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A Study of Inflammatory and Non-Inflammatory markers in COVID-19 infected Patients

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ABSTRACT

COVID-19 is highly transmissible in humans with mild flu-like symptoms, but some patients, especially the elderly and people with underlying diseases, evolve critical condition and rapidly develop acute respiratory distress syndrome, respiratory failure, multiple organ disorder and death. The rapid viral replication of SARS-COV-2 gives rise to inflammatory response, cellular destruction and induces the release of cytokines and chemokines then activate immune responses, leading to cytokine storms and aggravations. The RT-PCR test remains gold standard as it detect virus nucleic acid but it is time consuming and has a high prevalence of false negative results. Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality. Para-clinical investigations including laboratory tests and radiologic findings play an important role in early diagnosis and treatment monitoring of severe acute respiratory syndrome and COVID-19. This study aims to explore the evaluation of inflammatory and non-inflammatory parameters in the disease pathogenesis of COVID-19 and assess how their levels vary depending on the severity of the disease. By doing so, it gives clinicians a tool to group patients and predict prognosis and mortality. The inflammatory parameters included Ferritin, Lactate dehydrogenase (LDH), D-dimer, Interleukin 6 (IL6) and non-inflammatory parameters includes Glucose, Urea, Creatinine, SGOT, SGPT in Covid-19 infected patients. Total subjects were divided in three groups that is control, Group 1 is covid-19 positive patients without comorbidities and Group 2 is covid-19 positive patients with comorbidities. As compared to control Ferritin, LDH, IL6, D-Dimer significantly increased in Group 1 & Group 2, and further as compared with Group 1, these inflammatory parameters significantly elevated in Group 2. As compared to control, Blood Glucose, Urea, Creatinine, SGOT, and SGPT statistical not different in Group 1 but when compared with Group -2 these parameters significantly increased. Further as compared to Group 1 Blood Glucose, Urea, Creatinine, SGOT, and SGPT significantly increased in Group 2. As compared to control Total protein and Albumin statistically not different in Group 1 & Group 2, and there was no any statistical difference in the levels of

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Total protein and albumin in Group 1 and Group 2. This change of levels of parameters is used as an adjunct in clinical practice to guide treatment and admission to Intensive care unit and also it may improve prognosis and decrease the mortality rates.

Keywords: Covid 19, Ferritin, LDH, D-Dimer, Glucose, Urea, Creatinine, SGOT, SGPT, Protein.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a form of mild to severe respiratory disease caused by a virus belonging to the Coronaviridae family.[1] According to the current statistics of the WHO, the disease has involved all over the world, with over 160,074,267 confirmed cases and more than 3,325,260 deaths until May 13, 2021.[2] The symptoms occur in the initial phases of the disease, like fever, cough, and dyspnea.[3] Some patients of Covid-19 develop rapidly acute respiratory distress syndrome (ARDS) and additional severe complications with multiple organ failure[4], hence, timely diagnosis of patients is very essential.

The collected evidence has suggested that inflammatory responses play a critical role in the progression of Covid-19.[5] The rapid viral replication of SARS-CoV-2 provoked in to inflammatory response and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines.[6] These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations.[7] Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality.[8]

The real time reverse transcription polymerase chain reaction (RT-PCR) remains gold standard as it detect viral nucleic acid but it is very time consuming and has a high prevalence of false negative results.[9] Other laboratory tests, such as whole white blood cells (WBCs) count, neutrophil ratio, lymphocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, platelets, procalcitonin, creatine kinase (CK), myoglobin, SGOT, SGPT, Bilirubin, Creatinine, Cardiac troponin I, D-dimer, Albumin, LDH and several other laboratory tests have been reported to change in Covid-19 patients.[10]

The majority of previous reports were based on data from the general population of the SARS-CoV-2 laboratory results and limited information is available based on age difference. Since the laboratory medicine provides a crucial share for clinical decision making in many infectious diseases including COVID-19. Para-clinical investigations including laboratory tests and radiologic findings play an important role in early diagnosis and treatment monitoring of severe acute respiratory syndrome and COVID-19 (SARS-CoV-2). This study aims to explore the evaluation of inflammatory and non-inflammatory parameters in the disease pathogenesis of COVID-19 and assess how their levels vary depending on the severity of the disease. By doing so, it gives clinicians a tool to group patients and predicts prognosis and mortality. The inflammatory parameters included Ferritin, LDH, D-dimers, IL6 and non-inflammatory were Glucose, Urea, Creatinine, SGOT, SGPT, Total Protein and Albumin in Covid-19 infected patients.

