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Correlating inflammatory markers with clinical profile and final outcome in patients with Covid 19 admitted to a tertiary care setup

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Abstract

Background:The ongoing worldwide Coronavirus Disease 2019 (COVID-19) pandemic has posed a huge threat to global public health[1]. COVID-19 represents a spectrum of clinical severity ranged from asymptomatic to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death. Therefore, full monitoring the severity of COVID-19 and effective early intervention are the fundamental measures for reducing mortality.

Accumulating evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19 [3]. Inflammatory responses induce the release of cytokines and chemokines. These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations[4]. Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality. But the results are inconclusive, with various studies giving different results. Our study intends to correlate levels of inflammatory markers with severity of Covid 19 infection and its final outcome.

Methods and materials:This is a retrospective study which includes 818 patients admitted to our hospital during the second wave of Covid 19 pandemic with confirmed Covid 19 infections by RTPCR. Admitted patients included mild disease to severe Covid 19 infections. Those patients who have received standardized treatment according to hospital protocol were included in the study. Data was collected and entered in pre-designed proforma. Results obtained will be compiled in excel sheet and will be analyzed statistically.

Results: Total of 818 patients were admitted to our hospital between May to July 2021. Of which 341 had mild disease, 241 had moderate disease, 237 patients had severe disease on presentation.While looking into the final outcome of the disease, 175 patients died due Covid 19 pneumonia or its complication, 52 patients were discharged with oxygen support. Of 237 patients with severe disease 150 patients had CRP levels >75mg/dl. Of 175 patients who died, 121 had CRP levels >75 mg/dl. Of 237 patients with severe disease, 122 of them had D-dimer >1000 ng/ml. Of 175 patients who died with Covid 19, 103 of them had d-dimer levels >1000 ng/ml.CRP and D-dimer were significantly increased in patients with severe disease and in patients who died of Covid 19 with p value <0.0001.

Conclusion: Increasing levels of CRP and D-dimer were good predictors of severe disease in Covid 19. Also, increased levels of CRP and d-dimer were suggestive of poorer outcome of the disease in terms of mortality and morbidity in Covid 19 infection.

Keywords: Covid 19, CRP, D-dimer, disease severity

Introduction

The coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which is responsible for the disease COVID-19 (coronavirus disease 2019), has infected over 27 million people and has caused more than 5,393,000 deaths globally, as of December 2021. In India, around 3.48 Crore people are infected with Covid 19 and total of 4.78 lakh people have died due to Covid 19 infection.

Corona virus disease 2019 (COVID-19) pandemic that spread to the entire world and crumpled the world's economy. It exposed the loop holes that existed in our public health system. This novel human corona virus was first identified in Wuhan region of China in December 2019. This virus is a single-stranded ribonucleic acid (RNA) betacoronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as it shares an approximately 79% similarity at nucleotide level with severe acute respiratory syndrome coronavirus (SARS-CoV)[2].

SARS-CoV-2 spreads primarily via respiratory droplets that are transmitted from person to person who are in close contact. The median incubation period is around 5.4 days. Clinically its symptoms vary from asymptomatic, mild respiratory infection to severe acute respiratory distress including death.

About 20% of people infected with Covid 19 develop severe disease[7].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. From what is known at the moment, patients with COVID-19 disease who have comorbidities, such as hypertension or diabetes mellitus, are more likely to develop a more severe course and progression of the disease. Furthermore, older patients, especially those 65 years old and above who have comorbidities and are infected, have an increased admission rate into the intensive care unit (ICU) and mortality from the COVID-19 disease6. But we have seen that even young adults with no comorbidities have developed severe disease including death. Therefore, it becomes necessary to monitor patients and identify those who are going to develop severe disease so early intervention could be done to reduce the mortality and morbidity.

