Correlation between serum C-reactive protein level with severity of the disease in Covid-19 patients.

[1]Asmabi Tousif Imadad Devale, Associate Professor, Department of Biochemistry Prakash institute of medical Science & Research, UrunIslampur, Dist-Sangli, Maharashtra.

[2]Amit D Sonagra, Assistant Professor, Department of Biochemistry, AIIMS, Rajkot.

[3]Shireen Swaliha Quadri, Associate Professor, Department of Physiology, SIMS, Shimoga, Karnataka

[4]Anupriya Deshpande, Professor and Head, Department of Physiology, Prakash institute of Medical Science & Research, UrunIslampur, Dist-Sangli, Maharashtra.

[5]Tousifimadad Devale, Consultant medical oncologist, Mahatama Gandhi Cancer Hospital, Miraj, Maharashtra

Corresponding Author: Anupriya Deshpande, Professor and Head, Department of Physiology, Prakash institute of Medical Science & Research, UrunIslampur, Dist-Sangli, Maharashtra.

Abstract

Background: COVID-19 has emerged as a rapidly spreading global pandemic with increased burden on health care. Biomarkers have always played an important role in clinical decision making in various infectious diseases. It is crucial to assess the role of biomarkers in evaluating severity of disease and appropriate allocation of resources.

Objectives: To find the levels of serum CRP in confirmed Covid-19 patients and to compare their levels in patients with mild to moderate disease and patients with severe disease who required ICU care for management.

Methods: A Cross sectional study was carried out on 261 confirmed cases of Covid-19, in whom Serum levels of Random Glucose (SRG), Creatinine, Urea, C-reactive protein (CRP) were measured.

Results: To assess the association between CRP level and severity of disease along with their hospital outcome, 261 confirmed COVID-19 patients were recruited. They were divided into two groups, Group I were Covid-19 Patients (222) with mild to moderate disease and Group II Covid-19 patients(39)with severe disease who required ICU care for management. CRP levels were significantly increased with p value <0.005 in group II when compared to group I.

Conclusion: Findings of our study suggest that determination of biochemical parameters like CRP at the time of hospitalization helps in predicting the severity of disease and need for ICU for better treatment management and prevention of adverse outcome.

Keywords: Severe acute respiratory syndrome, Covid-19, C- reactive protein, Intensive care unit.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has become the focus of attention worldwide. It is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] First case of COVID-19 was reported in late December 2019 in Wuhan, China, since then it has aggressively spread across the world and dramatically impacted people's health and daily life.[2] This outbreak has been a challenge for clinicians and researchers alike.

COVID-19 infection has a variable clinical presentation from asymptomatic to milder symptoms, including fever, dry cough, dyspnoea, myalgia, sore throat and headache, to more severe and emergent manifestations including confusion, chest pain, hypoxemia, pneumonia and other complications requiring intensive care unit (ICU) admission and mechanical ventilation.[3-5] Diarrhoea, anosmia and agues as well as neurologic manifestations have also been reported in a few studies.[6-8] As the number of infected and fatal cases is rising across the globe, there is a pressing need to investigate the clinical, radiological, and laboratory characteristics, and more importantly, the mortality risk factors in severe COVID-19 patients.

In an effort to aid medical management, researchers all over the globe have been toiling hard to search for predictors of COVID-19 disease severity to identify and stratify them accordingly. Insights into disease pathogenesis and methods to rapidly discern and assess COVID-19 infection are evolving. Laboratory biomarkers are economical, faster and feasible to obtain. As such, they have been the preferred modality to monitor and predict outcomes and prognosis of disease.[9-11] Understanding the variation and profile of specific biomarkers as a function of different COVID-19 outcomes would help in the development of a risk stratified approach in the care of patients with this illness. With the surge in COVID-19 cases across the globe due to its highly contagious nature, there have been numerous studies reporting on the predictors of disease severity in COVID-19 patients.

