ORIGINAL ARTICLE

RELATIONSHIP OF PRIOR PULMONARY TUBERCULOSIS WITH THE OCCURRENCE OF COVID-19 PNEUMONIA: REVIEW OF 500 PLUS HRCT CHEST SCANS FROM TWO DIFFERENT CENTRES OF SINDH, PAKISTAN

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Background: COVID-19 pandemic has severely affected the entire world. However, its severity and mortality rate are lesser in developing countries, including Pakistan. This study aims to determine the association of prior pulmonary tuberculosis with COVID-19 pneumonia. **Methods:** This cross-sectional study was conducted at two centres of Sindh, Pakistan. 521 HRCT chest performed from 1st May to 31st July 2020 were included and marked as "COVID-19 group". 761 HRCT chest performed during the first six months of 2019 were retrospectively evaluated to determine the prevalence of prior pulmonary tuberculosis and marked as the "pre-COVID-19 group". Previous pulmonary tuberculosis was documented as evidenced by clinical history, ATT intake and HRCT findings. Chi-square test was used to determine the association of prior pulmonary tuberculosis with COVID-19 pneumonia. A *p*-value of ≤0.01 was considered statistically significant. **Results:** In the "COVID-19 group", 4.9% (n=26) patients had prior pulmonary tuberculosis. In the "pre-COVID-19 group", 9.8% (n=75) patients had prior pulmonary tuberculosis with a confirmed history of tuberculosis in 8.9% (n=68) and without documented history in 0.9% (n=7) cases. A significant *p*-value of 0.001 was obtained with a confidence interval of 99%. **Conclusion:** Prior pulmonary tuberculosis might have a protective effect against COVID-19 pneumonia which could be due to developed antibodies secondary to exposure to prior tuberculosis or BCG vaccination. Our results warrant further consideration due to the potential public-health benefits that can be achieved in our fight against the novel pandemic.

Keywords: COVID-19; Pandemic; Prior pulmonary tuberculosis; HRCT, RT-PCR; Immunity

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INTRODUCTION

In December 2019, the epidemic of Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread in Wuhan city of China.[1] Soon it engulfed the entire world, challenging the global health care system and was acknowledged as a 'public health emergency of international concern' by the World Health Organization (WHO). Later on, due to the rapidly evolving crisis and magnitude of the disease spread, WHO characterized COVID-19 as a "pandemic" on 11th March 2020.[2] As of 9th August 2020, there are 19,847,798 cases worldwide with 730,371 deaths. In Pakistan, the first case of COVID-19 was diagnosed on 26th February 2020. There are confirmed 284,121 cases and 6,082 deaths until 9th Augest.[3]

According to the WHO COVID-19 situation report, the severity of pandemic is lower in developing countries, including Pakistan. The trained innate immunity could be a possible reason for this phenomenon. These countries have adopted national vaccination policies like Bacille Calmette–Guerin (BCG) and the oral polio vaccines.[4–6] Approximately 80% of the population of the developing countries test positive for BCG, which is an attenuated form of the bacterium that causes tuberculosis. Hence, it is biologically conceivable to assume that exposure to tuberculosis infection may induce a non-specific protective effect against COVID-19.[7] However, many researchers fear that in high tuberculosis burden countries co-infection with tuberculosis could negatively impact the local population. Tuberculosis is already existing as an undeclared pandemic with approximately a quarter of the world population assumed to have a latent disease. The combination of tuberculosis and COVID-19 pandemics and the impact of COVID-19 on patients with prior pulmonary tuberculosis is unknown so far.[8] The present study was designed to determine the association of prior pulmonary tuberculosis with COVID-19 pneumonia.

MATERIAL AND METHODS

This cross-sectional study was conducted at the National Medical Centre, Karachi and Super Diagnostic Centre, Hyderabad, Pakistan. The ethical

approval of the study was obtained from the Institutional Review Boards of these centres.

