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Original Research Article

Correlation of Inflammatory Markers with Radiological Findings in Novel COVID-19 Diseased Patients in a Tertiary Care Centre in South India

K. Tamilmani[1], M. Subarathi[2], K.R. Minu Meenakshi Devi[3], V. Yogeswari*

[1]Associate Professor of Biochemistry, Govt. Villupuram Medical College, Villupuram
[2]Associate Professor of Biochemistry, Govt. Madurai Medical College, Madurai
[3]Associate Professor of Biochemistry, Govt. Coimbatore Medical College, Coimbatore
*Associate Professor, Department of Biochemistry, Govt. Vellore Medical College, Vellore

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Corresponding author: Dr. V. Yogeswari
Conflict of interest: Nil

Abstract

Background: In December 2019, SARS-COV-2 infection emerged in Wuhan, China causing COVID-19 and subsequently spread throughout the globe. Systemic inflammation has been reported as a predictor for COVID-19 outcomes. Elevated levels of inflammatory markers are shown to be associated with endothelial dysfunction, cytokine storm and coagulopathy in COVID-19. Raised inflammatory markers influences the mortality in severe Covid-19.

Objectives: The aim of the study is to correlate the inflammatory markers with CT severity score among COVID-19 patients.

Materials and Methods: Retrospective cross–sectional study conducted among 250 patients admitted in the COVID 19 isolation wards confirmed by RT-PCR. The study was conducted over a period of six months (April 2021 to September 2021) based on data's from the central laboratory registers in Biochemistry & CT Severity Score from the medical records.

Results: Statistically significant elevation in Ferritin, CRP, LDH and D dimer among the severely affected group of patients is noted, all four markers are positively correlated with CT scores & increases with increase in the disease severity. It is observed that SpO_2 decreases with increase in the severity of the disease.

Conclusion: In this study we found significant correlation of the raised inflammatory markers and the CT severity score and the disease severity which highlights the prognostic significance of the inflammatory markers that would guide us in the diagnosis and management of critically ill patients at the earliest.

Keywords: Inflammation, Cytokine storm, Pneumonia, Ferritin, D- Dimer, LDH, CT severity score.

Introduction

Coronavirus disease 2019 (COVID-19) is a novel infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan and has quickly spread across the world. The mortality rate in critically ill patients with COVID-19 is high. Novel COVID-19 infection was declared a pandemic by WHO[1] and its death toll has been more compared to SARS or MERS.

Its a new disease with almost no established understanding of pathophysiology. CRP is one of the valuable biomarker to anticipate the severity of COVID-19 cases [2]. Serum ferritin levels are used as a marker of inflammation in COVID-19 patients because of its pro-inflammatory effects causing cytokine storm[3].

Cytokine storm is associated with high mortality in COVID-19 patients. D-Dimer is elevated in COVID-19 patients due to coagulopathy [4]. D-Dimer is used as a prognostic marker in severe cases of pneumonia [5]. LDH release from lung tissue is high in ARDS-hall mark of the disease[6]

Hence this study will determine the correlation of serum inflammatory markers-CRP, D-Dimer, Ferritin and LDH with CT severity score in COVID-19 patients between mild/moderate and severe/critical patients, which may help to identify critical cases and perform appropriate clinical intervention early

Aim

To correlate the serum inflammatory markers and SpO_2 with radiological findings in the COVID 19 patients.

Results

Primary objective: To determine the levels of serum inflammatory markers-CRP, D-Dimer, Ferritin and LDH among mild, moderate and severe COVID-19 patients

Secondary objective: To determine the correlation of the various inflammatory markers with radiological findings in all categories of COVID-19 patients

Methodology

This was conducted as a retrospective -Cross-sectional study. Convenient random sampling was done. The sample size was estimated with n master software. The minimum samples required for the study is estimated as 250 at 5% level of significance and 90% power. This study was conducted in the Department of Biochemistry, Department of General Medicine and radiology in Govt Vellore Medical College.

Ethical clearance was obtained from the Ethics committee of this institute.

Laboratory data's of COVID19 patients confirmed by RT PCR technique admitted between April to August 2021 from the central laboratory services registers in Biochemistry and pathology were included in the study. COVID-19 cases without radiological findings or normal inflammatory markers are excluded from the study Lab number, age, gender was noted.

