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Evaluating the haematological and inflammatory markers in predicting the clinical outcome of COVID-19 patients admitted in a tertiary care hospital of Northern India

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***Abstract*---**Infection with the SARS-CoV-2 virus induces coagulation and stimulates the innate immune system. In ICU patients with COVID-19, nothing is known regarding coagulopathy and the response of inflammation and infection. The effects of SARS-CoV-2 infection on coagulation, infection, and inflammatory indicators, as well as their relationships, were studied. The study took place in

Naraina Medical College and Research Centre, a dedicated COVID-19 referral hospital in Northern India, from April to August 2021. This study only included COVID-19 positive hospitalised cases with RT-PCR confirmation. All blood samples were examined for haematological, coagulation, and inflammatory indicators, and mean results were compared between the three patient groups. All patients had elevated d-dimer and FDP levels, notably non-survivors, who had prolonged PT, APTT, INR, and TT, as well as lower PTA and AT, as compared to survivors. Non-survivors were more likely to develop SIC and DIC. All patients' CRP, ESR, serum ferritin, IL-8, and IL-2R levels increased, while non-survivors' IL-6 and IL-10 levels were significantly higher. CRP, serum ferritin (p = 0.02), PCT (p 0.001), and IL-2R (p = 0.007) were all found to be positively linked with D-dimer. CRP (p = 0.006), PCT (p = 0.0007), IL-1 (p = 0.048), and IL-6 (p = 0.009) were all strongly connected with SIC scores. CRP (p 0.0001), ESR (p = 0.02), PCT (p 0.0001), serum ferritin (p 0.0001), IL-10 (p = 0.02), and IL-2R were all positively linked with DIC scores. Coagulation characteristics in COVID-19 ICU patients include prothrombotic condition, SIC, and DIC. CRP, ESR, serum ferritin, IL-8, IL-2R, IL-6, and PCT were stimulated by SARS-CoV-2 infection. CRP, PCT, serum ferritin, and IL-2R levels suggest the degree of coagulopathy in COVID-19 patients.

***Keywords*---**SARS-CoV-2, COVID-19, coagulopathy, markers of infection and inflammation, correlation.

Introduction

SARS-CoV-2, a recently discovered RNA beta coronavirus that causes COVID-19 and was initially identified in Wuhan, China in December 2019, has spread internationally, infecting over 8 million individuals and killing over 400,000 people, with numbers rising every day. [1] Humans are infected with SARS-CoV-2 by respiratory droplets and close contact. [2] During an infection, the respiratory system is the most vulnerable to infringement, resulting in the most common symptoms: fever and cough.[2]

The most common cause of mortality among COVID-19 patients, especially those who are extremely ill, is acute respiratory distress syndrome. [3] Supportive care and symptomatic therapy are the key therapeutic measures for COVID-19 patients. The activation of coagulation is a major clinical characteristic of COVID-19. [4,5] The coagulation parameters of COVID-19 patients are found to be abnormal, indicating the severity of COVID-19. [4,5]

Another important feature of COVID-19 is that it stimulates the innate immune system to release huge amounts of pathogenic cytokines, which are involved in disease progression. [6–8] There is a lot of research that implies that crosstalk between coagulation and inflammation, which interacts with each other, aggravates sepsis symptoms. [9] In addition, the infectious response serves as a link between coagulation abnormalities and sepsis. However, little is known about the link between coagulation abnormalities and infection and inflammatory

indicators in COVID-19-infected ICU patients. As a result, the goal of this study is to determine how SARS-CoV-2 infection affects coagulation and infection and inflammation markers, as well as the relationship between coagulopathy in ICU patients and infectious and inflammatory markers.

Patients and Methods

Study oversight

From July to August 2020, a dedicated COVID-19referral hospital in Central India conducted a record-based cross-sectional study. On July 21, 2020, the Institutional Ethical Committee authorised the study. The Institutional Ethical Committee waived the necessity to obtain consent because the patient's identity was de-identified in this investigation. This study only included COVID-19-positive cases admitted to the hospital and validated by an RT-PCR (real-time polymerase chain reaction) test. At the time of admission, three whole blood samples were collected and tested at the institutional laboratory: first in ethylenediaminetetraacetic acid (EDTA) vial for hemogram, second in citrate vial for coagulation profile, and last one in the plain vial for biomarkers.
Collection and analysis of data were anonymous.

