Coagulation Abnormalities in Covid-19 Positive Patients at Covid Hospital of Hassan Institute of Medical Sciences, Hassan

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ABSTRACT

BACKGROUND

Throughout the world, millions of people are affected by corona virus disease 2019 (Covid-19). 16 % of infected Covid-19 people may need hospitalisation. Patients with severe respiratory or systemic manifestations are at increased risk of venous thromboembolism. Thrombocytopenia, elevated D-Dimer, prolonged prothrombin time, and features of disseminated intravascular coagulation laboratory findings are included in initial reports on Covid-19 patients' blood samples.

METHODS

This cross-sectional study was conducted at pathology laboratory, Hassan Institute of Medical Sciences, Hassan, between June 01, 2020 to August 29, 2020. 4096 patients' blood samples with Covid-19 positivity in Covid Hospital of Hassan Institute of Medical Sciences, Hassan, were analysed in detail and statistical reports were derived from the fresh samples for platelet count, prothrombin time and D-Dimer. The results were compared with severity of infection.

RESULTS

Analysis of 4096 Covid-19 blood sample results, revealed significant abnormal mean values in critical cases for platelet count in which it was severely decreased (35,000 cells / cumm), prothrombin time was prolonged for more than 180 seconds and D-Dimer values were 3.74 microgram per ml.

CONCLUSIONS

As the pandemic is spreading, we highlight the importance of laboratory and clinical findings of coagulation disorders in Covid-19 infected patients. To prevent death of Covid-19 infected patients, noticing the laboratory findings related to coagulation will help in early detection of critical patients. This is very important for relevant treatment and may prevent mortality in Covid-19 infected patients.

KEYWORDS

Coagulation, Coronavirus, Venous Thromboembolism (VTE), Prothrombin Time, Disseminated intravascular coagulation (DIC)

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BACKGROUND

Coronaviridae virus family consisting of a positive-strand RNA virus causes severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2.[1]

This virus is having high rate of transmission and known for much contagious infection. As per the reports from WHO, more than 9,65,000 patients with Covid-19 have undergone death till the month of September 2021 and is advancing still without any hindrance.[2] Covid-19 patients with immunosuppressed or immunocompromised status shall be having more dangerous situation and may go for very bad prognosis. As most of the countries are having this infection, providing proper health facility and prevention of death to the infected people has resulted in severe impact in health care system. Due to these reasons, measures that are taken for proper treatment of Covid-19 infection shall be of lengthy process and are becoming problematic conditions in elderly individuals.[3] Severe Covid-19 infection results in distinctive type of coagulopathy. Covid-19 infection death rates are more in patients with significantly elevated circulating D-Dimer levels.[4] In such cases, there shall be presence of diffuse deposition of extracellular fibrin in multiple organs like lungs, liver, kidney and other visceral organs. In addition, there will be presence of distended micro blood vessels and capillaries with deposition of micro thrombi with fibrin threads.[5]

Severe Covid-19 infection with critical situation develops disseminated intravascular coagulation (DIC). In such cases, there shall be a prolonged prothrombin time (PT), severe thrombocytopenia in addition to increased D-Dimer values. Laboratory findings have shown that 70 % of such cases may result in death. Not only this, they may have decreased life span. In such situations, it calls for more attentive critical care management.[6]

Objectives

1. To study the results of platelet count, PT and D-Dimer in Covid-19 patients' blood samples.
2. To compare the values of platelet count, PT and D-Dimer in critically ill Covid-19 patients and non-critically ill Covid-19 patients.

METHODS

This cross-sectional observation study was conducted at central laboratory of Hassan Institute of Medical Sciences, Hassan, between June 01, 2020 to August 29, 2020 of about 03 months' duration. The study protocol was approved by the ethical and research committee. A confirmed case of Covid-19 was defined as a positive result on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of pharyngeal swab specimens. Patient data collected included clinical history, hospital length of stay, bleeding events, arterial and venous thrombotic events and anticoagulation administered. 4096 blood samples were collected as a time bound sampling size. On receiving fresh, adequate Covid-19 blood samples to the Department of Pathology laboratory, samples were classified as below based on patient history, and categorisation by clinicians.

1. Asymptomatic Cases (AS): Patients' blood samples without any symptoms and signs where they had history of contacts with primary Covid-19 cases or coming on their own.

2. Influenza Like Illness (ILI): Patient with history of fever, running nose, sore throat, cough with or without sputum production and other mild symptoms related to corona illness.

3. Severe Acute Respiratory Illness (SARI): Patient with high grade fever, chills, dyspnoea, severe cough with expectoration and other symptoms of corona which impaired the daily routine life activities.

4. Critical Cases (CC): Covid-19 patient's fresh blood samples obtained from very severely ill cases with marked variation in abnormal values of vital parameters, oxygen saturation, intubation of trachea, assisted mechanical respiration and monitoring and supervision with additional extra care by attending doctors.