We included all HRCT chest scans of diagnosed and suspected cases of COVID-19 performed from 1st May to 31st July 2020 and marked it as the "COVID-19 group". The rationale for screening scans was to isolate highly suspected cases in a PCR resource-constrained environment and triage patients of the emergency department who required urgent intervention or hospitalization. The COVID-19 status of a patient was established by the reverse transcription-polymerase chain reaction (RT-PCR) in the acute phase and COVID-19 total antibodies in the later stage of the disease. According to the inclusion criteria, we included scans of patients who (a) tested positive on COVID-19 RT-PCR and had positive pulmonary findings, (b) tested positive on anti COVID antibodies and had positive pulmonary findings, (c) demonstrated CO-RADS 3 and 4 features on HRCT and tested positive on subsequent RT-PCR or anti-COVID antibodies and (d) demonstrated CO-RADS 5 features on HRCT regardless of laboratory confirmation (as per the Fleischner Society Guidelines for imaging during the COVID-19 pandemic).[9] We excluded the screening HRCT chest scans of patients with CO-RADS 3 and 4 findings who tested negative on two consecutive RT-PCR. Secondly, COVID-19 positive patients with mild symptoms, normal chest radiographs and O^2 saturation of more than 95% were not scanned, therefore, they were not included in this study.

In the second group, we included all HRCT chest scans performed during the first six months of 2019 and marked it as the "pre-COVID-19 group". We retrospectively evaluated these scans and available clinical data to determine the prevalence of prior pulmonary tuberculosis before the arrival of the pandemic. The relevant clinical information including age, gender, symptoms and diagnosis were retrieved by detailed analysis of the patients' electronic medical records.

All HRCT chest were performed on Toshiba Astelion 16 slicer and Canon Aquilion Start 16 slicer CT scanners, respectively. Patients were scanned in a supine position during end-inspiration. No intravenous contrast material was used. The scans were reconstructed to 1.25-mm thin slices. Multiplanar reconstructions were obtained using the multiplanar reformatting technique on the workstation. Images were reviewed independently by two experienced radiologists. The scans in the COVID-19 group were reported using COVID-19 Reporting and Data System (CO-RADS).[10]

The Statistical Package for the Social Sciences, Version 21.0 (IBM, USA) was used for data entry, analysis and interpretation. Quantitative variables like age were displayed as Mean±Standard Deviation (SD). Qualitative variable such as gender, radiological features and diseases were expressed as frequency and percentages. Both groups of patients were divided into four categories according to age criteria, i.e., young (0–24 years), young adults (25–54 years), adults (55–64 years) and older adults (65 years and above). Chi-square test was used to determine the association of prior pulmonary tuberculosis with COVID-19 pneumonia. A *p*-value of ≤0.01 (99% Confidence Interval) was considered statistically significant.

RESULTS

During our study period, 555 HRCT chest scans of diagnosed and highly suspected cases of COVID-19 were performed**.** After excluding 5.9% (n=34) screening HRCT by utilizing the exclusion criteria, a total of 521 scans were included in the "COVID-19 group". These comprised of 89.3% (n=465) diagnostic and 10.1% (n=53) screening scans. There were maximum scans in the CO-RADS 6 categories 89.3% (n=465) [Table-1]. In the "COVID-19 group", there were 72.5% (n=383) males with a mean age of 51.0±13.52 years and 27.9% (n=138) females with a mean age of 55.0±14.96 years [Table-2]. The male to female ratio was 2.7:1. Majority of patients were young adults 59.5% (n=310) aged 25–54 years. There was confirmed history or mark of BCG vaccination in 85.2% (n=444) cases. The COVID-19 positive status of 94.8% (n=441) patients was confirmed using RT-PCR in 88.2% (n=465) and anti COVID antibodies in 11.3% (n=53) cases. Most common findings of COVID-19 pneumonia comprised of ground glass opacification (GGO) 97.3% (n=514), consolidation 56.8% (n=300), subpleural septal thickening 74.2% (n=392), fluffy nodules 24.6% (n=130), crazy paving 14.9% (n=78) and thoracic lymph nodes 12.09% (n=63) [Table-3]. There was typical bilateral peripheral pulmonary involvement in 83.6% (n=436) scans [Figure-2]. Curvilinear subpleural bands were noted frequently [Figure-3]. We diagnosed prior pulmonary tuberculosis in 4.9% (n=26) scans in the "COVID-19 group" as evidenced by clinical history, ATT intake and HRCT features of upper lobe fibrosis 4.9% (n=26), pleural thickening 3.8% (n=20), calcified mediastinal lymphadenopathy 4.9% (n=26), and calcified granulomas 4.9% (n=26) [Table-4] [Figure-3]. No patient had radiological evidence of active pulmonary tuberculosis.

