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ORIGINAL ARTICLE

Risk factors of SARS-CoV-2 infection and complications from COVID-19 in lung cancer patients

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Abstract

Background Identifying lung cancer patients at an increased risk of getting SARS-CoV-2-related complications will facilitate tailored therapy to maximize the benefit of anti-cancer therapy, while decreasing the likelihood of COVID-19 complications. This analysis aimed to identify the characteristics of lung cancer patients that predict for increased risk of death or serious SARS-CoV-2 infection.

Patients and methods This was a retrospective cohort study of patients with lung cancer diagnosed October 1, 2015, and December 1, 2020, and a diagnosis of COVID-19 between February 2, 2020, and December 1, 2020, within the Veterans Health Administration. Serious SARS-CoV-2 infection was defined as hospitalization, ICU admission, or mechanical ventilation or intubation within 2 weeks of COVID-19 diagnosis. For categorical variables, differences were assessed using X^2 tests, while Kruskal–Wallis rank-sum test was used for continuous variables. Multivariable logistic regression models were fit relative to onset of serious SARS-CoV-2 infection and death from SARS-CoV-2 infection.

Results COVID-19 infection was diagnosed in 352 lung cancer patients. Of these, 61 patients (17.3%) died within four weeks of diagnosis with COVID-19, and 42 others (11.9%) experienced a severe infection. Patients who had fatal or severe infection were older and had lower hemoglobin levels than those with mild or moderate infection. Factors associated with death from SARS-CoV-2 infection included increasing age, immune checkpoint inhibitor therapy and low hemoglobin level.

Conclusions The mortality of lung cancer patients from COVID-19 disease in the present cohort was less than previously reported in the literature. The identification of risk factors associated with severe or fatal outcomes informs management of patients with lung cancer who develop COVID-19 disease.

Keywords Lung cancer · COVID-19 disease · Outcomes · Risk factors · Mortality

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel beta coronavirus that originated in China and has affected the entire world with coronavirus disease 2019 (COVID-19). While the case fatality rate of COVID-19 varies based on factors including the availability of testing and methods of mortality attribution, certain populations are at an increased risk of developing complications from COVID-19 [1–3]. Patients with cancer are one such group, with mortality estimates ranging from 13 to 29% [4–9], much higher than the typical mortality in COVID-19 patients. Factors, such as older age, advanced tumor stage, recent adjuvant chemotherapy, and multiple comorbidities, need for ICU support, elevated D-Dimer, and LDH and elevated lactate blood levels have been associated with

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severe COVID-19 outcomes [10, 11]. Only a few studies have studied outcomes of SARS-CoV-2 infection specifically in patients with lung cancer; these have reported a mortality rate of approximately 30% [12–14]. The risk factors for developing complications from COVID-19 disease in patients with lung cancer are not clear as most of the aforementioned studies have not separated risk factors specifically by cancer type. Hence, there is an urgent need for identifying those lung cancer patients at an increased risk of getting SARS-CoV-2 infection and subsequently developing complications.

To that end, we hypothesized that baseline clinical and laboratory characteristics are associated with risk of developing serious COVID-19 infection and developed multivariable models that (1) identify the clinical and laboratory characteristics of cancer patients that predict for increased risk of serious SARS-CoV-2 infection, and (2) identify the clinical and laboratory characteristics of cancer patients that predict for increased risk of death from SARS-CoV-2 infection. Identification of patients at an increased risk of SARS-CoV-2 infection will allow their oncology team to alter or delay treatment of the cancer to maximize the benefit of cancer therapy, while minimizing the risk of COVID-19-related complications.

Methods

Data sources and patient population

We conducted a retrospective cohort study using data from the VA COVID-19 Shared Data Resource, the VA Cancer Registry, and the VA Corporate Data Warehouse (CDW), which centralizes electronic health record data for patients seen at VA facilities nationwide [15]. We included patients with a diagnosis of lung cancer in the VA Cancer Registry (ICDOSite = 'LUNG/BRONCHUS') between October 1, 2015 and December 1, 2020, and a diagnosis of COVID-19 as recorded in the VA COVID-19 Shared Data Resource between February 2, 2020 and December 1, 2020. We considered data in the electronic health record collected between October 1, 2015 and December 1, 2020.

Ethics

The study was approved by the VA Boston Institutional Review Board (IRB) as an exempt human research study prior to data collection and analysis. Due to the sensitive nature of the data collected for this study, requests to access the data set are limited to qualified VA-affiliated researchers.

Study variables and outcome

We considered two outcomes: onset of serious SARS-CoV-2 infection and death from SARS-CoV-2 infection. Onset of serious SARS-CoV-2 infection was defined as the first occurrence of any of the following within 2 weeks after COVID-19 diagnosis: (a) hospitalization, (b) ICU admission, or (c) utilization of respiratory support (mechanical ventilation or intubation). Unplanned hospitalizations were determined using a previously defined algorithm [16]. ICU admission was defined as a subset of hospitalizations where the specialty ward is either "Surgical ICU" or "Medical ICU". Respiratory support was determined based on the presence of a current procedural terminology (CPT) or ICD-10 procedure code for intubation or mechanical ventilation (Supplementary Table 1). Death from SARS-CoV-2 infection was defined as death occurring within four weeks after COVID-19 diagnosis.

