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Role of biochemical parameters in predicting the severity of disease in patients with Covid-19

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Abstract: *Background:* The world is currently witnessing a drastic disruption of everyday life due to the rapid progression of the corona virus disease 2019 (COVID-19) pandemic. However, the information on risk factors predicting the prognosis and mortality due to covid-19 is limited. *Objectives:* To find the levels of serum CRP, D-Dimer, and LDH in confirmed Covid-19 patients and compare their levels in patients who do not require invasive mechanical ventilation (IMV) and with patients required IMV for the treatment management. *Methods:* A Cross sectional study was carried out on 106 confirmed cases of Covid-19, in whom Random blood sugar (RBS), Creatinine, Urea, C- reactive protein (CRP), D-Dimer and Lactate Dehydrogenase (LDH) were measured. *Results:* To assess the clinical utility of CRP, D-Dimer and LDH for predicting hospital outcome in Covid-19 Patients, they were divided into two groups, Group I were Covid-19 Patients who did not require ventilation and Group II Covid-19 patients needed invasive mechanical ventilation for the management. CRP and D-Dimer levels were significantly increased with p value <0.05 in group II when compared to group I, but the levels of LDH did not show a statistical significant difference in group I and group II. *Conclusion:* Our study advocates that determination of biochemical parameters like CRP, D-Dimer and LDH at the time of hospitalization helps in predicting the severity of disease and need for IMV leading to better treatment management and prevention of adverse outcome.

Keywords: Covid-19, C- reactive protein, D-Dimer and Lactate Dehydrogenase, Severe Acute Respiratory Syndrome.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is one of the deadliest pandemic that has disseminated the whole world from Wuhan, China. It is the greatest global public health crisis since 1918 influenza outbreak [1]. World health organization named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as coronavirus disease 2019 (COVID-19) [2]. Currently, the number of individuals with COVID-19 is still soaring worldwide. As of November 3, 2020, according to the WHO, confirmed COVID-19 patients exceeded 46 million with over 1.2 million deaths worldwide [3]. India is among the top countries reported more than 9.6 million cases with 1.42 lack mortality till November 2020 [4].

Majority of the patient infected by COVID-19 have mild illness and small number of them progress to severe cases in a shorter period of time and die of multiorgan failure, especially the elderly patients with co-morbidities [5-6]. The diagnostic tests that can be used to predict the development of severe disease play a vital role for the treatment and prognosis of COVID-19 infection. In a multitude of blood test and imaging conducted on these patient biochemical parameters like CRP, D-Dimer and LDH are measured in many health care settings.

CRP is a pro-inflammatory marker, increased in the blood under the influence of cytokine interleukin (IL6). High levels of CRP > 50mg/dl are observed in bacterial infection, cardiovascular diseases and other inflammatory states. It can also be used as prognostic marker for the underlying disease. D- Dimer are peptide fragments produced by the degradation of fibrin. Their concentration in blood is very low, and high levels are seen in diseases involving production and breakdown of fibrin clots [7-8].

Lactate dehydrogenase (LDH) is an enzyme that converts lactate to pyruvate in the cells of most body tissues. Increased serum LDH levels seen in conditions, such as hemolysis, liver diseases, sepsis, cancer and severe infections. Nowadays, there was much evidence suggesting that the serum LDH levels serve as a non-specific indicator of cellular death in many diseases. However, the current information about dynamic change of LDH in COVID-19 pneumonia was very still [9]. The present study is carried out to evaluate the role of CRP, D-Dimer and LDH in predicting the severity of infection and need for IMV in COVID-19 patients.

Material and Methods

Source of Data: A cross sectional study was carried out on 106 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 [10].

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 study subjects. Serum was separated by centrifugation and used for estimation of RSG, Serum Creatinine, blood urea, CRP, D-dimer, and LDH.

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, D-dimer: kit based on Latex Enhanced Immune Turbidimetry. LDH: UV kinetic method.

Statistical Analysis: The data was collected and 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 for statistical significance. Results are expressed as Mean, SD, and range values for continuous data, number and percentage for discrete data.

Results

A total of 106 patients with confirmed COVID-19 infection were enrolled in this study. Among the patients 37 were females and 69 were males, the average age was 51-56years. To assess the clinical utility of CRP, D-Dimer and LDH for predicting hospital outcome in Covid-19 Patients, they were divided into two groups, Group I were Covid-19 Patients who did not require ventilation and Group II Covid-19 patients needed invasive mechanical ventilation for the management. CRP and D-Dimer levels were significantly increased with p value <0.05 in group II when compared to group I, but the levels of LDH did not show a statistical significant difference in group I and group II (Table 1).

