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Factors Affecting COVID-19 Outcomes in Cancer Patients: A First Report From Guy's Cancer Center in London

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Background: There is insufficient evidence to support clinical decision-making for cancer patients diagnosed with COVID-19 due to the lack of large studies.

Methods: We used data from a single large UK Cancer Center to assess the demographic/clinical characteristics of 156 cancer patients with a confirmed COVID-19 diagnosis between 29 February and 12 May 2020. Logistic/Cox proportional hazards models were used to identify which demographic and/or clinical characteristics were associated with COVID-19 severity/death.

Results: 128 (82%) presented with mild/moderate COVID-19 and 28 (18%) with a severe case of the disease. An initial cancer diagnosis >24 months before COVID-19 [OR: 1.74 (95% CI: 0.71–4.26)], presenting with fever [6.21 (1.76–21.99)], dyspnea [2.60 (1.00–6.76)], gastro-intestinal symptoms [7.38 (2.71–20.16)], or higher levels of C-reactive protein [9.43 (0.73–121.12)] were linked with greater COVID-19 severity. During a median follow-up of 37 days, 34 patients had died of COVID-19 (22%). Being of Asian ethnicity [3.73 (1.28–10.91)], receiving palliative treatment [5.74 (1.15–28.79)], having an initial cancer diagnosis >24 months before [2.14 (1.04–4.44)], dyspnea [4.94 (1.99–12.25)], and increased CRP levels [10.35 (1.05–52.21)] were positively associated with COVID-19 death. An inverse association was observed with increased levels of albumin [0.04 (0.01–0.04)].

Conclusions: A longer-established diagnosis of cancer was associated with increased severity of infection as well as COVID-19 death, possibly reflecting the effects a more advanced malignant disease has on this infection. Asian ethnicity and palliative treatment were also associated with COVID-19 death in cancer patients.

Keywords: COVID-19, cancer, SARS-CoV-2, outcomes, directed acyclic graph

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INTRODUCTION

In the context of cancer, the COVID-19 pandemic has led to a series of challenging decisions that must be made (1, 2). Patient visits to the cancer clinic increase the potential risk of infection when the alternative is self-isolation at home, and some cancer treatments may predispose patients to moderate or severe harmful effects of COVID-19 (3, 4). Current precautionary management decisions being made for cancer patients are based on assumptions supported by limited evidence, based on small case series from China and Italy (5–13) and larger series from New York (14, 15) and a recent consortium of 900 patients from over 85 hospitals in the USA, Canada, and Spain (16). As a result of their limited sample sizes, most studies were not able to distinguish between the effects of age, cancer, and other comorbidities on COVID-19 outcomes in this population (17, 18). Moreover, the case series from New York analyzed which patient characteristics are associated with COVID-19 death, but only made a comparison with non-cancer patients (14, 15). The first results of the COVID-19 and Cancer Consortium provide insights from a large cohort in terms of COVID-19 mortality, though a wide variety of institutions with different COVID-19 testing procedures were included (16). In addition, recently published prognostic studies in COVID-19 positive patients have been judged to be at high risk of bias, mainly due to non-representative selection of control patients, exclusion of patients who had not experienced the event of interest by the end of the study, high risk of model overfitting, and limited information on model building strategies used (19).

It can be difficult to confidently diagnose COVID-19 symptoms in cancer patients, as presenting features of the infection are often similar to cancer symptoms and treatment-related adverse events (17, 20). This may result in a delayed or missed COVID-19 diagnosis, which could lead to the confounding of cases and infection mortality rates, as well as late interventions for more life-threatening diseases (21). In addition, COVID-19 may be a barrier to dignified and humane end-of-life cancer care (17). Finally, the pandemic is causing huge service reconfiguration for both curative and palliative oncology care, resulting in fewer clinic visits due to social distancing (22), cessation of screening, and delays or changes in treatments that will inevitably have serious impacts on cancer-related mortality and morbidity (17, 21). Our recent systematic review reported there is currently no definitive evidence that specific cytotoxic drugs are contraindicated in cancer patients infected with COVID-19 (23).

Larger studies with multivariate models are urgently warranted to further explore this intersection of COVID-19 and cancer in terms of clinical outcomes, so as to inform oncological care during this outbreak and potential future pandemics (24). Guy's Cancer Center in South-East London, which treats ∼8,800 patients annually, including 4,500 new diagnoses, is one of the largest Comprehensive Cancer Centers in the UK and is currently at the epicenter of the UK COVID-19 epidemic.

