(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 4, Page No: 894-902
July-August 2021

IJMSCR

A Study Correlating Inflammatory Markers and Co-Morbidities In Covid-19 Patients

Dr. C. Arulmurugan[1], Dr. M. Nikita[2], Dr. Lakhan Parajiya[3]
Associate Professor, Assistant Professor, Post Graduate
Department of General Medicine, Vinayaka Mission's Medical College and Hospitals, Salem, Tamil Nadu

***Corresponding Author:**
Dr. M. Nikita
Assistant Professor, Department of General Medicine, Vinayaka Mission's Medical College and Hospitals, Salem, Tamil Nadu

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

BACKGROUND: It is believed that COVID-19, in those with underlying health conditions or comorbidities, has an increasingly rapid and severe progression, often leading to death. People with chronic obstructive pulmonary disease (COPD) and other respiratory illnesses are also at higher risk for severe illness from COVID-19 disease. The elderly population, with chronic health conditions like diabetes and cardiovascular or lung disease, are at a higher risk of developing severe illness and also at an increased risk of death if they become ill.

AIM AND OBJECTIVE:

To understand the correlation between comorbidities and inflammatory markers and to reduce avoidable prolonged morbidity and mortality.

MATERIALS AND METHODS: This retrospective analytical study was conducted in VMKV medical college and hospitals, Salem. All the covid-19 cases with co-morbidities admitted from august 2020 to September 2020 were included. The patients were selected based on inclusion and exclusion criteria. In all those patients, inflammatory markers were estimated and analysed. Fifty patients were included in the study group after applying exclusion criteria.

RESULTS: In our study males accounted for 74% and females accounted for 25 %. In our study, the person with the mild, moderate, severe disease according to CT grading are 30%, 27%, and 44% respectively. In this study, the mean CRP in males before treatment was 58.4 and it decreased after treatment to 25.5, whereas in females mean CRP was 28.6 before and 7.8 after treatment. So, the mean CRP is in a slightly higher range in men both before and after treatment. The mean ESR in men is 54.6 mm before treatment and that of after treatment is 31.6mm/hr, in females it is 41.8mm/hr and 26.8mm/hr before and after treatment respectively. The mean NLR in males is 6.06 and 3.79 before and after treatment respectively, and that of the female is 4.19 and 3.23 before and after treatment respectively. The mean RDW in men is 14.8 and 13.8 before and after treatment respectively, like that of women were 15.3 and 1.5 before and after treatment respectively. Mean serum Total Cholesterol (268.88 ± 29.23 mg/dl), Triglyceride (192.12 ± 56.42 mg/dl), Very Low-Density Lipoprotein Cholesterol (38.42 ± 11.28 mg/dl) were significantly higher in covid -19 patients. Total Cholesterol (182.56 ± 21.33 mg/dl), Triglyceride (115.71 ± 32.11mg/dl), Low Density Lipoprotein Cholesterol (107.68 ± 9.55 mg/ dl), Very Low-Density Lipoprotein Cholesterol (23.14 ± 6.42 mg/dl). On the other hand value of mean serum, High-Density Lipoprotein Cholesterol was lower before treatment (40.7 ± 2.21 mg/dl) after treatment (51.74 ± 5.36mg/dl). The mean serum ferritin level was high in covid -19 patients 554.4 ± 223.3 ng/ml after treatment it has 227.8 ± 183.8 ng/ml. D-dimer elevation (≥0.50mg/L) was seen in 74.6% (85/100) of the patients. D-dimer level of >2.14 mg/L predicted in-hospital mortality with a sensitivity of 88.2% and specificity of 71.3% (AUC 0.85; 95% CI=0.77-0.92).