We determined age at COVID-19 diagnosis, gender, race, and ethnicity from structured data in the CDW, as well as urban status (urban, rural, and highly rural) of each patient's home address and the region of the VA facility where each patient was tested for SARS-CoV-2. Smoking status was defined using health factors [17]. We extracted date of diagnosis with lung cancer, histology, and stage from the VA Cancer Registry; for patients with multiple records of lung cancer in the registry, we used the first record with a date of diagnosis within our study period. We determined utilization of systemic therapy (chemotherapy, hormone therapy, immunotherapy, or targeted therapy) based on pharmacy records in the CDW, utilization of radiation therapy for lung cancer based on procedure codes (Supplementary table 1) in 1 week proximity to a ICD-10 diagnosis code related to lung cancer (Supplementary Table 1), and utilization of surgical resection for lung cancer by identifying surgical records with a principal-associated diagnosis of lung cancer. We tabulated presence or absence of each type of therapy in the 6 months prior to COVID-19 diagnosis and determined the most recent type of therapy prior to COVID-19 diagnosis. The presence of individual comorbidities, including acute myocardial infarction (AMI), chronic obstructive pulmonary disease (COPD), diabetes, hypertension, and stroke, was derived from diagnosis and procedure codes in the year prior to each patient's first COVID-19 test using Centers for Medicare and Medicaid Services Chronic Conditions Warehouse algorithms adapted for use in the VA [17] (Also, available at Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse: condition categories. https://www2.ccwdata.org/web/guest/about-ccw Accessed October 01, 2020). Finally, we identified laboratory test results from the specimen taken most recently prior to COVID-19 diagnosis for complete blood count (white cell count, platelets,

hemoglobin); absolute neutrophil and absolute lymphocyte counts; neutrophil-to-lymphocyte ratio (NLR); electrolytes (sodium chloride, potassium chloride, and chloride); liver function (AST, ALT, and alkaline phosphatase); and kidney function (creatinine). Laboratory test results were categorized using pre-specified cutoffs detailed in Supplementary Table 2.

Statistical analysis

Baseline characteristics were summarized in the full cohort and patient assigned an outcome group as either those without serious SARS-CoV-2 infection, patients with serious SARS-CoV-2 infection but no death, or patients who died following SARS-CoV-2 infection. For categorical variables, differences in proportion across these groups were assessed using chi-squared tests. For continuous variables, between-group differences were assessed using the Kruskal–Wallis rank-sum test.

Multivariable logistic regression models were fit relative to the two outcomes of interest (i.e., onset of serious SARS-CoV-2 infection and death from SARS-CoV-2 infection). The index date was the date of diagnosis of COVID-19. For onset of serious SARS-CoV-2 infection, follow-up time was censored by death (if it occurred prior to onset of SARS-CoV-2 complications) or the end of the study period (December 1, 2020). For death from SARS-CoV-2 infection, follow-up time was censored by the end of the study period. All variables described above were included in each model.

Results

We identified 352 lung cancer patients diagnosed with COVID-19 between February 2, 2020 and December 1, 2020. Of these, 61 patients (17.3%) died within four weeks of diagnosis with COVID-19, and 42 others (11.9%) experienced a severe infection.

The demographics of this cohort are described in Table 1. The majority of the patients were male ($n=337$; 95.7%) with a median age of 72.6 years (IQR: 69–77.3 years). Whites made up of almost two thirds of this cohort (n = 234; 66.5%), while Blacks comprised of 29% ($n=102$). Hispanic or Latino ethnicity was noted in 3.4% of this cohort ($n=12$). Nearly half of the cohort consisted of current smokers ($n=158$; 44.9%), while another 42.6% of the cohort were former smokers ($n=150$). Adenocarcinoma was the most common histology seen ($n=142$; 40.3%) and the most recent treatment received in almost 80% of the cohort was an immune checkpoint inhibitor. Twenty-two patients (6.2%) received radiation therapy, while 8 patients (2.3%) underwent surgery in the 6 months preceding their COVID-19 diagnosis. The most common comorbidities seen in our cohort were hypertension (73.3%), COPD (54.3%) and diabetes (42%).

Patients who had fatal or severe infection were older than those with mild/moderate infection (median age: 76.1 and 73.0 years, vs. 72.0 years; $p<0.001$). Patients who suffered a fatal or severe infection were also more likely than patients with mild/moderate infection to exhibit low hemoglobin levels (62.3% and 52.4%, vs. 37.8%, $p=0.001$). In addition, 57.4% of patients who died within four weeks of SARS-CoV-2 infection suffered from diabetes, compared to 40.6% of patients with mild/moderate infection ($p=0.01$).

We used multivariable logistic regression to evaluate the relationship between these baseline characteristics and the odds of experiencing serious SARS-CoV-2 infection, or death within four weeks of infection (Table 2). Older patients had increased odds of experiencing severe infection or death (OR: 1.09; 95% CI 1.04–1.14; $p<0.001$). Patients who had anemia (OR: 2.8; 95% CI 1.47–5.33; $p=0.002$ also had increased odds of severe infection or death. Gender, race, ethnicity, histology, recent surgery or radiation, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, acute myocardial infection, and other laboratory values were not associated with an increased risk of severe/fatal infection.

In addition, we prepared a multivariable logistic regression model to indicate the odds of death within four weeks of infection (Table 3). Older patients had an increased risk of death (OR: 1.11; 95% CI 1.05–1.18; $p<0.001$) from SARS-CoV-2 infection. Patients who most recently underwent checkpoint inhibitor therapy also had increased odds of fatal infection (OR: 6.43; 95% CI 1.76–23.44; $p=0.005$). The presence of anemia too associated with increased odds of fatal infection (OR: 2.4; 95% CI 1.02—5.61; $p=0.044$). Factors associated with lower odds of death following infection include elevated alkaline phosphatase levels (OR: 0.19; 95% CI 0.04–1; $p=0.05$). Gender, race, ethnicity, histology, stage at diagnosis, previous surgery or radiation therapy, diabetes, hypertension, history of stroke, and other laboratory parameters were not associated with mortality from SARS-CoV-2 infection.