In the "pre-COVID-19 group", out of 761 patients, 71.6% (n=545) were males with a mean age of 50.0±14.0 years and 29% (n=216) were females with a mean age of 52.0±15.0 years [Table-5]. The male to female ratio was 2.5:1. Majority of patients were young adults 62.7% (n=477). A total of 35.9%

(n=273) HRCT scans were reported normal without any significant finding. The top five most prevalent diseases in a descending order included interstitial lung disease 12.4% (n=94), chronic obstructive pulmonary disease 10.9% (n=83), prior pulmonary tuberculosis 9.9% (n=75), active and miliary tuberculosis 5.4% (n=41) and pneumonia 4.1% (n=31) [Figure-1]. 9.9% (n=75) scans demonstrated HRCT features of prior pulmonary tuberculosis with a documented clinical history of anti-tuberculous drugs in 8.9% (n=68). In 0.9% (n=7) patients, there was no documented history of tuberculosis. However, they demonstrated characteristic HRCT features of prior pulmonary tuberculosis [Figure-4]. Variable combinations of upper lobe fibrosis 9.4% (n=72), pleural thickening 7.8% (n=60), calcified lymphadenopathy 9.7% (n=74), and calcified granulomas 9.7% (n=74) were noted. Figure-5 shows characteristic features of miliary tuberculosis in the "pre-COVID-19 group".

We observed prior pulmonary tuberculosis in 4.9% (n=26) scans in the "COVID-19 group" and 9.8% (n=75) scans in the "pre-COVID-19 group". The negative and positive cases of COVID-19 and prior pulmonary tuberculosis in both groups were plotted in a 2×2 contingency table [Table-6]. The expected values were calculated from the observed values. The Chi-square statistic was 10.02. A significant *p*-value of 0.001 was obtained with a confidence interval (CI) of 99%.

Table-1: Distribution of cases according to CO-RADS criteria in the "COVID-19 group"

		(n)	(%)
CO-RADS	CO-RADS 6	465	89.3
	CO-RADS 3	4	0.8
	CO-RADS 4	25	4.8
	CO-RADS 5	27	5.2

Table-2: Distribution of patients by age and gender in the "COVID-19 group" [expressed as Number (n), Mean±SD and Percentage (%)]

COVID-19 group		(n)	Mean± SD	(%)
Age Groups	Youth (0-24 years)	6	24±0 years	1.2
	Young Adults (25–54 years)	310	44±7 years	59.5
	Adults (55–64 years)	88	58±3 years	16.9
	Older Adults (65+)	117	71±8 years	22.5
Gender				
	Male	383	51.0±13.52 years	72.5
	Female	138	55.0±14.96 years	26.1
	Total	521	52±14 years	100.0

Table-3: HRCT chest findings in the "COVID-19 group" [expressed as Number (n) and Percentage (%)]

HRCT Findings	COVID-19 group	
	(n)	(%)
Ground glass opacification	514	98.7
Interstitial septal thickening	392	98.2
Consolidation	300	97.7
Fluffy nodules	130	94.9
Crazy paving	78	14.9
Nodes	63	90.0
Halo sign	39	84.8
Bronchial wall thickening	31	81.6
Cavitation	31	81.6
Pleural effusion	22	75.9
Reversed halo sign	8	53.3
Pericardial effusion	8	53.3

