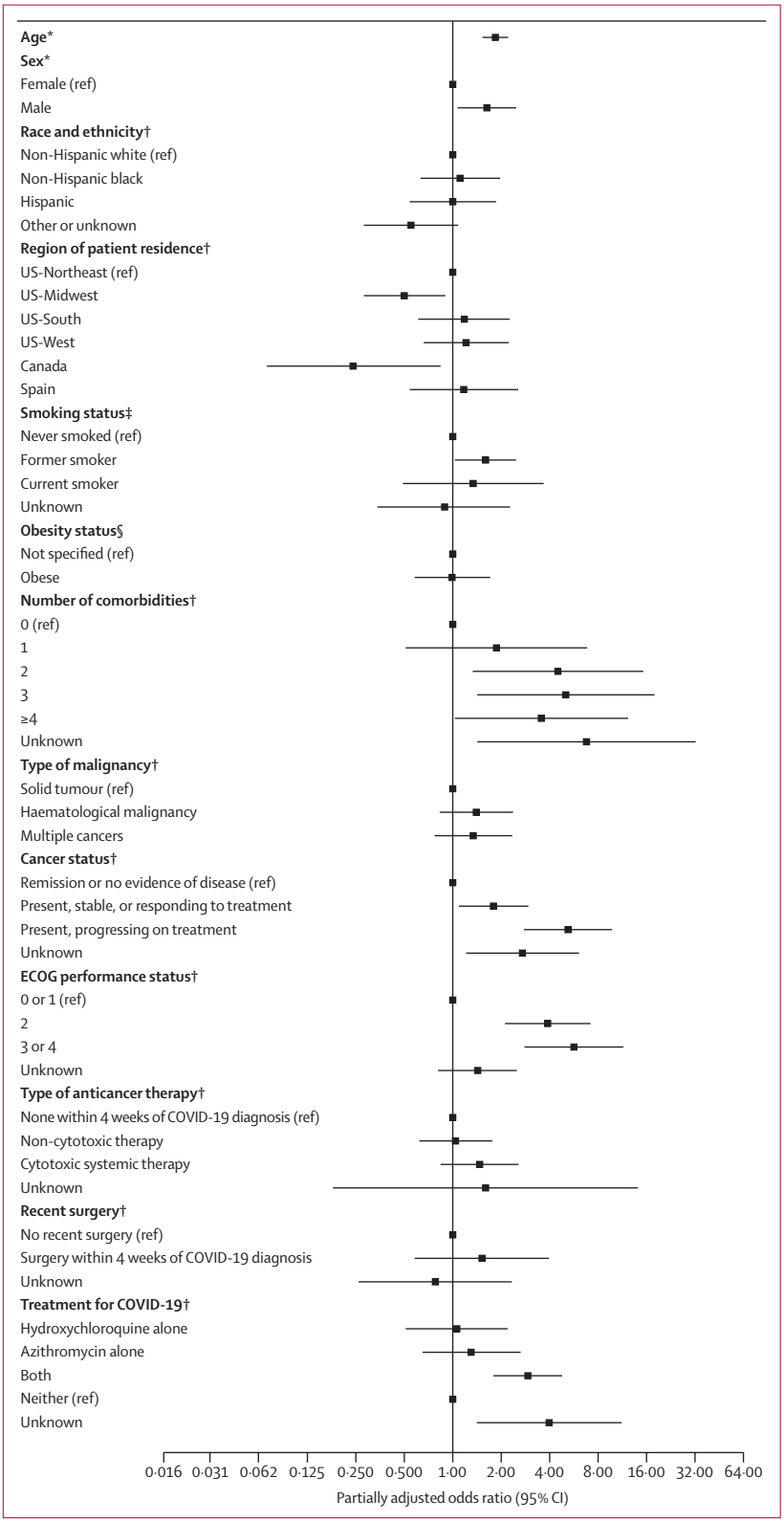

Figure 1: **Forest plot of factors associated with 30-day all-cause mortality**
Data are partially adjusted odds ratios, with 95% CIs. ECOG=Eastern Cooperative Oncology Group. *Adjusted for sex, smoking status, and obesity. †Adjusted for age, sex, smoking status, and obesity. ‡Adjusted for age, sex, and obesity. §Adjusted for age, sex, and smoking status.

