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Analysis of Clotting Factors in COVID 19: A Study in Indian Patients in a Tertiary Hospital

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Coronavirus 2019(COVID 2019) is a global pandemic and may trigger coagulation dysfunction with extensive micro thrombosis. This study was conducted to evaluate the basic coagulation parameters in symptomatic patients with and without SARI in COVID.It was a prospective comparative cross sectional study to study the prognostic role of these markers in patients with and without SARI (severe acute respiratory illness) and survivors versus non survivors. Demographic characteristics , detailed medical history and platelets, prothrombin time (PT),activated thromboplastin time (APTT), fibrinogen and D dimer was recorded and analysed in both these groups. The independent group t-test and Mann -Whitney U test was used to analyse continuous variables. ROC was plotted for significant variables to obtain area under curve. The average PT for survivors was 14.6s and non survivors was 29.4s and the difference statistically significant. The area under curve for PT was 0.751 and at a cut off value of 13s had a sensitivity of 75% and specificity of 62.5% for predicting severe COVID with SARI. The median value for aPTT for non survivors was 35.5 (IQR 32.5-42.1) and for survivors it was 31.9 (IQR 29.5-35.7) and was significant. The mean values of D dimer for patients without and with SARI was 384 and 2168 mcg/ml and the difference was statistically significant (p=0.00). The D dimer test was the single most test distinguishing survivors and non survivors with an AUC of 0.844.The levels of fibrinogen and CRP was higher in patients with severe COVID and was statistically significant (p=0.001) and (p=0.028).The platelet count was lower in patients with severe COVID but difference was not statistically significant. The basic coagulation markers have a prognostic significance in treatment of COVID atients with and without SARIp.

Keywords: COVID 19; Coagulation Profile; D dimer; SARI; aPTT; PT,2.

Coronaviruses are enveloped nonsegmented positive stranded RNA viruses belonging to the family Coronaviridae and the order Nidovirales.[4] The virus spreads through direct contact of infected surfaces or through human to human contact through air borne droplet spread.[5,6] The virus has a mean incubation period of 5.2 days.[7] Most common symptoms include nausea, vomiting, fever, fatigue, dry cough, dyspnoea, myalgia, diarrhea, sore throat, rhinorrhea and chest pain.[8,9,10]Increased mortality in COVID patients is related to severe symptoms like pneumonia, acute respiratory distress syndrome and multi organ failure.[11,12] In severe cases, patients may develop acute respiratory distress syndrome (ARDS), with coagulation predominant-type coagulopathy. [13]

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The coronavirus causing COVID-19 may trigger coagulation dysfunction because it induces abundant release of pro-inflammatory cytokines in various tissues, which can lead to systemic inflammatory response syndrome that damages the microvascular system and thereby activates the coagulation system, leading to generalised small vessel vasculitis and extensive microthrombosis1.[14,15] Patients with severe COVID-19 may be at high risk of venous thromboembolism, which may be present in up to 25% of such patients.[16] Risk may be exacerbated by the dehydration due to fever and diarrhea, hypotension, and prolonged bed rest characteristic of the disease, all of which are risk factors for coagulation.[17]Chinese studies have revealed markedly prolonged PT/APTT and elevated D dimer in nonsurvivors in comparision to COVID 19 survivors.[13,18] The coagulation parameters have not been completely reported in patients with and without SARS in Indian literature so far. Hence this research project was undertaken to ascertain the differences in coagulation parameters in symptomatic patients with and without SARI.

Aims and objectives

1. To evaluate the basic coagulation parameters in symptomatic patients with and without SARI
2. To study the prognostic role of the basic coagulation parameters in both the clinical forms of disease.

MATERIALS AND METHODS

This study was a prospective comparative cross sectional study which was undertaken in COVID patients admitted to Father Muller Medical College Hospital over a period of one year from April 2020- April 2021. The Institutional Ethics Committee clearance and prior written informed consent was obtained from the study participants.

The sample size was 96 (48 in each group)

Inclusion criteria

Adult COVID patients admitted to ward and ICU of this hospital with symptoms of nausea, vomiting, fever, fatigue, dry cough, dyspnoea, myalgia, diarrhea, sore throat, rhinorrhea and chest pain.

Exclusion criteria

Asymptomatic COVID patients, pregnant COVID patients and paediatric COVID patients.

At the time of admission to the hospital, blood sample was collected for platelets, prothrombin time (PT), activated thromboplastin time (APTT), fibrinogen and D dimer. Demographic characteristics, detailed medical history and basic coagulation was recorded and was analysed. Platelet analysis was done in Beckman Coulter LH 750. PT, APTT and fibrinogen was analysed in ACL TOP 500 and ACL TOP 300.D dimer was analysed by an automated latex enhanced immunoassay on the ACL TOP.

