Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/15351
DOI URL: http://dx.doi.org/10.21474/IJAR01/15351

RESEARCH ARTICLE

A STUDY ON THE CLINICAL PROFILE OF PATIENTS WITH COVID 19 WITH SPECIAL REFERENCE TO D DIMER AND FERRITIN AND THEIR CORRELATION WITH THE SEVERITY OF THE DISEASE

Dr. Naruttam Sonowal[1], Dr. Nirmita Saikia[2], Dr. Uttam Kumar Nath[3] and Dr. Anju B. Teli[4]

1. Associate Professor, Dept of Medicine, Jorhat Medical College.
2. Registrar, Dept of Medicine, Jorhat Medical College.
3. Assistant Professor, Dept of Medicine, Jorhat Medical College.
4. Professor, Dept of Biochemistry, Jorhat Medical College.

Manuscript Info

Manuscript History
Received: 10 July 2022
Final Accepted: 14 August 2022
Published: September 2022

Abstract

Aim: The purpose of the study is to evaluate the clinical characteristics of COVID 19 and to determine the correlation between severity of the disease and the level of D DIMER and ferritin, in patients admitted in Jorhat Medical College and Hospital-

Materials and Methods: A total of 241 patients diagnosed to be cases of COVID 19 were recruited from the Covid ward of Jorhat Medical College.

Results: Study results showed 49.59% patients had fever and 42.56% patients had respiratory distress. The mean D-dimer levels in mild, moderate and severe were 0.72(g/L),1.33(g/L) and 1.76(g/L) respectively. There was statistically significant difference among the 3 groups with p value <0.0001. The mean ferritin level in mild, moderate and severe were 168.83 ng/ml, 327.62 ng/ml and 681.10 ng/ml respectively. There was statistically significant difference among the 3 groups with p value <0.0001. Serum D dimer and ferritin levels were also found to be increased in patients with higher CT severity score.

Conclusion: Serum D dimer and ferritin levels can be used as predictors of severity of covid 19 and the outcome in hospitalised patients.

1.Introduction:-

In December 2019, health officials from Wuhan, China first reported the occurrance of a novel coronavirus disease caused by Severe Acute Respiratory Syndrome Coronavirus 2(SARS COV2).(1) This highly contagious disease started spreading rapidly and within a few months it spread across almost all the countries and continents. The World Health Organization(WHO) declared it as a pandemic on 11th March, 2020.(2) Globally, as of 26 August 2022, there have been 596,873,121 confirmed cases of COVID-19, including 6,459,684 deaths, as reported by WHO.(3) A number of research trials have been going on to understand the entire spectrum of the novel disease. The clinical manifestations of COVID-19 include fever, cough, diarrhea, dyspnea, fatigue and pneumonia(4) Some patients also present with headache, anosmia, myalgia, vomiting, anorexia, etc.(5) Most of the cases recover quite well. However a section of people especially those with associated comorbidities have been found to be severely affected and develop acute respiratory failure, acute kidney injury, multiorgan dysfunction and even death.(6) There

Corresponding Author:- Dr. Nirmita Saikia
Address:- Dept of Medicine, Jorhat Medical College.

is no definite data so far as to how and why there is striking variations in the way a particular patient respond to the disease process, irrespective of age, sex, ethnicity and lifestyle. Existing literature suggest among all complications of covid 19,there is a high risk of venous thromboembolism in patients, owing to the the severe inflammatory response and other features of critical illness.(7) Several prognostic biomarkers like CRP, leucocytes, procalcitonin, urea, troponins and D-dimer, and low levels of eGFR have been studied and evaluated to predict the severity and outcome of the disease.(8) Knowledge about the role of these biomarkers as predictors of severity in the disease process is extremely important to assess and identify the vulnerable people who are at risk of developing serious complications requiring ICU care or long term hospital in-admissions.

The present study has been undertaken to evaluate the clinical features of covid 19 patients and the association between common biomarkers and severity of the disease.

