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Original Research Article

GROUND GLASS OPACITIES IN LUNG CANCER PATIENTS POSITIVE FOR COVID-19

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Abstract: *This study was designed to evaluate radiological features of COVID-19 and early lung cancer through High-resolution computed tomography (HRCT) and demonstrated the disparity between them. A retrospective was conducted in the COVID-19 ward, Oncology & Radiology ward of CH& UCHS Lahore & Shifa International Hospital Islamabad & NMU & H Multan from October 14, 2019, to October 14, 2020. A total of 100 COVID-19 patients and 300 patients with pulmonary ground-glass opacities undergoing lung surgery (control group) were included in the study. After propensity score-matched analysis, patients were divided into two groups with 80 matched pairs each. Both groups' clinical, pathological, epidemiological, and radiological characteristics (evaluated through HRCT) were compared. It was observed that COVID-19 patients presented more definite symptoms, were mostly younger men, and had higher BMI (body-mass index). After the radiological analysis of the matched patients, it was revealed that single-lesion patients constituted 17% of COVID-19 cases and 89% of lung cancer cases. Patients in both groups mainly presented peripheral lesions. COVID-19 lesions had more lobes and segments and had various types with patchy forms. On the other hand, lung cancer tended to have only one type and had an oval form. Both COVID-19 and lung cancer showed ground-glass opacities with similar but independent characteristics. These characteristics, combined with pathogen detection, short-term CT examination, and laboratory tests, will aid in improved diagnosis.*

Keywords: COVID-19, Lung cancer, Radiology, Propensity score analysis, Ground-glass opacity

Introduction

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) caused COVID in 2019, and WHO declared it a global health emergency on January 30, 2020 (DECLARATION, 2001). The virus infected 8,525,000 people and caused 456,000 deaths till June 20, 2020. The pathogenesis of this infection usually has three stages. During the early stage, the virus binds to angiotensin-converting enzyme 2 (ACE-2), infecting nasal cells and leading to a low inflammatory response. Afterward, the virus reaches the respiratory airways, and clinical manifestations appear by this time. Lastly, the virus infects alveolar cell Type-II of the lungs by entering gas exchange units. Almost 20% of infected individuals reach this stage and have pulmonary infiltrates, severe disease including acute respiratory distress syndrome (ARDS), and frank lung injury develops in some cases (Wu et al., 2020). Rapidly transmitting virus calls for establishing consensus guidelines for preventing transmission and facilitating diagnosis (Miao et al., 2020). At current gold standard for its diagnosis is virus gene sequencing and Real-time polymerase chain reaction (RT-PCR). Still, these procedures are time-consuming, resulting in an extended diagnostic cycle (Covid et al., 2019). Different stages of COVID-19 are remarkably demonstrated by chest high-resolution computed tomography (HRCT) (Covid et al., 2019). Consolidative pulmonary opacities or patchy ground-glass opacities (GGOs) are mainly observed on CT scans. Consolidation and

enlargement of GGOs imply an increase in pneumonia (Chung et al., 2020). Along with having a central role in the evolution of the extent of pulmonary involvement in the disease, thoracic Ct significantly detects false-negative COVID-19 patients having nucleic acid tests because diagnostic CT findings are observed in these patients (Xie et al., 2020).

Early stages of lung cancer have been effectively screened using low-dose CT (LDCT). Potentially malignant lesions are indicated by GGOs on this CT (Team, 2013). It may be difficult to distinguish early lung cancer from COVID -19 because of the similarity of CT finding in both, particularly in nucleic acid-positive and asymptomatic patients. According to some reports, patients with both COVID-19 and early lung cancer did not show symptoms of pneumonia. Few were surgically treated but had severe life-threatening pneumonia (Tian et al., 2020) Therefore, it is essential to differentiate between two diseases, which GGOs indicate. In this study, we will evaluate the radiological features of COVID-19 and early lung cancer through High-resolution computed tomography (HRCT) and demonstrate the disparity between them.

Methods

A retrospective was conducted from October 14, 2019, to October 14, 2020, in the COVID-19 ward, Oncology, and radiology ward of CH & UCHS Lahore, Shifa International Hospital Islamabad & NMU & H Multan for one year. A total of 100 COVID-19 patients and 300 patients with pulmonary ground-glass opacities undergoing lung surgery (control group) were included in the study. Epistle 2000 software was used to calculate sample size by considering the 90% power of the test. A consecutive non-probability sampling technique was used. People with neurological disorders, chronic illness, and cancer in other areas were excluded. Medical records of the patients were used to obtain demographic data, symptoms, history, CT findings, and laboratory tests. Patients were also interviewed to obtain data do not present in the record. Standard chest protocol was followed for CT examinations: the patient was laid in a supine position, arms were raised, and the patient was asked to hold their breath. The following characteristics were analyzed in each patient: lung lesion type, lesion distribution, lesion form, number of affected lobes, frequency of lobe affected, number of segments affected, frequency of segment affected, and other findings like air bronchogram, tree-in-bud, centrilobular nodules, bronchial dilation, reticular pattern, cystic change, subpleural linear opacity, pleural retraction, pleural effusion, lymphadenopathy, and vessel convergence sign. Trained radiologists evaluated CT scans. The study was conducted after approval Ref# 11-108 dated 23-09-2019 from the ethical board.

