

Original Articles

Radiological Patterns Integration with Duration of Illness in COVID-19 Pneumonia as 'Evolved' and 'Evolving' Radiological Phenotypes: A Single Center Experience

Shital Patil¹, Neel Tandel², Laxman Kasture³, Gajanan Gondhali⁴

Abstract

Background: Radiological phenotypes are radiological patterns or observable characteristics of COVID-19 pneumonia.

Methods: Prospective observational study, included 3000 COVID-19 RT-PCR confirmed cases with lung involvement documented and categorized on HRCT thorax at entry point as mild, moderate and severe as per lung segment involvement bilaterally and follow up CT thorax imaging at six months post discharge from hospital. Radiological phenotypes were categorized as 'Evolved' and 'Evolving' as per radiological features and analysed with inflammatory markers and interventions required in indoor setting including ventilatory support. 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. Statistical analysis is done by using Chi square test.

Results: In study of 3000 COVID-19 RT PCR confirmed pneumonia, 'Evolved' and 'Evolving' radiological phenotype patterns were observed in 36.66% and 63.33% respectively. Duration of illness, laboratory parameters at entry point (CRP, IL-6, ferritin, LDH, D-dimer) & interventions required in indoor unit has significant association with Radiological phenotypes [$p < 0.00001$] HRCT severity score at entry point & Post COVID-19 lung fibrosis or sequelae has significant association with radiological phenotypes. [$p < 0.00001$]

Conclusions: Radiological phenotypes have documented very crucial role in initial assessment of COVID-19 pneumonia. Evolved and Evolving differentiation have documented important step in management of these cases in indoor and outdoor setting.

Keywords: COVID-19 pneumonia, Radiological phenotypes, Evolved, Evolving, Inflammatory marker



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Background:

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}

Pan et al described four temporal stages of acute and subacute COVID-19 on CT images, including an initial phase in which abnormalities manifest as GGOs, may be unilateral, and tend to lack the characteristic peripheral lung distribution. Patients often experience progression from day 5 to day 8, when pulmonary opacities become more extensive and confluent with more common bilateral lung involvement.⁸ The peak stage occurs around 9–13 days and features more extensive consolidation, which parallels the evolution of acute lung injury.⁹ This dovetail with investigators finding that abnormalities on chest radiographs are most extensive 10–12 days after symptom onset.¹⁰ There is variation among patients, but beginning at about 2 weeks, many enter the absorption stage. During this period, consolidation may

wane, and other manifestations absent in the earlier phases of acute infection, such as linear opacities, a reverse halo sign, and a so-called crazy-paving pattern, may emerge.¹¹

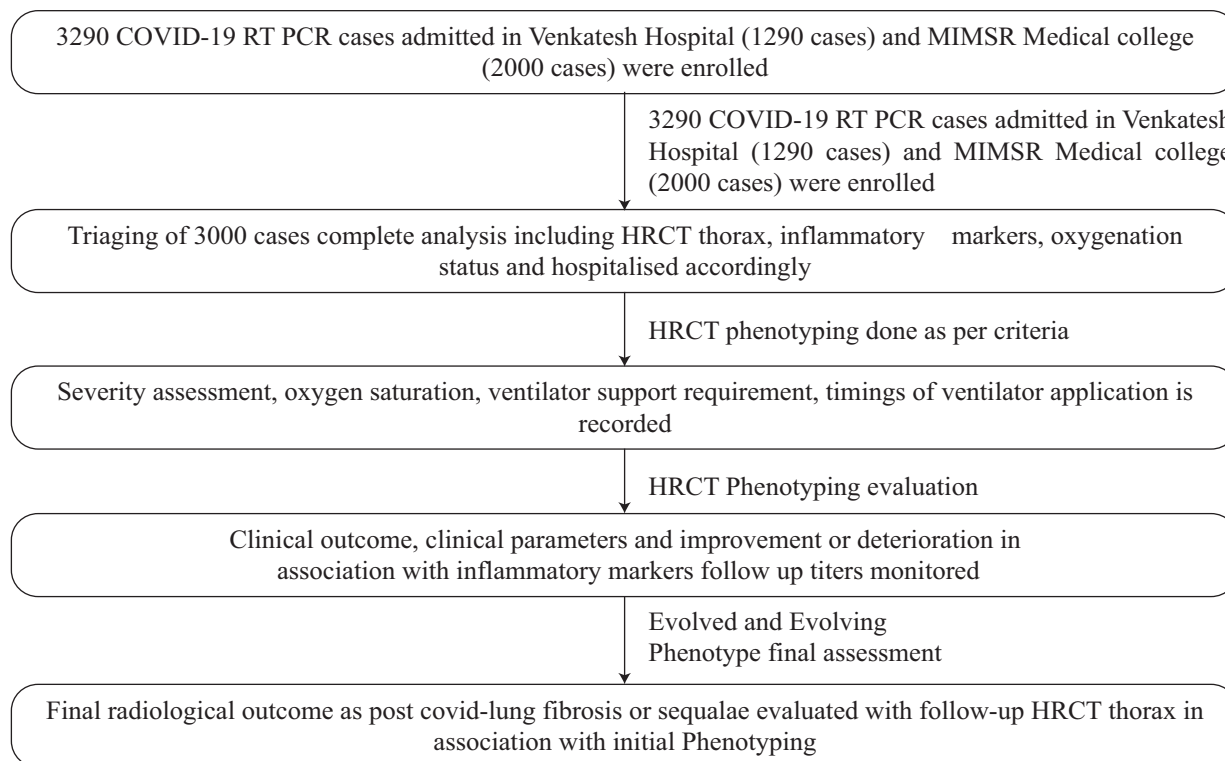
CT severity scoring tool is universally accepted tool for assessment in COVID-19 pneumonia along with laboratory and clinical parameters.¹² In addition, a significant percentage of patients with asymptomatic infection may have parenchymal involvement at CT that overlaps in severity with that of symptomatic 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.^{13,14}

