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Brief Report: Impact of anti-cancer treatments on outcomes of COVID-19 in patients with thoracic cancers: a CCC19 registry analysis

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Abstract

Introduction: Patients with thoracic cancers have one of the highest mortality rates among patients with cancer and COVID-19. Data evaluating the impact of recent anti-cancer therapies on COVID-19 outcomes in patients with thoracic cancers are confined to heterogenous studies with limited follow-up data. We leveraged data from the COVID-19 and Cancer Consortium (CCC19) (NCT04354701) to analyze the impact of recent anti-cancer therapies on the clinical outcomes of COVID-19 in patients with thoracic cancers.

Methods: The CCC19 registry was queried for adult patients with thoracic cancer and laboratory-confirmed SARS-CoV-2 infection. Patients with low-quality data were excluded. The primary outcome was six-level ordinal scale of COVID-19 severity. Secondary outcome was 30-day all-cause mortality. Patients were stratified by the receipt of any anti-cancer treatment within 3 months prior to COVID-19 into chemotherapy alone; chemotherapy with immunotherapy; chemotherapy and radiation; chemotherapy and targeted therapy; immunotherapy alone; targeted therapy alone, other combinations, and locoregional therapy only. Multivariable logistic regression was used to test the association of these treatments with the outcomes after adjustment for key clinical and demographic covariates.

Results: From January 2020 to December 2021, 927 patients with thoracic cancer met the inclusion criteria. Median age was 70 years (Interquartile range [IQR] (62–77 years)), 54% were female, 79% were former or current tobacco users, and 49% had pulmonary comorbidities. At median follow up time of 59 days (IQR 27–180 days), 52% (N=482) of patients received at least one anti-cancer therapy <3 months prior to COVID-19 diagnosis. Immunotherapy alone was the most prevalent treatment exposure (19%; N=93). 30-day all-cause mortality was 22% and overall mortality was 30%. Patients who received locoregional therapy and cytotoxic chemotherapy alone had higher 30-day all-cause mortality (37%, and 27% respectively). On the other hand, patients who received immunotherapy or targeted therapy had numerically lower 30-day all-cause mortality (15% and 17% respectively). On multivariable analysis, only recent chemotherapy use was significantly associated with COVID-19 severity (aOR 2.54; 95% CI 1.41–4.56). None of the other treatment modalities were significantly associated with COVID-19 severity or 30-day all-cause mortality. Among the patients who used baseline steroids of 10 mg or more of prednisone equivalent (12%), there was no significant interaction for COVID-19 severity and 30-day all-cause mortality.

Conclusion: We report a large study evaluating the clinical outcomes of COVID-19 in the context of recent anti-cancer treatments for thoracic cancers. Only recent chemotherapy use was associated with the primary outcome of COVID-19 severity. The study provides reassuring data that patients receiving anti-cancer treatments even in the context of palliative treatment appear not to have a significantly higher risk of mortality.

Keywords

Thoracic cancers; COVID-19; immunotherapy; targeted therapy; chemotherapy

Introduction

Patients with thoracic cancer and coronavirus disease 2019 (COVID-19) have one of the highest risks of complications and death[1,2]. Though novel COVID-19 therapies and vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have significantly lowered COVID-19 mortality and morbidity for the general population, patients with thoracic cancer remain highly vulnerable[3]. In the early phase of the COVID-19 pandemic, large scale registries such as Cancer and COVID-19 (CCC19) and TERAVOLT, dedicated to investigating the impact of COVID-19 in all patients with cancer and patients with thoracic malignancies respectively, provided crucial data on prognostic factors associated with COVID-19 severity and mortality[4,5]. To date, only few studies have specifically focused on the impact of recent anti-cancer treatments in patients with thoracic cancers on COVID-19 mortality, but shed little light on its impact on COVID-19 severity[4,6,7]. As focus shifts towards mitigating the severity of COVID-19 in patients with cancer, identifying adverse prognostic factors for COVID-19 severity in the context of treatments specific to thoracic cancer are needed to develop therapeutic strategies of maximal effect. Here, we analyze comprehensive treatment data from the CCC19 registry in patients with thoracic cancers, assessing the impact of specific anti-cancer treatments on COVID-19 severity through use of an ordinal scale.