Table 1. Group statistics

	Moderate Vs Severe Cases	N	Mean	Std. Deviation	Std. Error Mean
PT	Moderate	48	12.8417	3.37190	.48669
	Severe	48	21.3104	31.41860	4.53488
INR	Moderate	48	1.1438	.29556	.04266
	Severe	48	1.8483	2.72371	.39313
aPTT	Moderate	48	37.8875	35.36448	5.10442
	Severe	48	42.3188	38.89234	5.61363
Fibrinogen	Moderate	48	458.1667	166.26732	23.99862
	Severe	48	621.4583	286.98869	41.42325
Platelet	Moderate	48	265770.8333	124442.9699	17961.79554
	Severe	48	198958.3333	130473.9247	18832.28889
DDimer	Moderate	48	382.5417	492.35197	71.06489
	Severe	48	2168.2083	3320.43931	479.26413
CRP	Moderate	48	46.6608	60.04235	8.66637
	Severe	48	112.7206	123.35552	17.80484

The COVID patients was divided into 2 groups according to presence or absence of severe SARI requiring ICU care The clotting factors was compared between these 2 groups of patients and also survivors and non survivors . The case definition of severe SARI was defined as those patients requiring ICU care with saturation less than 90 % on room air requiring non-invasive or invasive ventilation.

Statistical analysis

The sample size of 96 was calculated based on the standard deviation 151 of fibrinogen in admitted COVID patients and standard deviation of 83 in outpatient (in reference to previously done study), mean difference of 70, alpha error 5% for 80% power, 2 sided test, sample size required for each group is 48.[19] This was calculated using Master 2 software, CMC, Vellore.

Data was analysed using unpaired t test if the results follow normal distribution or else Mann Whitney test will be used. $P<0.05$ is considered to be significant. Data was analysed using SPSS version 20.

Statistical analysis

Continuous variables were expressed as mean and SD or median and IQR The independent group t test was used to analyse normally distributed continuous variables, and the Mann-

Table 2. Group statistics

	Non Survivor Vs Survivor	N	Mean	Std. Deviation
PT (survivor Vs Nopn Survivor)	Survivors	80	14.6100	13.11189
	Non Survivors	16	29.4063	46.29603
INR (Survivor Vs Non Survivor	Survivors	80	1.2924	1.13967
	Non Survivors	16	2.5144	4.01809
aPTT (Survivor Vs Non Survivor	Survivors	80	35.7925	27.59943
	Non Survivors	16	61.6563	63.9037
Fibinogen (Survivor vs Non Survivor)	Survivors	80	518.4875	227.27500
	Non Survivors	16	646.4375	317.42106
Platelet (Survivor vs Non Survivor)	Survivors	80	237600.0000	130760.2502
	Non Survivors	16	206187.50000	134452.5784
DDimer (survivor vs Non Survivor)	Survivors	80	927.4875	2344.09279
	Non Survivors	16	3014.8125	2755.96904
CRP (Suvivor vs Non Survivors	Survivors	80	62.1549	78.14500
	Non Survivors	16	167.3700	154.77387

Group statistics	Non Survivor Vs Survivor	Std. Error Mean
PT (survivor Vs Nopn Survivor)	Survivors	1.46595
	Non Survivors	11.57401
INR (Survivor Vs Non Survivor	Survivors	.12742
	Non Survivors	1.00452
aPTT (Survivor Vs Non Survivor	Survivors	3.08571
	Non Survivors	15.97509
Fibinogen (Survivor vs Non Survivor)	Survivors	25.41012
	Non Survivors	79.35526
Platelet (Survivor vs Non Survivor)	Survivors	14619.44041
	Non Survivors	33613.14460
DDimer (survivor vs Non Survivor)	Survivors	262.07754
	Non Survivors	688.99226
CRP (Suvivor vs Non Survivors	Survivors	8.73688
	Non Survivors	38.69347

Whitney U test was used to analyse non-normally distributed continuous variables. Categorical variables were presented as frequency rates and percentages and analysed using ÷² test or Fisher's exact test as appropriate. Receiver Operative characteristic curves were plotted for significant variables to obtain area under curve.

RESULTS

In our study the values of the levels of all five parameters were elevated in non survivors as compared to survivors.