Blood samples belonging to AS, ILI, SARI were considered as noncritically ill samples and the remaining Covid-19 cases as critically ill sample. The collected blood samples were subjected for platelet count, prothrombin time and D-Dimer immediately in fresh state. 4096 fresh Covid-19 blood samples were subjected for platelet count analysis by Cell Dyn Ruby five-part automated cell count analyser, prothrombin time (PT) by automated coagulometer Operon SL 1000 C and D-Dimer tests by Abott Architect Ci 4100 done according to the standard operating procedure manual guidelines. Values were noted in different type of blood sample. Significant abnormal values were informed to the treating clinician for appropriate management. Relevant statistical parameters were used to calculate the results of the study. The data was analysed in terms of proportion, mean values and test of significance for comparison of our study reports.

Fresh blood samples of all Covid-19 patients were included, and Covid-19 blood samples received after 01 hour of collection were excluded from the study.

RESULTS

The age group ranged from 01 year to 90 years. The total number of blood samples subjected for investigations for coagulation abnormalities were 4096. The maximum number of samples were seen in age group of 41 to 50 years (19.31 %). For males it was in 41 to 50 years (20.38 %) and for females it was in 31 to 40 years (19.51 %). [Table 01]

On detailed analysis, of 4096 blood samples [Table 02] the contribution of asymptomatic cases (AS), influenza like

illness (ILI), severe acute respiratory illness (SARI) and critical cases (CC) were 1084 (26.46 %), 1762 (43.01 %), 991 (24.19 %) and 259 (6.32 %) respectively. Maximum number of asymptomatic cases (22.69 %) were seen in 31 to 40 years and no cases in 81 to 90 years of age group. ILI cases were more commonly seen in 31 to 40 years (19.46 %) and very minimal case (01 case) in 81 to 90 years of age group. SARI cases were more common in 41 to 50 years (21.08 %) and only in two cases from 81 to 90 years of age group. Maximum number of CC (28.57 %) were seen in 61 to 70 years and no cases in 01 to 20 years of age group. One or the other conditions like, chronic obstructive lung diseases, history of uncontrolled diabetes mellitus and hypertension of longer duration, previous history of heart attack and cardiac disorders, immunocompromised or immunosuppressed status, patients with renal dialysis, cirrhosis, chronic bed hidden patients were having history in critical cases.

Age (In Years)	Male - Number of Covid-19 Blood Sample	Female - Number of Covid-19 Blood Sample	Total
01 - 10	79	68	147
11 - 20	206	193	399
21 - 30	432	298	730
31 - 40	442	336	778
41 - 50	484	307	791
51 - 60	437	275	712
61 - 70	214	174	388
71 - 80	74	68	142
81 - 90	6	3	9
Total Number	**2374**	**1722**	**4096**

Table 1. Distribution of Covid-19 Blood Sample with Respect to Age and Sex

Age (In Years)	Asymptomatic	Influenza Like Illness	Severe Acute Respiratory Illness	Critical Cases	Total
01 - 10	53	73	21	00	147
11 - 20	122	229	48	00	399
21 - 30	237	328	162	03	730
31 - 40	246	343	173	16	778
41 - 50	226	297	209	59	791
51 - 60	141	305	201	65	712
61 - 70	57	148	109	74	388
71 - 80	02	38	66	36	142
81 - 90	00	1	2	6	9
Total Number	**1084**	**1762**	**991**	**259**	**4096**

Table 2. Classification and Typing of Number of Blood Samples with Respect to Age

For all the received fresh Covid-19 blood samples in pathology laboratory the following tests were performed according to standard procedure for coagulation abnormality. For each tests, control samples results were also noted.

1. Platelet Count (PC).
2. Prothrombin Time (PT).
3. D–Dimer (DD).

After subjecting the blood samples of 4096 Covid-19 positive cases, results were correlated with the type of blood samples and correlated with severity of infection. In addition to these tests for all the samples routine international normalized ratio (INR) values for coagulation and activated partial thromboplastin time were also noted.

Sl. No.	Type of Sample	Platelet Count (Lakh Cells / Cumm)		
		Min	Average	Max
1	Control	2.16	2.86	3.56
2	AS	1.58	1.74	1.90
3	ILI	0.85	1.01	1.19
4	SARI	0.56	0.69	0.82
5	CC	0.18	0.35	0.52

Table 3. Minimum, Average and Maximum Values of Platelet Count of 4096 Blood Samples

Sl. No.	Type of Sample	Prothrombin Time (in second)		
		Min	Average	Max
1	Control	12.3	12.6	12.9
2	AS	12.4	12.8	13.2
3	ILI	12.6	13.5	14.4
4	SARI	18.4	21.4	24.4
5	CC	> 180	> 180	> 180

Table 4. Minimum, Average and Maximum Values of Prothrombin Time of 4096 Blood Samples