Material and Methods

This study utilized data from CCC-19 registry, a multi-institutional collaboration of investigators collecting data on patients with any history of cancer and COVID-19 (NCT04354701). This study was exempt from Institutional Review Board (IRB). Deidentified data was collected on REDCap survey-based questionnaire with database housed at Vanderbilt University. The study schema and details on data elements are described previously[8]. The registry (data lock on January 1, 2022) was queried for adult patients (18 years or older) with thoracic cancers and laboratory confirmed SARS-CoV-2 infection by PCR. Quality control criteria were applied to exclude patients with non-invasive cancers, incomplete follow-up or missing outcomes data, and low quality data (quality score ≥ 5)[9]. All patients with thoracic cancers (i.e., lung, thymoma, mesothelioma) irrespective of histology or disease stage were included in the analysis. Patients who received any anti-cancer therapy within 3 months prior to COVID-19 diagnosis were stratified as follows: cytotoxic chemotherapy (hereafter, chemotherapy) alone, chemotherapy and immunotherapy, chemotherapy and radiation, immunotherapy alone, targeted therapy alone,

targeted therapy and chemotherapy, other modality combinations (e.g., immunotherapy + targeted), locoregional therapy only (surgery or radiation only) and no anti-cancer therapy. No recent anti-cancer therapy group includes patients who did not receive any anti-cancer treatment (surgery, radiation or any systemic treatment) within 3 months of COVID-19 diagnosis. This includes a heterogenous group of patients who had completed all intended therapies, patients on treatment breaks, and patients who had chosen to forego further anticancer therapy.

The primary outcome was a six-level ordinal scale of COVID-19 severity based on most severe reported disease statuses assessed over total follow-up time: none of the following/ambulatory, hospitalized without oxygen requirement, hospitalized with oxygen requirement, ICU admission, mechanical ventilation, and death from any cause, assessed over total follow-up time. For example, patients who were admitted to the ICU without mechanical ventilation and did not die are classified as 'ICU admission', whereas patients who were admitted to the ICU with mechanical ventilation and did not die are classified as 'received mechanical ventilation'. Our secondary outcome was 30-day all-cause mortality from COVID-19 diagnosis.

Baseline prognostic variables identified *a priori* included age, sex, race/ethnicity, country of patient residence, body mass index, smoking status, comorbidities, Eastern Cooperative Oncology group (ECOG) performance status (PS), cancer status at COVID-19 diagnosis, treatment intent, metastasis status, baseline corticosteroid use (10 mg or more of prednisone dose-equivalent [PDE]), types of COVID-19 treatments (remdesivir, hydroxychloroquine, corticosteroids, tocilizumab, others), and calendar time of COVID-19 diagnosis (every 4-months; from January 2020 through December 2021).

To evaluate the association of different systemic treatments with primary and secondary outcomes, we performed multivariable logistic regression after adjustment for the following covariates that were selected a priori: age, sex, race, comorbidities, cancer status, cancer type, COVID-19 treatment, ECOG PS, smoking status, geographic location, and time of diagnosis. Ordinal logistic regression with an offset for (log) follow-up time was used for the primary outcome, while binary logistic regression was used for the secondary outcome. We did not adjust for anti-COVID-19 treatments due to suspected confounding by indication. We considered interactions among metastatic status, intent of therapy, and baseline steroid use.

Results

From January 2020 through December 2021, 14,777 patients with a history of any cancer and COVID-19 were evaluable. Following quality control measures, 927 patients with thoracic cancers ((non-small cell lung cancer (n = 660), small cell lung cancer (n = 88), lung cancer not otherwise specified (NOS) (n = 148), mesothelioma (n = 12), or thymus cancer (n = 19)) and COVID-19 were included in the final analysis (Supplementary figure 1). The median age was 70 years [Interquartile range (IQR)- 62–77 years], with a majority being female (54%), of non-Hispanic white ethnicity (59%), and US residence (90%) (Table 1). Key clinical characteristics included previous smoking history (79%), pulmonary

comorbidities (49%), ECOG PS 2 or more (22%), and cancer status [in remission (30%), active and progressing (23%)], metastatic disease (43%) and palliative intent treatment (36%) (Table 1).

Half (52%) of patients received at least one anti-cancer treatment within 3 months prior to COVID-19 diagnosis. Immunotherapy alone (N=93), followed by chemotherapy alone (N=75), were the most prevalent systemic therapies (Table 1). After a median follow up time of 59 days from COVID-19 diagnosis, 67% of patients required hospitalization, with19% requiring mechanical ventilation. Overall mortality was 30% and 30-day all-cause mortality was 22% (Supplementary Table 1). Patients receiving immunotherapy or targeted therapy had lower 30-day all-cause mortality (15% and 17% respectively). In patients receiving chemotherapy and targeted therapy, the 30-day all-cause mortality rate was only 12%, however, it was limited by small number of patients (N=33). On the other hand, patients receiving chemotherapy alone or in combination with immunotherapy or radiation had higher 30-day all-cause mortality (Figure 1 and Supplementary Table 1).