Serum ferritin, D-Dimer, CRP, LDH done by immunoturbidimetry method was recorded. Complete hemogram reports were also collected from these patients. Clinical data and CT Severity Score for the same patients were obtained from the medical records and statistical analysis was done.

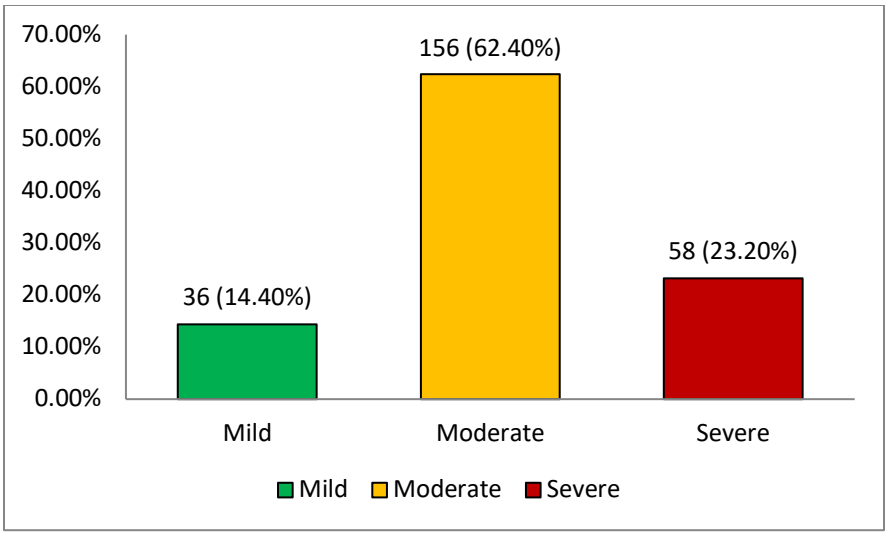

Figure 1: Distribution of cases based on the severity of COVID 19 across the study population (N = 250)

Figure 1 shows that among the study population, 14.4% had only milder form of disease; nearly 2/3rd (62.4%) had moderately severe form of disease and 23.2% of the study population had severe disease.

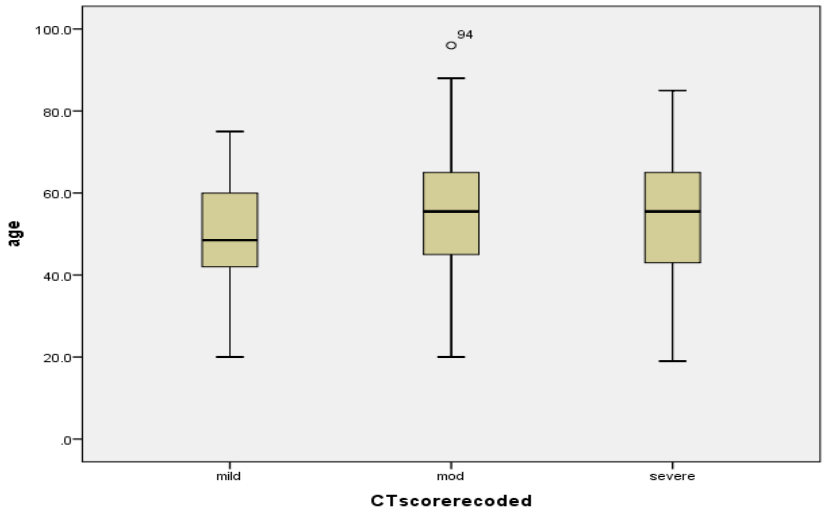

Figure 2: Age distribution of the study population based on the severity of the disease

The above Box and whisker plot shows that the median age of the study population with less severe disease is 48.5 years with the range of 42 to 60 years. The median age of patients with moderately severe disease is 55.5 years with the range of 45 to 65 years. The median age of patients with severe disease is 55.5 years with the range of 42.75 to 65.25 years.