2.Methods:-

2.1 Study design and participant

A total of 241 hospitalized patients with confirmed SARS COV infection admitted in covid ward of JMCH from 1ST JUNE,2021- 31ST AUGUST,2021 were included, after giving their consent to be a part of the study. Patients with age less than 18 years and those with pregnancy, cancer, hematologic malignancy,chronic liver disease, acute coronary syndrome, surgery or trauma within 30 days, and patients without reports of D-dimer and ferritin upon admission were excluded from the study.

2.2 Data Collection Tools:

Relevant data was collected retrospectively through electronic nursing and medical records using standardized data collection form. Following data were collected- age, gender, hospital ID no., presenting complaints, level of oxygen saturation at the time of admission, level of D dimer and Ferritin at the time of admission, HRCT thorax alongwith other investigations as relevant for the case.

2.3 Research Methodology:-

Complete records of history and general and systemic examination were analysed. Reports of following Investigations were collected from medical records retrospectively-
Biochemical- CBC,RBS,LFT,RFT,D-Dimer,ferritin,CRP,electrolytes.

The following laboratory normal range were considered- serum ferritin- 11-306.8 ng/ml, D dimer- <0.5g/L.

Patients were categorized as mild, moderate and severe covid 19 pneumonia according to WHO criteria as follows-

1. Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging, with SpO2>94% on room air at sea level.
2. Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) 90-94% on room air at sea level.
3. Severe Illness: Individuals who have SpO_2 <90% on room air at sea level, respiratory frequency >30 breaths/min or severe respiratory distress.(9)

HRCT thorax reports of 56 patients were assessed. In all cases, a semiquantitative CT severity scoring proposed by Li et al. was done, according to which, both lungs were divided into five lobes, and each lobe was assessed individually. The abnormalities that were considered significant for the disease included the following: ground-glass opacity, consolidation, nodule, reticulation, interlobular septal thickening, crazy-paving pattern, linear opacities, subpleural curvilinear line, bronchial wall thickening, lymph node enlargement, pleural effusion, and pericardial effusion.

Each lobe was assigned CT score from 0 to 5, depending on the percentage of the involved lobe: score 0 – 0% involvement; score 1 – less than 5% involvement; score 2 – 5% to 25% involvement; score 3 – 26% to 49% involvement; score 4 – 50% to 75% involvement; score 5 – greater than 75% involvement.

The overall CT score was the sum of the points from each lobe and ranges from 0 to 25 points. (10)
Sum of individual lobar score indicates the overall severity of five lobes as detailed in Table 1.

Table 1:-

SCORE	CT SEVERITY
<8	MILD
9-16	MODERATE
>16	SEVERE

3.Statistical Analysis

Data were recorded into a preformed and pretested proforma. Statistical analysis was done by MS excel 07 and GRAPHPAD INSTAT software. Data were expressed as mean and standard deviation. One way ANOVA analysis with post test was performed to compare the difference in mean D dimer levels and mean ferritin levels between each category of severity stage. P value <0.05 is considered significant.

4.Results And Observations:-

4.1 Clinical characteristics of patients

In this study, 120(49.59%) patients had fever and 103(42.56%) patients had respiratory distress. Other symptoms were cough(40.08%), headache(30.99%), diarrhea(24.38%) and myalgia (6.61%).

Table 2:-

Symptoms	Number of patients affected (%)
Fever	120(49.59%)
Cough	97(40.08%)
Respiratory distress	103(42.56%)
Myalgia	16(6.61%)
Diarrhea	59(24.38%)
Headache	75(30.99%)
Anosmia	74(30.58%)

4.2 Number of patients associated with comorbididties

0ut of 241 patients, 80 (33.19%) patients had diabetes and 93 (38.59%) patients had hypertension. Other associated co morbidities were COPD(19.91%), renal dysfunction (10.37%) and hypothyroidism (30.29%).

Table 3:-

Comorbid condition	No.of patients (male)	No. of patients (female)	Total(%)
DM	52	28	80(33.19%)
HTN	64	29	93(38.59%)
COPD	30	18	48(19.91%)
RENAL DYSFUNCTION	18	7	25(10.37%)
HYPOTHYROIDISM	44	29	73(30.29%)

4.3 Number of patients in various categories

Based on SPO2, 84(34.86%) patients were categorized as mild, 69(28.63%) patients as moderate and 88(36.51%) patients as severe.

