Early CT imaging markers of COVID-19 progression

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Research

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Abstract

Background: Early recognition of patients who are prone to develop severe or critical COVID-19 pneumonia may improve its management and modify its outcome by better treatment regimens.

Objective: To investigate Computed Tomography (CT)-based early markers of COVID-19 progression.

Material and methods: Thirty-two COVID-19 patients were retrospectively enrolled, including 23 moderate cases who remained moderate until being cured and discharged from hospital, and 9 progressive cases who started with moderate pneumonia and later progressed to severe or critical pneumonia. Clinical and CT data in the early course of disease were reviewed and compared. The association between early features and progression of COVID-19 were analyzed.

Results: The multivariate logistic regression analysis revealed that the progression of COVID-19 were significantly associated with older age and higher CT score of the right lower lobe in the early CT images. After adjustment for relevant covariates, the relationship between CT score of the right lower lobe and COVID-19 progression persisted (odds ratio 19.28, 95% confidence interval 1.07 - 348.34).

Conclusions: Higher CT Score of the right lower lobe in early images and older age appeared to be promising biomarkers for early prediction of COVID-19 prognosis. Extensive involvement of the right lower lobe at the early stage may suggest a high risk of progression.

Introduction

Emerging in late December 2019 in Wuhan, China, coronavirus disease 2019 (COVID-19) has rapidly spread to 199 countries around the world and become a global health threat. As of March 28, 2020, there had been 522343 confirmed cases and 24531 deaths worldwide [1, 2]. The causative agent was identified to be a novel coronavirus currently termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. Although most of people with COVID-19 have a mild clinical course, severe pneumonia occurred in 15.7% of cases [4]. Severe and critical COVID-19 patients have higher incidences of acute respiratory distress syndrome (ARDS) and serious complications, and have a high likelihood of admission to intensive care [5]. It has been reported that the mortality of severe COVID-19 is high (28%- 62%) [6–8], and even higher (81%) among those requiring mechanical ventilation [6, 9]. Treatment of severe and critical COVID-19 patients remains an arduous challenge in current clinical practice [6].

Early recognition of patients who are prone to develop severe and critical COVID-19 may improve its management and modify its outcome by better treatment regimens. Therefore, early prediction of progression is of utmost importance. Practicable biomarkers of evolving illness severity are urgently required to enable timely intervention. Chest computerized tomography (CT) provides a powerful noninvasive mean for the diagnosis and treatment monitoring for COVID-19, which shows diverse patterns with both lung parenchyma and interstitium involved. However, the correlation between CT findings and clinical progression, and the predictive value of baseline CT for disease outcome are not well

understood as of to date [10–13]. Therefore, in this study, we compared the differences of baseline CT features of moderate and progressive patients at the onset of COVID-19 pneumonia, exploring potential imaging marker tracking COVID-19 progression since the early stage of the disease.

Material And Methods

This retrospective study was approved by the Institutional Review Board of People's Hospital of Guangxi Zhuang Autonomous Region, and the requirement for informed consent was waived.

Study Subjects

We performed a retrospective review of 32 consecutive patients with COVID-19 in People's Hospital of Guangxi Zhuang Autonomous Region from January 2020 to March 2020. The diagnosis was established according to the Diagnosis and Treatment Guidelines of COVID-19 in China (trial version fifth) [14], and confirmed by positive real time reverse transcriptase polymerase chain reaction of SARS-CoV-2 in throat swabs or samples from lower respiratory tract. Inclusion criteria required clinical and chest CT data at the beginning of symptoms to evaluate characteristics in the early course of disease. Patients without abnormal manifestations on CT were excluded.

The patients were grouped based on the illness severity defined by the National Health Commission of China. The severe/critical cases met at least one of the following [14]: 1) breathing rate ≥ 30 breaths per minute; 2) pulse oximeter oxygen saturation $\leq 93\%$ in a resting state; 3) arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) ≤ 300 mmHg; 4) respiratory failure ($\text{PaO}_2 < 60$ mmHg when breathing ambient air) occurred and mechanical ventilation required; 5) hemodynamic shock; 6) patients with other organ failure needed intensive care unit monitoring and treatment. Five mild patients with normal CT were not included in the study, so the rest cases were placed in moderate group.