On multivariable analysis, chemotherapy use with in 3 months of COVID-19 diagnosis was the only treatment significantly associated with COVID-19 severity (aOR 2.54; 95% CI 1.41–4.56) (Table 2). In addition, older age, per decade (aOR 1.17; 5% CI 1.08–1.26), male gender (aOR 1.76; 95% CI 1.31–2.36), BMI >27 (aOR 1.11; 95% CI 1.01–1.22), pulmonary comorbidities (aOR 1.47; 95% CI 1.08–1.99), ECOG 2 or more (aOR 4.92; 95% CI 3.08–7.86) and active and progressing cancer (aOR 4.54; 95% CI 2.88–7.16) was associated with higher COVID-19 severity (Table 2). Diagnosis of COVID-19 in later stages of the pandemic was associated with lower COVID-19 severity. Baseline steroid use of more than 10 mg/day of prednisone or equivalent was not associated with any significant interaction. Significant interactions were noted among several COVID-19 treatments, including steroids, remdesivir and hydroxychloroquine.

As opposed to COVID-19 severity, recent cytotoxic chemotherapy exposure had a weaker association with 30-day all-cause mortality (secondary outcome) that was no longer statistically significant. None of the anti-cancer treatments were significantly associated with 30-day mortality. Other variables associated with higher COVID-19 severity were also associated with higher 30-day mortality. (Table 2).

Discussion

Using CCC19 registry data, we investigated the effects of anti-cancer treatment modalities in patients with thoracic cancers on ordinal outcomes of COVID-19 severity and 30-day-all-cause mortality. Our study represents the second largest cohort of its kind, only behind the TERAVOLT[7]. TERAVOLT is a cross-sectional study focused on evaluating prognostic variables affecting mortality in patients with thoracic cancers and COVID-19. However, the study did not report prognostic factors associated with COVID-19 severity[7]. In contrast, our study used a novel ordinal scale of COVID-19 severity to capture the spectrum of clinically significant complications of COVID-19 across a longer follow-up time. Furthermore, the granular information on the exposure to all types of cancer treatment prior to COVID-19

lends itself for a more nuanced analysis on the impact of these treatments on COVID-19 outcomes that is clinically relevant.

Our analysis showed that recent exposure to cytotoxic chemotherapy was significantly associated with increased COVID-19 severity but had no effect on 30-day all-cause mortality. These findings differ from those of earlier studies involving CCC19, where chemotherapy exposure was associated with both COVID-19 severity and 30-day all-cause mortality, though such results included hematologic malignancies with several chemotherapy regimens and shorter follow-up time[9]. Our findings are also in broad agreement with studies where recent chemotherapy when used alone or combined with any other treatment modality, or receipt of immunotherapy or targeted therapy did not appear to significantly affect COVID-19 mortality[7,11,12]. More research is necessary to elucidate the effects of chemotherapy on COVID-19 severity.

As opposed to previous research, history of smoking was not significantly associated with poorer outcomes after adjustment[10], but like prior studies, presence of pulmonary comorbidities did demonstrate an association with severe COVID-19, without significantly affecting 30-day all-cause mortality[10].

In our study, we observed a high overall mortality among patients with thoracic cancer and COVID-19 at 30%, comparable to other large cohorts involving patients with thoracic cancers and COVID-19 (22–42%)[4,6,7]. Of note, a large proportion of patients in our study were diagnosed early in the pandemic (~79% of patients before January 2021) which may reflect the disproportionately larger impact of COVID-19 in the early phase of the pandemic and the subsequent discovery of novel treatments directed against SARS-CoV-2 infection. Similarly, our findings also show an improvement in mortality and COVID-19 severity over the pandemic period[7,13].

Importantly, our study showed that established poor-prognostic factors like demographics (age and male gender); ECOG PS of 2+, active and progressing cancer, were the strongest predictors of both COVID-19 severity and 30-day all-cause mortality[4,6,7]. Baseline corticosteroid use (>10 mg of PDE) was not associated with any significant interactions for both the outcomes, while any corticosteroid use (irrespective of dose) was significantly associated with mortality in earlier studies[4,6]. More research is needed to ascertain the impact of baseline corticosteroids on COVID-19 severity in the context of specific anti-cancer treatments.

