ORIGINAL ARTICLE

Clinical Profile and Outcomes of All Admitted COVID-19 Positive Patients with Primary Lung Cancer in a Tertiary Government COVID-19 Referral Center: A Retrospective Cohort Study

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ABSTRACT

Background. COVID-19 infection poses a continuing challenge especially to those already with prior lung disease. To analyze such patients' profile is essential in today's health care management.

Objective. The study aimed to compare the outcomes of COVID-19 confirmed patients with and without primary lung cancer in terms of hospital stay, recovery, and mortality.

Methods. The study employed a retrospective cohort design. Chart review of all adult COVID-19 patients in Philippine General Hospital from January 2021 to June 2021 was done. A matched cohort study was conducted between COVID-19 patients with and without primary lung cancer.

Results. Among the 953 COVID-19 patients, there were 14 patients with primary lung cancer. In terms of length of hospital stay, patients with primary lung cancer had shorter days from 1.32 to 15.1 days compared to 2.28 to 18.36 days in patients without primary lung cancer (p-value 0.271). Furthermore, they had 64% recovery rate compared to 78% in those without primary lung cancer (p-value 0.118). In terms of overall mortality rate, primary lung cancer patients had 36% rate as compared to 22% in the non-lung cancer group (p-value 0.119). Diabetes mellitus, mild to severe COVID, Remdesivir, and antibiotic use were associated with longer hospital stay while oxygen support via nasal cannula and invasive ventilation led to shorter hospital stay. Age above 50 years, chronic liver disease, other malignancy, shortness of breath, oxygen support via face mask, high flow nasal cannula, invasive ventilation, antibiotic use, hemoperfusion and nebulization showed a decrease chance of recovery while on contrary, Remdesivir showed an increase chance of recovery. An increase mortality rate was seen among age above 50 years, chronic liver disease, other malignancy, shortness of breath, oxygen support via facemask, high flow nasal cannula, invasive ventilation, antibiotics, hemoperfusion, and nebulization, in contrast to a decrease in Remdesivir therapy.

Conclusions. Among all admitted COVID-19 patients, primary lung cancer patients were associated with shorter hospital stay (8.21+6.89days), lower rate of recovery (64%), and higher mortality rate (36%) as compared to those without primary lung cancer. However, based on the computed p-values for each outcome, these differences are not statistically significant.

Keywords: COVID-19, lung cancer, lung neoplasm, outcome

Poster presentations – Asia Pacific Society Respirology 2023, November 2023, Singapore; 43rd PCCP Annual Chest Convention, March 2024, Manila, Philippines.

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become a pandemic and a burden to global health. COVID-19 can cause a range of symptom severity with potential progression to respiratory failure and acute respiratory distress syndrome. A number of co-morbidities such as cardiovascular, metabolic, and respiratory conditions carry a higher risk of severe COVID-19.[1]

COVID-19 infection poses a continuing challenge to the world, and especially to those already with prior lung disease. One of the alarming concerns is the apparent high burden of COVID-19 infection among patients with lung cancer. A multicenter retrospective cohort study by Tian and colleagues done in China and published in 2021 noted 23 cases of lung cancer out of 13,077 patients with COVID-19 and showed that 78% of lung cancer patients had severe clinical outcome with a mortality rate of 39%.[2] Another study by Luo J et al.[3] showed that COVID-19 was severe in patients with lung cancer with 62% hospitalized, and 25% died. Although severe, COVID-19 accounted for a minority of overall lung cancer deaths during the pandemic (11% overall). In the same study, patient-specific determinants of COVID-19 severity such as smoking status and chronic obstructive pulmonary disease (COPD) were identified. Cancer-specific features, including prior thoracic surgery/radiation and recent systemic therapies did not impact severity. In a study by Calles et al.[4], there was a statistically significant association with mortality for oxygen saturation at diagnosis, ECOG performance status, number of comorbidities, stage IV disease, number of metastatic sites, progressive disease, and elevated CRP and fibrinogen.

In contrast to the above findings, a study by Rolfo et al.[5] in November 2021 did not find any difference in terms of severity in patients with lung cancer with COVID-19. Result of this study was similar with the TERAVOLT study.[6] Most studies so far have found no association between recent cancer therapy and increased mortality among patients with cancer and COVID-19.[7] An analysis by the COVID-19 and Cancer Consortium, in general, found no association between 30-day all-cause mortality and recent surgery, recent noncytotoxic therapy, or recent cytotoxic therapy.[8]

Data on the impact of SARS-CoV-2 infection on patients with cancer is limited. Although previous reports on patients with cancer infected with SARS-CoV-2 have suggested a higher mortality rate compared with the general population, the applicability of such data is hampered by small sample sizes. Given the global burden of lung cancer, the high number of COVID-19 cases in the Philippines as well as the heterogenous results of different studies regarding lung cancer and COVID-19, to analyze patients' profile is essential in today's health care management. To date, there is no local data or published studies regarding the clinical profiles and outcomes of COVID-19 positive patients with lung cancer. This study has no direct benefits to the participants. However, the results of this study will greatly aid clinicians to understand better the relationship of the two diseases and can be used in the management of future patients with COVID-19 infection with primary lung cancer.

OBJECTIVES

General Objectives

This study aimed to compare the outcomes of COVID-19 confirmed patients who have primary lung cancer and patients without primary lung cancer in terms of hospital stay, recovery, and mortality.

