

Original Article

CT Severity Radiological Phenotypes (CTS) Assessment in COVID-19 Pneumonia as 'Inconsistent Predictor of Disease Severity': A Large Tertiary Care Center Study in India

Shital Patil¹, Pravin Bhagat², Rajesh Bobade³, Uttareshvar Dhumal⁴, Laxman Kasture⁵, Gajanan Gondhali⁶

Abstract:

Introduction: Radiological phenotypes are radiological patterns or observable characteristics of COVID-19 pneumonia. Various phenotypic classifications have been reported in literature. CT severity radiological phenotypes are widely used and universally accepted radiological phenotypic methods. Robust data is available regarding role of HRCT in COVID-19 pneumonia and we have evaluated role of CT severity in assessing natural course of COVID-19 illness during its evolution and follow-up.

Methods: Prospective, Observational study, included 3000 COVID-19 RT-PCR confirmed cases with lung involvement documented and radiological severity phenotypes categorized on HRCT thorax as mild, moderate and severe as per lung segment involvement bilaterally (scoring tool 0-25 score, mild 1-7, moderate 8-15 and severe 16-25). Radiological CT severity phenotypes were evaluated in correlation with interventions such as oxygen support and oxygen plus ventilatory support requirement during hospitalization. Age, gender, comorbidity, laboratory parameters and use of BIPAP/NIV in COVID-19 cases and outcome as with or without lung fibrosis were key observations. Final radiological outcome documented in follow up CT thorax imaging done at six months of discharge from hospital. Statistical analysis is done by using Chi square test.

Results: In study of 3000 cases, 'mild, moderate and severe' radiological CT severity phenotypes were documented as 13.33%, 48.33% & 38.34 % respectively. CT severity has documented significant association with duration of illness at entry point [$p < 0.00001$] Duration of illness (<7 days, 7-14 days and >14 days) plays a crucial role in predicting radiological CT severity phenotypes. CT severity has documented significant association with laboratory parameters at entry point (d-dimer, CRP, IL-6) [$p < 0.00001$] and interventions required in indoor unit. [$p < 0.00001$] Post COVID-19 lung fibrosis or sequelae has significant association with radiological CT severity phenotypes. [$p < 0.00001$] Covariates such as age, gender, diabetes mellitus, IHD, Hypertension, COPD, Obesity has significant association with radiological CT severity phenotypes. [$p < 0.00001$]

Conclusion: Radiological CT severity phenotypic differentiation has documented very crucial role in initial assessment and during triaging of these cases in indoor and outdoor setting. Although CT severity is best predictor of severity it has showed 'inconstancy' in predicting disease severity, targeting interventions and predicting early and long-term outcomes in COVID-19 pneumonia.

Key words: COVID-19 pneumonia, Radiological phenotypes, CT severity, post covid lung fibrosis, Inflammatory marker

DOI: <https://doi.org/10.3329/jom.v25i1.70528>

Copyright: © 2024 Patil S. This is an open access article published under the Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not changed in any way and it is not used for commercial purposes.

Received: 4.4.23;

Accepted: 8.11.23

-
1. Professor, Pulmonary Medicine, MIMSR Medical College, Latur India
 2. Assistant Professor, Internal Medicine, MIMSR Medical College, Latur India
 3. Assistant Professor, Internal Medicine, MIMSR Medical College, Latur India
 4. Associate Professor, Radiodiagnosis, MIMSR Medical College, Latur India
 5. Professor and Head, Radiodiagnosis, MIMSR Medical College, Latur India
 6. Professor, Pulmonary Medicine, MIMSR Medical College, Latur India

Corresponding Author: Dr. Shital Patil, Associate Professor & Head, Pulmonary Medicine, MIMSR Medical College, Latur, Maharashtra State, India. Email. drsvpatil1980@gmail.com

Introduction:

COVID-19 is the first corona virus related global pandemic caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the history of mankind after endemic-epidemic SARS (severe acute respiratory syndrome) and MERS (middle east respiratory syndrome) reported in last two decades. First COVID-19 radiological imaging was published with data of initial cases of pandemic documented classical radiological patterns and then afterwards diagnostic trends were evolved. [1] Although COVID-19 RT PCR (real time reverse transcription polymerase chain) test is gold standard to confirm diagnosis, high resolution thoracic imaging (HRCT thorax) has documented role in assessment of COVID-19 cases in outdoor and indoor settings. Initially, radiology experts have documented limited role of HRCT imaging in COVID-19 in presence of atypical opacities due to overlapping nature with other respiratory infections leading to acute lung injury. The sensitivity of HRCT, when compared with RT-PCR, has been previously studied and was shown to be higher than RT-PCR. [2,3]

Typical COVID-19 lung parenchymal involvement described as predominant ground glass opacities (GGOs) and consolidations in peripheral and subpleural portion of any lobe, predominantly involving lower lobes.[4] Atypical Radiological patterns in COVID-19 has been documented as bronchopneumonia, multifocal consolidations, necrotizing pneumonia, cavitations with GGOs with or without consolidations. [5] The opacities are usually ground-glass opacities (GGOs), sometimes with areas of consolidation, and are often nodular or mass like, thereby resembling an organizing pneumonia pattern. [6,7] CT severity scoring tool is universally accepted tool for assessment in COVID-19 pneumonia along with laboratory and clinical parameters. [8] In addition, a significant percentage of patients with asymptomatic infection may have parenchymal involvement at CT that overlaps in severity with that of symptomatic patients, and CT severity scores of clinically severe cases of COVID-19 pneumonia may overlap with those of moderate clinical severity, underscoring limitations in drawing clinical conclusions from CT severity alone. [9,10]

In present study, we have studied correlation of universally accepted CT severity grading tool with clinical parameters, laboratory inflammatory markers, interventions required in indoor units and final outcome in COVID-19 pneumonia cases.

Methods:

Ethical approval:

This study was approved by the Institutional Review Board / Ethics Committee at Venkatesh Hospital and Critical Care Center Latur India and MIMSR Medical college Latur India, (Approval number: VCC/159-2020-2021; Approval date 11/11/2020)

Data source:

Prospective, observational, 24 weeks follow up study conducted during July 2020 to June 2021 in MIMSR Medical College Latur and Venkatesh Hospital Latur India. Present study included 3000 COVID-19 reverse transcription–polymerase chain reaction (RT PCR) confirmed cases admitted in the critical care unit with primary objective to find out the role of CT severity phenotypes in managements of COVID 19 pneumonia. Primary objectives were to find the role of CT severity phenotypes in predicting severity of illness, targeting interventions in indoor and critical care units, assessing response to therapy and secondary objectives were to find its role in analyzing post-covid fibrosis or sequelae. Total 3000 cases were enrolled in study after IRB approval and written informed consent of all included cases were taken at respective centers of study in Venkatesh Hospital and MIMSR Medical college Latur. [Figure 1].