METHODS

Study Population

Guy's Cancer Cohort, a research ethics committee approved research database (Reference number: 18/NW/0297) of all routinely collected clinical data of cancer patients at Guy's and St Thomas' NHS Foundation Trust (GSTT), forms the basis of this observational study (25). The database contains routinely collected prospective and retrospective demographic/clinical data on all cancer patients treated at Guy's Cancer Center. We have an established clinical database for all cancer patients tested for COVID-19 either in outpatient clinics or ward settings since 29 February 2020. Using the unique hospital number, these databases were merged prior to anonymization for research purposes. We assessed outcomes included in the core outcome sets currently being developed for COVID-19 to ensure all relevant information is collected in our COVID specific database (26).

We have included cancer patients who received a diagnosis of COVID-19 from a positive PCR test from 29th February to 12th May 2020. Until 30 April 2020, a COVID-19 test was ordered for cancer patients if they presented with symptoms necessitating hospitalization or if they were scheduled to undergo a cancer-related treatment. From 1 May 2020, COVID-19 testing was introduced as a part of standard care, with about 25% of patients being swabbed daily depending on staff and testing kit availability. A total of 1,507 patients were tested between 29 February and 12 May 2020, of whom 156 had COVID-19 (10%).

Statistical Methods

In this analysis of our data, we had three aims:

1) To describe demographic and clinical characteristics of COVID-19 positive cancer patients, in terms of their COVID-19 and cancer diagnoses.
2) To identify which demographic and/or clinical factors were associated with COVID-19 severity in cancer patients.
3) To identify which demographic and/or clinical factors were associated with COVID-19 death in cancer patients.

Descriptive statistics were used to address the first aim. Most variables had several categories for the purpose of these descriptive analyses but were collapsed for the purpose of regression analyses due to the sample size of our cohort. Socio-economic status (low, middle, high) was determined based on the English Indices of Multiple Deprivation for postcodes (27). Lymphocyte count ($\times 10^9$) was categorized as $\leq$0.5, 0.6–0.8, 0.9–1.2, and $>$1.2 based on the Common Terminology Criteria for Adverse Events v.5 (CTCAE). For the other laboratory variables, we created tertiles instead of clinical cut-offs due to cancer patients already having abnormal values for most of these blood markers (Ferritin, C-reactive protein, and albumin). Radical treatment was defined as those patients with a chance of long-term survival or cure.

For the second aim, we conducted logistic regression analyses. Mild/moderate COVID-19 was defined as pneumonia with or without sepsis (i.e., those patients managed on the ward), whereas severe COVID-19 was defined as acute respiratory

distress syndrome (ARDS) or septic shock (i.e., those patients where severity reached the criteria for Intensive Care Unit admission, if deemed clinically appropriate). These definitions were based on the WHO COVID-19 classification (28). The models used to quantify the association between each factor and COVID-19 severity were defined through a directed acyclic graph (DAG) (**Figure A1**). Each factor was individually set as the main exposure variable in the model in order to determine the minimal adjustments required for each factor (**Table A1**).

The third research aim was addressed with Cox proportional hazards regression analyses, whereby the models were defined as above (**Table A1**). Follow-up was defined from the date of COVID testing until death or 12 May 2020.

All statistical analyses were conducted with STATA version 15.1.

RESULTS

Demographic and Clinical Characteristics of COVID-19 Positive Cancer Patients

One hundred and twenty-eight patients (82%) presented with mild/moderate COVID-19 and 28 patients (18%) with severe COVID-19 (**Table 1**). More patients were male (58%) and aged 60+ (68%; median age: 67). However, 14% of the cancer population was aged <50 years ($n = 21$; median age: 41). When stratified by COVID grade, more male cancer patients presented with severe disease (68%). Most patients were from a lower socio-economic background (81%). With respect to ethnicity, about half were White, 22% were Black ($n = 32$), and 4% were of Asian ($n = 6$) origin. When stratified by COVID grade, a slightly larger proportion of patients from a white ethnic background had severe COVID (57%). Hypertension was the most reported comorbidity (47%), followed by diabetes mellitus (22%), renal impairment (19%), and cardiovascular disease (19%). However, benign lung conditions were more commonly reported for those who presented with severe COVID-19 (29 vs. 13% in those with mild COVID-19).