Methods:

Ethical approval & Data Source:

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/11-2020-2021; Approval date 12/07/2020). 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 critical care unit with primary objective to find out role of radiological phenotypes as ‘Evolved’ and ‘Evolving’ in correlation with radiological presentations. (Figure 1).

Study design: Figure 1 : Flow of the study



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.
2. **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 HRCT during follow up. COVID-19 cases died during hospitalization or before 24 weeks of discharge from hospital were excluded.

Case definitions for radiological phenotypes in this study formulated by expert group of teaching faculties in two tertiary care institutes were:

A) Evolved phenotype:

1. Radiological criteria- predominant consolidations unilateral or bilateral, peripheral, subpleural with minimal or negligible ground glass opacities. Consolidations are classically having ‘limiting sign’ i.e., line of demarcation between normal lucent and abnormal opaque lung parenchyma.
2. Laboratory criteria in correlation with HRCT findings- abnormal inflammatory markers such as IL-6, CRP, LDH, Ferritin and D-Dimer. Values of these inflammatory markers are less than fourfold.
3. Clinical assessment and interventions required in correlation with HRCT thorax- hypoxia (oxygen saturation less than 90% at room air), tachypnea (respiratory rate above 24 breaths per minute) and

tachycardia (heart rate above 100 per minute) were present in few cases. Duration required for clinical improvement is less than 2 weeks and very few cases required oxygen supplementation at home due to hypoxia at discharge.

4. Interventions required in these cases with typical HRCT findings: interventions as oxygen supplementation and Ventilatory support as HFNC, NIV and Invasive ventilatory support in indoor units. Majority of cases responded to oxygen supplementation with or without ventilatory support.

In present study we have identified Evolved radiological phenotypes according to duration of illness shown in images. (Image 1-4)

