Hypoalbuminemia in Severe COVID-19 Post Recovery Patients

Kameran Mohammed Ali
Sulaimani Polytechnic University
Ayad M. Ali
University of Garmian
Hassan Mohammad Tawfeeq
Sulaimani Polytechnic University
Grazziela Figueredo
University of Nottingham
Hassan Muhammad Rostam (hassan.al-bewani1@nottinggham.ac.uk)
University of Nottingham

Research Article

Keywords: COVID-19 post recovery patients, Serum albumin, ESR, CRP

Posted Date: October 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-90507/v1

Version of Record: A version of this preprint was published on April 8th, 2021. See the published version at https://doi.org/10.1002/jmv.27002.

Abstract

Pandemic Coronavirus disease 2019 (COVID-19) is a contagious disease affecting more than 200 countries, territories and regions. Thousands of studies have dealt with all aspects of the disease but little is known about post recovery status of the patients. Here, we examined ESR, CRP and serum albumin biomarkers in severe and mild-moderate COVID-19 post recovery patients. In severe group patients, serum albumin had a strong negative correlation with both ESR and CRP (R^2= -0.861), (R^2= -0.711) respectively. Also, there was a positive correlation between ESR and CRP (R^2=0.85) in the same group. However, there was no correlation among mild-moderate group patients in those biomarkers. In addition, no correlation recorded between severe and mild-moderate groups. This finding concludes the sustained elevation of ESR and CRP with decreased serum albumin level in severe COVID-19 post recovery patients.

Introduction

The outbreak of the coronavirus disease 2019 (COVID-19) is an infectious disease, with an etiological agent of a novel coronavirus, SARS-CoV-2, named for the similarity of its symptoms to those induced by the severe acute respiratory syndrome [1]. The disease appeared in late December 2019 in Wuhan, China [2]and within 3 months of its discovery, the disease spread rapidly worldwide [3,4]. Accordingly, on 11th of March 2020, the World Health Organization (WHO) announced COVID-19 as a pandemic disease [5].

COVID-19 can cause flu-like symptoms including; fever, cough, dyspnea, myalgia, and fatigue. More serious forms can cause severe pneumonia, respiratory failure, multi-organ dysfunction and death [6,7]. Gastrointestinal symptoms such as diarrhea, nausea and vomiting have also been described, along with loss of the sense of taste and smell [8,9]. Since the initial outbreak, great efforts from scientists have taken place to understand the pathophysiology and progression of the disease [8,10,11].

The clinical manifestations of COVID-19 infected patients are categorized as mild, moderate, severe, and critical [12]. The majority of affected patients (81%) suffer mild/moderate symptoms, whereas, severe and critical cases comprise 14% and 5% of infected cases, respectively [13].

Several biological markers have been found to correlate with the severity of COVID-19, including high C-reactive protein (CRP) level, high erythrocyte sedimentation rate (ESR) level and low level of serum albumin (hypoalbuminemia) [8,14-16]. These biomarkers in parallel with the clinical symptoms can be used to interpret more confidently the likely progression and severity of the disease [17]. CRP is an exquisitely sensitive systemic marker for acute-phase response to inflammation, infection, and tissue damage [18] . It has been reported that CRP levels are positively related to the severity of COVID-19 [19]. Another study illustrated a high ESR level in patients suffering severe COVID-19 symptoms when compared to non-severe groups, due to an increase in inflammation in severely affected patients [14]. In addition, other studies considered the serum albumin level as a vital indicator in severe COVID-19 patients [16,20].

Since the appearance of the disease, much research has been conducted on COVID-19 patients [8,10,11,17]. However, millions of people have recovered and limited follow-up studies have focused on the post recovery health status to check their biological markers [21]. Here, we studied the levels of ESR, CRP and serum albumin in severe COVID-19 post recovery patients and compared with a mild-moderate COVID-19 post recovery group.

