Original Article

Relationship between Post Covid 19 Duration and Biomarkers: A Retrospective Study in Hospitalised Patients

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How to cite this article: Pradnya Bagalkote1, Rekha Sharma. Relationship between Post Covid 19 Duration and Biomarkers: A Retrospective Study in Hospitalised Patients. Indian Journal of Public Health Research and Development / Vol. 16 No. 2, April-June 2025.

Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), now known as coronavirus disease 2019 (COVID-19) were initially reported in Wuhan, China and rapidly spread throughout world in December 2019. The present retrospective study was postulated to assess the relationship between the post COVID 19 duration and biomarkers.

Methods: About 369 subjects diagnosed as COVID-19 infection confirmed by "Nasopharyngeal Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive for SARS-CoV2" of all disease severity and admitted to Viveka Hospitals, Nagpur, Maharashtra, INDIA were included in the study. The laboratory investigations viz., D-Dimer, ferritin and C-reactive protein (CRP) and Lactate dehydrogenase (LDH) recorded at the time of admission, after 15th day and 30th day of discharged were retrieved from the hospital records. The relationship was computed using Paired t-test and the confidence interval was set at 95%. The study was initiated after approval from the Institutional Ethics Committee of Viveka Hospitals, Nagpur.

Results: The mean D Dimer and ferritin values showed significant ($p = 0.000$) decrease after 15 days of discharge and CRP and LDH showed insignificant ($p>0.05$) increase and decrease respectively as compared to day of admission. After 30th days of discharge D Dimer increased significantly ($p = 0.000$) and ferritin and CRP decreased insignificantly ($p>0.05$).

Conclusion: It can be concluded from the study that COID19 biomarkers responds differently after 15th and 30th days of discharge. The suitable changes in medical protocols after 15th day and 30th days of discharge can reduce morbidity amongst the COVID 19 patients.

Keywords: COVID-19, biomarkers, D-Dimer, Ferritin, C-Reactive Protein (CRP), Lactate dehydrogenase (LDH)

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Submission date: October 18, 2024 **Acceptance dat**e: December 11, 2024 **Published date: March 11, 2025**

Introduction

Coronaviruses are a large family of viruses that may cause respiratory illnesses in humans ranging from common colds to more severe conditions such as Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS). 'Novel coronavirus' is a new, previously unidentified strain of coronavirus. The novel coronavirus involved in the 2019 outbreak has been named SARS-CoV-2 by the World Health Organization (WHO). The first known case of COVID-19 originated from the city of Wuhan in Hubei Province, China. From there, it has spread to every inhabited continent worldwide. As of 30 April 2023, the COVID-19 pandemic has resulted in over 6.9 million deaths worldwide. [1]

For severe COVID-19 disease, major risk factors include age, male sex, obesity, smoking, and comorbid chronic conditions such as hypertension, type 2 diabetes mellitus, and others like chronic obstructive pulmonary disease (COPD), immunodeficiency, and malignancies. [2,3,4,5,6,7,8]

The accurate and reliable estimation of Oxidant/ Antioxidant levels in COVID-19 patients, utilizing biomarkers such as LYM, ferritin, D-dimer, WBC, and CRP, can facilitate the diagnosis and prognosis. [9] Comorbidities are medical conditions that coexist alongside a primary diagnosis and affect health, including treatment and outlook. Common comorbidities among hospitalized people include hypertension, diabetes and chronic lung disease. [10]

The review of literature shows that no studies have been undertaken on duration of COVID 19 and biomarkers hence, it was postulated to study the relationship between duration of COVID 19 and biomarkers amongst patients admitted in hospitals.

Material and Methods

It was a retrospective study conducted by retrieving data of 369 subjects[11] diagnosed as COVID-19 infection and were admitted to Viveka Hospitals, Nagpur, Maharashtra, INDIA designated for COVID-19 patients' isolation in the period from 1st of April 2020 to 31st of July 2021. All patients were given Standard Medical protocol as given by Ministry of Health and Family Welfare for Covid-19.[12]

Inclusion Criteria: The study included all adults (> 18 years old) hospitalized in Non-ICU isolated patients with COVID-19 infection confirmed by "Nasopharyngeal Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive for SARS-CoV2" of all disease severity.

