RESEARCH ARTICLE

COVID 19 Severity Correlation between Inflammatory Markers and High Resolution Computerised Tomography

Authors
Ashaq Parrey, Abir Aijaz, Mohd Ismail, Mir Sadaqat, Manzoor Koka, Murtaza Noor, Basharat Ahmad, Hilal Bhat, Yasmeen Amin.

Corresponding author:
Ashaq Parrey

Email: chogalpora@gmail.com

Abstract

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission associated with the seafood market in Wuhan, China. Later it was recognized that human to human transmission played a major role in the subsequent outbreak. The Inflammatory responses caused by viral replication of SARS-CoV-2 with cellular destruction can recruit macrophages and monocytes and lead to the release of cytokines and chemokines.These inflammatory markers then attract immune cells and activate immune responses, leading to cytokine storms .Many such inflammatory markers have been attributed to determine the severity of SARS-CoV-2 disease and mortality associated with it. The Inflammatory markers such as serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID-19 disease.

Aims and objectives

The aim of the study was to find out correlation between inflammatory markers and HRCT chest severity in hospitalised COVID-19 patients.

Results and conclusion.

The study supported the existing data that high load of inflammatory markers is associated with more severe COVID-19 lung disease and indirectly high mortality ,out of four inflammatory markers which included D Dimer ,IL6,Serum ferritin and LDH we found three markers IL6,Serum ferritin and LDH has significant relation with CT severity

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission associated with the seafood market in Wuhan, China. Later it was recognized that human to human transmission played a major role in the subsequent outbreak [1]. The novel coronavirus designated as SARS-CoV-2 after emerging in the city of Wuhan, China caused an outbreak of unusual viral pneumonia. Being highly transmissible, this novel coronavirus disease has spread fast all over the world [2, 3]. On March 11, 2020, the WHO declared COVID-19 a global pandemic [4]. The clinical presentation of SARS-CoV-2 vary from asymptomatic carriers to patients requiring assisted ventilatory support, and ICU admissions with increased mortality which is an unusual and unprecedented challenge [5,6].

High-resolution non contrast Computerised Tomography (HRCT) chest imaging plays an important role in the early disease detection and quantification of disease severity by using scoring system, particularly in patients with false-negative RT-PCR results, as well as in managing and monitoring the course of disease [7].Prognosis can also be affected by the severity of the disease in the critically ill patients allowing appropriate selection of early involvement of the intensive care [8,9]. Studies have explored the pulmonary involvement on the chest CT images using both visual and software quantitative assessments [10].

Severe or critical SARS-CoV-2 is strongly linked with mortality[11] and the high mortality rate amongst these cases is linked with SARS-CoV-2 infection-induced hyper inflammation of the innate and adaptive immune systems and the resulting cytokine storm, a cytokine release syndrome (CRS)-like syndrome in severe/critical COVID-19 cases [12,13,14,15]. Studies have reported that the inflammatory parameters are closely linked to the COVID-19 severity and mortality [16,17,18,19].

With each passing day of COVID 19 Pandemic evidence is accumulating that inflammatory responses play an important role in the severity of COVID-19. The Inflammatory responses caused by viral replication of SARS-CoV-2 with cellular destruction can recruit macrophages and monocytes and lead to the release of cytokines and chemokines.These inflammatory markers then attract immune cells and activate immune responses, leading to cytokine storms . Many inflammatory markers have been attributed to determine the severity of SARS-CoV-2 disease and mortality associated with it. The Inflammatory markers such as serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID-19 disease. IL-6, is a pleiotropic cytokine important in regulating immunological and inflammatory responses. Abnormally increased levels of such cytokines or chemokines can cause tissue damage, resulting in respiratory and multiple organ failure [20,21,22].

Patients with severe diseases have been reported to have increased plasma concentrations of proinflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP) 1α, and tumour necrosis factor (TNF)-α [23,24,25].

The Patients with severe COVID-19 disease may lead to formation of blood clots, which leads to vessel constriction and ultimately can result in pulmonary embolism or large-vessel

ischemic stroke, in addition to ischemia in fingers and toes [26,27].

