Utility of ferritin, procalcitonin, and C-reactive protein in severe patients with coronavirus disease 2019

Bo Zhou (✉ zb_bob@stu.xjtu.edu.cn)

the First Affiliated Hospital of Xi'an Jiaotong University

Jianqing She

the First Affiliated Hospital of Xi'an Jiaotong University

Yadan Wang (✉ yadan_wang@hust.edu.com)

Huazhong University of Science and Technology

Xiancang Ma (✉ maxiancang@163.com)

the First Affiliated Hospital of Xi'an Jiaotong University

Research article

Keywords: COVID-19, Biomarkers, C-reactive protein, Ferritin, Procalcitonin

Posted Date: April 22nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-23645/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Objectives It is of clinical significance to evaluate the disease severity and investigate possible biomarkers of COVID-19. In this study, we aim to describe the clinical characteristics of infection makers in severe and very severe patients with COVID-19.

Methods This is a single center, observational analysis. We enrolled 48 in-hospital severe patients with COVID-19 admitted to the West District of Union Hospital of Tongji Medical College and analyzed infection biomarkers in 20 patients who had been tested for ferritin, PCT, CRP, etc.

Results We noted significantly increased CRP (1.48mg/L [IQR: 16.69-2.74] vs. 57.98mg/L [IQR: 38.335-77.565], $P<0.05$), PCT(0.05ng/ml [IQR: 0.03-0.06] vs. 0.21ng/ml [IQR: 0.11-0.42], $P<0.05$) and ferritin (291.13ng/ml [IQR: 102.1-648.42] vs. 1006.16ng/ml [IQR: 408.265-1988.25]) in severe COVID-19. For blood count, significant increase was noticed in neutrophil count ($3.75 \times 10^9/L$ [IQR: 3.42-4.93] vs. $8.11 \times 10^9/L$ [IQR: 5.675-8.905], $P<0.05$); and decrease was seen in lymphocyte count ($1.62 \times 10^9/L$ [IQR: 0.7-1.73] vs. $0.68 \times 10^9/L$ [IQR: 0.385-1.04], $P<0.05$), and platelet count ($214 \times 10^9/L$ [IQR: 184-247] vs. $147 \times 10^9/L$ [IQR: 126-202.5], $P<0.05$) in severe COVID-19.

Conclusions The serum levels of CRP, PCT and ferritin are markedly increased in very severe compared with severe COVID-19. Increased CRP, PCT and ferritin level might correlate to secondary bacterial infection and associated with poor clinical prognosis.

Background

The outbreak of coronavirus disease 2019 (COVID-19) has caused global attention¹⁻⁶. Up to 12th March, 80981 laboratory-confirmed cases in China and 46728 outside China have been documented, with a total of 4734 deaths⁷. Due to its rapid spread worldwide⁸, COVID-19 was declared as a public health emergency by the World Health Organization⁹⁻¹³.

Although most patients have mild symptoms and good prognosis, severe COVID-19 cases may present with acute respiratory distress syndrome (ARDS) and systemic inflammation. Thus, it is urgent to evaluate the disease severity and investigate possible biomarkers so as to make fast and correct clinical decisions. One recent study has pointed out that the patients with COVID-19 usually have increased serum C-reactive protein (CRP) (58.3%), lactate dehydrogenase (LDH) (57.0%) and erythrocyte sedimentation rate (ESR) (41.8%)¹⁴. But more evidence regarding other infection markers in COVID-19 needs further study. Of note, previous studies have established ferritin as a possible inflammation marker in pneumonia, associating with the progression of bacterial and viral infection. However, no evidence has been released how ferritin is altered in COVID-19.

In the present single center, observational analysis, we explored the infection biomarkers, including ferritin, procalcitonin (PCT), and CRP in in-hospital patients with severe and very severe COVID-19. We

aim to describe the clinical characteristics of infection makers in severe and very severe patients with COVID-19.