The most frequently reported tumor types were urological/gynecological (29%), followed by hematological (18%) and breast (15%) (**Table 2**). The first group ($n = 45$) comprised of 21 prostate, 8 renal, 5 bladder, and 11 gynecological cancers. Of the 28 hematological malignancies, four (14.3%) were myeloid and 24 (85.7%) were lymphoid. Of all cancer patients tested for COVID-19, 80 were positive after their cancer-related hospital admission (51%), of which 61 were solid tumors (76%) and 19 were hematological cancers (24%). When stratified by COVID-19 severity, the largest proportion of cancers presenting with severe COVID were hematological (36%). A large proportion of patients had advanced cancer (40% stage IV) and were diagnosed with their malignancy in the last 12 months (46%).

Overall, 39% of patients were receiving palliative treatment, 25% were receiving radical treatment, and 12% were treatment naive. Treatment distributions were reasonably comparable between COVID-19 severity groups. Of the 81 patients on systemic treatment within the last 2 years, 54 were in a palliative setting; of these, 50% were 1st line, 33% 2nd line, and 13% on ≥3rd treatment line. However, the majority of severe COVID-19 patients were on third line metastatic treatment. **Table 2** provides further details on the cancer characteristics.

Forty six percentage of the cancer patients diagnosed with COVID-19 in this cohort presented with a cough and 52% had a fever. Most patients were molecularly diagnosed within seven days of their initial symptoms (58%) (**Table 3**). More patients in the severe COVID-19 group presented with C-reactive protein (CRP) values in the highest tertile (46 vs. 22% for mild/moderate disease). Similarly, they had a lower lymphocyte count [43 vs. 21% in the lowest category (≤0.5)] and lower albumin levels (39 vs. 22% in the lowest tertile).

Factors Associated With COVID-19 Severity in Cancer Patients

The odds ratios (ORs) for the associations between the various demographic and clinical factors and COVID-19 severity status are shown in **Table 4**. There was a non-statistically significant indication that those patients who were diagnosed with cancer more than 24 months ago were at a higher risk of presenting with severe COVID-19 as compared to those diagnosed during the last 24 months [OR: 1.74 (95% CI: 0.71–4.26)]. With respect to symptom presentation, those presenting with a fever, dyspnea, or gastro-intestinal symptoms were at a higher risk of having severe COVID-19 as compared to those without these symptoms [OR: 6.21 (1.76–21.99), 2.60 (1.00–6.76), and 7.38 (2.71–20.16), respectively].

Factors Associated With COVID-19 Death in Cancer Patients

During a median follow-up of 37 days (IQR: 18–49), 34 cancer patients had died of COVID-19 (22%) (**Table 5**). Several cancer patient characteristics were found to be positively associated with risk of COVID-19 death: being of Asian ethnicity [as compared to white—HR: 3.73 (95% CI: 1.28–10.91)], receiving palliative treatment [as compared to no active treatment—HR: 5.74 (95% CI: 1.15–28.79)], time since cancer diagnosis >24 months [as compared to ≤24 months—HR: 2.14 (95% CI: 1.04–4.44)], presenting with dyspnea [as compared to no dyspnea—HR: 4.94 (95% CI: 1.99–12.25)], and having high CRP levels [3rd tertile vs. 1st tertile—HR: 10.35 (95% CI: 1.05–52.21)]. In addition, an inverse association with death from COVID-19 was observed with normal albumin levels [3rd tertile vs. 1st tertile—HR: 0.04 (95% CI: 0.01–0.04)].

DISCUSSION

Using multivariate modeling based on a directed acyclic graph, this study reports on a large cohort of COVID-19 positive cancer patients from a single institution. Low SES, hypertension, and diabetes were common in cancer patients with COVID-19. Age, sex, ethnicity, SES, and current cancer treatment were found to not be associated with severity of COVID-19 infection in cancer patients. However, receipt of a cancer diagnosis more than 24 months previously (as compared

TABLE 1 | Demographic characteristics of COVID-19 positive cancer patients.