Our study has several limitations. The study population includes a heterogeneous group of patients with thoracic malignancies with exposure to different treatment modalities across disease settings. There was no consensus definition on what constitutes active therapy in relation to the timing of COVID-19 diagnosis, therefore, we used the time interval of 3-months prior to COVID-19 diagnosis to define recent treatment exposure to accommodate and capture both early and late effects of anti-cancer treatments on COVID-19 severity and mortality. We did not have sufficient power to observe associations of individual chemotherapy regimens and warrants further exploration. Furthermore, our timeframe for most of the data collection corresponds to early phases of the pandemic when vaccines

were not widely available, variants were being tracked and when our understanding of COVID-19 management was limited. Our results were not adjusted for phase of the pandemic and vaccination status, which can have a substantial effect on COVID-19 morbidity and mortality in patients with cancer[3,14], such effects may be reflected in the poorer outcomes we report. Nonetheless, our study used a robust data quality measure to provide detailed information collected by health care professionals pertaining to the impact of specific cancer treatments on COVID-19 severity. We used a novel ordinal scale to capture the entire spectrum of clinically relevant complications of COVID-19 in a large and geographically diverse patients with thoracic cancers with comprehensive follow-up. While tailored discussions are critical to balance the risks and benefits of cancer therapy, our study provides the basis for future research to further investigate the impact of chemotherapy on COVID-19 severity, while providing reassuring data for not withholding other systemic treatments. As the pandemic continues to evolve with new emerging strains and resulting fluctuations in disease burden, our study may provide the basis for cancer care providers to develop individualized treatment plans for patients with thoracic cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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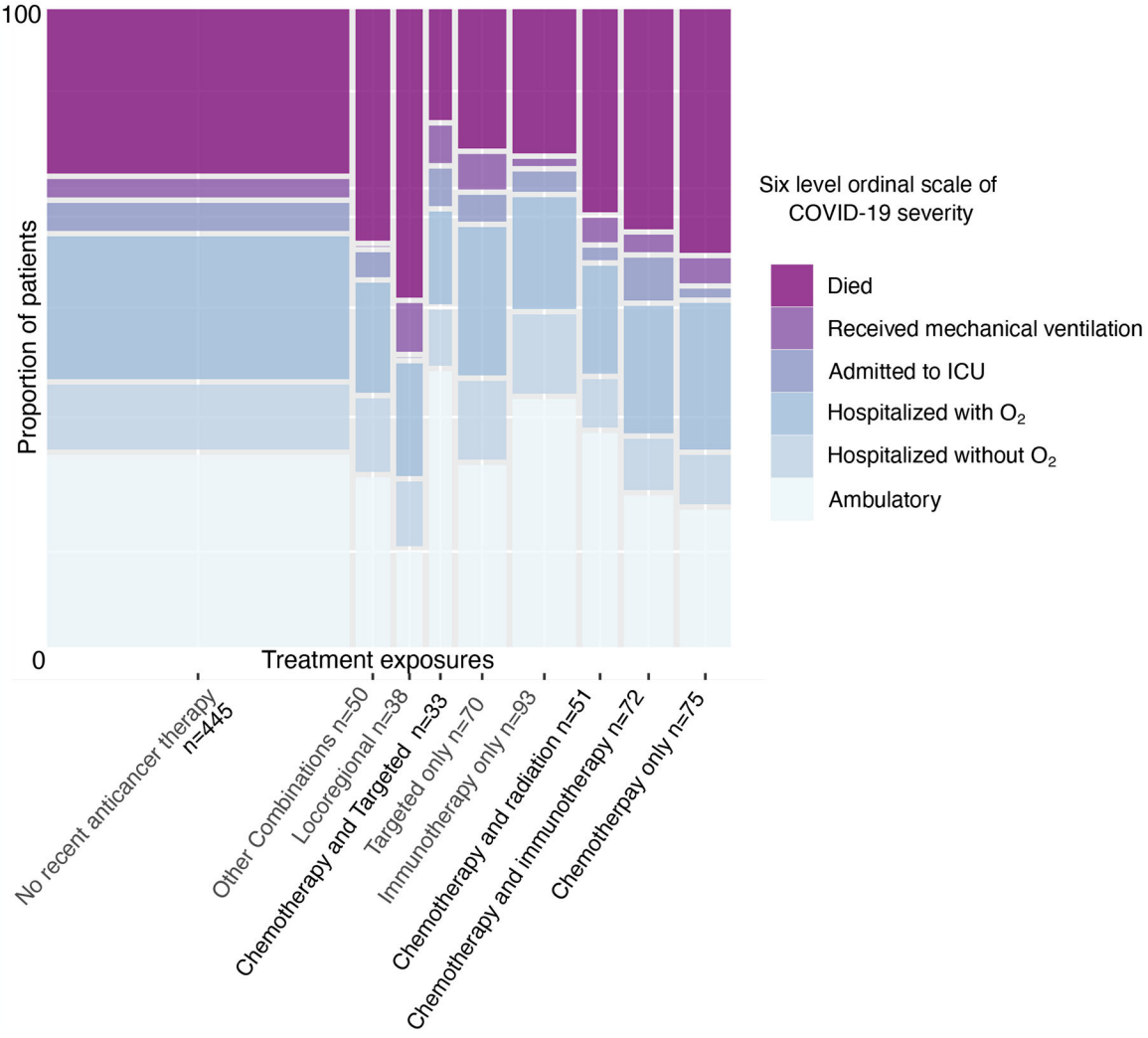