Furthermore, there are no reliable prognostic indicators for predicting disease severity and progression. Recognizing markers of disease severity may thus profoundly help to detect at-risk patients. Several retrospective analyses have reported the clinical characteristics and outcomes of hospitalized patients with COVID-19.[12-14] Derangements in laboratory markers of inflammatory response, including C-reactive protein (CRP), have been identified as predictors of clinical severity and complications.[15-17] CRP is an acute-phase, nonspecific marker of inflammation/infection which has been found to broadly correlate with disease severity and treatment response across a variety of infectious and noninfectious conditions.[18] Elevated CRP levels have been previously reported in severe acute respiratory syndrome, Middle East respiratory syndrome, H1N1 influenza.[19-21] Recent studies have reported that CRP levels are elevated in patients with COVID-19 and may correlate with severity of disease and disease progression.[18,22] As such, CRP holds promise as a potential prognostic biomarker. The aim of the study is to evaluate the clinical utility of CRP in predicting the severity of COVID-19 and need for intensive care and further complications.

Material and Methods

Source of Data: A cross sectional study was carried out on 261 Confirmed positive cases of Covid-19 who were admitted in the Prakash institute of medical

science and research centre, Urun Islampur between June – November 2020. This study was approved by institutional ethical committee. All the cases were confirmed Covid-19 positive by real time reverse transcriptase polymerase chain reaction (RT-PCR) assay in nasal and pharyngeal swab specimen.[11]

Data collection: After taking informed consent, Cases were subjected to medical examination and blood investigations. General health characteristics such as Age, Sex, history of travel, exposure to any other patient with similar illness were noted. History of Diabetes, hypertension and any other co morbid condition was recorded.

Biochemical investigations: A random blood sample of about 3ml was drawn from all the patients recruited for the study. Serum was separated by centrifugation and used for estimation of RSG, Serum Creatinine, blood urea and CRP.

Methods of Estimation**:** RSG: Glucose Oxidase Peroxidase, Serum Creatinine: Kit based Jaffe's method, Blood Urea: Modified Berthelot's Method. CRP: Turbidimetric Method using a reagent kit Tubilatex,

Statistical analysis: The data was collected, compiled and analyzed using SPSS statistical package version 17.0. Pearson's correlation test was performed to examine various correlations. Unpaired t-test was used for two group comparison. For all the tests, p value of < 0.05 was considered as statistically significant. Results were expressed as Mean, SD, and range values for continuous data, number and percentage for discrete data.

Results

A total of 261 patients with confirmed COVID-19 infection were enrolled in this study. Among the total patients enrolled for the study, 92 were females and 169 were males, the average age being 51-65years. To assess the clinical utility of CRP in predicting hospital outcome, Covid-19 Patients were divided into two groups-

Group I Covid-19 patients with mild to moderate disease (n=222)

Group II Covid-19 patients with severe illness who required ICU admission for the management. (n=39)

Table 1: Distribution of patients according age, serum levels of RBS, urea, creatinine, and CRP

	Group	N	Mean	Std. Deviation	Std. Error Mean	p (value)
Age (years)	1	222	62.95	12.174	1.949	
	2	39	53.34	13.947	0.936	>0.05
SRG (mg/dl)	1	222	173.590	87.9344	14.0808	
	2	39	157.681	83.5895	5.6102	>0.05
Urea (mg/dl)	1	222	39.436	25.8057	4.1322	
	2	39	30.539	11.2212	0.7531	<0.05
S. Creatinine (mg/dl)	1	222	1.231	0.5996	0.0960	
	2	39	0.990	0.3685	0.0247	<0.05

CRP (mg/L)	1	222	63.418	30.2199	4.8391	
	2	222	42.965	28.9036	1.9399	0.0001

There was no significant difference in the age, and SRG level between Group I and group II (p value>0.05).

The levels of serum Urea, Creatinine were significantly increased in group II when compared to group 1, and the levels of CRP were significantly increased with p value <0.0001 in group II when compared to group I.

12 out of 39 patients who were admitted in ICU died after developing various complications.

Discussion

Covid-19 is a pandemic infectious disease which has spread rapidly across the globe and became an urgent public health challenge. According to WHO's report, the pandemic will continue at least for years [23]. Clinical and epidemiological features have been reported by many studies,[24,25] but the knowledge about the biochemical parameters predicting the severity and mortality of the disease is reported by very few studies. Thus the aim of this study is to find out the predictive value of CRP in assessing the severity of COVID-19, need for intensive care and associated mortality.

Patients were divided into 2 groups based on the severity of the disease. Group 1 included the patients having mild to moderate disease and did not require ICU admission, whereas group 2 included the patients who developed severe disease and required ICU admission for the management. A total of 261 confirmed COVID-19 patients were recruited for the study. Serum CRP level was estimated at the time of admission. Among the 261patients, 222 had mild to moderate disease, 39 developed severe disease and required ICU admission for the management, 12 of them died after developing complications.