Table-2: The Average age in Group I was 51years and group II was 56years. Among the Group I patients, 5 and in group II, 6 patients were suffering from diabetes mellitus and 3 had chronic kidney disease.

Table-1: Levels of CRP, D-Dimer and LDH in Group I and Group II			
Parameters	**Group I**	**Group II**	**P value**
No of Patients	84	14	
CRP	43.94 ± 29.39	74.8818 ± 33.45	<0.05
D-Dimer	1.55±1.7	3.43 ± 3.42	<0.05
LDH	615.03±275.664	665.74±290.872	>0.05

Table-2: General Characteristics and Routine Biochemical parameters		
	Group I	**Group II**
No of Patients	84	14
Age(Average)	51years	56years
Diabetes	5	6
CKD	0	3
RBS	122±55	174.45±89.3
Urea	27.3±12.6	31±14.3
Creatinine	0.9±0.33	1.03±0.45

Among the 106 Covid-19 cases, 80 patients had mild to moderate disease and recovered within 2weeks of acquiring infection and got discharged and 4 patients developed complications and did not survive. 14 patients required IMV and 4 among them died. Total 8 patients developed complications and did not survive (Figure 1). We also compared the levels of CRP, D-dimer and LDH among the survival and non-survived group (Table 3). But unlike other studies we could not find a statistical significant difference in the levels of CRP, D-Dimer and LDH between those who survived and non survived Covid-19 patients, may be because sample size is small in our comparison groups. Studies with larger sample size are required to find out the risk factors associated with the severity and mortality of Covid-19 disease.

Fig-1: Distribution of Cases in Group I and Group II and Total death.

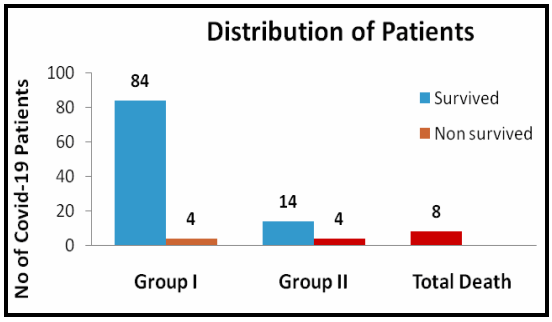

Table-3: Comparison of Levels of CRP, D-Dimer and LDH among the covid-19 patients who survived and non-survived			
Parameters	**Survived**	**Non Survived**	**P value**
No of Patients	98	8	
CRP	46.7219± 31.22	61.16± 34.24	>0.05
D-Dimer	1.86±2.25	1.59± 0.67	>0.05
LDH	624.37±275.052	609.00±305.366	>0.05

Discussion

The pandemic infectious disease Covid-19 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 [11]. Clinical and epidemiological features have been reported by many studies [10, 12-14], but the knowledge about the biochemical parameters predicting the severity and mortality of the disease is reported by vary few studies. Thus the aim of this study is to find out the levels CRP, D-Dimer and LDH and compare the levels between patients with mild and severe COVID-19 infection. We divided the patient into two groups based on requirement of Invasive mechanical ventilation for the management of COVID-19 disease. Group 1 included the patients having mild to moderate disease and did not require ventilation. And group 2 included the patients who developed

severe disease and required Invasive mechanical ventilation for the management. We found statistical higher levels (p value <0.05) of CRP and D-Dimer in group 2 patients when compared to group 1. Our findings are in accordance with previous studies [1, 2, 10, 15-16].

We also compared the levels of serum CRP, D-Dimer and LDH in patients who survived and with those did not survive due to Covid-19 diseases and found high levels of these parameters in patients who did not survive but were not statistical significant (p value>0.5) unlike the study reported by yongsheng Huang and et all, may be because of small comparison groups. High levels of inflammatory markers are critical indicators of underlying systemic vasculitis processes and dysregulation of coagulation mechanism that leads to parenchymal lesions in vital organs [17].

CRP is nonspecific acute phase reactant used clinically as a biomarker for different inflammatory and infectious conditions [18]. Studies have shown a direct association between the level of CRP with the inflammation and severity of disease [19-20]. Hence suggesting that CRP levels can be most effective and sensitive biomarker in predicting the COVID-19 disease progression.