Data Collection

Data included age, gender, comorbidities (hypertension, diabetes mellitus, heart disease, cerebrovascular diseases, and chronic obstructive pulmonary disease), symptoms, clinical sign, laboratory findings, and CT images were obtained from medical records. Both clinical and radiological parameters at the initial stage were used to gather information on early features that may be related to COVID-19 progression. Time from initial CT examination to severe/critical pneumonia development, and time from symptom onset to severe/critical pneumonia development were calculated.

Ct Scanning Protocol

CT examinations were performed on a 64-detector row SOMATOM go. Top (Siemens Healthineers, Erlangen, Germany), or a 64-detector row Revolution Frontier ES (GE Healthcare, China Branch, Beijing,

China), with the following parameters: tube voltage: 120 kVp, tube current with the automatic milliamperage technology: 32–250 mAs, pitch: 1.5 or 1, tube rotation time: 0.5 s or 0.75 s, matrix: 512 × 512, slice thickness: 0.6 mm, reconstruction thickness: 1.0 mm. Unenhanced CT scans were obtained for all patients.

Image Viewing And Evaluation

Three chest radiologists with 6, 9 and 11 years of experience who were blinded to the clinical data evaluated the CT findings in consensus. For each of the 32 patients, the initial chest CT images were analyzed for the following points: 1) number of the lesions, indicated as single lesion or multiple lesions; 2) site of the lesions, indicated as right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), and left lower lobe (LLL); 3) range of lobe involvement: indicated as single lobe involvement, 2 lobes involvement, 3 lobes involvement, 4 lobes involvement, and 5 lobes involvement; 4) transverse distribution of the lesion: described as peripheral, central, and peripheral and central; 5) lesion density, described as ground glass opacity (GGO), consolidation, mixed GGO and consolidation; 6) types of lesion density: classified as 1, 2, and 3; 7) shape of the lesion: described as round, fan-shaped, rectangular, bat-wing, and irregular; 8) other following characteristics: interlobular septal thickening, air bronchogram, microvascular dilation sign, fibrotic streaks, pulmonary emphysema, thickening of pleura, pleural retraction sign, pleural effusion, and lymphadenopathy; 9) extent of lesions: to quantify the extent of lesions and the degree of involvement, a thin section CT score was assigned on the basis of all abnormal areas involved. Each lobe was assigned a score that was based on the following: score 0, denoted no involvement; score 1, < 25% involvement; score 2, 25% to less than 50% involvement; score 3, 50% to less than 75% involvement; and score 4, $\geq$ 75% involvement. There was a score of 0–4 for each lobe, with a total possible score of 0–20 (Figs. 1 and 2).

Statistical Analysis

All statistical analyses were performed with the SPSS 17.0 software package (SPSS Inc., Chicago, IL, United States). Categorical variables were described as frequency rates and percentages, and quantitative variables were described using mean $\pm$ SD or median (inter quartile range, IQR) values. The Fisher exact test were used for categorical variables. For quantitative variables, independent sample *t* test was used for normally distributed data, and Mann-Whitney *U* test was used for non- normally distributed data. Subsequent univariate and multivariate logistic regression analysis were performed to further identify the initial clinical parameters and baseline CT features associated with the progression of COVID-19 pneumonia. *P*-values < 0.05 were considered significant.

Results

Clinical Characteristics

A total of 32 patients were included in the study, 9 (28.1%) were progressive cases who later progressed from moderate cases to severe/critical cases, and 23 (71.9%) were moderate cases who remained moderate until being cured and discharged. The clinical characteristics of the patients are shown in Table 1. The mean time from initial CT examination to severe/critical pneumonia development was 5 days, and that from symptom onset to severe/critical pneumonia development was 9 days.