Specific Objectives

1. To describe the demographic and clinical profile of patients with COVID-19 in terms of: age, sex, smoking status, co-morbidities, COVID-19 vaccination status, signs and symptoms, COVID-19 severity, COVID-19 medications taken prior to admission, type of oxygen support, antiviral use, concurrent treatment
2. To describe lung cancer profile of patients in terms of: radiologic imaging, histopathology, time diagnosed, ECOG Karnofsky index, disease activity status, lung cancer related sequelae, lung cancer treatment prior to admission
3. To determine which among the demographic and clinical factor/s is/are statistically associated with the patients' outcome in terms of hospital stay, recovery, and mortality.

METHODS

Study Design

The study employed a retrospective cohort design. Chart review of all adult COVID-19 patients in Philippine General Hospital (PGH) admitted from January 2021 to June 2021 was done through the Medical Records Section of the hospital. Then, a matched cohort study was conducted between COVID-19 patients with and without primary lung cancer based on their baseline characteristics and outcomes. The entire study was conducted over a period of six months from ethics approval to final manuscript writing.

Study Site

The study was conducted in PGH which is a tertiary state-owned and operated by the University of the Philippines Manila, designated as the National University Hospital and a primary COVID-19 referral center. The hospital caters to both charity and private cases.

Participants of the Study

The study included all COVID-19 confirmed patients aged 18 years old and above admitted from January 2021 to June 2021 with the diagnosis of primary lung cancer.

Inclusion Criteria

Patients are at least 18 years old and above with confirmed positive COVID-19 Real Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) or Rapid Antigen Test (RAT) result with presence of symptoms.

Exclusion Criteria

Exclusion criteria included patients with incomplete or unavailable medical records.

Operational Definition of Term

Recovery is a term used to describe patient's outcome after being discharged improved from the hospital.

Data Collection Procedure

All admitted adult COVID-19 patients from January 2021 to June 2021 in PGH were included in the study. Age, sex, smoking status, co-morbidities, COVID-19 vaccination status, signs and symptoms, COVID-19 severity, medications prior to admission, type of oxygen support, antiviral therapy, concurrent treatment, and outcomes were extracted from patient medical records. The diagnosis of primary lung cancer was based on previous work-up such as chest imaging and histopathology results with or without treatment. Time of diagnosis, ECOG Karnofsky index at baseline, disease activity status, lung cancer related sequelae and lung cancer treatment prior to admission were documented. A foreseen limitation in data collection was the unavailability of actual imaging studies for viewing. However, the researchers made use of written imaging results and interpretation. No potential confounders, modifiers or biases were identified.

Collection of data commenced upon approval from the Ethics Board. Data collection form via Microsoft Excel for ease of documentation was used to collect the necessary variables and outcomes needed in the study. Data were transcribed into the primary investigator's laptop which was password-protected. This was kept in a secure location within the study site. All data transcribed were shared with the statistician through secure means. Data collected will be kept for a maximum of ten years. The files will be deleted from the system and the hard drive used to store the data will be reformatted. Cases of incomplete or missing data were excluded in the analysis. Only the investigators and the hired research assistant were involved in reviewing the charts and collecting the data. The research assistant was granted authority to access medical records by the investigators and was trained to ensure measures of privacy and confidentiality. All data were kept anonymous and have no identifying codes that could link the data to the subject.

Data Analysis Plan

In describing the clinical profile of patients, descriptive statistics was used. The mean and standard deviation were used to describe the continuous variables while frequency and percent were used for categorical data.

The identification of risk factors associated with the outcome made use of binary logistic regression and results will present the respective odds as well as the 95% Confidence Interval ratio for length of hospitalization, recovery, and death.

Sample Size

Sample size computation for this study was done in Epi Info version 7.1.4.0 with the following assumptions: (1) the total population size of COVID-19 patients with lung cancer is large; (2) the outcome, rate of mortality among COVID-19 lung cancer patient is 0.70% (Passaro et al.[9]); (3) the desired precision is 5%. In a computation for the rate of mortality among lung cancer patients with COVID-19 carried out at <5% level of significance, a sample size of at least 11 patients is needed.

Ethical Considerations

The study was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) panel for ethics review and approval. The study commenced after approval from the review board. All investigators were certified with Good Clinical Practice training. The data set was anonymized and no identification of any individual was allowed (Data Privacy Act of 2012). The said data was stored in a password-protected laptop and hard drive.

A waiver of informed consent process was requested from the UPMREB panel for this study since there were no to minimal anticipated risks for the patients whose data were included in the study and the waiver will not adversely affect the rights and welfare of the participants in accordance to the National Ethical Guidelines of Health and Health-related Research 2017. During the review of medical records, no personal information was recorded and only non-sensitive data were collected. Conducting the informed consent process for this research was impractical since the study will be retrospective. There were no case of breach of privacy reported to the PGH Data Privacy Officer. Data derived from this research will only be used for academic purposes and will hopefully be shared in medical journals to add to the current knowledge regarding COVID-19 and lung cancer. There were no conflict of interest for this study. No incentives in the form of cash or token were given to the included patients or physicians involved in caring for the patients.

RESULTS

All admitted COVID-19 positive patients in PGH from January 2021 to June 2021 who have satisfied the inclusion criteria were included in the study as shown in Figure 1. Among 953 patients, 14 patients have primary lung cancer. The demographic and clinical profile of the patients with and without primary lung cancer is shown in Table 1.