The mean age of the study population among the patients with mild disease was found to be 48.83 $\pm$ 13.93 yrs; among the moderately severe cases it is 54.63 $\pm$ 15.56 yrs and in the severe cases mean age was found to be 53.69 $\pm$ 15.38 yrs.

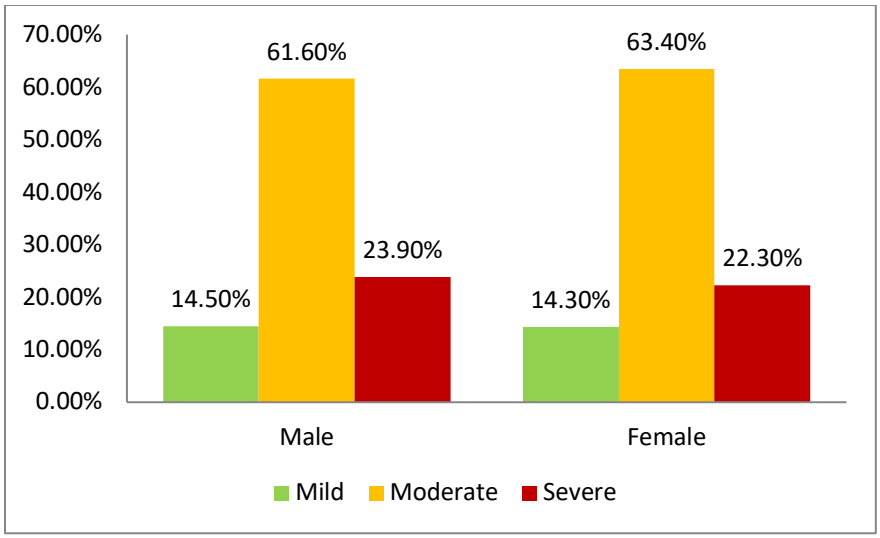

Figure 3: Distribution of the study population gender wise based on the severity (N = 250)

Figure 3 shows that in both the males and females moderately severe cases constitutes the major proportion (61.6% and 63.4%) respectively followed by severe cases (23.9% and 22.3%) respectively and the least proportion is constituted by milder cases (14.5% and 14.3%)

Table 1: Distribution of Comorbidity among the study population

Severity of CT score	Diabetes			Hypertension		
	Yes	No	p value	Yes	No	p value
Mild	5 (13.9%)	31 (86.1%)		0	36 (100%)	
Moderate	42 (26.9%)	114 (73.1%)		5 (3.2%)	151 (96.8%)	
Severe	11 (19%)	47 (81%)	0.17	2 (3.4%)	56 (96.6%)	0.54

*** p < 0.05 represents statistical significance**

Table 1 shows that among those with milder disease, 13.9% had Diabetes. Around one fourth (26.9%) of those with moderate disease had Diabetes whereas 19% of those with severe disease had Diabetes. But the difference was not statistically significant.

It also shows that among those with milder disease, none had Hypertension. Only 3.2% of those with moderate disease had Hypertension whereas 3.4% of those with severe disease had Hypertension. Here also the difference was not statistically significant.

Table 2: Laboratory markers in the study population based on the severity of the disease.

S. No.	Variable	Median (Range)
1	**SpO_2**	
	Mild CT score	0.96 (0.90 – 0.98)
	Moderate CT score	0.95 (0.88 – 0.97)
	Severe CT score	0.92 (0.80 – 0.95)
2	**Ferritin (ng/ml)**	
	Mild CT score	179 (110 – 254)
	Moderate CT score	308 (205 – 455.75)

	Severe CT score	558.50 (295.50 – 795)
3	**CRP (mg/dl)**	
	Mild CT score	4.08 (3 – 14)
	Moderate CT score	27.5 (13.22 – 57.50)
	Severe CT score	47.5 (34 - 79.25)
4	**D dimer (ng/ml)**	
	Mild CT score	244 (160.75 – 363.50)
	Moderate CT score	556 (294.5 – 1201.50)
	Severe CT score	885.50 (545.50 – 2617.50)
5	**LDH (U/L)**	
	Mild CT score	198 (136 – 347.25)
	Moderate CT score	344.50 (230.75 – 466.75)
	Severe CT score	404 (318.75 – 478.50)

Table 2 shows the median range of the various laboratory parameters observed in the patients. It is observed that SpO_2 decreases with increase in the severity of the disease. The other parameters like Ferritin, CRP, D dimer and LDH all increases with increase in the disease severity.