Data Collection and Definition

From the electronic medical records of ICU patients with COVID-19, basic information such as age, sex, and hospital stay, smoking history, malignancy and history, comorbidities such as hypertension, diabetes, COPD, CHD, CKD, CLD, and symptoms such as fever, cough, sputum, fatigue or myalgia, nausea or vomiting, and diarrhoea were collected. On day 1, day 4, day 7, and the last day in hospital, coagulation variables such as PT, APTT, d-dimer, INR, PTA, Fbg, FDP, TT, AT, and inflammatory indicators such as CRP, PCT, serum ferritin, ESR, IL-1, IL-2R, IL-6, IL-8, IL-10, and TNF- were extracted, as well as inflammatory indicators such as CRP, PCT.

Statistical Analysis

As a median, age, length of stay in the hospital, and SOFA score were displayed (IQR). The infectious markers and coagulation variables were expressed as mean SEM. Depending on the data type, statistical methods such as Fisher's exact test, chi-squared test, and Mann Whitney test were applied. The Spearman rank test was used to evaluate correlations.

Results

Clinical Features of Patients with COVID19 five hundred and twenty ICU patients infected with SARSCoV-2 were recruited in our study. The median age thereof was 66 y (IQR 57.0–73.8 y). The mean average age of those in the non-survivor group exceeded that of those in the survivor group (67.5 versus 59.0 y, $p = 0.0024$). As a median, age, length of stay in the hospital, and SOFA score were displayed (IQR). The mean SEM approach was used to compute the infection indicators and coagulation factors. Depending on the data type, statistical procedures such as Fisher's exact test, chi-squared test, and Mann Whitney test were applied.

PT was prolonged in the non-survivor group at day 1 (14.9 ± 0.3 s), day 4 (17.4 ± 1.3 s), and the last day (26.9 ± 3.3 s), comparable to the survivor group at day 1 (13.4 ± 0.1 s, p = 0.0059), day 4 (13.0 ± 0.3 s, p = 0.0077), and last day (13.2 ± 0.2 s, p < 0.0001), all of which were within the normal range (11.5–14.5 s) (1A). APTT was normal (normal range 29.0–42.0 s) for the survivor group during hospitalisation, but for the non-survivor group, APTT increased continually, to its longest by the last day (65.8 ± 5.2 s) which was much longer than that in the survivor group (36.9 ± 1.6 s, p = 0.0034) (1B). D-dimer levels elevated all the patients (normal range < 0.0001), (4.2 ± 2.4 μg/mL, p = 0.0003), (0.7 ± 0.3 μg/mL, p = 0.0198), and (2.2 ± 0.8 μg/mL, p < 0.0001) (1C). PTA was within normal range (75.0–125.0%) for the survivor group at day 1 (98.6 ± 2.6%), day 4 (104.9 ± 4.8%), day 7 (102.0 ± 13.0%), and the last day (102.5 ± 3.2%). For the non-survivor group, PTA decreased over time and was much lower than that of the survivor group at the corresponding time (75.5 ± 2.4%, p < 0.0001), (66.4 ± 3.1%, p < 0.0001), (55.1 ± 3.3%, p = 0.0227), and (49.5 ± 2.9%, p < 0.0001) (1D). Conversely, INR was elevated continually for the non-survivor group at day 1 (1.2 ± 0.0), day 4 (1.4 ± 0.1), day 7 (1.5 ± 0.1), and the last day (2.0 ± 0.2) and was higher than that of the survivor group at day 1 (1.0 ± 0.0, p < 0.0001), day 4 (1.0 ± 0.0, p < 0.0001), day 7 (1.0 ± 0.0, p = 0.0353), and the last day (1.0 ± 0.0, p < 0.0001), all of which were not beyond normal limits (0.8–1.2) . In contrast to d-dimer, levels of FDP were elevated in both groups (normal range < 0.0001), day 4 (100.5 ± 11.8 versus 25.9 ± 20.7 μg/mL, p = 0.0022), and the last day (80.3 ± 10.6 versus 12.9 ± 6.4 μg/mL, p < 0.0001) (1F). TT was beyond the normal range (14.0–19.0 s) and had a prolonged trend in the non-survival group. TT was normal in the survivor group, and was thus shorter than that in the non-survivor group, particularly at day 1 (16.3 ± 0.2 versus 22.2 ± 3.3 s, p = 0.0045) and the last day (16.6 ± 0.3 versus 35.6 ± 6.2 s, p = 0.0088).