Inclusion criteria: COVID-19 RT-PCR confirmed cases, above the age of 18 years and hospitalized in the study centers were included. Cases with comorbidities, and irrespective of severity and oxygen saturation status were also included in the study.

Exclusion criteria: Those cases not willing to give consent, not able to perform HRCT thorax at entry point and not willing to remain in follow-up or to perform HRTC during follow up. COVID-19 cases died during hospitalization or before 24 weeks of discharge from hospital were excluded.

Methodology:

Case definitions for radiological phenotypes as mild, moderate, severe were done according to the CO-RADS [8] which is a categorical CT assessment scheme for patients suspected of having COVID-19 definition and evaluation: Coronavirus disease 2019 (COVID-19) Reporting and Data System (CO-RADS) provided a standardized assessment scheme that simplifies reporting with a five-point scale of suspicion for pulmonary involvement of COVID-19 at chest CT. CO-RADS provides a level of suspicion for pulmonary involvement of COVID-19 based on the features seen at unenhanced chest CT. The level of suspicion increases from very low (CO-RADS category 1) to very high (CO-RADS category 5). Two additional categories encode a technically insufficient examination (CO-RADS category 0) and RT-PCR–proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at the time of examination (CORADS category 6). HRCT Thorax to assess severity of lung involvement as per COVID-19 Reporting and Data System (CO-RADS)¹¹ and categorized as Mild if score <7, moderated if score 8-15 and severe if score >15 or 15-25.

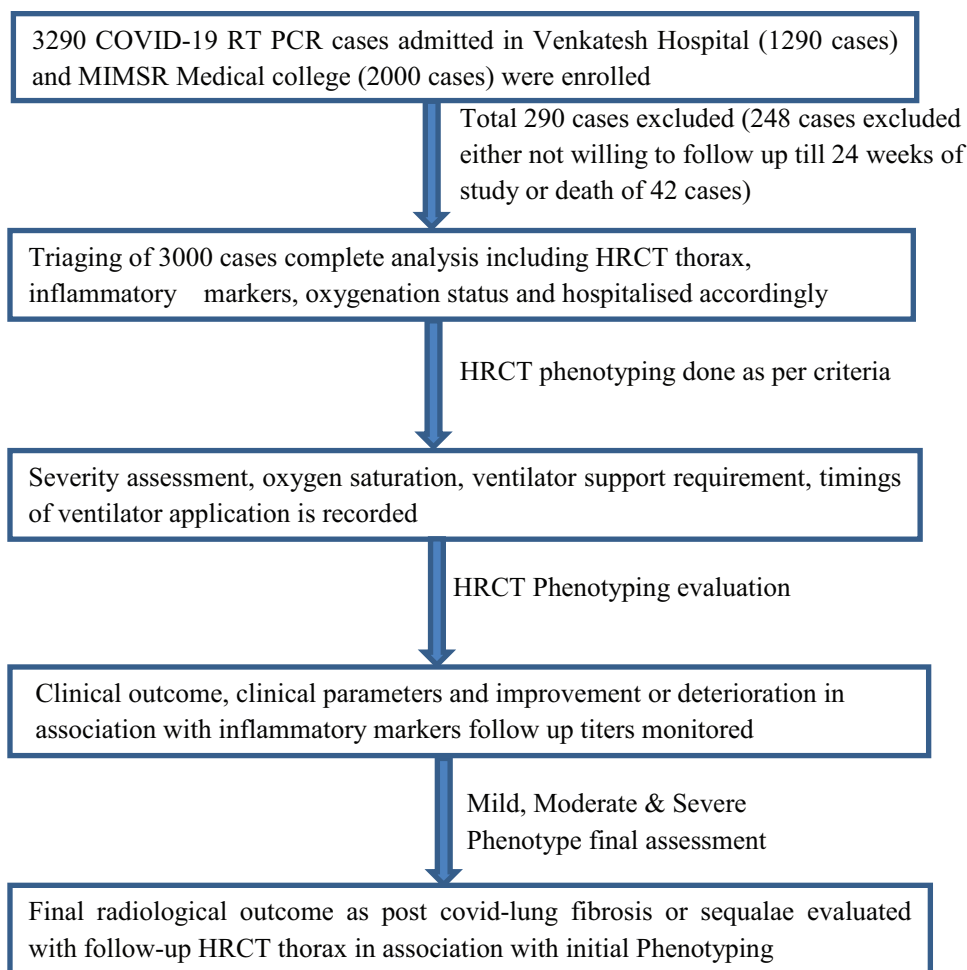
Radiological opacities in COVID-19 pneumonia were classified as GGOs, consolidations, GGOs plus consolidations and crazy paving types and included in mild CT severity (Image 1-2), moderate CT severity (Image 3-4) and Severe CT severity (Image 5-7) phenotypes.

Correlation of CT severity (mild, moderate, severe) with clinical parameters, laboratory parameters and interventions required with radiological outcomes at 24 weeks of discharge from hospital:

1. Clinical assessment and interventions required in correlation with HRCT thorax severity phenotypes. Clinical assessment (oxygen saturation at room air, heart rate and respiratory rate at entry point) and CT severity were correlated and triaging done accordingly to decide place of management in indoor settings such as ward, low dependency and high dependency units, intensive care units.
2. Routine biochemistry and hematological workup with viral inflammatory markers as CRP, Ferritin, LDH, IL-

6 & D-Dimer titers done in all cases. Inflammatory markers analysis was done at entry point and repeated every 72 hours to assess response to treatment. Laboratory parameters assessment was done in correlation with HRCT severity phenotypes.

3. Interventions required in indoor units were correlated with CT severity phenotypes. Intervention as oxygen supplementation, high flow nasal canula, BIPAP/NIV and Invasive ventilatory support requirement were correlated with CT severity phenotypes. Timings of interventions, interventions according to durations of illness in comparison with CT severity phenotypes were recorded.
4. Final clinical outcomes were monitored in all and radiological outcome at 24 weeks were monitored in selected cases those required interventions (oxygen, HFNC, BIPAP/NIV) in indoor period or required oxygen supplementation at home or having respiratory difficulty observed in post covid care units during follow up.