Propensity score matched (PSM) analysis was performed between both groups to minimize bias resulting from non-randomized data collection. A multivariable logistic regression model with covariates was used to calculate each patient's propensity score. This model showed significant baseline differences, including age, gender, body mass index (BMI), tumor history, digestive disease, and cardio-cerebrovascular disease. Wilcoxon rank-sum test was used for comparing continuous variables between both groups. These were represented as median (interquartile range (IQR)). Categorical variables were compared using Fisher's exact test or Pearson's Chi-squared test. R-software was used for statistical analysis. *P-value* <0.05 was statistically significant.

Results

A total of 300 patients with early lung cancer and 100 patients with COVID-19 were included in the study. Subjects in the COVID-19 group were younger and had higher BMI than those with lung cancer. Commodities like digestive disease, tumor history, and cardiovascular disease were much lower in patients with COVID-19. The clinical and demographic data before and after PSM are shown in Table-I. After propensity score-matched analysis, patients were divided into two groups with 80 matched pairs each. Before PSM, most COVID-19 patients had an exposure history, some traveled to pandemic areas, and some had close contact with infected patients. Pneumonia symptoms, including fever, cough, snot, dyspnea, sputum, muscle soreness, diarrhea, and chest distress, were more

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prevalent in COVID-19 patients than in those with lung cancer. According to laboratory tests at the time of admission, patients with COVID-19 had lower white blood cell count and lymphocyte count and higher aspartate aminotransferase than those with lung cancer. D-dimer, alanine aminotransferase, and Neutrophil count did not significantly vary between the groups. The difference in laboratory findings, the incidence of symptoms, and exposure history were consistent after PSM. Nevertheless, the incidence of muscle soreness and dyspnea were no longer much different in the two groups. D-dimer and neutrophil counts reached a significant difference.

Table-I: Clinical and Demographic Characters of Subjects included in the study

Variables	Before PSM			After PSM		
	COVID-19 n=100	Lung Cancer n=300	P value	COVID-19 n=80	Lung Cancer n=80	P value
Sex (%)			<.0001			1.00
Male	55 (55%)	105 (35%)		38 (48%)	38 (47%)	
Female	45(45%)	195 (65%)		42 (52%)	42 (53%)	
Age (years), median	47(37-56)	59 (50-67)	<.0001	51(42-58)	53(42-61)	.77
BMI kg/m2, median	25(22-27)	24(22-26)	.014	24(22-26)	24(23-27)	.71
History of exposure (%)			<.0001			<.0001
Contact with an infected person	31 (31%)	0 (0%)		24 (30%)	0 (0%)	
History of travel to the epidemic area	54 (54%)	0(0%)		46 (57%)	0 (0%)	
Comorbidity (%)						
Cardiovascular disease	18 (18%)	84 (28%)	.027	17 (21%)	18 (22%)	.88
Digestive disease	5 (5%)	36 (12%)	.034	6 (7%)	5 (6%)	1.00
Endocrine disease	6 (6%)	27 (9%)	.35	6 (7%)	3 (4%)	.41
Neuropathy	0 (0%)	6 (2%)	.19	0 (0%)	2 (2%)	.50
Respiratory disease	2 (2%)	12 (4 %)	.34	2 (2%)	3 (3%)	.68
Tumor history	1 (1%)	21 (7%)	.0087	2 (2%)		1.00
Symptoms (%)						
Fever	78(78%)	3 (1%)	<.0001	67 (82%)	0 (0%)	<.0001
Cough	59(59%)	15 (5%)	<.0001	46 (58%)	6 (7%)	<.0001
Sputum	32 (32%)	6 (2%)	<.0001	23 (29%)	1 (2%)	<.0001
Dyspnea	2 (2%)	0(0%)	.026	2 (2%)	0(0%)	.50
Snot	4(4%)	0(0%)	.00062	3 (4%)	0 (0%)	.060
Chest distress	10(10%)	3 (1%)	<.0001	9(11%)	1 (2%)	.020
Diarrhea	8 (8%)	0(0%)	<.0001	5 (6%)	0 (0%)	.014
Laboratory findings, median						
White blood cell	4.7 (3.7-6.1)	5.2 (4.4-6.1)	.00027	4.6 (3.4-5.8)	5.5 (4.6-6.5)	.0001
Neutrophil	2.65 (2.0-4.0)	2.82 (2.31-3.61)	.16	2.70(1.90-4.00)	3.08 (2.50-3.70)	.032
Lymphocyte	1.30 (.99-1.66)	1.71 (1.40-2.1)	<.0001	1.20 (.91-1.60)	1.75 (1.51-2.11)	<.0001
Alanine aminotransferase	20.1 (14.1-34.0)	20.0 (15.0-27.0)	.11	18.6 (13.4-33)	20.0(15.0-30.0)	.85
Aspartate aminotransferase	24.0 (20.0-35.5)	21 (18.0-26.0)	<.0001	24 (20-34.5)	21.0 (17.0-25.0)	<.0001
D-dimer	.26 (.19-.53)	.25(.19-.38)	.29	.28 (.20-.64)	.22(.17-.33)	.017
Viral nucleic acid detection	100 (100%)	NA	NA	80 (100%)	NA	NA