CONCLUSION: Ferritin was the most prominent inflammatory marker in our study. It is an iron-storing protein, responsible for releasing it in a controlled way. In inflammatory processes, a great production of ferritin occurs, inducing a decrease in serum iron, believed to decrease the availability of iron to microorganisms. For this reason, ferritin in critically ill patients may be increased, and it is associated with severity in some illnesses. Inflammatory markers levels are comparable to the degree of severity both by radiological and microbiological criteria (P-value < 0.001). The level of CRP correlates with disease activity. The concentration of serum total cholesterol, triglycerides, LDL-Cholesterol, VLDL-Cholesterol and decreases the level of HDL-Cholesterol, hypoxia and endotoxin stimulate inflammatory cells to release a variety of inflammatory mediators, resulting in injuries of vascular endothelial cells leading to a significant increase in plasma D-dimer levels.

Keywords: Coronavirus; COVID-19; hsCRP, d-dimer, serum ferritin, lipid profile

INTRODUCTION

A SARS-CoV-2 virus was identified in Wuhan, China, in December 2019. Since then, the virus has made its way across the world to affect more than 180 countries. It has infected humans in all age groups, both males and females while spreading through communities at an alarming rate. The nature of this virus is still to be learned; however, clinical manifestations range from a common cold to more severe diseases such as bronchitis, pneumonia, severe acute respiratory distress syndrome (ARDS), multi-organ failure, and even death. [1] The pathogen has been identified as a novel single-stranded ribonucleic acid (RNA) betacoronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which shares an approximately 79% similarity at the nucleotide level with severe acute respiratory syndrome coronavirus (SARS-CoV). As of March 21, 2020, a total of 266, 073 confirmed cases from 150 countries and territories were reported, including 11,183 deaths. COVID-19 represents a spectrum of clinical severity ranging from asymptomatic to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death.[2] These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations.[3] Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality. Inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID-19.[4] The inflammatory response is classified as local or systemic. In systemic inflammation, the inflammation spreads and affects other systems than the organ of origin. Inflammation can be evaluated by cytological or biochemical variables and different markers are associated with either type of inflammation.[5] Inflammation is incorporated into the definition of both chronic obstructive pulmonary disease (COPD) and asthma but the inflammatory response differs somewhat. Both diseases have chronic local inflammation, with airway remodelling but its localization, the inflammatory cells involved, mediator profiles and the therapeutic response may vary. The pro-inflammatory state due to activation of macrophages and release of Cytokines by expanded adipocytes plays an important role in the pathogenesis of this syndrome.[6] This pro-inflammatory state can be documented by estimating the level C-Reactive Protein in serum. Here we performed a meta-analysis based on the current scientific literature to compare the levels of inflammatory markers between severe patients and non-severe patients with COVID-19. Our study will highlight the association of inflammatory markers with the severity of COVID-19 and assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.[7]

MATERIALS AND METHODS: This retrospective analytical study was conducted in Vinayak Mission's Kirupananda Variyar medical College and Hospitals, Salem. All the COVID-19 cases with co-morbidities admitted from august 2020 to September 2020 were included. The patients were selected based on inclusion and exclusion criteria. In all those patients, inflammatory markers were estimated and analyzed. Fifty patients were included in the study group after applying exclusion criteria.

Inclusion Criteria:

- All Covid-19 Positive Patients
- All-Age Groups
- Male and Female Sexes and patients with all Comorbidities.

Exclusion Criteria:

- Non-Covid Pneumonia.

Clinically, the severity of the COVID–19 patients was classified into mild, moderate, severe, and critically ill according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6th ed.) by the National Health Commission of China. Radiologically, the area of affected lungs consistent with viral pneumonia in each patient's first chest CT after admission was measured and classified into ≤30%, 31–50%, and ≥50% of the total lung area. Haematological parameters such as serum ferritin, lipid profile, d-dimer level was analysed for patients.

STATISTICAL ANALYSIS

Statistical analysis was done using Microsoft Excel and SPSS software with the help of a statistician. P-value is used to assess the significance of the correlation between variables.