Result And Discussion

COVID-19 infected patients can be assessed clinically by using quantitative measurements of numerous biomarkers such as, ESR, CRP, and serum albumin. Monitoring those biomarkers play a key role in checking pathological development and helping prognosis and outcomes of the disease [22].

In this study, all cases were identified by RT-PCR and categorized into two groups (Mild-moderate and severe COVID-19 post recovery groups). ESR, CRP, and serum albumin were measured in both groups, and we found that albumin had a strong negative correlation with ESR (R^2= -0.861) and CRP (R^2= -0.711) in the severe COVID-19 post recovery group (Table 1).

The hypoalbuminemia was seen predominantly in severe COVID-19 cases compared with mild cases [23]. However, no study has been conducted yet for evaluating the levels of albumin and its effect on the health of COVID-19 post recovery patients. In our study, we found a persistent hypoalbuminemia in severe COVID-19 post recovery patients.

Although the mechanisms for hypoalbuminemia in COVID-19 have not been studied thoroughly [24], albumin is a major serum protein produced by hepatic cells [24,25]and has a critical role in human health. Hypoalbuminemia is considered a sinister clinical sign in COVID-19 viral infection, that may be due to the release of the major acute-phase cytokines into the blood vessels during the cytokine storm, [16] or due to the increase of vascular permeability which allows the albumin to diffuse into the extravascular space [26]. Reduction in albumin synthesis may also be due to anorexia that is caused by the viral infection [16].

In the present study we found that ESR increased in all severe COVID-19 post recovery patients. Similar results were found by Pu, et al., [27] who observed an elevated level of ESR in a case study of a patient recovered from severe COVID-19 infection. This finding may justify the strong negative correlation between ESR and albumin because albumin retards the sedimentation of erythrocytes and decreases the rouleaux formation while hypoalbuminemia accelerates it [28], in contrary to other plasma proteins in which high level of them speed it up [29].

Our study revealed a high concentration of CRP in severe COVID-19 post recovery patients. A significant negative correlation was also found between albumin level and the inflammatory indicator, CRP (R^2= -711) (Table 1). Studies have determined a significant increase of CRP concentration in severe COVID-19 patients [30-32]. However, our data is the first study related to the COVID-19 post recovery patients. CRP is produced by the liver as a nonspecific immune protein and it is considered as a signal of systemic

inflammation [33] CRP level in serum also can be affected with the level of other serum proteins which are produced by liver cells [34,35].

Ponti et al. [36] found the severity of COVID-19 is positively correlated with ESR and CRP, while no study on both biomarkers after the recovery of COVID-19 patients has been recorded yet. Our data has revealed a positive correlation between ESR and CRP (R^2=0.85) in severe COVID-19 post recovery patients. Elevation of inflammatory biomarkers can be considered as a parameter for COVID-19 infection and its severity [37].

In the mild-moderate COVID-19 post recovery group, data showed non-significant positive correlation between ESR and CRP (0.6149). In addition, there was neither correlation between CRP and albumin (-0.3277) nor between ESR and albumin (-0.0504) (Table 1). Studies have revealed no/slight increase of ESR and CRP [36,38,39]while other studies showed inconsiderable decrease of serum albumin in mild-moderate COVID-19 patients [38,40]. Most importantly no studies conducted on post recovery patients addressing those markers. In mild-moderate COVID-19 patients the inflammatory proteins that have effect on ESR boosting maintain in their minimum level, subsequently ESR stays in their normal range [41]. Our study seems to be the first attempt to observe those biological markers in COVID-19 post recovery patients.

In Table 1 data analyses showed no correlation between mild-moderate and severe groups in COVID-19 post recovery patients when both groups compared in terms of ESR, CRP and serum albumin markers.

A study showed a significant difference in ESR, CRP and serum albumin between mild and severe COVID-19 patients. However, the difference between moderate and severe groups was observed only in ESR.