	Total ($n = 156$)		WHO COVID grade			
			Mild/moderate ($n = 128$)		Severe ($n = 28$)	
	n	%	*n*	%	*n*	%
Sex						
Male	90	57.70	71	55.50	19	67.90
Female	66	42.30	57	44.50	9	32.10
Age						
<50	21	13.50	16	12.50	5	17.90
50–59	29	18.60	24	18.80	5	17.90
60–69	43	27.60	35	27.30	8	28.60
70–79	35	22.40	28	21.90	7	25.00
≥80	28	17.90	25	19.50	3	10.70
Mean (SD)	65.18 (14.80)		65.74 (14.39)		62.62 (16.41)	
SES						
Low	126	80.80	106	82.80	20	71.40
Medium	1	0.60	1	0.80	0	0.00
High	16	10.30	12	9.40	4	14
Missing	13	8.30	9	7.00	4	14.30
Ethnicity						
White British	66	42.30	50	39.10	16	57.10
White other	12	7.70	9	7.00	3	10.70
Black Caribbean	8	5.10	8	6.30	0	0.00
Black African	15	9.60	14	10.90	1	3.60
Black other	12	7.70	9	7.00	3	10.70
Asian	6	3.80	4	3.10	2	7.10
Mixed	2	1.30	2	1.60	0	0.00
Other	5	3.20	4	3.10	1	3.60
Unknown	30	19.20	28	21.90	2	7.10
Comorbidities						
Hypertension	74	47.40	63	49.20	11	39.30
Diabetes mellitus	35	22.40	31	24.20	4	14.30
Lung conditions	25	16.00	17	13.30	8	28.60
Renal impairment	30	19.20	26	20.30	4	14.30
Liver conditions	3	1.90	3	2.30	0	0.00
CVD	29	18.60	24	18.80	5	17.90
Frailty	10	6.40	6	4.70	4	14.30
Chronic steroid use	4	2.60	4	3.10	0	0.00
No. of comorbidities						
0	43	27.60	34	26.60	9	32.10
1	48	30.80	40	31.30	8	28.60
2	33	21.20	28	21.90	5	17.90
3+	32	20.50	26	20.30	6	21.40
Smoking history						
Never	59	37.80	51	39.80	8	28.60
Current	11	7.10	9	7.00	2	7.10
Ex-smoker	39	25.00	31	24.20	8	28.60
Unknown	47	30.10	37	28.90	10	35.70
Medications						
Polypharmacy	68	43.60	57	44.50	11	39.30
NSAIDs	20	12.80	16	12.50	4	14.30
ACE/ARB	33	21.20	29	22.70	4	14.30
Beta-blockers	24	15.40	20	15.60	4	14.30

TABLE 2 | Tumor characteristics of COVID-19 positive cancer patients.

	Total ($n = 156$)		WHO COVID grade			
			Mild/moderate ($n = 128$)		Severe ($n = 28$)	
	n	**%**	***n***	**%**	***n***	**%**
Cancer type						
Urological/gynae	45	28.80	39	30.50	6	21.40
Gastro-intestinal	21	13.50	19	14.80	2	7.10
Hematological	28	17.90	18	14.10	10	35.70
Skin/head and neck/sarcoma	10	6.40	9	7.00	1	3.60
Central nervous system	11	7.10	10	7.80	1	3.60
Breast	24	15.40	21	16.40	3	10.70
Lung	17	10.90	12	9.40	5	17.90
Cancer stage						
I	17	10.90	17	13.30	0	0.00
II	23	14.70	21	16.40	2	7.10
III	22	14.10	18	14.10	4	14.30
IV	63	40.40	49	38.30	14	50.00
Missing	31	19.90	23	18.00	8	28.60
Risk category* ($n = 4$)						
Low	1	25.00	0	0.00	1	33.33
Intermediate	2	50.00	1	100.00	1	33.33
High	1	25.00	0	0.00	1	33.33
Treatment paradigm						
Treatment naive	18	11.50	16	12.50	2	7.10
Neoadjuvant	7	4.50	7	5.50	0	0.00
Adjuvant	8	5.10	8	6.30	0	0.00
Radical	38	24.40	28	21.90	10	35.70
Palliative	60	38.50	49	38.30	11	39.30
Watch and wait	7	4.50	7	5.50	0	0.00
Surveillance	12	7.70	10	7.80	2	7.10
Missing	6	3.80	3	2.30	3	10.70
Line of palliative treatment ($N = 54$)						
1	27	50.00	23	52.27	4	40.00
2	18	33.33	13	29.55	5	50.00
3	6	11.11	5	11.36	1	10.00
4	1	1.90	1	2.27	0	0.00
Missing	2	3.70	2	4.55	0	0.00
Systemic treatment ($N = 81$)						
Systemic chemotherapy	45	55.60	34	53.10	11	64.60
Immunotherapy	7	8.60	5	7.80	2	11.80
Biological	13	16.00	11	17.20	2	11.80
Targeted therapy	5	6.20	5	7.80	0	0.00
Combination therapy	11	13.60	9	14.10	2	11.80
Time since cancer diagnosis						
<3 months	41	26.30	34	26.60	7	25.00
3–12 months	30	19.20	25	19.50	5	17.90
12–24 months	20	12.80	18	14.10	2	7.10
>24 months	57	36.50	45	35.20	12	42.90
Performance status						
0	19	12.20	17	13.30	2	7.10
1	43	27.60	34	26.60	9	32.10
2	33	21.20	27	21.10	6	21.40
3	14	9.00	13	10.20	1	3.60
4	6	3.80	5	3.90	1	3.60

