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Original Article

Radiology Section

Association between Chest CT Severity Scores and SARS-CoV-2 Vaccination among COVID-19 Patients: A Cross-sectional Study from Pune, India

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ABSTRACT

Introduction: The novel Coronavirus disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is seen to primarily affect the human respiratory system. Chest CT Severity Score (CTSS) provides a semi-quantitative assessment of pulmonary involvement in COVID-19 patients. COVID-19 pandemic mitigation measures such as SARS-CoV-2 vaccination are being deployed worldwide. However, with the emerging variants of concern of SARS-CoV-2, a high prevalence of post vaccination breakthrough infections is seen.

Aim: To assess the association of CTSS with the vaccination status in a cohort of COVID-19 patients referred to a tertiary diagnostic centre and to evaluate the association of CTSS with other clinical parameters including co-morbidities in these patients.

Materials and Methods: This cross-sectional observational study was conducted at a tertiary care diagnostic imaging centre in the city of Pune, Maharashtra, India. Data of 1002 symptomatic, adult patients who underwent chest CT and SARS-CoV-2 Reverse Transcription Polymerase Chain Reaction (RT-PCR)/ Rapid Antigen Test (RAT) laboratory test between March 13, 2021 and June 22, 2021, were collected. COVID-19 Reporting and Data System (CO-RADS) categories and the corresponding semi-quantitative CTSS were calculated for each patient. Based on their vaccination status, patients were categorised into three groups: unvaccinated, partially vaccinated and fully vaccinated. The association of CTSS with various categories of vaccination status, demographics, co-morbidities and stages of the disease of the patients, was evaluated.

Results: Of the 1002 COVID-19 patients, 768 (76.6%) were unvaccinated, 190 (19.0%) were partially vaccinated and 44 (4.4%) were fully vaccinated. Mean CTSS in the fully vaccinated cohort was significantly lower (3.75±4.7) than that in the partially vaccinated (6.05±5.7) and unvaccinated (8.29±4.9) patients (mean 3.75 vs. 6.05 vs. 8.29, respectively; ($p<0.05$). Mean CTSS in patients with no co-morbidities was significantly lower than that in patients with hypertension and diabetes (7.12 vs. 8.75 vs. 10.39, respectively; ($p<0.05$).

Conclusion: Significant association was noted between the Chest CTSS and the vaccination status, age, gender, co-morbidities and stage of disease in this large cohort of COVID-19 patients. The study reiterates that full vaccination aids in reducing the severity of lung involvement in COVID-19 infection.

Keywords: Computed tomography, Coronavirus disease-2019, Diagnostic imaging, Immunisation, Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

High Resolution Computed Tomography (HRCT) of the chest plays a pivotal role in assessing the severity of lung involvement in novel Coronavirus disease-2019 (COVID-19) infection [1-3]. The COVID-19 Reporting and Data System (CO-RADS) and the corresponding CT Severity Score (CTSS) introduced by Radiological Society of the Netherlands provide a semi-quantitative assessment of virus induced pulmonary involvement [4,5].

Mass vaccination is considered to be an important tool for COVID-19 disease prevention. India's COVID-19 vaccination program was expanded to include all citizens ≥18 years of age, even as the country witnessed a massive surge in infections during the 2nd wave of the pandemic [6]. The ChAdOx1n CoV-19/Covishield and BBV152/Covaxin are the two vaccines approved for emergency use in India [7]. However, vaccines do not confer complete immunity against the viral disease and vaccine breakthrough infections are being reported [8,9].

Studies have reported that chest CTSS correlates with the extent of lung damage in COVID-19 patients and therefore, may be used as a novel indirect indicator of vaccine effectiveness in the real world settings [2,3,10]. Studies comparing the chest CTSS and vaccination status among Indian patients with COVID-19 infection are scarce (one of these studies was a preprint at the time of writing this paper) [11-13].

On this background, the present study aimed to assess the association between chest CTSS and vaccination status in a cohort of Indian patients with COVID-19 infection. The secondary objective of this study was to assess the correlation between CTSS and the clinical parameters including co-morbidities in these patients.

MATERIALS AND METHODS

This cross-sectional, observational study was conducted at the imaging clinics of a tertiary diagnostic centre, in Pune, Maharashtra, India, between March 13, 2021 and June 22, 2021. This tertiary care diagnostic imaging centre receives referrals from various parts of Pune district. The study was approved by Institutional Ethics Committee (ECR/311/INST/MH/2013/RR-19) and informed consent was obtained from all the patients.

Sample size calculation: Optimum sample size for the study was estimated using the formula: $N=(1.96)^2\ PQ/L^2$. Where, N=Sample size, 1.96=Standard normal deviate set corresponding to 95% confidence interval (CI), P=Percentage of vaccinated population in

Pune district till June 2021, Q=100-P and L=Permissible error in estimation i.e., 10% of P.

