Patients With Lung Cancer Have High Susceptibility of COVID-19: A Retrospective Study in Wuhan, China

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Abstract
Patients with lung cancer are presumed to be at high risk from COVID-19 infection due to underlying malignancy. A total of 31 COVID-19 patients with pre-diagnosed lung cancer and 186 age and sex matched COVID-19 patients without cancer in 6 hospitals in Wuhan, China were identified in our study. There was a significantly higher level of IL-6 in lung cancer group showed by multifactorial analysis. The restricted mean survival time in 10, 20, and 53 days in COVID-19 patients with lung cancer were ealier than non-cancer COVID-19 patients in the same observation time (all P values < 0.05). Our results indicated that pre-diagnosed lung cancer was associated with higher morbidity and mortality in COVID-19 patients.

Introduction

Since late December of 2019, the whole world has been hit by 2019 novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of June, in 2020, more than 6,000,000 individuals were infected with this new virus causing a fatality rate of about 6.9%. Mounting evidence from recent reports has demonstrated that patients with cancer have the higher morbidity and

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death rate of COVID-19 compared to non-cancer individuals.[1,2] However, the relationship of a certain cancer type with the risk of COVID-19 remains inconclusive. Interestingly, it has been reported that individuals with lung cancer had the greatest infection rate of SARS-CoV-2 among all cancer patients.[3,4] Therefore, in this study, We sought to investigate the risk posed by COVID-19 to lung cancer population, and identify factors that placed lung cancer patients at highest risk of fatality from COVID-19.

Materials and Methods

Study Design and Participants

This multi-center study was performed in 6 hospitals designated for COVID-19 patients in Wuhan from January 1, 2020 to March 1, 2020 (listed in the Supplementary Appendix). COVID-19 was diagnosed according to the WHO interim guidance.[5] Over all, 31 COVID-19 patients with pre-diagnosed lung cancer were collected in our study. An age and sex-matched cohort of 186 patients at a 6:1 ratio of non-cancer to cancer COVID-19 patients from the same time period and from the same hospital system was also obtained after propensity matching and used as control to estimate the increased risk posed to lung cancer population. The study was approved by the institutional ethics review board and the need for informed consent was waived.

Data Collection

Patient medical records were obtained from the electronic medical records of the above 6 hospitals. Collected medical records included demographic characteristics, symptoms, signs, underlying comorbid conditions, laboratory results and clinical outcomes. Three independent physicians who had been taking care of patients with SARS-CoV-2 infection from each hospital double-checked the medical records to confirm data accuracy. Nasopharyngeal swabs were obtained for nucleic acid test of SARS-CoV-2 infection. Four primary outcomes were analyzed including: death, admission into the intensive care unit (ICU), development of severe symptoms, and utilization of invasive mechanical ventilation. The clinical destination of severe symptoms follow the 5th edition of 2019 Novel Coronavirus Disease (COVID-19) Diagnostic criteria published by the National Health Commission in China (listed in the Supplementary Appendix).

Statistical Analysis

For categorical data, percentages of patients in each category were calculated. The Wilcoxon rank sum test was used to compare continuous data and Fisher's exact test was used to compare categorical data from different categories without multi-test adjustment. Time from onset of symptoms to severe outcomes was investigated using survival analysis, with follow-up from initial onset of symptoms until the last day of follow-up. Multivariable Cox regression was conducted to estimate the hazard ratios and their corresponding 95% confidence interval. The Kaplan-Meier product-limit estimator was used to conduct survival analysis. All survival analyses were conducted using Lifelines 0.24.0 in Python environment.