New York City region (NY, USA) have reported specifically on outcomes in patients with cancer.[4,13] An aggregate-level analysis of 334 patients with cancer from the Mount Sinai Health System reported an 11% rate of death and 11% rate of intubation.[13] A series of 218 patients with cancer from the Montefiore Health system reported a case fatality rate of 28%, although the authors acknowledged a bias towards more severe cases.[4] Taken together with our cohort from multiple institutions, these findings have important policy implications including, but not limited to, the need for increased surveillance and testing for SARS-CoV-2, minimising health-care system exposure, and reconsideration of procedures and treatments in patients with cancer. Notably, health-care systems are screening asymptomatic individuals before many cancer treatments, and we anticipate that as the CCC19 cohort grows, separate analysis of asymptomatic individuals who have been screened will be necessary.

Important subgroups of patients with cancer appear to be at increased risk for adverse outcomes. In addition to the previously reported risk factors of age and sex in the general COVID-19 population,[6,14,15] ECOG performance status of 2 or higher and active cancer seem to be associated with an increased risk of worse outcomes from COVID-19 in patients with cancer. Although moderate or poor ECOG performance status is well known to have a deleterious effect on overall outcomes, an ECOG performance status of 2 is not always considered a contraindication to aggressive therapy for active cancer.[16,17] Our study highlights the potentially additive negative effect of COVID-19 in this susceptible population. Some potential implications of this finding include acceleration of advanced care planning and patient and family discussions on restricting aggressive interventions, such as mechanical ventilation.[18] The American Society of Clinical Oncology has issued guidance on ethical considerations pertaining to resource-limited situations during the SARS-CoV-2 pandemic.[19]

Although an ECOG performance status of 2 was relatively uncommon in this cohort, the presence of active (measurable) cancer was common. From our analysis, active cancer might be a risk factor associated with worse COVID-19 outcomes, especially in patients who have progressive disease. In our cohort, patients with progressive cancer died at a numerically higher rate without ICU admission than among those who were admitted to an ICU, and the reverse pattern was seen for patients in remission. This finding, and the numerically higher rate of deaths without ICU admission in patients aged 75 years and older and those receiving treatment with palliative intent, suggests that aggressive interventions might have already been reduced in these subpopulations. And similarly to patients with moderate or poor ECOG performance status, careful conversations about the risks and benefits of continuing anticancer therapy will urgently be required in these subpopulations. Conversely, the absence of an association between 30-day all-cause mortality and recent surgery, recent non-cytotoxic therapy,