MATERIAL & METHODS

The present study was carried out in the Department of Biochemistry BRIMS Bidar. The RT-PCR positive with symptoms and Control subjects with RT-PCR negative selected from COVID-19 hospital BRIMS Bidar. The COVID-19 positive patients divided in to two groups without and with comorbidities[11] like hypertension and diabetic were included based on clinical presentation of the patients at the time of admission. Total 150 subjects in between 50 to 70 age group were included in the study, out of which 50 were healthy control with RT-PCR negative and 50 were without comorbidities and 50 with comorbidities COVID-19 infected patients. The informed written consent with history, clinical examination, diet and

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previous treatment history was taken from the patients and control subjects. The study was approved by institutional ethical committee.

The following clinical severity and assessment parameters were used to classify the patient.[12]

Inclusion Criteria

- Newly diagnosed cases with RT-PCR positive and not on treatment.
- Covid-19 positive patients without comorbidities in the age group of 50 to 70 yrs.
- Covid-19 positive patients with comorbidities such as diabetes & hypertension in the age group of 50 to 70 yrs.
- Radiological evidence (CT) of pneumonia with no signs of severe disease was included.
- Healthy control with RT-PCR Negative in the age group of 50 to 70 yrs

Exclusion Criteria

- Patients addicted to alcohol or drug abuse.
- Any other concurrent drug intake, which alter the study parameters

Sample Collection and Analysis

Oro-nasopharyngeal swab-based testing using RT-PCR was employed for laboratory confirmation of COVID-19. A case was labelled as confirmed positive if RT-PCR testing showed a positive result, irrespective of clinical signs or symptoms. Blood samples from patients and control were collected from anticubital vein, with all aseptic precautions, using 10 ml disposable syringe. The blood was collected in the tubes for the analysis of inflammatory and non-inflammatory parameters. Blood samples were centrifuged at 3000 rpm for 10 minutes and serum was transferred to another tube. These serum samples were analysed on Beckman AU-480 Fully Autoanalyzer, ERBA ECL 760 coagulation analyser & Semi-Automatic UPT 3A Hotgen POCT Immunoassay Analyzer for all parameters.

Estimation of Inflammatory parameters

The estimation of ferritin was determined by Immuno-turbidimetric method on Beckman coulter analyser and determination of Lactate dehydrogenase (LDH) by kinetic UV method on Beckman coulter analyser.[13,14] The Ferritin and LDH reagent kits were purchased from Beckman Coulter Biomedical Limited Ireland Cat no-OSR6150 & OSR6126.The determination of D-Dimer was done by Immuno-turbidimetric method on ERBA ECL 760 coagulation analyser & reagent kit purchased from ERBA diagnostics Germany (TRANSASIA Biomedicals Ltd Cat no. EHL00011).[15] The determination of Interlukin-6 (IL-6) were done by UP-converting Phosphor technology (Sandwich Immuno-chromatography method) on Semi-Automatic UPT 3A Hotgen POCT Immunoassay Analyzer and reagents kits were purchased from Beijing Hotgen Biotech co, Ltd China Cat no.HGUPT09 & HGUPT02.[16]

Estimation of Non-Inflammatory parameters

The determination of Glucose by enzymatic UV (Hexokinase method).[17] The determination of Urea by Kinetic UV method.[18] The determination of Creatinine by Kinetic UV (Jaffes method).[19] The SGOT and SGPT determined by Kinetic UV method.[20,21] The determination of Total Protein & Albumin by photometric colour test method.[22,23] All the estimations were analysed by Beckman coulter analyser. The reagents kits were purchased from Beckman Coulter Biomedical Limited Ireland.

The statistical analysis was carried by Microsoft office 2019 and SPSS software version 18.1-2017. The probability values $P < 0.001$ was considered as significant and also data were expressed in mean ±SD.

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RESULTS

Standard Characteristics of the two groups enrolled in the study are reported in Table no-1. There was no statistical difference in Age as compared control with Group 1 & Group 2 ($P > 0.05$), as well as compared to Group 1 with Group 2 ($P > 0.05$). We observed significant difference in SpO2 as compared to control with Group 1 & Group 2 ($P < 0.001$), as well as significant difference in SpO2 levels observed in Group 1 with Group 2. HRCT score also highly significant in Group 2 as compared with Group 1.