Percentage of vaccinated population in Pune district till June 2021 (P), was calculated using the formula: P=total number of SARS-CoV-2 vaccinations done in Pune district till June 2021 i.e., 32, 17, 978 persons×100/total population of Pune district i.e.,1,00,89,916 persons, estimated in accordance with the Aadhaar uidai.gov.in December 2020 data [14-16]. Thus, the sample size calculated for this study was 820 patients [Table/Fig-1]. Taking into consideration the possible loss to follow-up of 20 % in an urban setting, the estimated optimum sample size for this study was further increased to 984 patients [Table/Fig-1]. The present study therefore included 1002 patients with COVID-19 infection.

P (%)	Q=100-P	L=10% of P	N=(1.96)² PQ/L²	Loss to follow-up=20% of N	Optimum sample size=N+Loss to follow-up
31.9	68.1	3.19	820=(1.96)²×31.9×68.1/(3.19)²	164	984 =820+164

[Table/Fig-1]: Optimum sample size calculation using the formula: N=(1.96)² PQ/L².
P: Percentage of vaccinated population in Pune district till June 2021; Q: 100-P; L: Permissible error in estimation i.e., 10% of P; N: Sample size; 1.96: Standard normal deviate set corresponding to 95% confidence interval

Inclusion criteria:

- Age ≥18 years;
- Patients suspected to have symptoms of COVID-19 infection;
- Patients who were referred for HRCT chest between March 2021 and June 2021;
- Patients with a positive SARS-CoV-2 Reverse Transcription Polymerase Chain Reaction (RT-PCR)/Rapid Antigen Test (RAT).

Exclusion criteria: Pregnant women, patients <18 years of age and patients with a negative RT-PCR/RAT test were excluded from the study.

Study Procedure

Data collection: Clinical data, laboratory data (SARS-CoV-2 RT-PCR/RAT tests) and vaccination data of the study patients were collected from electronic medical records, patient's clinical history sheets, and from telephonic interviews. Clinical information collected from all study patients included: age, gender, co-morbidities and stage of illness based on the time interval between onset of symptoms and acquisition of chest HRCT scan.

Chest HRCT evaluation: As a standard of practice, non contrast chest HRCT scans of the COVID-19 patients were performed on a multidetector CT scanner (Philips Ingenuity 128 Slice CT; Philips Healthcare, Amsterdam, Netherlands and GE 32 Slice; GE Healthcare, Waukesha, USA) with the patient in supine position, during end inspiration. Scanning parameters were in line with the manufacturer's standard recommendations for a routine thorax scan. All CT images were reconstructed to thin slices using the Multiplanar Reformatting (MPR) technique. Appropriate infection prevention and control measures were arranged for the CT technologists and the patients.

The HRCT images of the COVID-19 patients were independently examined on standardised workstations, by two radiologists with 15 years' experience in reporting chest CT images. These radiologists were blinded to the vaccination as well as co-morbidity status of the study patients. Chest CT scores for the first 30 study patients were recorded by the two radiologists independently. Intra Class Correlation (ICC), which is a useful statistic for estimating Inter-Rater Reliability (IRR), was calculated for these reads. The ICC for the initial 30 chest HRCT reads were found to be 0.997 with average measures (p-value=0.0001) and the estimated IRR was 99.7% [Table/Fig-2]. Hence,the chest HRCT scans of the remaining study patients, were randomly assigned to the two experienced radiologists for independent interpretation and scoring of the HRCT images.

Variables	Intra Class Correlation (ICC)ᵃ	95% Confidence interval		p-value
		Lower bound	Upper bound	
Single measure	0.995ᵇ	0.990	0.998	0.0001
Average measure	0.997ᶜ	0.995	0.999	0.0001

[Table/Fig-2]: Calculation of Intraclass correlation coefficient (ICC) for the first 30 study patients.
Two way mixed effects model where people effects are random and measures effects are fixed.
a. Type C intraclass correlation coefficients using a consistency definition the between measure variance is excluded from the denominator variance
b. The estimator is the same, whether the interaction effect is present or not
c. This estimate is computed assuming that the interaction effect is absent, as it is not estimable otherwise

Chest CT images of these patients were evaluated using the standard, international nomenclature based on COVID-19 Reporting and Data System (CO-RADS) [Table/Fig-3a] [4]. Further, in patients with characteristic findings of COVID-19 lung involvement, a semi-quantitative CT severity scoring was performed; using the scoring system which depends on the visual assessment of the extent of anatomic involvement (on a scale from 0-5) of each of the 5 lobes of the lungs [Table/Fig-3b] [17]. The total CTSS is the sum of the individual lobar scores and it ranges from 0=no involvement to 25 maximum involvement [17]. Based on the total CTSS, the severity of lung involvement in the patients was further graded into mild (CTSS of 0-8), moderate (CTSS of 9-15) and severe (CTSS of 16-25) categories. Thereafter, CT scans were further categorised into five stages based on the duration of time interval between initial symptoms' onset and performance of chest HRCT [Table/Fig-3c] [18].