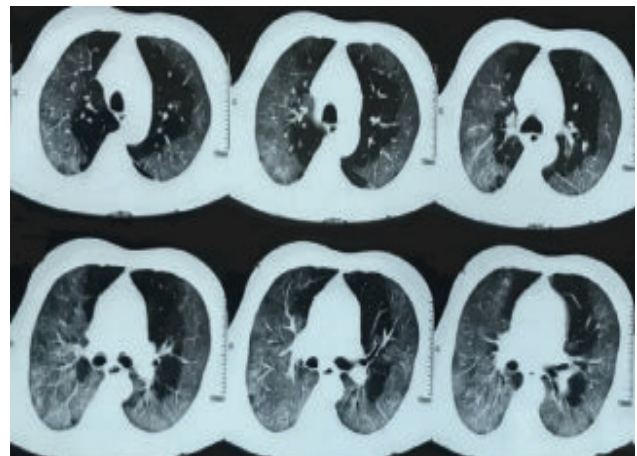


Image 1 Evolving phenotype showing GGOs and crazy paving

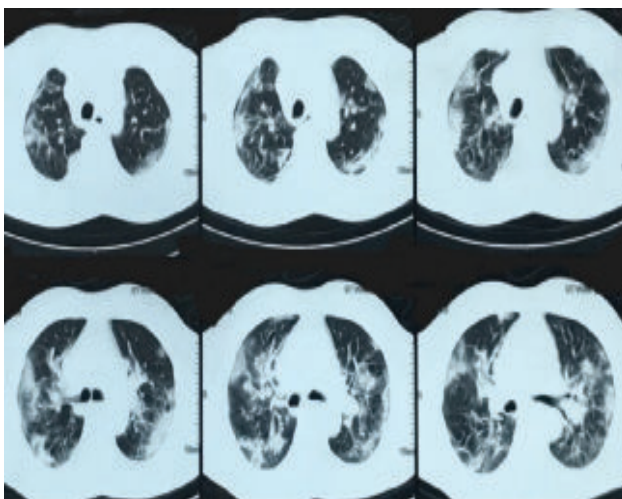


Image 2 Evolved phenotype showing bilateral consolidations

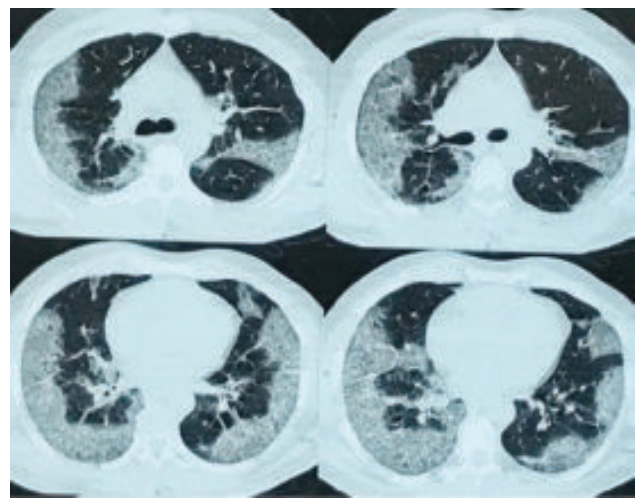


Image 3 Evolved phenotype showing consolidation with line of demarcation

B) Evolving phenotype:

1. Radiological criteria- predominant ground glass opacities, unilateral or bilateral, multifocal, peripheral, subpleural with minimal or negligible consolidations. Ground glass opacities are without ‘limiting sign’ i.e., no line of demarcation between normal lucent and abnormal opaque lung parenchyma. Some of these cases are having GGOs and interstitial marking due to thickened interlobular septa called as crazy paving pattern.
2. Laboratory criteria in correlation with HRCT findings- abnormal inflammatory markers such as IL-6, CRP, LDH, Ferritin and D-Dimer. Values of these inflammatory markers are more than fourfold.
3. Clinical assessment in correlation with HRCT thorax- hypoxia (oxygen saturation less than 90% at room air),

tachypnea (respiratory rate above 24 breaths per minute) and tachycardia (heart rate above 100 per minute) were present in proportionately majority of cases. Duration required for clinical improvement is more than 2 weeks and majority cases required oxygen supplementation at home due to hypoxia at discharge.

4. Interventions required in these cases with typical HRCT findings- interventions as oxygen supplementation and Ventilatory support as HFNC, NIV and Invasive ventilatory support in indoor units. Majority of cases required to oxygen supplementation with ventilatory support.

In present study we have identified Evolving radiological phenotypes according to duration of illness shown in images. (Image 4-6).