Exclusion Criteria: The study excluded all adults (> 18 years old) hospitalized in ICU isolated patients with COVID-19 infection confirmed by "Nasopharyngeal Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive for SARS-CoV2" of all disease severity.

The laboratory investigations viz., D-Dimer, Ferritin, C-reactive protein(CRP) and Lactose dehydrogenase (LDH) recorded at the time of admission, after 15 day and 30th day of discharge were retrieved from the hospital records.

Statistical Analysis: Data was analysed using Paired t test and the confidence interval was set at 95%. The study was initiated after approval from the Institutional Ethics Committee of Viveka Hospitals, Nagpur, with Reg. No. ECR/1639/INST/MH/2021, Dated 20th Feb 2024.

Observation and Results

D-Dimer and Duration of COVID 19

An elevated D-dimer in COVID-19 patients has been reported by several scientists. [13,14,15] The statistical analysis of the mean D dimer values of patients according to the duration of COVID19 has been presented in Table 1.

Table 1: D Dimer levels of COVID-19 Patients

SN	COVID 19 Biomarkers	Mean	Std. Deviation	Paired t test Value	P value
1.	D-DIMER ng/ml	785.50	980.43	9.154	0.000
	D DIMER After 15th Day ng/ml	293.00	316.53		
2.	D-DIMER ng/ml	785.50	980.43	8.684	0.000
	D DIMER After 30th Day ng/ml	335.66	275.90		
3.	D DIMER After 15th Day ng/ml	293.00	316.53	-2.083	0.038
	D DIMER After 30th Day ng/ml	335.66	275.90		

The data presented in Table 1 shows that the D-Dimer values after 15th day of discharge (t =9.154, p= 0.000) and 30th day after discharge (t=8.684, p=0.000) were significantly lower than the mean D-Dimer values on admission. However, the comparison between the D-Dimer values of 15th and 30th days, showed significant increase (t=2.083, p=0.038).

An elevated D-dimer in patients of COVID-19 infection and the patients with serum D-dimer ≥400 ng/ml predicted fatal outcome in COVID-19 patients. [15] The elevated D-dimer values (≥0.5 mg/L) were associated with nearly three fold higher risk of poor outcomes in COVID-19 patients (pooled-OR: 3.39; 95% CI: 2.66–4.33; p<0.00001. [16]In a retrospective, multicentre cohort study reported the d-dimer levels greater than 1·0 µg/mL (18·42, 2·64–128·55; p=0·0033) on admission in COVID- 19 patients. [3] Old patients with SARS-CoV-2 tend to show increased levels of D-Dimer compared with younger patients.[17,18]

In the present study the D Dimer values were observed between 1.27 to 7500 ng/dl whereas several scientists reported serum d Dimeras > 400 ng/ml, 1·0 µg/mL and (≥0.5 mg/L) respectively as risk of poor outcomes in COVID 19patients.[16,3,15] This indicates that the D-Dimer values of the present study were considerably high as compared to the reported studies. However, no mortality was observed amongst them.

Ferritin and Duration of COVID 19

Ferritin has a very crucial role in COVID-19 pneumonia in predicting the severity of illness and assessing response to treatment during hospitalization.[19] Serum ferritin levels were closely related to the severity of COVID-19 and serum ferritin ≥200 ng/ml predicted fatal outcome in COVID-19 patients.[20,3,15,17,21,13] The statistical analysis of the mean ferritin values of patients according to the duration of COVID 19 has been presented in Table 2.

Table 2: Ferritin levels of COVID-19 Patients

SN	COVID 19 Biomarkers	Mean	Std. Deviation	Paired t test Value	P value
1	Ferritin (ng/ml)	371.82	458.23	3.713	0.000
	Ferritin After 15 days(ng/ml)	255.26	475.81		
2	Ferritin (ng/ml))	371.82	458.23	5.959	0.000
	Ferritin After 30 Days(ng/ml)	215.89	221.70		
3	Ferritin After 15 days(ng/ml)	255.26	475.81	1.605	0.109
	Ferritin After 30 Days(ng/ml)	215.89	221.70		

The data presented in Table 2 shows that the mean Ferritin value of patients on admission was 371.82±458.23 ng/ml which significantly decreased on 15th (t=3.713, p=0.00) and 30th days of discharge (t=5.959, p=0.00). However, the comparison between the Ferritin values of 15th and 30th days, showed an insignificant decrease (t=1.605, p=0.109).