Aims and objectives

The aim of the study was to find out correlation between inflammatory markers and HRCT chest severity in hospitalised COVID-19 patients

Materials and methods

The study was conducted in Medicine department of SMHS Hospital Government Medical Collage Srinagar, it was a prospective study extended for a period of 3 months from May 2021 to Aug 2021.

All the patients admitted in hospital with COVID-19 disease had Hypoxemia (SPO2 <93%) which was primary reason for admission, all the patients underwent for baseline investigations and inflammatory Markers on day one of admission which included IL 6, DDimer , CRP, Ferritin and LDH.

A total of 103 patients with confirmed COVID 19 by RTPCR went for HRCT Chest on day five of illness for severity of lung involvement who were already investigated for inflammatory markers on day one of admission.

Inflammatory markers (IL6,D Dimer,CRP,LDH) were analysed using Abbott analyser by micro particle immune assay and chemoimmunofluorscense method and Non contrast High resolution Computerised tomography (HRCT) lungs was analysed by visual 25 point scoring system.

The Data of the study was analysed by using SPSS 23 software.

Results

1. The study involved 103 patients, males 68 (66%) and females 35 (34%) with mean age of 52 years (Minimum age 17 years and maximum 19 years) Table 1.

	Frequency	Percent	Valid Percent	Cumulative Percent
Males	68	66.0	66.0	66.0
Females	35	34.0	34.0	100.0
Total	103	100.0	100.0	

Table 1. Showing gender distribution in studied population.

2. The oxygen was required in all patients as all patients were hypoxemic on admission, mean Oxygen requirement was at the rate of 6.2Litters (Ltrs) with the minimum of 2 Ltrs and a maximum of 14Ltrs Table 2.

	N	Minimum	Maximum	Mean	Std. Deviation
Oxygen requirement	103 103	2.00	14.00	6.2330	3.04606

Table 2.Showing Oxygen requirement of studied patients.

3. The minimum total leukocyte (TLC) count of Studied patients was 3300 and maximum of 21000 with a mean of 9227 Table 3.

	N	Minimum	Maximum	Mean	Std. Deviation
Total Leukocyte count	103 103	3300.00	21000.00	9227.2816	4249.25696

Table 3.Showing Total leukocyte count of studied patients

4. The mean D Dimer of patients was 1540ng/ml (Minimum 12 and Maximum 9000). Normal D dimer less than 500ng/ml was seen in 33 % (34 Patients) D-Dimer of 500-1000ng/ml was seen in 21.4 (22 patients) and more than 1000 ng/ml was seen in 45.4 % (46 patients)Table 4 .There was no significant correlation between CT severity and D-Dimer lavel table 5,however more than 66% patients had high D Dimer lavels.

	N	Minimum	Maximum	Mean	Std. Deviation
D Dimer	103 103	12.00	9000.00	1540.40	1789.1

Table 4. showing maximum, minimum and mean D Dimer in studied population

Correlations

		CT Severity	D Dimer
CT Severity	Pearson Correlation	1	.022
	Sig. (2-tailed)		.823
	N	103	103
D Dimer	Pearson Correlation	.022	1
	Sig. (2-tailed)	.823	
	N	103	103

Table 5.showing pearsons correlation between CT Severity and D Dimer lavel.

5. The Minimum CT Severity score was 1/25 and Maximum CT severity score was 21/25 with a mean of 7.8/25 Table. 6.

Mild disease with CT severity of <7/25 was seen in 60 patients (58.2%) score.Moderate disease with CT Severity of >7/25 but < 14/25 was seen in 27 Patients (26.2%) and severe disease with CT Severity score of more than 14/25 was seen in 16 patients (15%)

	N	Minimum	Maximum	Mean	Std. Deviation
CT severity N	103 103	1.00	21.00	7.7864	4.87420

Table 6. Showing CT Severity in studied patients.

6. The minimum level of Interleukin 6 (IL6) was 0.18pg/ml and maximum was 44pg/ml with the mean of 4.67 Table 7.

There was significant relation between IL6 and CT severity with Correlation significant at the 0.01 level Tables 8.