Study design: **Figure 1:** Flow of the study

Inflammatory markers analysis: Analysis of inflammatory markers were done in Rosch automated biochemistry analyzer. Values of these inflammatory markers were considered significant in presence of four-fold raised titers. We have correlated inflammatory markers titers with cut off of four-fold rise with radiological phenotypes and interventions required during hospitalization.

1. CRP titer: Normal values up to 6 mg/L. (0-6 mg/L)
2. LDH titer: Normal value up to 470 mg/L (90-470 mg/L)
3. Ferritin titer: Normal value up to 14-250ng/ml in males, and Female in age <45 years old 6-160ng/ml and age ≥45 years old 5-200ng/ml
4. D-dimer titer: Normal value up to value up to 470 mg/L (70-470 mg/dL)
5. IL-6 titer: Normal value up to <7 pg/mL (0-7 pg/ml)

Statistical Analysis:

The statistical analysis was done by using chi-square test in R-3.4 software. Significant values of χ^2 were seen from probability table for different degree of freedom required. *P* value was considered significant if it was below 0.05 and highly significant in case if it was less than 0.001.

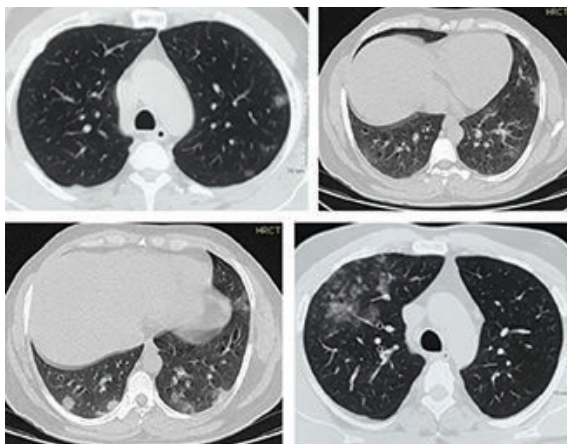


Figure 1: Mild CTS early GGOs with minimal consolidation

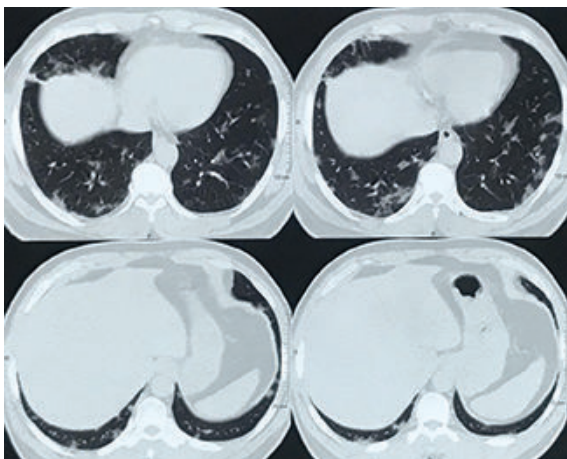


Figure 2: Mild CTS phenotype bilateral consolidation

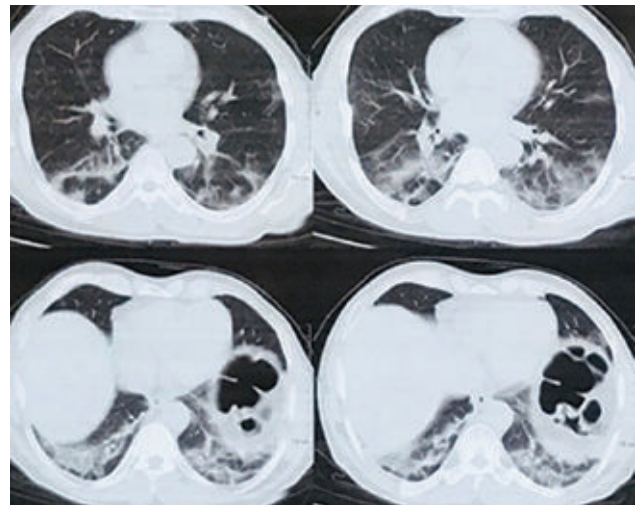


Figure 3: Moderate CTS GGOs predominant

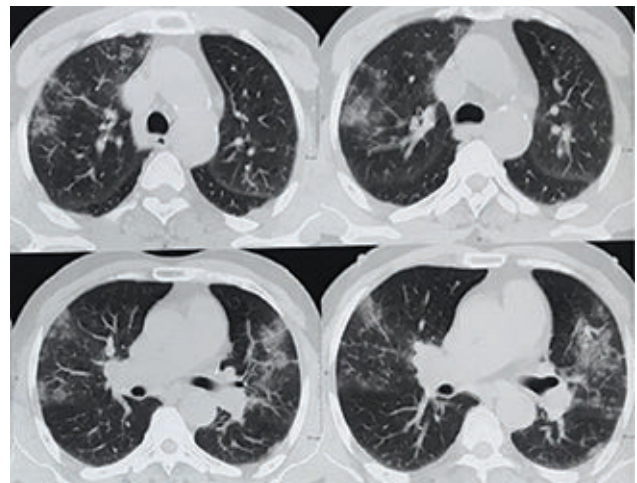


Figure 4: Moderate CTS phenotype GGOs plus consolidation

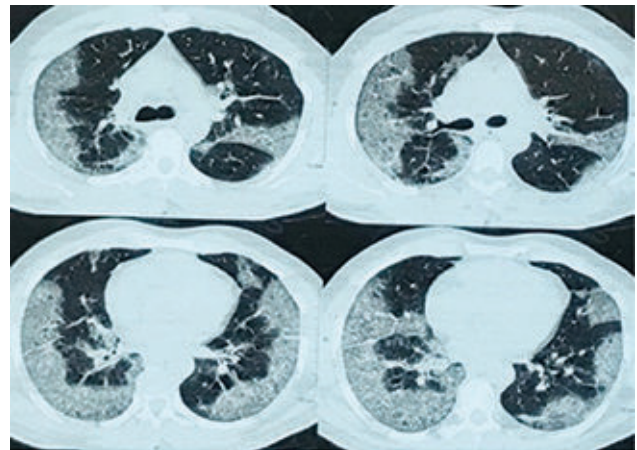


Figure 5: Severe CTS phenotype consolidation crazy paving

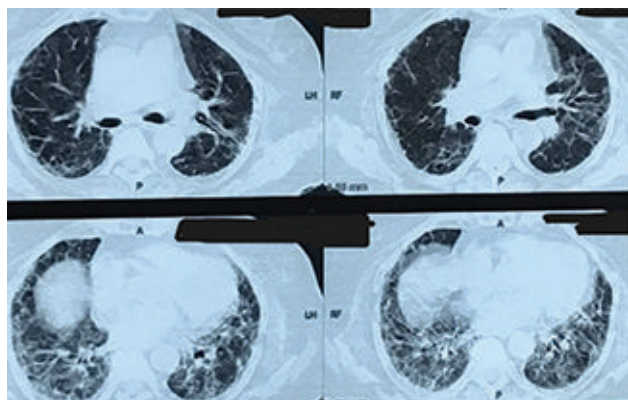


Figure 6: Severe CTS Phenotype GGOs with consolidations with necrotizing type

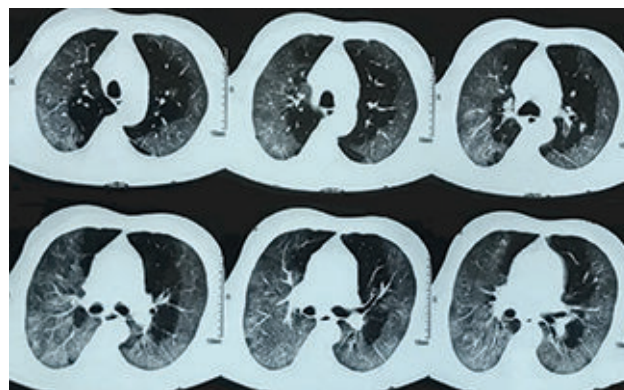


Figure 7: Severe CTS Phenotype bilateral consolidations

Results: Covariates

Table 1. Other variables and CRP titer in COVID-19 Pneumonia cases (n=3000)

COVID-19 RT PCR positive (n=3000)	Mild (n=400)	Moderate (n=1450)	Severe (n=1150)	Analysis
Age >50 years (n=1285)	165	668	452	$\chi^2=12.45p< 0.00197$
Age <50 years (n=1715)	235	782	698	
Male gender (n=1835)	177	986	672	$\chi^2=80.30p< 0.00001$
Female gender (n=1165)	223	464	478	
Diabetes mellitus (n=731)	81	312	338	$\chi^2=25.82p< 0.00001$
Without diabetes (n=2269)	319	1138	812	
Hypertension (n=310)	51	118	141	$\chi^2=14.67p< 0.00065$
Without Hypertension (n=2690)	349	1332	1009	
COPD (n=118)	45	12	61	$\chi^2=99.40p< 0.00001$
Without COPD (n=2882)	355	1438	1089	
IHD (n=298)	35	95	168	$\chi^2=47.25p< 0.00001$
Without IHD (n=2702)	365	1355	982	
Obesity (n=218)	49	61	108	$\chi^2=42.59p< 0.00001$
Without obesity (n=2782)	351	1389	1042	