A ferritin cut-off value at 272.5 ng/ml. COVID -19 patients with elevated ferritin levels had a higher incidence of severity illness (50.0 vs 2.9%) and liver injury (52.3 vs 20.0%) when compared with patients with normal ferritin levels (p < 0.05).[21] The elevated ferritin group showed longer viral clearance time (median 16 vs 6 days, p < 0.001) and in-hospital length (median 18 vs 10 days, p < 0.001)).[22]In ROC analysis, the level of ferritin ≥264.5 ng/ml predicted severe COVID-19 with 73.9% sensitivity and 94.2% specificity. [23]

In the present study the ferritin levels of patients ranged between 54.819ng/ml to 178.282 ng/ml during admission and were above the cut-off value[21] however, none of COVID 19 patients were critical. There after, the ferritin levels decreased considerably after 15 and 30 days and ranged between -8.946ng/ mlto 88.535ng/ml. Studies comparing ferritin level on admission between COVID-19 patients between survivors and non-survivors demonstrated that non-survivors showed ferritin levels on admission around 1400 ng/mL, which is between 3 and 4 times higher than that observed in survivors.[24] The higher levels of 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.[3]

C-Reactive Protein (CRP) and Duration of COVID 19

C-Reactive Protein(CRP) was found to be an independent determinant factor for severe COVID-19 patients. [3,20,16,15] The mean CRP values of patients on admission, 15th day and 30th days of discharge have been presented in Table 3.

Table 3: CRP levels of COVID-19 Patients

SN	COVID 19 Biomarkers	Mean	Std. Deviation	Paired t test Value	P value
1	CRP (mg/l)	59.52	143.13	0.902	0.368
	CRP After 15 days	67.35	196.20		
2	CRP (mg/l)	59.52	143.13	1.574	0.116
	CRP After 30 Days	46.49	64.82		
3	CRP After 15 days	67.35	196.20	1.933	0.054
	CRP After 30 Days	46.49	64.82		

The data presented in Table 3 shows that the mean CRP value of patients on admission was 59.52±143.13 mg/l which on 15th day of discharge increased to 67.35±196.20mg/l and decreased to 46.49±64.82 mg/l on 30th day. The CRP values after 15th day of discharge (t =0.902, p= 0.368) and 30th day after discharge (t=1.574, p=0.116) were insignificantly lower than the mean CRP values on admission. However, the comparison between the CRP values of 15th and 30th days, showed a significant decrease (t=1.933, p=0.054).

The average CRP level of deceased patients reported was 137.79 mg/l, while the average CRP level of survivors was 14.37 mg/l.[25] The CRP levels above 30 mg/L were significantly associated with an increased risk of developing severe COVID-19 for those who have higher ages and comorbidities (ARR 3.99, 95% CI: 1.35– 11.82; p=0.013).[26]A study also predicted fatal outcome in COVID-19 patients with Serum CRP ≥30ng/ml. [15]

In the present study the CRP levels on admission ranged between5 to100 mg/l and were very high as compared to the reported values. According to a study, COVID-19 patients exhibited higher median CRP levels at baseline [58 (IQR: 2.0–127.8) mg/L] that decreased significantly to 2.4 (IQR: 1.4–3.9) mg/L after 40 days after symptom onset (p<0.0001). [26] Similarly, in the present study, the CRP values were found to be decreased on 30th day of discharge, but at a slower pace.

Lactate dehydrogenase (LDH) and Duration of COVID 19

Several scientists have reported the increased LDH levels to the development of COVID-19 disease. [27,28,3,29,30,17,18,16] The mean LDH values of patients on admission, 15th day of discharge have been presented in Table 4.

Table 4: LDH levels of COVID-19 Patients

SN	COVID 19 Biomarkers	Mean	Std. Deviation	Paired t test Value	P value
1	LDH (U/Liter)	309.71	638.23	0.635	0.526
	LDH After 15 days	307.58	638.37		

In the present study, the initial LDH value was 309.71 + 638.23 u/l, which decreased after 15th day of discharge but the statistical analysis did not show any significant difference between them (t= 0.63, p=0.526). Fatal outcome in COVID-19 patients with Serum LDH ≥400 U/L had been predicted.[15] LDH > 731 U/L significantly predicted mortality in an adjusted multivariate analysis while LDH < 425 U/L was associated with lower rates of ICU admission.[17] However, in the present study, the LDH levels were

less than the critical values reported, which shows the less severity of COVID 19 patients.