	N	Minimum	Maximum	Mean	Std. Deviation
Interleukin 6 Valid N (list wise)	103 103	.18	44.00	4.6653	7.46715

Table 7 showing minimum, maximum and mean IL6 levels in studied patients.

Correlations

		CT Severity	IL6
CT Severity	Pearson Correlation	1	.714**
	Sig. (2-tailed)		.000
	N	103	103
IL6	Pearson Correlation	.714**	1
	Sig. (2-tailed)	.000	
	N	103	103

**. Correlation is significant at the 0.01 level (2-tailed).

Table 8. Showing Pearson Correlation between CT Severity and IL6.

7. The minimum serum Ferritn lavel was 21ng/ml and maximum 2579ng/ml with the mean of 279.4 table 9.There was significant correlation between serum ferritin and CT severity (Correlation is significant at the 0.01 level) Table 10.

	N	Minimum	Maximum	Mean	Std. Deviation
Serum ferritin Valid N (listwise)	103 103	21.00	2579.00	279.4272	448.64962

Table 9 showing Minimum, maximum and mean Serum Ferritin in studied patients.

		CT severity	Ferritin
CT Severity	Pearson Correlation	1	.725**
	Sig. (2-tailed)		.000
	N	103	103
Ferritin	Pearson Correlation	.725**	1
	Sig. (2-tailed)	.000	
	N	103	103

Correlation is significant at the 0.01 level (2-tailed).

Table 10 showing Pearson Correlation between CT Severity and serum Ferritin.

8. The minimum LDH level was 14.7and maximum 2041 wit mean of 290 tables 11.

There was significant correlation between LDH and CT severity Table 12.

	N	Minimum	Maximum	Mean	Std. Deviation
LDH	103	14.70	2041.00	289.8592	372.95677
Valid N (listwise)	103				

Table 11 showing Minimum maximum and mean LDH in studied population

Correlation is significant at the 0.01 level (2-tailed).

Table 10 showing Pearson Correlation between CT Severity and serum Ferritin.

8. The minimum LDH level was 14.7and maximum 2041 wit mean of 290 tables 11.

There was significant correlation between LDH and CT severity Table 12.

		VAR00031	VAR00028
CT Severity	Pearson Correlation	1	.816**
	Sig. (2-tailed)		.000
	N	103	103
LDH	Pearson Correlation	.816**	1
	Sig. (2-tailed)	.000	
	N	103	103

**. Correlation is significant at the 0.01 level (2-tailed).

Table 12 showing Pearson Correlation between CT severity and LDH

Discussion.

A high-resolution CT (HRCT) chest imaging plays a pivotal and essential role in the early disease detection COVID 19 disease, particularly in patients with false-negative RT-PCR results, as well as in managing and monitoring the course of disease [28].The quantitative severity of COVID Pneumonia can be assessed using a visual method or software that determines the percentage of affected lung volumes using the deep learning algorithms [29,30,31].

In our study we found significantly positive correlation between CT Severity and IL6, CT Severity and Serum ferritin,CT severity and LDH ,however no significant correlation was seen between CT severity and D Dimer.

Eight studies [32-38]comparing 543 COVID-19 patients who died during follow-up with 1713 who remained alive during the same period found that on admission, patients who subsequently died showed significantly higher white blood cell count (WMD: 4.11, 95% CI: 3.25–4.97), CRP (WMD: 74.18, 95% CI: 56.63–91.73), PCT (WMD: 0.26, 95% CI: 0.11–0.42), erythrocyte sedimentation rate (WMD: 10.94, 95% CI: 4.79–17.09), and IL-6 (WMD: 59.88, 95% CI: 19.46–100.30)

The levels of these cytokines have been found higher in severe cases when compared with the moderate cases [39], which suggests the necessity of IL-6 detection for early prediction of severity [40].in our study we found a positive correlation between IL6 and CT severity which is consitant with other studies[41,42]