In study of 3000 COVID-19 RT PCR confirmed pneumonia, males were 61.16% (1835/3000) and females were 38.83% (1165/3000), age >50 were 42.83% (1285/3000) cases and age <50 were 57.16% (1715/3000) cases. Significant association observed in radiological CT severity phenotypes such as 'mild, moderate and severe with variables such as age [p<0.00197], gender [p<0.00001], diabetes mellitus [p<0.00001], IHD [p<0.00001], Hypertension [p<0.00065], COPD [p<0.00001], Obesity [p<0.00001] in study cases. (Table 1).

Results: core observations

In study of 3000 cases, 'mild, moderate and severe' radiological CT severity phenotypes were documented as

13.33%, 48.33% & 38.34 % respectively. (Table 2). Significant association was documented in radiological CT severity phenotypes and duration of illness at entry point. [p<0.00001] Duration of illness (<7 days, 7-14 days and >14 days) plays a crucial role in predicting radiological CT severity phenotypes (Table 3) Laboratory parameters at entry point showed significant association with radiological CT severity phenotypes. [p<0.00001] (Table 4). Significant association documented between radiological CT severity phenotypes and interventions required in indoor unit. [p<0.00001] (Table 5). Post COVID-19 lung fibrosis or sequelae has significant association with radiological CT severity phenotypes. [p<0.00001] (Table 6).

Table 2. Radiological presentation phenotypes-severity assessment (N=3000)

	Present (n=3000)	Percentage
Mild	400	13.33
Moderate	1450	48.33
Severe	1150	38.33

Table 2. Duration of illness (DOI) at entry point during hospitalization and Radiological CT severity phenotypes in COVID-19 pneumonia cases (n=3000)

Duration of illness	Mild (n=400)	Moderate (n=1450)	Severe (n=1150)	Analysis
<7 days (n=1562)	210 (52.50%)	765 (52.75%)	587 (51.04%)	$\chi^2=51.16$ p<0.00001
8-15 days (n=882)	135 (33.75%)	465 (32.06%)	282 (24.52%)	
>15 days (n=556)	55 (13.75%)	220 (15.17%)	281 (24.43%)	

Table 4. Association of Radiological CT severity phenotypes with inflammatory markers assessment in COVID-19 pneumonia cases

	Mild (n=400)	Moderate (n=1450)	Severe (n=1150)	Analysis
Laboratory parameters (CRP, IL-6, ferritin, LDH, D-dimer) more than four-fold (n=2750)	218 (54.50%)	1411 (97.31%)	1121 (97.47%)	$\chi^2=834.63$ p<0.00001
Laboratory parameters (CRP, IL-6, ferritin, LDH, D-dimer) less than four-fold (n=250)	182 (45.50%)	39 (2.68%)	29 (2.52%)	

Table 5. Association of Radiological CT severity phenotypes with interventions during hospitalization in COVID-19 pneumonia (n=3000)

	Mild (n=400)	Moderate (n=1450)	Severe (n=1150)	Analysis
Oxygen (n=1144)	52 (13.00%)	667 (46.00%)	425 (36.95%)	$\chi^2=1403.66$
Oxygen plus ventilatory support (n=1306)	16 (4.00%)	594 (40.96%)	696 (60.52%)	p<0.00001
No oxygen or ventilator (n=550)	332 (83.00%)	189 (13.03%)	29 (2.52%)	

Table 6. Association of Radiological CT severity phenotypes at entry point and its correlation with post-covid lung fibrosis (n=622)

