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Role of D-Dimer in Covid-19 pneumonia: sensitive marker of inflammation, predictor of mechanical ventilation, thromboembolic events and early marker of post covid-lung fibrosis; Prospective Multicentric, Observational, Interventional study in tertiary care setting in India

Shital Patil[1], Manojkumar Bhadake[3], Abhijit Acharya[2], Ganesh Narwade[4]

[1] *Associate Professor, Pulmonary Medicine, MIMSR Medical College, Latur-413512, Maharashtra, India*
[2] *Associate Professor, Internal Medicine, MIMSR Medical College, Latur-413512, Maharashtra, India*
[3] *Associate Professor, Pathology Department, MIMSR Medical College, Latur-413512, Maharashtra, India*
[4] *Associate Professor, Pulmonary Medicine, MIMSR Medical College, Latur-413512, Maharashtra, India*

Abstract

Introduction: Covid-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. **Materials and methods:** Multicentric, prospective, observational and interventional study included 1000 covid-19 cases confirmed with RT PCR. All cases were assessed with HRCT thorax, oxygen saturation, inflammatory marker as D-Dimer at entry point and follow up. Age, gender, Comorbidity and use BIPAP/NIV and outcome as with or without lung fibrosis were key observations. In selected cases, lower limb venous doppler and CT pulmonary angiography to rule out DVT or PTE. Statistical analysis is done by using Chi square test. **Observations and analysis:** Age (<50 and >50 years) and gender (male versus female) has significant association with D-Dimer level. [p<0.00001] & [p<0.010] respectively. CT severity score at entry point with D-Dimer level has significant correlation. [p<0.00001] D-Dimer level has significant association with duration of illness prior to hospitalization. [p<0.00001] Comorbidities have significant association with D-Dimer level. [p<0.00001] D-Dimer level has significant association with oxygen saturation. [p<0.00001] BIPAP/NIV requirement has significant association with D-Dimer level. [p<0.00001] Timing of BIPAP/NIV requirement during hospitalization has significant association with D-Dimer level. [p<0.00001] Follow-up D-Dimer titer during hospitalization as compared normal & abnormal to entry point level has significant association with post-covid lung fibrosis, deep vein thrombosis and pulmonary thromboembolism. [p<0.00001]. **Conclusion:** D-Dimer has documented very crucial role in covid-19 pneumonia in predicting severity of illness and assessing response to treatment during hospitalization and follow up titers have significant role in step-up or step-down interventions in critical care setting.

Keywords: Covid-19 Pneumonia, D-Dimer, Lung Fibrosis, Deep Vein Thrombosis, Pulmonary Embolism, Inflammatory Marker.

INTRODUCTION

The current pandemic of coronavirus disease 2019 (covid-19) caused by SARS-CoV-2, originally emerged from China, has documented 274,628,461 confirmed cases and 5,358,978 deaths globally, and 34,752,164 confirmed cases 478,007 deaths in India [1]. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Task Force on covid-19 has been established to synthesize up-to-date information on the epidemiology, pathogenesis, and laboratory diagnosis and monitoring of covid-19, as well as to develop practical recommendations on the use of molecular, serological, and biochemical tests in disease diagnosis and management [2,3].

Covid-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Although Lung is the primary target organ involvement in corona virus disease-19 (covid-19), many patients were shown pulmonary and extrapulmonary manifestations of diseases variably during first and second wave, which occurred as resultant pathophysiological effects of immune activation pathway and direct virus induced lung damage. In covid-19 pneumonia pathophysiology constitutes different pathways like immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues. Covid-19, the pandemic disease caused by infection with the novel virus, SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) can now be added to the already extensive list of conditions that may be associated with elevated D-dimer. The discovery that D-dimer may be elevated in covid-19 was first reported by physicians in Wuhan, China where the epidemic started. A study of 191 patients with covid-19, who were hospitalized in Wuhan during January 2020 at the outset of the pandemic, revealed that D-

***Corresponding author:**
Dr. Shital Patil
Associate Professor, Pulmonary Medicine, MIMSR Medical College, Latur-413512, Maharashtra, India
Email:
Drsvpatil1980@gmail.com

dimer was elevated in many of these patients and the magnitude of the elevation was greatest in those who did not survive [4].