The age range of patients with primary lung cancer was 27 to 78 years old, with 71% belonging in the 50 years and above age range, and with male predominance. Although

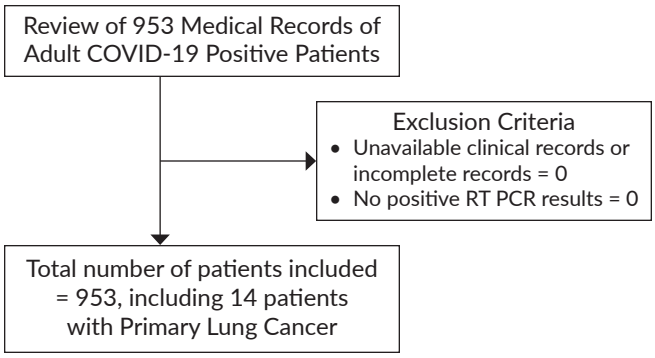

Figure 1. Flow diagram of patients included and excluded from the study after chart review.

the non-lung cancer group also illustrated predominance of patients age 50 years and above, this group showed an almost equal gender distribution. This gender difference however was not statistically significant. There were no active smokers documented in the lung cancer group and roughly 14% only had history of smoking with mean pack per year of 7.2 ± 3.96. In the non-lung cancer group, 5% were active smokers and 19% were previous smokers with mean pack years of 16.86 ± 22.24. Statistically, there was a significantly higher rate of number of pack years smoking history in those without lung cancer. Medical comorbidities such pulmonary tuberculosis (29%, p-value 0.003) and malignancy (100%, p-value 0.000) were significantly higher among those with lung cancer. On

Table 1. Demographic and Baseline Characteristics of Patients with COVID-19 Stratified by the Presence of Primary Lung Cancer

Characteristics	Total Patients	Non-Lung Cancer	Lung Cancer	*P*-value
Subject, N (%)	953	939	14	
Age, N (%)				
<50 years of age	353 (37%)	349 (37%)	4 (29%)	0.254
50 and above years of age	600 (63%)	590 (63%)	10 (71%)	0.254
Gender, N (%)				
Male	478 (50%)	470 (50%)	8 (57%)	0.299
Female	475 (50%)	469 (50%)	6 (43%)	0.305
Smoking, N (%)				
Active/Current	44 (5%)	44 (5%)	0 (0%)	0.203
Previous	185 (19%)	183 (19%)	2 (14%)	0.313
Pack years (IQR)	24.06+26.2	16.86+22.24	7.2+3.96	0.010
Co-morbidities, N (%)				
Hypertension	470 (49%)	465 (50%)	5 (36%)	0.153
Diabetes Mellitus	**274 (29%)**	**274 (29%)**	**0 (0%)**	**0.008**
Bronchial Asthma	72 (8%)	72 (8%)	0 (0%)	0.141
COPD	19 (2%)	19 (2%)	0 (0%)	0.295
Pulmonary Tuberculosis	**80 (8%)**	**76 (8%)**	**4 (29%)**	**0.003**
Cardiovascular Disease	72 (8%)	72 (8%)	0 (0%)	0.141
Chronic Kidney Disease	90 (9%)	90 (10%)	0 (0%)	0.112
Chronic Liver Disease	9 (1%)	9 (1%)	0 (0%)	0.356
Malignancy	**68 (7%)**	**54 (6%)**	**14 (100%)**	**0.000**
COVID-19 vaccination status				
Vaccinated	51 (5.35%)	51 (5.43%)	0 (0%)	0.317
Unvaccinated	902 (94.65%)	888 (94.57%)	14 (100%)	0.317
Systemic signs and symptoms, N (%)				
Fever	**505 (53%)**	**501 (53%)**	**4 (29%)**	**0.033**
Cough	575 (60%)	567 (60%)	8 (57%)	0.403
Shortness of breath	**69 (7%)**	**66 (7%)**	**3 (21%)**	**0.020**
Dyspnea	489 (51%)	483 (51%)	6 (43%)	0.262
Fatigue	**57 (6%)**	**50 (5%)**	**7 (50%)**	**0.000**
Anorexia	70 (7%)	70 (7%)	0 (0%)	0.144
Diarrhea	120 (13%)	120 (13%)	0 (0%)	0.076
COVID-19 Severity, N (%)				
Mild	169 (17.73%)	167 (17.78)	2 (14%)	0.367
Moderate	217 (22.77%)	214 (22.79)	3 (21%)	0.467
Severe	311 (32.63%)	306 (32.59%)	5 (36%)	0.402
Critical	256 (26.86%)	252 (26.84)	4 (29%)	0.442
Medications prior to admission				
Lin Hua	14 (1%)	14 (1%)	0 (0%)	0.323
Ivermectin	5 (1%)	5 (1%)	0 (0%)	0.392
Others, will specify	0 (0%)	0 (0%)	0 (0%)	-

Table 1. Demographic and Baseline Characteristics of Patients with COVID-19 Stratified by the Presence of Primary Lung Cancer *(continued)*

Characteristics	Total Patients	Non-Lung Cancer	Lung Cancer	*P*-value
Oxygen support				
O_2 support via NC	161 (17%)	158 (17%)	3 (21%)	0.324
O_2 support via FM	243 (25%)	239 (25%)	4 (29%)	0.395
High flow nasal cannula	41 (4%)	40 (4%)	1 (7%)	0.299
Non-invasive ventilation	0 (0%)	0 (0%)	0 (0%)	-
Mechanical ventilation	**72 (8%)**	**69 (7%)**	**3 (21%)**	**0.024**
COVID-19 Treatments, N (%)				
Anti-viral agents				
Remdesivir	446 (47%)	439 (47%)	7 (50%)	0.404
Favipiravir	1 (0%)	1 (0%)	0 (0%)	0.451
Molnupiravir	0 (0%)	0 (0%)	0 (0%)	-
Tocilizumab	**412 (43%)**	**409 (44%)**	**3 (21%)**	**0.049**
Antibiotics (specify)	**679 (71%)**	**666 (71%)**	**13 (93%)**	**0.036**
Chest physiotherapy	913 (96%)	900 (96%)	13 (93%)	0.402
Hemoperfusion	71 (7%)	71 (8%)	0 (0%)	0.142
Systemic steroids (Dexamethasone)	**568 (60%)**	**563 (60%)**	**5 (36%)**	**0.033**
Concurrent treatments				
Mucolytics	**571 (60%)**	**559 (60%)**	**12 (86%)**	**0.024**
Nebulization	37 (4%)	36 (4%)	1 (7%)	0.262
SABA/SAMA inhalers	549 (58%)	536 (57%)	13 (93%)	0.004