Thus, understanding the pathogenesis of the disease becomes necessary. Studies suggest an underlying florid inflammatory response to the virus as a pivotal role in manifesting severe disease[3]. Inflammatory responses are triggered by rapid viral replication of SARS-CoV-2 and cellular destruction that recruit macrophages and monocytes and induce the release of cytokines and chemokines. These cytokines and chemokines then attract immune cells and activate immune responses, leading to cytokine storms and aggravations[4].As a result, various inflammatory markers rise in response to the disease. Increasing levels of 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 associated with the high risks of the developing severe disease[5]. But the results are inconclusive, with various studies giving different results.

The underlying inflammatory flare in Covid 19 was found to be associated with microvascular thrombosis resulting in ARDS and various extrapulmonary manifestation like, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic complications. This is attributed to direct viral toxicity, underlying endothelial dysfunction and thromboinflammation leading to microcirculation dysfunction leading to multiorgan dysfunction. Increasing levels of markers of coagulation like D-dimer hence helps to identify patients who are going to develop procoagulant state.

Here in our study we correlated inflammatory markers like CRP and D-dimer levels with

severity of the disease and also with its final outcome in the form of death or oxygen dependency during discharge.

Aims and Objectives

1. To correlate levels of CRP and D-dimer with severity of Covid 19 infection.
2. To correlate levels of CRP and D-dimer with final outcome of Covid 19 infection.

Methods and Materials

This is a retrospective study which includes 818 patients admitted to our hospital during the second wave, (between May to July 2021) of Covid 19 pandemic with confirmed Covid 19 infections by RTPCR. Admitted patients includes mild to severe disease caused by Covid 19 infections. Those patients who have received standardized treatment according to hospital protocol were included in the study. Those patients who could not be given standardized treatment because of their underlying comorbidities were excluded from the study. Data was collected and entered in pre-designed proforma. This included details of the patient like existing comorbidities, symptoms and vitals during admission, details of necessary investigation done, treatment received in the hospital and the final outcome of the patient. Results obtained was compiled in excel sheet and analyzed statistically.

Inclusion criteria

1. Patient admitted with confirmed Covid 19 infections by RTPCR.
2. Patients who have received standardized treatment as per protocol.

Exclusion criteria

Those not eligible to receive standardized protocol due to underlying comorbidities.

Statistical analysis

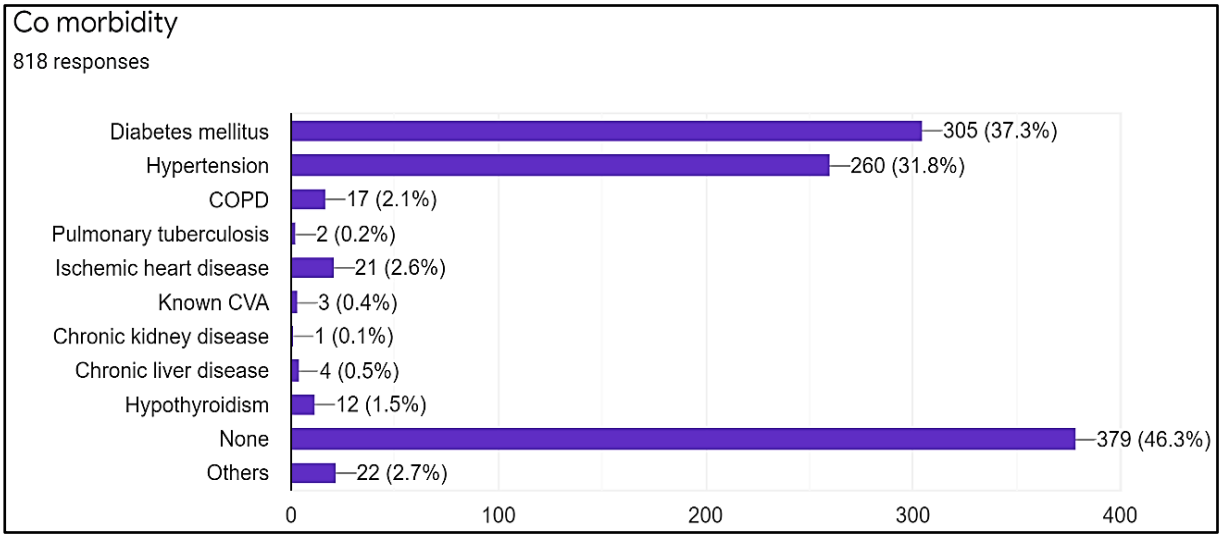
Data collected was entered in Microsoft excel sheet. SPSS software version 21 was used for statistical analysis. Data were analyzed using Chi-square test to determine the association between the variables. A p-value of <0.01 was considered as significant.