Table-4: HRCT features of prior pulmonary tuberculosis in the "COVID-19 group" [expressed as Number (n) and Percentage (%)]

HRCT features of prior pulmonary tuberculosis	[n]	(%)
Upper lobe fibrosis	26	5.0%
Pleural thickening	20	3.8%
Calcified nodes	26	5.0%
Calcified granulomas	26	5.0%

Table-5: Distribution of patients by age and gender in the "pre-COVID-19 group" [expressed as Number (n), Mean±SD and Percentage (%)]

		Age		
		(n)	Mean± SD	%
Age Groups	**Youth (0-24 years)**	22	22±2 years	2.9%
	Young Adults (25-54 years)	477	43±7 years	62.7%
	Adults (55 - 64 years)	114	58±years	15.0%
	Older Adults (65+)	148	72±9 years	19.4%
Gender	**Male**	545	50±14 years	71.6%
	Female	216	52±15 years	28.3%
	Total	761	50±14years	100.0%

Table-6: Chi-square 10.02. *p*-value 0.0001. Since *p*-value (0.001< 0.01), we reject the null hypothesis with 99% confidence interval. There is a significant association between prior pulmonary tuberculosis and COVID-19 pneumonia. Values expressed as Numbers (n).

Observed Values		COVID-19 (n)		Total (n)	Expected Values		COVID-19 (n)		Total (n)
		Yes	No				Yes	No	
Tuberculosis (n)	Yes	26	75	101	Tuberculosis (n)	Yes	41	60	101
	No	495	686	1,181		No	480	701	1,181
Total (n)		521	761	1,282	Total (n)		521	761	1,282

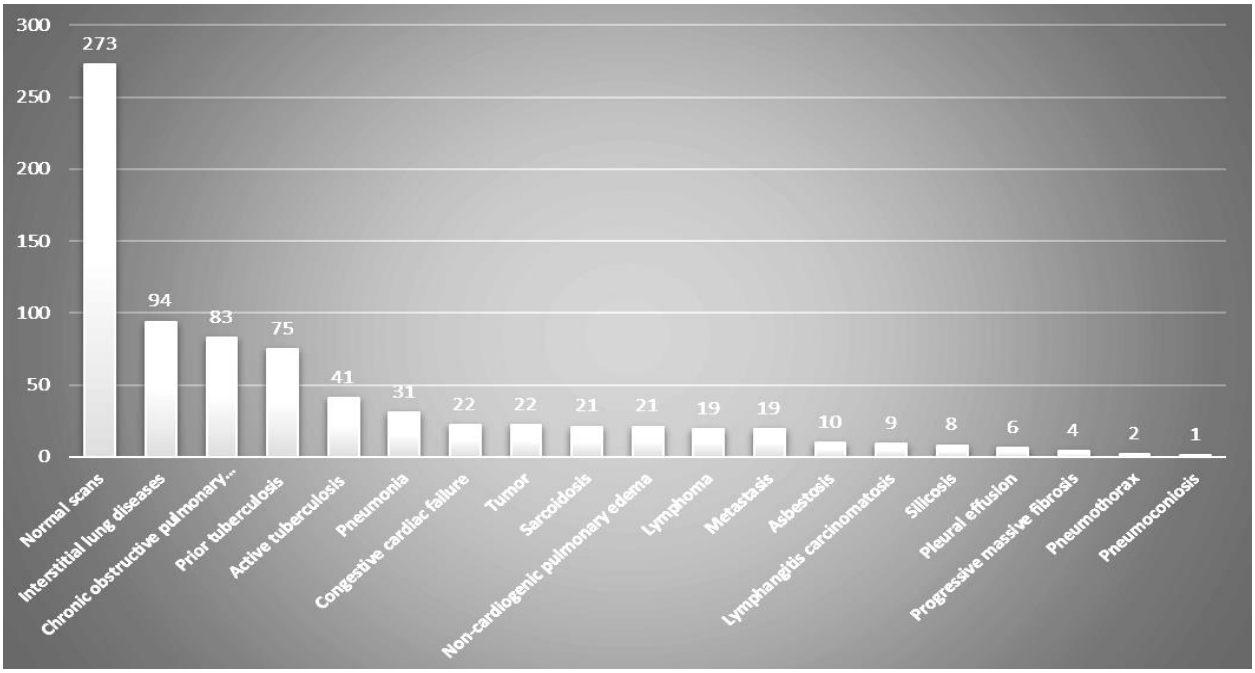

Figure-1: Distribution of diseases in the "Pre-COVID-19 group" [expressed as Number (n)]