Table 4:-

CATEGORY	NO. OF CASES
MILD	84
MODERATE	69
SEVERE	88

4.4 Level of D-Dimer in various categories of patients

In this study, the mean D-dimer levels in mild, moderate and severe were 0.72(g/L),1.33(g/L) and 1.76(g/L) respectively. There was statistically significant difference among the 3 groups with p value <0.0001. On the other hand, 0.39% of mild category, 62.32% of moderate category and 71.59% of severe category patients had raised serum levels of d dimer.

Table 5:-

SEVERITY	PATIENTS WITH NORMAL D DIMER	PATIENTS WITH RAISED D DIMER	MEAN D DIMER LEVEL(g/L)
MILD	51(60.71%)	33(0.39%)	0.72
MODERATE	26(37.68%)	43(62.32%)	1.33
SEVERE	25(28.41%)	63(71.59%)	1.76

4.5 **Level of ferritin in various categories of patients:**

In this study,15.48% of mild category, 31.88% of moderate category and 78.41% of severe category patients had raised serum levels of ferritin. The mean ferritin level in mild, moderate and severe were 168.83 ng/ml, 327.62 ng/ml and 681.10 ng/ml respectively. There was statistically significant difference among the 3 groups with p value <0.0001.

Table 6:-

SEVERITY	PATIENTS WITH NORMAL FERRITIN	PATIENTS WITH RAISED FERRITIN	MEAN FERRITIN LEVEL(ng/ml)
MILD	71(84.52%)	13(15.48%)	168.83
MODERATE	47(68.12%)	22(31.88%)	327.62
SEVERE	19(21.59%)	69(78.41%)	681.10

4.6 **Number of patients in various categories of Ct severity score**

Based on the CT severity score, patients with CT score <8, 9-16 and > 16 were categorized as mild , moderate and severe respectively.

In the present study, out of 53 patients whose HRCT Thorax reports were analysed, 7 patients were mild, 30 patients were moderate while 16 patients belonged to severe category.

Table 7:-

CT SCORE	SEVERITY	NUMBER OF PATIENTS
<8	MILD	7
9-16	MODERATE	30
>16	SEVERE	16

4.7 **Correlation of D-dimer,ferritin and Ct severity score**

The mean ferritin level in mild, moderate and severe categories (based on ct severity score) were 138.09 ng/ml, 310.52 ng/ml and 853.33 ng/ml respectively. There was statistically significant difference among the 3 groups with p value <0.0001.

Similarly, the mean d dimer level in mild, moderate and severe categories (based on ct severity score) were 0.5 g/L, 1.15g/L and 2.79g/L respectively. There was statistically significant difference among the 3 groups with p value <0.0001.

Table 8:-

SEVERITY	CT SEVERITY SCORE	MEAN D DIMER (g/L)	MEAN FERRITIN(ng/ml)
MILD	<8	0.5	138.09
MODERATE	9-16	1.15	310.52
SEVERE	>16	2.79	853.33

4.8 **Correlation of CT severity score and outcome of patients**

In this study, out of 53 patients whose HRCT Thorax reports were analysed, all 10 patients belonging to mild category were discharged. Out of 30 moderate cases, 14 patients (46.67%) were discharged while 16 patients (53.33%) expired. Out of 16 severe cases, 6 patients(37.5%) were discharged and 10 patients(62.5%) expired.