Table 3: Correlation of CT scores with other laboratory parameters

Variable	Pearson's Correlation Coefficient (r)	95% CI	p value
Spo2	- 0.299	- 0.399 to - 0.177	**< 0.01**
Ferritin	0.497	0.400 to 0.590	**< 0.01**
CRP	0.336	0.232 to 0.448	**< 0.01**
D dimer	0.278	0.152 to 0.396	**< 0.01**
LDH	0.320	0.200 to 0.420	**< 0.01**

*** p < 0.05 represents statistical significance**

Table 3 shows that Spo2 is negatively correlated to CT score severity (SpO_2 decreases when the severity increases) and the other parameters are positively correlated with the CT severity score and the results are all statistically significant.

Table 4: Correlation of CT scores among patients with mild severity with other laboratory parameters

Variable	Pearson's Correlation Coefficient (r)	95% CI	p value
Spo2	- 0.203	- 0.486 to 0.183	0.23
Ferritin	0.195	- 0.229 to 0.580	0.256
CRP	0.404	0.203 to 0.569	**0.015**
D dimer	0.188	0.071 to 0.473	0.272
LDH	0.377	0.127 to 0.626	**0.023**

*** p < 0.05 represents statistical significance**

Table 4 shows that correlation of laboratory parameters with CT scoring among mild cases. Statistically significant correlation of CT score is noted only with CRP and LDH, both of which are positively correlated with the CT score.

Table 5: Correlation of CT scores among patients with moderately severe disease with other laboratory parameters

Variable	Pearson's Correlation Coefficient (r)	95% CI	p value
Spo2	- 0.206	- 0.369 to - 0.032	**0.01**
Ferritin	0.199	0.035 to 0.360	**0.01**
CRP	0.147	0.037 to 0.270	0.067
D dimer	0.145	- 0.024 to 0.302	0.072
LDH	0.236	0.090 to 0.370	**0.003**

*** p < 0.05 represents statistical significance**

Table 5 shows that correlation of laboratory parameters with CT scoring among moderately severe cases. Statistically significant correlation of CT score is noted with SpO_2, Ferritin and LDH. SpO_2 is observed to be negatively correlated with CT scores. Ferritin and LDH are positively correlated with CT scores.

Table 6: Correlation of CT scores among patients with severe disease with other laboratory parameters

Variable	Pearson's Correlation Coefficient (r)	95% CI	p value
Spo2	- 0.141	- 0.350 to 0.078	0.290
Ferritin	0.391	0.148 to 0.600	**0.002**
CRP	0.169	- 0.093 to 0.413	0.205
D dimer	0.265	- 0.061 to 0.529	**0.044**
LDH	0.171	- 0.148 to 0.510	0.200

*** p < 0.05 represents statistical significance**

Table 6 shows that correlation of laboratory parameters with CT scoring among severe cases. Statistically significant correlation of CT score is noted with Ferritin and D dimer both of which are positively correlated with CT scores.

Discussion

SARS-CoV-2 is spread primarily via respiratory droplets. Infection may be spread by asymptomatic, presymptomatic, and symptomatic carriers. The lungs are the main organs affected leading to pneumonia and respiratory failure in severe cases that may need mechanical ventilation. Occasionally patient may present with gastro-intestinal, cardiac and neurologic symptoms with or without lung involvement.

The process of entry of coronaviruses into the host is facilitated by the host cell proteins namely Transmembrane protease serine and lysosomal cathepsin through the following mechanisms: proteolytic cleavage of ACE2 receptor that stimulates viral uptake and cleavage of coronavirus spike glycoproteins which turns on the glycoprotein for host cell entr. [7]

Elevations in more traditional biochemical markers of acute infection, including C-reactive protein (CRP) and ferritin (both positive acute phase reactants), as well as decrease in lymphocytes and significant elevations in neutrophils, are evident which are the result of overproduction of proinflammatory cytokines.[8]. Chen *et al* showed that the mean level of C reactive protein was found to be higher in the severely affected patients compared to the mild group (Chen *et al*., 2020).[9]. In this study the

median range of CRP is significantly higher for the severe category.