Table 1. Correlation analysis between ESR, CRP and albumin. In Sever COVID-19 post recovery group and mild-moderate COVID-19 post recovery group. Also, Correlation analysis between severe and mild-moderate COVID-19 post recovery groups, n=46 patients.

	ESR Severe	CRP Severe	serum Albumin Severe	ESR Mild-moderate	CRP Mild-moderate	serum Albumin Mild-moderate
ESR Severe	1.0000	0.8534	0.8610	0.1206	0.0868	-0.3505
CRP Severe	0.8534	1.0000	-0.7114	-0.0487	-0.0457	-0.3242
serum Albumin Severe	-0.8610	-0.7114	1.0000	0.0784	0.1265	0.2419
ESR Mild-moderate	0.1206	-0.0487	0.0784	1.0000	0.6149	-0.0504
CRP Mild-moderate	0.0868	-0.0457	0.1265	0.6149	1.0000	-0.3277
serum Albumin Mild-moderate	-0.3505	-0.3242	0.2419	-0.0504	-0.3277	1.0000

In conclusion we found a prolonged increase of ESR, CRP and decrease of serum albumin in severe COVID-19 post recovery patients. We also discovered a strong negative correlation of albumin with both ESR and CRP in the group. Therefore replacing albumin and ESR/CRP de-escalation is vitally recommended for the physician to avoid further consequences to COVID-19 post recovery patients.

Materials And Methods

Real-Time Reverse Transcription Polymerase Chain Reaction Assay for SARS-CoV-2

A total of 46 hospitalized patients were included in this study (the study committed to the ethical consideration). The diagnostic tests were performed for each patient, and pharyngeal swab samples collected for extracting 2019-nCoV RNA. After collection, the total RNA was automatically extracted within 45 seconds using the Qiagen EZ1 Advanced XL system (Qiagen, Hilden, Germany). Then, the presence of SARS-CoV-2 was detected by real-time RT-PCR amplification of SARS-CoV-2 open reading frame 1ab (ORF1ab) and envelope (E) genes fragments using PowerChek SARS-CoV-2 Real-Time PCR Kit (Kogenebiotech, Seoul, Korea). Conditions for amplifications were 50 °C for 30 min, 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1 min. When two target genes (ORF1ab, E) tested positive by specific real-time RT-PCR, the case would be transferred to the laboratory for confirmation. A cycle threshold value (Ct-value) ≤ 36.7 was defined as a positive test, and the Ct-value of > 36.7 was defined as a negative test or recovered.

COVID-19 Severity Category

The criteria for severity of COVID-19 were defined according to the diagnosis and treatment protocol for novel coronavirus pneumonia (Version 7) as mild, moderate and severe [42]. **Mild cases -** the patient shows mild clinical symptoms with no sign of pneumonia on imaging; **moderate cases -** the patient shows fever

and respiratory symptoms with radiological findings of pneumonia; **severe cases -** cases have any of the following criteria, respiratory distress (≧30 breaths/min), oxygen saturation ≤93% at rest, arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≦300 mmHg (l mmHg = 0.133 kPa).

Based on the above criteria patients were divided into two groups; 23 mild-moderate cases and 23 severe cases. Within 2-4 weeks of post recovery, blood samples were collected from each participant.

Biological marker Test

Biological marker tests including CRP and serum albumin were assessed for mild/moderate and severe groups using an automated multiparametric analyzer (cobas c111, Roche Diagnostics, Germany) and ESR were tested by Westergren method [43].

Statistical Analysis

Pearson correlation and polynomial regressions were employed to understand the relationship between ESR, SRP and serum albumin biomarkers.

Declarations

Conflict of interests: No

Author contribution: KMA and AMA have performed lab work, HMT and HMR have contributed in the writing. GF has analyzed the data.

References

1 Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine* **382**, 727-733, doi:10.1056/NEJMoa2001017 (2020).

2 who.org. *Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update*, <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/> (2020).