Methods

Study design and participants

This is a single center, observational analysis. We enrolled 48 in-hospital severe patients with COVID-19 admitted to the West District of Union Hospital of Tongji Medical College in the 7th floor ward from February 5th to February 25th, 2020, and analyzed infection biomarkers in 20 patients who had been tested for ferritin, PCT, CRP, etc. COVID-19 was diagnosed upon admission based on the New Coronavirus Pneumonia Prevention and Control Program (4th edition) published by the National Health Commission of China⁶. Severe COVID-19 was defined as having either one of the following criteria: 1) Respiratory distress with respiratory rate more than 30 times/min; 2) Oxygen saturation $\leq 93\%$ in resting state; 3) $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ ($1 \text{ mmHg} = 0.133 \text{ kPa}$). And very severe COVID-19 was defined as having either one of the following criteria: 1) Respiratory failure in need of mechanical ventilation; 2) Shock; 3) Other organ dysfunction. Patients with previous medical history of acute coronary syndrome were excluded. The study was approved by the ethics committee of the local hospital and data were collected retrospectively.

Data collection and infection biomarker measurement

Demographic and epidemiological data including age, sex, and disease history were collected upon admission. Real-time polymerase chain reaction testing was used to detect COVID-19 according to the recommended protocol in the laboratory department of the hospital¹⁵. Serum samples were collected from the patients upon admission, and blood count, CRP, PCT, and ferritin were tested by the laboratory department.

Statistical analysis

All statistical analyses were performed by SPSS for Windows 25.0 (SPSS Inc. Chicago, IL). Data were presented as percentages for categorical variables and median $\pm$ IQR (Inter Quartile Range) for continuous variables, unless otherwise indicated. Simple t test was used to compare continuous variables which are in normal distribution. Mann-Whitney U test was used to compare continuous variables which do not conform to the normal distribution. Fisher's exact test was used to compare categorical variables. Fisher's exact test was used to compare categorical variables. A value of $p < 0.05$ was considered statistically significant.

Results

9 patients with severe and 11 with very severe COVID-19 were included in this analysis. Baseline data for the cases enrolled were shown in Table 1. The median age was 59yrd (inter quartile range [IQR]:46–61) among severe COVID-19 group and 57yrd (IQR:45-71.5) among very severe group. The male percentage

was much higher (3 [33.33%] of 9 vs. 8 [72.73%] of 11) in very severe group. Kidney and liver function showed no statistical significance with regards to creatine (59.9 $\mu\text{mol/L}$ [IQR: 53.3–60.9] vs. 71.8 $\mu\text{mol/L}$ [IQR: 61.85–89.2]), aspartate Aminotransferase (AST) (27 U/L [IQR: 18–30] vs. 45 U/L [IQR: 28.5–67]) and alanine aminotransferase (ALT) (36 U/L [IQR: 27–57] vs. 45 U/L [IQR: 27–97.5]).

All patients were tested for infection markers including LDH, CRP, PCT, ferritin and blood count (Table 2). We noted significantly increased LDH (195 U/L [IQR: 170–226] vs. 411 U/L [IQR: 346.5–578], $P < 0.001$), CRP (1.48 mg/L [IQR: 16.69–2.74] vs. 57.98 mg/L [IQR: 38.335–77.565], $P < 0.05$), PCT (0.05 ng/ml [IQR: 0.03–0.06] vs. 0.21 ng/ml [IQR: 0.11–0.42], $P < 0.05$) and ferritin (291.13 ng/ml [IQR: 102.1–648.42] vs. 1006.16 ng/ml [IQR: 408.265–1988.25]). For blood count, significant increase was noticed in neutrophil percentage (67.6% [IQR: 61.8–76.4] vs. 86.7% [IQR: 82–92.35], $P < 0.01$) and neutrophil count ($3.75 \times 10^9/\text{L}$ [IQR: 3.42–4.93] vs. $8.11 \times 10^9/\text{L}$ [IQR: 5.675–8.905], $P < 0.05$); and decrease was seen in lymphocyte percentage (22.7% [IQR: 17.4–27.4] vs. 8% [IQR: 4.85–13], $P < 0.05$), lymphocyte count ($1.62 \times 10^9/\text{L}$ [IQR: 0.7–1.73] vs. $0.68 \times 10^9/\text{L}$ [IQR: 0.385–1.04], $P < 0.05$), and platelet count ($214 \times 10^9/\text{L}$ [IQR: 184–247] vs. $147 \times 10^9/\text{L}$ [IQR: 126–202.5], $P < 0.05$).