According to the CT scan results, ten patients with COVID-19 had negative radiological findings. One thousand lung lesions were observed in 100 COVID -19 patients. Four hundred lesions were observed in 300 lung cancer patients. Peripheral lesions were predominantly present in both groups (760/1000 in COVID-19, 296/400 in lung cancer). The proportion of consolidation, mixed GGO, and pure GGO were 15%, 59%, and 28%, respectively, in COVID-19 patients, while in lung cancer patients, these proportions were 6%, 48%, and 47%. CT findings between both groups were quantitatively compared (Table II). The form, type, number, specific features, and distribution of lesions before and after PSM were comparable. Among the matched groups, a single lesion was present in 14/80 COVID-19 patients and 71/80 patients with lung cancer. More lobes and segments were involved in COVID-19 patients compared to lung cancer patients. More than one type of lung lesion was found in the majority of COVID-19 patients (54/80, 67%), while patients with lung cancer either had mixed GGO (32/80, 40%) or pure GGO (40/80, 50%). COVID-19 patients had patchy lesions, while those with lung cancer had oval lesions. Pleural effusion and lymphadenopathy were observed in 6/80 (8%) and 3/80 (4%) patients. Cystic change and air bronchogram were present in both groups.

Table II: Radiological Findings

Variables	Before PSM			After PSM		
	COVID-19 n=100	**Lung cancer n=300**	**P value**	**COVID-19 n=80**	**Lung cancer n=80**	**P value**
Single lesion	17 (17%)	261 (87%)	<.0001			<.0001
No. of involved lobe, median	5 (2-7)	1 (1-1)	<.0001	14 (17%)		<.0001
No. of segments involved, median	7 (2-13)	1 (1-1)	<.0001			<.0001
Type of lesion						
Pure GGO	4 (4%)	141 (47%)	<.0001	1 (1%)	40 (50%)	<.0001
Mixed GGO	17 (17%)	126 (42%)	<.0001	17 (21%)	32 (40%)	.0013
Consolidation	3 (3%)	12 (4%)	.95	3 (4%)	2 (2%)	.45
Pure and mixed GGO	34(34%)	18 (6%)	<.0001	26 (32%)	4 (5%)	<.0001
Pure GGO and consolidation	1 (1%)	3 (1%)	1.00	1 (1%)	1 (1%)	1.00
Mixed GGO and consolidation	16 (16%)	3 (1%)	<.0001	10 (12%)	2 (2%)	.0044
Pure and mixed consolidation	20 (20%)	0 (0%)	<.0001	19 (24%)	0 (0%)	<.0001
Form of lesion						
Oval	4 (4%)	189 (63%)	<.0001	4 (5%)	53 (66%)	<.0001
Patchy	49 (49%)	90 (30%)	<.0001	43 (54%)	24 (30%)	.00026
Oval and patchy	36 (36%)	21 (7%)	<.0001	27 (34%)	3 (4%)	<.0001
No lesion	11 (11%)	0 (0%)	<.0001	6 (7%)	0 (0%)	.0033
Distribution of lesion						
Unilateral lung	17 (17%)	285 (95%)	<.0001	75 (94%)	78 (97%)	<.0001
Bilateral lung	72 (72%)	15 (5%)	<.0001	59 (74%)	2 (3%)	<.0001
No lesion	7 (7%)	0 (0%)	<.0001	6 (7%)	0 (0%)	.0033
Lymphadenopathy	4 (4%)	0(0%)	.0011	3 (4%)	0 (0%)	.060
Pleural effusion	7 (7%)	0(0%)	<.0001	6 (8%)	1 (1%)	.014

COVID-19 patients had more frequent air bronchogram, while cystic changes were rare. Moreover, reticular pattern, bronchial dilation, subpleural linear opacity, tree-in-bud, and centrilobular nodules were observed in COVID-19 patients, while none were in lung cancer patients. On the other hand, lung cancer patients had vessel convergence signs, pleural retraction, and lobulated signs, while COVID-19 patients did not show any of these.