Volume 4, Issue 4; July-August 2021; Page No 894-902

A statistically significant correlation is one in which Pearson correlation is used to assess the strength of correlation between variables. Pearson correlation: > 0.5 - Strong correlation, 0.3 to 0.5 - Moderate correlation, < 0.3 - Weak correlation.

Chi-square Test: Chi-square test is performed between two groups and its statistical significance is calculated. The chi-square ($\chi 2$) test of independence is used to test for a statistically significant relationship between two categorical variables. The term "degrees of freedom" is used to refer to the size of the contingency table on which the value of the Chi-Square statistic has been computed value is calculated using the Excel CHITEST function: If P-value ≤ 0.05 → statistically significant, if P-value > 0.05 → statistically insignificant.

RESULTS:

In our study males accounted for 74% and females accounted for 25 %. In our study, the mean age distribution is 40 years with a maximum of 70 years and minimum age of 18 years. The males were more in number in mild disease and severe disease. Males and females are equal in number in moderate disease. In our study, the person with the mild, moderate, severe disease according to radiological grading are 30%, 27%, and 44% respectively

TABLE :1 CRP LEVELS

PARAMETER	SEX	BEFORE TREATMENT	AFTER TREATMENT
CRP	Male	58.4+/-29.8	23.5+/- 15.3
	Female	28.6+/- 23.4	7.8 +/- 10.2

Table :1 In this study the mean CRP in males before treatment was 58.4 and it decreased after treatment to 25.5. whereas in females mean CRP was 28.6 before and 7.8 after treatment. The mean CRP is in a slightly higher range in men both before and after treatment. CRP values >10 mg/l were found in 26 patients during the first week and in five patients after day 7

TABLE:2 ESR LEVELS

PARAMETER	SEX	BEFORE TREATMENT	AFTER TREATMENT
ESR	Male	54.6+/ 24.5	31.6 +/- 7.39
	female	41.8 +/-10.7	26.85 +/- 5.17

Table:2 The mean ESR in men is 54.6 mm/before treatment and that of after treatment is 31.6mm/hr.in females it is 41.8mm/hr and 26.8mm/hr before and after treatment respectively. The highest median ESR values were found after 4–5 days and occurred 1–2 days later than the peak CRP values. The ESR strongly correlated with the CRP value on days 3–6 (Pearson coefficient = 0.55–0.71, P<0.001), but there was no correlation on days 7 and 10. A statistically significant correlation was also found on days 14 and 21

Volume 4, Issue 4; July-August 2021; Page No 894-902

TABLE: 3 NEUTROPHIL-LYMPHOCYTE RATIO

PARAMETER	SEX	BEFORE TREATMENT	BEFORE TREATMENT
NLR	Male	6.06+/- 2.3	3.79 +/- 1.2
	Female	4.19 +/- 1.27	3.23 +/-0.56

Table :3 The mean NLR IN males is 6.06 and 3.79 before and after treatment respectively, and that of the female is 4.19 and 3.23 before and after treatment respectively. the median neutrophil-to-lymphocyte ratio (NLR) value of the severe patients was dramatically higher than that of the non-severe patients (10.4 vs 2.6; $P < .001$). The NLR value equal to 5 was a boundary value worthy of reference because more than 80% of severe patients had an NLR value greater than 5 and over 80% of non-severe patients had an NLR value less than 5. The NLR value of these COVID-19 patients was positively and respectively correlated with the values of C-reactive protein ($R = .5921$, $P < .001$), NLR was found to be an independent risk factor for severe COVID-19 pneumonia in the heavy group (OR = 1.264, 95% CI: 1.046~1.526, $P = .015$). The calculated AUC using ROC for NLR was 0.831, with an optimal limit of 4.795, the sensitivity of 0.83, and the specificity of 0.75, which is highly suggestive of NLR being a marker for the early detection of deteriorating severe COVID-19 infection.