Figure 1.

Distribution of clinical outcomes in patients with thoracic cancer based on the six-level ordinal scale of COVID-19 severity stratified by types of anti-cancer treatment exposures.

Table 1.

Clinical Characteristics of patients with thoracic cancer and COVID-19 receiving anti-cancer treatments.

Characteristics	All patients	Chemotherapy alone	Chemotherapy and immunotherapy	Chemotherapy and radiation	Immunotherapy alone	Targeted therapy alone	Chemotherapy and targeted therapy	Locoregional therapy only	Other combinati
	N = 927	N = 75	N = 72	N = 51	N = 93	N = 70	N = 33	N = 38	N = 50
Age [Median (IQR)]	70 (62–77)	68 (60–73)	66 (60–73)	69 (62–73)	70 (62–75)	69 (59–78)	61 (55–68)	68 (62–76)	66 (56–71)
Sex									
Female	497 (54%)	41 (55%)	36 (50%)	28 (55%)	40 (43%)	45 (64%)	25 (76%)	17 (45%)	25 (50%)
Male	430 (46%)	34 (45%)	36 (50%)	23 (45%)	53 (57%)	25 (36%)	8 (24%)	21 (55%)	25 (50%)
Race/Ethnicity									
Non-Hispanic White	550 (59%)	35 (47%)	49 (68%)	33 (65%)	54 (58%)	37 (53%)	11 (33%)	24 (63%)	32 (64%)
Non-Hispanic Other	261 (28%)	23 (31%)	16 (22%)	12 (24%)	29 (31%)	17 (24%)	12 (36%)	11 (29%)	15 (30%)
Hispanic	93 (10%)	14 (19%)	4 (6%)	3 (6%)	8 (9%)	14 (20%)	9 (27%)	3 (8%)	3 (6%)
Missing/Unknown	23 (2%)	3 (4%)	3 (4%)	3 (6%)	2 (2%)	2 (3%)	1 (3%)	0 (0%)	0 (0%)
Country of patient residence									
Non-US	91 (10%)	19 (25%)	5 (7%)	2 (4%)	12 (13%)	13 (19%)	3 (9%)	1 (3%)	2 (4%)
US	836 (90%)	56 (75%)	67 (93%)	49 (96%)	81 (87%)	57 (81%)	30 (91%)	37 (97%)	48 (96%)
Smoking status									
Never	177 (19%)	15 (20%)	4 (6%)	9 (18%)	9 (10%)	37 (53%)	17 (52%)	6 (16%)	12 (24%)
Former/Current	730 (79%)	57 (76%)	68 (94%)	41 (80%)	84 (90%)	30 (43%)	14 (42%)	32 (84%)	38 (76%)
Missing/Unknown	20 (2%)	3 (4%)	0 (0%)	1 (2%)	0 (0%)	3 (4%)	2 (6%)	0 (0%)	0 (0%)
BMI [Median (IQR)]	27 (23–30)	26 (23–28)	26 (24–30)	26 (23–31)	27 (22–30)	28 (24–30)	27 (24–28)	27 (22–30)	28 (24–32)
Comorbidities									
Diabetes mellitus	246 (27%)	23 (31%)	14 (19%)	13 (25%)	31 (33%)	19 (27%)	6 (18%)	13 (34%)	13 (26%)
Pulmonary comorbidities	453 (49%)	33 (44%)	34 (47%)	23 (45%)	47 (51%)	19 (27%)	8 (24%)	21 (55%)	19 (38%)
Cardiovascular comorbidities	253 (27%)	19 (25%)	24 (33%)	12 (24%)	18 (19%)	17 (24%)	3 (9%)	11 (29%)	9 (18%)
Renal comorbidities	116 (13%)	12 (16%)	7 (10%)	4 (8%)	9 (10%)	4 (6%)	4 (12%)	7 (18%)	7 (14%)
Missing/Unknown	6 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (2%)	2 (3%)	0 (0%)	0 (0%)	1 (2%)
ECOG performance status prior to infection									
0	196 (21%)	12 (16%)	13 (18%)	10 (20%)	19 (20%)	19 (27%)	8 (24%)	6 (16%)	12 (24%)