Results

Total of 818 patients were admitted to Subbaiah institute of medical science, Shivamogga, during the second wave (between May to July 2021) of Covid 19 pandemic. Of which 538 were male patients and 280 were female.

Age wise distribution showed 119 (14.5%) were between 31-40 years, 179 (21.9%) patients were between 41-50 years, 190 (23.2%) patients were between 51-60 years. 174 (21.3%) were between 61-70 yrs. This suggests that majority of patients admitted were aged less 60yrs which goes against the fact that Covid 19 was more symptomatic in those aged more than 60 yrs.

Of all patients admitted, 305 were known type 2 diabetes mellitus, 260 patients known hypertensive, 21 were suffering from ischemic heart disease. Details of comorbidities is shown in bar chart.



Of the 818 patients admitted 341 had mild disease, 241 had moderate disease, 237 patients had severe disease on presentation.The most common symptom at presentation was cough (80.8%) followed by fever (74.8%). Breathlessness was seen in 35.3% patients and myalgia was seen in 21.3% of them. Majority of patients 63% (523) presented to the hospital within 3 to 7 days of symptom onset.

Of final outcome of the disease, 175 patients died due Covid 19 pneumonia or its complication, 52 patients were discharged with oxygen support.

Table 1: Final_outcome_of_the_disease by Severity_of_covid_19_infection

Final outcome of the disease	**Severity of Covid 19 infection**			
Frequency Col Pct.	**Mild [SpO2>94%]**	**Moderate [SpO2 94-90%]**	**Severe [SpO2 <90%]**	**Total**
Death due to Covid 19 or it's complications	4 1.18	18 7.47	153 64.56	175
Discharged with home oxygenation	10 2.94	17 7.05	25 10.55	52
Discharged with no oxygen support	326 95.88	206 85.48	59 24.89	591
Total	340	241	237	818

While correlating CRP with disease severity, it was seen that higher levels of CRP was seen with increasing severity of the disease and this was proved to be statistically significant. Of 237 patients with severe disease 150 patients had CRP levels >75mg/dl. In mild disease out of 340 patients only 51 had CRP levels >75mg/dl.

Table 2: CRP_Levels by Severity_of_covid_19_infection

CRP Levels	**Severity of Covid 19 infection**			
FrequencyCol Pct.	**Mild [SpO2 >94%]**	**Moderate [SpO2 94-90%]**	**Severe [SpO2 <90%]**	**Total**
0-10 mg/dl	111 32.65	44 18.26	15 6.33	170
11-50 mg/dl	142 41.76	68 28.22	45 18.99	255
51-75 mg/dl	36 10.59	48 19.92	27 11.39	111
76-125 mg/dl	34 10.00	51 21.16	76 32.07	161

>125mg/dl	17 5.00	30 12.45	74 31.22	121
Total	340	241	237	818
Chi square test Chi square value=183.12 P value =<0.0001				

While correlating CRP with final outcome of the disease again we found that higher levels of CRP was seen in patients who died due to Covid 19 disease. Of 175 patients who died, 121 had CRP levels >75 mg/dl. Of 591 patients who got discharged from hospital without oxygen support only 137 of them had CRP >75mg/dl. Also the levels of CRP was higher in patients who were dependent on oxygen during discharge from hospital when compared to those who got discharged without oxygen support. Both the values were found to be statistically significant with p value of <0.0001. This suggest that higher the CRP levels poorer the prognosis of the disease.