a) CO-RADS categories and the corresponding level of suspicion for pulmonary involvement in COVID-19, as assessed on chest HRCT scans [4]

CO-RADS category	Level of suspicion for pulmonary involvement in COVID-19	CT features
0	Not interpretable	Technically insufficient scan
1	Very Low	Normal/Non infectious
2	Low	Typical for infections other than COVID-19
3	Equivocal/Indeterminate	Suggesting COVID-19, but may be seen in some other diseases as well
4	High	Imaging abnormalities suspicious for COVID-19
5	Very high	Characteristically seen in COVID-19
6	Proven (SARS-CoV-2 RT-PCR positive)	-

b) Score of individual lobes of lungs on chest HRCT [17]

Individual lobar score	Percentage of involvement of a lobe of lung
0	No involvement
1	<5%
2	5-25%
3	26-49%
4	50-75%
5	>75%

c) Stages of lung involvement on chest HRCT based on the duration of time interval between initial symptoms' onset and performance of the CT scan [18]

Stages	Number of days between initial symptoms' onset and performance of chest HRCT
Stage-1	0-4 days
Stage-2	5-9 days
Stage-3	10-14 days
Stage-4	15-21 days
Stage-5	>21 days

[Table/Fig-3 a-c]: Various classifications and scores used for categorisation of chest HRCT scans of study patients.
CO-RADS: COVID-19 reporting and data system; COVID-19: Coronavirus disease 2019; HRCT: High resolution computed tomography; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RT-PCR: Reverse transcription polymerase chain reaction

Vaccination status: The study patients were categorised into the following three groups, based upon their vaccination status at the time of a positive laboratory confirmation of COVID-19 infection.

1) **Unvaccinated** (never received a COVID-19 vaccine dose);
2) **Partially vaccinated** (received one dose of a two dose vaccine series, or <14 days elapsed after the 2nd dose);
3) **Fully vaccinated** (received two doses of a two dose vaccine series and ≥14 days elapsed since the second dose).

STATISTICAL ANALYSIS

Statistical analysis of the data was perfomed using Epi info software. Descriptive statistics of patient's demographics and clinical results were reported as numbers (n) and percentages (%). Quantitative continuous variables were presented as mean±standard deviation. Analysis of Variance (ANOVA) test was applied to assess the significance of association between mean CTSS and various categories of vaccination status and clinical parameters of the study participants. Kruskal-Wallis test was used for confirmation of results of multiple comparisons. The differences in grades of chest CTSS between the various categories of patients based on their demographic, co-morbidity and vaccination status and stage of disease; were examined using Chi-square (χ^2) test. Multivariate linear regression analysis was used to determine the association of CTSS with the vaccination status (unvaccinated or vaccinated), co-morbidity status (presence or absence of co-morbidity) and stages of disease on CT. For all the statistical tests; p-value <0.05 was considered statistically significant.

RESULTS

Mean age of the 1002 patients enrolled for the study was 49.0 years±15.6 years and men constituted 64.4% of the study population. Study patients were classified into three age group categories based on the prioritisation of vaccination among the Indian population as per the directives of National Expert Group on Vaccine Administration for COVID-19 (NEGVAC) [6].

Co-morbidity data was available in 949/1002 patients. Amongst these, 249 (26.2%) patients had some co-morbidities: either hypertension or Diabetes Mellitus (DM), or a combination of both DM and hypertension, which depicts the baseline demographic and clinical characteristics of the patients [Table/Fig-4].

