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TO COMPARE THE LEVELS OF ADVANCED MARKERS IN COVID-19 PATIENTS

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Abstract: -

Background: - Coronavirus disease 2019 (COVID-19) was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early December 2019. The illness starts out as a respiratory condition with a range of outcomes, including full recovery and long-term sequelae like respiratory difficulties, heart problems, stroke, and death. The goal of the current investigation was to evaluate the levels of advanced markers like inflammatory and non-inflammatory markers to check the severity and, consequently, gauge the prognosis of patients with COVID-19 infection.

Materials and methods: - 144 patients with COVID-19 were included in the study group A and B, and was validated by nasopharyngeal swab RT-PCR for SARS-CoV-2. Information was gathered from medical records. Correlation analysis were carried out and variables compared.

Results- As per statistical analysis, C-reactive protein (P = 0.001), ferritin (P = 0.0001), D-dimer (P = 0.001), lactate dehydrogenase (P = 0.001), aspartate aminotransferase (P= 0.004), and total bilirubin (P = 0.006) levels were found significantly increased in both the groups. Leukocytosis, neutropenia, lymphopenia, and an elevated neutrophil-to-lymphocyte ratio (P = 0.001) were also seen in both the groups.

Conclusion: - Indicators of organ involvement in COVID 19 infection can be assessed via growing levels of inflammatory markers demonstrate that the illness has moved from group A to group B. Leukocytosis, neutrophilia, lymphopenia, and a raised NLR were among the inflammatory markers that were altered in the current study. CRP, ferritin, LDH, and D-dimer levels were also elevated. Increased levels of transaminases and total bilirubin suggest organ (liver) involvement.

Key words: - Inflammatory markers, COVID-19, SARS-CoV-2, rt PCR.

1.0 Introduction

The SARS-CoV-2 coronavirus is the culprit behind the 2019 coronavirus sickness (COVID-19). On March 11, 2020, the illness became a worldwide epidemic after starting in Wuhan, the Chinese province of Hubei. The disease spread quickly both within the individual and within the community, making it impossible for the efforts attempted to prevent or contain it to be effective (1). The patient

is asymptomatic yet contagious during the virus's incubation period, which lasts between two days and two weeks. Depending on the prevalence of metabolic diseases such obesity, diabetes mellitus, hypertension, and chronic obstructive pulmonary disease, among others, the illness severity might range from mild to moderate by the time patients start experiencing symptoms (2).
When a virus infects a host, a series of inflammatory reactions are triggered to fight the infection. The inflammatory reaction is not stopped by scavenging the virus alone; it also harms tissues at the area where the viral pathogen has spread as well as distant organs from the site of infection. The heart, liver, central nervous system, blood arteries, and lungs are just a few of the different organs that are often affected in people with COVID-19. Clinicians may be guided as to the extent or severity of the disease by an estimate of the extent of disease to these organs. These characteristics enable effective illness management to be started at the appropriate time (1). In order to determine the liver function abnormalities and advanced inflammatory biomarkers that may be used to diagnosis the severity and subsequently gauge the prognosis of patients with COVID-19 infections, the current retrospective investigation was conducted.

2.0 Materials and methods

2.1 Study setup and design. The current study was a retrospective (P = 0.001) study, the data was collected from the regional hospital, Bareilly, UP from Oct. 2020 to Feb. 2022. Only those patients' records were collected whose positive sample was determined and confirmed by reverse transcription-PCR of nasopharyngeal swabs (assessed at one of the laboratories that the Indian Council of Medical Research has approved for RNA virus nucleic acid amplification tests).