Table 1: Distribution and Clinical Characteristics of Covid-19 Positive patients and Control groups

Parameters	Control Subjects	Group-1 COVID-19 positive atients without Comorbidities	Group-2 COVID-19 positive atients with Comorbidities
Age (Year)	64.38 ± 2.68	65.35 ± 3.72$^{\Psi}$	69.38± 1.72$^{\Psi\$}$
SpO_2 at room air	98±1.00	95±1.14*	75± 2.18*#
HRCT Severity Score	NA	06± 2.12	20± 1.14#

Table no-2 shows, As compared to control Ferritin, LDH, IL6, D-Dimer significantly increased in Group 1 & Group 2 Covid-19 positive patients ($P < 0.001$). Further as compared to Group 1, Ferritin, LDH, IL6, D-Dimer significantly increased in Group 2 Covid-19 positive patients ($P < 0.001$).

As compared to control, Blood Glucose, Urea, Creatinine, SGOT, and SGPT statistical not different in Group 1 Covid-19 patients ($P > 0.05$), but when compared with Group -2 these parameters significantly increased ($P < 0.001$). Further as compared to Group 1, Blood Glucose, Urea, Creatinine, SGOT, and SGPT significantly increased in Group 2 Covid-19 positive patients.

We also observed that as compared to control Total protein & Albumin statistically not different in Group 1 & Group 2 Covid-19 positive patients ($P > 0.05$). Further as compared with Group 1, Total protein & Albumin statistically not different Group 2 Covid-19 positive patients ($P > 0.05$).

Table 2: The Serum Levels of Inflammatory and Non-Inflammatory markers in Covid-19 Patients and Control group

Parameters	Groups		
	Control subjects Mean Age (64.38 ± 2.68)	Group -1 COVID-19 positive patients without Co-morbidities (Mean Age 65.35 ± 3.72)	Group-2 COVID-19 positive patients with Co-morbidities (Mean Age 69.38± 1.72)
Ferritin (μg/L)	120±15	256±25*	546±70*#
LDH (U/L)	180±20	327±17*	576.8±62*#
IL6 (pg/ml)	1.34±3.50	15±0.5*	28.8±5*#
D-Dimer (ng/ml)	1.20±0.20	350±24*	744.6±357*#
Blood Glucose (mg/dl)	102.5±17	120±10$^{\Psi}$	260.3±88*#
Urea (mg/dl)	28.6±12	30±08$^{\Psi}$	50.5±32*#

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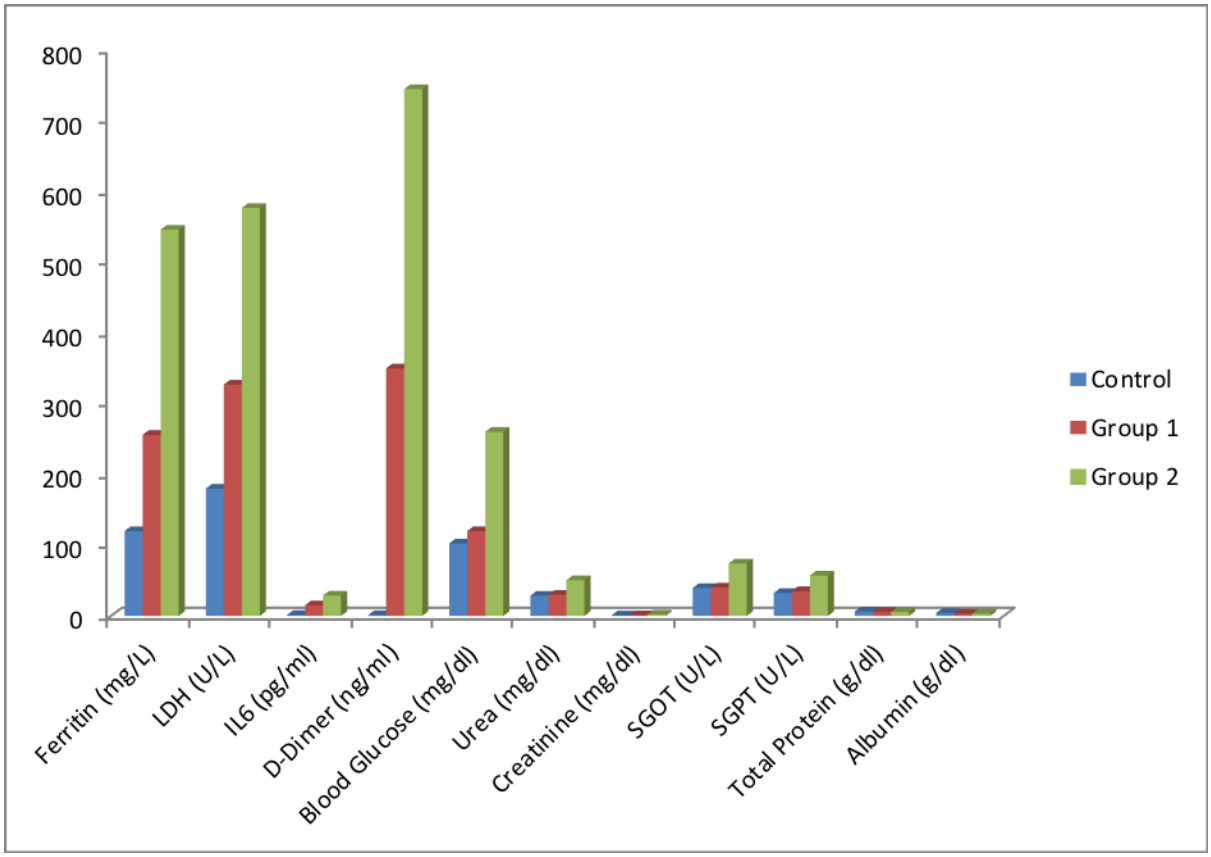
Creatinine (mg/dl)	0.79±0.6	0.9±01$^{\Psi}$	2.07±0.5*#
SGOT (U/L)	39.42±5	40.20±8$^{\Psi}$	74.2±24*#
SGPT (U/L)	32.46±7	35.14±7$^{\Psi}$	57.06±22*#
Total Protein (g/dl)	6.5± 1.5	5.9± 1.3$^{\Psi}$	5.8± 1.6$^{\Psi\$}$
Albumin (g/dl)	4.1±1	3.3±0.5$^{\Psi}$	3.1±0.9$^{\Psi\$}$