Table 2. Characteristics of Primary Lung Cancer

	Values
Diagnosis	
Radiologic imaging of pulmonary mass	14 (100%)
Histopathology	
Classify as non-small cell lung carcinoma based on TNM Staging	14 (100%)
Classify as small cell lung carcinoma limited or extensive stage	0 (0%)
Time diagnosed	
Within 12 months	8 (57%)
More than 12 months	5 (36%)
Status	
Active	
Recently diagnosed	8 (57%)
Ongoing treatment	9 (64%)
Dormant	1 (7%)
ECOG Karnofsky Index at Baseline (during Admission)	1.23+1.59
Lung cancer-related sequelae	
Pleural effusion	12 (86%)
Pericardial effusion	5 (36%)
Obstructive pneumonia	5 (36%)
Intrapulmonary metastasis	3 (21%)
Metastatic disease (specify location)	10 (71%)
Lung cancer treatment (prior to admission)	
Chemotherapy	7 (50%)
Immunotherapy	0 (0%)
Targeted therapy	0 (0%)
Hormonal therapy	0 (0%)
Radiotherapy	8 (57%)
Tube placement/Surgery	9 (64%)

the other hand, diabetes mellitus (29%, p-value 0.008) was significantly higher among those without lung cancer. There were 51 non-lung cancer patients who received COVID-19 vaccination while none on the lung cancer group. This difference was, however, not statistically significant. As for the symptom present during admission, there was a significantly higher rate of shortness of breath (21%, p-value 0.020) and fatigue (50%, p-value 0.000) among those with lung cancer. Furthermore, fever (29%, p-value 0.033) was significantly higher among those without lung cancer. As for COVID-19 severity classification, both groups had predominance of the severe type. Also, all patients with lung cancer had no COVID-19 medications taken prior to admission.

As for oxygen support on admission, there was significantly higher rate of mechanical ventilation use (21%, p value 0.024) among those with lung cancer. During the course of hospital stay, there was significantly higher rate of antibiotic use (93%, p value 0.036) among those with lung cancer. Moreover, there was significantly higher rate of Tocilizumab (44%, p value 0.049) and systemic steroids (60%, p value 0.033) under those without lung cancer. As for concurrent treatments, there was significantly higher rate of mucolytic (86%, p value 0.024) and SABA/SAMA inhaler use (93%, p value 0.004) among those with lung cancer. Antiviral, chest physiotherapy, hemoperfusion, and use of nebulization were not statistically significant risk factors.

Table 2 shows the characteristics of patients with primary lung cancer. All had documented radiologic imaging of pulmonary mass and histopathologic diagnosis of non-small cell lung carcinoma. Fifty-seven percent (57%) were active cases and were diagnosed within 12 months. Sixty-

four percent (64%) were currently undergoing treatment. There was one dormant patient who had been adjudged to be clinically quiescent for at least two years. Average ECOG at baseline of the 14 patients was 1.23+1.59. There were 12 patients who have pleural effusion, five have pericardial effusion, five have obstructive pneumonia, three have intra-pulmonary metastasis and 10 have pleural metastasis. As for the treatment received prior to admission, 50% underwent chemotherapy and 57% had radiotherapy. There were nine patients who underwent surgical procedures including two lobectomy, three chest tube insertions, three thoracentesis, and one pericardiostomy.

As for Table 3, the logistic regression analysis revealed that among the factors, there was an increased chance for

Table 3. Risk Factors for Longer Hospital Stay

Characteristics	Odds Ratio	95% CI Lower limit - Upper limit	*P*-value
Age of more than 50 years	1.238	0.818 - 1.874	0.312
Gender, Male	0.856	0.587 - 1.248	0.419
Active Smoking	1.269	0.834 - 1.932	0.267
Co-morbidities, N (%)			
Hypertension	1.000	0.799 - 1.251	1.000
Diabetes Mellitus	**1.581**	**1.081 - 2.314**	**0.018**
Bronchial Asthma	1.080	0.569 - 2.048	0.814
COPD	1.063	0.334 - 3.385	0.918
Pulmonary Tuberculosis	0.712	0.387 - 1.312	0.276
Cardiovascular Disease	1.493	0.821 - 2.712	0.189
Chronic Kidney Disease	1.539	0.886 - 2.676	0.126
Chronic Liver Disease	2.842	0.669 - 12.066	0.157
Malignancy	1.029	0.523 - 2.025	0.935
COVID-19 Vaccination	2.016	0.224 - 18.15	0.532
Systemic signs and symptoms, N (%)			
Fever	0.687	0.464 - 1.017	0.061
Cough	0.739	0.495 - 1.103	0.138
Shortness of breath	0.732	0.36 - 1.49	0.389
Dyspnea	1.187	0.773 - 1.821	0.434
Fatigue	0.734	0.508 - 1.061	0.100
Anorexia	0.709	0.36 - 1.395	0.319
Diarrhea	1.115	0.675 - 1.839	0.671
Others	0.653	0.434 – 0.985	0.420
COVID-19 classification			
Mild to Severe	3.006	1.456 - 6.209	0.003
Medications prior to admission			
Lin Hua	0.348	0.072 - 1.691	0.191
Oxygen support			
O_2 support via NC	**0.551**	**0.305 - 0.996**	**0.048**
O_2 support via FM	0.760	0.436 - 1.326	0.334
High flow nasal cannula	0.753	0.313 - 1.814	0.528
Non-invasive ventilation	0.078	**0.021 - 0.281**	**0.001**
Mechanical ventilation	0.000	0	1.000
COVID-19 Treatments, N (%)			
Anti-viral agents			
Remdesivir	**2.071**	**1.256 – 3.413**	**0.004**
Favipiravir	0.000	0	1.000
Molnupiravir	0.000	0	1.000
Tocilizumab	1.181	0.82 - 1.702	0.371
Antibiotics (specify)	**2.455**	**1.3 - 4.633**	**0.006**
Chest physiotherapy	0.566	0.272 - 1.176	0.127
Hemoperfusion	1.509	0.836 - 2.723	0.172
Systemic steroids			
Dexamethasone	1.354	0.718 - 2.554	0.349
Methylprednisone	0.000	0	1.000
Hydrocortisone	0.000	0	1.000
Concurrent treatments			
Mucolytics	1.302	0.8 - 2.12	0.288
Nebulization	1.609	0.761 - 3.4	0.213
LABA/LAMA inhalers	0.799	0.511 - 1.248	0.324