We found statistically higher levels (p value<0.0001) of CRP in group 2 patients who were in ICU when compared to group 1 patients. Our findings are in accordance with previous studies.[24,26-29] High levels of inflammatory markers are critical indicators of underlying systemic vasculitis and dyes regulation of coagulation mechanism that leads to parenchymal lesions in vital organs.[30]CRP is a non-specific acute phase reactant induced by IL-6in the liver. Elevated CRP levels are directly correlated with level of inflammation and disease severity. Hence, it is an important biomarker in diagnosis and assessing these verity of infectious diseases.[31]Meta-analysis of 20 studies including 4843 COVID-19 patients, reporting impact of elevated CRP (>10 mg/L) on outcomes showed that there is nearly fourfold higher risk of poor outcomes inCOVID-19 patients with elevated CRP (pooled-OR:3.97; 95% CI:2.89–5.45; p<0.00001).[10]

Some studies suggested that an early elevation in C-reactive protein (CRP) greater than 15 mg/l provides a marker of disease severity and levels greater than 200 mg/l on admission are independently associated with five times the odds of death.[32]Inpatients with sepsis, elevated CRP level >100 mg/L has been identified as an independent predictor of ICU and 30-day mortality as well as length of ICU stay in patients who fulfillSepsis-3 criteria.[33] Elevated CRP values have been reported in viral respiratory illnesses such as SARS, MERS-CoV, and H1N1, and have been reported to correlate with disease severity and predictors of disease progression.[19,20] Similarly, CRP levels have been reported to be elevated in hospitalized patients

with COVID-19, and to correlate with severity of disease and mortality.

In one retrospective study, CRP and IL-6 values on admission were independent predictors of disease severity, while in a small prospective study IL-6 and CRP levels correlated with the development of respiratory failure.[22,34] Another small retrospective study reported a correlation between mortality and CRP values in diabetic patients with COVID-19.[35]few researchers have reported a direct association between the level of CRP with the inflammation and severity of disease,[36] suggesting that CRP levels can be most effective and sensitive biomarker in predicting the COVID-19 disease progression.

The findings of our study suggest that determination of serum CRP along with the other routine laboratory tests is useful for predicting high risk and need for ICU care in the early stage to prevent the adverse outcome of Covid-19 disease.

Conclusion

Study of biomarkers is essential for identifying high risk categories following Covid-19 diagnosis for optimal resource allocation, to improve the clinical management and prevention of serious complications. CRP is widely available, easy to obtain, and inexpensive. Our study advocates that determination of biochemical parameters like CRP at the time of hospitalization helps in predicting the severity of disease and need for ICU care, leading to better treatment management and prevention of adverse outcome.

Limitations and Future Suggestions

In Our study we collected sample from a single center and has short sample size, thus it may lack generalizability. Furthermore consequent missing clinical data was another limitation therefore, subsequent clinical studies with larger sample sizes and multiple CRP level measurements, especially at different treatment times, should be performed to confirm our findings.

References

1. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-n CoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536-544.

2. Zhu NA, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl JmMed 2020;382:727-733.

3. W-jG, Z-y N, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020.

4. The Novel Coronavirus Pneumonia Emergency Response Epidemiology T. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. China CDC Weekly 2020;2:113–22.

5. Zaim S, Chong JH, Sankaranarayanan V, et al. COVID-19 and multiorgan response. Curr Probl Cardiol 2020;45:100618.

6. Giacomelli A, Pezzati L, Conti F, et al. Self-Reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clin Infect Dis 2020;71:889–90.

7. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:766–73.

8. Kaur N, Gupta I, Singh H, et al. Epidemiological and clinical characteristics of 6635 COVID-19 patients: a pooled analysis. SN Compr Clin Med 2020:1048–52.

9. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a systematic review and current update. Acta Neurol Scand 2020;**142**:14–22.

10. Malik P, Patel U, Mehta D, et al. BMJ Evidence-Based Medicine. doi:10.1136/bmjebm-2020-111536.

11. Aronson JK, Ferner RE, Review B-AG. Biomarkers-A general review. Curr Protoc Pharmacol 2017;**76**:9.23.1-9.23.17.

12. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China [Internet]. JAMA. 2020; 323(13):1239.