Characteristics	All patients	Chemotherapy alone	Chemotherapy and immunotherapy	Chemotherapy and radiation	Immunotherapy alone	Targeted therapy alone	Chemotherapy and targeted therapy	Locoregional therapy only	Other combinati
1	340 (37%)	35 (47%)	33 (46%)	21 (41%)	50 (54%)	31 (44%)	12 (36%)	11 (29%)	19 (38%)
2+	208 (22%)	22 (29%)	21 (29%)	11 (22%)	19 (20%)	12 (17%)	5 (15%)	11 (29%)	14 (28%)
Unknown	182 (20%)	6 (8%)	5 (7%)	9 (18%)	5 (5%)	8 (11%)	8 (24%)	10 (26%)	5 (10%)
Missing	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Baseline steroids									
10 mg PDE or less per day	56 (6%)	8 (11%)	8 (11%)	3 (6%)	7 (8%)	3 (4%)	4 (12%)	1 (3%)	5 (10%)
More than 10 mg PDE per day	107 (12%)	9 (12%)	24 (33%)	9 (18%)	8 (9%)	4 (6%)	9 (27%)	5 (13%)	12 (24%)
None	703 (76%)	48 (64%)	30 (42%)	35 (69%)	73 (78%)	61 (87%)	16 (48%)	29 (76%)	32 (64%)
Missing/Unknown	61 (7%)	10 (13%)	10 (14%)	4 (8%)	5 (5%)	2 (3%)	4 (12%)	3 (8%)	1 (2%)
COVID Treatments									
Hydroxychloroquine as COVID-19 treatment, ever	151 (16%)	10 (13%)	16 (22%)	8 (16%)	17 (18%)	9 (13%)	6 (18%)	10 (26%)	8 (16%)
Azithromycin as COVID-19 treatment, ever	172 (19%)	15 (20%)	14 (19%)	5 (10%)	21 (23%)	17 (24%)	7 (21%)	12 (32%)	10 (20%)
Steroids as COVID-19 treatment, ever	311 (34%)	23 (31%)	30 (42%)	20 (39%)	27 (29%)	25 (36%)	11 (33%)	14 (37%)	20 (40%)
Remdesivir as COVID treatment, ever	165 (18%)	11 (15%)	14 (19%)	12 (24%)	12 (13%)	13 (19%)	2 (6%)	8 (21%)	10 (20%)
Tocilizumab as COVID-19 treatment, ever	29 (3%)	2 (3%)	1 (1%)	2 (4%)	1 (1%)	2 (3%)	0 (0%)	2 (5%)	3 (6%)
COVID-19 treatments other than hydroxychloroquine, azithromycin, steroids, remdesivir, or tocilizumab	82 (9%)	4 (5%)	5 (7%)	6 (12%)	10 (11%)	8 (11%)	2 (6%)	6 (16%)	6 (12%)
Missing/Unknown	34 (4%)	4 (5%)	3 (4%)	1 (2%)	3 (3%)	2 (3%)	2 (6%)	0 (0%)	1 (2%)
Cancer status									
Remission/NED	274 (30%)	3 (4%)	3 (4%)	5 (10%)	5 (5%)	6 (9%)	0 (0%)	10 (26%)	2 (4%)
Active, stable/ responding	316 (34%)	32 (43%)	37 (51%)	22 (43%)	63 (68%)	45 (64%)	16 (48%)	6 (16%)	21 (42%)
Active, progressing	216 (23%)	31 (41%)	20 (28%)	17 (33%)	18 (19%)	18 (26%)	11 (33%)	12 (32%)	20 (40%)
Unknown	119 (13%)	8 (11%)	12 (17%)	7 (14%)	7 (8%)	1 (1%)	6 (18%)	10 (26%)	7 (14%)
Missing	2 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Metastasis status									
Metastatic	397 (43%)	44 (59%)	58 (81%)	18 (35%)	64 (69%)	50 (71%)	26 (79%)	9 (24%)	40 (80%)