Conclusion

The mean D Dimer and ferritin values showed significant (p=0.000) decrease after 15 days of discharge and CRP and LDH showed insignificant (p>0.05) increase and decrease respectively as compared to day of admission. After 30th days of discharge D Dimer increased significantly (p=0.000) and ferritin and CRP decreased insignificantly (p>0.05).The biomarkers showed different trends when compared between 15th day and 30th day of discharge, the D-Dimer increased significantly (p= 0.000) and CRP decreased significantly (p= 0.000) whereas ferritin decreased insignificantly (p>0.05). It can be concluded from the study that COID19 biomarkers responds differently after 15th and 30th days of discharge. The suitable changes in medical protocols after 15th day and 30th days of discharge can reduce morbidity amongst the COVID 19 patients.

Study Limitations: The study was limited to the COVID-19 Non-ICU patients of all disease severity.

Future Research Recommendations: Future studies can be carried out on effects of supplementations on biomarkers and nutritional status of patients. In depth studies can be carried out on the biomarkers.

Conflict of interest: Nil

Source of funding: Nil

References

1. https://www.who.int/ westernpacific/ healthtopics/ detail/ coronavirus, Retrieved on December 10,2021.
2. Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., … Song, Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Internal Medicine.2020,180(7), 934–943.
3. 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. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. Lancet (London, England).2020,395(10229), 1054–1062.
4. Garibaldi, B. T., Wang, K., Robinson, M. L., Zeger, S. L., Bandeen-Roche, K., Wang, M. C., Alexander, G. C., Gupta, A., Bollinger, R., & Xu, Y. Comparison of time to clinical improvement with vs without remdesivir treatment in hospitalized patients with COVID-19. JAMA Network Open, 4(3).2021, e213071.
5. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using open safely. Nature. ;584(7821).2020, 430–436.
6. Cucinotta D, Vanelli M .WHO declares COVID-19 a pandemic. Acta Biomed .2020,91(1), 157–160.
7. Gao Y, Ding M, Dong X. et al. Risk factors for severe and critically ill COVID-19 patients: A Review. Allergy. 2021,76(2),428–455.
8. CDC. 2019 Novel Coronavirus, Wuhan, China. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/about/index.html. January 26, 2020
9. Tahir Huyut M, Huyut Z, İlkbahar F, Mertoğlu C. What is the impact and efficacy of routine immunological, biochemical and hematological biomarkers as predictorsof COVID-19 mortality?IntImmunoPharmacol. 2022 ,105:108542
10. www.clevelandclinic.com,https://my.clevelandclinic.org/,2021,Dec 10
11. https://www.scienceimpactpub.com/journals/index.php/jei/article/view/481
12. https://covid19dashboard.mohfw.gov.in/ pdf/ClinicalGuidanceon Diagnosisand ManagementofDiabetesatCOVID19 Patient Managementfacility.pdf
13. Pasini, E., Corsetti, G., Romano, C., Scarabelli, T. M., Chen-Scarabelli, C., Saravolatz, L., & Dioguardi, F. S. (2021). Serum metabolic profile in patients with long-covid (pasc) syndrome: clinical implications. Frontiers in Medicine. (2021),8, 714426. https://doi.org/10.3389/fmed.2021.714426
14. Bivona, G., Agnello, L., & Ciaccio, M. Biomarkers for prognosis and treatment response in covid-19 patients. Annals of laboratory medicine.2021,41(6), 540–548. https://doi.org/10.3343/alm.2021.41.6.540
15. Yousaf, M., Abujaber, A. A., Almughalles, S., Thomas, M. M., & Hameed, M. A. (2024). Predictive value of D-dimer in assessing the risk of pulmonary embolism (PE) in Covid-19. Qatar Medical Journal.2024(2), 6. https://doi.org/10.5339/qmj.2024.qitc.6

16. Malik, F. T., Ishraquzzaman, M., Kalimuddin, M., Choudhury, S., Ahmed, N., Badiuzzaman, M., Ahmed, M. N., Banik, D., Huq, T. S., & Al Mamun, M. A. Clinical presentation, management and in-hospital outcome of healthcare personnel with covid-19 disease. Cureus.2020,12(8), e10004. https://doi.org/10.7759/cureus.10004

17. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., et al. Epidemiologicalandclinical characteristics of 99 cases of 2019 novel coronavirus pneumonia inWuhan, China: a descriptive study. Lancet.395.2020,(10223),507–513.