Fisher's exact test was then applied to compare the rate with abnormal LDH, CRP, PCT, ferritin and blood count between severe and very severe COVID-19, and relative risk was calculated. The results showed that PCT and PLT count had statistical significance ($P < 0.05$), and CRP, ferritin and LY% had towards statistical significance ($P = 0.07$) (Table 3), indicating that PCT, CRP, ferritin, LY% and PLT count might be possible markers for the progression of disease in severe and very severe COVID-19.

Discussion

In this observational study, we have focused on the infection markers in severe and very severe patients with COVID-19. The serum levels of LDH, CRP, PCT and ferritin are markedly increased in very severe patients compared with severe COVID-19, suggesting that increased LDH, CRP, PCT and ferritin level might stand for more severe secondary bacterial infection and exacerbated COVID-19. Moreover, lymphocyte count is decreased in very severe patients compared with severe COVID-19, indicating that lower lymphocyte count correlate to poor prognosis in COVID-19.

In the present analysis, we firstly evaluated serum ferritin levels in COVID-19, which are significantly elevated during critical infection. The function of ferritin including iron binding and storage is associated with the immune and inflammatory response¹⁶. The reasons of increased ferritin include bacterial and/or viral infection, hemochromatosis and long-term transfusion¹⁷. When bacterial and/or viral infection takes place, the increase of serum ferritin is related to the release of iron in the reticuloendothelial system, the decrease of the ability of transporting ferritin in liver and spleen, and increased synthesis and release of intracellular ferritin^{18,19}. Some studies showed that patients with bacterial infection had higher ferritin level compared to viral infection^{20,21}. Previous review has also proposed a model that the inflammatory

response to viral (IL-18/ferritin) presents as specific plasma patterns of immune biomarkers¹⁷. Moreover, elevation of serum ferritin levels predicts a poor outcome in hospitalized patients with influenza infection¹⁶. In the present study, the patients in severe and very severe COVID-19 both exhibits increase serum ferritin level, but the serum ferritin in very severe COVID-19 group is significantly higher than that of severe COVID-19 group. The increased ferritin might indicate severe secondary bacterial infection in COVID-19, and might be utilized as a marker of poor prognosis.

As we known, when inflammation or tissue damage happens, CRP can be significantly increased in serum, which is usually used as a unique inflammatory marker in the current clinical practice²². On the other hand, PCT, as the precursor of calcitonin, is a kind of glycoprotein without hormone activity, which is significantly higher in bacterial infection, but remain normal or slightly increased in viral infection^{22, 23}. Consistently, our study shows that CRP and PCT are markedly increased in severe and very severe COVID-19, and significantly higher in very severe COVID-19. This further correlates to the implication of the serum ferritin alteration, that most of severe patients in COVID-19 have viral infection and secondary bacterial infection.

One important limitation of the present study is that we have only observed infection biomarkers in limited COVID-19 patients; the small sample size have prevented us from reaching diagnostic value of infection markers in very severe COVID-19. Secondly, the present study hasn't evaluated the relationship between infection matkers and prognosis of all the patients enrolled. With more clinical information acquired from COVID-19 patients, further large population-based prospective studies coul provide further evidence how infection biomarkers are altered and what it indicate in COVID-19.

Conclusion

In the present study, we investigated the infection markers in patients with severe and very severe COVID-19, including serum levels of CRP, PCT and serum ferritin. Higher levels of CRP, PCT and serum ferritin in very severe COVID-19 as compared to severe COVID-19 might be correlated to secondary bacterial infection, protection from which could be of vital importance for reducing the mortality rate in very severe COVID-19.

Abbreviations

ARDS	Acute respiratory distress syndrome
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
CDC	Chinese Center for Disease Control and Prevention
CRP	C-reactive protein

COVID-19	Coronavirus disease 2019
ESR	Erythrocyte sedimentation rate
IQR	Inter quartile range
LDH	Lactate Dehydrogenase
PCT	Procalcitonin

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was obtained from all participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding

This study was funded by the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University, China (No.XJTU1AF-CRF-2018-025).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

BZ, XM and YW collected the clinical and laboratory data. JS processed statistical analysis. JS and BZ drafted the manuscript. BZ, XM and YW revised the final manuscript. BZ, XM and YW is responsible for all clinical and laboratory data.

Acknowledgments

We thank all patients involved in the study.