Fibrin degradation products (FbDP) are a highly heterogeneous group of soluble fragments that appear in the circulation as a result of two simultaneous physiological processes: 1) Coagulation, resulting in the conversion of soluble fibrinogen into insoluble stabilized fibrin by the enzymes thrombin and factor XIIIa, 2) Fibrinolysis, resulting in the dissolution of the fibrin clot by the enzyme plasmin. The D-dimer fragment is the terminal product of this process [5]. A number of subsequent studies conducted around the world have confirmed that D-dimer is elevated in those with severe covid-19 and highest in those who are most critically ill and those who do not survive. Much covid-19 research over the past months has been directed at understanding the significance of D-dimer elevation and the covid-19 related coagulopathy that is presumed responsible for the elevation [4].

D-dimer has been extensively investigated for the diagnosis, monitoring, and treatment of venous thromboembolism (VTE) for which it is used routinely [6]. D-dimer levels are also elevated in conditions of chronic inflammation, such as active malignancy, rheumatoid arthritis, sickle cell disease, and asthma [7]. In the setting of covid-19, D-dimer has been reported to be higher in subjects who are critically ill or those who expire [8-12].

In present study, we have utilized D-Dimer as a basic marker in laboratory panel workup in all covid patients and analyzed as 'core marker' for assessment of coagulation status with other markers of inflammation IL-6, CRP and ferritin during follow up in all admitted patients to assess response to therapy and predictor of post-covid fibrosis, which can be promptly evaluated and treated to have successful treatment outcome.

MATERIALS AND METHODS

Multicentric, prospective, and observational study conducted during July 2020 to May 2021, in MIMSR Medical College and Venkatesh Hospital Latur India, included 1000 covid-19 cases confirmed with RT PCR, to find out role of D-Dimer in predicting severity of illness, assessing response to therapy and outcome as post-covid fibrosis & predicting DVT/PTE in covid-19 pneumonia cases admitted in critical care unit. Total 1000 cases were enrolled in study after IRB approval and written informed consent of patient.

Inclusion criteria: Covid-19 patients, confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centers, including those with comorbidities and irrespective of severity and oxygen saturation were included in the study.

Exclusion criteria: Those not willing to give consent, not able to perform D-dimer and not willing to remain in follow-up were excluded.

All study cases were undergone following assessment before enrolling in study

1. Covid-19 RT PCR test performed in all cases, if first test results were negative and radiological features clearly documenting pneumonia, we have repeated RT PCR test and enrolled all cases with positive Covid-19 RT-PCR test.

2. HRCT Thorax to assess severity of lung involvement, and categorized as Mild if score <7, moderated if score 8-15 and severe if score >15 or 15-25.

3. Clinical assessment as- vital parameters like heart rate, oxygen saturation, respiratory rate, blood pressure and documentation of respiratory adventitious sounds.

4. Laboratory parameters- complete blood counts, liver functions, blood sugar level, renal functions, ECG.

5. Viral inflammatory markers like D-Dimer, CRP, IL-6 assessed at entry point and repeated whenever required during course of illness. Normal and abnormal parameter readings were considered as per pathological laboratory standard.

6. Entry point D-Dimer titer was utilized as assessment tool of severity of illness with clinical parameters.

7. If D-Dimer analysis was normal at entry point, then D-Dimer titer was repeated on day of discharge from hospital or done during hospitalization if clinical course deteriorates.

8. If D-Dimer analysis was abnormal at entry point, we repeated on every 72 hours as follow up to assess severity, progression of illness and also titer level utilized to assess response to medical treatment.

9. In selected cases, with abnormal D-dimer or persistent tachycardia, subjected to lower limb venous doppler to rule out DVT, and or CT Pulmonary angiography to rule out pulmonary thromboembolism.

10. Follow-up HRCT thorax was done after twelve weeks or 3 months of discharge from hospital for analysis of post covid lung fibrosis in selected cases with abnormal D-Dimer level at discharge and required BIPAP/NIV during hospitalization and cases required oxygen supplementation at home.

D-Dimer titer assessment

Normal values: Normal values 70-470 mg/dL.

Interpretation of results

1. Normal: D-Dimer value up to 470 mg/L

2. Positive: value above 470 mg/dL

3. Significant: two-fold raised D-Dimer level

4. Highly significant: four-fold raised D-Dimer level

5. Follow up significance: values raised or decreased in two-to-four-fold change

The statistical analysis was done using chi-squared test. Significant values of $\chi 2$ were seen from probability table for different degree of freedom required. *P* value was considered significant if it was below 0.05 and highly significant in case if it was less than 0.001.

Observations and analysis

In present study, 1000 covid-19 pneumonia cases confirmed by covid-19 RT PCR, males were 650/1000 and females were 350/1000, age >50 were 600 cases and age <50 were 400 cases.

CT severity score at entry point with D-Dimer level has significant correlation in covid-19 pneumonia cases [p<0.00001] [Table 1].