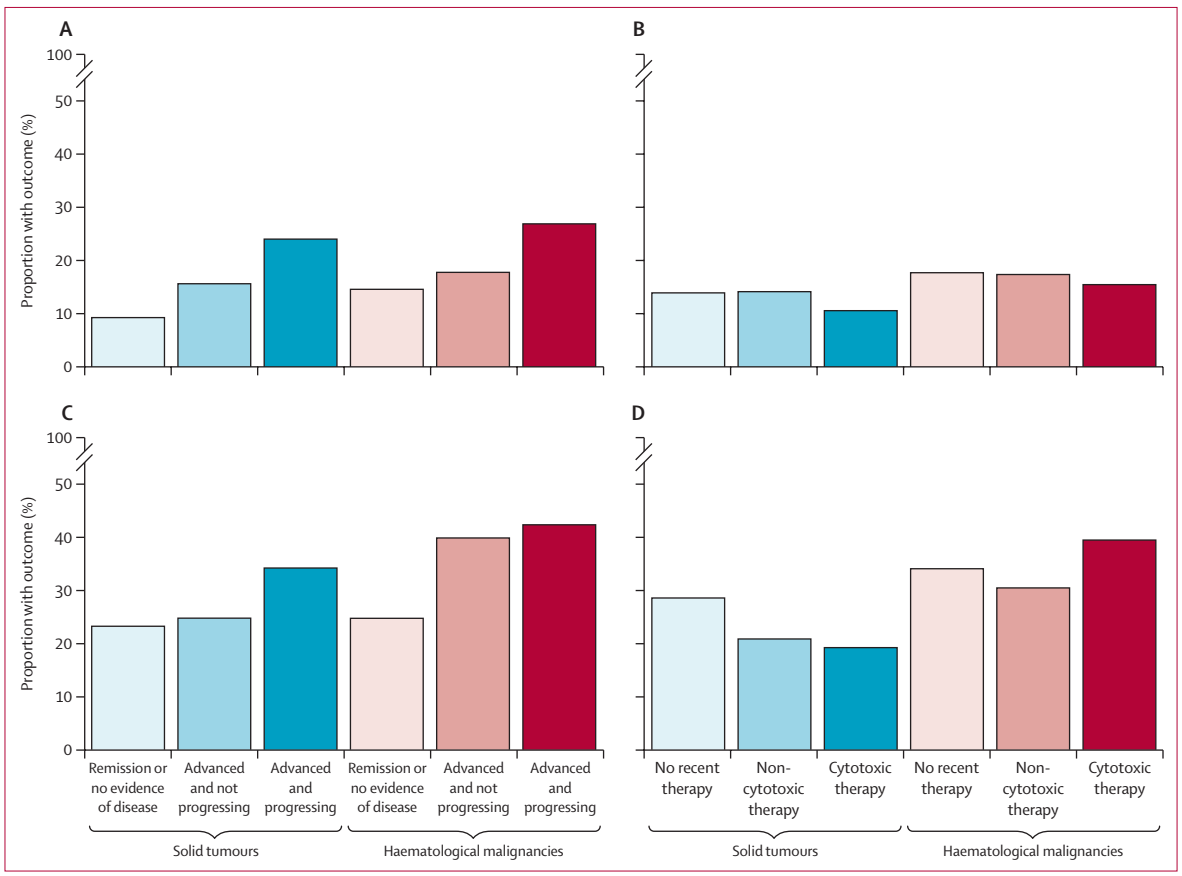

Figure 2: **Primary and composite secondary outcome by cancer type, cancer status, and anticancer therapy**
Mortality as a function of cancer type and status (A) and cancer type and therapy type (B). Composite outcome as a function of cancer type and status (C) and cancer type and therapy type (D). Results are descriptive; no statistical analyses were applied.

or recent cytotoxic systemic therapy suggests that curative surgical resections, adjuvant chemotherapy, and maintenance chemotherapy could continue during the SARS-CoV-2 pandemic with extreme caution, although this finding should not be interpreted as a recommendation.

Some of the observations reported here potentially have a biological basis—eg, smoking in particular has previously been implicated in inflammatory lung disease and SARS-CoV-2 biology.[20–23] Former smoking was associated with increased mortality in the baseline analysis and in the elastic net regression; no conclusions can be drawn about current smoking due to the small number of events. Human and animal models suggest that the alveolar epithelial cells in the lungs of smokers might have increased angiotensin-converting enzyme 2 (ACE2) expression, which might increase mucus-secreting goblet cells.[24] Although the potential systemic dysregulation of ACE2 is not yet fully understood, downregulation caused by SARS-CoV-2 viral binding to this receptor could lead to increased angiotensin II, which can cause acute lung injury and other systemic effects.[25] SARS-CoV-2 is similar to other coronaviruses, including the severe acute respiratory syndrome (SARS) CoV that led to the SARS outbreak in 2003.[26] Cell entry of both of these viruses appears to rely on protein binding to ACE receptors on host cells, with an additional required proteolytic step to allow fusion of the viral and cellular membranes. This proteolytic step is dependent on transmembrane serine protease 2 (TMPRSS2).[27] TMPRSS2 expression is regulated by the androgen receptor in the prostate.[28,29] Androgens have been hypothesised to also regulate TMPRSS2 expression in lung tissue, potentially explaining the increased mortality in male patients from COVID-19 seen consistently across national health departments to varying degrees.[30] Further analysis is needed of the observed association between male sex and 30-day all-cause mortality, which might be driven by biological differences between the sexes versus differences in high risk jobs, professional exposure, or other factors.[31]

Notably, we did not find any association between recent surgery and 30-day all-cause mortality, as previously described in a smaller case series.[2] Given that delays in elective cancer surgeries might lead to deleterious outcomes, this finding should be taken into consideration if policies to delay treatments are being implemented, while acknowledging that many other factors exist that should be considered, such as surge capacity and provider availability.[32,33] As the CCC19 cohort increases and matures,

additional factors can be examined in greater detail, such as myelosuppression associated with cytotoxic chemotherapy, immune activation associated with immunotherapy, and risks specific to some cancer diagnoses and regimens.

Our study has some limitations, such that some observations should be interpreted with caution. Some notable regional variations in the primary and secondary outcomes exist. The Spanish subgroup had no ICU admissions and no patients put on mechanical ventilation, but had ten deaths. The Canadian subgroup had the highest proportion of patients admitted to hospital, yet had the numerically lowest rate of deaths of any of the regional subgroups. These findings, including the reduced risk of 30-day all-cause mortality associated with residence in Canada and the US-Midwest probably reflect regional differences in the response to COVID-19, and different timelines of the local pandemic, and deserve further study. Higher numbers of comorbidities were significantly associated with increased mortality; however, the number of events in the reference group was very low (three deaths). This variable also had a high inflation factor, indicating significant collinearity with other variables in the model. A cancer status of unknown was also associated with increased mortality, intermediate between the groups of present, stable, or responding, and present, progressive disease. These patients are likely to be a distinct subgroup—eg, having scans with mixed or equivocal findings or having recently started a new anticancer therapy without re-assessment.