Discussion

Thousands of people have been affected by the COVID-19 pandemic worldwide. The major challenge is ensuring the specificity and sensitivity of the diagnosis. CT scan, in addition to the nucleic acid test, is a practical diagnostic method for COVID-19. Additionally, despite the negative nucleic acid test, COVID-19 still could be present (Fang et al., 2020; Huang et al., 2020). It is very important to differentiate the early stages of lung cancer from COVID-19. GGO-appearing CT scans show attenuation and damage to the alveoli. Imaging results matched pathological findings like proteinaceous exudes and alveolar edema, where multinucleated giant cells, vascular congestion, and inspissated secretion were seen in the airspaces. Additionally, alveolar activity was decreased due to the proliferation of interstitial fibroblasts and pneumocytes (Tian et al., 2020). GGO is predominantly found in the radiographic image of both early lung cancer and COVID-19. Both could demonstrate patchy or oval, unilateral or bilateral GGO in the form of multiple or single lesions, which makes it challenging to discriminate between both. This similarity can confuse the surgeons and lead to inappropriate surgical intervention.

Despite these difficulties, differentiating characteristics are found in our study that will aid in reaching the correct diagnosis. This study shows that patchy bilateral GGOs are predominantly present in COVID-19, while oval unilateral GGOs are present in lung cancer. Distribution and shape are consistent with past studies (Bernheim et al., 2020). COVID-19 can be distinguished by reticular pattern, bronchial dilation, subpleural linear opacity, tree-in-bud, and centrilobular nodules. On the other hand, lung cancer is featured by vessel convergence, cystic change, pleural retraction, and lobulated signs. During the

initial stage of COVID-19, classical GGO and occasional consolidation are observed; another study confirmed this finding (Hanif et al., 2021). After five days, lesions lesion increases in size with disease progression, and additional features like crazy paving pattern, reverse halo sign, and fibrous stripe begin to appear; an increase in GGO is related to progressing malignancies (Chang et al., 2020). Though these are subtle differences are of high value in distinguishing these diseases; however, diagnosis of COVID-19 requires thorough assessment, epidemiological investigation, laboratory tests, and clinical symptoms. Patients with shortness of breath, fever, myalgia, and cough should be focused on (Chang et al., 2020). Travel history to epidemic areas and contact with those infected with COVID-19 are also considered during diagnosis. Above all, the nucleic acid test remains the gold standard for a definite diagnosis (Nicholls et al., 2003). It is essential and clinically significant to analyze the distinction between CT findings of early lung cancer and COVID-19. GGO in CT scans can help diagnose asymptomatic COVID-19 patients and those with negative nucleic acid pneumonia, thus limiting transmission and decreasing missed diagnosis rates. Patients with lung cancer should be extensively evaluated to exclude COVID-19 before surgery. The possibility of misdiagnosing COVID-19 as lung cancer and vice versa should be reduced. Rash decision exposed the patient to COVID-19 and surgical trauma. Upon reaching a definitive diagnosis, treatment of COVID-19 should be prioritized (Zhang et al., 2020).

COVID-19 has monopolized human and economic resources of the health system worldwide and has affected the diagnosis and treatment of lung cancer, leading to poor prognosis (Talic et al., 2021; Wong et al., 2022). COVID-19 pneumonia is more severe in oncological patients and has worse complications (Fusco et al., 2021; Mitrev et al., 2021). Despite overlapping and similar findings, the combination of radiological and clinical findings can lead to differential diagnoses. It is important to understand the classic radiological feature of COVID-19 phases on HRCT (Kostakoglu et al., 2021; Tabassum et al., 2022). Atypical findings like vessel invasion, lymphadenopathies, and unresponsiveness to therapy are associated with lung cancer. The radiological features of lung cancer and COVID-19 discussed in our study can be used for developing protocols for early diagnosis and intervention to improve life expectancy. However, this study has a few limitations like a small sample size and shorter study period, due to which more detailed studies are required to validate our results.

Conclusion

The distinctive features of GGOs in patients with early-stage lung cancer and COVID-19, along with laboratory tests, patient history, and pathogen detection, will aid in differential diagnosis and lower the rate of miss diagnosis.

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Conflict of interest

The authors declared absence of conflict of interest.

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