**For myeloid malignancies only.*

TABLE 3 | COVID-19 presentation of COVID-19 positive cancer patients.

	Total ($n = 156$)		WHO COVID grade			
			Mild/moderate ($n = 128$)		Severe ($n = 28$)	
	n	%	*n*	%	*n*	%
Symptoms						
Cough	72	46.20	57	44.50	15	53.60
Fever	81	51.90	59	46.10	22	78.60
Dyspnoea	55	35.30	41	32.00	14	50.00
Gastro-intestinal symptoms	25	16.00	13	10.20	12	42.90
Time between first symptom and diagnosis						
<7 days	90	57.70	71	55.50	19	67.90
7–14 days	27	17.30	22	17.20	5	17.90
>14 days	14	9.00	11	8.60	3	10.70
Missing	25	16.00	24	18.80	1	3.60
Care setting						
Outpatient	36	23.10	36	28.10	0	0.00
Inpatient	105	67.30	90	70.30	15	53.60
ITU	13	8.30	0	0.00	13	46.40
Missing	2	1.30	2	1.60	0	0.00
Laboratory values*						
Ferritin (μg/L)						
T1 (80–793)	18	11.50	14	10.90	4	14.30
T2 (891–1,442)	18	11.50	13	10.20	5	17.90
T3 (1,596–5,958)	17	10.90	10	7.80	7	25.00
Missing	103	66.00	91	71.10	12	42.90
CRP (mg/L)						
T1 (3–41)	44	28.20	38	29.70	6	21.40
T2 (42–117)	39	25.00	30	23.40	9	32.10
T3 (126–508)	41	26.30	28	21.90	13	46.40
Missing	32	20.50	32	25.00	0	0.00
Lymphocytes ($\times 10^9$)						
≤0.5	39	25.00	27	21.10	12	42.90
0.6–0.8	38	24.40	30	23.40	8	28.60
0.9–1.2	27	17.30	25	19.50	2	7.10
>1.2	27	17.30	21	16.40	6	21.40
Missing	25	16.00	25	19.50	0	0.00
Albumin (g/L)						
T1 (20–32)	39	25.00	28	21.90	11	39.30
T2 (33–38)	43	27.60	32	25.00	11	39.30
T3 (39–57)	34	21.80	32	25.00	2	7.10
Missing	40	25.60	36	28.10	4	14.30

**Distribution shown in tertiles (T).*

to within 24 months) and presenting with fever, dyspnea, or gastro-intestinal symptoms were linked with higher odds of developing severe illness as compared to mild/moderate COVID-19. Higher levels of CRP and ferritin were also associated with more severe COVID-19 disease in infected cancer patients. During a median follow-up of 37 days, the following cancer patient characteristics were found to be positively associated with COVID-19 death: Asian ethnicity, palliative treatment, initial cancer diagnosis >24 months, dyspnea at presentation, and high CRP levels. Normal serum albumin levels were inversely associated with death from COVID-19 in cancer patients.

Demographic and Cancer Characteristics

Several retrospective cohort studies published using data from hospitals situated in Wuhan, China, Northern Italy, Canada, and the USA have reported on the clinical characteristics of COVID-19 positive cancer patients with sample sizes varying from 9 to 85, two slightly larger series of >200 patients, and a big data

TABLE 4 | Odds Ratios and 95% confidence intervals for COVID-19 severity in cancer patients.