Post-covid Covid pneumonia fibrosis	Mild (n=400)	Moderate (n=1450)	Severe (n=1150)	Analysis
Pulmonary fibrosis present (n=622)	24 (6.00%)	282 (19.44%)	316 (27.47%)	$\chi^2=86.12$ p<0.00001
Pulmonary fibrosis absent (n=2378)	376 (94.00%)	1168 (80.55%)	834 (72.52%)	

Discussion:**1. CT severity 'mild, moderate & severe' Phenotypes in Study cases:**

In present study, 'mild, moderate and severe' radiological CT severity phenotypes were documented as 13.33%, 48.33% & 38.34 % respectively. This is universally accepted CT severity assessment tool bases on anatomical extent of disease. This scoring tool is single point assessment of anatomical involvement and devoid of giant assessment of laboratory and clinical parameters. CT is sensitive test with limited specificity as reported in previous studies. [2,3] CT findings will help in analyzing disease severity in correlation with inflammatory laboratory markers and clinical parameters. [12-16] Anatomical extent of involvement correlates very well with disease severity and laboratory parameters as documented in our study. [17-21]

2. CT severity 'mild, moderate & severe' Phenotypes in Study cases and its correlation with duration of illness:

Significant association was documented in radiological CT severity phenotypes and duration of illness at entry point. [p<0.00001] Duration of illness (<7 days, 7-14 days and >14 days) plays a crucial role in predicting radiological phenotype i.e., as duration of illness increases, we have observed a shift from mild to severe phenotype. Temporal association between radiological patterns in COVID-19 disease and duration illness as observed in early phase disease with predominant radiological abnormalities such as GGOs and in later phase GGOs were progressed and evolved into consolidations. [22] CT Severity at entry point is purely based on radiological involvement and may underpredict chances of progression if not compared with clinical and laboratory parameters. Majority of cases in second week of illness have progressed to severe category if clinical and laboratory assessment are not made in timely as observed in present study. This will result in pickup of disease in advanced stage, and importantly this was not possible to repeat CT after every third day as laboratory parameters can be repeated, which will help in composite assessment of disease severity as observed and documented in present study. This may be explained by facts of immune dysregulation due to COVID-19 manifested as GGOs predominantly observed in first week of illness as observed in mild category and switched to consolidations with minimal GGOs as in moderate and severe category during second and third week of illness as corelated with inflammatory markers monitoring during hospitalization in indoor unit. Various Authors have documented observations similar to our study and reported that GGOs with consolidations with duration of illness 1-3 weeks which indicates severe disease. [23-24] Crazy paving documented

5-30% of COVID-19 cases is the hallmark of peak of disease with consolidation and GGOs and marker of severe disease. [25] Authors have reported crucial role of clinical and laboratory parameters along with CT severity phenotypes as composite assessment for more precise assessment of disease severity. [26-30]

3. CT severity 'mild, moderate & severe' Phenotypes in Study cases and its correlation with laboratory inflammatory markers during hospitalization:

Inflammatory parameters at entry point (CRP, IL-6, Ferritin, LDH, D-dimer) showed significant association with CT severity phenotypes. [p<0.00001] Importantly, we have documented more than four-fold increased inflammatory markers in 218/400 (54.50%) cases in mild, 1411/1450 (97.31%) cases in moderate & 1121/1150 (97.43%) in severe phenotype. Laboratory parameters were in correlation to anatomical extent and pattern of involvement such as GGO and associated consolidation with necrosis. Studies have documented inflammatory markers (CRP, Ferritin, LDH, IL-6, D-Dimer) titer analysis has positive correlation with radiological patterns, severity assessment, interventions required and outcomes in COVID-19 pneumonia. [31-35] Surprisingly, we have documented more than four-fold increased inflammatory markers in 182/400 (45.50%) cases in mild, 39/1450 (2.68%) cases in moderate & 29/1150 (2.52%) in severe phenotype. Up to half of the cases in mild and very few cases in moderate and severe category were having less than four-fold increase in inflammatory markers. Similarly, authors have reported role of inflammatory markers in COVID-19 pneumonia cases in predicting severity in association with CT findings. [36-40] Author have documented similar observation and reported modest increase in inflammatory markers which is indicator of controlled inflammation. [41] Thus, there is disproportionate levels of inflammatory markers in various CT severity phenotypes which will appropriately guide severity if assessed combine, and isolated CT severity will either underestimate or overpredict severity.

4. CT severity 'mild, moderate & severe' Phenotypes in Study cases and its correlation with interventions required during hospitalization:

In present study, significant association documented in radiological CT severity phenotypes with interventions required in indoor unit [p<0.00001]. Previously published data supports our findings and correlated with interventions required in indoor units with CT findings and inflammatory markers. [26-35] Interestingly, a greater number of cases in mild category of CT severity required oxygen and oxygen

plus ventilatory support would be because of more GGOs and more inflammatory component resulting into more hypoxia as correlated with laboratory and clinical parameters. Surprisingly, Proportionate number of cases in moderate phenotype either required oxygen or ventilatory support and up to 13.03% cases doesn't require any of these interventions. Rational for this observation would be predominant GGOs more inflammatory surge as documented with more than four-fold increased inflammatory markers, and those doesn't require interventions were having predominant consolidation resulting into controlled inflammation with less than fourfold rise in inflammatory markers and less oxygen diffusion defect manifested as hypoxia. Authors have observed similar findings in their studies. [41-43] Lastly, 97.42% (310/1100) of cases in Severe CT severity phenotype require either oxygen or oxygen plus ventilatory support. Rational for this observation would be more consolidations and without or with minimal GGOs or crazy paving and more cases in this category were having more than four-fold inflammatory markers. Still, 2.52% (29/1150) cases don't require oxygen or oxygen plus ventilatory support and that too correlated with inflammatory markers and presence of minimal GGOs with crazy paving in this category. Similarly, authors have reported role of CT findings in predicting requirement of interventions in intensive care units in correlation with inflammatory markers. [26-35,41-43]