C-reactive protein is an acute-phase inflammatory protein produced by the liver and regulated at the transcriptional level by the cytokine IL-6 and IL-1 [43] SARS-CoV-2 shares similar clinical features with Middle East respiratory syndrome coronaviruss [44] and in patients with severe Middle East respiratory syndrome coronavirus pneumonia, increasing in C-reactive protein levels correlated with clinical deterioration.[45]

The importance of identifying this (IL 6) elevated biomarker also lies in the potential use of an antibody against IL-6 such as tocilizumab, which has been reported to effectively improve clinical symptoms and repress the deterioration of severe and critically ill patients with COVID-19.[46] Few studies have reported isolated IL-6 expression in COVID-19 patients, suggesting that elevated IL-6 and other cytokine levels correlated with severity of this disease, [47-49].Our study incorporated all the four major inflammatory markers for correlation with CT severity score and found that the levels of IL6 correlated with severity of COVID 19 disease on HRCT chest.

Elevated LDH levels have been associated with worse outcomes in patients with other viral infections in the past [52-53] 40% of patients with COVID-19 disease have been reported to present with increased LDH levels and elevated LDH has been associated with a higher risk of ARDS and need for intensive care and mortality [54].Our study was consistent with above studies as the levels of LDH correlated positively with CT Severity of COVID- 19 Disease

Ferritin an acute-phase protein a key mediator of immune dysregulation that contributes to cytokine storm and it has been reported that fatal outcomes by COVID – 19 are accompanied by cytokine storm Serum ferritin can be used as a prognostic marker for tissue damage or acute infections [55]. Thereby those with elevated ferritin have high probability to experience serious complications [56].In our study we found the similar results the high levels of Ferritin was associated with high CT severity score (Table10). It is suggested that hyperferritinemia in COVID-19 patients is

most likely due to the cytokine storm as in secondary hemophagocytic lymphohistiocytosis.[57]

Many studies from different countries have consistently found elevated levels of D-dimer in patients with SARS-COV-2 pneumonia [58], However in our study no significant correlation was found between CT Severity and D dimer levels.

Conclusion

The study supported the existing data that high load of inflammatory markers is associated with more severe COVID-19 lung disease and indirectly high mortality ,out of four inflammatory markers which included D Dimer ,IL6,Serum ferritin and LDH we found three markers IL6,Serum ferritin and LDH has significant relation with CT severity.

References.

1. Wu, J. T., Leung, K. & Leung, G. M. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet **395**, 689–697 (2020).
2. Hui, D. S. et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan, China. Intl. J. Infect. Dis. **91**, 264–266 (2020).
3. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation report – 51. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10 (2020).
4. Liu J., Yu H., Zhang S. The indispensable role of chest CT in the detection of coronavirus disease 2019 (COVID-19) European Journal of Nuclear Medicine and Molecular Imaging. 2020,
5. Emedicine.medscape.com. Coronavirus Disease 2019 (COVID-19) Clinical Presentation: History, Physical Examination, Complications. https://emedicine.medscape.com/article/2500114-clinical. [Google Scholar]
6. Thomas-Rüddel D., Winning J., Dickmann P., et al. "Coronavirus disease 2019" (COVID-19): update für anästhesisten und intensivmediziner märz 2020. Der Anaesthesist. 2020;69(4):p. 225.
doi: 10.1007/s00101-020-00758-x. [PubMed] [CrossRef] [Google Scholar]
7. Leonardi A., Scipione R., Alfieri G., et al. Role of computed tomography in predicting critical disease in patients with covid-19 pneumonia: a retrospective study using a semiautomatic quantitative method. European Journal of Radiology. 2020;130:p. 109202. doi: 10.1016/j.ejrad.2020.109202.
8. Meng L., Qiu H., Wan L., et al. Intubation and ventilation amid the COVID-19 outbreak. Anesthesiology. 2020;132(6):p. 1317. doi: 10.1097/ALN.0000000000003296.
9. Zhang H.-t., Zhang J.-s., Zhang H.-h., et al. Automated detection and quantification of COVID-19 pneumonia: CT imaging analysis by a deep learning-based software. European Journal of Nuclear Medicine and Molecular Imaging. 2020;47(11):p. 2525.
doi: 10.1007/s00259-020-04953-1.
10. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X., Cheng Z., Yu T., Xia J., Wei Y., Wu W., Xie X., Yin W., Li H., Liu M., Xiao Y., Gao H., Guo L., Xie J., Wang G., Jiang R., Gao Z., Jin Q., Wang J., Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
11. Weiss P., Murdoch D.R. Clinical course and mortality risk of severe COVID-19. Lancet. 2020;395(10229):1014–1015. doi: 10.1016/S0140-6736(20)30633-4. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
12. Cummings M.J., Baldwin M.R., Abrams D. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763–1770. doi: 10.1016/S0140-6736(20)31189-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
13. Henderson L.A., Canna S.W., Schulert G.S. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheum. 2020
doi: 10.1002/art.41285. [Published online on May 10] [PMC free article] [PubMed] [CrossRef] [Google Scholar]
14. Moore J.B., June C.H. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473–474. doi: 10.1126/science.abb8925. [PubMed] [CrossRef] [Google Scholar]
15. Channappanavar R., Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm

and immunopathology. Semin Immunopathol. 2017;39(5):529–539. doi: 10.1007/s00281-017-0629-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. Chen R., Sang L., Jiang M. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol. 2020 doi: 10.1016/j.jaci.2020.05.003. [published online on May 11] [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Qin C., Zhou L., Hu Z. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762–768. doi: 10.1093/cid/ciaa248. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
18. Lv Z., Cheng S., Le J. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. Microb Infect. 2020;22(4-5):195–199. doi: 10.1016/j.micinf.2020.05.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
19. Wang Y., Lu X., Li Y. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med. 2020 Jun 1;201(11):1430–1434. doi: 10.1164/rccm.202003-0736LE. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Chollet-Martin S., Jourdain B., Gibert C., Elbim C., Chastre J., Gougerot-Pocidalo M.A. Interactions between neutrophils and cytokines in blood and alveolar spaces during ARDS. Am J Respir Crit Care Med. 1996;154(3 Pt 1):594–601. doi: 10.1164/ajrccm.154.3.8810592. [PubMed] [CrossRef] [Google Scholar]
21. Gupta K.K., Khan M.A., Singh S.K. Constitutive inflammatory cytokine storm: a major threat to human Health. J Interferon Cytokine Res. 2020;40(1):19–23. doi: 10.1089/jir.2019.0085. [PubMed] [CrossRef] [Google Scholar]
22. Tanaka T., Narazaki M., Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a016295. doi: 10.1101/cshperspect.a016295. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Zhou Y., Fu B., Zheng X., Wnag D., Zhao C., Qi Y., Sun R., Tian Z., Xu X., Wei H. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Journal. 2020
24. Qin C., Zhou L., Hu Z., Zhang S., Yang S., Tao Y., Xie C., Ma K., Shang K., Wang W., Tian D.S. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Journal. 2020 doi: 10.1093/cid/ciaa248.
25. Wadman, M. C.-F., J, Kaiser, J & Matacic, C. How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. Science https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes (2020).
26. Oxley, T. J. et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N. Engl. J. Med. **382**, e60 (2020).
27. Liu J., Yu H., Zhang S. The indispensable role of chest CT in the detection of coronavirus disease 2019 (COVID-19) European Journal of Nuclear Medicine and Molecul Imaging. 2020, https://www .ncbi.nlm.nih.gov/pmc/ articles/PMC7118704/#CR2 , In press. [PMC free article] [PubMed] [Google Scholar]
28. Li K., Fang Y., Li W., et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19) European Radiology. 2020;30(8):4407–4416. doi: 10.1007/s00330-020-06817-

6. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Huang L., Han R., Ai T., et al. Serial quantitative chest CT assessment of COVID-19: deep-learning approach. Radiology: Cardiothoracic Imaging. 2020;2(2):p. e200075.
doi: 10.1148/ryct.2020200075. https://pubs.rsna.org/doi/10.1148/ryct.2020200075. [CrossRef] [Google Scholar]
30. Lessmann N., Sánchez C. I., Beenen L., et al. Automated assessment of CO-rads and chest CT severity scores in patients with suspected COVID-19 using artificial intelligence. Radiology. 2020:p. 202439. doi: 10.1148/radiol.2020202439. https://pubs.rsna.org/doi/10.1148/radiol.2020202439. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
31. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl) 2020;133:1261–7.
32. Chen G, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. J Clin Invest. 2020b;130(5):2620–9
33. Gao Y, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020;92(7):791–6.
34. Tao L, et al. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019.
35. Gong J, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia.
36. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan China: a retrospective cohort study. Lancet 2020;395:1054–62.
37. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
38. Wang Y, Lu X, Chen H, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020;201:1430–4.Cited Here |View Full Text | PubMed | CrossRe
39. An W, Xia F, Chen M, et al. Analysis of clinical features of 11 death cases caused by COVID-19. J Pract Med 2020;1–6.
40. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect 2020;80:639–45.
41. Tu WJ, Cao J, Yu L, et al. Clinicolaboratory study of 25 fatal cases of COVID-19 in Wuhan. Intensive Care Med 2020;46:1117–20.
42. He XW, Lai JS, Cheng J, et al. Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients. Chin J Cardiol 2020;1–9.
43. Black S., Kushner I., Samols D. C-reactive protein. J Biol Chem. 2004;279(47):48487–48490.
doi: 10.1074/jbc.R400025200. [PubMed] [CrossRef] [Google Scholar]
44. Khalid I., Alraddadi B.M., Dairi Y. Acute management and long-term survival among subjects with severe Middle East respiratory syndrome coronavirus pneumonia and ARDS. Respir Care. 2016;61(3):340–348. doi: 10.4187/respcare.04325. [PubMed] [CrossRef] [Google Scholar]
45. Cheng Z.J., Shan J. Novel coronavirus: where we are and what we know. Infection. 2019;48(2):155–163. doi: 10.1007/s15010-020-01401-y. 2020. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
46. Xu X., Han M., Li T. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S

A. 2020;117(20):10970–10975. doi: 10.1073/pnas.2005615117
47. Chen C.Y., Lee C.H., Liu C.Y., Wang J.H., Wang L.M., Perng R.P. Clinical features and outcomes of severe acute respiratory syndrome and predictive factors for acute respiratory distress syndrome. J Chin Med Assoc. 2005;68(1):4–10. [PMC free article] [PubMed] [Google Scholar]
48. Chiang C.H., Shih J.F., Su W.J., Perng R.P. Eight-month prospective study of 14 patients with hospital-acquired severe acute respiratory syndrome. Mayo Clin Proc. 2004;79(11):1372–1379. [PMC free article] [PubMed] [Google Scholar]
49. Tao R.J., Luo X.L., Xu W. Viral infection in community acquired pneumonia patients with fever: a prospective observational study. J Thorac Dis. 2018;10(7):4387–4395. [PMC free article] [PubMed] [Google Scholar]
50. Chen G, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. J Clin Invest. 2020b;130(5):2620–9.
51. Tao L, et al. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019. https://doi.org/10.1101/2020.03.01.20029769. Posted on medRxiv 10 Mar 2020.
52.Gong J, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. https://doi.org/10.1101/2020.02.25.20025643. Posted on medRxiv 27 Feb 2020.
53. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Amer J Hematol. (2020) 95:834–47. doi: 10.1002/ajh25829
54. Kernan K.F., Carcillo J.A. Hyperferritinemia and inflammation. Int Immunol. 2017;29(9):401–409. doi: 10.1093/intimm/dxx031.
55. Manuel V and Christian CR. Ferritin levels and Covid -19. Pan American journal of Public Health. 2020; (44): e72. https://doi.org/10.26633/RPSP.2020.72
56. Mehta P., McAuley D.F., Brown M. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–1034. doi: 10.1016/S0140-6736(20)30628-0. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
57. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Cui S, Chen S, Li X, Liu S, Wang F J Thromb Haemost. 2020 Jun; 18(6):1421-1424.
58. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study.Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B Lancet. 2020 Mar 28; 395(10229):1054-1062.