Results

Table 1 shows the demographic and clinical characteristics of the 31 COVID-19 patients with lung cancer.The mean age of the overall population was 67.26 years (standard deviation
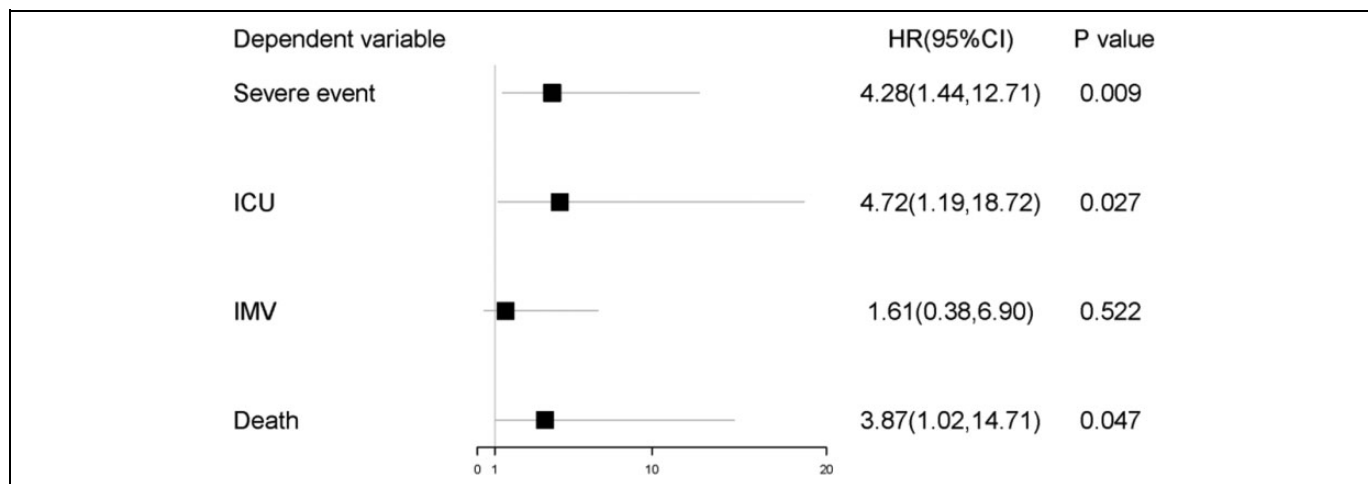
Table 1. Demographics and Clinical Characteristics of COVID-19 Patients With Lung Cancer.

Characteristics	N.(%)
Age	67.26 ± 8.40
Gender	
Male	25 (80.6%)
Female	6 (19.4%)
Smoking History	
Current	5 (16.13%)
Former	10 (32.26%)
Never	16 (51.61%)
Drinking	5 (16.13%)
Comorbidities	
Hypertension	9 (29.03%)
Diabetes	4 (16.13%)
Cardiovascular disease	4 (12.90%)
Cerebrovascular disease	2 (6.45%)
COPD	3 (9.68%)
Pathological Type	
Squamous cell carcinoma	7 (22.58%)
Adenocarcinoma	14 (45.16%)
Mixed	2 (6.45%)
Pathological Stage	
I	9 (33.33%)
II	2 (6.45%)
III	4 (12.90%)
IV	12 (38.71%)
Anti-cancer Treatments	
Surgery	7 (22.58%)
Radiotherapy	8 (25.81%)
Chemotherapy	10 (32.26%)
Targeted therapy	3 (9.68%)
Immunotherapy	4 (12.90%)
Signs at oneset	
Fever (temperature ≥37·3°C)	21 (67.74%)
Cough	8 (25.81%)
Expectoration	5 (16.13%)
Myalgia	3 (9.67%)
Abdominal pain or Diarrhea	3 (9.67%)
Shortness of breath	6 (19.35%)
Outcomes	
Severe illness	17 (54.8%)
ICU	10 (32.26%)
IMV	5 (16.13%)
Death	8 (25.81%)

Data are presented as mean (SD) or n (%). Anti-Cancer treatments present treatments within 3 months before the onset of COVID-19 symptoms. Abbreviations: COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; IMV = invasive mechanical ventilation.

Figure 1. Associations of severe conditions in COVID-19 patients with lung cancer and without cancer. Hazard ratio, 95% CI and p values denoted the comparison between COVID-19 patients with lung cancer and age and sex-matched non-cancer COVID-19 patients. Abbreviations: ICU = intensive care unit, IMV = invasive mechanical ventilation.

[SD]: 8.40 years), including 25 males and 6 females. Among the lung cancer patients, adenocarcinoma was the most frequent pathological type (14, 45.16%), followed by squamous cell carcinoma (7, 22.58%) and mixed cinoma (2, 6.45%). Ten patients (38.71%) were diagnosed with stage IV cancer. The most common symptoms on admission were fever (21, 67.74%), Cough(8, 25.81%) and Shortness of breath (6, 19.35%). There was a significantly higher level of IL-6 in lung cancer group with an average of 67.43 pg/ml (95% CI: 30.25-104.61 pg/ml) increase showed by multifactorial analysis, compared to non-cancer Covid-19 patients (Supplementary Table2).

Compared with COVID-19 patients without cancer, patients with lung cancer had higher observed severe events (OR 4.28, 95% CI [1.44, 12.71], p = 0.009), higher rates of ICU admission (HR 4.72, 95% CI [1.19, 18.72], p = 0.027) and higher death rates (HR 3.87, 95% CI [1.02, 14.71, p = 0.047) (Figure 1). To evaluate the time-dependent evolution of the disease, we also conducted survival analysis on occurrence of any severe condition which included death, ICU admission, having severe/critical symptoms and utilization of invasive mechanical ventilation (Supplementary Figure 1). Figure 2 demonstrates the time line of different events for COVID-19 patients with lung cancer with death and other severe events marked in the Figure. In general, patients with lung cancer deteriorated more rapidly than those without cancer.