5. Does CT severity 'mild, moderate & severe' Phenotypes predict long term radiological outcome?

We have documented post COVID-19 lung fibrosis or sequelae has significant association with radiological CT severity phenotypes. [p<0.00001]. We have assessed those cases required oxygen supplementation for more than one week during hospitalization, cases required ventilatory support, high flow nasal canula and those cases required oxygen and or non-invasive ventilation (NIV) at home for post covid lung sequelae or fibrosis after 24 weeks of discharge from hospital. Studies have reported similar observations and documented post covid fibrosis in correlation with CT severity, inflammatory markers and interventions required. [37-41] Post covid sequelae was documented more commonly in severe CT severity phenotypes in 27.47% (316/1150) cases. We have done retrospective analysis radiological patterns shown more post covid lung fibrosis. Radiological patterns with more consolidations with or without necrosis, with or without crazy paving and minimal GGOs were predominantly associated with post covid lung fibrosis. We have further checked the indoor records and noted more than four-fold raised inflammatory markers in these cases & revealed that nearly

all cases required ventilatory support requirement due to more hypoxia. Another possible explanation for post covid sequelae in these cases would be hypoxia and inflammation go hand in hand, and both works synergistically to release profibrogenic inflammatory markers hypoxia inducible transcription factor indirectly assessed by raised LDH titer. Authors have reported similar observations in their studies. [44-47] Post covid sequelae was documented in 19.44% (282/1450) cases in moderate CT severity phenotypes. Retrospective analysis of these cases shown more GGOs with or without consolidation and very well correlated with inflammatory markers and interventions required during hospitalization. Similarly, Authors have documented that post covid sequelae is well predicted with inflammatory markers and patterns of lung disease on CT imaging. [44-48] Interestingly, 6.0% (24/400) cases in mild CT severity phenotypes were having post covid lung sequel. These radiological outcomes were really not predicted on CT patterns at entry points, but these complications were easily predicted after correlation with inflammatory markers and interventions required in indoor unit. Thus, isolated CT severity at entry point is inadequate indicator of future radiological outcomes.

6. Association of covariates with CT severity 'mild, moderate & severe' Phenotypes:

In present study, age and gender has documented significant association with CT severity radiological phenotypes with more involvement in male gender. Reason for more male preference to COVID-19 illness is not known and considered as by chance or hormonal factors protects female gender from severe COVID-19 illness. These findings need further research. Various authors have documented similar observations in their studies. [26-39, 42-48] In present study, covariates such as diabetes mellitus, IHD, Hypertension, COPD and Obesity with CT severity radiological phenotypes which has been correlated with published data. [26-39, 42-49]

Limitation of present study:

Our study is having enough sample size and analyzed role of radiological phenotypes in correlation with laboratory and clinical marker in assessment and management in indoor units. First limitation is confounding factors leading to raised inflammatory markers were not analyzed in study. Second limitation is in notifying exact duration of illness in correlation with radiological patterns, because we have taken entry point CT findings and duration of illness as variables with complete reliability on attendants and patients. Third limitations multivariate analysis of inflammatory markers with individual marker is not done in correlation with radiological phenotypes. Fourth limitation is we have

considered interventions used during indoor period such as oxygen and ventilatory support at entry point and during course of hospitalization but we have considered CT thorax findings at entry point. We have not performed repeat CT thorax due to cost constraint to analyze CT findings during hospitalization. Time trends with timings of interventions and CT findings is not exactly available. Lastly, post covid radiological outcomes were studied in those cases with special cases those have documented aggressive interventions required in indoor and oxygen supplementation at home after discharge with or without comorbidities.

Pitfalls of universally acceptable HRCT severity scoring system in COVID-19 pneumonia as per present study analysis:

Universally accepted HRCT severity scoring tool bases on topographical involvement of lung segments in bilateral lung lobes is not suited for routine care in indoor units as per our observations.

1. Inappropriate estimation of severity due to lack of correlation to clinical and laboratory parameters. CT Severity is based on anatomical involvement in both lungs. This is pure radiological estimation without assessment of clinical and laboratory parameters. Authors have described 'Evolved and Evolving' and 'Easy to treat and Difficult to treat' radiological phenotypes with more precise assessment in comparison with clinical and laboratory parameters and considered as best 'Composite index' to assess COVID-19 cases. [50-53]
2. HRCT severity is gross estimation of anatomical involvement of segments of lung. Cases with high CT severity scoring may have stable clinical and laboratory parameters while cases with just Minimal to mild disease according to CT may have very grossly deranged laboratory parameters with deteriorated clinical status
3. GGO and consolidation are two radiological patterns commonly described in COVID pneumonia and included in CT severity scoring tool. GGO is indicator of early disease and indicates advanced disease in presence of concurrent consolidation in CT imaging. Consolidation is marker of advanced disease and well-defined borders indicates less severe disease in spite of high CT severity in scoring method.
4. Proportionately large number of cases with mild disease and predominant GGO have been progressed to advanced disease as COVID evolves with or without treatment and in few cases resolved completely after treatment.
5. Similarly, large number of covid cases with advanced disease were not required aggressive interventions in indoor period and easily recovered and few of them progressed to require more integrations and mortality documented in this class of patients. CT severity in these cases is just gross estimation of risk and unable to predict poor outcome unless combined with clinical and laboratory parameters
6. Thus, CT severity is best predictor of severity but it indicates "static severity indicator" or it tells severity at "some point" and very poor predictor of final outcome. CT severity is poor predictor of Temporal assessment of severity unless it is combined with clinical and Laboratory assessment which is called as composite index in COVID.
7. Composite index is best tool to assess severity, predict need for interventions, guide in triaging the cases during management in decision making to admit in wards, ICU with or without interventions and predict final radiological and clinical outcome.

Conclusions:

Radiological CT severity Phenotypic categorization is a simple, sensitive and more widely studied and universally accepted classification system. Limitation of this method is its 'static and only' radiological assessment criteria and not 'dynamic and clinical and laboratory parameters' included 'composite index' criteria which is temporal assessment over a period of time as disease process evolves and not a single point assessment. Radiological CT severity phenotypes will predict disease severity as per the anatomical extent of disease and this actually either overestimate in severe category and underestimates in mild category. Thus, quote 'one size fit to all' will not suit conventional CT severity scoring tools and phenotypes.