	OR*	95% CI
Sex		
Male	1.00	Ref
Female	0.59	(0.25–1.40)
Age		
≤60	1.00	Ref
>60	0.82	(0.35–1.93)
SES		
Low	1.00	Ref
Middle	N/A	N/A
High	2.11	(0.51–8.67)
Ethnicity		
White	1.00	Ref
Black	0.40	(0.13–1.28)
Asian	1.55	(0.26–9.16)
Other	0.52	(0.06–4.57)
Number of comorbidities		
0	1.00	Ref
1	1.09	(0.29–4.07)
2	1.04	(0.23–4.68)
3+	1.26	(0.29–5.41)
P for trend	0.776	
Smoking history		
Never	1.00	Ref
Ever	1.39	(0.36–5.33)
Cancer type		
Solid	1.00	Ref
Hematological	3.14	(0.70–14.03)
Treatment paradigm		
No active treatment	1.00	Ref
Radical/curative	2.76	(0.34–22.16)
Palliative	3.40	(0.50–23.20)
Time since cancer diagnosis		
≤24 months	1.00	Ref
>24 months	1.74	(0.71–4.26)
Performance status		
0–2	1.00	Ref
3+	0.33	(0.04–2.64)
Symptoms		
Cough	1.27	(0.53–3.01)
Fever	6.21	(1.76–21.99)
Dyspnea	2.60	(1.00–6.76)
GI symptoms	7.38	(2.71–20.16)
Time between first symptom and diagnosis		
<7 days	1.00	Ref
7–14 days	0.85	(0.28–2.54)
>14 days	1.02	(0.26–4.02)
CRP (mg/L)		
T1 (3–41)	1.00	Ref
T2 (42–117)	1.95	(0.19–20.25)
T3 (126–508)	9.43	(0.73–121.12)
Lymphocytes (×10^9)		
≤0.5	1.00	Ref
0.6–0.8	0.49	(0.06–3.73)
0.9–1.2	0.27	(0.03–2.34)
>1.2	0.63	(0.07–5.84)
Albumin (g/L)		
T1 (20–32)	1.00	Ref
T2 (33–38)	1.13	(0.18–7.00)
T3 (39–57)	0.07	(0.01–0.96)

(Continued)

TABLE 4 | Continued

Adjustment as defined by the DAG (Table A1**).*

Consortium including over 85 institutions and 900 patients (5–12, 16). The median age reported in these studies was similar to our study, with a range from 63 to 72 years. A larger proportion of male patients has been observed. Lung cancer was the most commonly reported cancer in the Zhang et al. (5), Yu et al. (8), Yang et al. (10), and Stroppa et al. (11) studies, but only accounted for 11% in our patient population. Zhang et al. (5) estimated that in their cohort, 29% of patients tested positive for COVID-19 following hospital admission, whereas this was estimated at 51% in our cohort. Interpretation of this statistic is difficult given the latency between exposure and manifestations of infection, meaning patients diagnosed after admission may have been infected outside of the hospital. Several studies (6, 10) noted that hypertension, diabetes, and coronary heart disease were the most commonly reported comorbidities.

Our cancer cohort is similar in distribution of age, sex, and comorbidities to the case series reported to date. The ethnicity and SES of our COVID-19 positive cancer patients are most likely a reflection of the catchment area of our Cancer Center in South-East London (29), covering more deprived boroughs (Lambeth and Southwark). Based on the number of cancer patients treated at our Cancer Center in 2019, about 49% of patients are of a White ethnic background. Variations observed with the published data in terms of cancer type, stage, and treatment may be a reflection of clinical practice (e.g., intensity of treatment and frequency of hospital visits), of relative cancer incidence, or of extent of treatment changes introduced as mitigation in the face of the emerging pandemic. For example, the most recently reported age-standardized lung cancer incidence rates for males and females in Wuhan are 54.1 and 19.1 per 100,000, whereas these are estimated to be 37.5 and 24.3 per 100,000 in London (30). Early modification and prioritization of treatment was introduced at our center, in accordance with now-published guidance (31).

COVID-19 Characteristics and Severity

Comparably to our study, both the Zhang and the Du studies also reported fever, cough, shortness of breath, and dyspnea as common clinical features (5, 6). As in the Chinese cohort of 85 fatal cases, our severe COVID-19 patients had comparable

TABLE 5 | Hazard Ratios and 95 %Confidence intervals for COVID-19 death in cancer patients.

