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CT-based staging and prognosis of novel coronavirus (COVID-19) pneumonia: correlation with blood glucose levels

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Abstract. – OBJECTIVE: Based on the latest epidemic situation and field experience, this study aims to explore the correlation of computed tomography (CT) stages and blood glucose level in patients with novel coronavirus pneumonia (COVID-19).

PATIENTS AND METHODS: The clinical data of first and multiple CT imaging re-examination and blood glucose levels from 62 confirmed cases of COVID-19 were collected for a retrospective analysis to determine the correlation between glucose level and CT-based staging.

RESULTS: Of the 62 COVID-19 patients, 48 cases of early stage and 14 cases of advanced stage were found in the CT data of the first diagnosis. These 62 cases were currently under follow-up (17-32 days): 18 cases in early stage-resorption stage, 25 cases in early stage-advanced stage-resorption stage, 12 cases in advanced stage-resorption stage, 5 cases in early stage -advanced stage-severe stage-resorption stage, and 2 cases in advanced stage-severe stage-resorption stage. Among them, the CT of 14 patients with advanced stage at the first diagnosis showed multiple stage lesions (advanced stage + early stage) at the same time. Patients presented with statistically significant changes in blood glucose at early stage-resorption stage, early stage-advanced stage-resorption stage, advanced stage-resorption stage, and early stage-advanced stage-severe stage-resorption stage ($p<0.05$). However, no statistically significant alterations were observed in the glucose level of patients with advanced stage-severe stage-resorption stage ($p>0.05$).

CONCLUSIONS: Alteration of blood glucose is positively correlated with CT-based staging of COVID-19. Blood glucose is of great value in clinical diagnosis of COVID-19 and in determining the stage and prognosis of this disease.

Key Words:
Novel coronavirus pneumonia, COVID-19, Computed tomography, Tomography, Blood glucose, Disease course, Diagnosis.

Introduction

At the end of 2019, the 2019 Novel Coronavirus (COVID-19) has broken out and is propagating across the globe[1]. SARS-CoV-2 belongs to Beta Coronavirus[2,3]. Patients infected with SARS-CoV-2 mainly present with pulmonary inflammation, which is called Novel Coronavirus Pneumonia (hereinafter referred to as COVID-19). SARS-CoV-2 is highly contagious and the population is generally susceptible. Patients usually have a history of epidemiological exposure, mainly manifested as symptoms of lower respiratory tract infections, such as dry cough, fever, and dyspnea[4]. In severe cases, acute respiratory distress syndrome (ARDS) and sepsis may occur[5]. Most patients have a favorable prognosis, and the elderly or those with chronic underlying diseases have a poor prognosis[3]. At present, the patient's epidemiological exposure history, clinical manifestations (fever, normal or reduced early stage white blood cell count, reduced lymphocyte count, any two of them) and typical pneumonia imaging features are clinically used as criteria for suspected cases of SARS-CoV-2 infection or clinical diagnosis[6]. Combined with the etiological evidence of the respiratory tract or blood specimens (real-time fluorescent RT-PCR), a positive SARS-CoV-2 nucleic acid can be confirmed[3]. An increasing number of authoritative journals at home and abroad have reported the important value of CT in the diagnosis and treatment of COVID-19[7]. However, in the course of the disease, CT is self-limiting in determining the disease course, and blood glucose test is convenient and fast. Therefore, the joint examination of the two should be applied to determine the course of the disease, which provides a high clinical value.

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Patients and Methods

Baseline Characteristics

A total of 62 confirmed patients with SARS-CoV-2-positive nucleic acid test between 2020.01.22 and 2020.03.22 were collected in the Ningbo First Hospital, including 21 males and 41 females, aged from 32 to 85 years, with a mean age of 60.7 years. Thirty-five patients (56.45%) had chronic diseases such as heart disease, hypertension, and diabetes, and 27 patients (43.55%) had no chronic medical history. There were 30 cases of fever, 21 cases of cough and sputum, 16 cases of dyspnea, 3 cases of chest tightness and pain, 6 cases of diarrhea, and 2 cases were asymptomatic. The study was conducted under the approval of the Ethics Committee of Ningbo First Hospital. All participating patients signed informed consent documentation.