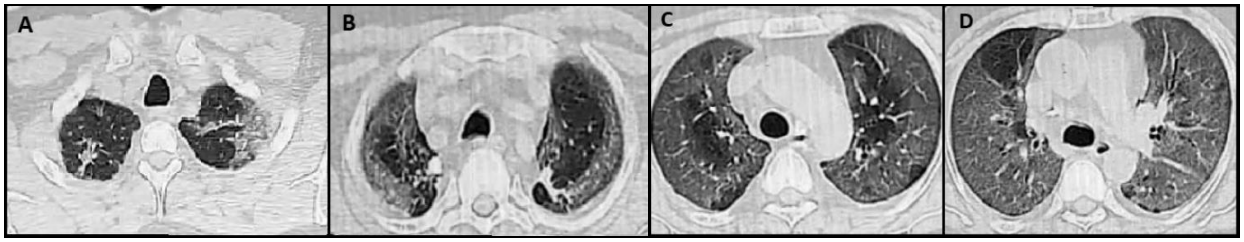

Figure-2: A 45-year-old female with high-grade fever and dyspnea in the "COVID-19 group". Positive COVID-19 RT-PCR. Documented history of tuberculosis and anti-tuberculous treatment. Axial images of HRCT chest show bilateral diffuse ground-glass opacification with peripheral preponderance consistent with CO-RADS 6. Left upper lobe fibrosis with calcified granuloma in the right apical region with calcified lymph nodes suggesting prior pulmonary tuberculosis.

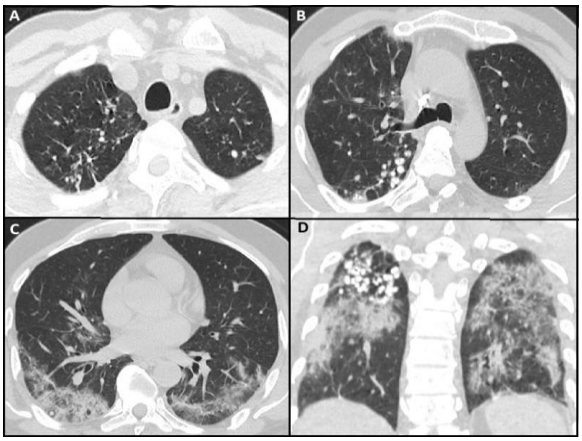

Figure-3: A-57-years old male with fever and dry cough for last 10 days in the "COVID-19 group". Positive COVID-19 RT-PCR. He had pulmonary tuberculosis 20 years back. Axial (A, B & C) and coronal (D) images of HRCT shows bilateral upper lobe fibrosis and calcification with calcified mediastinal nodes. There are subpleural ground glass haze and consolidation bilaterally. Findings are consistent with CORADS 6.

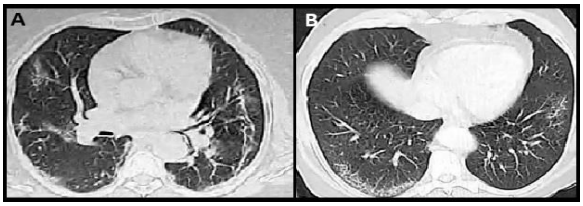

Figure-4: Axial (A, B) images of screening HRCT of two different patients from "COVID-19 group", showing typical curvilinear subpleural bands and patchy ground-glass opacification in bilateral basal regions. CO-RADS 5. Subsequent IgM anti-COVID antibodies were positive.