Variable	Number of deaths ($n = 34$)	HR*	95% CI
Sex			
Male	22	1.00	Ref
Female	12	0.73	(0.36–1.47)
Age			
≤60	9	1.00	Ref
>60	25	1.34	(0.63–2.87)
SES			
Low	26	1.00	Ref
Middle	0	N/A	
High	3	1.03	(0.29–3.60)
Ethnicity			
White	21	1.00	Ref
Black	5	0.51	(0.19–1.35)
Asian	4	3.73	(1.28–10.91)
Other	2	1.52	(0.35–6.49)
Number of comorbidities			
0	9	1.00	Ref
1	8	1.20	(0.39–3.74)
2	8	1.92	(0.58–6.34)
3+	9	1.14	(0.34–3.82)
P for trend		0.749	
Smoking history			
Never	15	1.00	Ref
Ever	9	1.00	(0.97–1.03)
Cancer type**			
Solid	27	1.00	Ref
Hematological	7	0.22	(0.05–1.05)
Treatment paradigm			
No active treatment	2	1.00	Ref
Radical/curative	6	1.35	(0.21–8.57)
Palliative	19	5.74	(1.15–28.79)
Time since cancer diagnosis			
≤24 months	15	1.00	Ref
>24 months	17	2.14	(1.04–4.44)
Performance status			
0–2	20	1.00	Ref
3+	5	0.56	(0.15–2.02)
Symptoms			
Cough	16	1.00	(0.48–2.09)
Fever	21	1.63	(0.72–3.68)
Dyspnea	21	4.94	(1.99–12.25)
GI symptoms	8	1.44	(0.64–3.26)
Time between first symptom and diagnosis			
<7 days	23	1.00	Ref
7–14 days	6	0.86	(0.35–2.11)
>14 days	2	0.54	(0.13–2.29)
CRP (mg/L)			
T1 (3–41)	4	1.00	Ref
T2 (42–117)	9	2.87	(0.61–13.48)
T3 (126–508)	18	10.35	(1.05–52.21)
Lymphocytes (×10^9)			
≤0.5	11	1.00	Ref
0.6–0.8	12	0.84	(0.21–3.38)
0.9–1.2	4	0.96	(0.20–4.57)
>1.2	4	0.75	(0.14–4.12)
Albumin (g/L)			
T1 (20–32)	18	1.00	Ref
T2 (33–38)	8	0.50	(0.17–1.47)
T3 (39–57)	1	0.04	(0.01-0.42)

*Adjustment as defined by the DAG (**Table A1**).*

***Unadjusted due to missingness not allowing to run fully adjusted model as per the DAG.*

laboratory findings: decreased lymphocytes, increased CRP, and decreased albumin (6).

Severe events were reported for 54% of the study population and mortality for 29% in the Zhang study, as compared to 18 and 22% in our cohort. Zhang et al. also reported that recent treatment within 14 days was associated with an increased risk of developing severe events (28 days) (5). This difference with our observations may be attributed to different definitions of severe events, as it was not entirely clear how these were defined by Zhang et al. As highlighted by Wynants et al. in their assessment of current statistical models published for COVID-19 (19), there is a need for consistent use of outcome definitions. However, our observations of a positive association with CRP levels is in line with most COVID-19 studies published to date (32). Apart from the CCC-19 Consortium (16), no study to date has specifically looked at COVID-19 severity at presentation in COVID-19 positive cancer patients and hence our observation of an association with time since cancer diagnosis and presenting symptoms needs further validation in other large cohorts with homogenous definitions of inclusion criteria, testing strategies, and outcome measures. However, it is possible that time since cancer diagnosis is also a reflection of the extent of the disease and progression along the palliative patient pathway from diagnosis to death.

COVID-19 Death

The study by Yu et al. reported three deaths (25%) (8). In the larger series from New York, Mehta et al. reported an overall case fatality rate of 28%, with 37% for hematological malignancies and 25% for solid tumors (14). The CCC-19 Consortium reported a 30-day mortality rate due to COVID-19 of 13% (16). In our cohort, the overall case fatality rate was 22%, with 25% for hematological cancers and 21% for solid tumors. As more than 85 institutions were included in the CCC-19 Consortium (16), it is possible that differences in COVID-19 practice as well as cancer treatments between the

numerous centers may explain the slightly lower death rate as compared to reports from single center studies. Moreover, our median follow-up is 37 days as compared to 21 days for the Consortium. The heterogeneity between centers may also explain why performance status was found to be associated with COVID-19 outcomes, an observation not identified in our single center cohort.