Characteristics	All patients	Chemotherapy alone	Chemotherapy and immunotherapy	Chemotherapy and radiation	Immunotherapy alone	Targeted therapy alone	Chemotherapy and targeted therapy	Locoregional therapy only	Other combinati
Non-metastatic	484 (52%)	26 (35%)	13 (18%)	29 (57%)	21 (23%)	19 (27%)	5 (15%)	28 (74%)	8 (16%)
Missing/Unknown	46 (5%)	5 (7%)	1 (1%)	4 (8%)	8 (9%)	1 (1%)	2 (6%)	1 (3%)	2 (4%)
Treatment intent									
Curative	198 (21%)	23 (31%)	14 (19%)	31 (61%)	25 (27%)	8 (11%)	11 (33%)	26 (68%)	12 (24%)
Palliative	335 (36%)	50 (67%)	53 (74%)	18 (35%)	64 (69%)	57 (81%)	21 (64%)	7 (18%)	35 (70%)
Missing/Unknown	394 (43%)	2 (3%)	5 (7%)	2 (4%)	4 (4%)	5 (7%)	1 (3%)	5 (13%)	3 (6%)
Timing of COVID diagnosis									
Jan - Apr 2020	235 (25%)	20 (27%)	21 (29%)	12 (24%)	26 (28%)	15 (21%)	16 (48%)	8 (21%)	16 (32%)
May - Aug 2020	270 (29%)	14 (19%)	21 (29%)	16 (31%)	30 (32%)	16 (23%)	7 (21%)	16 (42%)	13 (26%)
Sep - Dec 2020	221 (24%)	23 (31%)	15 (21%)	13 (25%)	16 (17%)	25 (36%)	4 (12%)	5 (13%)	10 (20%)
Jan - Apr 2021	101 (11%)	12 (16%)	9 (12%)	5 (10%)	11 (12%)	5 (7%)	3 (9%)	4 (11%)	5 (10%)
May - Aug 2021	67 (7%)	4 (5%)	3 (4%)	5 (10%)	5 (5%)	6 (9%)	2 (6%)	4 (11%)	5 (10%)
Sep - Dec 2021	33 (4%)	2 (3%)	3 (4%)	0 (0%)	5 (5%)	3 (4%)	1 (3%)	1 (3%)	1 (2%)

Abbreviations: Interquartile range (IQR); United States (US); Body mass index (BMI); Eastern Cooperative Oncology Group (ECOG); prednisone daily equivalent (PDE); no evidence of disease (NED)

Table 2.

Adjusted associations of baseline prognostic factors including exposures to cancer treatment with COVID 19 severity (primary) and 30-day all-cause mortality (secondary) among patients with thoracic cancer.