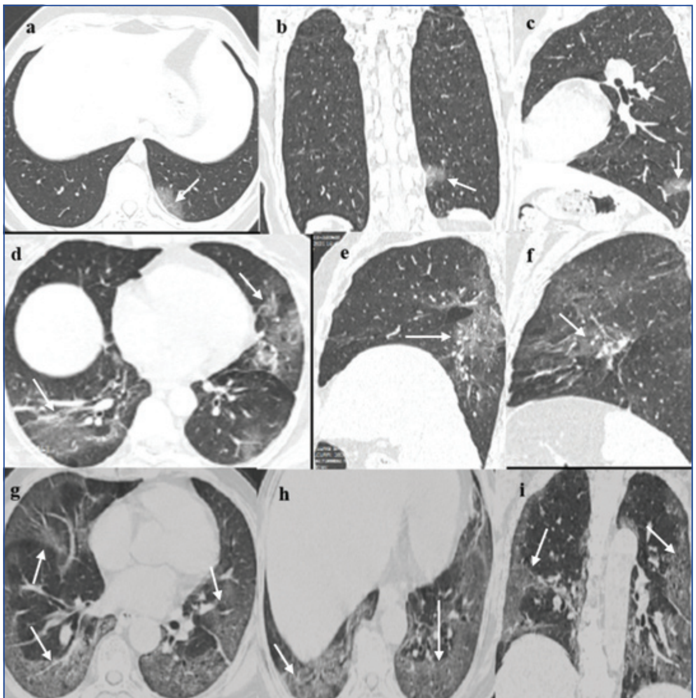
Characteristics	Number of patients, n (%)
Total number of study patients	1002 (100)
Age in years	
Mean±standard deviation* (Range)	49.0 years±15.6 (18-90)
Age group (years) classified into three groups	
18-44	416 (41.6)
45-59	299 (29.8)
≥60	287 (28.6)
Gender	
Male	645 (64.4)
Female	357 (35.6)
Co-morbid conditions (949/1002 patients)	
No co-morbidities	700 (73.8)
Diabetes Mellitus (DM)	80 (8.4)
Hypertension	99 (10.4)
DM+Hypertension (DM+HTN)	70 (7.4)

[Table/Fig-4]: Demographic and clinical characteristics of the patient cohort.
*All data are expressed as numbers (percentage) or mean±standard deviation

Out of the 1002 patients, 768 (76.6%) were unvaccinated. Details of the categorisation of the study cohort depending on their CTSS, stage of lung involvement on CT and vaccination status are presented in [Table/Fig-5]. Various grades of severity of lung involvement seen on the chest HRCT images of the study patients with COVID-19 infection are illustrated in [Table/Fig-6]. Breakthrough infections (defined as SARS-CoV-2 infections occurring ≥14 days after completing the second dose of a two dose COVID-19 vaccination series); occurred in 44 (4.4%) patients.

Categories of study patients	Number of patients, n (%)
CTSS categories (n=1002)	
Mild (CTSS of 0-8)	590 (58.9)
Moderate (CTSS of 9-15)	315 (31.4)
Severe (CTSS of 16-25)	97 (9.7)
Staging of lung involvement on CT scan * (n=1002)	
Stage 1 (0-4 days)	251 (25.0)
Stage 2 (5-9 days)	678 (67.7)
Stage 3 (10-14 days)	51 (5.1)
Stage 4 (15-21 days)	15 (1.5)
Stage 5 (>21 days)	7 (0.7)
Vaccination status (n=1002)	
Unvaccinated	768 (76.6)
Partially vaccinated†	190 (19.0)
Fully vaccinated‡	44 (4.4)
Type of vaccine received (n=234)	
ChAdOx1 nCoV- 19 /Covishield	207 (88.5)
BBV152/Covaxin	27 (11.5)
Doses of vaccine received (n=234)	
1st dose	178 (76.1)
2nd dose	56 (23.9)

[Table/Fig-5]: Details of patient categorisation based on their chest CTSS, CT stage of disease and vaccination status.
*Staging of lung involvement on CT scan based on time interval between initial symptom's onset and CT scan acquisition. †Received 1st dose of a two dose vaccine series, or <14 days elapsed after the 2nd dose
‡Received two doses of a two dose vaccine series and ≥14 days elapsed since the second dose; CTSS: CT severity score



[Table/Fig-6]: Chest HRCT imaging features in study patients with COVID-19 infection: Axial (a), coronal (b) and sagittal (c) thin sections of unenhanced HRCT chest demonstrate mild sub pleural ground glass opacity (GGO) (indicated by white arrows), involving the left lower lobe in a patient with mild CTSS of 2. Bilateral, patchy, peripheral and peri broncho vascular, multi lobe GGOs (white arrows), seen on the axial (d) and sagittal sections of the right (e) and left lung (f) in another patient with moderate CTSS of 12. Axial (g,h) and coronal (i) CT sections show bilateral, diffuse areas of crazy paving pattern and peripheral consolidations in the middle and lower lobes (white arrows) of a patient with severe CTSS of 17.

Association of CTSS with age groups and gender: The study results showed significant difference in the mean CTSS when all the age group categories in the study population were compared together (p<0.01). Mean CTSS of the persons ≥60 years of age was higher than that of persons in the 45-59 years age group and 18-44 years age group (Mean CTSS 9.34 vs. 8.35 vs. 6.00, respectively) [Table/Fig-7a]. Similarly, significant difference was observed in the grades of chest CTSS of patients depending upon their age group categories. As depicted in [Table/Fig-7b], moderate as well as severe grades of CTSS were increasingly seen in the 45-59 years and ≥60 years age group categories.