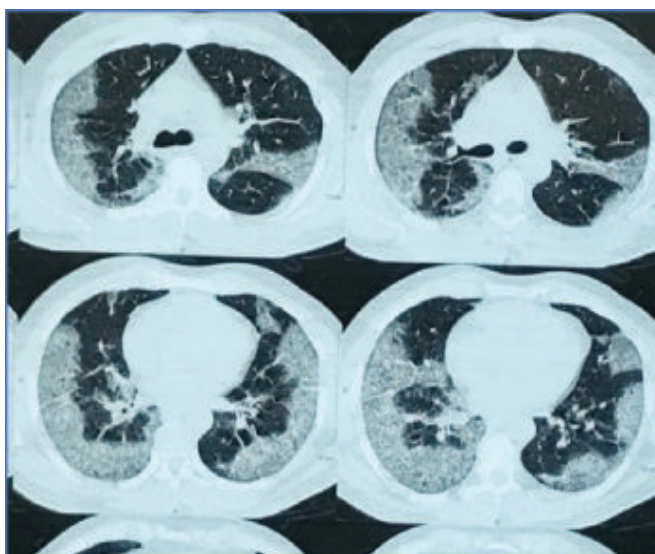


Image 4 Evolved and Evolving phenotype

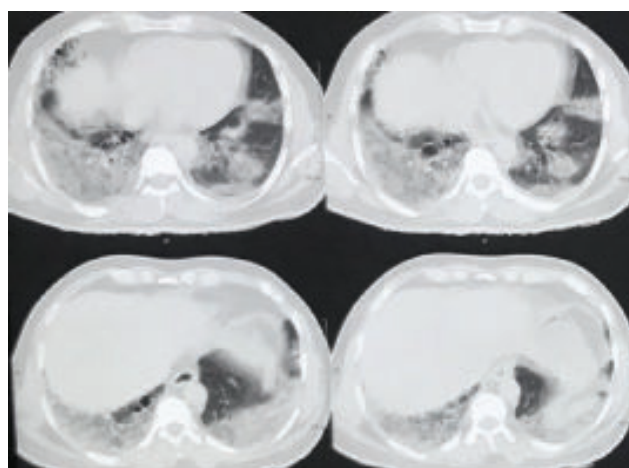
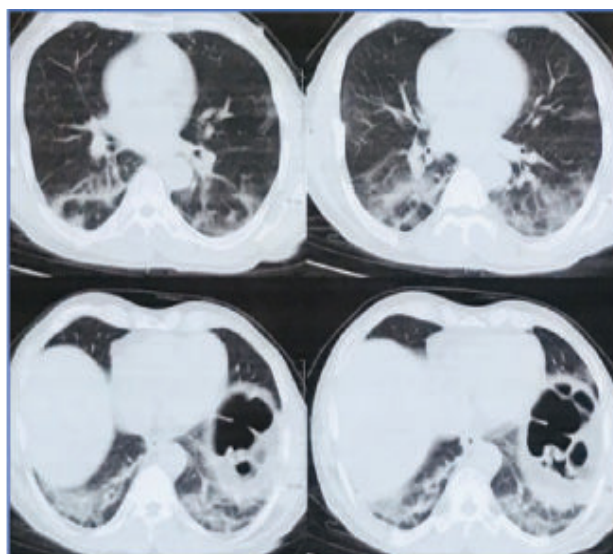


Image 5 Evolving phenotype showing bilateral GGOs with dense consolidations

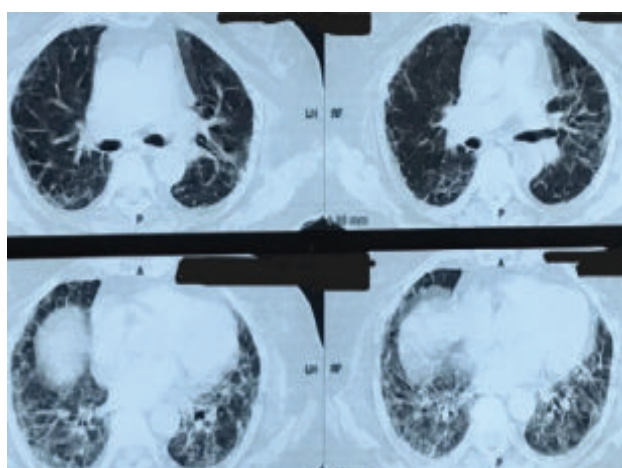


Image 6 Evolving phenotype showing bilateral GGOs with consolidations with necrotizing type

All study cases were undergone following assessment before enrolling in study:

COVID-19 RT PCR test was performed on nasopharyngeal samples collected with all standard institutional infection control policies and enrolled only RT PCR positive cases. HRCT Thorax to assess severity of lung involvement as per COVID-19 Reporting and Data System (CO-RADS)^[20], and categorized as Mild if score <7, moderated if score 8-15 and severe if score >15 or 15-25. Clinical assessment and routine biochemistry and hematological workup with viral inflammatory markers as CRP, Ferritin, LDH, IL-6 titers. (Figure 1). Values of these inflammatory markers were considered significant in presence of four-fold raised titers.