Table 3: CRP_Levels by Final_outcome_of_the_disease

CRP Levels	**Final outcome of the disease**			
Frequency Col Pct.	**Death due to Covid 19 or it's complications**	**Discharged with home oxygenation**	**Discharged with no oxygen support**	**Total**
0-10 mg/dl	4 2.29	8 15.38	158 26.73	170
11-50 mg/dl	29 16.57	10 19.23	216 36.55	255
51-75 mg/dl	21 12.00	10 19.23	80 13.54	111
76-125 mg /dl	55 31.43	13 25.00	93 15.74	161
>125mg /dl	66 37.71	11 21.15	44 7.45	121
Total	175	52	591	818
Chi square test Chi square value=163.82 P value =<0.0001				

While comparing CRP with duration of hospital stay we found that higher levels of CRP was seen in patients with longer hospital stay due to increased severity and this was found to be statistically significant.

Table 4: CRP_Levels by Duration_of_hospital_stay

CRP Levels	**Duration of hospital stay**				
Frequency Col Pct.	**5 to 7 days**	**7 to 14 days**	**< 5days**	**> 2 weeks**	**Total**
0-10 mg/dl	77 26.01	72 22.09	17 11.04	4 9.52	170
11-50 mg/dl	109 36.82	103 31.60	35 22.73	8 19.05	255
51-75 mg/dl	38 12.84	43 13.19	25 16.23	5 11.90	111
76-125 mg /dl	44 14.86	67 20.55	38 24.68	12 28.57	161
>125mg /dl	28 9.46	41 12.58	39 25.32	13 30.95	121

Total	296	326	154	42	818
Chi square test Chi square value=56.34 P value =<0.0001					

We also compared D-dimer levels with disease severity and final outcome. We found that higher levels of D-dimer were seen in patients with moderate to severe pneumonia. Also, D-dimer levels were higher in those who died due to Covid 19 disease. It was also found that D-dimer levels were higher in patients with severe disease who got discharged on oxygen support than in those who were weaned off from oxygen before discharge. This suggest that higher D-dimer levels correlatedwith higher mortality and morbidity from Covid 19 infection.

Table 5: D_Dimer_levels by Severity_of_covid_19_infection

D Dimer levels	**Severity of Covid 19 infection**			
Frequency Col Pct.	**Mild [SpO2 >94%]**	**Moderate [SpO2 94 - 90%]**	**Severe [SpO2 <90%]**	**Total**
<500 ng/ml	182 53.53	104 43.15	52 21.94	338
500-1000 ng/ml	88 25.88	69 28.63	63 26.58	220
1001-2000 ng/ml	51 15.00	32 13.28	27 11.39	110
2001-3000 ng/ml	10 2.94	7 2.90	15 6.33	32
3001-4000 ng/ml	6 1.76	14 5.81	11 4.64	31
4001-5000 ng/ml	0 0.00	3 1.24	10 4.22	13
>5000 ng/ml	3 0.88	12 4.98	59 24.89	74
Total	340	241	237	818
Chi square test Chi square value= 158.63 P value =<0.0001				

Table 6: D_Dimer_levels by Final_outcome_of_the_disease

D Dimer levels	**Final outcome of the disease**			
Frequency Col Pct.	**Death due to Covid 19 or it's complications**	**Discharged with home oxygenation**	**Discharged with no oxygen support**	**Total**
1001-2000ng/ml	22 12.57	9 17.31	79 13.37	110
2001-3000 ng/ml	13 7.43	1 1.92	18 3.05	32
3001-4000 ng/ml	6 3.43	6 11.54	19 3.21	31
4001-5000 ng/ml	3 1.71	3 5.77	7 1.18	13
500-1000 ng/ ml	44 25.14	14 26.92	162 27.41	220
<500 ng/ml	28 16.00	17 32.69	293 49.58	338
>5000 ng/ml	59 33.71	2 3.85	13 2.20	74