Table 4. Risk Factors for Recovery

Characteristics	Odds Ratio	95% CI Lower limit - Upper limit	*P*-value
Age of more than 50 years	**0.532**	**0.31 - 0.912**	**0.022**
Gender, Male	0.863	0.551 - 1.353	0.521
Active Smoking	1.162	0.698 - 1.937	0.564
Co-morbidities			
Hypertension	1.060	0.679 - 1.655	0.798
Diabetes Mellitus	0.883	0.546 - 1.427	0.612
Bronchial Asthma	1.861	0.744 - 4.654	0.184
COPD	0.807	0.227 - 2.873	0.741
Pulmonary Tuberculosis	1.555	0.724 - 3.338	0.257
Cardiovascular Disease	0.605	0.29 - 1.261	0.180
Chronic Kidney Disease	0.589	0.3 - 1.153	0.122
Chronic Liver Disease	**0.205**	**0.043 - 0.986**	**0.048**
Malignancy	**0.235**	**0.112 - 0.493**	**0.001**
COVID-19 vaccination	0.392	0.049 - 3.105	0.375
Systemic signs and symptoms			
Fever	0.987	0.611 - 1.594	0.958
Cough	1.467	0.897 - 2.401	0.127
Shortness of breath	**0.440**	**0.21 - 0.923**	**0.030**
Dyspnea	0.618	0.362 - 1.055	0.078
Fatigue	0.714	0.46 - 1.109	0.134
Anorexia	1.318	0.587 - 2.958	0.504
Diarrhea	1.105	0.584 - 2.093	0.758
Others	0.622	0.361 - 1.07	0.860
COVID-19 classification			
Mild to Severe	0.442	0.159 - 1.23	0.118
Medications prior to admission			
Lin Hua	0.997	0.234 - 4.251	0.997
Ivermectin	0.531	0.073 - 3.888	0.533
Others, will specify			
Oxygen support			
O_2 support via NC	0.443	0.195 - 1.006	0.052
O_2 support via FM	**0.121**	**0.058 - 0.255**	**0.001**
High flow nasal cannula	**0.103**	**0.038 - 0.282**	**0.001**
Non-invasive ventilation	0.000	0	1.000
Mechanical ventilation	**0.005**	**0.002 - 0.015**	**0.001**
COVID-19 Treatments, N (%)			
Anti-viral agents			
Remdesivir	**3.647**	**1.955 - 6.804**	**0.001**
Favipiravir	0.000	0	1.000
Molnupiravir	0.000	0	1.000
Tocilizumab	0.906	0.473 - 1.736	0.766
Antibiotics (specify)	**0.360**	**0.151 - 0.857**	**0.021**
Chest physiotherapy	1.578	0.614 - 4.058	0.344
Hemoperfusion	**0.288**	**0.15 - 0.553**	**0.001**
Systemic steroids	0.827	0.361 - 1.895	0.653
Concurrent treatments			
Mucolytics	1.269	0.683 - 2.357	0.450
Nebulization	**0.279**	**0.12 - 0.653**	**0.003**
SABA/SAMA inhalers	0.834	0.472 - 1.473	0.531