13. Roxby AC, Greninger AL, Hatfield KM, et al. Outbreak Investigation of COVID-19 Among Residents and Staff of an Independent and Assisted Living Community for Older Adults in Seattle, Washington. JAMA Intern Med [Internet] 2020; Available from: http://dx.doi.org/10.1001/jamainternmed.2020.2233

14. Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and Ventilator Mortality among Critically Ill Adults With Coronavirus Disease 2019. Crit Care Med [Internet] 2020; Available from: https://doi.org/10.1097/CCM. 0000000000004457 PMID: 32452888

15. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China [Internet]. JAMA. 2020; 323(13):1239.

16. Roxby AC, Greninger AL, Hatfield KM, et al. Outbreak Investigation of COVID-19 Among Residents and Staff of an Independent and Assisted Living Community for Older Adults in Seattle, Washington. JAMA Intern Med [Internet] 2020; Available from: http://dx.doi.org/10.1001/jamainternmed.2020.2233

17. Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and Ventilator Mortality among Critically Ill Adults with Coronavirus Disease 2019. Crit Care Med [Internet] 2020; Available from: https://doi.org/10.1097/CCM. 0000000000004457 PMID: 32452888

18. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med 1999; 17(6):1019–25. https://doi.org/10. 1016/s0736-4679(99)00135-3 PMID: 10595891

19. Wang J-T, Sheng W-H, Fang C-T, et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerg Infect Dis 2004; 10(5):818–24.

20. Ko J-H, Park GE, Lee JY, et al. Predictive factors for pneumonia development and progression to respiratory failure in MERS-CoV infected patients. J Infect 2016; 73(5):468–75.

21. Vasileva D, Badawi A. C-reactive protein as a biomarker of severe H1N1 influenza. Inflamm Res 2019;68(1):39–46. https://doi.org/10.1007/s00011-018-1188-x PMID: 30288556

22. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol [Internet] 2020;Available from: https://doi.org/10.1016/j. jaci.2020.05.008 PMID: 32425269

23. Huang Y, Lyu X, Li D, Wang L, Wang Y, Zou W, et al. (2020) A cohort study of 676 patients indicates D-dimer is a critical risk factor for the mortality of COVID-19. PLoS ONE 15(11): e0242045.

24. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497–506

25. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 02: 25-29.

26. Ullah W, Thalambedu N, Haq S, Saeed R, Khanal S, Tariq S et al. Predictability of CRP and D-Dimer levels for in hospital outcomes and mortality of COVID-19. Journal of Community Hospital Internal Medicine Perspectives.2020;10(5):402-408.

27. Wang F, Zhang H, Sun Z. The laboratory tests and host immunity of COVID-19 patients with different severity of illness.JCI Insight. 2020;5(10):e137799.

28. Tomlins J, Hamilton F, Gunning S, Sheehy C, Moran E, MacGowan A. Clinical features of 95 sequential hospitalised patients with novel coronavirus 2019 disease (COVID-19), the first UK cohort. J Infect. 2020; 81(2):e59–e61.

29. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. International Journal of Infectious Diseases.2020;95: 304–307.

30. Ponti G,Maccaferri M, Ruini C, Thomasi A,Thomari O. Biomarkers associated with COVID-19 disease progression. Critical Reviews in Clinical Laboratory Sciences. https://doi.org/10.1080/10408363.2020.1770685.

31. Chalmers S, Khawaja A, Wieruszewski PM, et al. Diagnosis and treatmentof acute pulmonary inflammation in critically ill patients: the role ofinflammatory biomarkers. WJCCM 2019;8:74–96.

32. T. Haitao, J. V. Vermunt, J. Abeykoon et al., "COVID-19 and sex differences: mechanisms and biomarkers," Mayo Clinic Proceedings, vol. 95, no. 10, pp. 2189–2203, 2020.

33. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol 2018; 9:754. https://doi.org/10.3389/fimmu.2018.00754 PMID: 29706967

34. Koozi H, Lengquist M, Frigyesi A. C-reactive protein as a prognostic factor in intensive care admissions for sepsis: A Swedish multicenter study. J Crit Care 2020; 56:73–9.

35. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China [Internet]. Intensive Care Medicine. 2020; 46:846–8.

36. Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. Diabetes Care [Internet] 2020;Available from: http://dx.doi.org/10.2337/dc20-0660