Total	175	52	591	818
Chi square test Chi square value= 211.01 P value =<0.0001				

Discussion

A retrospective study was conducted involving 818 Covid 19 patients admitted to our hospital during the second wave of pandemic. Patients were categorized into mild moderate and severe disease according to Spo2 and respiratory rate proposed by the ministry of health, Government of India. Details of the patients which included their age, previous comorbidities, symptoms and its duration of onset was noted. Details of treatment given was also documented. Patients who were given treatment according to standardized hospital protocol were included in the study. Patients who did not receive treatment according to the protocol were excluded from the study. Patients CRP and D-Dimer levels were entered. Final outcome of the disease in form death due to Covid 19 or its complication, discharge from hospital with oxygen support and discharge without oxygen support were noted.

The most common symptom at presentation was cough (80.8%) followed by fever (74.8%). Breathlessness was seen in 35.3% patients and myalgia was seen in 21.3% of them. Majority of patients 63% (523) presented to the hospital within 3 to 7 days of symptom onset.

While correlating CRP with disease severity we found that CRP levels proportionately increased in moderate and severe disease. Of 237 patients with severe disease 150 patients had CRP levels >75mg/dl. In mild disease out of 340 patients only 51 had CRP levels >75mg/dl. This found to be statistically significant with p value <0.0001. This finding was similar to studies like Gong, J., Dong, H., Xia, QS. *etal*. were they found CRP increased in severe disease with cutoff value of 30[8]. Another meta-analysis was conducted by Ji Pan MD et al. where fifty-six studies involving 8719 COVID-19 patients was done to find the association of inflammatory markers with severe disease, they found that inflammatory markers increased with severe disease when compared to mild disease[9]. In another study by Jain P et al. where they studied 63 patients and compared their inflammatory markers with disease severity, they found that CRP levels were significantly increased in patients who had severe disease[10].

We also correlated CRP levels with final outcome of the disease. We found that CRP was significantly increased in patients who died due to Covid 19. Of 175 patients who died, 121 had CRP levels >75 mg/dl. Of 591 patients who got discharged from hospital without oxygen support only 137 of them had CRP >75mg/dl. Even in those who survived from severe Covid 19 it was found that CRP levels (24 out of 52 patients) was significantly increased in patients who got discharged from hospital with oxygen support than in those who got discharged without oxygen support, thus suggesting that high levels of CRP correlating longer morbidity from the disease.

While comparing D-dimer levels, of 237 patients with severe disease 122 of them had D-dimer >1000 ng/ml. Of 175 patients who died with Covid 19, 103 of them had d-dimer levels >1000 ng/ml. This was similar to study by LitaoZang*et al*. [11]. Where out of 343 patients enrolled in the study, 67 patients had D-dimer ≥2.0 µg/mLand 267 patients D-dimer <2.0 µg/mL on admission. 13 deaths occurred during hospitalization. Patients with D-dimer levels ≥2.0 µg/mL had a higher incidence of mortality when comparing with those who with D-dimer levels <2.0 µg/mL. In another study by Poudel A *et al*. [12]182 patients were included in the study out of which 34(18.7%) died during the hospital stay. In them D-dimer levels among surviving patients was 1.067 µg/ml (±1.705 µg/ml), whereas that among patients who died was 3.208 µg/ml (±2.613 µg/ml). Thus, suggesting that higher levels of D-dimer on admission were suggestive of higher mortality.

Conclusion

Increasing levels of CRP and D-dimer were good predictors of severe disease in Covid 19. Also, increased levels of CRP and d-dimer were suggestive of poorer outcome of the disease in terms of mortality and morbidity in Covid 19 infection.

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