Table 5. Risk Factors for Mortality

Characteristics	Odds Ratio	95% CI Lower limit - Upper limit	*P*-value
Age of more than 50 years	**1.784**	**1.049 - 3.035**	**0.033**
Gender, Male	1.146	0.735 - 1.788	0.548
Active Smoking	0.827	0.498 - 1.373	0.462
Co-morbidities			
Hypertension	0.946	0.61 - 1.465	0.802
Diabetes Mellitus	1.051	0.654 - 1.689	0.836
Bronchial Asthma	0.541	0.22 - 1.33	0.181
COPD	1.410	0.407 - 4.881	0.588
Pulmonary Tuberculosis	0.685	0.322 - 1.455	0.325
Cardiovascular Disease	1.737	0.84 - 3.593	0.136
Chronic Kidney Disease	1.799	0.926 - 3.498	0.083
Chronic Liver Disease	**5.255**	**1.109 - 24.896**	**0.037**
Malignancy	**3.882**	**1.886 - 7.989**	**0.000**
COVID-19 Vaccination	2.902	0.45 - 18.732	0.263
Systemic signs and symptoms			
Fever	1.066	0.664 - 1.712	0.790
Cough	0.706	0.434 - 1.15	0.162
Shortness of breath	**2.374**	**1.139 - 4.949**	**0.021**
Dyspnea	1.600	0.946 - 2.704	0.079
Fatigue	1.360	0.881 - 2.099	0.165
Anorexia	0.767	0.348 - 1.69	0.510
Diarrhea	0.893	0.476 - 1.675	0.725
Others	1.544	0.906 - 2.63	0.110
COVID-19 classification			
Mild to Severe	2.140	0.787 - 5.818	0.136
Medications prior to admission			
Lin Hua	1.007	0.236 - 4.305	0.992
Ivermectin	2.055	0.285 - 14.804	0.475
Others, will specify			
Oxygen support			
O_2 support via NC	2.051	0.921 - 4.565	0.078
O_2 support via FM	**7.609**	**3.686 - 15.707**	**0.000**
High flow nasal cannula	**9.303**	**3.459 - 25.02**	**0.000**
Non-invasive ventilation	0.000	0	1.000
Mechanical ventilation	**151.923**	**54.656 - 422.291**	**0.000**
COVID-19 Treatments, N (%)			
Anti-viral agents			
Remdesivir	**0.286**	**0.155 - 0.526**	**0.000**
Favipiravir	0.000	0	1.000
Molnupiravir	0.000	0	1.000
Tocilizumab	1.139	0.619 - 2.094	0.676
Antibiotics (specify)	**2.332**	**1.014 - 5.364**	**0.046**
Chest physiotherapy	0.769	0.307 - 1.928	0.575
Hemoperfusion	**3.195**	**1.675 - 6.097**	**0.000**
Systemic steroids			
Dexamethasone	1.179	0.524 - 2.651	0.691
Methylprednisone			
Hydrocortisone			
Concurrent treatments			
Mucolytics	0.830	0.451 - 1.527	0.548
Nebulization	**3.033**	**1.302 - 7.068**	**0.010**
SABA/SAMA inhalers	1.150	0.658 - 2.009	0.624

patients with diabetes mellitus (OR=1.581, P=0.018), with mild to severe COVID-19 (OR=3.006, P=0.003), and who received Remdesivir (OR=2.071, P=0.004) and antibiotics (OR=2.455, P=0.006) to have longer hospital stay.

In contrast, there was a decrease of 45% among those on oxygen support via nasal cannula (OR=0.551, P=0.048) and a decrease of 92% among those on non-invasive ventilation (OR=0.078, P=0.001) with regard to the chance of longer hospitalization stay. Age, gender, smoking, COVID-19 vaccination, medications prior to admission, Tocilizumab, chest physiotherapy, hemoperfusion, systemic steroids, mucolytics, nebulization, and SAMA/SABA inhaler did not show statistical significance.

As for Table 4, the logistic regression analysis revealed that among the factors, age 50 years and above (OR=0.532, P=0.022), with chronic liver disease (OR=0.205, P=0.048), with non-pulmonary malignancy (OR=0.235, P=0.001), with shortness of breath during admission (OR=0.44, P=0.03), with oxygen support via face mask (OR=0.121, P=0.001), with high flow nasal cannula (OR=0.103, P=0.001), with invasive ventilation (OR=0.005, P=0.001), with antibiotic use (OR=0.36, P=0.021), with hemoperfusion (OR=0.288, P=0.001), and with nebulization (OR=0.279, P=0.003) showed a decrease chance of recovery while Remdesivir (OR=3.647, P=0.001) showed an increase chance of recovery. The rest of the risk factors did not show statistical significance for recovery.

For Table 5, the logistic regression analysis revealed that among the factors, there was an increase mortality rate among age more than 50 years (OR=1.784, P=0.033), with chronic liver disease (OR=5.255, P=0.037), with other non-pulmonary malignancy (OR=3.882, P=0), with shortness of breath (OR=2.374, P=0.021), with oxygen support via FM (OR=7.609, P=0), with high flow nasal cannula (OR=9.303, P=0), with invasive ventilation (OR=151.923, P=0), with antibiotics (OR=2.332, P=0.046), with hemoperfusion (OR=3.195, P=0), and with nebulization (OR=3.033, P=0.01). On contrary, Remdesivir use (OR=0.286, P=0) showed a significant mortality benefit. Other risk factors did not show statistical significance on mortality.

Among all COVID-19 patients included in the study as shown in Table 6, the 14 patients with primary lung cancer had shorter length of hospital stay from 1.32 to 15.1 days compared to 2.28 to 18.36 days in patients without primary lung cancer. Furthermore, 9 patients with primary lung cancer were discharged improved with recovery rate of 64%. Thus, this was lower compared to the 78% or 729 patients without lung cancer who were discharged improved. In terms of overall mortality rate, patients with primary lung cancer had 36% rate as compared to the 22% in the non-lung cancer group. In addition, patients with primary lung cancer had higher number of deaths with 21.4% during day 0 of hospitalization as compared to 6.6% in the non-lung cancer group. Based on the computed p-values for each outcome, all of these differences are not statistically significant.

DISCUSSION

Previous literatures showed heterogenous results regarding outcomes of COVID-19 patients with lung cancer. This study had shown that COVID-19 positive patients with primary lung cancer have shorter hospital stay, lower rate of recovery, and higher mortality as compared to those without primary lung cancer. However, based on the computed p-values for each outcome, these differences were not statistically significant.

Length of Hospital Stay

In our study, the length of hospital stay in patients with lung cancer was 1.32 to 15.1 days.