2.2 Selection of patients

To remove biasness, analysis of medical record from Oct. 2020 to Feb. 2022 was done and patients who were older than 18 years with positive rt- PCR test were included in the study. This retrospective study excluded the patients whose outcomes were unknown after being released against medical recommendation. Patients' selection from the medical record for the study based on peripheral oxygen saturation, respiratory rate, and CT scan results. The respiration rates for patients were >30 breaths/min, respectively, with oxygen saturations of >90% (3). After careful analysis of medical records, the authors have decided to divide the selected 144 patients into two groups on the basis of viral loads of Corona virus in the samples. The patients having low viral load were considered as weakly positive and represented in group A whereas patients having high viral load were present in Group B. Importantly, the viral load of the patients were analysed by the rt PCR under authorized laboratory of Uttar Pradesh government.
The patients were also graded using a chest CT scan. The extent of each lung lobe's involvement was evaluated and categorized by Bernheim et al. (4). The total severity score was given as the sum of the five lung lobes' involvement and ranged from 0 to 20. The total severity was determined by the sum of the Lobar scores: a total score of 7 included in group A and >18 included in group B (4).

2.3 Data collection

Data were gathered manually by looking over hospital case sheets, looking into electronic patient data systems, and looking up discharge summaries in a transcription database. A daily clinical assessment, initial laboratory tests like a complete blood count, liver function tests like bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, C-reactive protein (CRP), and the detection of bilirubin in the urine, as well as information on symptoms like fever, throat pain, cough, dyspnea, diarrhea, and anosmia was done as per medical records. All the biochemical parameters and inflammatory markers were investigated via laboratory accredited by National Accreditation Board for Testing and Calibration Laboratories. Additionally, data on chest imaging, drugs taken (steroids, heparin, remdesivir, and antibiotics), oxygen support, organ dysfunction, secondary sepsis, and the outcome were gathered from the medical records. Clinical severity, higher inflammatory marker levels, high D-dimer levels, prolonged hospital stay, and patient condition after discharge were the study's main outcomes of interest.

2.4 Ethics declaration: - According to the institutional regulatory body, the institutional ethics committee of Rajshree Medical research Institute, Bareilly, UP. has approved the current retrospective study.

2.5 Statistical analysis: - Reversible de-identification of patients was done for analysis's sake. Statistical investigation. One-way ANOVA was used to assess between-group differences in variables, and Tukey's post hoc analysis followed. Pearson's correlation analysis was used to determine the relationship between the variables. The threshold for statistical significance was set at P 0.05.

3.0 Results

144 participants (66 men and 78 women) with confirmed COVID-19 infection were included in the analysis of the current study. The patients' median age ranged from 35 to 74 years, or 51 years. From the total of 144 patients, 68 had mild COVID-19 infection (Group A), 76 severe COVID-19 infection (Group B). In Table I, the study population's demographic and laboratory baseline data are shown. The most frequent clinical symptoms that patients presented with were fever, sore throat, cough, dyspnea, diarrhea, anosmia, and myalgia, in that order of incidence. Importantly, patients in the younger age group, who ranged in age from 18.85 to 24.50 years, fully recovered (Data not shown in the table). Patients from group A to group B had leukocytosis along with increasing neutrophilia, lymphopenia, and an elevated neutrophil-to-lymphocyte ratio (NLR (P = 0.001)). Table I lists the concentrations of liver function indicators in the study groups. In the groups i.e group A to group B, there was a significantly significant rise in AST (P = 0.004), ALT (P = 0.002), and total bilirubin levels (P = 0.006).

The NLR (P = 0.001) and D-dimer (P = 0.001) levels were found significant in between the groups. Table 1 displays the correlation of various inflammatory markers with liver function indicators. For the neutrophil count (P = 0.001), CRP (P = 0.001), and LDH levels (P = 0.001), the **De Rittis ratio** was found to be high. Table I displays the CI of the major hematological, inflammatory, and liver function markers in the study groups. Table I shows the findings of the correlation analysis between the De Ritisti ratio and various inflammatory and liver function markers. The De Ritis ratio showed positive associations with total bilirubin and AST and negative connections with serum albumin and ALT among the liver function markers tested. The De Ritis ratio showed a positive link with D-dimer levels and a negative correlation with hemoglobin levels and the WBC count when compared to the inflammatory markers (P = 0.46). Table I displays the findings of the link between the NLR and other inflammatory markers as well as liver function markers. The neutrophil count, CRP, ferritin, D-dimer, and LDH levels all showed positive associations with NLR, while the lymphocyte and monocyte counts showed negative connections (not shown in table). NLR showed a positive connection with ALT and a negative correlation with serum albumin levels when compared to liver function indicators.