PT

On admission the mean level of PT in patients with and without SARI 12.8s and 21.3s. When interpreted with INR the mean values were 1.1 and 1.8. The difference in the mean values apart from being statistically significant (p=0.006) and also clinically different with moderate patients having a mean value within normal range for our laboratory(10-13s) and the severe cases well above that. Our finding is similar to Song JC[15] et al who hypothesized that these are due to liver involvement as there was significant abnormality in the liver enzymes of patients with COVID.

The average PT for survivors was 14.6 and the non survivors was 29.4s and the difference was statistically significant. Area under the curve for PT (survivors non survivor)was 0.751 and at a cut off value of 13s PT alone had a sensitivity of 75 % and a specificity of 62.5% for predicting those with severe covid. A cut off value of 16s had sensitivity to 39.6%. specificity of 95.8 % in predicting death This finding is similar to those described by Cui S et al[16] in whose study the multivariate regression analysis showed the difference in PT inpatients with SARI who survived and did not survive was not significant.

Area under the curve

The prolongation of PT is understandable. One of the mechanisms of COVID induced coagulopathy (CIC) is the over expression of tissue factor (TF) by the endothelial cells secondary to the cytokine release. Binding activation and consumption of factor VII by TF is probably the main reason for this. It can be inferred that the consumption of factor VII occurs more severely in SARI than in non SARI cases due to stronger cytokine response in them.

aPTT

The difference in aPTT among the moderate and sever cases was not statistically significant. This finding is similar to other studies. However the difference was significant when aPTT was survivors was compared with non survivors. (p=0.003) The median value for non survivors was 35.5 (IQR 32.5-42.1) and for survivors it was 31.9 (IQR 29.5-35.7) This finding is similar to that of study done by Huang C [11] et al.

Table 3.

		Levene's Test for Equality of Variances		t-test Equality of Means	
		F	Sig	t	Df
PT	Equal Variances assumed Equal Variances not assumed	7.767	.006	-1.857-1.857	9448.083
INR	Equal Variances assumed Equal Variances not assumed	7.531	.007	-1.782-1.782	9448.107
aPTT	Equal Variances assumed Equal Variances not assumed	.815	.369	-.584-.584	9493.163
Fibrinogen	Equal Variances assumed Equal Variances not assumed	12.653	.001	-3.411-3.411	9475.356
Platelet	Equal Variances assumed Equal Variances not assumed	1.092	.299	2.5672.567	9493.790
DDimer	Equal Variances assumed Equal Variances not assumed	18.579	.000	-3.686-3.686	9449.066
CRP	Equal Variances assumed Equal Variances not assumed	4.957	.028	-3.336-3.336	9468.087

It has been suggested that CIC be categorized into three stages beginning with stage of high d-dimer and nerar normal PT and aPTT, followed by increasing PT and aPTT with high dDimer and finally with features of Classic DIC as described by International Society of Thrombosis and Hemostasis (ISTH) It is possible that the non survivors in our case had progressed to second stage as compared to our survivors . It is interesting to note that the difference in the aPTT between survivors with and without SARI was also not significant as well as between the SARI survivors and non survivors.

33.9 cut off 21 severe patients and 18 moderate patients

>33.9s in 11/16 non survivors(68.5%) 36.25% (of survivors 29/80)

D Dimer (D-DU) (non survivor vs survivor and Non Sari vs Sari). The mean values of D dimer for patients without and with SARI as 384 and 2168 mcg/ml and the difference was highly significant. The IQR of D dimer in survivors and

Table 4.

		t-test Equality of Means		
		Sig. (2-tailed)	Mean Difference	Std. Error Difference
PT	Equal Variances assumed	0.066	-8.46875	4.56093
	Equal Variances not assumed	0.069	-8.46875	4.56093
INR	Equal Variances assumed	0.078	-0.70458	0.39544
	Equal Variances not assumed	0.081	-0.70458	0.39544
aPTT	Equal Variances assumed	0.561	-4.43125	7.58735
	Equal Variances not assumed	0.561	-4.43125	7.58735
Fibrinogen	Equal Variances assumed	0.001	-163.29167	47.87295
	Equal Variances not assumed	0.001	-163.29167	47.87295
Platelet	Equal Variances assumed	0.012	66812.5	26024.627
	Equal Variances not assumed	0.012	66812.5	26024.627
DDimer	Equal Variances assumed	0	-1785.6667	484.50421
	Equal Variances not assumed	0.001	-1785.6667	484.50421
CRP	Equal Variances assumed	0.001	-66.05979	19.80197
	Equal Variances not assumed	0.001	-66.05979	19.80197