In contrast, a retrospective analysis by Luo et al.[3] reported a longer and more severe course of COVID-19 disease in lung cancer patients than in the general United States population. The findings of a shorter hospital stay might be due to the higher mortality rate on admission at the emergency room. According to the large cohort study by Dai M et al.[10], compared with all other patients, patients with primary or metastatic tumors in the lungs were more prone to rapid clinical deterioration on SARS-CoV-2 infection.

Specifically, our study showed that there was an increased chance for patients with diabetes mellitus, mild to severe COVID-19, Remdesivir and antibiotics use to have longer hospital stay. Diabetes was an independent risk factor for mortality in patients with SARS-CoV with higher disease severity and poor prognosis.[11] However, data regarding length of stay was inadequate at present. According to Luo[3], the median time to recovery of patients requiring non-ICU hospitalization and ICU care was 18 days for mild cases, 34 days for non-ICU hospitalization, and less than 14 days in critical cases. To note, mild to severe cases have longer hospital stay in comparison to ICU patients. Currently, there is still limited data on the length of hospital stay among those treated with antibiotic. On the other hand, outcome of Remdesivir use was different from the findings of the NIH

Table 6. Outcomes of COVID-19 Confirmed Patients with and without Primary Lung Cancer in Terms of Hospital Stay, Recovery and Mortality

Outcomes, N (%)	Non-Lung Cancer	Lung Cancer	*P*-value
Length of hospital stay (IQR)	10.32+8.04	8.21+6.89	0.271
Discharged / Recovered	729 (78%)	9 (64%)	0.118
Death	210 (22%)	5 (36%)	0.119

clinical trial[12] that suggests although it was not statistically significant, patients receiving Remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less [hazard ratio 1.52 (95% confidence interval 0.95–2.43)]. According to this trial, the median time to recovery was 11 days for patients treated with Remdesivir compared with 15 days for those who received a placebo. Although this belongs to the range of length of hospital stay observed in our study, still it is considerably lower than those without lung cancer.

In addition, another significant finding in our study was a decrease of 45% among those on oxygen support via nasal cannula and a decrease of 92% among those on invasive ventilation with regard to the chance of longer hospitalization stay. According to Dai M et al.[10], in patients affected by lung cancer, the average time (means/SD days) for those in need of an ICU admission was 10 days while those with critical symptoms was 8.55 days. This is significantly shorter compared to the average recovery time of 14 days.

Recovery

In terms of recovery, our study showed 64% chance of recovery which is lower than the non-lung cancer group. However, this percentage is close to the findings in the study of Luo where recovery occurs in approximately 65% of the patients. Despite the burden of COVID-19 disease in lung cancer patients, more than half of them achieved recovery, including those who initially required invasive ventilation.[3]

Our study showed that among the factors, age 50 years and above, with chronic liver disease, with non-pulmonary malignancy, with shortness of breath during admission, with oxygen support via face mask, with high flow nasal cannula, with invasive ventilation, with antibiotic use, with hemoperfusion, and with nebulization showed a decrease chance of recovery. These findings are similar with the study of Lee[13] that COVID-19-positive cancer patients are older age, harboring ≥2 comorbidities, more frequently developing respiratory failure, compared to the general population. Currently, there is no specific validated treatment for COVID-19, and management comprises of supportive and symptomatic care, and instituting recommended infection prevention and control measures. There were anecdotal reports and preclinical data supporting the investigation of potentially efficacious drugs.

In addition, our study noted that remdesivir showed an increase chance of recovery. Patients who received Remdesivir had a 31% faster time to recovery than those who received placebo (p <0.001). Specifically, the median time to recovery was 11 days for patients treated with Remdesivir compared with 15 days for those who received a placebo. This finding was also similar in the analytical study by Beigel J et al.[14], where patients who received Remdesivir were found to be more likely to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity).

Mortality

Lung cancer represents a clinical scenario characterized by an increased risk of pulmonary complications, severe lung injury, and high mortality from COVID-19, due to pathophysiological, clinical, and treatment-related risk factors.[9] In our study, mortality rate was noted to be 36% on the lung cancer group. This was close to the findings of the multicenter observational TERAVOLT study[6] where COVID-19 mortality rate of 33% in patients with pleuropulmonary neoplasms. In addition, a retrospective analysis study by Tian et al.[2] in China where 23 patients with lung cancer had 39% mortality rate and 78% had severe clinical outcome. Furthermore, the study by Rugge et al.[15] showed the lung cancer was associated with fourfold risk of death from SARS-CoV-2. Similar findings were also noted in the study of Rogado et al.[16]

Among the factors, there was an increase mortality rate among age more than 50 years, with chronic liver disease, with other malignancy, with shortness of breath, with oxygen support via FM, with high flow nasal cannula, with invasive ventilation, with antibiotics, with hemoperfusion, and with nebulization. Results were similar to the study of Passaro et al.[9] and Yu et al.[17] with age older than 65 years and presence of comorbidities associated with an increased risk of death. In addition, the study of Ozer[18] observed that higher comorbidity scores and increased oxygen requirement with mechanical ventilation were associated with increased mortality (p <0.004 and <0.001, respectively). However, with regard to hemoperfusion, result was contradictory to the study of Mikaeili et al.[19] where a significant mortality rate reduction in the perfused group especially among those with a P/F ratio more than 75 (37.1% vs. 63.6%, p = 0.02).

On contrary, Remdesivir use (OR=0.286, P=0) showed a significant mortality benefit. In the study of Jaroszewicz et al.[20], study shows that patients with malignancies could benefit from early Remdesivir therapy, with a decrease in 28-day in-hospital mortality of 80%.