Table 1
Baseline clinical characteristics between moderate group and progressive group

Parameter	Moderate (n = 23)	Progressive (n = 9)
Age (y)*	35.8 ± 13.6	61.1 ± 15.2
Sex (male)	5 (22%)	3 (30%)
Onset of symptoms to severe/critical pneumonia hospital (d)	0	9
Baseline CT examination to severe/critical pneumonia (d)	0	5
Comorbidities*	1 (4%)	4 (44%)
Hypertension	1 (4%)	2 (22%)
Diabetes mellitus	0	1 (11%)
Cerebrovascular diseases	0	1 (11%)
Oxygenation index (mmHg)	489.5 ± 192.6	502.9 ± 341.9
White blood cell count($\times 10^9/L$)	6.6 ± 2.0	6.9 ± 1.8
Hemoglobin (g/L)	116.6 ± 16.9	109.2 ± 24.3
Neutrophil ratio (%)	54.9 ± 14.8	58.3 ± 12.4
Lymphocyte ratio (%)	33.3 ± 13.7	26.4 ± 14.7
Creatinine ($\mu\text{mol/L}$)	59.9 ± 14.8	67.4 ± 15.1
Erythrocyte sedimentation rate (s)	33.7 ± 21.2	47.5 ± 29.2
Data are expressed as mean ± SD or n (%).		
* Significance of difference between parameters from moderate and progressive groups.		

Compared with the moderate group, the progressive cases were significantly older (mean age 61.1 ± 15.2 years vs 35.8 ± 13.6 years; $P < 0.01$) and had more comorbidities of hypertension, diabetes mellitus, and cerebrovascular diseases ($P = 0.02$). No significant differences were observed in gender, oxygenation index, white blood cell count, hemoglobin, neutrophil ratio, lymphocyte ratio, creatinine, and erythrocyte sedimentation rate between the two groups.

Ct Findings

There were significant differences between the two groups in the total CT score of both lungs ($P < 0.01$), the CT scores of each lung lobe, and incidence of right middle lobe involvement ($P < 0.01$) and all lobes involvement ($P < 0.01$).

No significant differences were observed in number of the lesions, transverse distribution of the lesion, lesion density, shape of the lesion, interlobular septal thickening, air bronchogram, microvascular dilation sign, fibrotic streaks, pulmonary emphysema, thickening of pleura, pleural retraction sign, pleural effusion, and lymphadenopathy between the two groups. The CT Features were present in Table 2.

Table 2
CT Features between moderate group and progressive group

Parameter	Moderate (n = 23)	Progressive (n = 9)
Number of lesions		
Single	2 (9%)	1 (11%)
Multiple	21 (91%)	8 (89%)
Lesion distribution		
Peripheral	17 (74%)	4 (44%)
Peripheral and central	6 (26%)	5 (56%)
Density		
GGO	12 (52%)	5 (56%)
Mixed	19 (83%)	8 (89%)
Consolidation	6 (26%)	2 (22%)
Number of types of density		
1 type of density	12 (52%)	4 (44%)
Only GGO	5 (22%)	1 (11%)
Only mixed	7 (30%)	3 (30%)
Only consolidation	0	0
2 types of density	10 (43%)	4 (44%)
GGO + mixed	0	3 (30%)
Mixed + consolidation	4 (17%)	1 (11%)
GGO + consolidation	6 (26%)	0
3 types of density	1 (4%)	1 (11%)
Total CT score of the pulmonary involvement*	4 (2–5)	10 (5.5–15.5)
CT score of RUL*	1 (0–1)	1 (1–3)
CT score of RML*	1 (0–1)	1 (1–3)
Data are expressed as n (%) and median (interquartile range). GGO = ground-glass opacity. Mixed = GGO and consolidation. RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe (RLL), LUL = left upper lobe, LLL = left lower lobe.		
* Significance of difference between parameters from moderate and progressive groups.		