TABLE 1 -LEVELS OF INFLAMMATORY MARKERS AND NON-INFLAMMATORY MARKERS OF THE STUDY PARTICIPANTS

DEMOGRAPHIC PROFILE OF STUDY PARTICIPANTS					
Diagnostic parameters	GROUP A	GROUP B	P- value	SE	CI
Age	38.53±12.55	41.87±15.43	**<0.001**	----	---
Sex M/F	32/36	34/42	0.04	----	----
Hospital stay	6.1±3.5	21.4±6.7	**<0.00001**	----	----
LEVELS OF INFLAMMATORY MARKERS OF THE STUDY PARTICIPANTS					
Hb (g%)	15.22±6.72	11.55±4.30	0.02	0.084	0.56 to 0.91
Total WBC count (Cells/ mm^3)	7342 (2,200-19,100)	9431 (3,600-36,500)	**<0.001**	0.024	0.21 to 0.45
Neutrophil count (%^{age})	78.49±19.26	82.30±15.24	**<0.001**	0.016	0.12 to 0.55

NLR	2.54 (0.25-25.95)	6.76 (2.12-71.06)	**<0.001**	0.54	0.41 to 0.76
ESR (mm/h)	14 (1-89)	45 (9-59)	0.04	0.78	0.49 to 0.89
CRP(mg/L)	0.66 (0.1-98)	9.80 (0.9-87.6)	**<0.001**	0.82	0.33 to 0.98
Ferritin (ng/L)	165.3 (8.3-5433.0)	533.4 [64.8-8907.0]	**0.0001**	0.81	0.46 to 0.91
D-Dimer (mg/L)	0.47 (0.01-32.00)	1.59 (0.53-64.87)	**<0.001**	0.65	0.46 to 0.82
LEVELS OF NON-INFLAMMATORY MARKERS OF THE STUDY PARTICIPANTS					
LDH (U/L)	246 (12-756)	376 (187-878)	**<0.001**	0.67	0.64 to 0.85
AST (U/L)	13 (6-178)	17 (12-183)	**0.004**	0.61	0.58 to 0.87
ALT(U/L)	43 (14-128)	55 (32-198)	**0.002**	0.60	0.49 to 0.88
S. Albumin (g/dL)`	3.54±0.22	3.82±0.12	0.06	0.57	0.44 to 0.75
Total Bilirubin (mg/dL)	0.22 (0.15-2.12)	0.63 (0.4-3.5)	**0.006**	0.87	0.38 to 0.77
Direct Bilirubin(mg/dL)	0.06 (0.04-11.0)	0.17 (0.03-1.65)	0.43	0.91	0.49 to 0.88
Urea (mg/dL)	12(11-67)	32 (21-108)	**0.002**	0.77	0.36 to 0.92
Creatinine (mg/dL)	0.12 (0.05-2.12)	0.73 (0.2-2.5)	**0.006**	0.25	0.15 to 0.47
ALP (mg/dL)	54 (11-168)	76 (32-328)	**0.006**	0.47	0.56 to 0.72
De Rittis ratio	1.21 (0.45-3.13)	0.97 (0.45-2.35)	0.46		

Note –

- Diagnostic values of various parameters are expressed as the mean ± SD in between the groups and are also expressed as the median and range. Hb:- hemoglobin; WBC:- white blood cell; NLR :- neutrophil-to-lymphocyte ratio; ESR:- erythrocyte sedimentation rate; CRP:- C-reactive protein, LDH :- lactate dehydrogenase.
- Values in bold font indicate statistically significant differences (P<0.05); SE, standard error; CI, confidence interval.