Table 1: Correlation of CT severity (at entry point) and D-Dimer in covid-19 cases (n=1000)

CT severity	Normal D-Dimer (n=320)	Abnormal D-Dimer level (n=680)	Analysis
<8 score (n=300)	190	110	Chi test value 224.87

9-15 (n=300)	90	210	p<0.00001
>15 (n=400)	40	360	

D-Dimer level has significant association with duration of illness in covid-19 pneumonia cases. [p<0.00001] [Table 2].

Table 2: Duration of illness (Doi) at entry point during hospitalization and D-Dimer level in covid-19 pneumonia cases (n=1000)

Duration of illness	Normal D-Dimer (n=320)	Abnormal D-Dimer (n=680)	Analysis
<7 days (n=340)	30	310	Chi test value 185.65 p<0.00001
8-15 days (n=460)	160	300	
>15 days (n=200)	130	70	

Significant association in D-Dimer and COIVD-19 pneumonia has been documented with variables like age, gender, diabetes mellitus, IHD, Hypertension, COPD, Obesity [p<0.00001] [Table 3].

Table 3: Other variables and D-Dimer level in Covid-19 Pneumonia cases (n=1000)

COVID-19 RT PCR Positive (n=1000)	D-Dimer level Normal (n=320)	D-Dimer level Abnormal (n=680)	Chi Test Value and P Value
Age >50 years (n=600)	140	460	χ2=51.77 p< 0.00001
Age <50 years (n=400)	180	220	
Male gender (n=650)	190	460	χ2=6.5 p< 0.010
Female gender (n=350)	130	220	
Diabetes mellitus (n=600)	150	450	χ2=33.77 p< 0.00001
Without diabetes (n=400)	170	230	
Hypertension (n=210)	160	50	χ2=238.55 p< 0.00001
Without Hypertension (n=790)	160	630	
COPD (n=150)	100	50	χ2=97.46 p< 0.00001
Without COPD (n=850)	220	630	
IHD (n=200)	110	90	χ2=60.77 p< 0.00001
Without IHD (n=800)	210	590	
Obesity (n=160)	20	140	χ2=33.28 p< 0.00001
Without obesity (n=840)	300	540	

D-Dimer level has significant association with oxygen saturation in covid1-19 pneumonia cases. [p<0.00001] [Table 4].

Table 4: Oxygen saturation at entry point and D-Dimer level in Covid-19 pneumonia cases (n=1000)

Oxygen saturation	Normal D-Dimer level (n=320)	Abnormal D-Dimer level (n=680)	Analysis
>90% (n=210)	110	100	Chi test value 60.37 p<0.00001
75-90% (n=490)	150	340	
<75% (n=300)	60	240	

BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with D-Dimer level. [p<0.00001] [Table 5].

Table 5: Correlation of BIPAP use with D-Dimer level in covid-19 pneumonia cases (n=1000)

BIPAP/NIV	Normal D-Dimer (n=320)	Abnormal D-Dimer level (n=680)	Analysis
BIPAP/NIV required (n=600)	155	445	Chi test value 26.21 p<0.00001
BIPAP/NIV not required (n=400)	165	235	

Timing of BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with D-Dimer level. [p<0.00001] [Table 6].

Table 6: BIPAP/NIV initiation time at entry point and D-Dimer level covid-19 pneumonia cases (n=600)

BIPAP Used (n=600) With Duration Of Illness	Abnormal D-Dimer level (n=290)	Four-fold raised D-Dimer level (n=310)	Analysis
Entry point <1days (n=180)	110	70	Chi test value 31.30 p<0.00001
3- 7 days (n=310)	150	160	
After 7 days (n=110)	30	80	

Follow-up D-Dimer titer during hospitalization as compared to entry point abnormal D-Dimer has significant association in post-covid lung fibrosis [p<0.00001] [Table 7].

Table 7: Abnormal D-Dimer level at entry point (n=680) and follow up and its correlation with post-covid lung fibrosis

Post-covid Covid pneumonia fibrosis	D-Dimer titer increased/abnormal at entry point (n=400)	D-Dimer titer fourfold increased during follow up (n=280)	Analysis
Pulmonary fibrosis present (n=210)	40	170	Chi test value 198.45 p<0.00001
Pulmonary fibrosis absent (n=470)	360	110	

Follow-up D-Dimer titer during hospitalization as compared to entry point normal D-Dimer has significant association in post-covid lung fibrosis [p<0.00001] [Table 8].