A strong association with 30-day all-cause mortality was observed in the subgroup treated with the combination of azithromycin plus hydroxychloroquine; this same effect was not seen in the subgroups treated with either drug alone. This combination was commonly used in patients who met the composite endpoint, possibly on the basis of the non-randomised study by Gautret and colleauges.[34] Therefore, hydroxychloroquine plus azithromycin might not be the cause of increased mortality, but instead were given to patients with more severe COVID-19. On the other hand, the US Food and Drug Administration have documented their concerns about the risk of prolonged QT intervals when combining these medications.[35] Although our findings cannot be considered conclusive due to an inherent bias caused by the primarily retrospective nature of the study, these data still highlight the importance of establishing the aggregated risks and benefits of these medications in a prospective randomised trial setting before widespread application.[36]

This is primarily a retrospective cohort study designed for rapid patient accrual and data collection in an urgent global crisis. The lack of precise timing for events, as was required to meet IRB and General Data Protection Regulation requirements, introduces uncertainty into the exact timing of diagnostic, therapeutic, and outcome intervals. Although participating sites were strongly urged to comprehensively identify patients with concurrent cancer and COVID-19 diagnoses, selection bias is likely given that patients who are tested are generally symptomatic, and thresholds for testing are lower in hospital settings. Community practices are somewhat underrepresented in this initial sample; therefore, this cohort might reflect more severe cases of COVID-19. We were unable to adjust for all the a priori potential prognostic variables in the multivariable models due to low numbers of events. Finally, we were not able to do an analysis comparing our cohort with patients with cancer without COVID-19 and patients without cancer with COVID-19. Such an analysis would better place the current data into a larger context.

In summary, this study of patients with cancer and COVID-19 reinforces several important considerations for clinical care, and emphasises the urgent need for more data. Longer-term follow-up and larger sample sizes are needed to more completely understand the effect of SARS-CoV-2 on outcomes in patients with cancer.

Contributors

NMK, TKC, DPS, AD, DRR, GdLL, PG, CAP, SP, MAT, GHL, BIR, and JLW conceived and designed the study. DPS, YS, NMK, JLW, SMR, DRR, GHL, SSh, and C-YH designed the statistical analysis plan. YS, SMR, C-YH, and JLW analysed the data and developed the figures and tables. ZB, GB, TB-S, MAB, NB, MBL, DC, SADP, DBD, PCE, AE, DFa, DFl, MDG, MJG, EAG, APG, SG, NH, TRH, JEH, EH, AK, ARK, CAL, CL, BL, TM, RRM, RAM, AKM, MFM, OAP, PP, NAP, KR, LRR, RR, MS, AS, SAS, JAS, JS, KES-G, SSu, DCV, FHW, LBW, JT-YW, EW-B, ZX, AY, PPY, AYZ, and LZ coordinated data contributions at their respective sites, each of which contributed at least ten cases to the consortium. SM provided study project management. All authors contributed intellectual content during the drafting and revision of the work and approved the final version.

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in International Patent Application number PCT/US2018/12209, entitled "PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response," filed Jan 3, 2018 (claiming priority to US Provisional Patent Application No 62/445,094, filed Jan 11, 2017) and International Patent Application Number PCT/US2018/058430, entitled "Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy," filed Oct 31, 2018 (claiming priority to US Provisional Patent Application No 62/581,175, filed Nov 3, 2017). TKC's institution (Dana-Farber Cancer Institute) might have received additional independent funding of drug companies or royalties potentially involved in research around the subject matter of this Article. TKC has mentored several non-US citizens on research projects with potential funding (in part) from non-US sources or foreign components. 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Data sharing

Aggregate de-identified patient data with site identifiers removed and geographical region of patient residence masked to a level no smaller than US Census Divisions will be made publicly available for any purpose beginning 6 months and ending a minimum of 36 months after publication of this Article through the CCC19 website. Individual de-identified patient data with site identifiers removed and geographical region of patient residence masked to a level no smaller than US Census Divisions will be made available to researchers who provide a methodologically sound proposal, whose proposed use of the data has

been approved by an independent review committee identified for this purpose. Proposals can be submitted beginning 6 months and up to 36 months after publication of this Article. Proposals should be directed to sanjay.mishra.1@vumc.org; to gain access, data requestors will need to sign a data access agreement.