Discussion

Almost 30% of lung cancer patients with COVID-19 infection either developed complications or died. The case fatality rate for lung cancer patients in the present cohort was 17.3%. In contrast to previous studies, the case fatality rate in our series was significantly lower. As discussed earlier, two previous analyses suggested that the case fatality rate in lung cancer patients was greater than 30% [12–14]. The first analysis by Tagliamento et al. was a meta-analysis of all previously published studies [12]. Interestingly, they

Table 1 Patient characteristics in the full sample and in patients experiencing each outcome

Variable	Full sample	Non-serious SARS-CoV-2 infection	Serious SARS-CoV-2 infection but no death	Death from SARS-CoV-2 infection	*P*
Number of Observations	352	249	42	61	
Age, mean [IQR]	72.58 [69.04—77.27]	72.01 [68.56—76.13]	73.01 [70.87—76.96]	76.12 [72.48—82.52]	< 0.001
Gender (female), *n* (%)	15 (4.3%)	11 (4.4%)	4 (9.5%)	0 (0.0%)	0.061
Race, *n* (%)					
White	234 (66.5%)	166 (66.7%)	25 (59.5%)	43 (70.5%)	0.403
Black	102 (29.0%)	69 (27.7%)	16 (38.1%)	17 (27.9%)	
Other or Unknown	16 (4.5%)	14 (5.6%)	1 (2.4%)	1 (1.6%)	
Ethnicity, *n* (%)					
Not Hispanic or Latino	334 (94.9%)	233 (93.6%)	42 (100.0%)	59 (96.7%)	0.438
Hispanic or Latino	12 (3.4%)	11 (4.4%)	0 (0.0%)	1 (1.6%)	
Unknown	6 (1.7%)	5 (2.0%)	0 (0.0%)	1 (1.6%)	
Rurality, *n* (%)					
Rural	83 (23.6%)	57 (22.9%)	9 (21.4%)	17 (27.9%)	0.810
Urban	267 (75.9%)	190 (76.3%)	33 (78.6%)	44 (72.1%)	
Unknown	2 (0.6%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	
Year of diagnosis, *n* (%)					
2015	18 (5.1%)	15 (6.0%)	1 (2.4%)	2 (3.3%)	0.357
2016	46 (13.1%)	31 (12.4%)	7 (16.7%)	8 (13.1%)	
2017	70 (19.9%)	53 (21.3%)	8 (19.0%)	9 (14.8%)	
2018	72 (20.5%)	53 (21.3%)	9 (21.4%)	10 (16.4%)	
2019	86 (24.4%)	61 (24.5%)	7 (16.7%)	18 (29.5%)	
2020	50 (14.2%)	28 (11.2%)	8 (19.0%)	14 (23.0%)	
Unknown	10 (2.8%)	8 (3.2%)	2 (4.8%)	0 (0.0%)	
Histology, *n* (%)					
Adenocarcinoma	142 (40.3%)	99 (39.8%)	21 (50.0%)	22 (36.1%)	0.270
Squamous cell carcinoma	8 (2.3%)	6 (2.4%)	1 (2.4%)	1 (1.6%)	
Large cell carcinoma	90 (25.6%)	68 (27.3%)	11 (26.2%)	11 (18.0%)	
Other or UNKNOWN	112 (31.8%)	76 (30.5%)	9 (21.4%)	27 (44.3%)	
Stage at diagnosis, *n* (%)					
I	122 (34.7%)	95 (38.2%)	11 (26.2%)	16 (26.2%)	0.552
II	25 (7.1%)	17 (6.8%)	2 (4.8%)	6 (9.8%)	
III	36 (10.2%)	26 (10.4%)	4 (9.5%)	6 (9.8%)	
IV	15 (4.3%)	9 (3.6%)	2 (4.8%)	4 (6.6%)	
Unknown	154 (43.8%)	102 (41.0%)	23 (54.8%)	29 (47.5%)	
Smoking status, *n* (%)					
Current	158 (44.9%)	23 (37.7%)	117 (47.0%)	18 (42.9%)	0.771
Former	150 (42.6%)	28 (45.9%)	103 (41.4%)	19 (45.2%)	
Never	25 (7.1%)	5 (8.2%)	18 (7.2%)	2 (4.8%)	
Unknown	19 (5.4%)	5 (8.2%)	11 (4.4%)	3 (7.1%)	
Most recent treatment, n (%)					
Checkpoint Inhibitor	284 (80.7%)	207 (83.1%)	34 (81.0%)	43 (70.5%)	0.198
Chemotherapy	40 (11.4%)	22 (8.8%)	5 (11.9%)	13 (21.3%)	
Targeted	26 (7.4%)	18 (7.2%)	3 (7.1%)	5 (8.2%)	
No prior treatment	2 (0.6%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	
Radiation in last 6 months, *n* (%)	22 (6.2%)	13 (5.2%)	3 (7.1%)	6 (9.8%)	0.397
Surgery in last 6 months, *n* (%)	8 (2.3%)	5 (2.0%)	1 (2.4%)	2 (3.3%)	0.836
Acute myocardial infarction, *n* (%)	3 (0.9%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	0.535
Chronic obstructive pulmonary disease, *n* (%)	191 (54.3%)	134 (53.8%)	28 (66.7%)	29 (47.5%)	0.155

Table 1 (continued)