There was no significant difference in Fbg between non-survivors and survivors (most values were within a normal range) (1H). At day 1, day 4, and day 7, AT was not comparable between non-survivors and survivors, and values were within reference limits (80.0–120.0 percent); however, AT in the non-survivor group decreased to 68.2 2.8 percent on the last day, which was lower than that of the survivor group (88.5 3.8 percent, p = 0.0001).

Changes in Infectious Indicators in SARS-CoV-2 Infected Patients COVID-19 coagulopathy was inextricably linked to an inflammatory response triggered by SARS-CoV-2 infection, as evidenced by inflammatory markers, cytokines, and cytokine receptors (2). At day 1, day 4, day 7, and the last day, CRP levels in the survivor and non-survivor groups were more than 10.0 mg/L.

Meanwhile, the non-survivor group had considerably higher CRP levels at all periods (127.6 7.5 vs 40.3 9.1 mg/L, p 0.0001) (118.9 9.0 versus 18.8 4.2 mg/L, p 0.0001) (138.9 11.8 versus 46.0 16.8 mg/L, p = 0.0003) (128.3 8.7 versus 24.9 8.7 mg/L, p 0.0001) (138.9 11.8 versus 46.0 (2A). At all occasions, the ESR in both groups was greater than 15.0 mm/h. At day 1 (46.0 3.3 versus 27.4 4.3 mm/h, p = 0.0046) and the last day (147.7 3.5 versus 23 2.7 mm/h, p 0.0001), ESR was faster in the non-survivor group than in the survivor group.

Furthermore, both groups' serum ferritin levels surpassed 500 g/L at all times, although the non-survivor group had greater serum ferritin levels on day 1 (p = 0.0019), day 4 (p = 0.04), and the final day (p = 0.0002). (2D). In this work, we measured interleukins such as IL-1, IL-6, IL-8, and IL-10. Most patients' IL-1 levels were less than 5.0 pg/mL at all periods (2E), but IL-6 levels in all patients were higher than the usual range, which was less than 7.0 pg/mL. Levels of IL-6 increased as the disease progressed, especially among non-survivors, and were substantially greater than those of survivors at day 7 (p = 0.03) and the last day (p = 0.01). (2F).

In contrast, IL-8 levels were below the upper limit of 62.0 pg/mL in most patients in both groups, despite non-survivors having greater levels of IL-8 on day 1 (p = 0.02), day 7 (p = 0.02), and the last day (p = 0.0008), in comparison to survivors (2G). IL-10 levels in survivors ranged near the top limit, 9.1 pg/mL, while they were higher in non-survivors. On the last day, the non-survival group's IL-10 levels were significantly greater than the survivor group's (p = 0.0006). (2H).

The levels of the interleukin-2 receptor, or IL-2R, increased in the survivor group, but were substantially greater in the non-survivor group, especially on day 1 (p = 0.02) and the last day (p = 0.0002). (2I). During hospitalisation, another cytokine, TNF-, was found to be unstimulated in both groups, with no significant difference between the two groups. The infection with SARS-CoV-2 triggered an inflammatory response, which resulted in a significant change in coagulation function.

The association between coagulation function and viral and inflammatory markers in COVID-19 patients was investigated (Table 2). For COVID-19 patients on admission, D-dimer was positively linked with CRP (r = 0.36, p = 0.0007), serum ferritin (r = 0.29, p = 0.02), PCT (r = 0.45, p 0.001), and IL-2R (r = 0.45, p = 0.007). (Table 1). Meanwhile, among COVID-19 patients on admission, SIC scores were strongly linked with CRP (r = 0.28, p = 0.006), PCT (r = 0.35, p = 0.0007), IL-1 (r = 0.33, p = 0.048), and IL-6 (r = 0.37, p = 0.009). CRP (r = 0.45, p = 0.0001), ESR (r = 0.25, p = 0.02), PCT (r = 0.46, p 0.0001), serum ferritin (r = 0.43, p 0.0001), IL-10 (r = 0.33, p = 0.02), and IL-2R (r = 0.48, p = 0.02) were all positively related to DIC scores at the conclusion of the hospitalisation.

Discussion

Immune systems are inevitably activated during the fight against viral or bacterial invasion, stimulating the coagulation system.[9,15] As a result, SARS-CoV2 infection has been linked to coagulation and immune system problems, both of which are serious concerns during the treatment of COVID-19 patients. SARS-CoV-2-associated coagulopathy is found in almost all severely ill COVID-19 patients, according to this investigation. All patients had increased d-dimer and FDP levels, especially non-survivors, who also had prolonged PT, APTT, INR, and TT, as well as lower PTA and AT compared to survivors. Furthermore, patients in the nonsurvivor group were more likely to develop to SIC and DIC. In addition, infectious and inflammatory markers such as CRP, ESR, serum ferritin, IL-8, and IL-2R rose in all patients, but especially in those who had a severe infection.