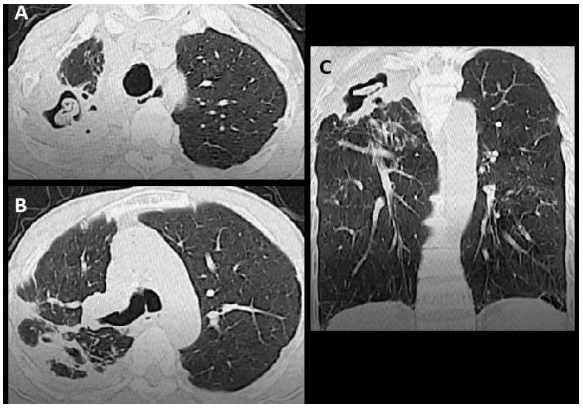

Figure-4: A 36-year-old male with fever from the "pre-COVID-19 group". He had history of treated pulmonary tuberculosis. Axial (A, B) and coronal (C) images of HRCT chest shows volume loss in the right upper lobe with pleural thickening and fibrotic bands. A cavity is also noted with gravity dependent soft tissue area suggesting aspergilloma.

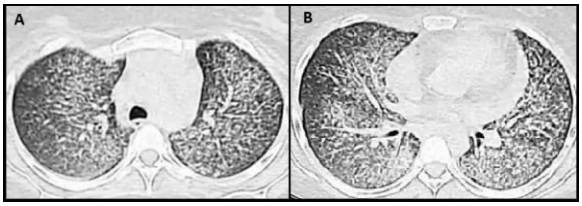

Figure-6: A 78-years-old male with low-grade fever, productive cough and weight loss from the "pre-COVID-19 group". GeneXpert was positive. Axial (A, B) images of HRCT chest show innumerable miliary nodules in both lungs representing miliary tuberculosis.

DISCUSSION

COVID-19 has adversely affected the lives of millions of people around the globe, especially those with comorbid conditions.[9] According to the WHO COVID-19 situation report, the severity of pandemic and mortality rate is lower in developing countries, including Pakistan.[8] The trained immunity due to vaccination policies like BCG could be a possible explanation for this outcome. This vaccine is an attenuated form of the bacteria that causes tuberculosis, and hence it is plausible to assume that exposure to tuberculosis infection may also induce a non-specific protective effect against COVID-19. Moreover, there could be an additive effect of BCG vaccination and prior tuberculosis on the overall less severity of COVID-19 pandemic in Pakistan. The BCG vaccination program was initiated in Pakistan in 1949 and has been a constant part of the Extended Program of Immunization since 1970.[4–6,11,12]

Tuberculosis is the world's biggest killer among infectious diseases. However, the experience of concomitant COVID-19 and tuberculosis remains very limited. Patients with existing lung damage may suffer from more severe forms of COVID-19 pneumonia with a higher risk of fatal complications.[13,14] Many fears that in high tuberculosis burden countries co-infection with tuberculosis could negatively impact the clinical outcome of these patients. Unfortunately, Pakistan ranks 5th amongst the topmost tuberculosis burden countries and 4th amongst the highest multidrug-resistant tuberculosis countries.[15] WHO reports, the incidence, prevalence and mortality of tuberculosis in Pakistan as 230 per 100 000, 310 per 100,000 and 39 per 100,000, respectively. This shows 410,000 newly diagnosed cases and 69,000 deaths each year due to tuberculosis.[16,17] Qadeer et al estimated the incidence and prevalence rate of all forms of tuberculosis to be 231 (95% confidence interval (CI), 189-277) and 364 (95%CI, 154-611) per 100,000 population, respectively.[18] The prevalence significantly increased

with age and was highest in Sindh which is the centre of the tuberculosis epidemic in Pakistan.[18]