Abbreviations:

RT PCR- real time reverse transcription polymerase chain, HRCT-high resolution computerised tomography, CRP C-reactive protein, SpO2 oxygen saturation, LDH lactate dehydrogenase, IL-6 Interleukin-6, CT-computerised tomography, SARS-CoV-2 severe acute respiratory syndrome-corona virus-2 BIPAP/NIV- bilevel positive airway pressure/non-invasive ventilation

References:

1. Kanne JP. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: key points for the radiologist. *Radiology* 2020; 295(1): 16–17.
2. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus

- disease 2019 (COVID-19) in China: A report of 1014 cases. *Radiology*. 2020 doi: 10.1148/radiol.2020200642
3. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: Comparison to RT-PCR. *Radiology*. 2020;296: E115–7.
 4. Jeûrey P, Kanne, Harrison Bai, Adam Bernheim, Michael Chung, Linda B. Haramati, David F. Kallmes, Brent P. Little, Geotûrey Rubin, and Nicola Sverzellati COVID-19 Imaging: What We Know Now and What Remains Unknown *Radiology* 2021 299:3, E262-E279
 5. Patil S, Gondhali G, Patil R. Radiological Phenotypes' In Covid-19 Pneumonia: Retrospective, Multicentric Study Of 6000 Cases In Tertiary Care Setting In India. *Chest*. 2022 Jun;161(6): A537.
 6. Chung M, Bernheim A, Mei X, CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* 2020; 295(1): 202–207.
 7. Simpson S, Kay FU, Abbara S, Radiological Society of North America expert consensus statement on reporting chest CT findings related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA—secondary publication. *J Thorac Imaging* 2020; 35(4): 219–227.
 8. Mathias Prokop, Wouter van Everdingen, Tjalco van Rees Vellinga, Henriëtte Quarles van Ufford, Laurant Stöger, Ludo Beenen, Bram Geurts et al. COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19—Definition and Evaluation. *Radiology* 2020 296:2, E97-E104
 9. Li K, Chen D, Chen S. Predictors of fatality including radiographic findings in adults with COVID-19. *Respir Res* 2020; 21(1): 146
 10. Zhang R, Ouyang H, Fu L. CT features of SARS-CoV-2 pneumonia according to clinical presentation: a retrospective analysis of 120 consecutive patients from Wuhan city. *Eur Radiol* 2020; 30(8): 4417–4426
 11. Liu KC, Xu P, Lv WF, Qiu XH, Yao JL, Gu JF, et al. CT manifestations of coronavirus disease 2019: A retrospective analysis of 73 cases by disease severity. *Eur J Radiol* 2020;126:108941.
 12. Patil S, Narwade G, Dhupal U. The Role of initial and follow-up C-reactive protein titer in COVID-19 pneumonia: A single center study of 1000 cases in a tertiary care setting in India. *J Adv Lung Health* 2023; 3:17-24
 13. Patil S, Bhadake M, Narwade G, Patil R. Correlation of LDH with duration of illness, disease severity, ventilatory support and lung fibrosis in covid-19 pneumonia: a single center experience of 1000 cases in tertiary care setting in India. *Ital J Emerg Med* 2022; 11:95-103
 14. Patil S, Acharya A, Gondhali G, Narwade G. Serial interleukin 6 titer monitoring in COVID 19 pneumonia: Valuable inflammatory marker in assessment of severity, predicting ventilatory support requirement, and final radiological outcome – Prospective observational study in tertiary care setting in India. *J Assoc Pulmonologist* 2022; 5:2-8
 15. Patil S, Gondhali G, Acharya A. Role of ferritin as “Core Marker” in the assessment of severity, response to therapy and predicting outcome in COVID-19 pneumonia: A large, two-center, prospective, observational study of 1000 cases in tertiary care setting in India. *Indian J Respir Care* 2022; 11:253-60.
 16. Patil S, Khule S, Toshniwal S. Role of D-Dimer in assessing severity, monitoring, and predicating outcome in COVID-19 pneumonia: A single center study. *Glob J Health Sci Res* 2023; 1:31-7
 17. Patil, S., Gondhali, G., & Acharya, A. (2022). Serial CRP (C-reactive protein) Monitoring in COVID-19 Pneumonia for the Assessment of Severity, Ventilatory Support Requirement and Predicting Early Lung Fibrosis. *Journal of Medicine*, 23(2), 112–120.
 18. Patil S, Bhadake M, Narwade G, Acharya A. Role of lactate dehydrogenase in COVID19 pneumonia: a single tertiary care center follow-up experience of 1000 cases in India. *J One Health Res* 2023;1(1):7-14
 19. Patil SV, Gonghali G, Acharya A. Role of initial and follow-up IL-6 (Interleukin-6) titre in COVID-19 pneumonia: A single center experience. *Electron J Gen Med*. 2022;19(5): em390.
 20. Patil S, Toshniwal S, Acharya A, Narwade G. Role of “Ferritin” in COVID-19 pneumonia: Sensitive marker of inflammation, predictor of mechanical ventilation, and early marker of post COVID-lung fibrosis – A prospective, observational, and interventional study in a tertiary care setting in India. *Muller J Med Sci Res* 2022; 13:28-34
 21. Patil S, Acharya A, Gondhali G, Narwade G. Role of ‘Serial D-Dimer Level’ in predicting Severity and outcome in COVID-19 pneumonia: A Prospective multicentric Observational Study of 1000 cases in Tertiary Care Setting in India. *EJMA* 2022;2(2):73–80.
 22. Wang Y., Dong C., Hu Y., Li C., Ren Q., Zhang X., Shi H., Zhou M. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology*. 2020;296: E55–E64.
 23. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020; 8:420–422.
 24. Kanne JP. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: key points for the radiologist. *Radiology*. 2020; 295:16–17.