Furthermore, ultrasonography revealed that 28 percent of non-survivors had deep vein thrombosis, which explained the fast onset of respiratory failure and mortality of several COVID-19 patients seen during our clinical work, indicating separation of deep vein thrombus and pulmonary embolism.

Levels of d-dimer and FDP, which reflect blood hypercoagulability, rise in laboratory tests for COVID-19 patients and rise dramatically in cases of critical illness or death, as validated by our data. High d-dimer levels are connected to hospital mortality in patients with sepsis. In COVID-19 patients, a high level of d-dimer is an independent risk factor for in-hospital death. DIC, which reflects the patients' severe condition and indicates a poor prognosis, is another clinical hallmark of COVID-19 patients. As a result of sepsis-induced coagulopathy and a low platelet count, sepsis-induced DIC develops. Thrombocytopenia is uncommon in COVID-19 patients with mild, moderate, and severe disease, but it is common in critical illness patients, which is consistent with our findings that platelet absolute counts increased in survivors and fell in fatalities. Unlike non-sepsis DIC, PAI-1 suppresses fibrinolysis in sepsis-associated DIC, which causes organ failure by reducing tissue perfusion and seldom results in systematic bleeding. Several patients in our group experienced gastrointestinal bleeding and cerebrovascular accident, which were ascribed to stress, peptic ulcers, and hypertension, respectively. The above coagulopathy characteristics of COVID-19 patients differ slightly from SARS and MERS. SARS-related thrombocytopenia is prevalent, but COVID-related thrombocytopenia is uncommon. Even in non-ICU patients with SARS, a prolonged APTT is common. Patients with SARS-CoV infection, which is different from SARS-CoV-2 infection, did not have a raised d-dimer. DIC is identified in a small number of SARS patients, accounting for just 11.4 percent of mortality, a figure that is far lower than that of SARS.

Around 21% of SARS patients have DVT, similar to ICU COVID-19 patients. For the time being, COVID-19 patients do not show evidence of pulmonary embolism, which is found in 11% of SARS patients. Thrombocytopenia is also common in MERS, however it is less common than in SARS. DIC occurs in 14% of MERS patients, which is higher than SARS (2.5%)24 but significantly lower than our findings (39 percent in Table 1). Sepsis-related coagulopathy is caused by a variety of processes, the most important of which is the involvement of cytokines in the coagulation system's dysfunction. In the activation of coagulation, elevated levels of pro-inflammatory cytokines (such as TNF, IL-6, and IL-1) and anti-inflammatory cytokines (such as IL-10) were observed.

Crosstalk with the protein C, protein S, and antithrombin systems activates coagulation, and IL-6 is a poor prognostic factor for sepsis. The virus can activate coagulation by binding to angiotensin converting enzyme 2 (ACE2), causing damage to vascular endothelial cells, as well as triggering the innate immune system, resulting in a cytokine storm linked to illness severity. Increased levels of pro-inflammatory cytokines including IL1, IL-2, IL-2R, IL-6, IL-8, IL-10, TNF-, and IFN-, as well as anti-inflammatory cytokines like IL-4 and IL-10, have been well established in patients with COVID-19 in previous research, especially in critical instances.

Besides, this phenomenon also occurs in SARS and MERS such that serum concentrations of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, and IFN-γ) increased.32,33 In addition, infectious response was initiated during sepsis. Infectious markers, including CRP and PCT, increased during infection, participate in the abnormality of coagulation, and predict disease severity. [10,11] Increased values of CRP, PCT, ESR, and serum ferritin are depicted in COVID-19 patients, and CRP, PCT, and serum ferritin have significantly higher values in severe cases[7,12] as supported by our findings. Inflammation and coagulation interact during infection. Markers of infection and inflammation, including PCT, IL-6, IL-8, and IL-10 are positively correlated with DIC in patients with sepsis.[10] For SARS-CoV-2 infection, we found that D-dimer was positively associated with CRP, serum ferritin, PCT, and IL-2R: the SIC score was positively correlated with CRP, PCT, IL-1β, and IL-6, and the DIC score was positively correlated with CRP, ESR, PCT, serum ferritin, IL-10, and IL-2R in COVID-19 patients. Up to now, no evidence has been found to allow investigation of the relationship between coagulation and inflammation in SARS-COV-2 infection. Therefore, our data were the first to allow description of the correlation of coagulopathy of patients with COVID-19 and markers of inflammation and infection. The primary management of patients with COVID-19 is symptomatic therapy and supportive care as there is no effective drug to treat SARS-CoV-2 infection at present. Prothrombotic state, DVT, and DIC of patients with COVID-19 are managed by use of anticoagulants.