Table 8: Normal D-Dimer level (n=320) at entry point and follow up and its correlation with post-covid lung fibrosis

Post-Covid Covid Pneumonia Fibrosis	D-Dimer Normal at Entry Point and Remained less Than Fourfold (n=120)	D-Dimer Titer Fourfold Increased During Follow up (n=200)	
Pulmonary fibrosis present (n=40)	5	35	Chi test value 12.19 p<0.00048
Pulmonary fibrosis absent (n=280)	115	165	

Follow-up D-Dimer titer during hospitalization as compared to entry point abnormal D-Dimer has significant association in presence of deep vein thrombosis [p<0.00001] [Table 9].

Table 9: Abnormal D-Dimer level at entry point (n=680) and its correlation with follow up titer with deep vein thrombosis

DVT (Deep Vein Thrombosis)	D-Dimer Titer Increased/Abnormal at Entry Point (n=400)	D-Dimer Titer Fourfold Increased During Follow up (n=280)	Analysis
DVT present (n=210)	40	170	Chi test value 198.45 p<0.00001
DVT absent (n=470)	360	110	

Follow-up D-Dimer titer during hospitalization as compared to entry point normal D-Dimer has significant association with pulmonary thromboembolism [p<0.00001] [Table 10].

Table 10: Normal D-Dimer level (n=320) at entry point and its correlation with follow up titer with pulmonary thromboembolism

PTE (Pulmonary Embolism)	D-Dimer Normal at Entry Point and Remained less Than Fourfold (n=120)	D-Dimer Titer Fourfold Increased During Follow up (n=200)	
PTE present (n=40)	5	35	Chi test value 12.19 p<0.00048
PTE absent (n=280)	115	165	

DISCUSSION

Correlation of CT severity (at entry point) and D-Dimer in covid-19 cases

In present study, CT severity score at entry point with D-Dimer level has significant correlation in covid-19 pneumonia cases, score <8, 8-15 and >15 documented normal and abnormal D-Dimer level as in 190/110, 90/210 and 40/360 respectively of total 1000 study cases [p<0.00001] We observed that CT severity is best visual assessment and indirect marker of inflammation which can be collaborated with D-dimer, and as CT severity score increases, D-dimer level also increases, which is a marker of coagulation abnormality. Numerous studies [13-20]. have documented similar observation.

Duration of illness (Doi) at entry point during hospitalization and D-Dimer level in COVID-19 pneumonia cases (n=1000)

In present study, D-Dimer level has significant association with duration of illness in covid-19 pneumonia cases, Doi <7 days, 8-15 days and >15 days of onset of symptoms documented normal and abnormal D-Dimer levels in 30/310, 160/300 and 130/70 cases respectively [p<0.00001] As duration of illness in COVID-19 pneumonia increases, ongoing inflammation increases and having abnormal D-Dimer level due to abnormal coagulation cascade stimulation. Studies by various author [14-26]. have documented similar observation. We have also documented that; entry point abnormal D-Dimer with other inflammatory markers like CRP and IL-6 with duration of illness more than a week or 7 days is predictor of prolonged hospital stay with requirement of ventilatory requirement in intensive care unit. Similar observation has been documented in various studies [21-25].

Correlation of BIPAP use with D-Dimer level in covid-19 pneumonia cases (n=1000)

In present study, BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with D-Dimer level; cases received BIPAP/NIV during hospitalization were documented normal and abnormal D-Dimer level in 155/445, 165/235 cases respectively [p<0.00001] We have documented positive correlation with hypoxia and resulting in need of ventilatory support during hospitalization with abnormal D-Dimer level. Similarly various authors [14-25]. have observed that abnormal or high D-dimer is predictor of poor outcome and these patients require aggressive interventions like BIPAP/NIV, mechanical ventilation or ECMO in due course and persistent high level denotes higher chances of mortality.

Correlation of Oxygen saturation at entry point and D-Dimer level in Covid-19 pneumonia cases (n=1000)

In present study, D-Dimer level has significant association with oxygen saturation in covid-19 pneumonia cases; cases with oxygen saturation >90%, 75-90%, and <75% observed as normal and abnormal D-Dimer level in 110/100, 150/340 and 60/240 cases respectively [p<0.00001] We have documented positive correlation with hypoxia at entry point during hospitalization and abnormal D-Dimer level which is similar to studies by various authors [14-20]. Low Oxygen saturation or hypoxia is independent predictor of poor outcome in covid-19 pneumonia, as hypoxia is trigger for deranged coagulation secondary to increase in hypoxia-inducible transcription factor which will increase D-Dimer level, Numerous studies [21-25]. have documented similar observation.