Parameter	Moderate (n = 23)	Progressive (n = 9)
CT score of RLL*	1 (1–1)	3 (1–3.5)
CT score of LUL*	0 (0–1)	1 (1–1)
CT score of LLL*	1 (1–1)	3 (1–4)
Interlobular septal thickening	20 (87%)	9 (100%)
Air bronchogram sign	1 (4%)	1 (11%)
Microvascular dilation sign	22 (96%)	9 (100%)
Pulmonary emphysema	1 (4%)	0
Thickening of pleura	19 (83%)	9 (100%)
Pleural retraction sign	18 (78%)	8 (89%)
Pleural effusion	1 (4%)	3 (30%)
Unilateral pleural effusion	0	1 (11%)
Bilateral pleural effusion	1 (4%)	2 (22%)
Lymphadenopathy	5 (22%)	3 (30%)
pulmonary artery enlargement	1 (4%)	1 (11%)
Frequency of lobe involvement		
RUL	14 (61%)	8 (89%)
RML*	5 (22%)	8 (89%)
RLL	20 (87%)	9 (100%)
LUL	12 (52%)	8 (89%)
LLL	19 (83%)	8 (89%)
Number of lobes involved		
1 lobe involved	4 (17%)	1 (11%)
Only RLL	3 (13%)	1 (11%)
Only LLL	1 (4%)	0

Data are expressed as n (%) and median (interquartile range). GGO = ground-glass opacity. Mixed = GGO and consolidation. RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe (RLL), LUL = left upper lobe, LLL = left lower lobe.

* Significance of difference between parameters from moderate and progressive groups.

Parameter	Moderate (n = 23)	Progressive (n = 9)
2 lobes involved	3 (13%)	0
RUL + LLL	1 (4%)	0
RLL + LLL	2 (9%)	0
3 lobes involved	4 (17%)	0
RUL + RLL + LLL	1 (4%)	0
RUL + LUL + LLL	1 (4%)	0
RML + RLL + LLL	2 (9%)	0
4 lobes involved	4 (17%)	0
RUL + RML + RLL + LUL	1 (4%)	0
RUL + RML + RLL + LLL	1 (4%)	0
RUL + RLL + LUL + LLL	2 (9%)	0
RML + RLL + LUL + LLL	1 (4%)	0
5 lobes involved*	7 (30%)	8 (89%)
Shape		
Round	16 (70%)	4 (44%)
Fan-shaped	14 (61%)	8 (89%)
Rectangular	11 (48%)	5 (56%)
Bat wing	0	3 (30%)
Irregular	16 (70%)	8 (89%)
Strip	0	1 (11%)
Number of types of shape		
1 type of shape	6 (26%)	2 (22%)
Round	2 (9%)	0
Fan-shaped	1 (4%)	1 (11%)

Data are expressed as n (%) and median (interquartile range). GGO = ground-glass opacity. Mixed = GGO and consolidation. RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe (RLL), LUL = left upper lobe, LLL = left lower lobe.

* Significance of difference between parameters from moderate and progressive groups.

Parameter	Moderate (n = 23)	Progressive (n = 9)
Rectangular	0	0
Bat wing	0	1 (11%)
Irregular	3 (13%)	0
2 types of shape	6 (26%)	1 (11%)
Round + irregular	3 (13%)	0
Round + fan-shaped	2 (9%)	1 (11%)
Fan-shaped + rectangular	1 (4%)	0
3 types of shape	8 (35%)	3 (33%)
Round + fan-shaped + rectangular	1 (4%)	0
Round + fan-shaped + irregular	6 (26%)	1 (11%)
Fan-shaped + rectangular + irregular	2 (9%)	2 (22%)
4 types of shape	2 (9%)	2 (22%)
Round + fan-shaped + rectangular + irregular	2 (9%)	1 (11%)
Fan-shaped + rectangular + bat wing + irregular	0	1 (11%)
5 types of shape	0	2 (22%)
Round + fan-shaped + rectangular + bat wing + irregular	0	1 (11%)
Round + fan-shaped + rectangular + strip + irregular	0	1 (11%)
Data are expressed as n (%) and median (interquartile range). GGO = ground-glass opacity. Mixed = GGO and consolidation. RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe (RLL), LUL = left upper lobe, LLL = left lower lobe.		
* Significance of difference between parameters from moderate and progressive groups.		