References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X and Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-

- Infected Pneumonia in Wuhan, China. *JAMA*. 2020.
2. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC and Zhang YZ. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020.
 3. Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine A. [An update on the epidemiological characteristics of novel coronavirus pneumonia COVID-19]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41:139-144.
 4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X and Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020.
 5. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Li M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JTK, Gao GF, Cowling BJ, Yang B, Leung GM and Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020.
 6. National Health Commission of China. New coronavirus pneumonia prevention and control program (4th edn). Jan 22, 2020. <http://www.gov.cn/zhengce/zhengceku/2020-01/28/5472673/files/0f96c10cc09d4d36a6f9a9f0b42d972b.pdf> (in Chinese).
 7. National Health Commission of the People's Republic of China. <http://www.nhc.gov.cn>.
 8. Liu Y, Gayle AA, Wilder-Smith A and Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med*. 2020.
 9. Thompson RN. Novel Coronavirus Outbreak in Wuhan, China, 2020: Intense Surveillance Is Vital for Preventing Sustained Transmission in New Locations. *J Clin Med*. 2020;9.
 10. Du Z, Wang L, Cauchemez S, Xu X, Wang X, Cowling BJ and Meyers LA. Risk for Transportation of 2019 Novel Coronavirus Disease from Wuhan to Other Cities in China. *Emerg Infect Dis*. 2020;26.
 11. Backer JA, Klinkenberg D and Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. *Euro Surveill*. 2020;25.
 12. Liao X, Wang B and Kang Y. Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichuan Province, China. *Intensive Care Med*. 2020.
 13. Eurosurveillance Editorial T. Note from the editors: World Health Organization declares novel coronavirus (2019-nCoV) sixth public health emergency of international concern. *Euro Surveill*. 2020;25.
 14. Rodríguez-Morales AJC-O, J.A.; Gutiérrez-Ocampo, E.; Villamizar-Peña, R.; Holguín-Rivera, Y.; Escalera-Antezana, J.P.; Alvarado-Arnez, L.E.; Bonilla-Aldana, D.K.; Franco-Paredes, C.; Henao-Martínez, A.F.; Paniz-Mondolfi, A.; Lagos-Grisales, G.J.; Ramírez-Vallejo, E.; Suárez, J.A.; Zambrano, L.I.; Villamil-Gómez, W.E.; Balbin-Ramón, G.J.; Rabaan, A.A.; Harapan, H.; Dhama, K.; Nishiura, H.; Kataoka, H.; Ahmad, T.; Sah, R. . Clinical, Laboratory and Imaging Features of COVID-19: A Systematic Review and Meta-analysis. Preprints 2020, 2020020378 (doi: 10.20944/preprints202002.0378.v3). .

15. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, Bleicker T, Brunink S, Schneider J, Schmidt ML, Mulders DG, Haagmans BL, van der Veer B, van den Brink S, Wijsman L, Goderski G, Romette JL, Ellis J, Zambon M, Peiris M, Goossens H, Reusken C, Koopmans MP and Drosten C. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill.* 2020;25.
16. Lalueza A, Ayuso B, Arrieta E, Trujillo H, Folgueira D, Cueto C, Serrano A, Laureiro J, Arevalo-Canas C, Castillo C, Diaz-Pedroche C, Lumbreras C and group I. Elevation of serum ferritin levels for predicting a poor outcome in hospitalized patients with influenza infection. *Clin Microbiol Infect.* 2020.
17. Slaats J, Ten Oever J, van de Veerdonk FL and Netea MG. IL-1beta/IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections. *PLoS Pathog.* 2016;12:e1005973.
18. Kernan KF and Carcillo JA. Hyperferritinemia and inflammation. *Int Immunol.* 2017;29:401-409.
19. Senjo H, Higuchi T, Okada S and Takahashi O. Hyperferritinemia: causes and significance in a general hospital. *Hematology.* 2018;23:817-822.
20. Sanaei Dashti A, Alizadeh S, Karimi A, Khalifeh M and Shoja SA. Diagnostic value of lactate, procalcitonin, ferritin, serum-C-reactive protein, and other biomarkers in bacterial and viral meningitis: A cross-sectional study. *Medicine (Baltimore).* 2017;96:e7637.
21. Kawamata R, Yokoyama K, Sato M, Goto M, Nozaki Y, Takagi T, Kumagai H and Yamagata T. Utility of serum ferritin and lactate dehydrogenase as surrogate markers for steroid therapy for *Mycoplasma pneumoniae* pneumonia. *J Infect Chemother.* 2015;21:783-9.
22. Choi YJ, Jeon JH and Oh JW. Critical combination of initial markers for predicting refractory *Mycoplasma pneumoniae* pneumonia in children: a case control study. *Respir Res.* 2019;20:193.
23. Memar MY, Varshochi M, Shokouhi B, Asgharzadeh M and Kafil HS. Procalcitonin: The marker of pediatric bacterial infection. *Biomed Pharmacother.* 2017;96:936-943.