High-Resolution Computed Tomography (Hrct) Scanning Method and Image Processing

Philips Brilliance 16 and Siemens Sensation 16 spiral CT machines were adopted for HRCT scanning. All patients undergoing scanning were in the supine position with their arms raised and their heads advanced. Individuals to be detected hold their breath at the end of inspiration and were scanned continuously from the thoracic inlet to the lower margin of adrenal gland. The scanning parameters are listed as follows: tube voltage = 120 kV, tube current = 200-300 mA, scanning collimator width = 1 mm × 16 mm, pitch = 0.75, layer thickness and layer distance = 5 mm. The lesions were reconstructed after conventional scanning. The reconstruction layer thickness and interval were 1 mm or 2 mm, and the bone algorithm and standard algorithm were used for reconstruction.

Blood glucose level was measured by a Hitachi 7060 automatic biochemical detector through the glucose oxidase method. Notably, the whole blood glucose concentration ≥ 7.0 mmol/L was considered as hyperglycemia.

Ct-Based Staging of COVID-19

CT signs of COVID-19 patients were analyzed after image processing. The location, morphology, distribution, extent, density, and internal structure of the lesions were observed, such as thickened lobular septum and central nodules of the lung lobules. The relationship between lesions and bronchial blood vessels, the condition of stripe signs, and the presence of solid component signs were determined. Morphological changes and imaging signs were observed in patients with dynamic follow-up.

According to the extent of the lesion and CT findings, COVID-19 can be divided into 4 stages. (1) Early stage: focal ground-glass opacity (GGO) was not distributed across segments, but multiple lesions may occur. (2) Advanced stage: the lesions were distributed across segments and had a large range of GGO, including paving stone sign and mixed GGO and solid component signs. There were also solid component signs, regardless of the size of the range. (3) Severe stage: it developed from the advanced stage, and the lesion area had increased significantly on the basis of previous examination. The CT manifestation was "butterfly sign" and even "white lung". (4) Resorption stage (or recovery stage): the main manifestation was the narrowed lesion range and the lightened density on the basis of the previous stage, and the characteristic stripe sign appeared.

Index Observation

The changes of blood glucose in different CT stages of the same patient were compared and analyzed.

Statistical Analysis

The data obtained were analyzed with SPSS 13.0 (Chicago, IL, USA) statistical software. Chi-square test was used for comparison in count data. The measurement data were expressed as mean ± standard deviation. Paired *t*-test or independent sample *t*-test was conducted for comparison between two groups. One-way analysis of variance (ANOVA) was performed for comparison among multiple groups, followed by least-significant difference (LSD) post-hoc test. The difference was statistically significant at $p < 0.05$.

Results

Ct-Based Staging Analysis

Of the 62 COVID-19 patients, 48 cases of early stage and 14 cases of advanced stage were found in the CT data of the first diagnosis. These 62 cases were currently under follow-up (17-32 days): 18 cases in early stage-resorption stage, 25 cases in early stage-advanced stage-resorption stage, 12 cases in advanced stage-resorption stage, 5 cases in early stage -advanced stage-severe stage-resorption stage, and 2 cases in advanced stage-severe stage-resorption stage. Among them, the CT of 14

patients with advanced stage at the first diagnosis showed multiple stage lesions (advanced stage + early stage) at the same time. A total of 134 lesions (including 68 GGO, 45 paving stone-like signs, 20 mixed GGO and solid component signs, and 1 solid component sign) were found by initial CT examination of 57 COVID-19 patients. A short-term re-examination of CT revealed that 58 of the 68 GGOs were gradually and completely absorbed, and 10 of them were first converted to mixed GGO and solid component, and later an examination revealed that they were transformed into stripe signs. The 45 paving stone-like signs were successively transformed into mixed GGO and solid component signs, and later into stripe signs according to re-examination. For the 20 GGO and solid component signs, GGO was gradually resorbed, and the solid signs changed to stripe shadows.

Analysis of Changes in Blood Glucose Levels

In the detection of blood glucose levels in different CT stages, patients presented with statistically significant changes in blood glucose at early stage-resorption stage, early stage-advanced stage-resorption stage, advanced stage-resorption stage, and early stage-advanced stage-severe stage-resorption stage ($p < 0.05$). However, no statistically significant alterations were observed in the glucose level of patients with advanced stage-severe stage-resorption stage ($p > 0.05$) (Table I).