18. Zhang, L., Yan, X., Fan, Q., Liu, H., Liu, X., Liu, Z., & Zhang, Z.D-Dimer levels on admission to predict in-hospital mortality in patients with covid-19. journal of thrombosis and haemostasis: JTH.2020, 18(6),1324–1329.

19. Ahmed, S., Ansar Ahmed, Z., Siddiqui, I., Haroon Rashid, N., Mansoor, M., & Jafri, L. Evaluation of serum ferritin for prediction of severity and mortality in COVID-19- a cross sectional study. Annals of Medicine and Surgery.2021, 63, 102163.

20. Liu, F., Li, L., Xu, M., Wu, J., Luo, D., Zhu, Y., Li, B., Song, X., & Zhou, X. Prognostic value of interleukin-6, c-reactive protein, and procalcitonin in patients with COVID-19. Journal of Clinical Virology: The Official Publication of The Pan American Society forClinical Virology.(2020),127, 104370.

21. Cao, P., Wu, Y., Wu, S., Wu, T., Zhang, Q., Zhang, R., Wang, Z., & Zhang, Y. Elevated serum ferritin level effectively discriminates severity illness and liver injury of coronavirus disease 2019 pneumonia. Biomarkers: Biochemical Indicators of Exposure, Response, And Susceptibility to Chemicals.2021, 26(3), 207–212.

22. Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J., & HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England).2020, 395(10229), 1033–1034.

23. Bozkurt, F. T., Tercan, M., Patmano, G., BingolTanrıverdi, T., Demir, H. A., &Yurekli, U. F. Can Ferritin levels predict the severity of illness in patients with COVID-19? Cureus.2021, 13(1), e12832.

24. Gómez-Pastora, J., Weigand, M., Kim, J., Wu, X., Strayer, J., Palmer, A. F., Zborowski, M., Yazer, M., & Chalmers, J. J.Hyperferritinemiain critically ill covid-19 patients - is ferritin the product of inflammation or a pathogenic mediator? ClinicaChimica Acta; International Journal of Clinical Chemistry.(2020),509, 249–251.

25. Abdullah, A. J., Arif, A. T., Rahman, H. A., Sofihussein, K. Q., Hadi, J. M., Aziz, J. M. A., Tofiq, S. S., & Mustafa, A. M. Assessing serum c-reactive protein as a predictor of COVID-19 outcomes: a retrospective cross-sectional study. Annals of Medicine and Surgery.2023,85(7), 3359–3363.

26. Gebrecherkos T, Challa F, Tasew G, Gessesse Z, Kiros Y, Gebreegziabxier A, Abdulkader M, Desta AA, Atsbaha AH, Tollera G, Abrahim S, Urban BC, Schallig H, Rinke de Wit T, Wolday D. Prognostic value of c-reactive protein in sars-cov-2 infection: a simplified biomarker of COVID-19 severity in northern ethiopia. Infect Drug Resist. 2023,16:3019-3028

27. Ferraris, A. M., Giuntini, P., & Gaetani, G. F. Serum lactic dehydrogenase as a prognostic tool for non-hodgkin lymphomas. Blood.1979,54(4), 928–932.

28. Xiang, J., Zhou, L., He, Y., & Wu, S. LDH-A Inhibitors as remedies to enhance the anticancer effects of parp inhibitors in ovarian cancer cells. Aging.2021, 13(24), 25920–25930.

29. Li, C., Ye, J., Chen, Q., Hu, W., Wang, L., Fan, Y., Lu, Z., Chen, J., Chen, Z., Chen, S., Tong, J., Xiao, W., Mei, J., & Lu, H.Elevated lactate dehydrogenase (ldh) level as an independent risk factor for the severity and mortality of COVID-19. Aging. 2020,12(15), 15670–15681.

30. Mao Manyun , Dian Yating , Sun Yuming , Chen Wangqing , Zhu Wu , Deng Guangtong.Lactate dehydrogenase predicts disease progression outcome in COVID-19 patients treated with azvudine.Frontiers in Cellular And Infection Microbiology.2023, 13.