The neutrophil-to-lymphocyte ratio appears to be a useful indicator of disease prognosis and management. Progressive lymphopenia was observed in the severely affected. It was probably due to depletion through TNF-α-mediated apoptosis or even direct cytopathic injury. The degree of lymphopenia may address the severity of the disease and the onset of complications. The monocyte to lymphocyte ratio and Platelet lymphocyte ratio are the other predictors for progression to ARDS [10,11] Another finding in our study is lower level of platelets in majority of cases which was identified as an independent risk factor for severe COVID-19, which was in agreement with the study published by Zhe Zhu *et al*. [12]

Viral infection causes tissue hypoxia which leads to accumulation of lactic acid resulting in metabolic acidosis. Also the lactic acid stimulates the monocytes to produce inflammatory mediators and thereby LDH is elevated as a response to homeostasis. In our study, there was significantly higher median range for LDH among the severely infected patients and positively correlated with CT Score. There was positive correlation between LDH and neutrophils count according to the study by Eman T Ali. Elevated lactic acid values was associated with a worse overall outcome of patients according to the study by Aditi parimoo *et al*.[13,14]

Epidemiological studies demonstrated that COVID-19 patients causes elevation of acute phase reactants such as ESR, CRP, IL-6, and ferritin and rapidly activates the innate immune response.[15] This hyperinflammatory immune response mimics a macrophage activation syndrome (MAS) which is characterized by high CRP, neutrophilia, and hyperferritinemia.[16,17] Significant increase in ferritin levels in blood has been found in the severe group which is considered as an independent risk factor for acute respiratory distress syndrome. Inflammatory cytokines cause the imbalance of coagulation and fibrinolysis in the alveoli, which may activate the fibrinolysis system and then increase the level of D-dimer [18,19]. Several critically ill patients have been reported to develop coagulopathy, antiphospholipid antibodies, and arterial and venous thrombotic events such as cerebral infarction.[20] Higher levels of these inflammatory markers suggest that uncontrolled systemic inflammation can be considered one of the major causes of disease severity in SARS-CoV-2 infection. These markers have been proposed for the early identification of patients developing a cytokine storm and for their subsequent monitoring and prognostication.

The majority of patients are reported to exhibit diffuse bilateral pneumonia surrounded with ground-glass opacity either progressing or coexisting with consolidation [21] The lower respiratory tract was found to hold a higher overall viral load than the upper respiratory tract according to the study by Wölfel *et al*., 2020[22]. Pathological findings observed in the infected lungs were the proteinaceous exudates in lung tissues, development of pulmonary edema, bilateral diffuse alveolar damage ,interstitial thickening, infiltration of T cells or inflammatory monocytes[23] (Wölfel *et al*., 2020)

CT findings of COVID-19 pneumonia change over time with different presentations according to the phase and severity of lung infection. The evolution of lung abnormalities was classified into four stages (early 0–4 days, progressive 5–8 days, peak 9–13 days, and absorption ≥ 14 days) according to time periods. Each of the 5 lung lobes was visually scored from 0 to 5 as follows: 0, no involvement; 1, < 5% involvement; 2, 25% involvement; 3, 26%–

49% involvement; 4, 50%–75% involvement; and 5, > 75% involvement [24] The total CT score ranged from 0 to a maximal value of 25. Stage 2 was characterized by an increase of GGO extent, with a crazy-paving pattern On the opposite, in stage 3, consolidation was the main feature with a decreased GGO ratio, The transformation of GGO into linear consolidation is typical for an evolution towards organizing pneumonia[25]. Patients with lower CTSS, lower pulmonary artery CT diameter, and round shape opacity had lower mortality.

Conclusion

In this study we found significant correlation of the raised inflammatory markers and the CT severity score and the disease severity which highlights the prognostic significance of the inflammatory markers that would guide us in the diagnosis and management of critically ill patients at the earliest.