a) Age group of patients in years	Mean CTSS±SD	Number of patients (N)
18-44	6.00±5.177	416
45-59	8.35±5.511	299
≥ 60	9.34±5.801	287
Total	7.66±5.645	1002

p=0.0001 (p<0.01) by ANOVA test and Kruskal-Wallis Test (applied to confirm the results by ANOVA)

b) Grades of CTSS based on severity of lung involvement	Number (n) and percentage (%) of patients in different age group categories (in years)			Total
Variables	18-44 years n (%)	45-59 years n (%)	≥ 60 years n (%)	n (%)
Mild (0-8)	300 (72.1)	165 (55.2)	125 (43.6)	590 (58.9)
Moderate (9-15)	96 (23.1)	97 (32.4)	122 (42.5)	315 (31.4)
Severe (16-25)	20 (4.8)	37 (12.4)	40 (13.9)	97 (9.7)
Total	416 (100.0)	299 (100.0)	287 (100.0)	1002 (100.0)

p=0.0001 (p<0.01) by Chi-square test

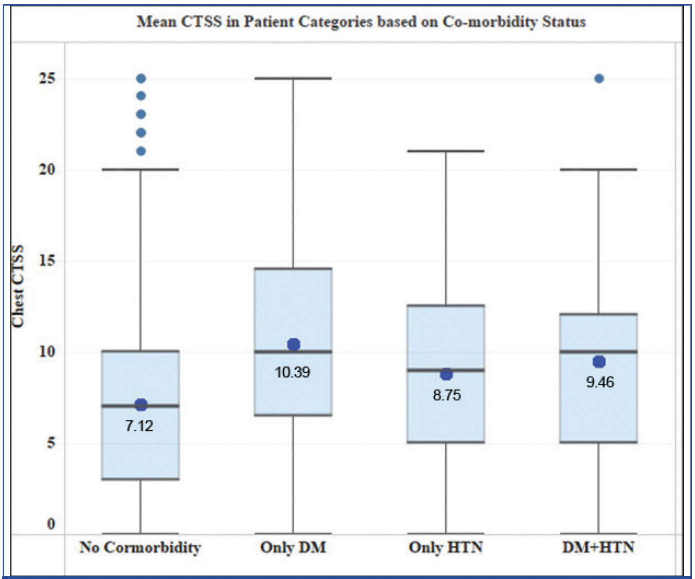
[Table/Fig-7]: Comparison of Mean CTSS (a) and grades of CTSS (b) amongst different age group categories of patients.

The mean CTSS in male patients was significantly higher than that in the female patients (Mean CTSS 8.0 vs. 7.05 respectively) (p=0.01, p<0.05). Mild grade of CTSS was seen in greater percentage of female patients (64.1%); as compared to male patients (56%). Significant difference was detected in the grades of CTSS when compared together, based on the gender of study participants (p=0.027, p<0.05).

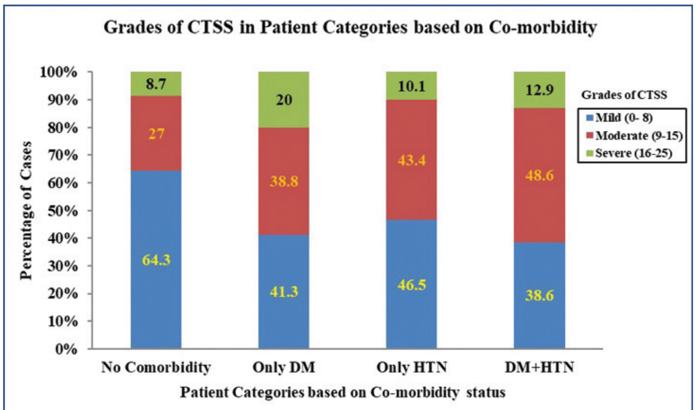
Association of CTSS with co-morbidities: Mean CTSS in patients with no co-morbidity was significantly lower than that in patients with comorbidities such as hypertension alone, hypertension with diabetes mellitus and diabetes alone (7.12 vs. 8.75 vs. 9.46. vs. 10.39, respectively (p<0.05) [Table/Fig-8]. Mild CTSS was seen in majority of the patients (64.3%) with no co-morbidities; whereas, highest percentage of cases (20%) with severe CTSS were seen in patients with diabetes mellitus [Table/Fig-9]. Significant difference was seen in the mean CTSS as well as in the grades of CTSS, when all groups were compared together, based on their co-morbidity status (p<0.01).

Association of CTSS with vaccination status: Majority of the vaccinated persons in the study cohort belonged to >60 years and 45-59 years age group. Breakthrough infections were identified in 44 (4.4%) of the vaccinated cohort. When multiple comparisons were made, mean CTSS was significantly higher in the unvaccinated cohort (mean±SD:8.29±4.9) versus the partially vaccinated patients (mean±SD:6.05±5.7) versus the fully vaccinated patients (mean±SD:3.75±4.7) (p<0.01) [Table/Fig-10]. The difference in mean CTSS between the partially vaccinated and fully vaccinated groups was also found to be significant (p=0.035, p<0.05).