4.0 Discussion

Acute respiratory distress syndrome, respiratory failure, acute liver injury, renal injury or failure, and cardiovascular manifestations are some of the systemic manifestations with multiorgan failure and septicaemia that are seen when COVID-19 infection progresses to severe disease (5). Only a small number of patients have an insufficient pro-inflammatory response, which causes severe clinical symptoms. The term "cytokine response syndrome" (CRS) or "cytokine storm syndrome" (CSS) is used to describe this manifestation (1, 6). The current study showed that patients with severe disease were between the ages of 51.47 and 8.16, which was the time when problems started to manifest. Males have been more affected by COVID-19 than females, which may be related to the higher occurrence of diseases in men. In addition, a potential confounder is that significantly more male patients than female patients were admitted to the hospital. In the current study, there were 32 and 34 of males who had mild, moderate, or severe illness, respectively (Table I). The number of days spent in the hospital was 6.1 ± 3.5, and 21.4±6.7 in the groups A and B, respectively (Table I).

In the study by Ali et al. (6), it was discovered that older people had a higher risk of acquiring serious disease, especially those who had underlying co-morbidities. Patients with serious illness needed to stay in the hospital for a long time, usually in the intensive care unit (ICU) with mechanical ventilation (6). Age, concomitant conditions, symptom severity, and lymphopenia level all have an impact on how the disease manifests itself clinically. Longer hospital stays have been linked to increased risk of complications and subsequent bacterial infections in patients (7, 8). It has been determined that the median ages of survivors and non-survivors are 54 and 70 years old, respectively (9). Patients with severe outcomes have a median age of 65 and a male preponderance of 75% (10). As previously shown, a chest CT scan of COVID-19 patients has revealed different patterns and levels of lung involvement. Although it has been found that male patients with severe COVID-19 infection had lower levels of testosterone and dihydrotestosterone than other male patients with COVID-19 infection, the function of these hormones is yet unknown (11). In order to begin early ICU care with

assisted mechanical breathing in patients with COVID-19, multiorgan failure is evaluated. Radiological and clinical aspects have been reported to benefit from routine laboratory blood tests (12). The COVID-19 cases in the current study had serially rising total WBC counts; these rises were statistically significant and more prominent in the Group B as compare to Group A. Additionally, in the Group B as compare to Group A, significantly more progressive lymphopenia was seen (P = 0.0001; Table I). In individuals with group A and group B COVID-19 infection, there were statistically significant drops in the monocyte (P = 0.01) and eosinophil (P = 0.02) counts (not shown). Significantly higher levels of WBC and other CBC parameters found in our retrospective study has a correlation with widespread systemic inflammation that causes multiorgan damage and thrombotic, vascular, and ischemic injuries. Hyperinflammation causes the disease to escalate to a severe form with serious consequences (13, 14). The direct harm to lymphocytes that results in altered lymphocyte structure and/or function may be the cause of lymphopenia. Thus, even in moderate cases of infection, lymphopenia may be thought of as a distinguishing feature of SARS-CoV-2 infection. The level of lymphopenia may be a good indicator of the severity of the condition and when problems may start to appear (12). T-lymphocyte apoptosis is influenced by interleukin-6 (IL-6). Lung inflammation results in an overconsumption of lymphocytes, which is caused by CSS-induced bone marrow inhibition of lymphocyte production (11, 13, 16).

The neutrophil count increased statistically significantly (P = 0.001) in the study, especially between group A and group B (P = 0.006). With regard to infection severity i.e group B patients, the NLR also progressively rose (P = 0.001; Table I). Lymphopenia was thought to be a more accurate predictor of the outcome of COVID-19 infection than neutrophilia, as measured by the NLR. Studies have shown that patients in the ICU with high viral load had significantly increased WBC counts, neutrophil absolute counts, NLRs, and platelet-to-lymphocyte ratios (7, 18). Both survivors and non-survivors had normal absolute neutrophil counts, albeit survivors' neutrophil counts were considerably lower than non-survivors', according to Zhao et al. (9). It has been found that patients with moderate to severe infections and a WBC count >10,000 cells/mm3 need inpatient care (10). The prognosis is worse, as was previously shown, the lower the lymphocyte count and the longer the lymphopenia lasts (19).