Variable	Full sample	Non-serious SARS-CoV-2 infection	Serious SARS-CoV-2 infection but no death	Death from SARS-CoV-2 infection	*P*
Diabetes, *n* (%)	148 (42.0%)	101 (40.6%)	12 (28.6%)	35 (57.4%)	0.010
Hypertension, *n* (%)	258 (73.3%)	180 (72.3%)	30 (71.4%)	48 (78.7%)	0.574
Stroke, *n* (%)	19 (5.4%)	13 (5.2%)	2 (4.8%)	4 (6.6%)	0.901
White cell count, *n* (%)					
Low	27 (7.7%)	21 (8.4%)	3 (7.1%)	3 (4.9%)	0.872
Normal	320 (90.9%)	225 (90.4%)	38 (90.5%)	57 (93.4%)	
Unknown	5 (1.4%)	3 (1.2%)	1 (2.4%)	1 (1.6%)	
Platelet count, *n* (%)					
Low	48 (13.6%)	8 (13.1%)	32 (12.9%)	8 (19.0%)	0.305
Normal	288 (81.8%)	48 (78.7%)	206 (82.7%)	34 (81.0%)	
Elevated	16 (4.5%)	5 (8.2%)	11 (4.4%)	0 (0.0%)	
Absolute neutrophils count, *n* (%)					
Low	9 (2.6%)	7 (2.8%)	1 (2.4%)	1 (1.6%)	0.769
Normal	262 (74.4%)	187 (75.1%)	33 (78.6%)	42 (68.9%)	
Elevated	45 (12.8%)	31 (12.4%)	3 (7.1%)	11 (18.0%)	
Unknown	36 (10.2%)	24 (9.6%)	5 (11.9%)	7 (11.5%)	
Absolute lymphocytes count, *n* (%)					
Low	92 (26.1%)	59 (23.7%)	10 (23.8%)	23 (37.7%)	0.312
Normal	236 (67.0%)	174 (69.9%)	28 (66.7%)	34 (55.7%)	
Elevated	3 (0.9%)	2 (0.8%)	0 (0.0%)	1 (1.6%)	
Unknown	21 (6.0%)	14 (5.6%)	4 (9.5%)	3 (4.9%)	
Neutrophil-to-lymphocyte ratio (NLR), *n* (%)					
Normal	136 (38.6%)	19 (31.1%)	104 (41.8%)	13 (31.0%)	0.197
Elevated	168 (47.7%)	29 (47.5%)	116 (46.6%)	23 (54.8%)	
Unknown	48 (13.6%)	13 (21.3%)	29 (11.6%)	6 (14.3%)	
Sodium, *n* (%)					
Low	80 (22.7%)	52 (20.9%)	7 (16.7%)	21 (34.4%)	0.149
Normal	252 (71.6%)	179 (71.9%)	34 (81.0%)	39 (63.9%)	
Elevated	2 (0.6%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	
Unknown	18 (5.1%)	16 (6.4%)	1 (2.4%)	1 (1.6%)	
Potassium, *n* (%)					
Low	12 (3.4%)	9 (3.6%)	0 (0.0%)	3 (4.9%)	0.519
Normal	193 (54.8%)	132 (53.0%)	25 (59.5%)	36 (59.0%)	
Elevated	13 (3.7%)	10 (4.0%)	0 (0.0%)	3 (4.9%)	
Unknown	134 (38.1%)	98 (39.4%)	17 (40.5%)	19 (31.1%)	
Chloride, *n* (%)					
Low	18 (5.1%)	13 (5.2%)	0 (0.0%)	5 (8.2%)	0.536
Normal	158 (44.9%)	110 (44.2%)	23 (54.8%)	25 (41.0%)	
Elevated	28 (8.0%)	19 (7.6%)	4 (9.5%)	5 (8.2%)	
Unknown	148 (42.0%)	107 (43.0%)	15 (35.7%)	26 (42.6%)	
ALT, *n* (%)					
Normal	330 (93.8%)	235 (94.4%)	41 (97.6%)	54 (88.5%)	0.134
Elevated	19 (5.4%)	13 (5.2%)	1 (2.4%)	5 (8.2%)	
Unknown	3 (0.9%)	1 (0.4%)	0 (0.0%)	2 (3.3%)	
AST, *n* (%)					
Normal	336 (95.5%)	240 (96.4%)	41 (97.6%)	55 (90.2%)	0.131
Elevated	13 (3.7%)	8 (3.2%)	1 (2.4%)	4 (6.6%)	
Unknown	3 (0.9%)	1 (0.4%)	0 (0.0%)	2 (3.3%)	

Table 1 (continued)

Variable	Full sample	Non-serious SARS-CoV-2 infection	Serious SARS-CoV-2 infection but no death	Death from SARS-CoV-2 infection	*P*
Alkaline phosphatase, *n* (%)					
Normal	310 (88.1%)	216 (86.7%)	37 (88.1%)	57 (93.4%)	0.675
Elevated	41 (11.6%)	32 (12.9%)	5 (11.9%)	4 (6.6%)	
Unknown	1 (0.3%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	
Creatinine, *n* (%)					
Normal	261 (74.1%)	193 (77.5%)	30 (71.4%)	38 (62.3%)	0.080
Elevated	88 (25.0%)	53 (21.3%)	12 (28.6%)	23 (37.7%)	
Unknown	3 (0.9%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	
Hemoglobin, *n* (%)					
Low	154 (43.8%)	94 (37.8%)	22 (52.4%)	38 (62.3%)	0.001
Normal	198 (56.2%)	155 (62.2%)	20 (47.6%)	23 (37.7%)	

found that the case fatality rate in studies that included more than 100 patients, was lower than that seen in smaller series. They found that the case fatality rate was 32.4% (95% CI 26.5–39.6%) when they included all studies, but this decreased to 22.7% (95% CI 11.8–43.8%) when they excluded studies with < 100 patients, suggesting a possible bias in reporting. The latter estimate is similar to the findings from our cohort, which included over 352 patients. When compared to the patients in the aforementioned TERAVOLT cohort, the patients in the present cohort were older (IQR: 69–77.3 years vs. 61.8–75 years), more likely to be male (95.7% vs. 70%), be exposed to tobacco (87% vs. 81%) and be diagnosed with stage I lung cancer (34.7% vs. 8%) [18]. Similarly, when compared to the patient demographics in the Spanish GRAVID study, the patients in the present cohort were more likely older (mean age 72.6 vs. 67.1 years), be likely to be male (95.7% vs. 74.3%) and be diagnosed at a stage I disease (34.7% vs. 10%) [14].