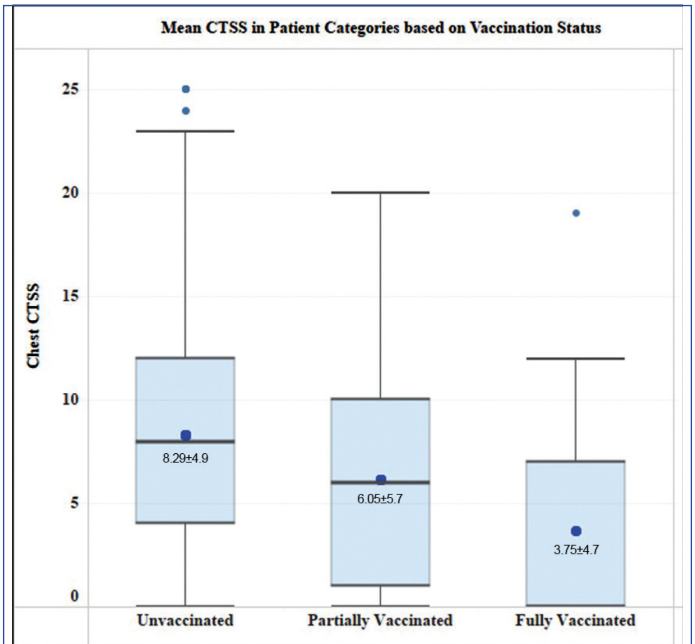
The percentage distribution of mild, moderate and severe grades of CTSS amongst the unvaccinated, partially vaccinated and fully vaccinated groups of patients is illustrated in [Table/Fig-11]. Majority of the fully vaccinated patients (86.4%) demonstrated mild CTSS; whereas highest percentage of severe CTSS (11.5%) was reported in the unvaccinated patient group. This difference in the grades of



[Table/Fig-8]: Box plots showing comparison of Mean chest CTSS between patient categories based on co-morbidity status.
Blue dot within the box: Mean CTSS, Blue dots outside the box: Outliers, Black horizontal line within the box: Median CTSS.
DM: Diabetes mellitus; HTN: Hypertension; DM+HTN: Diabetes mellitus+Hypertension

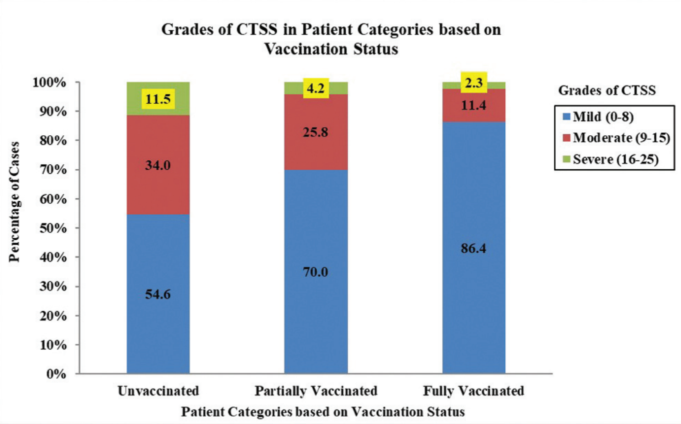


[Table/Fig-9]: Stacked column chart showing percentage distribution of grades of chest CTSS in patient categories based on co-morbidity status.
DM: Diabetes mellitus; HTN: Hypertension; DM+HTN: Diabetes mellitus+Hypertension



[Table/Fig-10]: Box plots showing comparison of Mean CTSS between patient categories based on vaccination status.
Blue dot within the box: Mean CTSS, Blue dots outside the box: Outliers, Black horizontal line within the box: Median CTSS

CTSS observed in the different patient categories depending on their vaccination status, was statistically significant (p<0.01).



[Table/Fig-11]: Stacked column chart showing percentage distribution of grades of chest CTSS in patient categories based on vaccination status.

Association of CTSS with the two types of COVID-19 vaccines: Amongst the vaccinated cohort, 207 (88.5%) patients had received Covishield and 27 (11.5%) persons had received Covaxin. The difference between mean CTSS of patients who had received Covishield (Mean±SD:5.61±4.9) and that of patients who had received Covaxin (Mean±SD: 5.67±4.6); was statistically insignificant (p=0.954, p>0.05).

Association of CTSS with stage of lung involvement on CT: Statistically significant difference was noted in the mean CTSS among the five stages of lung involvement on CT based on the period between onset of symptoms and acquisition of CT scan (p<0.01), [Table/Fig-12].