Discussion

Elevated Blood Glucose and Its Mechanism in COVID-19

The metabolism of blood glucose is regulated by a variety of hormones in the body. Insulin promotes the transfer of glucose from the blood into the tissue cells and lowers blood glucose levels[8]. Glucagon, glucocorticoids, growth hormone, and catecholamines, etc. can all raise blood glucose levels. When suffering from COVID-19 pneumonia, especially severe pneumonia, the body appears neurological and endocrine disorders under the stress responses, which induce the massive release of catecholamine hormones, glucagon, and glucocorticoids. Norepinephrine and epinephrine can increase glucagon secretion. Glucocorticoids can promote increased gluconeogenesis[9] and accelerated breakdown of glycogen. In addition, the sensitivity of tissues to insulin commonly decreases under stress, so blood glucose increases.

Ct Staging and Imaging Manifestations of COVID-19

At present, there is no uniform standard for COVID-19 imaging staging at home and abroad. Based on previous literature[10] and the characteristics of cases in Ningbo First Hospital, the authors recommend that COVID-19 can be roughly divided into four stages: early stage, advanced stage, severe stage and resorption stage (recovery stage), according to the onset time, clinical manifestations, lesion range and CT manifestations, as well as the course of the disease.

Early stage

The early stage of mostly COVID-19 represents day 1 to day 3 after the onset of symptoms. CT manifestations are single or multiple patchy or nodular GGO, with sub-pleural multiple patch GGO being the most common. There are often air bronchograms and thickened bronchial walls, and the boundaries are still clear. Early-stage COVID-19 manifested as single or multiple nodules with mixed GGO as the main part, and the boundaries were blurred with "halo sign", and some showed "thickened blood vessel" sign. The authors conclude that the pathological mechanism

Table I. Quantitative analysis of glucose level changes in different CT stages.

CT Stages	n	Glucose level (mmol/L)	p
Early stage-resorption stage	18	6.14 ± 1.58/7.60 ± 1.32	0.021
Early stage-advanced stage-resorption stage	25	7.03 ± 2.10/13.04 ± 4.51/7.87 ± 2.66	<0.0001
Advanced stage-resorption stage	12	10.59 ± 2.62/6.58 ± 1.60	0.0002
Early stage-severe stage-advanced stage-resorption stage	5	7.52 ± 1.38/13.60 ± 2.56/22.30 ± 4.01/8.48 ± 1.43	<0.0001
Advanced-severe-resorption stage	2	16.40 ± 6.79/23.80 ± 6.36/10.15 ± 3.32	0.201

at this stage may be alveolar septal capillary dilatation and congestion, fluid exudation in the alveolar cavity, and interlobular interstitial edema.

Advanced stage

The advanced stage of COVID-19 mostly represents day 4 to day 7 after the onset of symptoms. Compared with the early-stage CT findings, the lesion range was further expanded, the density became denser, and fusion or mass-like consolidation appeared. If there is no previous CT film as a comparison, the CT image exhibits multi-segment distribution clump or fused solid shadow, or higher density of GGO, concurrent with thickening of the lobular septum of the lung, and the interstitial line of the lobular parenchyma (paving stone sign), which the authors also classified as advanced stage. Sometimes there is a little pleural effusion. The pathological mechanism at this stage is the accumulation of a large amount of cell-rich exudate in the alveolar cavity, vasodilation and exudation in the interstitial blood vessels, both of which lead to exacerbation of alveolar and interstitial edema. Cellulose-like exudation connected each alveolar through the alveolar septum, showing a tendency to fuse and clump. In the later stage, the cellulose-like exudation of the alveolar cavity and the capillary congestion in the alveolar wall subsided and gradually became consolidated.

Severe stage. The severe stage of COVID-19 mostly represents the 1-2 weeks after the onset of symptoms. In severe cases, diffuse lesions of both lungs are often present. The CT image showed a large patchy or fusion-like consolidation with symmetrical distribution of the two lungs, showing "butterfly sign" or "upside-down butterfly sign" (Figure 1), and even presenting with "white lung". The pathological mechanism at this stage is that the scope of cellulose-like exudation in the alveolar cavity of the advanced stage is further expanded.

Resorption stage (recovery stage)

The COVID-19 resorption stage (recovery stage) is mostly the 2-3 weeks after the onset of symptoms, or even earlier. The main manifestations of CT: (1) The density of GGO becomes lighter, and is gradually completely resorbed, or GGO is completely resorbed, leaving a few stripe or small patchy consolidation signs (Figure 2). (2) Consolidation shadows are gradually replaced by GGO, stripe or strip shadows to form organizing lesions of chronic inflammation. The scope of the lesions is reduced, and further resorbed and disappeared. The pathological mechanism at this stage is that the cellulose-like exudation in the alveolar cavity is gradually resorbed, and the alveolar cavity is re-inflated, or a little organizing lesion remain.