25. Wong KT, Antonio GE, Hui DSC, et al. Thin-section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. *Radiology*. 2003; 228:395–400.
26. Patil S, Khule S, Patil D, Toshniwal S. Role of C-Reactive protein in COVID-19 pneumonia as “A jack of all trades is a master of none!”: A single-center experience of 2000 cases. *J Assoc Pulmonologist Tamilnadu* 2022; 5:106-12.
27. Patil, S. ., Khule, S. ., & Patil, D. . (2023). Role of Initial and Follow-up LDH Titer in COVID-19 Pneumonia: A Single Center Experience of 2000 Cases in Tertiary Care Setting in India. *Journal of Medicine*, 24(1), 10–17.
28. Shital Patil, Abhijit Acharya, Gajanan Gondhali. Does IL-6 level help in assessment of severity in COVID-19 Pneumonia, and predicting radiological outcome? Tertiary care center experience of 1000 COVID-19 cases in India. *JMR* 2022; 8(2):62-68
29. Patil, S., Gondhali, G. & Acharya, A. “Serial ferritin titer” monitoring in COVID-19 pneumonia: valuable inflammatory marker in assessment of severity and predicting early lung fibrosis — prospective, multicentric, observational, and interventional study in tertiary care setting in India. *Egypt J Intern Med* 34, 75 (2022).
30. Shital Patil, Manojkumar Bhadake, Abhijit Acharya, Ganesh Narwade. Role of D-Dimer in Covid-19 pneumonia: sensitive marker of inflammation, predictor of mechanical ventilation, thromboembolic events and early marker of post covid-lung fibrosis; Prospective Multicentric, Observational, Interventional study in tertiary care setting in India. *JMR* 2022; 8(2):50-55
31. Patil S, Dhumal U, Bhadake M. Role of CRP in COVID-19 pneumonia: A single-center experience of 1000 cases in a tertiary care setting in India. *J Med Sci Res* 2022; 5:430-6
32. Patil, Shital; Patil, Deepak1; Khule, Shubhangi2. Role of Initial and Follow-Up Lactate Dehydrogenase Titer in Coronavirus Disease 2019 Pneumonia: A Single-Center Experience. *CHRISMED Journal of Health and Research* 10(1):p 79-85, Jan–Mar 2023
33. Patil, Shital1; Gondhali, Gajanan2; Acharya, Abhijit3. Role of interleukin-6 in coronavirus disease 2019 pneumonia: sensitive marker of inflammation, a predictor of ventilatory support and early marker of post-coronavirus disease lung fibrosis. A single center experience. *The Egyptian Journal of Chest Diseases and Tuberculosis* 72(3):p 346-354, July-September 2023.
34. Patil S, Dhumal U, Acharya A. Correlation of ferritin with the duration of illness, disease severity, oxygenation status, ventilatory requirement, and lung fibrosis in COVID-19 pneumonia: A single-center experience of 1000 cases in tertiary care setting in India. *Adesh Univ J Med Sci Res* 2022; 4:86-93.
35. Patil S, Acharya A, Gondhali G, Narwade G. Does follow-up D-dimer level help in predicting oxygenation status, ventilatory support requirement, lung fibrosis, and thromboembolic events in coronavirus disease 2019 pneumonia? A prospective observational study in a tertiary care setting in India. *Ann Afr Med* 2023;22:286-92
36. Wang Y., Dong C., Hu Y., Li C., Ren Q., Zhang X., Shi H., Zhou M. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology*. 2020;296: E55–E64.
37. Ojha V., Mani A., Pandey N.N., Sharma S., Kumar S. CT in Coronavirus Disease 2019 (COVID-19): A Systematic Review of Chest CT Findings in 4410 Adult Patients. *Eur. Radiol.* 2020; 30:6129–6138.
38. Di Meglio L., Carriero S., Biondetti P., Wood B.J., Carrafiello G. Chest Imaging in Patients with Acute Respiratory Failure Because of Coronavirus Disease 2019. *Curr. Opin. Crit. Care.* 2022; 28:17–24.
39. Li J., Yan R., Zhai Y., Qi X., Lei J. Chest CT Findings in Patients with Coronavirus Disease 2019 (COVID-19): A Comprehensive Review. *Diagn. Interv. Radiol.* 2021; 27:621–632.
40. Saeed GA, Gaba W, Shah A, Al Helali AA, Raidullah E, Al Ali AB, Elghazali M, Ahmed DY, Al Kaabi SG, Almazrouei S (2021) Correlation between chest CT severity scores and the clinical parameters of adult patients with COVID-19 pneumonia. *Radiol Res Pract* 2021:6697677.
41. M. Ackermann, S. E. Verleden, M. Kuehnel et al., “Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19,” *New England Journal of Medicine*, vol. 383, no. 2, p. 120, 2020.
42. Xie J, Covassin N, Fan Z, et al. Association between hypoxemia and mortality in patients with COVID-19. *Mayo Clin Proc.* 2020;95(6):1138-1147.
43. Nuevo-Ortega P, Reina-Artacho C, Dominguez-Moreno F, et al. Prognosis of COVID-19 pneumonia can be early predicted combining age-adjusted Charlson Comorbidity Index, CRB score and baseline oxygen saturation. *Scientific Reports.* 2022; 12:1-2.
44. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the development of pulmonary fibrosis using serial thin-section CT and clinical features in patients discharged after treatment for COVID-19 pneumonia. *Korean J Radiol.* (2020) 21:746–55.
45. Shital Vishnu Patil, Gajanan Gondhali, Rajesh Patil Post-Covid-19 Lung Fibrosis: Study Of 600 Cases in Tertiary Care Setting in India *European Respiratory Journal* 2021 58: PA3776; DOI: 10.1183/13993003.congress-2021.PA3776

46. Antonio GE, Wong KT, Hui DS, Wu A, Lee N, Yuen EH, et al. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. *Radiology*. (2003) 228:810–5.
47. Patil, S.; Gondhali, G.; Patil, R.; Kasture, L. Post-COVID-19 lung fibrosis: Study of 600 cases in tertiary care setting in India. *American Journal of Respiratory and Critical Care Medicine*; 203(9), 2021.
48. Zhang D, Zhang C, Li X, Zhao J, An C, Peng C, et al. Thin-section computed tomography findings and longitudinal variations of the residual pulmonary sequelae after discharge in patients with COVID-19: a short-term follow-up study. *Eur Radiol*. (2021) 31:7172–83
49. Shital Vishnu Patil, Rajesh Patil, Gajanan Gondhali. Effect of hyperglycemia on post-Covid-19 lung fibrosis: Study of 600 cases in tertiary care setting in India. *European Respiratory Journal* 2021 58: PA3777
50. Patil S, Gondhali G, Patil R. Radiological Phenotypes' in Covid-19 Pneumonia: Retrospective, Multicentric Study Of 6000 Cases In Tertiary Care Setting In India. *Chest*. 2022 Jun;161(6): A537.
51. S. Patil, R. Patil, G. Gondhali "Role of Radiological Phenotypes" in Diagnosis, Treatment and Assessment of Covid-19 Pneumonia: Multicentric Study of 6000 Cases in Tertiary Care Setting in India. *Am J Respir Crit Care Med* 2022;205: A2963
52. Patil S, Dhupal U, Patil D, Acharya A. Easy-to-treat and difficult-to-treat radiological phenotypes in coronavirus disease 2019 pneumonia: A single-center experience. *Radiol Infect Dis* 2023;10:19-29
53. Patil, S., Tandel, N., Kasture, L., & Gondhali, G. (2023). Radiological Patterns Integration with Duration of Illness in COVID-19 Pneumonia as 'Evolved' and 'Evolving' Radiological Phenotypes: A Single Center Experience. *Journal of Medicine*, 24(2), 71–81.