	COVID-19 Severity		30-day Mortality	
Predictors	***Odds Ratios*** [a]	***CI***	***Odds Ratios*** [b]	***CI***
Recent chemotherapy with immunotherapy[c]	1.06	0.58 – 1.93	1.03	0.50 – 2.14
Recent chemotherapy with radiation[c]	0.68	0.34 – 1.36	1.21	0.55 – 2.70
Recent chemotherapy with targeted therapy[c]	0.73	0.32 – 1.69	0.50	0.15 – 1.70
Recent chemotherapy, only [c]	**2.54**	**1.41 – 4.56**	1.23	0.58 – 2.60
Recent immunotherapy, only[c]	0.58	0.34 – 0.99	0.53	0.25 – 1.11
Recent locoregional therapy, only[c]	2.11	0.90 – 4.96	1.74	0.75 – 4.03
Other combinations of recent therapy[c]	1.01	0.50 – 2.05	0.90	0.37 – 2.14
Recent targeted therapy, only[c]	1.19	0.65 – 2.16	1.20	0.52 – 2.77
Age, per decade[c]	0.58	0.38 – 0.89	0.69	0.38 – 1.26
Age, per decade (quadratic)	**1.17**	**1.08 – 1.26**	**1.15**	**1.03 – 1.28**
Race (Hispanic)	0.65	0.39 – 1.08	1.01	0.50 – 2.05
Race (Non-Hispanic Other)	1.07	0.76 – 1.52	1.24	0.80 – 1.92
Sex (Male)	**1.76**	**1.31 – 2.36**	**1.64**	**1.12 – 2.40**
Region (Non-US)	1.16	0.69 – 1.95	1.62	0.82 – 3.19
BMI <27	0.93	0.87 – 0.99	0.98	0.90 – 1.05
BMI >27	**1.11**	**1.01 – 1.22**	1.05	0.93 – 1.18
Smoking status (Ever)	1.08	0.71 – 1.63	0.93	0.52 – 1.67
Cardiovascular comorbidities (yes vs no)	1.16	0.81 – 1.67	0.99	0.63 – 1.55
Renal disease (yes vs no)	1.19	0.75 – 1.90	1.32	0.78 – 2.23
Diabetes (yes vs no)	1.24	0.88 – 1.74	0.98	0.63 – 1.53
Pulmonary comorbidities (yes vs no)	**1.47**	**1.08 – 1.99**	1.26	0.84 – 1.87
ECOG Score (1)	1.08	0.73 – 1.59	1.41	0.76 – 2.61
ECOG Score (2+)	**4.92**	**3.08 – 7.86**	**3.63**	**1.93 – 6.82**
ECOG Score (Unknown)	1.37	0.86 – 2.18	1.56	0.80 – 3.04
Cancer status (active and stable/responding)	1.46	0.96 – 2.23	1.48	0.83 – 2.66
Cancer status (active and progressing)	**4.54**	**2.88 – 7.16**	**3.31**	**1.86 – 5.89**
Cancer status (unknown)	4.53	2.73 – 7.52	3.06	1.63 – 5.74
Baseline steroids <= 10 mg PDE/day	0.98	0.52 – 1.84	1.33	0.63 – 2.83
Baseline steroids > 10 mg PDE/day	1.15	0.68 – 1.95	1.20	0.67 – 2.16
Remdesivir as a COVID-19 treatment, ever[e]	**4.94**	**3.23 – 7.54**	**1.95**	**1.09 – 3.50**
Hydroxychloroquine as a COVID-19 treatment, ever[e]	**6.74**	**4.20 – 10.81**	**1.97**	**1.15 – 3.38**
Azithromycin as a COVID-19 treatment, ever[e]	1.01	0.66 – 1.54	1.19	0.73 – 1.94

	COVID-19 Severity		30-day Mortality	
Predictors	***Odds Ratios*** [a]	***CI***	***Odds Ratios*** [b]	***CI***
Tocilizumab as a COVID-19 treatment, ever[e]	0.98	0.43 – 2.24	0.94	0.34 – 2.58
Steroids as a COVID-19 treatment, ever[e]	**3.30**	**2.30 – 4.74**	**1.74**	**1.09 – 2.78**
Other COVID-19 treatments[e]	1.38	0.84 – 2.26	0.85	0.42 – 1.74
COVID Diagnosis (May - August 2020)	0.40	0.26 – 0.60	0.40	0.25 – 0.66
COVID Diagnosis (September - December 2020)	0.14	0.09 – 0.22	0.22	0.12 – 0.42
COVID Diagnosis (January - April 2021)	0.19	0.11 – 0.34	0.21	0.10 – 0.46
COVID Diagnosis (May - August 2021)	0.18	0.09 – 0.34	0.33	0.14 – 0.75
COVID Diagnosis (September - December 2021)	0.25	0.11 – 0.58	0.18	0.04 – 0.73

Abbreviations: confidence interval (CI); United States (US); Body mass index (BMI); Eastern Cooperative Oncology Group (ECOG); prednisone daily equivalent (PDE)

[a]Odds ratios >1 indicate higher COVID-19 severity.

[b]Odds ratios >1 indicate higher odds of 30-day all-cause mortality.

[c]Within 3 months of COVID-19 diagnosis.

[d]Obtained from a linear regression spline with a knot at age 40 years, such that odds ratios for ‘Age <40 years’ correspond to the per-decade difference in age for ages <40 years and odds ratios for ‘Age >40 years’ correspond to the per-decade difference in age for ages >40 years.

[e]The model for COVID-19 severity also included anti-COVID-19 treatments due to suspected confounding by indication.