Relationship Between Changes in Blood Glucose Levels and Ct Staging in COVID-19

The blood glucose level of 48 early stage patients was 6.75 mmol/L. The stress changes at early stage in the body are not intense, so blood glucose levels are generally normal or not high. In 14 advanced stage patients, the blood glucose level was significantly higher than normal, and

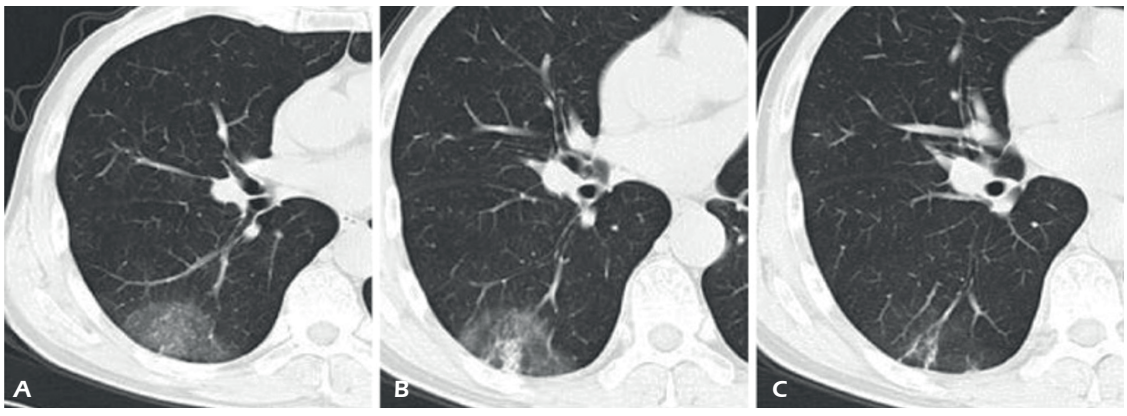

Figure 1. Chest CT images of a 37-year-old female COVID-19 patient at different stages. **A**, The patient had fever for 3 days. CT scan at the initial diagnosis shows focal GGO under the pleura in the dorsal segment of the right lower lobe (early stage). **B**, A re-examination of the chest CT on the 5th day of the disease course reveals wedge-shaped consolidation in the right lower lobe; **C**, Re-examination on the 12th day of the course shows that most of the lesions in the lower lobe of the right lung were resorbed at the same layer, leaving a few stripe shadows.

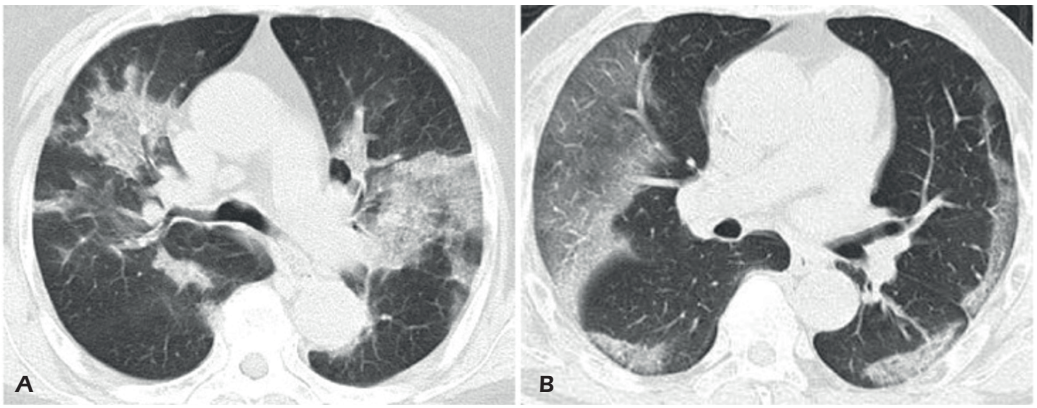

Figure 2. Chest CT images of "butterfly sign" or "upside-down butterfly sign" for typical severe-stage COVID-19. **A**, A chest CT image of an 80-year-old female COVID-19 patient. Chest CT re-examination shows that the two hilums are symmetrically distributed with large clumps of or fusion-like consolidation, showing "butterfly sign". **B**, A chest CT image of a 57-year-old male COVID-19 patient. Chest CT shows that GGO was distributed symmetrically and extensively under the pleura on both lateral sides of the lungs, with the long axis parallel to the pleura showing an "upside-down butterfly sign".