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References

1. World Health Organization . WHO characterizes COVID-19 as a pandemic. March 11, 2020; https://www.who.int/emergencies/diseases/novel%2010coronvirus%20102019/events%2010as%2010they%2010happen. Accessed Jan, 2021.
2. Guyi Wang, Chenfang Wu, Quan Zhang, Fang Wu, Bo Yu, JianleiLv, et al. C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation. Open Forum Infect Dis. 2020;7(5):1-5.
3. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. Research J Med Sci. 2014;19(2) :164–74.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.
5. Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, Martinez I. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. Chest. 2004;126(4):1087–92.
6. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med. 2020;38(9):1722-26.
7. Zhang Q., Xiang R., Huo S., Zhou Y., Jiang S., Wang Q., et al. Molecular Mechanism Of Interaction Between SARS-Cov-2 And Host Cells And Interventional Therapy. Signal. Transduct. Targeted Ther. 2021;6: 1–19.
8. Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. Immunity. 2020;53(1):19–25.
9. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia (In Chinese). Zhonghua Jie He He Hu Xi Za Zhi 2020b;43(3):203–8
10. Peng J, Qi D, Yuan G, Deng X, Mei Y, Feng L, et al. Diagnostic Value of Peripheral Hematologic Markers for Coronavirus Disease 2019 (COVID19): A Multicenter, Cross-Sectional Study. J Clin Lab Anal. 2020; 34(10): e23475.

11. Kordzadeh-Kermani E, Khalili H and Karimzadeh I: Pathogenesis, clinical manifestations and complications of COVID-19. Future Microbiol. 2020; 15: 1287-1305.
12. Zou X, Li S, Fang M, Hu M, Bian Y, Ling J, Yu S, Jing L, Li D, Huang J. Acute physiology and chronic health evaluation II score as a predictor of hospital mortality in patients of coronavirus disease 2019. Crit Care Med. 2020;48:e657.
13. Eman T. Ali Azza Sajid Jabbar, Hadeel S. Al Ali Saad Shaheen Hamadi, Majid S. Jabir, and Salim Albukhaty. Extensive Study on Hematological, Immunological, Inflammatory Markers, and Biochemical Profile to Identify the Risk Factors in COVID-19 Patients, International Journal of Inflammation. 2022.
14. Aditi Parimoo, Ashutosh Biswas, Upendra Baitha, Gaurav Gupta, Shivam Pandey, Piyush Ranjan, Vandana Gupta, Debarchan Barman Roy, Bindoo Prakash, Naveet Wig, Dynamics of Inflammatory Markers in Predicting Mortality in COVID-19, world academy of sciences journal 2020;3: 52.
15. Huang I, Pranata R, Lim MA, et al. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis 2020;14:1753466620937175
16. McGonagle D., Sharif K., O'Regan A. & Bridgewood C. Te Role of Cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun. Rev. 2020; 19: 102537.
17. Karakike, E. & Giamarellos-Bourboulis, E. J. Macrophage activation-like syndrome: A distinct entity leading to early death in sepsis. Front. Immunol. 2019; 10: 55.
18. Gandini O, Criniti A, Ballesio L, et al. Serum Ferritin is an independent risk factor for acute respiratory distress syndrome in COVID-19. J Infect. 2020; 81:979-97.
19. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18:1094-9.
20. Li XY, Du B, Wang YS. The key points in treatment of the critical coronavirus disease 2019 patient. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43: E026.
21. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020; 382: e38
22. Cui, N., Zou, X., and Xu, L. Preliminary Ct Findings of Coronavirus Disease 2019 (Covid-19). Clin. Imaging. 2020; 65: 124–132.
23. Wölfel, R., Corman, V. M., Guggemos, W., Seilmaier, M., Zange, S., Müller, M. A., et al. Virological Assessment of Hospitalized Patients with Covid- 2019; 2020; Nature, 581: 465–469.
24. Pan F., Ye T., Sun P., Gui S., Liang B., Li L. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) Pneumonia. Radiology. 2020.
25. Kligerman S.J., Franks T.J., Galvin J.R. From the Radiologic Pathology Archives: Organization and fibrosis as a response to lung injury in diffuse alveolar damage, organizing pneumonia, and acute fibrinous and organizing pneumonia. Radiographics. 2013; 33:1951–1975