3 Park, S. E. Epidemiology, virology, and clinical features of severe acute respiratory syndrome - coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). *Clin Exp Pediatr* **63**, 119-124, doi:10.3345/cep.2020.00493 (2020).

4 Hoffmann, M. *et al.* SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **181**, 271-280.e278, doi:10.1016/j.cell.2020.02.052 (2020).

5 who.org. *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020*, <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020> (2020).

6 Wu, Z. & McGoogan, J. M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* **323**, 1239-1242, doi:10.1001/jama.2020.2648 (2020).

7 Guan, W.-j. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine* **382**, 1708-1720, doi:10.1056/NEJMoa2002032 (2020).

8 Chen, N. *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet* **395**, 507-513, doi:10.1016/S0140-6736(20)30211-7 (2020).

9 Wang, D. *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* **323**, 1061-1069, doi:10.1001/jama.2020.1585 (2020).

10 Polak, S. B., Van Gool, I. C., Cohen, D., von der Thüsen, J. H. & van Paassen, J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Modern Pathology*, doi:10.1038/s41379-020-0603-3 (2020).

11 Yang, S. *et al.* Clinical and CT features of early stage patients with COVID-19: a retrospective analysis of imported cases in Shanghai, China. *European Respiratory Journal* **55**, 2000407, doi:10.1183/13993003.00407-2020 (2020).

12 Wu, D., Wu, T., Liu, Q. & Yang, Z. The SARS-CoV-2 outbreak: What we know. *International Journal of Infectious Diseases* **94**, 44-48, doi:10.1016/j.ijid.2020.03.004 (2020).

13 Sun, P. *et al.* Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. *Journal of Medical Virology* **92**, 612-617, doi:10.1002/jmv.25735 (2020).

14 Zeng, F. *et al.* Association of inflammatory markers with the severity of COVID-19: A meta-analysis. *International Journal of Infectious Diseases* **96**, 467-474, doi:10.1016/j.ijid.2020.05.055 (2020).

15 Gao, Y. *et al.* Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *Journal of Medical Virology* **92**, 791-796, doi:10.1002/jmv.25770 (2020).

16 Ramadori, G. Hypoalbuminemia: an underestimated, vital characteristic of hospitalized COVID-19 positive patients? *Hepatoma Research* **6** (2020).

17 Pierce, J. D., McCabe, S., White, N. & Clancy, R. L. Biomarkers: an important clinical assessment tool. *Am J Nurs* **112**, 52-58, doi:10.1097/01.naj.0000418926.83718.28 (2012).

18 Pepys, M. B. & Hirschfield, G. M. C-reactive protein: a critical update. *The Journal of Clinical Investigation* **111**, 1805-1812, doi:10.1172/JCI18921 (2003).

19 Chen, L. *et al.* [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. *Zhonghua Jie He He Hu Xi Za Zhi* **43**, E005, doi:10.3760/cma.j.issn.1001-0939.2020.0005 (2020).

20 Li, J. *et al.* Plasma albumin levels predict risk for nonsurvivors in critically ill patients with COVID-19. *Biomarkers in Medicine* **14**, 827-837, doi:10.2217/bmm-2020-0254 (2020).

21 Balachandar, V. *et al.* Follow-up studies in COVID-19 recovered patients - is it mandatory? *Science of The Total Environment* **729**, 139021, doi:https://doi.org/10.1016/j.scitotenv.2020.139021 (2020).

22 Kermali, M., Khalsa, R. K., Pillai, K., Ismail, Z. & Harky, A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. *Life Sci* **254**, 117788, doi:10.1016/j.lfs.2020.117788 (2020).

23 Zhang, Y. *et al.* Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver International* **40**, 2095-2103, doi:10.1111/liv.14455 (2020).

24 Rothschild, M. A., Oratz, M. & Schreiber, S. S. Serum albumin. *Hepatology* **8**, 385-401, doi:10.1002/hep.1840080234 (1988).