Factors Associated With Progression

Table 3 showed the results of univariate and multivariate logistic regression analyses on relationship to the progression of COVID-19 pneumonia. Based on univariate logistic regression analyses, the clinical characteristics and CT features of age, comorbidities, total CT score of both lungs, CT scores of each lung lobe, and incidence of all lobes involvement were correlated with the progression of COVID-19 pneumonia. However, only the CT score of right lower lobe and age were confirmed to be associated with COVID-19 progression in subsequent multivariate logistic regression analyses. After adjustment for age

and other relevant covariates, the relationship between CT score of right lower lobe and COVID-19 progression persisted, odds ratio = 19.28 (95% confidence interval 1.07–348.34).

Table 3
Univariate and Multivariate Logistic Regression Analyses of Baseline Clinical and CT features for Progression of COVID-19 pneumonia

Parameter	Univariate			Multivariate		
	OR	95%CI	P Value	OR	95%CI	P Value
Age (y)	1.18	1.05–1.32	< 0.01	1.25	1.01–4.53	0.04
Comorbidities	17.6	1.60–193.4	0.02			
CT score of RUL	3.86	1.24–11.95	0.02			
CT score of RML	2.78	1.10–7.08	0.03			
CT score of RLL	6.84	1.83–25.54	< 0.01	19.28	1.07–348.34	0.04
CT score of LUL	2.71	1.21–6.06	0.02			
CT score of LLL	4.28	1.44–12.74	< 0.01			
Total CT score	1.55	1.11–2.17	0.01			
RML involved	7.33	0.78–68.48	0.08			
All lobes involved	18.29	1.91–175.34	0.01			
Odds Ratio = OR, CI = Confidence interval						

Discussion

The severe/critical patients have worse prognosis and higher mortality than the moderate patients. Therefore, it is essential to perform active intervention for COVID-19 cases who are more likely to progress before developing into severe/critical stages, and the key lies in the early assessment of potential risk of progression [15]. This study demonstrated that older age and higher CT score of right lower lobe in the early images were risk factors for the progression of COVID-19. They may be promising biomarkers for predicting the progression of COVID-19. Such an early identification of patient at risk of progression would be of paramount clinical importance, because it could allow for the design and implementation of personalized preventive and therapeutic strategies, thereby improving the prognosis and reducing the mortality.

In this study, we found that older age was risk factor for the progression of COVID-19 pneumonia. Previous studies have generally assumed that the elderly were more seriously ill after infection [1, 6, 7, 16, 17]. Older people are more likely to develop disease progression, which may be the result of their weakened immune function [5]. In our study, the rate of underlying disease was significantly associated

with the progression based on univariate logistic regression analyses, but subsequent multivariate analysis negated the significance of it. Some previous studies on COVID-19 pneumonia showed that the rate of underlying disease was not significantly different between nonemergency group and emergency group [17]. However, some other previous studies showed that people with underlying disease were more seriously ill after infection [16]. The differences between these studies may have been due to patients selection bias, sample sizes, different research parameters, and different statistical methods (e.g., some of these studies did not use multivariate analysis).

Most patients with COVID-19 pneumonia had GGO or mixed GGO and consolidation, interlobular septal thickening, and vascular enlargement in the lesion, and the lesions were more likely peripheral distribution, bilateral involvement, and multifoca [12, 13, 18–22]. In our study, above CT features of COVID-19 pneumonia were not associated with the progression, indicating that above CT features in early-phase were not risk factors of the progression of COVID-19 pneumonia. Some previous studies showed that the CT findings of consolidation, linear opacities, crazy paving pattern, bronchial wall thickening, high total CT scores of involvement, lymphnode enlargement, pericardial effusion, and pleural effusion were features of severe/critical COVID 19 pneumonia, and were related to the severity of disease [16]. In this study, above CT features of severe/critical COVID-19 pneumonia were not associated with the progression based on initial baseline Chest CT. However, the CT score of right lower lobe in the early images was strongly related to the progression, independently of the age. It is unclear at this time why more severe involvement of right lower lobe in the early images was associated with COVID-19 deterioration. The phenomenon may be related to the deeper location and higher load of the culprit virus. Since the right mainstem bronchus is shorter, wider, and more vertical in direction than the left, the anatomical feature may facilitate the invasion of virus, which has been proposed in the cases of influenza pneumonia [23] and H7N9 pneumonia [24]. Besides, the right lower lobe, which included 5 lung segments, seemed to make the largest contribution to ventilation, thus facilitating aspiration of SARS-CoV-2 [25]. The extensive lesions of the right lower lung in the early phase may reflect more viral colonization that leads to further dissemination and progression of the infection. Another possible explanation was the exudation process of COVID-19, which was more obvious than in SARS. Pathological autopsy in COVID-19 patients showed massive foam mucus exudates in the lung [26]. In addition, acute exudation was especially evident among rapidly progressing cases [26]. Based on these observations [27], we deduced that exudation in the early phase of severe COVID-19 may be active. The massive exudate may easily accumulate in the right lower lung through the vertical right bronchus, resulting in more extensive lesions of right lower lung in CT images. Accordingly, in the early course of COVID-19, high CT Score of the right lower lobe may also suggest an active exudative inflammation that constituted the pathophysiological basis of pulmonary dysfunction.