Restricted mean survival time (RMST) is a well-established measure that can be interpreted as the average event-free survival time up to a pre-specified, clinically important time point.[6-8] We conducted the analysis of RMST between Covid-19 patients with lung cancer and without cancer. The observation time points were 10, 20, and 53 days from admission day (Table 2). Our data showed that in the 10 days observation time, COVID-19 patients with lung cancer developed severe conditions 1.6 days earlier, required ICU admission 0.9 days earliern than non-cancer COVID-19 patients (all P values < 0.05). COVID-19 patients with lung cancer developed severe conditions 3.7 days earlier, required ICU admission 3.1 days earlier, use invasive mechanical ventilation and death 1.1 days ealier ealier than non-cancer COVID-19 patients in the 20 days of observation time (all P values < 0.05). Furthermore, in the 53 days observation time, lung cancer patients had 17.3 days earlier of developing severe conditions, 11.6 days earlier of admission into ICU and 7.8 days of death than non-cancer patients (all P values < 0.05).

Discussion

The morbidity and mortality of lung cancer ranks the first among all malignant tumors worldwide. Over 3.8 million were diagnosed as lung cancer in 2014 in China.[9,10] Furthermore, patients with lung cancer had a more severe outcome when co-infected influenza or respiratory diseases such as bronchopneumonia or pneumonia.[11] Therefore, we believe that lung cancer is a risk factor for COVID-19-related pneumonia.[12] Jacobo Rogado *et al* investigated 17 COVID-19 patients with lung cancer among 1878 COVID-19 patients and found that lung cancer patients have a higher mortality rate than general population. Furthermore, univariate and multivariate logistic regression revealed that combined treatment with hydroxychloroquine and azithromycin significantly improved the outcome of Covid-19 in lung cancer patients.[13] However, limited information is known about the clinical characteristics and outcomes of lung cancer patients with COVID-19. Our study indicated that there was a significantly higher level of IL-6 in lung cancer group and that the restricted mean survival time in COVID-19 patients with lung cancer were earlier than non-cancer patients.

From the results of multicenter cohort study, patients with pre-existing lung cancer had the severe outcomes including
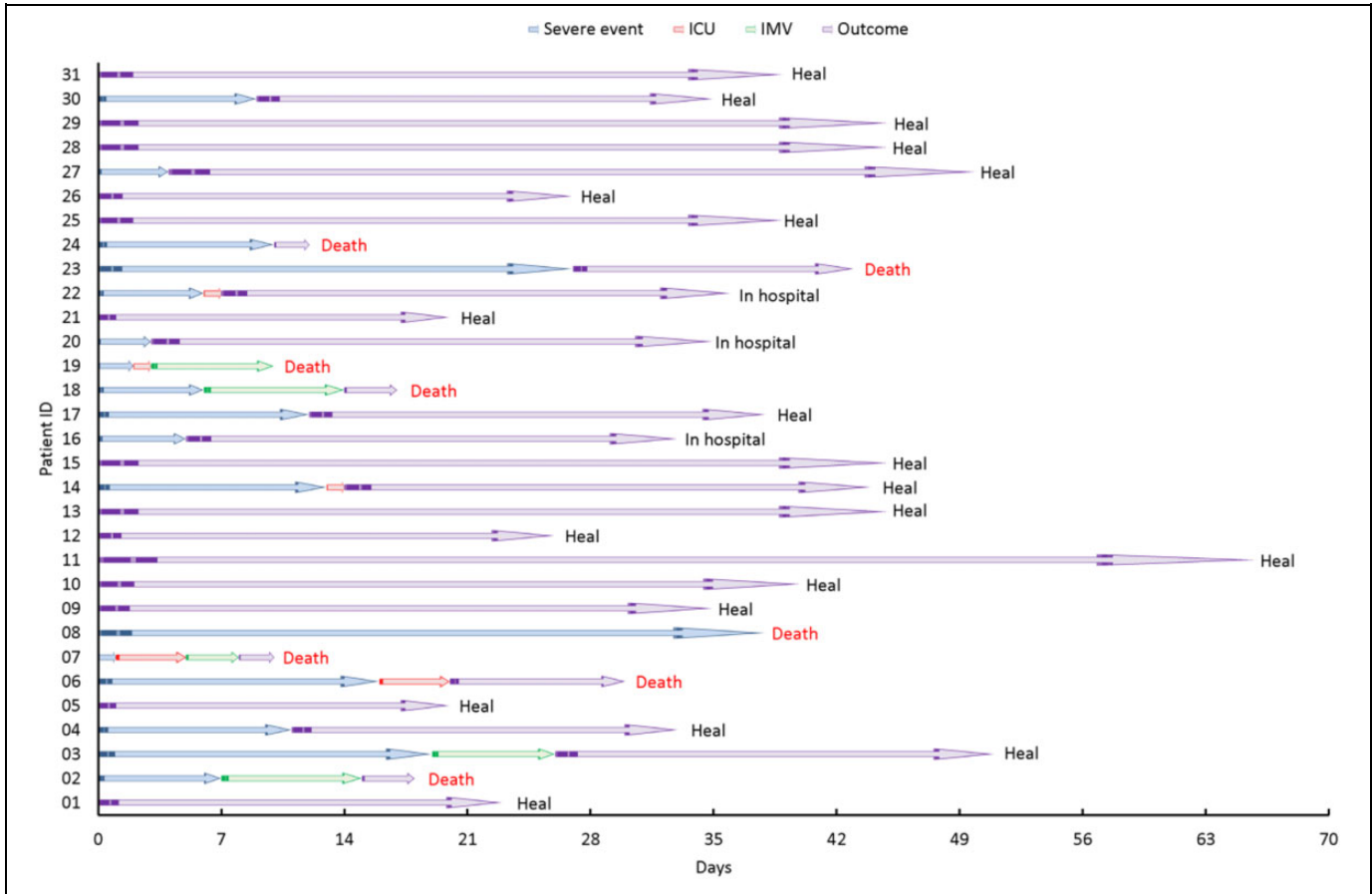
Figure 2. Timeline of events for COVID-19 patients with lung cancer. Severe event, ICU admission, IMVand death are marked in the Figure. Abbreviations: ICU = intensive care unit, IMV = invasive mechanical ventilation.