TABLE: 4 RED CELL DISTRIBUTION WIDTH

PARAMETER	SEX	BEFORE TREATMENT	BEFORE TREATMENT
RDW	Male	14.8+/-1.5	13.8 +/- .98
	female	15.3 +/- 1.7	13.5 +/- 0.72

Table:4 The mean RDW in men is 14.8 and 13.8 before and after treatment respectively, likethat of women were 15.3 and 1.5 before and after treatment respectively. Elevated RDW (>14.5%) was associated with increased mortality risk in patients of all ages. The RR for the entire cohort was 2.73, with a mortality rate of 11% in patients with normal RDW (1173) and 31% in those with an elevated RDW (468). The RR in patients younger than 50 years was 5.25 (normal RDW, 1% [n = 341]; elevated RDW, 8% [n = 65]); 2.90 in the 50- to 59-year age group (normal RDW, 8% [n = 256]; elevated RDW, 24% [n = 63]); 3.96 in the 60- to 69-year age group (normal RDW, 8% [n = 226]; elevated RDW, 30% [104]); 1.45 in the 70- to 79-year age group (normal RDW, 23% [n = 182]; elevated RDW, 33% [n = 113]); and 1.59 in those ≥80 years (normal RDW, 29% [n = 168]; elevated RDW, 46% [n = 123]).

Volume 4, Issue 4; July-August 2021; Page No 894-902

TABLE :5 LIPID PROFILE

NAME OF PARAMETER	BEFORE TREATMENT	BEFORE TREATMENT	P-value
Total Cholesterol mg/dl	268.88 ± 29.23	182.56 ± 21.33	<0.05
Triglyceride mg/dl	192.12 ± 56.42	115.71 ± 32.11	<0.05
VLDL-Cholesterol mg/dl	38.42 ± 11.28	23.14 ± 6.42	<0.05
LDL-Cholesterol mg/dl	189.76 ± 15.74	107.68 ± 9.55	<0.05
HDL-Cholesterol mg/dl	40.7 ± 2.21	51.74 ± 5.36	<0.05

Table :5 Mean serum Total Cholesterol (268.88 ± 29.23 mg/dl), Triglyceride (192.12 ± 56.42 mg/dl), Very Low-Density Lipoprotein Cholesterol (38.42 ± 11.28 mg/dl) were significantly higher in covid -19 patients. Total Cholesterol (182.56 ± 21.33 mg/dl), Triglyceride (115.71 ± 32.11mg/dl), Low Density Lipoprotein Cholesterol (107.68 ± 9.55 mg/ dl), Very Low-Density Lipoprotein Cholesterol (23.14 ± 6.42 mg/dl). On the other hand value of mean serum High Density Lipoprotein Cholesterol was lower before treatment (40.7 ± 2.21 mg/dl) after treatment (51.74 ± 5.36mg/dl).

TABLE :6 SERUM FERRITIN (ng/ml) LEVEL

	BEFORE TREATMENT	BEFORE TREATMENT	Wilcoxon test	p-value
Ferritin (ng/ml) Median (IQR) Mean ± SD	554.4 ± 223.3 ng/ml.	227.8 ± 183.8 ng/ml.	-3.677	< 0.001*

Table:6 The mean serum ferritin level was high in covid -19 patients 554.4 ± 223.3ng/ml after treatment it has 227.8 ± 183.8 ng/ml. serum ferritin levels in group 1 patients were lower than in group 2 patients. In addition, the degree of decline in the 1st-month serum ferritin levels (from peak levels) in group 1 patients was higher (76% vs. 49%, P = 0.039) Data are presented as the number of subjects with the percentage in parenthesis. Continuous variables were transformed into categorical variables using median or mean cut-off values or upper normal limit values for the univariate analyses.