the disease progressed further than early stage, which was synchronized with CT manifestations. At this time, glucagon, glucocorticoids, growth hormone, and catecholamine hormones in the patient's body began to be released, resulting in increased blood glucose. Twelve patients with advanced stage progressed further to severe stage, and their blood glucose level further elevated or remained unchanged as compared to the advanced stage, and a few cases showed a decline. The authors speculate that the incidence of abnormal elevation in blood glucose is appreciably increased in pneumonia concurrent with systemic inflammatory response syndrome (SIRS) or multiple organ failure (MOF). Moreover, the incidence of abnormal elevation in blood glucose and blood glucose levels would increase in parallel with the aggravation of the disease. In addition, we also found that a more severe condition made it more difficult for blood glucose levels to return to normal after treatment.

Conclusions

It should be noted that the four CT stages of the disease course are not indispensable. In clinical practice, most patients only experience early stage-advanced stage-resorption stage, and only a few patients experience the severe stage. There are also patients whose course changes directly from early stage to resorption stage. Understanding the changes in blood glucose levels and CT staging can provide very important multidisciplinary references for further clinical treatment, especially in patients at severe stage. In summary, considering the close relationship between CT staging and changes in blood glucose levels can provide us with great help in further diagnosis and treatment of COVID-19.

Ethics Statement

The study was conducted under the approval of the Ethics Committee of Ningbo First Hospital. All participating patients signed informed consent documentation.

Author' Contributions

Chengcheng Xu conceived and designed the study, Xinzhong Ruan and Qiuli Huang collected the data, Zhenya Zhao and Li Ru analyzed the data and wrote the manuscript. Chengcheng Xu, Xinzhong Ruan, Qiuli Huang, Zhenya Zhao and Li Ru assisted with the data analyses and participated in the writing of the manuscript. Xueqin Chen contributed to revising the manuscript. All authors read and approved the final manuscript.

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Data Availability

The data obtained and/or analyzed during the current study were available from the corresponding authors on reasonable request.

Consent for Publication

Not applicable.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019) - recent trends. Eur Rev Med Pharmacol Sci 2020; 24: 2006-2011.
2) Comba A, Dunn PJ, Kish PE, Kadiyala P, Kahana A, Castro MG, Lowenstein PR. Laser capture microdissection of glioma subregions for spatial and molecular characterization of intratumoral heterogeneity, oncostreams, and invasion. J Vis Exp 2020; 158: 10.3791/60939. doi: 10.3791/60939.
3) New Coronavirus Pneumonia Diagnosis and Treatment Program, 2020. Available at: http://www.nhc.gov.cn/xcs/fkdt/202002/e84bd30142ab4d8982326326e4db22ea.shtml
4) Xu P, Sun GD, Li ZZ. Clinical characteristics of two human-to-human transmitted coronaviruses: Corona Virus disease 2019 vs. Middle East Respiratory Syndrome Coronavirus. Eur Rev Med Pharmacol Sci 2020; 24: 5797-5809.
5) Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 Janu-ary 2020. World Health Organization. Available at: https://www.who.int/publications/i/item/clinical-management-of-covid-19.
6) Yang CL, Qiu X, Zeng YK, Jiang M, Fan HR, Zhang ZM. Coronavirus disease 2019: a clinical review. Eur Rev Med Pharmacol Sci 2020; 24: 4585-4596.
7) Jacobi A, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review. Clin Imaging 2020; 64: 35-42.
8) Zhuang YG, Peng H, Huang F. A meta-analysis of clinical therapeutic effect of insulin glargine and insulin detemir for patients with type 2 diabetes mellitus. Eur Rev Med Pharmacol Sci 2013; 17: 2566-2570.
9) Whirledge S, Cidlowski JA. Glucocorticoids, stress, and fertility. Minerva Endocrinol 2010; 35: 109-125.
10) Loemology group of Chinese Society of Radiology; Committee on Infectious Disease Imaging Rb, Chinese Medical Doctor Association; Infection and Inflammation Radiology Society, Chinese Research Hospital Association. Guide to Imaging Diagnosis for New Coronavirus Pneumonia (First Edition, 2020). Journal of New Medicine 2020; 30: 22-34.