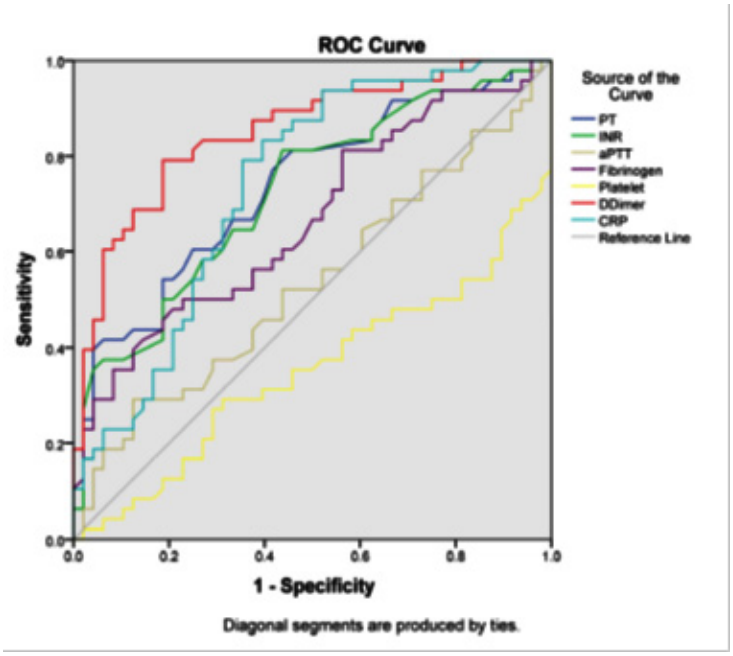
Table 5.

		t-test for Equality of Means 95% Confidence Interval of the Difference	
		Lower	Upper
PT	Equal Variances assumed	-17.52458	0.58708
	Equal Variances not assumed	-17.6387	0.7012
INR	Equal Variances assumed	-1.488974	0.08058
	Equal Variances not assumed	-1.49963	0.09046
aPTT	Equal Variances assumed	-19.49612	10.63362
	Equal Variances not assumed	-19.49788	10.63538
Fibrinogen	Equal Variances assumed	-258.34453	-68.2388
	Equal Variances not assumed	-258.65208	-67.93125
Platelet	Equal Variances assumed	15139.993	118485.01
	Equal Variances not assumed	15138.487	118486.51
DDimer	Equal Variances assumed	-2747.6611	-823.67221
	Equal Variances not assumed	-27759.281	-812.05201
CRP	Equal Variances assumed	-105.37707	-26.74251
	Equal Variances not assumed	-105.5731	-26.54648

non survivors was 196-817 and 1043-4961 and the median was 352 and 2080 between survivors and non survivors difference was statistically significant (p<0.001)

The D Dimer test was the single most important test distinguishing survivors and non Survivors with an AUC of. 0.844. At values if 382 the sensitivity and specificity was 93.8 and 51, 2. A cut off of 1000 ensured a 81.3 and 81.2% specificity. At 1711 it was 56.3 and 90% respectively. Our findings is similar to Gao Y.D. et al [20] also is the most common hematological abnormality reported in COVID-19 in a study done Asakura H, Ogawa H[21] . Elevated D-dimer level is a sign of excessive coagulation activation and hyperfibrinolysis which is a significant predictor of mortality due to venous thromboembolism both of the deep veins and in the pulmonary circulation the prevalence of which ranges from 0-54% as shown in a study by Suh et al[22]

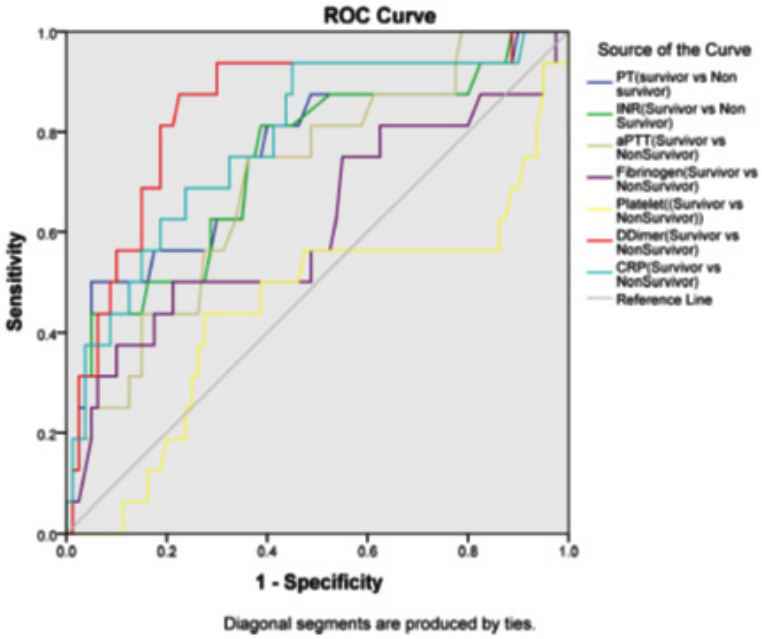
The mean levels of fibrinogen values in our study in moderate and severe cases was 458 and 621 respectively and the difference was significant (p =. 001) .The CRP The levels of fibrinogen and CRP was higher in patients with severe COVID and the difference was statistically significant whereas platelet values were lower but difference was not significant