TABLE 7. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF SEVERERITY OF INFECTION

Concomitant variable	Regression coefficient	SE	Wald	P-value	OR	Lower	Upper
CRP (X_1)	0.011	0.006	3.344	0.067	1.011	0.999	1.024
Age (X_2)	−0.038	0.011	12.158	0.000	0.962	0.942	0.983
Body temperature (X_3)	0.325	0.134	5.824	0.016	1.383	1.063	1.801
Expectoration (X_4)	−0.853	0.283	9.108	0.003	0.426	0.245	0.742
Dyspnea (X_5)	3.360	0.286	137.936	0.000	28.801	16.438	50.461

Volume 4, Issue 4; July-August 2021; Page No 894-902

NEUT (X_6)	0.005	0.003	2.324	0.127	1.005	0.999	1.011
Constant	−14.780	5.150	8.237	0.004	0.000		

CRP, C-reactive protein; NEUT, the proportion of neutrophils; AUC, the area under the curve; SE, standard error; OR, odds ratio; CI, confidence interval.

Table:7 With the severity of infection as the dependent variable, the CRP level, body temperature, expectoration, bacterial infection, viral infection, cough, gender, age, NEUT, and dyspnoea were used as covariates. Using multivariate logistic regression analysis, a preliminary regression model was established, and the covariates of bacterial infection, viral infection, cough, and gender were excluded (P>0.1). The regression model was assessed using a likelihood-ratio test and the goodness of fit of the regression model was demonstrated to be satisfactory (P<0.01>)

TABLE:8 D-DIMER LEVEL WITH SENSITIVITY & SPECIFICITY

The cutoff point for D-dimer (mg/L)	2.14
Area under curve	0.85
95% CI	0.77-0.92
Subjects with d-dimer > 2.14mg/L (%)	77 (31.2%)
Sensitivity (%)	88.2
Specificity (%)	71.3
Likelihood ratio	3.08

Table 8 D-dimer elevation (≥0.50mg/L) was seen in 74.6% (85/100) of the patients. D-dimer level of >2.14 mg/L predicted in-hospital mortality with a sensitivity of 88.2% and specificity of 71.3% (AUC 0.85; 95% CI=0.77-0.92).

TABLE:9 COMPARISON OF COMORBIDITY AMONG MILD & SEVERE SYMPTOMATIC PATIENTS IN CORRELATION WITH INFLAMMATORY MARKERS

Comorbidity (*n* (%))	ALLPATIENTS	MILD SYMPTOMATIC	SEVERE SYMPTOMATIC	P VALUE
Hypertension	16 (5.6)	6 (2.8)	10 (13.5)	0.002*
Diabetes	11 (4.6)	2 (0.9)	11 (14.9)	<0.001*
Heart disease	9 (3.2)	2 (0.9)	7 (9.5)	0.001*
Stroke	1 (1.9)	6 (2.8)	5 (6.8)	0.161
Thyroid disease	5 (2.4)	1 (0.5)	0 (0.0)	1.000
Chronic gastritis	3 (1.1)	2 (0.9)	1 (1.4)	1.000
Hyperuricemia	4 (1.4)	2 (0.9)	2 (2.7)	0.277

Table:9 Inflammatory markers such as serum ferritin, lipid profile, D-dimer level were compared with comorbidity conditions which have shown significantly higher levels in mild & moderate symptomatic patients. Significant difference between the two groups was observed in the median age

Volume 4, Issue 4; July-August 2021; Page No 894-902

(p = .001), ACCI score (p < .001), comorbidity categories (p < .001), and complications include hypertension (P = .002), diabetes (p < .001), and heart disease (p = .001).