Stages of lung involvement on CT based on the period between onset of symptoms and CT scan	Mean CTSS±SD	Number of patients
Stage 1 (0-4 days interval)	4.16±3.879	251
Stage 2 (5-9 days interval)	8.45±5.302	678
Stage 3 (10-14 days interval)	11.16±7.640	51
Stage 4 (15-21 days interval)	13.27±5.849	15
Stage 5 (>21days)	19.86±3.436	7
Total	7.66±5.645	1002

[Table/Fig-12]: Comparison of mean CTSS among stages of lung involvement on CT based on the period between symptom' onset and CT scan acquisition.
p=0.0001 (p<0.01) by ANOVA test and Kruskal-Wallis Test (applied to confirm the results obtained by ANOVA)

Further, occurrence of mild grade of CTSS in majority (89.3%) of the patients belonging to the fully vaccinated cohort with no co-morbidity, was demonstrated in the two-way cross tables. None (0%) of these patients recorded severe CTSS. On the contrary, a large percentage of unvaccinated patients with co-morbidity; demonstrated either moderate or severe CTSS [Table/Fig-13].

Co-morbidity status	Vaccination status	Grades of CTSS Number (N) and percentage (%) of patients			Total number of patients N=949* (100.0%)
		Mild (0-8) N=556, (58.6%)	Moderate (9-15) N=297, (31.3%)	Severe (16-25) N=96, (10.1%)	
No Co-morbidity	Unvaccinated	337 (60.6)	162 (29.1)	57 (10.3)	556 (100.0)
	Partially vaccinated	88 (75.9)	24 (20.7)	4 (3.4)	116 (100.0)
	Fully vaccinated	25 (89.3)	3 (10.7)	0	28 (100.0)
	Total	450 (64.3)	189 (27.0)	61 (8.7)	700 (100.0)
Only DM	Unvaccinated	15 (26.8)	27 (48.2)	14 (25.0)	56 (100.0)
	Partially vaccinated	14 (70.0)	4 (20.0)	2 (10.0)	20 (100.0)
	Fully vaccinated	4 (100.0)	0	0	4 (100.0)
	Total	33 (41.3)	31 (38.8)	16 (20.0)	80 (100.0)
Only HTN	Unvaccinated	21 (32.8)	35 (54.7)	8 (12.5)	64 (100.0)
	Partially vaccinated	20 (66.7)	8 (26.7)	2 (6.7)	30 (100.0)
	Fully vaccinated	5 (100.0)	0	0	5 (100.0)
	Total	46 (46.5)	43 (43.4)	10 (10.1)	99 (100.0)
DM+HTN	Unvaccinated	12 (30.8)	19 (48.7)	8 (10.1)	39 (100.0)
	Partially vaccinated	11 (45.8)	13(54.2)	0	24 (100.0)
	Fully vaccinated	4 (57.1)	2 (28.6)	1(14.3)	7 (100.0)
	Total	27 (38.6)	34 (48.6)	9 (12.9)	70 (100.0)

[Table/Fig-13]: Co-morbidity* Vaccination status * Grades of CTSS- two way cross tabulation.
CTSS: CT severity scores; DM: Diabetes mellitus; HTN: Hypertension
*N=949 as Co-morbidity data was available for 949 out of 1002 study patients

Taking into account, the confounding effect of all the included independent variables, multivariate linear regression analysis showed that presence of co-morbidity and higher stage of disease were associated with higher CTSS; whereas partially/fully vaccinated patients recorded lower CTSS when compared with unvaccinated patients (adjusted R^2 is 0.230) [Table/Fig-14].

R	R^2	Adjusted R^2	Standard error of the estimate	Change statistics				
				R^2 change	F change	df1	df2	Significant F change
0.482c	0.232*	0.230	4.999	0.039	47.875	1	945	0.0001

	Unstandardised coefficients		Standardised coefficients	t statistic	Significance
	B	Standard error	β (Beta)		
(Constant)	1.439	0.527		2.731	0.006
Stages of lung involvement based on duration of symptoms	3.367	0.257	0.376	13.089	0.0001
Vaccination status	-2.705	0.384	-0.205	-7.046	0.0001
Co-morbidity status	2.589	0.374	0.200	6.919	0.0001

[Table/Fig-14]: Multivariate regression analysis: with CTSS as a dependent variable and patient related factors such as 1) stages of lung involvement on CT based on duration of symptoms, 2) vaccination status and 3) co-morbidity status, as independent variables.
R^2: Coefficient of determination; F: F statistics; df: degrees of freedom; B: Unstandardised regression coefficient. β: Standardised regression coefficient
*R^2 is 0.232 i.e., 23.2% variation in CTSS is explained by the 3 factors: 1) stage of disease on CT chest based on symptom's duration, 2) vaccination status and 3) co-morbidity status of patients. This variation is significant with p=0.0001

DISCUSSION

In the course of evolution of the COVID-19 global pandemic, several studies have shown that various patient related factors such as age, gender, duration of symptoms, along with the number and type of co-morbidities; influence the clinical severity and outcomes of patients with COVID-19 infections [3,17-22]. Scientific literature till date has demonstrated the correlation between the clinical severity of COVID-19 disease and chest CTSS in COVID-19 patients [1-3,23-25].