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References

1 WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Geneva: World Health Organization, March 11, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed April 20, 2020).

2 Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21:** 335–37.

3 Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov* 2020; published online April 28. DOI:10.1158/2159–8290.CD-20–0422.

4 Miyashita H, Mikami T, Chopra N, et al. Do patients with cancer have a poorer prognosis of COVID-19? An experience in New York City. *Ann Oncol* 2020; published online April 21. DOI:10.1016/j.annonc.2020.04.006.

5 Blimark C, Holmberg E, Mellqvist U-H, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica* 2015; **100:** 107–13.

6 CDC. COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 343–46.

7 Desai A, Warner J, Kuderer N, et al. Crowdsourcing a crisis response for COVID-19 in oncology. *Nat Cancer* 2020: published online April 21. DOI:10.1038/s43018–020–0065-z.

8 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377–81.

9 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44:** 837–45.

10 Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15:** 361–87.

11 Zou H, Hastie T. RegularIZation and variable selection via the elastic net. *J R Statistic Soc B* 2005; **67:** 301–20.

12 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382:** 1708–20.

13 Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York hospital system. *Cancer Discov* 2020; published online May 1. DOI:10.1158/2159–8290.CD-20–0516.

14 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; **323:** 1061–69.

15 Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; published online April 22. DOI:10.1001/jama.2020.6775.

16 Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J Clin Oncol* 2013; **31:** 2849–53.

17 Macarulla T, Pazo-Cid R, Guillén-Ponce C, et al. Phase I/II trial to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel in combination with gemcitabine in patients with pancreatic cancer and an ECOG performance status of 2. *J Clin Oncol* 2019; **37:** 230–38.

18 Rosenbaum L. Facing Covid-19 in Italy - ethics, logistics, and therapeutics on the epidemic's front line. *N Engl J Med* 2020; **382:** 1873–75.

19 Marron JM, Joffe S, Jagsi R, Spence RA, Hlubocky FJ. Ethics and resource scarcity: ASCO recommendations for the oncology community during the COVID-19 pandemic. *J Clin Oncol* 2020; published online April 28. DOI:10.1200/JCO.20.00960.

20 Crotty Alexander LE, Shin S, Hwang JH. Inflammatory diseases of the lung induced by conventional cigarette smoke: a review. *Chest* 2015; **148:** 1307–22.

21 Strzelak A, Ratajczak A, Adamiec A, Feleszko W. Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: a mechanistic review. *Int J Environ Res Public Health* 2018; **15:** 1033.

22 Cai H. Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir Med* 2020; **8:** e20.

23 Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. *Tob Induc Dis* 2020; **18:** 20.

24 Smith JC, Sheltzer JM. Cigarette smoke triggers the expansion of a subpopulation of respiratory epithelial cells that express the SARS-CoV-2 receptor ACE2. *bioRxiv* 2020; published online March 31. DOI:10.1101/2020.03.28.013672 (preprint).

25 Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med* 2020; **382:** 1653–59.

26 Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; **348:** 1953–66.

27 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; **181:** 271–80.

28 Lin B, Ferguson C, White JT, et al. Prostate-localized and androgen-regulated expression of the membrane-bound serine protease TMPRSS2. *Cancer Res* 1999; **59:** 4180–84.

29 Afar DEH, Vivanco I, Hubert RS, et al. Catalytic cleavage of the androgen-regulated TMPRSS2 protease results in its secretion by prostate and prostate cancer epithelia. *Cancer Res* 2001; **61:** 1686–92.

30 Stopsack KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. *TMPRSS2* and COVID-19: serendipity or opportunity for intervention? *Cancer Discov* 2020; published online April 10. DOI:10.1158/2159–8290.CD-20–0451.

31 CDC. COVID-19 Response Team. Characteristics of health care personnel with COVID-19 - United States, February 12-April 9, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 477–81.

32 Samson P, Patel A, Garrett T, et al. Effects of delayed surgical resection on short-term and long-term outcomes in clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2015; **99:** 1906–12.

33 Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to surgery and breast cancer survival in the United States. *JAMA Oncol* 2016; **2:** 330–39.

34 Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; published online March 20. DOI:10.1016/j.ijantimicag.2020.105949.

35 US Food & Drug Administration. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. US Food & Drug Administration, April 24, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (accessed April 26, 2020).

36 Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. *medRxiv* 2020; published online April 23. DOI:10.1101/2020.04.16.20065920 (preprint).