The radiology departments across Pakistan routinely witness radiographs and HRCT scans of patients with active tuberculosis as well as sequelae of prior pulmonary tuberculosis. The typical findings of prior tuberculosis are apical pleural thickening and fibrosis, atelectatic pleuroparenchymal bands, and calcified granulomas, predominantly in the upper lobes. Calcified thoracic lymphadenopathy is a frequently reported finding.[19] Kamran *et al* reported apical pleural thickening as the most commonly seen abnormality on HRCT chest 75.3% (n=64) followed by fibrotic pleuroparenchymal bands 57.6% (n=49) in a screening study of tuberculosis in Pakistan.[20]

The RT-PCR is the most accurate diagnostic test for the detection of COVID-19.[21] HRCT chest plays a supporting role in the rapid diagnosis of COVID-19 and aids in the estimation of disease severity and prognosis.[10,22] It may be used as a tool for the rapid screening of patients with acute emergencies in a resource-constrained environment.[23] The typical imaging features of COVID-19 pneumonia are bilateral multifocal patchy or (GGO), pure consolidation, mixed GGO and consolidation, interstitial septal thickening and nodules in a peripheral distribution. Less common features in the later course of the disease may include bronchiectasis, bronchial wall thickening, cavitation, pleural effusion, pericardial effusion, pneumothorax, pneumomediastinum, and thoracic lymphadenopathy. Some classic radiological signs, including, "crazy paving", "halo sign" and "reversed halo sign" may also be encountered.[1,22,24,25]

Chaudhry *et al* conducted an epidemiological study to determine the temporal and spatial distribution of the initial 100 deaths due to COVID-19 in Pakistan. They reported maximum deaths (41%) in the 60–69 years group. Males were more prone due to their social activities in a male dominant society with male to female ratio of 3:1. Comorbid conditions were reported in 71% (n=71), including hypertension 67%, diabetes mellitus 45% and ischemic heart diseases 27%. They reported a combined history of tuberculosis and chronic obstructive pulmonary disease in (n=3/100) patients, constituting a total of 3%.[26]

Singh *et al* documented a case of a 76-years-old female patient who was concomitantly diagnosed with COVID-19 and tuberculosis. There was no documented history of prior tuberculosis. Her throat swab for SARS CoV-2 was positive on RT-PCR. Ziehl Neelsen staining of sputum was positive for acid-fast bacilli. GeneXpert of sputum detected rifampicin sensitive Mycobacterium tuberculosis complex. The patient was treated concurrently with four anti-tuberculous drugs regimen and hydroxychloroquine in along with antibiotics. Her CT chest demonstrated left lower lobe consolidation with air bronchogram and bilateral ground-glass opacification.[27]

Chen *et al* considered latent or active tuberculosis as a comorbidity for COVID-19. They suspected increased susceptibility of COVID-19, with more severity, and rapid progression to pneumonia in patients suffering from tuberculosis. The combination of these two bugs was associated with disease severity evidenced by 75% severe or critical and 22% mild or moderate cases (p=0.0049). The rate of disease progression and development of symptoms was also high in patients with concomitant tuberculosis.[13]

Stochino *et al* reported a modest impact of COVID-19 co-infection on the clinical course of tuberculosis. The comparison of post-COVID-19 chest radiograph with the latest available radiographs depicted reduction of tuberculous lesions in 63% (n=12) patients, worsening of lesions in 35% (n=7) patients and no interval change in one patient. Apart from fever, most patients had no significant clinical deterioration. Only one patient progressed to severe respiratory insufficiency and died. In most cases, tuberculous lesions did not increase, and only four patients had features of newly developed pneumonia. No patient required intensive care or mechanical ventilation.[8]