Further, National SARS CoV-2 vaccination drive is underway in India as part of the global efforts to abate the onslaught of the pandemic [6]. Even so, post vaccination breakthrough infections, mainly attributable to the emergence of new variants of SARS-CoV-2 virus; are being reported all over the world, as well as in India [8,9,26,27].

In these settings, the present study assessed the association between CTSS and vaccination status in RT-PCR/RAT confirmed, symptomatic COVID-19 patients, during the second wave of the pandemic in India. The association between CTSS and clinical parameters of these patients were also investigated. Results of this study demonstrated that patients with partial and full vaccination record significantly lower mean CTSS and also report lower percentage of patients with severe grade of CTSS; when compared with the unvaccinated patient population [Table/Fig-10,11]. These results corroborated with those of previously conducted, similar Indian studies comparing chest CTSS amongst the unvaccinated and vaccinated COVID-19 patients (one of these studies was a preprint at the time of writing this paper) [11-13]. In comparison with these studies, the present study included a larger cohort of patients.

In the present study, majority (86.4%) of the fully vaccinated patients with breakthrough infections, demonstrated mild CTSS and only 1 patient (2.3%) recorded severe CTSS. In line with previous literature reports, this data also illustrated that majority of the patients with post vaccination breakthrough infections suffer from mild disease [11-13,26,27]. All of the above mentioned results in the present study can be ascribed to the effectiveness of vaccines in preventing severe COVID-19 disease.

Patients of different age groups in the Indian population are receiving vaccines in a phased manner, as prioritisation of vaccination to the elderly population at an increased risk for developing severe COVID-19 infection; is crucial [6]. Therefore, the younger age group (18-44 years) made a sizeable contribution to the unvaccinated category (91.1%) in the current study cohort. Similar to the observations reported by previous studies, this study recorded a higher mean CTSS along with a greater percentage of patients with severe CTSS, in the middle aged (45-59 years) and elderly (>60 years) population [3,19]. One reason for this observation could be the stage of the pandemic when this study was conducted and another possible reason may be that COVID-19 infection elicits a stronger inflammatory response in the elderly population since they are more likely to have concomitant co-morbidities [19].

Higher mean CTSS and greater percentage of cases with moderate and severe grades of CTSS were seen in the male population in this study. Saeed GA et al., and Jin J-M et al., have reported in their respective studies that, men are at a higher risk of severe COVID-19 disease as compared to women and our results support their observation [3,20].

As expected, the authors of the present study found a significantly higher mean CTSS in patients with one or more co-morbidities, when compared with patients with no co-morbidities [Table/Fig-8] [21]. Also, severe CTSS was more commonly recorded in the patients with diabetes mellitus alone followed by patients with both DM and hypertension; further followed by those with hypertension alone [Table/Fig-9] [22]. Overall, these findings are in agreement with the existing literature reports that have documented the impact of co-morbidities on clinical outcomes of patients with COVID-19 [21,22]. In the current study cohort of breakthrough infections, the fully vaccinated patient with severe CTSS was 75 years of age and had co-morbidities such as diabetes and hypertension.

Pan F et al., and Ding X et al., in their respective studies found that the chest CT features and CT scores of patients with COVID-19, changed with duration of symptoms [17,18]. Consistent with these studies, the present study reported significantly lower mean CTSS and milder grades of CT scores in patients in the early stages of the disease. The mean CT scores were seen to progressively increase from stage 1 to stage 5.

Limitation(s)

The study cohort did not include asymptomatic and RT-PCR false negative persons; who are likely to promote spread of COVID-19 infection. Another limitation was self reporting and under reporting of co-morbidities in some of the enrolled patients. Data on obesity, ischaemic heart disease, chronic renal disease and prior lung disease was not available. Details about the clinical categorisation and treatment received by the study patients were also not available. Follow-up chest CT scans were performed in some patients on the basis of clinical indication. However, such serial chest CT scans were not included in the study analysis. Further multicentric studies involving larger groups of COVID-19 patients are recommended to validate the results of this study and to evaluate the impact of SARS-CoV-2 vaccination on the overall patient outcomes.

CONCLUSION(S)

Significant association between the chest CTSS and the vaccination status, age, gender, co-morbidities and stage of disease was seen, in this large cohort of COVID-19 patients from a tertiary care diagnostic centre in Pune, Maharashtra, India. This study conducted in real world settings, reiterates that full vaccination aids in reducing the severity of lung damage in COVID-19 infections. It therefore, underscores the role played by vaccines in curbing the current COVID-19 pandemic.

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