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 $\neq 2$ 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.

In study of 3000 COVID-19 RT PCR confirmed pneumonia, males were 61.16% and females were 38.83%, age >50 were 42.83% cases and age <50 were 57.16% cases. Significant association observed between radiological phenotypes 'Evolved and Evolving' with variables such as age, gender, diabetes mellitus, IHD, Hypertension, COPD, Obesity. Similarly, HRCT severity score at entry point has significant correlation with radiological phenotypes in COVID-19 pneumonia [$p < 0.00001$] (Table 1).

Table 1. Other variables and radiological phenotypes as Evolved and Evolving type in COVID-19 Pneumonia cases (n=3000)

COVID-19 RT PCR positive (n=3000)	Evolved (n=1100)	Evolving (n=1900)	Analysis
Age >50 years (n=1285)	288	997	$\chi^2=416.76p < 0.00001$
Age <50 years (n=1715)	812	497	
Male gender (n=1835)	339	1496	$\chi^2=673.46p < 0.00001$
Female gender (n=1165)	761	404	
Diabetes mellitus (n=731)	110	621	$\chi^2=194.51p < 0.00001$
Without diabetes (n=2269)	990	1279	
Hypertension (n=310)	40	270	$\chi^2=85.20p < 0.00001$
Without Hypertension (n=2690)	1060	1630	
COPD (n=118)	96	22	$\chi^2=105.63p < 0.00001$
Without COPD (n=2882)	1004	1878	
IHD (n=298)	196	102	$\chi^2=120.69p < 0.00001$
Without IHD (n=2702)	904	1798	
Obesity (n=218)	47	171	$\chi^2=23.10p < 0.00001$
Without obesity (n=2782)	1053	1729	
Mild as CT severity <8 score (n=400)	171	229	$\chi^2=179.44p < 0.00001$
Moderate as CT severity 9-15 (n=1450)	358	1092	
Severe as CT severity >15 (n=1150)	571	579	

Results: core observations

In radiological response phenotype, ‘Evolved’ and ‘Evolving’ patterns were observed in 36.66% and 63.33% respectively. (Table 2) Significant association was documented in radiological 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 easy to difficult phenotype. [Table 3]

Laboratory parameters at entry point (d-dimer, CRP, IL-6) showed significant association with radiological phenotypes as ‘Evolved’ and ‘Evolving’ pneumonia. [p<0.00001] (Table 4) In present study, significant association documented in radiological phenotypes as ‘Evolved’ and ‘Evolving’ pneumonia with interventions required in indoor unit. [p<0.00001] (Table 5) Post COVID-19 lung fibrosis or sequelae has significant association with radiological phenotypes. [p<0.00001] (Table 6)

Table 2. Radiological ‘Evolved’ and ‘Evolving’ phenotypes

	Present (n=3000)	Percentage (%)
Evolving (Predominant GGOs)	1900	63.33
Evolved (Predominant GGOs)	1100	36.66

Table 3. Duration of illness (DOI) at entry point during hospitalization and Radiological ‘Evolved’ and ‘Evolving’ phenotypes in COVID-19 pneumonia cases (n=3000)

Duration of illness	Evolved (n=1100)	Evolving (n=1900)	Analysis
<7 days (n=1562)	234 (21.27%)	1328 (69.89%)	$\chi^2=662.00$
8-15 days (n=882)	544 (49.45%)	338 (17.78%)	p<0.00001
>15 days (n=556)	322 (29.27%)	234 (12.31%)	

Table 4. Association of Radiological ‘Evolved’ and ‘Evolving’ phenotypes with inflammatory markers assessment

	Evolved (n=1100)	Evolving (n=1900)	Analysis
Laboratory parameters (CRP, IL-6, ferritin, LDH, D-dimer) more than four-fold (n=2750)	890 (80.90%)	1860 (97.89%)	$\div 2=263.12$ p<0.00001
Laboratory parameters (CRP, IL-6, ferritin, LDH, D-dimer) less than four-fold (n=250)	210 (19.09%)	40 (2.10%)	