Our analysis has the advantage of including all the patients within a large US database and is therefore, less likely to be susceptible to reporting bias. Another possible reason for this discrepancy could have been the stage distribution of patients in the present cohort, as a larger proportion were diagnosed with stage I disease. A third possibility could be that our cohort included patients diagnosed throughout 2020. It is possible that these patients may have had the benefit of being treated after more information was known about the pathophysiology of COVID-19 and therefore received more appropriate care.

In the present cohort, increasing age, prior immune checkpoint inhibitor therapy, and low hemoglobin level were associated with a severe/fatal SARS-CoV-2 infection. When we evaluated factors associated with mortality in our cohort, these same factors were associated with increased mortality, while elevated alkaline phosphatase was associated with decreased risk of mortality.

A prospective French study of 1230 cancer patients, of which 475 had confirmed COVID-19 disease, showed that male gender, metastatic disease, history of inflammatory or autoimmune disease receiving immunosuppressive treatments and lymphopenia were independent predictive factors for death, on multivariate analysis [19]. The TERAVOLT study, which is a global consortium studying the effect of SARS-CoV-2 in patients with thoracic cancers, has presented data on 400 patients so far [13]. In their updated analysis, age > 65, ECOG PS ≥ 1, use of steroids and anticoagulation prior to COVID-19 diagnosis were associated with increased risk of death [20]. The GRAVID study, which was a prospective, observational study of patients with lung cancer and PCR-confirmed COVID-19 diagnosis across 65 hospitals in Spain demonstrated a mortality rate of 32.7% [14]. They observed that a higher mortality rate among patients treated with corticosteroids during their hospitalization, while anticancer therapy, including immunotherapy, was not associated with an increased risk of hospitalization or death. However only 20% of their patients received an immune checkpoint inhibitor. They also found that patients with lymphocytopenia and high LDH had an increased risk of death, but the lymphocytopenia was most likely related to corticosteroid use, while an elevated LDH was most likely a marker of disease severity. A small report from Indonesia found that elevated neutrophil-to-lymphocyte ratio and elevated platelet to lymphocyte ratio were significantly associated with increased risk of death from COVID-19 infection in patients with non-small cell lung cancer [21]. In contrast, in our analysis, there was no association between laboratory parameters, other than hemoglobin and either severe infection or mortality from COVID-19 infection. Given the inherent nature of our population, which was overwhelmingly male, we were not able to find a gender difference in mortality or risk of severe disease.

Table 2 Multivariable logistic regression model of the odds of experiencing serious SARS-CoV-2 infection within 2 weeks after infection or death within 4 weeks of infection

	OR (95% CI)	*Z*	*P*	Sig
Age	1.09 (1.04–1.14)	3.59	< 0.001	***
Gender				
Male	Reference			
Female	1.84 (0.37–9.1)	0.75	0.453	
Race				
White	Reference			
Black	1.16 (0.57–2.39)	0.41	0.68	
Other or Unknown	0.59 (0.1–3.66)	< 0.01	0.575	
Ethnicity				
Not Hispanic or Latino	Reference			
Hispanic or Latino	0.22 (0.02–2.02)	< 0.01	0.179	
Unknown	0.94 (0.08–11.28)	< 0.01	0.963	
Rurality				
Rural	Reference			
Urban	0.6 (0.29–1.22)	< 0.01	0.157	
Unknown	0 (0-Inf)	< 0.01	0.995	
Histology				
Adenocarcinoma	Reference			
Large cell carcinoma	0.67 (0.11–4.29)	< 0.01	0.674	
Squamous cell carcinoma	0.55 (0.26–1.18)	< 0.01	0.127	
Other or Unknown	0.82 (0.42–1.62)	< 0.01	0.569	
Stage at Diagnosis				
I	Reference			
II	1.78 (0.54–5.87)	0.94	0.345	
III	1.48 (0.55–4.02)	0.77	0.44	
IV	4.72 (0.95–23.38)	1.9	0.057	*
Unknown	2.59 (1.22–5.49)	2.48	0.013	**
Smoking status				
Current	Reference			
Former	1.35 (0.72–2.55)	0.94	0.346	
Never	0.9 (0.27–3)	< 0.01	0.861	
Unknown	2.67 (0.68–10.4)	1.41	0.158	
Most recent treatment				
No prior treatment	Reference			
Checkpoint	2.2 (0.84–5.78)	1.6	0.11	
Chemotherapy	1.02 (0.32–3.26)	0.04	0.967	
Targeted	0 (0-Inf)	< 0.01	0.995	
Radiation in last 6 months	1.43 (0.46–4.41)	0.62	0.538	
Surgery in last 6 months	1.4 (0.26–7.71)	0.39	0.697	
Acute myocardial infarction	0 (0-Inf)	< 0.01	0.992	
Chronic obstructive pulmonary disease	1.66 (0.89–3.11)	1.58	0.113	
Diabetes	0.73 (0.38–1.38)	< 0.01	0.332	
Hypertension	0.77 (0.38–1.55)	< 0.01	0.462	
Stroke	1.52 (0.42–5.51)	0.63	0.527	
White cell count				
Normal	Reference			
Low	0.37 (0.09–1.49)	< 0.01	0.162	
Unknown	1.51 (0.13–17.1)	0.33	0.742	
Platelets count				
Normal	Reference			
Low	0.82 (0.34–2)	< 0.01	0.6	

Table 2 (continued)