DISCUSSION

There have been remarkable and variable cardiovascular complications of the coronavirus infection. In severe manifestations of COVID-19, increased D-dimer and its association with increased mortality have been observed.[8] Studies have suggested that an exacerbate systemic inflammatory response plus hypoxia may cause endothelial dysfunction and increased procoagulant activity, contributing to thrombus formation. This prothrombotic state, associated with systemic infection, is commonly known as sepsis-induced coagulopathy.[9] The D-dimer, a fibrin degradation product, is a relatively small protein fragment that is present in the blood following degradation of blood clots by fibrinolysis. The determination of circulating D-dimer concentrations is a sensitive test in clinical practice to diagnose thrombotic states, including pulmonary embolism and DIC [10]. Therefore, elevations in D-dimer levels in COVID-19 patients might be helpful to rapidly identify those that have high disease severity, pulmonary complications, and risk of venous thromboembolism in the setting of a pro-thrombotic state. This would assist with risk stratification and the early introduction of therapeutic measures that might reduce COVID-19 related morbidity and mortality. The NLR ratio elevated inactive disease and falls significantly in mild disease (p < 0.006) whereas in moderate and severe disease fall in its level is not significant (p = 0.5). Mean serum Total Cholesterol (268.88 ± 29.23 mg/dl), Triglyceride (192.12 ± 56.42 mg/dl), Very Low-Density Lipoprotein Cholesterol (38.42 ± 11.28 mg/dl) were significantly higher in covid -19 patients. Total Cholesterol (182.56 ± 21.33 mg/dl), Triglyceride (115.71 ± 32.11mg/dl), Low Density Lipoprotein Cholesterol (107.68 ± 9.55 mg/ dl), Very Low Density Lipoprotein Cholesterol (23.14 ± 6.42 mg/dl).[14] On the other hand value of mean serum High-Density Lipoprotein Cholesterol was lower before treatment (40.7 ± 2.21 mg/dl) after treatment (51.74 ± 5.36 mg/dl). Similar findings are reported by Han H, et.al [15]. Ferritin was the most prominent inflammatory marker in our study. It is an iron-storing protein, responsible for releasing it in a controlled way. In inflammatory processes, a great production of ferritin occurs, inducing a decrease in serum iron, believed to decrease the availability of iron to microorganisms. For this reason, ferritin in critically ill paediatric patients may be increased, and it is associated with severity in some illnesses a study conducted by Higgins JPet.al [16] shows that serum ferritin level has a sensitivity of 62.5% and specificity of 81.2% in prediction of mortality with (p-value = 0.002) with cut-off point > 550, while ejection fraction has a sensitivity of 83.3% and specificity of 87.5% in prediction of mortality with (p-value = < 0.001) with cut-off point ≤ 56%Also as shown in the same, serum ferritin level had a sensitivity of 68.4% and specificity of 66.7% in prediction of cardiac dysfunction with (p-value = 0.016) with cut-off point > 510.[17] Interestingly, we observed no significant associations between increasing SMD values and the age ratio between patients with more severe COVID-19 and those with milder forms, despite the established age-related increase in serum D-dimer concentrations [18] As patients with severe COVID-19 disease are also significantly older than subgroups with milder form, our findings suggest that the reported differences in serum D-dimer concentrations are independent of age differences in patients with different disease severity.[19] Although this further supports the presence of DIC as the primary marker of D-dimer elevations and COVID-19 severity, additional studies in cohorts with higher age ratios between patients with more severe COVID-19 and those with milder forms are required to confirm this proposition. [20] Pending further research to investigate the cause-effect relationship between serum D-dimer concentrations, COVID-19 disease severity, the onset of pulmonary complications, and clinical outcomes, the identification of D-dimer as a biomarker of COVID-19 severity is potentially clinically relevant.[21] For example, the rapid initiation of DIC therapies, instigated by high D-dimer concentrations and the presence of other diagnostic criteria, might provide additional therapeutic advantages in severe COVID-19 patients already receiving ventilatory and circulatory support. [23,24,25]

CONCLUSION

The level of CRP correlates with disease activity. The concentration of serum total cholesterol, triglycerides, LDL- Cholesterol, VLDL-Cholesterol and decreases the level of good Cholesterol i.e., HDL-Cholesterol.