Table 2. Restricted Mean Survival Time (RMST) Between COVID-19 Patients With Lung Cancer and Without Cancer.

Variables	Restricted days	Lung cancer	Non cancer	P value
Severe event	10	8.4 (7.5,9.4)	10.0 (10.0,10.0)	0.002
	20	14.1 (11.7,16.6)	19.7 (19.3,20.2)	<0.001
	53	29.5 (21.5,37.4)	46.8 (41.3,52.4)	<0.001
ICU	10	9.1 (8.5,9.8)	10.0 (10.0,10.0)	0.013
	20	16.9 (14.9,19.0)	20.0 (20.0,20.0)	0.003
	53	38.7 (31.5,45.8)	50.3 (46.2,54.5)	0.006
IMV	10	9.9 (9.8,10.1)	10.0 (10.0,10.0)	0.309
	20	18.9 (17.9,20.0)	20.0 (20.0,20.0)	0.043
	53	46.5 (41.4,51.7)	49.4 (45.5,53.3)	0.386
Death	10	NA	NA	NA
	20	18.9 (17.9,19.9)	20.0 (20.0,20.0)	0.034
	53	43.8 (38.2,49.5)	51.6 (49.3,53.9)	0.013

Notes: RMST is a kind of survial time measure method which can be estimated under a restricted period; ICU = intensive care unit; IMV = invasive mechanical ventilation.; N. A = not available.

ICU admission (32.3%), invasive mechanical ventilation (16.1%), and death (25.8%), which may be caused by low lung function and immunosuppression.

Recently, restricted mean survival time (RMST) has been proposed as an alternative measure of treatment effect that offers some advantages in design, analysis, and interpretation over the conventional measures, especially in studies among small number of patients.[14,15] In our study, we found in the observation time of 10, 20 and 53 days, COVID 19 patients with lung cancer patients developed severe conditions and death faster than non-cancer COVID 19 patients, which indicated lung cancer was associated with increased mortality among COVID-19 patients.

The main endogenous cytokine IL-6, has been suggested to be a prediction factor for severe condition of Covid-19 patients.[16,17] Lung cancer patients had a significant increase in IL-6 level compared to non-cancer patients when infected SARS-CoV-2.[18] This line of evidence may explain lung cancer patients develop more severe conditions than non-cancer patients during COVID-19 outbreak. According to pathological studies on the COVID-19 patients, there were desquamation of pneumocytes and hyaline membrane formation, implying that these patients had ARDS. ARDS induced by cytokine storm indicated that patients without lung cancer had stronger immune response.[19] Moreover, it is possible that certain anti-cancer treatments such as immunotherapy and chemotherapy can induce the release of a large amount of cytokines, which

can be toxic to normal cells, including lung epithelial cells, and therefore exacerbates the severity of illness.[20] However, due to the small number of patients in current study, further study with a large case population is required. In summary, our findings suggest that lung cancer is the risk factor associated with the prognosis of Covid-19 patients.

Author Contribution

Mengyuan Dai, Zhen Chen, Yan Leng and Meng Wu contributed equally to the article.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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