	OR (95% CI)	*Z*	*P*	Sig
Elevated	0.62 (0.16–2.45)	< 0.01	0.49	
Absolute Neutrophils count				
Normal	Reference			
Low	0.61 (0.06–5.92)	< 0.01	0.67	
Elevated	1.4 (0.57–3.47)	0.73	0.467	
Unknown	0.18 (0.02–1.51)	< 0.01	0.114	
Absolute Lymphocytes count				
Normal	Reference			
Low	0.98 (0.46–2.06)	< 0.01	0.952	
Elevated	1.36 (0.07–25.39)	0.21	0.836	
Unknown	1.04 (0.17–6.37)	0.04	0.97	
Neutrophil-to-lymphocyte ratio (NLR)				
Normal	Reference			
Elevated	1.54 (0.7–3.37)	1.07	0.283	
Unknown	8.27 (1.47–46.59)	2.39	0.017	**
Sodium				
Normal	Reference			
Low	1.69 (0.8–3.55)	1.37	0.169	
Elevated	0 (0-Inf)	< 0.01	0.994	
Unknown	0.18 (0.02–1.25)	< 0.01	0.083	*
Potassium				
Normal	Reference			
Low	0.43 (0.07–2.46)	< 0.01	0.341	
Elevated	0.08 (0.01–0.67)	< 0.01	0.02	**
Unknown	0.86 (0.44–1.67)	< 0.01	0.651	
Chloride				
Normal	Reference			
Low	0.57 (0.12–2.74)	< 0.01	0.483	
Elevated	1.28 (0.45–3.67)	0.46	0.647	
Unknown	0.93 (0.46–1.89)	< 0.01	0.847	
ALT				
Normal	Reference			
Elevated	1.11 (0.28–4.46)	0.15	0.879	
Unknown	8,254,893.44 (0-Inf)	< 0.01	0.994	
AST				
Normal	Reference			
Elevated	1.52 (0.28–8.07)	0.49	0.626	
Unknown	215.86 (3.22–14,463.2)	2.51	0.012	**
Alkaline phosphatase				
Normal	Reference			
Elevated	0.46 (0.17–1.28)	< 0.01	0.136	
Unknown	0 (0-Inf)	< 0.01	0.994	
Creatinine				
Normal	Reference			
Elevated	1.66 (0.86–3.17)	1.52	0.128	
Unknown	0 (0-Inf)	< 0.01	0.994	
Hemoglobin				
Normal	Reference			
Low	2.8 (1.47–5.33)	3.14	0.002	***

Significance: ***$p < 0.01$, **$0.01 <= p < 0.05$, *$0.05 <= p < 0.1$

Table 3 Multivariable logistic regression model of the odds of experiencing death from SARS-CoV-2 infection within 4 weeks after the infection

	OR (95% CI)	*Z*	*P*	Sig
Age	1.11 (1.05–1.18)	3.41	< 0.001	***
Gender				
Male	Reference			
Female	0 (0-Inf)	< 0.01	0.99	
Race				
White	Reference			
Black	0.69 (0.27–1.79)	< 0.01	0.445	
Other or Unknown	0.29 (0.02–3.68)	< 0.01	0.34	
Ethnicity				
Not Hispanic or Latino	Reference			
Hispanic or Latino	0.53 (0.05–5.72)	< 0.01	0.603	
Unknown	4.29 (0.25–72.33)	1.01	0.312	
Rurality				
Rural	Reference			
Urban	0.49 (0.19–1.25)	< 0.01	0.134	
Unknown	0 (0-Inf)	< 0.01	0.998	
Histology				
Adenocarcinoma	Reference			
Large cell carcinoma	0.54 (0.03–9.29)	< 0.01	0.673	
Squamous cell carcinoma	0.45 (0.15–1.31)	< 0.01	0.141	
Other or unknown	1.64 (0.69–3.89)	1.12	0.265	
Stage at diagnosis				
I	Reference			
II	3.29 (0.76–14.27)	1.59	0.112	
III	1.63 (0.39–6.73)	0.67	0.5	
IV	1.39 (0.2–9.92)	0.33	0.742	
Unknown	1.62 (0.56–4.65)	0.89	0.371	
Smoking status				
Current	Reference			
Former	1.33 (0.57–3.07)	0.66	0.51	
Never	0.68 (0.13–3.51)	< 0.01	0.646	
Unknown	1.65 (0.32–8.45)	0.6	0.548	
Most recent treatment				
No prior Treatment	Reference			
Checkpoint	6.43 (1.76–23.44)	2.82	0.005	***
Chemotherapy	1.72 (0.39–7.5)	0.72	0.472	
Targeted	0 (0-Inf)	< 0.01	0.997	
Radiation in last 6 months	2.4 (0.55–10.5)	1.16	0.245	
surgery in last 6 months	1.6 (0.16–15.81)	0.4	0.688	
Acute myocardial infarction	0 (0-Inf)	< 0.01	0.994	
Chronic obstructive pulmonary disease	0.74 (0.33–1.67)	< 0.01	0.466	
Diabetes	1.65 (0.69–3.95)	1.13	0.259	
Hypertension	0.91 (0.35–2.37)	< 0.01	0.847	
Stroke	1.64 (0.31–8.79)	0.58	0.565	
White cell count				
Normal	Reference			
Low	0.25 (0.03–1.94)	< 0.01	0.185	
Unknown	0.59 (0.03–12.37)	< 0.01	0.737	
Platelets count				
Normal	Reference			
Low	0.63 (0.2–1.95)	< 0.01	0.421	

Table 3 (continued)