Tables

Table 1: Baseline Information of the Patients Enrolled

Variable	Median(IQR)		P Value	Reference
	Severe	Very Severe		
Number	9	11		
Sex(Male%)	33.33%	72.73%	ns	
Age(yrs)	59(46-61)	57(45-71.5)	ns	
CRE($\mu\text{mol/L}$)	59.9(53.3-60.9)	71.8(61.85-89.2)	ns	57.0-111.0
AST(U/L)	27(18-30)	45(28.5-67)	ns	8-40
ALT(U/L)	36(27-57)	45(27-97.5)	ns	5-40
CK(U/L)	98(90-112)	186(90.5-244.5)	ns	24-194
CKMB(U/L)	9(9-17)	18(10-19)	ns	0-25

Abbreviations: IQR: inter quartile range; CRE: Creatine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK: Creatine Kinase; CKMB: Creatine kinase-MB; CK: Creatine Kinase; CKMB: Creatine kinase-MB.

Table 2: LDH, CRP, PCT and Blood Count in Severe and Very Severe Patients with COVID-19

Variable	Median(IQR)		P Value	Reference
	Severe	Very Severe		
LDH(U/L)	195(170-226)	411(346.5-578)	<0.001	109-245
CRP(mg/L)	1.48(16.69-2.74)	57.98(38.335-77.565)	<0.05	0-8
PCT(ng/ml)	0.05(0.03-0.06)	0.21(0.11-0.42)	<0.05	<0.05
FERR(ng/ml)	291.13(102.1-648.42)	1006.16(408.265-1988.25)	<0.05	4.62-204
WBC count($\times 10^9/\text{L}$)	6.07(5.48-7.22)	8.94(6.46-10.525)	ns	3.5-9.5
NE%	67.6(61.8-76.4)	86.7(82-92.35)	<0.01	40-75
LY%	22.7(17.4-27.4)	8(4.85-13)	<0.05	20-50
NE count($\times 10^9/\text{L}$)	3.75(3.42-4.93)	8.11(5.675-8.905)	<0.05	1.8-6.3
LY count($\times 10^9/\text{L}$)	1.62(0.7-1.73)	0.68(0.385-1.04)	<0.05	1.1-3.2
PLT count($\times 10^9/\text{L}$)	214(184-247)	147(126-202.5)	<0.05	125-350

Abbreviations: IQR: inter quartile range; LDH: Lactate dehydrogenase; CRP: C reactive protein; PCT: Procalcitonin; FERR: Ferritin; WBC: White Blood Cell; NE%: Neutrophil percentage; LY%: Lymphocyte percentage; NE count: Neutrophil count; LY count: Lymphocyte count; PLT count: platelet count.

Table 3: Risk ratio for severity of COVID-19

Variable	Odds Ratio	95% Confidence Interval			P value
LDH(U/L)	21.33	1.81	~	251.26	0.65
CRP(mg/L)	6.67	0.61	~	73.03	0.07
PCT(ng/ml)	4.57	0.41	~	51.14	0.03
FERR(ng/ml)	2.00	0.27	~	14.70	0.07
NE%	9.60	0.88	~	105.17	0.18
LY%	0.45	0.24	~	0.87	0.07
NE count(*10 ⁹ /L)	3.50	0.55	~	22.30	1.00
LY count(*10 ⁹ /L)	6.13	0.83	~	45.02	0.65
PLT count(*10 ⁹ /L)	1.50	0.95	~	2.38	0.00

Abbreviations: IQR: inter quartile range; LDH: Lactate dehydrogenase; CRP: C reactive protein; PCT: Procalcitonin; FERR: Ferritin; NE%: Neutrophil percentage; LY%: Lymphocyte percentage; NE count: Neutrophil count; LY count: Lymphocyte count; PLT count: platelet count.