Graph 1. ROC Curve

Table 6.

t-test Result Variable(s)	Area	a Std Error	Asymptotic Sig.b	Asymptotic 95% confidence Interval Lower Bound	Upper Bound
PT	.735	.051	.000	.635	.835
INR	.724	.052	.000	.623	.825
aPTT	.535	.059	.558	.418	.651
Fibrinogen	.667	.055	.005	.559	.775
Platelet	.350	.057	.011	.239	.461
DDimer	.852	.039	.000	.775	.928
CRP	.740	.051	.000	.639	.840



Graph 2. ROC Curve

Table 7.

Test Result Variables	Area	Std. Error	Asymptotic sig.	Asymptotic 95% Confidence
PT (survivor vs Non survivor)	.751	.073	.002	.607
INR (Survivor Vs Non Survivor	.738	.073	.003	.506
aPTT (Survivor Vs Non Survivor	.705	.069	.010	.570
Fibinogen (Survivor vs Non Survivor)	.615	.087	.147	.445
Platelet (Survivor vs Non Survivor)	.448	.090	.513	.272
DDimer (survivor vs Non Survivor)	.644	.057	.000	.732
CRP (Suvivor vs Non Survivors	.784	.064	.000	.658

DISCUSSION

The aim of the cross-sectional study was to analyze the association between the coagulation parameters on admission with the severity and survival of adult

COVID patients as thromboembolism and disseminated Intravascular Coagulation are an important cause of morbidity and mortality among COVID patients.

Early on it was discovered that the mechanism for development of DIC in patients with COVID differed from those commonly encountered during sepsis. It is believed that the release of cytokines especially the Interleukin -6(IL-6) is major contributor for development of macrovascular as well as microvascular thrombosis. The mechanism appears to be dual:1. IL -6 increases the endothelial expression of Tissue Factor, ii) Sars Co-V 2 by itself produces widespread endothelitis and also pyroptosis and apoptosis of endothelial cells.

The coagulation cascade activation that occurs I Covid can be identified by prolongation of Prothrombin Time, Activated Partial Thromboplastin Time (aPTT). The fibrinolysis that follows is represented by increased levels of D- Dimer and Fibrin Split Products (FSP). The other conventional laboratory parameters that are useful in monitoring of Covid patients is levels of

Lactate Dehydrogenase (LDH), Serum Ferritin, C- Reactive Protein(CRP) and Interleukin 6 levels.

In our study the values of the levels of all five parameters were elevated in non survivors as compared to survivors

On admission the mean level of PT in patients with and without SARI 12.8s and 21.3s. When interpreted with INR the mean values were 1.1 and 1.8. The difference in the mean values apart from being statistically significant (p=0.006) also clinically different with moderate patients having a mean value within normal range for our laboratory (10-13s) and the severe cases well above that. Our finding is similar to Zhang et al[23] who hypothesized that these are due to liver involvement as there was significant abnormality in the liver enzymes of patients with COVID.

The levels of fibrinogen and CRP was higher in patients with severe covid and the difference was statistically significant whereas platelet values were lower but difference was not significant.

Platelet values are known to be lower in patients with severe Covid and multiple mechanisms are proposed beginning with suppression of bone marrow to increased consumption. Lower platelet counts are associated with more severe disease and are useful if monitored serially[24]. Since we did not follow up platelet counts and it may be the reason that it was not statistically significant. In our study 20 severe and 6 moderate cases had levels below 1,50,000

Both fibrinogen and CRP elevation can be explained by the fact that they are acute phase reactants. Elevation of fibrinogen could also be an indicator of prothrombotic state as shown in study done by Thachil J[25] and in conjunction with elevated CRP gives credence to the connection between inflammation and coagulation.

CONCLUSION

Basic coagulation markers may have a prognostic implication in the treatment of Covid patients with and without SARI.

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Conflicting of Interests

There are no conflict of interest.

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