Correlation of BIPAP/NIV initiation time at entry point and D-Dimer level covid-19 pneumonia cases (n=600)

In present study, Timing of BIPAP/NIV requirement during course of covid-19 pneumonia in critical care setting has significant association with D-Dimer level; cases received BIPAP/NIV at entry point <1 day, 3-7 days and after 7 days of hospitalization were documented significance in four-fold raised D-Dimer level in 110/70, 150/160 and 30/80 cases respectively [p<0.00001] We have documented positive correlation with hypoxia and resulting in need of ventilatory support during hospitalization with abnormal D-Dimer level. Cases with high D-dimer would have required BIPAP/NIV early as compared with normal to slightly raised D-Dimer level, which is in correlation with studies [14-20]. documented similar observation.

Other important observation in this study

Correlation of Abnormal D-Dimer level at entry point (n=680) and follow up and its correlation with post-covid lung fibrosis, Deep vein thrombosis and pulmonary Thromboembolism:

In present study, Follow-up D-Dimer titer during hospitalization during hospitalization as compared to entry point abnormal D-Dimer has significant association in post-covid lung fibrosis [p<0.00001] i.e., D-Dimer at entry point to four-fold raised cases in presence or absence of pulmonary fibrosis were 40/170 and 360/110 cases respectively. Follow-up D-Dimer titer during hospitalization as compared to entry point abnormal D-Dimer has significant association in presence of deep vein thrombosis [p<0.00001] i.e., D-Dimer at entry point to four-fold raised cases in presence or absence of deep vein thrombosis were 40/170 and 360/110 cases respectively. We have observed that ongoing inflammation is the key for rise of D-dimer level irrespective of CT severity score as mild cases were also having significant rise in D-Dimer level as compared to advanced CT Severity, thus it will help in predicting progression of disease in due course during hospitalization and aggressive steps to be taken during management of these cases. Numerous studies [20-31]. have documented similar risk of poor outcome and adverse lung outcome as increased D-Dimer is an indication of severe inflammatory response and resulted in lung fibrosis in follow up of survivors of COVID-19 pneumonia.

Correlation of Normal D-Dimer level (n=320) at entry point and follow up and its correlation with post-covid lung fibrosis, Deep vein thrombosis and pulmonary Thromboembolism:

In present study, Follow-up D-Dimer titer during hospitalization during hospitalization as compared to entry point normal D-Dimer has significant association in post-covid lung fibrosis [p<0.00001] i.e., D-Dimer at entry point to four-fold raised cases in presence or absence of pulmonary fibrosis were 5/35 and 115/165 cases respectively. In this study, a small fraction of nonsevere patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, health care institutions should also pay close attention to the mild patients, identify progressors early, and provide appropriate treatment to reduce mortality. Follow-up D-Dimer titer during hospitalization as compared to entry point normal D-Dimer has significant association with pulmonary thromboembolism [p<0.00001] i.e., D-Dimer at entry point to four-fold raised cases in presence or absence of pulmonary thromboembolism were 5/35 and 115/165 cases respectively. Authors in various studies [14-25]. have documented similar observation.

Correlation of other variables and D-Dimer level in Covid-19 Pneumonia cases

In present study, age of patient i.e., <50 years and >50 years has significant association in covid-19 cases with normal and abnormal D-Dimer level [p<0.00001]. we have also documented gender of included cases has significant association in covid-19 cases with normal and abnormal D-Dimer level [p<0.010] documented significant differences in age, gender, comorbidities, respiratory symptom, neutrophil count, lymphocyte count, eosinophil count, and D-Dimer level. Studies by various author [14-26]. have documented similar observation.

In present study, comorbidities as Diabetes mellitus, COPD, Hypertension, IHD and obesity has documented significant association in covid-19 cases with normal and abnormal D-Dimer level at entry point. [p<0.00001] Numerous studies [14-31]. have documented similar observation.

CONCLUSION

D-Dimer is easily available, and universally acceptable inflammatory marker, which has documented very crucial role in covid-19 pneumonia in predicting severity of illness, and assessing response to treatment during hospitalization. D-Dimer has important role during interventions in intensive care unit, as follow up titers have significant role in step-up or step-down interventions in critical care setting. Correlating D-dimer with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome.

D-Dimer titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial D-Dimer has progressed to critical course and we have documented follow up titers has played crucial role with other inflammatory markers, and many times in second week of illness rising titers indicates ongoing coagulation abnormality, worsening of pneumonia, and increased inflammatory burden which will help to target therapy accordingly. D-Dimer follow-up titer can help in predicting progression of covid pneumonia, and assessing risk of post covid lung fibrosis.

Conflict of Interest

None declared.

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