Both at the beginning and throughout the SARS-CoV-2 infection, macrophages have been discovered to be crucial players (20, 21). The total WBC count, neutrophil count, ALT, CRP, ferritin, D-dimer, and LDH values all showed a positive connection with NLR. Lymphocyte, monocyte, and serum albumin levels all showed a negative connection with the NLR (Table I). Furthermore, the ESR significantly increased (P = 0.02; and 95% CI of 0.66-0.82 (P = 0.001). As inflammatory markers, ESR and CRP values can be utilized to evaluate the outcomes of patients with COVID-19 infection (12). It has been discovered that there is a strong negative association between albumin levels and ESR levels. An elevated ESR can result from increased fibrinogen in acute inflammatory situations. Because albumin has a suppressive impact on ESR, ESR tends to rise in COVID-19-infected patients, especially those with high load of virus and cause severe infection, when serum albumin levels fall (10, 22).

Alveolar injury is brought on by inflammation, and vascular endothelial response is triggered by hypoxia, which enhances thrombus formation (23). Acute phase protein transcription is enhanced by IL-6 via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway (24–26). Patients with COVID-19 who have a dysregulated immune response have significantly lower peripheral lymphocyte counts, which is indicative of a greater risk of subsequent bacterial infections (27). A considerable gradual increase in CRP was seen in the current study (P 0.001). The WBC count, D-dimer, CRP, and LDH levels were also discovered to be important in determining the prognosis of COVID-19 patients. As the disease severity increased, D-dimer levels significantly rose (P 0.001; Table I). It has been demonstrated that people with severe COVID-19 have higher levels of CRP as well as other pro-inflammatory cytokines, chemokines, and NLR. This may be because these people are experiencing a hyper-inflammatory response (28). When determining the prognosis of patients with severe COVID-19 infection, CRP values >10 mg/l may be helpful (29). The complicated combination between inflammatory and pro-thrombotic variables is thought to be what triggers the

condition of coagulopathy in SARS-CoV-2 infection (30). Disseminated intravascular coagulation is the outcome of endothelial inflammation and damage brought on by the coronavirus. D-dimer levels above 1 mg/l have been linked to poor disease development in patients (6, 12, 13, 31).

As the condition progressed to a severe form in the current investigation, ferritin levels showed a considerable rise (P = 0.0001; Table I). With a cut-off value of 173.60 ng/ml (P = 0.001) (Table I). As a positive acute phase protein, ferritin is thought to be a predictor of worse outcomes in people with SARS-CoV-2 infection (12, 32). LDH levels were found to have significantly increased in the current investigation (P 0.001; Table I). LDH is an impersonal indicator of tissue injury. According to research, 50% of infected people have elevated levels of CRP, LDH, ferritin, and ESR (9, 33, 34). These changes could be brought on by CSS's acute systemic immune response (13). D-dimer and LDH blood levels have been demonstrated to exhibit a considerable positive correlation with mortality in COVID-19 patients (10, 35). The NLR has been demonstrated to have a positive link with CRP, LDH, ferritin, D-dimer, and troponin-I levels in COVID-19 patients; these parameters may indicate the length of the hospital or ICU stay as well as illness outcomes (7).

During their clinical course, patients in group B has also frequently experienced liver damage (20, 36). Disseminated intravascular coagulation (DIC), hypoxia with hypoperfusion, and shock all contribute to COVID-19's potential to impact many organs (37). Patients with COVID-19 and probable liver inflammation or injury have also been shown to have elevated transaminases, bilirubin, and decreased levels of albumin and prealbumin. The liver was involved in COVID-19, which is a sign of a bad prognosis. Additionally, it has been discovered that several medications used to treat COVID-19 can worsen liver damage (13). As the disease severity increased in the current investigation, the levels of AST showed a consistent rise (P = 0.006; Table I). With a cut-off value of 71 U/l, additionally, there was a statistically significant rise in ALT levels (P = 0.003). Compared to AST, ALT was lower at 0.56 (Table I). Contrary to the findings of other investigations, the AST: ALT (De Ritis) ratio did not show a statistically significant difference (38–40). This could be because the distribution of research participants in the current study was not uniform throughout the different categories in the groups A and B, respectively.