25 Huang, J. *et al.* Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *Journal of Medical Virology* **92**, 2152-2158, doi:10.1002/jmv.26003 (2020).

26 Soeters, P. B., Wolfe, R. R. & Shenkin, A. Hypoalbuminemia: Pathogenesis and Clinical Significance. *Journal of Parenteral and Enteral Nutrition* **43**, 181-193, doi:10.1002/jpen.1451 (2019).

27 Li, J., Pu, S., Zhang, X., Liu, D. & Ye, B. The unexplained increasing of Erythrocyte Sedimentation Rate in a case recovered from COVID-19. (2020).

28 REINHART, W. H. & NAGY, C. Albumin affects erythrocyte aggregation and sedimentation. *European Journal of Clinical Investigation* **25**, 523-528, doi:10.1111/j.1365-2362.1995.tb01739.x (1995).

29 Tishkowski, K. & Gupta, V. in *StatPearls [Internet]* (StatPearls Publishing, 2020).

30 Qin, C. *et al.* Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clinical Infectious Diseases* **71**, 762-768, doi:10.1093/cid/ciaa248 (2020).

31 Li, X. *et al.* Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. *International Journal of Infectious Diseases* **94**, 128-132, doi:https://doi.org/10.1016/j.ijid.2020.03.053 (2020).

32 Chen, W. *et al.* Plasma CRP level is positively associated with the severity of COVID-19. *Annals of Clinical Microbiology and Antimicrobials* **19**, 18, doi:10.1186/s12941-020-00362-2 (2020).

33 Ramadori, G., Sipe, J. D. & Colten, H. R. Expression and regulation of the murine serum amyloid A (SAA) gene in extrahepatic sites. *The Journal of Immunology* **135**, 3645-3647 (1985).

34 Ramadori, G. & Christ, B. Cytokines and the Hepatic Acute-Phase Response. *Semin Liver Dis* **19**, 141-155, doi:10.1055/s-2007-1007106 (1999).

35 Perez, L. Acute phase protein response to viral infection and vaccination. *Archives of Biochemistry and Biophysics* **671**, 196-202, doi:https://doi.org/10.1016/j.abb.2019.07.013 (2019).

36 Ponti, G., Maccaferri, M., Ruini, C., Tomasi, A. & Ozben, T. Biomarkers associated with COVID-19 disease progression. *Critical Reviews in Clinical Laboratory Sciences* **57**, 389-399, doi:10.1080/10408363.2020.1770685 (2020).

37 Kermali, M., Khalsa, R. K., Pillai, K., Ismail, Z. & Harky, A. The role of biomarkers in diagnosis of COVID-19 – A systematic review. *Life Sciences* **254**, 117788, doi:https://doi.org/10.1016/j.lfs.2020.117788 (2020).

38 Jin, A. *et al.* Clinical characteristics of patients diagnosed with COVID-19 in Beijing. *Biosafety and Health* **2**, 104-111, doi:https://doi.org/10.1016/j.bsheal.2020.05.003 (2020).

39 Ghahramani, S. *et al.* Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. *European Journal of Medical Research* **25**, 30, doi:10.1186/s40001-020-00432-3 (2020).

40 Wang, D. *et al.* Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. (2020).

41 Sun, Y. *et al.* Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience. *Journal of Autoimmunity* **112**, 102473, doi:https://doi.org/10.1016/j.jaut.2020.102473 (2020).

42 medium.com. *The Official Chinese Government Guide to Diagnosing and Treating the Novel Coronavirus*, <https://medium.com/@balajis/the-official-chinese-government-guide-to-diagnosing-and-treating-the-novel-coronavirus-9d06868f8df4> (2020).

43 ICSH recommendations for measurement of erythrocyte sedimentation rate. International Council for Standardization in Haematology (Expert Panel on Blood Rheology). *Journal of Clinical Pathology* **46**, 198-203, doi:10.1136/jcp.46.3.198 (1993).