COVID-19 Profile

Majority of the patients with lung cancer (71%) belonged to the age range of 50 years old above with male predominance. This was similar in a study by Robilotti[21] with most patients were adults over the age of 60 years (234, 56%). Also, comparable findings were observed in the study of Luo[3] with mean age of 68 years, however, with predominance of female at 52%. In addition, in a descriptive analysis study by Marineillo et al.[22], patients entering the hospital emergency department for symptoms related to SARS-CoV-2 infection showed that COVID-19-positive cancer patients were older, harboring ≥2 comorbidities, more frequently developing respiratory failure, at higher rates of hospitalization, compared to the general population. In our study, pulmonary tuberculosis and other malignancy were significantly higher in patients with lung cancer. All were noted to be nonsmokers with 2% with history of smoking with mean pack per year

of 7.2 ± 3.96. On the other hand, a study by Luo[3] showed that most patients' median pack-year smoking history was 23.5 (range 0-120 pack-years). Also, in the TERAVOLT study[6], majority of patients' profile include median age of 68 years, ECOG performance status of 0–1, current or former smokers, had non-small-cell lung cancer, and were on therapy. In this study, cigarette smoking has been significantly associated with patients' mortality in multivariate analysis.

In our study, all lung cancer patients were unvaccinated and were admitted during the time that COVID-19 vaccination was not yet readily available to most patients. Data on vaccine safety among cancer patients are still limited since most trials exclude this vulnerable group.[23] To date, there are no data regarding coverage of immunocompromised patients such as those with primary lung cancer. On admission, there is significantly higher rate of shortness of breath and fatigue among those with lung cancer. In comparison to the study of Robilotti[21], the presenting symptoms, fever (78%) and cough (82%) were the most common, whereas shortness of breath (44%) and diarrhea (26%) were less common but not rare. In addition, in a study by Luoet al.[3], although symptoms such as cough (70%) and fever (59%) were common, the constellation of symptoms within a given patient at presentation were variable. Furthermore, Calles et al.[4] in 2020 has observed that all patients had at least one COVID-19-related symptom; cough (48%), shortness of breath (48%), fever (39%), and low-grade fever (30%) were the most common. Also, lung cancer patients also presented with atypical appearances of COVID-19. Both groups have predominance of the severe type. As for oxygen support on admission, there was significantly higher rate of Mechanical Ventilation use among those with lung cancer. This was different from the result in the study of Robilotti[21] where patients developed severe respiratory illness, including 47 (11%) who required high-flow oxygen and 40 (9%) who required mechanical ventilation. As for concurrent treatments, there was significantly higher rate of antibiotic use, mucolytic and SABA/SAMA inhaler use among those with lung cancer. Data is sparse regarding these above therapies.

Cancer Profile

According to Calles et a.l[4], multiple variables related to tumor status, clinical baseline conditions, and inflammation markers were associated with mortality but did not remain statistically significant in a multivariate model. According to American Lung Association's Lung Cancer and COVID-19 update in September 2021, so much is still unknown about the lasting impacts of the COVID-19 infection. Among COVID-19 confirmed patients with lung cancer, it would be difficult to discern if symptoms are due to COVID-19 infection or due to the underlying lung cancer.[24]

All patients included had histopathologic diagnosis of non-small cell lung carcinoma. Fifty-seven percent (57%) were active cases and were diagnosed within 12 months. Sixty-four percent (64%) are currently undergoing treatment. There was one dormant patient who had been adjudged to be clinically quiescent for at least two years. Based on the report at Zhongnan Hospital in Wuhan[17], 58.3% of the COVID-19 lung cancer patients had non-small cell lung cancer (NSCLC) and more than half of whom were on active therapy. In this similar study, one patient required ICU admission and three patients died. Thus, they concluded that patients with cancer had a higher risk of mortality compared with the community. According to the study by Haineala et al.[25], lung cancer was mainly non-small cell cancer (76%) with 74% of cases were undergoing treatment. Similar findings was observed in the study of Luo[3] with 92% have non-small cell carcinoma, followed by small cell cancer.

In this study, average ECOG at baseline of the 14 patients was 1.23+1.59 which is somewhat similar to the findings of Haineala[25] with ECOG of 0-2. According to the study of Ozer, et al.[18], in general, non-survivors had higher comorbidity scores, late-stage cancer, and worse ECOG performance status than survivors ($p < 0.005$). They reported no association between anti-cancer treatments and mortality from COVID-19 disease. No specific data for lung cancer was declared on this study with only 12% lung cancer.

As for the treatment received prior to admission, 50% underwent chemotherapy and 57% had radiotherapy. There were nine patients who underwent surgical procedures including two lobectomy, three chest tube insertions, three thoracentesis and one pericardiostomy. According to a study by Lou et al.[3], cancer-specific features, including prior thoracic surgery/radiation and recent systemic therapies did not impact severity. Patient-specific features, rather than cancer-specific features or treatments, are the greatest determinants of severity.

Limitations of the Study

The authors based the diagnosis of primary lung cancer solely on medical history and made use of written imaging results and interpretation. Some patients were not able to present actual imaging studies for viewing.

CONCLUSION

The study showed that among all admitted COVID-19 patients, those with primary lung cancer were associated with shorter hospital stay, lower rate of recovery, and higher mortality rate as compared to those without primary lung cancer. Patient's clinical profile and demographics may suggest their clinical outcome but are not specific. The results of this study will guide clinicians predict potential course and prognosis, and serve as a guide to help improve current care with emphasis on the vulnerability of lung cancer patients during this pandemic.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

The study was funded by the authors.

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