When the condition is severe or persistent, the De Ritis ratio is more likely to rise. Patients' hyperbilirubinemia has been linked to a changed De Ritis ratio, according to research (38). A De Ritis ratio 1.0 indicates moderate to severe liver damage, but values >1.0 are indicative of severe liver disorders (39, 40). The median De Ritis ratio reported by Zinellu et al in their study (39), which is comparable to that reported by Yazar et al in their cohort(37), was 1.33. Additionally, the De Ritis ratio cut-off value was discovered to be 1.38 in the study by Qin et al. (40); patients who had a De Ritis ratio >1.38 upon admission had significantly lower survival rates (41). The hepatocyte turnover may lead to a much greater concentration of AST in blood compared to ALT with the hepatic proportion of the AST:ALT ratio of 2.5:1. In contrast to ALT, which has a half-life of 36 h, AST has a shorter half-life of 18 h. As a result, healthy individuals have relatively identical serum levels of AST and ALT. ALT is solely found in the cytoplasm, but AST is found in both the cytoplasm and mitochondria, though at a significantly higher quantity than ALT (42). The total bilirubin, D-dimer, and AST levels in the current study showed positive correlations with the De Ritis ratio, while the hemoglobin, total WBC, serum albumin, and ALT levels showed negative correlations (Table I).

Between group A and group B instances in the current investigation, there was a significantly higher level of total bilirubin (P = 0.04; Table I). However, there was no statistically significant difference in the serum albumin levels between the groups (P = 0.09; Table I). With low blood levels in acute inflammation and an inverse relationship to the degree of systemic inflammation, albumin is thought to be a negative acute phase reactant (23). Serum albumin levels and illness severity have been observed to be negatively correlated in COVID-19 infection (43). In the current study, there was a considerable rise in LDH levels in severe cases but not in AST levels. Rhabdomyolysis brought on by a direct viral invasion of myocytes may be the cause of this. Additionally, it could be caused by T-cell-mediated injury as a symptom of CSS (11, 44), viral toxin-induced injury, viral antigen antibody immune complex deposition, or both. According to the severity of COVID-19, decreased

WBC counts and platelet counts, together with elevated NLR and ferritin levels, aid in determining the prognosis and the best course of treatment (44).

5.0 Conclusion

Depending on the disease's severity, COVID-19 disease is characterized by widespread inflammation and different tissue involvements. Therefore, rising levels of inflammatory markers and indicators of organ involvement, including liver involvement, show that the condition has advanced from group A to group B. Inflammatory markers such as leukocytosis, neutrophilia, lymphopenia, and an elevated NLR were altered in the current study, and inflammatory markers like CRP, ferritin, LDH, and D-dimer levels were also elevated. Transaminases levels and total bilirubin levels increased, indicating organ (liver) involvement. The total WBC count, monocytes, albumin, CRP, ALT, ferritin, D-dimer, and LDH levels all showed a link with the NLR. The De Ritis ratio did not show this kind of association. Therefore, in individuals with COVID-19, NLR and AST may be more accurate predictors of liver involvement than the De Ritis ratio in predicting systemic inflammation linked to liver injury or inflammation. The current study was conducted in the past. This made it impossible to acquire data on IL-6, prothrombin, partial thromboplastin time, etc. Additionally, because this was a single-center study, the population makeup and the severity of the patients who were admitted to the hospital would have had a significant impact on the study's conclusions. Because there were fewer patients in the groups, the findings regarding liver function may have been compromised.

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8.0 Patient consent for publication: - Not applicable.

9.0 Conflict of interest: - The authors declare that they have no competing interests.

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