Table 9:-

SEVERITY	CTSCORE	DISCHARGED	DEATH	TOTAL
MILD	<8	10	0	10
MODERATE	9-16	14	16	30
SEVERE	>16	6	10	16

5.Discussion:-

Covid 19 is a novel disease which has affected millions of people across the world. Existing data suggest most people remain asymptomatic while others can present mostly with cough, fever, shortness of breath, malaise and myalgia. Some can also have symptoms related to gastrointestinal and neurological system like vomiting, anorexia, headache, anosmia etc. Several research trials have been conducted to evaluate the importance of serum biomarkers like D dimer, ferritin, CRP, lymphocyte counts, etc. in the pathogenesis of the disease. Our study has aimed to study the clinical profile of patients with COVID 19 infection and to establish whether there is any correlation between serum biomarkers like D dimer and ferritin with the severity of the disease. D-dimers are one of the fragments produced when fibrin polymers are cleaved by plasmin at the D fragment site to break down clots.(11) Any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels. Conditions like deep vein thrombosis/pulmonary embolism, arterial thrombosis, disseminated intravascular coagulation, pregnancy, inflammation, cancer, chronic liver diseases, post trauma and surgery status, and vasculitis can result in increased D dimer levels. Our study excluded patients with these conditions. Ferritin is the intracellular storage form of iron. It also acts as an "acute phase reactant"and reflects the degree of both chronic as well as acute inflammation inside the body.(13) A higher ferritin level indicates an activated monocyte-macrophage system, immune dysregulation, with direct immune suppressive and pro-inflammatory effects that cause cytokine storm. The prevalence of various symptoms and complications in COVID 19 can be attributed to this cytokine storm syndrome.(13)

In our study, 49.59% patients had fever and 42.56% patients had respiratory distress. Other symptoms were cough(40.08%), headache(30.99%), diarrhea(24.38%) and myalgia (6.61%). The results were similar to the study conducted by Guan et al., comprising of 1099 patients, they the most common symptoms were fever (43.8%)and cough (67.8%).(1) Li et al. and Chen et al. also reported similar results.(4)(5)

Most of the patients had associated comorbidities like diabetes and hypertension. In this study, the mean D-dimer levels in mild, moderate and severe were 0.72(g/L),1.33(g/L) and 1.76(g/L) respectively. There was statistically significant difference among the 3 groups with p value <0.0001. A number of studies have reported increased D dimer levels in hospitalized covid 19 patients with critical illness and comorbidities. Between March 1, 2020 and April 8 2020, Berger et al conducted a study, among 2377 adults hospitalized with COVID-19 and found that patients with elevated presenting baseline D-dimer were more likely than those with normal D-dimer to have critical illness (43.9% versus 18.5%; adjusted odds ratio, 2.4 [95% CI, 1.9–3.1]; P<0.001).(12) In another study comprising of 1310 patients, conducted in Feb- May 2020, Hodges et al reported higher standardized absolute risk of death/ICU admission within 30 days in patients with higher levels of D dimer and other inflammatory markers.(8) Yao et al, in a study of 248 hospitalised patients, found that D-dimer levels significantly increased with increasing severity of COVID-19 as determined by clinical staging.

In our study, majority of patients in severe category had raised serum ferritin levels (78.41%) while only 15.48% of mild category had increased levels of serum ferritin. The mean ferritin level in mild, moderate and severe were 168.83 ng/ml, 327.62 ng/ml and 681.10 ng/ml respectively. There was statistically significant difference among the 3 groups with p value <0.0001. In a meta analysis conducted by Cheng et al., a total of 52 records involving 10, 614 COVID-19-confirmed patients between December 25, 2019, and June 1, 2020, were included and 18 studies were included in the qualitative synthesis. The ferritin level was significantly increased in severe patients compared with the level in non-severe patients [WMD 397.77 (95% CI 306.51-489.02), P < .001]. Non-survivors had a significantly higher ferritin level compared with the one in survivors [WMD 677.17 (95% CI 391.01-963.33), P < .001].(14) In another study by Qeadan et al., it was reported that out of 14,958

patients with a a valid serum ferritin level, patients with a ferritin ≥714.3 ng/mL had 3.7 (95% CI: 2.8–4.8) higher odds of in-hospital mortality compared to those with a lower ferritin value.(15)