	OR (95% CI)	*Z*	*P*	Sig
Elevated	3.07 (0.61–15.39)	1.36	0.174	
Absolute neutrophils count				
Normal	Reference			
Low	0.56 (0.02–15.63)	< 0.01	0.732	
Elevated	3.05 (0.93–9.97)	1.84	0.066	*
Unknown	0.21 (0.02–2.73)	< 0.01	0.232	
Absolute lymphocytes count				
Normal	Reference			
Low	2.13 (0.75–6)	1.42	0.155	
Elevated	1.17 (0.04–33.23)	0.09	0.927	
Unknown	1.65 (0.14–19.72)	0.4	0.692	
Neutrophil-to-lymphocyte ratio (NLR)				
Normal	Reference			
Low	0.74 (0.24–2.24)	< 0.01	0.594	
Elevated	4.23 (0.68–26.15)	1.55	0.121	
Sodium				
Normal	Reference			
Low	1.76 (0.66–4.69)	1.13	0.258	
Elevated	0 (0-Inf)	< 0.01	0.996	
Unknown	0.2 (0.01–3.59)	< 0.01	0.273	
Potassium				
Normal	Reference			
Low	1.37 (0.18–10.48)	0.3	0.762	
Elevated	0.27 (0.03–2.46)	< 0.01	0.247	
Unknown	0.81 (0.33–2.01)	< 0.01	0.657	
Chloride				
Normal	Reference			
Low	1.89 (0.27–13)	0.65	0.518	
Elevated	1.9 (0.46–7.85)	0.88	0.377	
Unknown	1.45 (0.56–3.78)	0.76	0.449	
ALT				
Normal	Reference			
Elevated	2.57 (0.53–12.36)	1.18	0.24	
Unknown	101,991,132.84 (0-Inf)	< 0.01	0.996	
AST				
Normal	Reference			
Elevated	1.65 (0.21–13.1)	0.48	0.634	
Unknown	604.8 (0.39–940,504.74)	1.71	0.088	*
Alkaline phosphatase				
Normal	Reference			
Elevated	0.19 (0.04–1)	< 0.01	0.05	**
Unknown	0 (0-Inf)	< 0.01	0.996	
Creatinine				
Normal	Reference			
Elevated	2.04 (0.9–4.63)	1.7	0.089	*
Unknown	0 (0-Inf)	< 0.01	0.996	
Hemoglobin				
Normal	Reference			
Low	2.4 (1.02–5.61)	2.02	0.044	**

There has been a lot of debate on the influence of immune checkpoint inhibitor therapy on outcomes from COVID-19 infection. On the one hand, immune checkpoint inhibitors can increase the robustness of the T-cell response and improve the ability to resist the impact of SARS-CoV-2 infection resulting in a good clinical outcome; they can also stimulate the development of a hyperimmune response and a severe systemic inflammatory state, which has been the hallmark of severe COVID-19 disease [22]. Clinical evidence on the effect of checkpoint inhibitors and COVID-19 outcomes has been mixed. A single-center, retrospective study of 423 patients with symptomatic COVID-19, found that treatment with immune checkpoint inhibitors (ICIs) predicted for hospitalization and respiratory illness [23]. In contrast, in another study of 69 patients with non-small cell lung cancer, Luo and colleagues did not find an association between PD-1 inhibition and an increased risk of severe COVID-19, defined as a composite rate of intensive care unit stay, intubation, transition to do not intubate status, and death [24]. In our cohort, the use of immune checkpoint inhibitor use was associated with an increased risk of severe SARS-CoV-2 infection and death from COVID-19 disease.

One interesting finding in our cohort was the finding that elevated alkaline phosphatase levels were associated with decreased risk of mortality. Previous studies that have studied association between elevated liver-associated enzyme and severity of COVID-19 infection, have noted that elevated liver enzymes were associated with poor outcomes. Chela et al. studied 14,138 patients from the Cerner Real-World Data™ de-identified COVID-19 patient cohort [25]. They found that elevated ALT, AST, and total bilirubin levels, but not elevated alkaline phosphatase levels, were associated either with COVID-19 mortality or risk of intubation. In another study from Poland involving 2184 patients, only an elevated AST level was associated with COVID-19-related mortality [26]. In this analysis too, alkaline phosphatase was not associated with COVID-19 outcomes. The main difference between these studies and ours is that the present study was focused only on patients with lung cancer. However, a clinical explanation for the observation that an elevated alkaline phosphatase protects against COVID-19 mortality in lung cancer patients is unclear, and this finding may simply be due to chance.

We did not find any association between race, ethnicity, place of residence, histology, the presence of chronic obstructive pulmonary disease, hypertension, history of acute myocardial infarction or stroke, thoracic radiation therapy, and outcomes from SARS-CoV-2 infection. While unexpected, this is not different from what has been reported earlier [13].

Our analysis has limitations. This was a retrospective cohort of patients collected using the VA in electronic medical record system and therefore suffers from the drawbacks of any retrospective analysis, a major drawback if the absence of stage in a large proportion of patients. This is most likely due to the nature of our database, which uses the cancer registry to identify the stage. Cancer registries usually lag actual diagnosis by at least 6 months and hence are unlikely to have staging information on more recently diagnosed patients. Unlike some of the prospective studies that we have discussed above, we were not able to identify various clinical factors that potentially could have been relevant for the identification of factors affecting outcomes. Additionally, the cohort only includes patients diagnosed with COVID-19 on or before December 1, 2022, prior to the emergency use authorization of COVID-19 vaccinations or COVID-19 specific treatments. As a result, we are unable to measure the effect of vaccination or COVID-19 specific treatments on outcomes for lung cancer patients.

Despite this, the present analysis is one of the largest data sets on lung cancer patients affected by COVID-19 disease. Since it includes the entire VA population, the odds of reporting bias are significantly reduced. Second, since this is a cohort of predominantly male veterans from the United States, the generalized ability of this information to female patients is limited, even though approximately 15% of this cohort was made up of women.

In conclusion, we found that the mortality of lung cancer patients from COVID-19 disease was less than what has been previously reported in the literature. Older age, anemia, and use of immune checkpoint inhibitors were associated with increased mortality in this cohort. These data will help guide treatment of lung cancer patients with COVID-19 disease during the current pandemic.

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Data availability statement Due to the sensitive nature of the data collected for this study, requests to access the data set are limited to qualified VA affiliated researchers.

Declarations

Conflict of interest AKG: Consultant: Genentech, AstraZeneca, G1 Therapeutics, Jazz Pharmaceuticals, Flagship Biosciences Research Support: Takeda, DSMC: Y-mAbs Therapeutics. MK: Executive Program Director of Oncology, Specialty Care Services, VHA, Department of Veterans' Affairs. The other authors do not have any conflicts of interest.