Table 5. Association of Radiological ‘Evolved’ and ‘Evolving’ phenotypes with interventions during hospitalization in COVID-19 pneumonia (n=3000)

	Evolved (n=1100)	Evolving (n=1900)	Analysis
Oxygen (n=1144)	695 (63.18 %)	449 (23.63%)	$\div 2=863.52$ p<0.000026
Oxygen plus ventilatory support (n=1306)	95 (8.63%)	1211 (63.73%)	
No oxygen or ventilator (n=550)	310 (28.18%)	240 (12.63%)	

Table 6. Radiological ‘Evolved’ and ‘Evolving’ phenotypes at entry point and its correlation with post-covid lung fibrosis (n=622)

Post-covid Covid pneumonia fibrosis	Evolved (n=1100)	Evolving (n=1900)	Analysis
Pulmonary fibrosis present (n=622)	324 (29.45%)	298 (15.68%)	$\div 2=80.38$ p<0.00001
Pulmonary fibrosis absent (n=2378)	776 (70.54%)	1602 (84.31%)	

Discussion:

1. Evolved and Evolving phenotypes in study cases:

We have observed important role of CT thorax in early diagnosis of COVID-19 pneumonia by analyzing GGOs in early stage of illness (less than one week) and in cases with duration of illness more than 2 weeks. In both scenarios chances of false negative RT PCR is high and we have repeated RT PCR to confirm diagnosis. Thus, 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. Anatomical extent of involvement correlates very well with disease severity and laboratory parameters as documented in our study.¹⁶⁻²⁷

2. Evolved and Evolving phenotypes in study cases and its correlation with duration of illness:

Duration of illness before hospitalization plays a crucial role in predicting radiological 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.²⁸ We have observed surprising distribution of COVID-19 cases in Evolved and Evolving phenotypes as per duration of illness. As duration of illness increases there would be more consolidation in imaging or resolving GGOs and consolidations as compared to predominant class. Duration of illness were considered in present study according to symptom onset reported by patient and attendants. Numerous authors have reported similar observation.^{29,30,31} Authors described hyaline membrane as probable mechanisms of GGOs in postmortem examination and documented GGOs as marker of advanced disease, organizing pneumonia with ARDS, and with risk of mortality and poor outcome.³²⁻³³

Interestingly, majority of cases in second & third week of illness were Evolved as compared to Evolving phenotype as observed in correlation with inflammatory markers and clinical parameters. This may be explained by facts of immune dysregulation due to COVID-19 manifested as GGOs predominantly observed in first week of illness and switched to consolidations with minimal GGOs during second and third week of illness as correlated with inflammatory markers. We have observed those cases with Evolving phenotype in third week were showing more lung parenchymal involvement with minimal GGOs plus consolidation with lucencies or breakdown suggestive of necrotizing type requiring ventilator support and aggressive interventions in indoor units. Authors have observed similar

findings^{15,34-35} 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.^{11,36}

3. Evolved and Evolving patterns in study cases and its correlation with laboratory inflammatory markers during hospitalization:

Laboratory parameters in Evolving category were predominantly four-fold raised due to more GGOs with other features such as more anatomical involvement and associated consolidation with necrosis. Studies have documented inflammatory markers titer analysis has positive correlation with radiological patterns, severity assessment, interventions required and outcomes in COVID-19 pneumonia.³⁷⁻⁴¹ Inflammatory markers titers were proportional to inflammation; more inflammation is observed in presence of GGOs in Evolving phenotype and less inflammation with minimal GGOs in Evolved phenotype were the probable mechanism for inflammatory pattern. Similarly, authors have reported role of inflammatory markers in association with CT findings.⁴²⁻⁴⁵ Very few cases (2.10%) cases in Evolving phenotype were shown less than four-fold raised inflammatory markers. Rationale for this would be lesser ongoing inflammation in presence of early GGOs in COVID-19 pneumonia which is indicator of controlled inflammation. Author have documented similar observation to our study.⁴⁶