All values are expressed as mean ±SD, * P < 0.001 highly significant as compared to control, # P < 0.001 highly significant as compared with Group 1, $^{\Psi}$P > 0.05 statistically not significant as compared with Control, $ P > 0.05 statistically not significant as compared with Group 1.



Graph 1: The Serum Levels of Inflammatory and Non-Inflammatory Parameters in controls, Group 1 & Group 2 covid-19 patients

DISCUSSION

An increase in these inflammatory markers is an early indicator of cytokine storm in these patients, which is a harbinger of a relatively poor prognosis and is associated with higher mortality in patients with COVID-19. Based on the findings of this present study we observed that, the increased levels of inflammatory parameters like Ferritin, LDH, IL6, D-Dimer, in COVID-19 infected patients in Group-1 & Group-2 as compared to control subjects & further these levels elevated and statistically significant in Group-2 as compared to Group-1 (Table-2 & Grapgh-1). Worldwide COVID-19 disease is rapidly expanding. The infected patients have mild and severe symptoms and a good prognosis, but some of them develop severe complications like acute respiratory distress syndrome (ARDS) which leads to multiorgan failure and death, hence timely diagnosis of patients is very essential.

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The inflammatory process consists of a series of metabolic and physiological changes due to acute phase reaction and it begins immediately after tissue injury. Among this variation in the concentration of various plasma inflammatory acute phase reaction, Ferritin, IL6, D-Dimer, LDH is the best known in clinical practice.[24] Several studies show that circulatory ferritin levels may play a critical role in inflammation.[25] In some previous studies ferritin levels were high in older peoples with co-morbidities which also associated with increased mortality.[26]

The lysis of cross linked fibrin originates D-Dimer with increasing levels indicating the activation of coagulation and fibrinolysis.[27] In the retrospective cohort study consist 191 patients found that D-Dimer levels > 1.0μg/ml were associated with increased mortality among COVID-19 patients. Some studies shows nearly 90% in patients with pneumonia had increased D-Dimer levels.[28] Further some researcher shows that levels of D-Dimer on admission was useful to triage patients with critical care[29], were as some authors shows that median D-Dimer levels were higher in ICU patients compared to non ICU patients.

Cytokines release syndrome (CRS) is an over magnified involving an immense release of pro-inflammatory mediators. The underlying mechanism of above pathological process is acute respiratory distress syndrome (ARDS).[30] Some studies revealed that the most common type of cytokine IL6 released by activated macrophages and increased in severe manifestations of COVID-19.[31] One metanalysis after assessing six studies shows mean IL6 levels were 2.9 fold higher in patients with complicated COVID-19 compared to those with non-complicated disease.[32] In his studies after analysis the outcome include ICU admission onset of ARDS and mortality, since the consistent rise of IL6 is correlated with disease severity. The enzyme LDH converts Lactate to pyruvate in glucose metabolism. The secretion of LDH is triggered by necrosis of the cell membrane indicating to viral infection or lung damage like pneumonia induced by SARS-COV-2.[33] There is potent evidence of linking of LDH to the progression of COVID-19 disease.[34] A study found significantly increased levels of LDH in ICU patients compared to non ICU patients, since continued high levels of LDH in the ICU patient's number of days post admission. Hence LDH may be predictor parameter of more severity of disease.[35] In some multicentre study consisting 1099 patients shows supporting evidence correlating extent of tissue damage and inflammation with increasing levels of LDH[36], further significantly higher levels of LDH reflected the severity of pneumonia when correlates with CT scan.[37] There is increasing confidence in using LDH as a biomarker to measure severity of COVID-19 infection.