In this study, the mean ferritin level in mild, moderate and severe categories (based on CT severity score) were 138.09 ng/ml, 310.52 ng/ml and 853.33 ng/ml respectively. There was statistically significant difference among the 3 groups with p value <0.0001. Similarly, the mean d dimer level in mild, moderate and severe categories (based on CT severity score) were 0.5 g/L, 1.15 g/L and 2.79 g/L respectively. There was statistically significant difference among the 3 groups with p value <0.0001. Our findings were consistent with the study conducted by Saeed et al., in December 2020, comprising of 902 covid 19 patients, where CT severity score was found to be positively correlated with lymphopenia, increased serum CRP, d-dimer, and ferritin levels ($p < 0.0001$).(16) Similar results were also reported by Kömürcüoğlu et al. where out of 480 hospitalised COVID 19 patients, in 277 patients who underwent HRCT thorax, a significant relationship was found between radiological scores in Thorax HRCT and lymphopenia, D-Dimer, SPO2, ferritin levels (Man Whitney U test, $p <0.01$).(17) Another study comprising of 130 patients, conducted by Yilmaz et al. also reported positive correlation between serum ferritin level and CT severity score.(18)

6.Limitations Of The Study

There are a few limitations in our study. Patients were not followed up after discharge for further progression of the disease. The association between serum d dimer levels, ferritin and ct severity score could not be assessed in all the patients.

Conclusion:-

In conclusion, COVID 19 patients can present with wide range of symptomatology. Serum biomarkers like D dimer and ferritin levels can be used as predictors of severity of covid 19 and the outcome in hospitalised patients.

References:-

1. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Disease 2019 in China. 2020;
2. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 – A systematic review. 2020;(January).
3. Asia S. COVID-19 Weekly Epidemiological Update. 2021;(February).
4. Li H, Wang J, Xu L, Zhao X, Feng J, Xu Y. Clinical analysis of 132 cases COVID-19 from Wuhan. 2020;1–5.
5. Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J. Clinical characteristics of 145 patients with corona virus disease 2019 (COVID‐19) in Taizhou , Zhejiang , China. Infection [Internet]. 2020;48(4):543–51.
6. 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. 2020;2(December 2019):1–11.
7. Mouhat B, Besutti M, Bouiller K, Grillet F, Monnin C, Ecarnot F, et al. Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. 2020;(July):1–11.
8. Hodges G, Pallisgaard J, Olsen MS, Mcgettigan P, Andersen M, Krogager M, et al. Association between biomarkers and COVID-19 severity and mortality : a nationwide Danish cohort study. 2020;
9. Clinical management Clinical management Living guidance COVID-19. 2021;(January).
10. Li K, Wu J, Wu F, Guo D, Chen L. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. 2020;55(6):1–5.
11. Manuscript A. NIH Public Access. 2015;29(1):17–24.
12. Berger JS, Kunichoff D, Adhikari S, Ahuja T, Amoroso N, Aphinyanaphongs Y, et al. Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. 2020;(October):2539–47.
13. Hussein AM, Taha ZB, Gailan A, Akram K, Qasim D, Jalal R, et al. Materials Today : Proceedings D-Dimer and Serum Ferritin as an Independent Risk Factor for Severity in COVID-19 Patients. Mater Today Proc [Internet]. 2021;(xxxx):11–3.
14. Cheng L, Li H, Li L, Liu C, Chen H, Li Y. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. 2020;(September):1–18.
15. Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic Values of Serum Ferritin and D-Dimer Trajectory in Patients with COVID-19. 2021;1–12.
16. Saeed GA, Gaba W, Shah A, Ahmed A, Helali A, Raidullah E, et al. Correlation between Chest CT Severity Scores and the Clinical Parameters of Adult Patients with COVID-19 Pneumonia. 2021;2021.

17. Komurcuoglu B, Susam S, Batum Ö. Correlation between chest CT severity scores and clinical and biochemical parameters of COVID-19 pneumonia. 2022;(June):497–503.
18. Yilmaz A, Sabirli R, Seyit M, Ozen M, Oskay A, Cakmak V. Association between laboratory parameters and CT severity in patients infected with Covid-19 : A retrospective , observational study. 2020;(January).