4. Evolved and Evolving patterns in study cases and its correlation with interventions required during hospitalization:

Previously published data supports our findings.³⁷⁻⁴¹ More cases in Evolving phenotype required oxygen and oxygen plus ventilatory support as compared to Evolved phenotype would be because of more GGOs with crazy paving pattern and more inflammatory component resulting into more hypoxia as correlated with HRCT with more than four-fold raised inflammatory markers. Secondly, very few cases in Evolving phenotype neither required oxygen or ventilatory support and rational for this observation would be early GGOs with less than four-fold increased inflammatory markers resulting into controlled inflammation and less oxygen diffusion defect manifested as hypoxia. Numerous Authors have observed similar findings in their studies.⁴⁷⁻⁴⁹ Surprisingly, 28.18% of cases in Evolved pneumonia phenotype doesn't 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 less than four-fold inflammatory markers. Still 8.63% cases required ventilatory support and 63.18% cases required oxygen support in Evolved phenotypes which is correlated

with inflammatory markers. Similarly, authors have reported matching observations to present study. [47-49]

5. Correlation of CT severity with Evolved and Evolving phenotypes:

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. Rational would be disproportionate inflammatory pattern, duration of illness, oxygenation status and interventions required in Evolved and Evolving categories in comparison to conventional CT severity scoring tool is pure anatomical assessment. Thus, Radiological phenotyping is superior to CT severity scaling as it will help in overall assessment of cases and considered as 'composite assessment'. As less anatomical area is involved in mild CT severity category, proportionately equal number of COVID-19 cases were in Evolved phenotype in comparison to Evolving phenotypes cases. Rational for same would be less inflammatory surge due to less lung parenchymal anatomical area involvement. Still in few numbers of cases were shown significant raised inflammatory markers with hypoxia and required oxygen supplementation with or without ventilatory support which is explained by predominant GGOs. Authors have overserved similar findings in their study.^{1,47-49} In moderate CT severity category, a greater number of cases were in Evolving in comparison to Evolved phenotypes, and CT severity has documented significant correlation with these radiological phenotypes. This could be explained by more GGOs, crazy paving with or without consolidation and necrosis in Evolving cases. Similar to our study, authors have documented similar observations.⁴⁷⁻⁴⁹ In this pandemic, CT severity scoring tool helped during initial assessment and triaging of these cases before hospitalization and treatment planning. This methodology was unable to predict course during hospitalization, interventions required during Indoor unit and to predict final outcome at entry point as compared to Evolved and Evolving radiological phenotype which involves 'composite assessment.'

6. Does radiological phenotype predict long term radiological outcome?

Lung fibrosis has been documented in 29.45% (324/1100) cases in 'Evolved' radiological phenotype and 15.68% (298/1900) in 'Evolving' radiological phenotype. 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 form hospital. Numerous authors have reported similar observations to our study.³⁷⁻⁴¹

We have done retrospective analysis of radiological patterns and 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. Authors have reported similar observations in their studies. [8, 50-53]

7. Association of covariates with radiological phenotypes:

In present study, age and gender has documented significant association with Evolved and Evolving 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.^{37-41, 50-53} In present study, covariates such as diabetes mellitus, IHD, Hypertension, COPD and Obesity with Evolved and Evolving radiological phenotypes which has been correlated with published data.^{37-41, 50-53}

8. Limitations of study:

Our study is having enough sample size and analyzed role of radiological phenotypes in correlation with laboratory and clinical marker in 'composite 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 with consideration of 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 documented aggressive interventions required in indoor stay and oxygen supplementation at home after discharge with or without comorbidities.

Conclusions and learning points:

Radiological patterns or phenotypes have documented important role in assessing disease severity in COVID-19

pneumonia. Evolved and Evolving phenotypes help in triaging the cases at entry point in correlation with clinical and laboratory inflammatory markers analysis. Phenotypic categorization is simple, sensitive and guided during treatment planning in indoor units. Phenotyping in Evolved category in correlation with laboratory and clinical parameters have documented role in predicting lesser need of aggressive interventions in comparison to Evolving phenotypes.

Radiological phenotyping is natural trend of evolution of COVID-19 pneumonia at entry point. Presence or absence of GGOs, consolidations and crazy paving with necrosis were key radiological markers in categorizing these phenotypes. Radiological phenotyping should be correlated with clinical and laboratory parameters for accurate analysis of severity assessment, duration illness prediction and inflammatory markers workup. Phenotyping will also help in monitoring of COVID-19 pneumonia cases and guide for necessary timely interventions in indoor units to have successful treatment outcome. Post covid fibrosis is reversible and should be labeled as sequela due to near total reversible nature.

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