The non- inflammatory parameters such as, Glucose, Urea, Creatinine, SGOT and SGPT statistically not significant in Group-1 COVID-19 positive patients as compared to control, but when compared with Group-2 these parameters significantly increased . Further as compared to Group 1, Blood Glucose, Urea, Creatinine, SGOT, and SGPT significantly increased in Group 2 Covid-19 positive patients (Table-2 & Graph-1).

Our results indicate that increase in blood glucose level in COVID-19 infected patients with comorbidities as compared to COVID-19 infected patients without comorbidities. These results suggest that the risk for poor outcomes and the distribution of tissue infection in COVID-19 may be due to poor glucose control. High glucose levels leads to osmotic diuresis with loss of electrolyte and hypovolemia which inhibit host cell defence.[38] Hyperglycemia induces the systems of advanced glycation and products binds to proteins, lipids and cellular membrane[39] and these glycated end products binds to cellular membrane could lead to endothelial dysfunction.[40] The retrospective study explained the outcome of COVID-19 patients admitted to two hospitals in china. In this study 605 patients were included, 114 died in the hospital having fasting blood glucose levels greater than 126mg/dl.[41] One researcher mentioned from his study that 1122 patients with COVID-19 including 194 with diabetes and uncontrolled hyperglycemia had a mortality rate 28% compared to a mortality rate 6.2% in other patients. These results shows that acute hyperglycemia may be independent risk factor

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for death and further suggest that management goal for glucose should aim for less than 180mg/dl.[42]

Wang et al, examined the levels of six laboratory parameters throughout 19 days of hospital admission in 138 patients with COVID-19 infection (38 with severe disease). He observed significant differences were noted between patients who needed admission in ICU and those who did not, mainly higher levels of LDH (2.1fold), ALT (1.5fold), AST (1.8fold), creatinine (1.1fold), D-Dimer (2.5fold).[43] As a result this parameters the rate of patients with abnormal values admitted to the ICU was over 3-fold higher than that of those who were not.[44] Similar findings produced from the article published by Liu et al, who found that disease severity may be predicted by increased values of LDH and decreased values of Albumin.[45] Hypoalbuminemia is multifactorial in critically ill patients and is allocated to increased capillary permeability, decreased protein synthesis and increased turnover, increased volume and distribution and increased expression of vascular endothelial growth factor.[46] But in our study we observed that as compared to control Total protein & Albumin statistically not different in Group-1 & Group-2) (Table-2 & Graph-1) Covid-19 positive patients. Further as compared with Group 1, Total protein & Albumin statistically not different Group 2 Covid-19 positive patients (Table-2 & Graph-1).

CONCLUSION

COVID-19 is a hyperinflammatory state associated with an increase in pro-inflammatory cytokines and raised inflammatory markers have prognostic significance in patients with COVID-19 disease are associated with a severe disease course and an adverse final outcomes. . Higher levels of these inflammatory markers, particularly later during the course of hospital admission, are associated with a higher likelihood of non-survival in these patients. This will help clinicians in the early identification of high-risk patients. Therefore, measuring the levels of these inflammatory markers early in the disease helps in prognosticating patient outcomes. This, in turn, helps in tailoring early, appropriate, efficient, and effective treatment of patients, which will lead to a significant reduction in mortality related to COVID-19. This change of levels of parameters is used as an adjunct in clinical practice to guide treatment and admission to Intensive care unit and also it may improve prognosis and decrease the mortality rates.

Limitations of Study

The study was conducted on small numbers of subjects. However, to understand the causative factors and underlying biochemical mechanism in elegant details need further elucidations. This research paper was approved by Ethical committee of BRIMS Bidar Karnataka-585401.

No Conflict of Interest

No Funding.

Acknowledgement

This study was approved by Institutional ethical committee. Patients' privacy was maintained at all times. Written consent consent form was taken from the patients as per our institutional guidelines

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