References

1. Richardson S, Hirsch JS, Narasimhan M et al (2020) Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 323(20):2052–2059. https://doi.org/10.1001/jama.2020.6775
2. Goyal P, Choi JJ, Pinheiro LC et al (2020) Clinical characteristics of Covid-19 in New York City. N Engl J Med 382(24):2372–2374. https://doi.org/10.1056/NEJMc2010419
3. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3
4. Ferrari BL, Ferreira CG, Menezes M et al (2021) Determinants of COVID-19 mortality in patients with cancer from a community oncology practice in Brazil. JCO Glob Oncol 7:46–55. https://doi.org/10.1200/GO.20.00444
5. Fillmore NR, La J, Szalat RE et al (2021) Prevalence and outcome of COVID-19 infection in cancer patients: a National Veterans Affairs Study. J Natl Cancer Inst 113(6):691–698. https://doi.org/10.1093/jnci/djaa159
6. Kuderer NM, Choueiri TK, Shah DP et al (2020) Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 395(10241):1907–1918. https://doi.org/10.1016/S0140-6736(20)31187-9
7. Lee LY, Cazier JB, Angelis V et al (2020) COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 395(10241):1919–1926. https://doi.org/10.1016/S0140-6736(20)31173-9
8. Zhang L, Zhu F, Xie L et al (2020) Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 31(7):894–901. https://doi.org/10.1016/j.annonc.2020.03.296
9. Ruthrich MM, Giessen-Jung C, Borgmann S et al (2021) COVID-19 in cancer patients: clinical characteristics and outcome-an analysis of the LEOSS registry. Ann Hematol 100(2):383–393. https://doi.org/10.1007/s00277-020-04328-4
10. Mehta V, Goel S, Kabarriti R et al (2020) Case fatality rate of cancer patients with COVID-19 in a New York Hospital System. Cancer Discov 10(7):935–941. https://doi.org/10.1158/2159-8290.CD-20-0516
11. Liang J, Jin G, Liu T et al (2021) Clinical characteristics and risk factors for mortality in cancer patients with COVID-19. Front Med 15(2):264–274. https://doi.org/10.1007/s11684-021-0845-6
12. Tagliamento M, Agostinetto E, Bruzzone M et al (2021) Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: a systematic review and meta-analysis. Crit Rev Oncol Hematol 163:103365. https://doi.org/10.1016/j.critrevonc.2021.103365
13. Garassino MC, Whisenant JG, Huang LC et al (2020) COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol 21(7):914–922. https://doi.org/10.1016/S1470-2045(20)30314-4
14. Provencio M, Mazarico Gallego JM, Calles A et al (2021) Lung cancer patients with COVID-19 in Spain: GRAVID study. Lung Cancer 157:109–115. https://doi.org/10.1016/j.lungcan.2021.05.014
15. Price LE, Shea K, Gephart S (2015) The Veterans Affairs's corporate data warehouse: uses and implications for nursing research and practice. Nurs Adm Q 39(4):311–318. https://doi.org/10.1097/NAQ.0000000000000118
16. Vincent BM, Wiitala WL, Burns JA et al (2018) Using Veterans Affairs Corporate Data Warehouse to identify 30-day hospital readmissions. Health Serv Outcomes Res Method 18(3):143–154. https://doi.org/10.1007/s10742-018-0178-3
17. Fillmore NR, DuMontier C, Yildirim C et al (2021) Defining multimorbidity and its impact in older United States Veterans newly treated for multiple myeloma. J Natl Cancer Inst 113(8):1084–1093. https://doi.org/10.1093/jnci/djab007
18. Haineala B, Zgura A, Badiu DC et al (2021) Lung cancer, Covid-19 infections and chemotherapy. In Vivo 35(3):1877–1880. https://doi.org/10.21873/invivo.12450
19. Assaad S, Zrounba P, Cropet C et al (2021) Mortality of patients with solid and haematological cancers presenting with symptoms of COVID-19 with vs without detectable SARS-COV-2: a French nationwide prospective cohort study. Br J Cancer 125(5):658–671. https://doi.org/10.1038/s41416-021-01452-4
20. Horn L, Whisenant JG, Torri V et al (2020) thoracic cancers international COVID-19 collaboration (TERAVOLT): impact of type of cancer therapy and COVID therapy on survival. J Clin Oncol 38(18_suppl):LBA111. https://doi.org/10.1200/JCO.2020.38.18_suppl.LBA111
21. Sutandyo N, Jayusman AM, Widjaja L et al (2021) Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as mortality predictor of advanced stage non-small cell lung cancer (NSCLC) with COVID-19 in Indonesia. Eur Rev Med Pharmacol Sci 25(10):3868–3878. https://doi.org/10.26355/eurrev_202105_25954
22. Burgaletto C, Brunetti O, Munafo A et al (2021) Lights and shadows on managing immune checkpoint inhibitors in oncology during the COVID-19 era. Cancers (Basel). https://doi.org/10.3390/cancers13081906
23. Robilotti EV, Babady NE, Mead PA et al (2020) Determinants of COVID-19 disease severity in patients with cancer. Nat Med 26(8):1218–1223. https://doi.org/10.1038/s41591-020-0979-0
24. Luo J, Rizvi H, Egger JV et al (2020) Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. Cancer Discov 10(8):1121–1128. https://doi.org/10.1158/2159-8290.CD-20-0596
25. Chela HK, Tallon EM, Baskett W et al (2023) Liver injury on admission linked to worse outcomes in COVID-19: an analysis of 14,138 patients. Transl Gastroenterol Hepatol 8:4. https://doi.org/10.21037/tgh-21-94
26. Tokarczyk U, Kaliszewski K, Kopszak A et al (2022) Liver function tests in COVID-19: assessment of the actual prognostic value. J Clin Med. https://doi.org/10.3390/jcm11154490