Tadolini *et al* shared the first global cohort of active or prior tuberculosis and post tuberculosis sequelae with COVID-19 under the umbrella of the Global Tuberculosis Network. They enrolled 49 patients from 8 countries. 53.0% (n=26) had tuberculosis before the detection of COVID-19, 28.5% (n=14) were diagnosed with COVID-19 followed by tuberculosis, and 18.3% (n=14) were concomitantly diagnosed with both diseases. In their study, 85.7% (n=42) patients had active tuberculosis and 14.3% (n=7) had sequelae of prior tuberculosis. 42% (n=21) patients had typical HRCT features of COVID-19. (15) In 19/49 (38.8%) patients COVID-19 appeared during the course of anti-tuberculosis treatment suggesting limited or no protection against COVID-19. In (n=9) patients a simultaneous diagnosis of COVID-19 and tuberculosis created a diagnostic challenge that was overcome by clinico-radiological correlation. In (n=14) patients, COVID-19 was detected before tuberculosis, which could be secondary to the potential contribution of COVID-19 towards the progression of the latent disease to active tuberculosis. In (n=7) patients, COVID-19 was detected with post tuberculosis sequelae. They recommended further studies with a larger sample

size to comprehend the impact of prior pulmonary tuberculosis on COVID-19.[28]

To the best of our knowledge, this is the first study to evaluate the association between prior pulmonary tuberculosis and COVID-19. The results reported here are from the province of Sindh, which is regarded as the centre of the tuberculosis epidemic in Pakistan. Considering the high tuberculosis burden of this region, we expected to encounter more patients of COVID-19 with active or prior pulmonary tuberculosis on HRCT scans. On the contrary, we found prior tuberculosis in 4.9% (n=26) scans in the "COVID-19 group" which is almost half the number of cases reported before the arrival of the pandemic, i.e., 9.8% (n=75) (*p*-value 0.001). Moreover, there were no cases of active tuberculosis in the "COVID-19 group" which strongly rejects the commonly created hype of increased susceptibility of COVID-19 in patients of tuberculosis. The results of our study are comparable to the epidemiological analysis of the initial 100 deaths of RT-PCR confirmed COVID-19 cases in Pakistan conducted by Chaudhry *et al*. They reported a combined history of tuberculosis and chronic obstructive pulmonary disease in only 3% deceased patients.[26] On the other side, these results may also suggest a possible protective impact of prior pulmonary tuberculosis in the current pandemic. This plausible protection could be due to developed antibodies from previous exposure to the disease or vaccination. Additionally, there could be an additive effect of BCG vaccination and prior tuberculosis exposure on the overall less severity of the current pandemic in Pakistan.

Our study reflects the initial stages of the pandemic, and longitudinal observations will be required to evaluate the relationship between COVID-19 and tuberculosis. Additionally, an amalgamation of multiple factors could be responsible for relatively less severity of this pandemic in our country. These may be a higher mean local temperature at the time of onset of the epidemic, more occurrence of disease in young adults, and high prevalence of other infectious diseases, such as malaria, dengue, rubella, and measles. These diseases and the vaccinations and medications administered to fight them may enhance the non-specific immunity or prevent the reproduction or function of SARS-CoV-2.

We accept the limitations of our study, such as small sample size and lack of proper follow-up due to patient isolation and nationwide lockdown. Similarly, we did not induct known cases of pulmonary tuberculosis. Instead, we evaluated the HRCT scans of diagnosed or suspected COVID-19 patients to establish its association with prior pulmonary tuberculosis. Nevertheless, considering the probable public-health benefits, our results indicate that this hypothesis warrants further consideration and should not be overlooked. If the exposure to tuberculosis, whether through vaccination or disease, produces a protective effect against COVID-19, it could have a significant impact in our fight against the current pandemic.

CONCLUSION

Prior pulmonary tuberculosis might have a protective effect against COVID-19 pneumonia which could be due to developed antibodies secondary to previous exposure to the mycobacterium or BCG vaccination. Considering the possible public-health benefits, our results warrant further consideration as they can significantly impact our fight against the COVID-19 pandemic.

Ethical considerations: Patients were not directly involved therefore informed written consent was not obtained.

Conflict of interest: All authors declare no competing interests.

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AUTHORS' CONTRIBUTION

NA, SH: Study conceptand design. NA, SH, MAM: Literature search. NA, MAM: Data collection. SH, NA, MAM: Drafting of the manuscript. NA, SH: Statistical analysis. NA, SH, MAM: Analysis and interpretation of data, Critical revision of manuscript and final approval.

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