Volume 4, Issue 4; July-August 2021; Page No 894-902

Hypoxia and endotoxin stimulate inflammatory cells to release a variety of inflammatory mediators, resulting in injuries of vascular endothelial cells leading to a significant increase in plasma D-dimer levels. Serum CRP level shows a higher significance among the various inflammatory markers studied. This suggests that D-dimer concentrations might be helpful to rapidly identify COVID-19 patients with a high risk of pulmonary complications and venous thromboembolism, facilitating the early initiation of effective therapies. However, further studies are required to confirm such findings in different geographical areas, using robust assessment methods, and to investigate the associations between D-dimer concentrations, COVID-19 disease progress, response to treatment, and overall clinical prognosis.

REFERENCES

1. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* (1994) 50:1088–101.
2. Bowden J, Tierney JF, Copas AJ, Burdett S. Quantifying, displaying, and accounting for heterogeneity i`xn the meta-analysis of RCTs using standard and generalized Q statistics. *BMC Med Res Methodol.* (2011) 11:41.
3. Channappanavar R, Perlman S: *Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. SEMIN IMMUNOPATHOL* 2017, *39(*5):529–539.
4. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* (2020) 130:2620–9.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, *et al: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet* 2020, *395(*10223):507–513.
6. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: a retrospective study. *BMJ.* (2020) 368:m1091.
7. Dai R, Kong Q, Mao B, Xu W, Tao R, Wang X, Kong Q, Xu J: *The mortality risk factor of community-acquired pneumonia patients with chronic obstructive pulmonary disease: a retrospective cohort study. BMC PULM MED* 2018, *18(*1).
8. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, Ferraz da Silva LF, Pierre de Oliveira E, Nascimento Saldiva PH, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost*. (2020) 18:1517–9.
9. Du Toit A. Outbreak of a novel coronavirus. *Nat Rev Microbiol.* (2020) 18:123.
10. Duval S, Tweedie R, Trim, Fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* (2000) 56:455–63.
11. Fruchter O, Yigal M, Kramer MR: *d-dimer as a Prognostic Biomarker for Mortality in Chronic Obstructive Pulmonary Disease Exacerbation. The American Journal of the Medical Sciences* 2015, *349(*1):29–35.
12. Grabinski LE, Baric RS: *Molecular pathology of emerging coronavirus infections. The Journal of Pathology* 2015, *235(*2):185–195.
13. Gre Goire Le Gal M, Marc Righini M, Pierre-Marie Roy M, Olivier Sanchez M, Drahomir Aujesky MM, Henri Bounameaux M, And Arnaud Perrier M: *Prediction of Pulmonary Embolism in the Emergency Department: The revised Geneva score. ANN INTERN MED* 2006, 144:165–171.
14. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, Qu J: *Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. FRONT MICROBIOL* 2019, *10:*2752.
15. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. (2020) 58:1116–20.
16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* (2002) 21:1539–58.
17. 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) 395:497–506.

Volume 4, Issue 4; July-August 2021; Page No 894-902

18. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England)* 2020, *395(*10223):497–506.

19. Lippi G, Bonfanti L, Saccenti C, Cervellin G: *Causes of elevated D-dimer in patients admitted to a large urban emergency department. EUR J INTERN MED* 2014, *25(*1):45–48.

20. Liu B, Li M, Zhou Z, Guan X, Xiang YJ. Can we use interleukin-6 (IL-6) blockade for coronavirus disease (2019)? (COVID-19)-induced cytokine release syndrome (CRS)? *Autoimmun*. (2020) 111:102452.

21. Liu M, He P, Liu HG, Wang XJ, Li FJ, Chen S, et al. Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi*. (2020) 43:209–14.

22. Olson JD. D-dimer: an overview of hemostasis and fibrinolysis, assays, clinical applications. *Adv Clin Chem*. (2015) 69:1–46. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: A pooled analysis. *Thromb Haemost*. (2020) 120:876–8.

23. Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Clement JL, Gomez E, Martinez I: *Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. CHEST* 2004, *126(*4):1087–1092.

24. Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG: *D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomized clinical trial. EUR J INTERN MED* 2012, *23(*5):436–441.

25. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol.* (2001) 54:1046–55.

Volume 4, Issue 4; July-August 2021; Page No 894-902