Previous studies showed that there were many differences in laboratory indicators between COVID-19 pneumonia and non-COVID-19 pneumonia patients, or between the moderate and severe/critical COVID-19 pneumonia patients [1, 5–7, 12, 16]. However, in our study, these initial laboratory indicators of oxygenation index, white blood cell count, hemoglobin, neutrophil ratio, lymphocyte ratio, creatinine, and erythrocyte sedimentation rate were not associated with the progression of COVID-19 pneumonia.

This study has several limitations. Firstly, data of the two groups were not balanced. The sample size of the progressive group was limited because most severe/critical patients presented with rapid deterioration and their early data was unavailable. Further studies with more patients especially progressive cases are warranted. Secondly, we had not performed further investigation of the pulmonary lesions early in the course of the disease, due to the lack of inspection equipment in temporary isolation wards. Bronchoscopy, bronchoalveolar lavage and lung biopsy are required to further confirm the nature of the lesions.

Conclusion

According to our findings, Higher CT Score of the right lower lobe in the early images and older age appeared to be promising biomarkers that may potentially be useful for early prediction of COVID-19 prognosis. Extensive involvement of the right lower lobe at the early stage may suggest a high risk of progression. Further prospective studies are required to confirm and interpret the association.

Declarations

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Authors' contributions

Y. Wei, Y. Lu, K. Ye, Y. Su, J. Yuan collected the clinical and CT imaging dataset. Y. Chen, Z. Fu, Y. Yang processed and analyzed the data. Y. Yang, X. Liao provided statistical analysis. Y. Chen, F. Xu, L. Ma, Q. Wu conceived the project. Y. Chen, N. Tang, G. Huang edited the paper.

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Availability of data and materials

Data sharing requests from appropriate researchers and entities will be considered on a case-by-case basis. Interested parties should contact the corresponding author.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of People's Hospital of Guangxi Zhuang Autonomous Region, and the requirement for informed consent was waived.

Consent for publication

All authors gave their consent for publication.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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Figures

Figure 1

CT features of COVID-19 Pneumonia. This figure shows CT features indicating the number, involvement, distribution, shape, and density of the lesions, pleura and interstitial changes caused by COVID-19 Pneumonia. A–D. 15-year-old woman. Baseline CT images showed multifocal round pure ground-glass

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Figure 2

Extent of lesions and the degree of involvement in three patients with COVID-19 Pneumonia. A–D. 59-year-old woman, progressive case. Baseline CT images showed multifocal mixed GGO and consolidation lesions involved in all the lobes of both lungs (white arrow). The CT score of right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe was 1, 1, 3, 1 and 1, respectively. The total CT score of both lungs was 7. E–H. 56-year-old woman, moderate case. Baseline CT images showed multifocal mixed GGO and consolidation lesions involved in all the lobes of both lungs (white arrow). The CT score of right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe was 1, 1, 1, 3 and 1, respectively. The total CT score of both lungs was 7. I–L. 30-year-old woman, moderate case. Baseline CT images showed multiple pure GGO lesions with obscure boundary involved in all the lobes of both lungs (white arrow). The CT score of right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe was 3, 1, 1, 2 and 1, respectively. The total CT score of both lungs was 8.