The increased levels of D-Dimer in COVID-19 disease may be because of severe Pneumonia causing increased inflammatory response and Hypoxia, triggering Coagulation and fibrinolysis, which is followed by hypercoagulability state leading to DIC and multiorgan failure [21-22]. In our study we found high levels of LDH in Group II when compared with group I but were of not statistical significant. Severe COVID-19 infections may cause cytokine-mediated tissue damage and LDH release [23]. Since LDH is present in lung tissue (isozyme 3), patients with severe COVID-19 infections can be expected to release greater amounts of LDH in the circulation, as a severe form of interstitial pneumonia, often evolving into acute respiratory distress syndrome [24].

The findings of our study suggest that determination of serum CRP, D-Dimer, LDH along with the other routine laboratory test are useful for predicting high risk and need for mechanical ventilation in the early stage to prevent the adverse outcome of Covid-19 disease. Early prediction of high risk cases will guide us in allocating the resources for these patients and prepare in advance as presently our health care facilities have been exhausting due to very rapid spread of Covid-19 disease. Our study has limitations of collecting sample from a single center and small sample size. Large scale research studies are required to support our findings.

Conclusion

Since the Covid-19 infection has become widespread. Never before have we experienced a health emergency like this, study of biomarkers is essential for determining high risk categories following Covid-19 diagnosis for optimal resource allocation, to improve the clinical management and prevention of serious complication. Our study advocates that determination of biochemical parameters like CRP, D-Dimer and LDH at the time of hospitalization helps in predicting the severity of disease and need for IMV leading to better treatment management and prevention of adverse outcome.

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References

1. 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.
2. 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.
3. Mirmohammadi S, Kianmehr A, Arefi M, Ismaila Z, Hark A. Biochemical parameters and pathogenesis of SARS-CoV-2 infection in vital organs: COVID-19 outbreak in Iran. *New Microbes and New Infections,* 2020; 38(C): 1-9.
4. World Health Organisation. Novel Coronavirus (COVID-19) situation. Accessed November 2020.

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

5. Chen N et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; 395(10223):507-513.
6. Agrawal A, Tyagi P, Mahavar S, Banerjee S, Sharma R, Bhandhari S et al. Study of hematological and biochemical parameters in a cohort of Indian COVID-19 patients admitted in a tertiary care centre. *Int J Adv Med,* 2020; 7(12):1840-1845.
7. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol,* 2018; 13(9):754.
8. Spyropoulos AC, Raskob GE. New paradigms in venous thromboprophylaxis of medically ill patients. *Thromb Haemost.* 2017; 117(9):1662-1670.
9. Wu M, Yao L , Wang Y, Zhu XY, Wang X, Tang P et al. Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-pneumonia). *Respiratory Research*, 2020; 21:171.
10. 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.
11. Huang Y, Lyu X, Li D, Wang L, Wang Y, Zou W, et al. A cohort study of 676 patients indicates D-dimer is a critical risk factor for the mortality of COVID-19. *PLoSONE*, 2020; 15(11): e0242045.
12. 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.
13. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy,* 2020; 02:20-23.
14. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. *Diagnosis (Berl).* 2020; 7(2):91-96.
15. 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.
16. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. *International Journal of Infectious Diseases,* 2020; 95:304-307.
17. Ponti G, Maccaferri M, Ruini C, Thomasi A, Thomari O. Biomarkers associated with COVID-19 disease progression. *Critical Reviews in Clinical Laboratory Sciences.* 2020; 57:6, 389-399.
18. Chalmers S, Khawaja A, Wieruszewski PM et al. Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: the role of inflammatory biomarkers. *WJCCM*, 2019; 8:74-96.
19. Liu F, Li L, Xu M et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol,* 2020; 127:104370-70.
20. Qin C, Zhou L, Hu Z et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis*, 2020;71:762-768.
21. Garcia-Olivé I, Sintes H, Radua J et al. D-Dimer in patients infected with COVID-19 and suspected pulmonary embolism. *Respir Med*, 2020; 169:106023.
22. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. *J Thromb Haemost*, 2018; 16:231-241.
23. Martinez-Outschoorn U.E., Prisco M., Ertel A. Ketones and lactate increase cancer cell "stemness," driving recurrence, metastasis and poor clinical outcome in breast cancer: achieving personalized medicine via metabolo-genomics. *Cell Cycle,* 2011; 10(8):1271-1286.
24. Kaplan B, Meier-Kriesche HU. Death after graft loss: an important late study endpoint in kidney transplantation. *Am J Transplant.* 2002; 2(10):970-974.

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