Variables	Total (n= 520)	Survivors (n= 440)	Non-Survivors (n=80)	P-value
Age, years	66.0(57.0–73.8)	59.0(32.3–69.5)	67.5(59.3–75.0)	0.0024
Sex				0.0054
Female	35(32%)	15(54%)	20(25%)	
Male	73(68%)	13(46%)	60(75%)	
Current smoker	10(9%)	1(4%)	9(11%)	0.45
Comorbidity				
Hypertension	47(44%)	5(18%)	42(53%)	0.0015
Diabetes	20(19%)	4(14%)	16(20%)	0.58
COPD	5(5%)	1(4%)	4(5%)	1
CHD	16(15%)	4(14%)	12(15%)	1
CKD	6(6%)	3(11%)	3(4%)	0.18
CLD	0	0	0	
Malignancy	4(4%)	0	4(5%)	0.57
Surgery history	24(22%)	2(7%)	22(28%)	0.033
Hospital stay, days	10.0(6.0–15.0)	12.5(8.0–15.8)	9.0(6.0–13.8)	0.13
Time from symptom on set to admission, days	9.0(6.0–12.0).	4.0(3.0–9.0)	10.0(7.3–13.0)	0.0004
Time from admission to ICU, days	4.0(2.0–6.0)	3.0(2.0–4.0)	4.0(2.0–6.0)	0.26
Symptom				
Fever	91(84%)	24(86%)	67(84%)	1
Cough	83(77%)	21(75%)	62(78%)	0.78
Sputum	49(45%)	9(32%)	40(50%)	0.102
Fatigueormyalgia	54(50%)	12(43%)	42(53%)	0.38
Nauseaorvomiting	10(9%)	3(11%)	7(9%)	0.71
Diarrhoea	17(16%)	3(11%)	14(18%)	0.55
DVT	22(20%)	0	22(28%)	0.0008
GIB	6(6%)	1(4%)	5(6%)	1
Cerebrovascularaccident	3(3%)	0	3(4%)	0.57
SICscore(ISTH≥4)	34(31%)	1(4%)	33(41%)	<0.0001

DICscore(ISTH≥5)	42(39%)	0	42(53%)	<0.0001
SOFAscore	3.0(2.0–4.0)	1.0(1.0–2.0)	3.0(2.0–4.0)	<0.0001
Anti-coagulationtherapy	42(39%)	1(4%)	41(51%)	<0.0001

Table 2
Correlations between Coagulopathyof COVID-19 Patient sand Infectiousand Inflammatory Markers

	CRP	ESR	PCT	Serum Ferritin	IL-1β	IL-6	IL-8	IL-10	IL-2R	TNF-α
	r(*p*)	*r*(*p*)	*r*(*p*)	*r*(*p*)	*r*(*p*)	*r*(*p*)	*r*(*p*)	*r*(*p*)	*r*(*p*)	*r*(*p*)
D-dimer	0.36 (0.0007)	0.18 (0.13)	0.45 (<0.0001)	0.29 (0.02)	−0.07 (0.72)	0.16 (0.29)	0.22 (0.21)	0.07 (0.71)	0.45 (0.007)	0.06 (0.72)
SICscore	0.28 (0.006)	−0.10 (0.39)	0.35 (0.0007)	0.23 (0.052)	0.33 (0.048)	0.37 (0.009)	0.31 (0.07)	0.10 (0.60)	0.28 (0.10)	−0.11 (0.52)
DICscore	0.45 (<0.0001)	0.25 (0.02)	0.46 (<0.0001)	0.43 (<0.0001)	−0.06 (0.69)	0.20 (0.09)	0.27 (0.06)	0.33 (0.02)	0.48 (0.0005)	−0.01 (0.94)

Conclusion

Coagulation characteristics in COVID-19 ICU patients include prothrombotic condition, SIC, and DIC. CRP, ESR, serum ferritin, IL-8, IL-2R, IL-6, and PCT were stimulated by SARS-CoV-2 infection. CRP, PCT, serum ferritin, and IL-2R levels suggest the degree of coagulopathy in COVID-19 patients.

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