Our observations of Asian ethnicity being associated with increased mortality from COVID-19 in cancer patients is of interest, given the recent speculations about the disproportionate effects of COVID-19 on Black, Asian, and minority ethnic communities (33) as well as the confounding factor of vitamin D deficiency (34). However, longer follow-up studies are required to disentangle the association between ethnicity and COVID-19 death in cancer patients.

Strengths and Limitations

Whilst this is one of the largest single center COVID-19 positive cancer cohorts to date, our sample size is still relatively modest and hence confidence intervals for some statistically significant observations are still wide. No firm conclusions in terms of prognostic modeling can be drawn as of yet (19). Current analyses aimed to generate further hypotheses on patient or tumor characteristics indicative of severity or of death from COVID-19 in the context of cancer. Our data for some of the patient characteristics is limited; for example, smoking status was missing for 29% of patients and hence likely underestimates the proportion of smokers. COVID testing in the UK has only been implemented gradually during the period of our data collection, and there is selection bias in favor of patients being tested as inpatients. Our analysis is likely to have missed cancer outpatients under our care diagnosed with COVID-19 at other hospitals—however this is most likely to be an even more important issue for global Consortia with many hospitals only adding a few cases to the overall dataset.

In light of these differences in COVID-19 management and cancer treatments between centers, it is important to note that our hospital has a specialized highly infectious disease unit with extracorporeal membrane oxygenation (ECMO) facilities, which ensured very experienced critical care management of COVID patients. A standard clinical approach was used, with concurrent antibiotics to cover bacterial infection and early escalation of treatment decisions, including appropriateness of ITU admission. No standard use of other agents (steroids or antivirals) was applied unless within the context of a clinical trial. Moreover, our general oncological approach was to maintain standard anti-cancer treatment (including surgery, radiotherapy, and systemic treatments) where it was safe and reasonable to do so. Our Cancer Center managed to continue oncology services throughout the COVID pandemic, whereas other Centers may have redeployed staff that precluded this.

It is also a strength of our study that we used clearly defined definitions of COVID-19 severity, as well as a DAG to develop the different models, as to date very limited knowledge is available regarding the intersection between COVID-19 and cancer (19). Detailed information on our modeling will help comparison with future studies with larger sample sizes and longer follow-ups.

CONCLUSION

Our analysis of one of the largest single center series of COVID-19 positive cancer patients to date confirms a similar distribution of age, sex, and comorbidities as reported for other populations. Reflecting the general population, presenting with fever, dyspnea, gastro-intestinal symptoms, higher levels of CRP, or ferritin were also indicators of COVID-19 severity in the cancer population. Similarly, we noted that dyspnea at presentation, high CRP levels, and low levels of albumin were associated with death from COVID-19. With respect to cancer specific observations, patients who have lived longer with their cancer were found to be more susceptible to a greater infection severity, possibly reflecting the effect of a more advanced malignant disease-as almost half of the severe cohort were on third line metastatic treatment-or the impact of this infection. The latter was also found to be associated with COVID-19 death in cancer patients, as were being of Asian ethnicity and receiving palliative treatment. Further validation will be provided from other large case series, as well as from those including longer follow-ups, to provide more definite guidance for oncological care.

DATA AVAILABILITY STATEMENT

Data can be obtained by researchers via an application to the Access Committee of Guy's Cancer Cohort. An application form can be obtained via Charlotte Moss, charlotte.moss@kcl.ac.uk.

ETHICS STATEMENT

Guy's Cancer Cohort, a research ethics committee approved research database (Reference Number: 18/NW/0297) of all routinely collected clinical data of cancer patients at Guy's and St Thomas' NHS Foundation Trust (GSTT), forms the basis of this observational study.

AUTHOR CONTRIBUTIONS

BR, CM, PR, DC, HW, FC, AH, KZ, FR, AS-L, DJ, SD, ML, SGh, ES, AD'S, SGo, DE, PF, DW, KR, MG, KB, RD, MS, and AS: data collection. BR, CM, SP, SI, PR, JS, SD, and MVH: study design. BR, CM, MVH, and SD: data analysis. MVH, BR, CM, SD, SP, RS, PR, JS, SK, and CH: manuscript drafting. All authors: final approval of manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01279/full#supplementary-material

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