Sl. No.	Type of Sample	D-Dimer (in Microgram / ml)		
		Min	Average	Max
1	Control	0.05	0.13	0.18
2	AS	0.18	0.21	0.26
3	ILI	0.78	0.46	0.74
4	SARI	0.70	1.21	1.72
5	CC	3.36	3.74	4.12

Table 5. Minimum, Average and Maximum Values of D-Dimer of 4096 Blood Samples

On analysis of these 4096 blood sample results significant abnormal mean values were noticed especially in critical cases for platelet count in which it was severely decreased (35,000 cells / cumm) [Table 03], prothrombin time was prolonged for more than 180 seconds [Table 04] and D-Dimer values were 3.74 microgram per ml [Table 05]. Results for platelet count showed that minimum, mean and maximum values for AS, ILI, SARI and CC gradually decreased respectively. Similarly, minimum, mean and maximum values for PT and D-Dimer in AS, ILI, SARI and CC samples gradually increased respectively. However, there was not much change in activated partial thromboplastin time values except in critical cases in which values were prolonged.

All the obtained results were noted and analysed in detail. Particular attention was given for the results of critically ill patient's blood samples. These abnormal values for platelet count, prothrombin time and D-Dimer especially in critical cases (Table 05) were compared with blood samples of noncritically ill AS, ILI and SARI patients in which values were abnormally significant with p value less than 0.05. Thus, these values can be used for prediction of severity of infection and prognosis of the diseased patients. Using these data, parameter, p value less than 0.05 was noticed to impart a high risk for severe Covid-19: especially in associated other comorbid conditions as already mentioned in critical cases.

DISCUSSION

Worldwide spread of infection from Wuhan, China by a new coronavirus strain, Coronavirus disease 2019 (Covid-19) or

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease is recently identified and spreading very rapidly throughout the world.[8] Usually, these patients will have fever (> 80 %), cough (> 60 %), and myalgia or fatigue (> 40 %) as initial presentation.[9] In present situation, various studies reveal that majority of the Covid-19 patients have minor illness. But, the disease presentations may also be asymptomatic. They can also have moderate to severe distress with complications like sepsis and death. Critical illness with secondary complications can occurs in 16 % of cases as in the study revealed by Guan et al.[10] In our study, results showed that involvement of male gender was more common and the median age was near 50 years. The same findings were noticed in C. Huang et al. study.[9]

Everywhere throughout the world, this disease is advancing at faster rate with many unknown things. In patients with severe Covid-19 infection, coagulation complications are known to occur and raises many issues in relation to treatment aspect. Still the exact mechanism is not known completely, the proper health care of the patients at the beginning stages is very important. So, these reasons, made us to review the available literature with respect to disorders of blood clot formation in patients of SARS-CoV-2. This was an attempt to make awareness about laboratory values and their significance with severe Covid-19 infection and the probable complications.

Our research values were almost correlating with that of preliminary reports like W.J. Guan et al. study on Covid-19 pandemic outcome patients developing thrombocytopenia (36.2 %). In our study, the results for D-Dimer values were higher in systemic inflammatory response syndrome (SIRS) (49.4 %) and critical cases (63.4 %). These results are very much near to the values for elevated D-Dimer (46.4 %), in severe and while these rates are even higher in patients with critical Covid-19 disease and (59.6), respectively by W.J. Guan et al. study. Disseminated intravascular coagulation (DIC) is known to occur in this severe type of Covid-19 infection. Many publications have revealed and supported this finding in critical cases of Covid-19 infection.[11] The laboratory evidentiary findings for the development of DIC were in the form of significantly increased values in the D-Dimer, fibrin split products and prothrombin time. Thus, in such conditions, patients had very bad prognosis.[12] According to the standard guidelines, Tang et al. study reported that 15 out of 21 non-survivors developed inevitable DIC in very severe cases of Covid-19 infection.

We also observed the similar findings for the presence of DIC especially in critical cases in which we also noticed that 148 patients had DIC out of 259 dead cases.[13] Like Chen et al. study,[13] our study values also showed significantly increased D-Dimer values, in critical cases most of them not survived. Our study findings showed that platelet count was very much decreased for critical cases of Covid-19 infection. Same findings were noted in Lippi et al. study.[14] Systemic inflammatory response and disturbance in the homeostasis in coagulation mechanisms can be caused by viral infections. These infections can cause decreased platelet count and elevated D-Dimer values. This may result in hyper responsiveness of coagulation cascade activation and thrombocytes.[15] Here, the probable mechanisms may be like dysfunction of endothelia cells, platelet activation, activation of tissue-factor pathway and other molecular factors that are involved in abnormal coagulation.[15,16] Activated platelets will react with leukocytes and enhance blood clot formation via formation of primary haemostatic plug.[17]

Increased coagulation status by this viral infection is due to activation of platelets. Such activated platelets will react with inflammatory cells like macrophages, monocytes, endothelial cells and lymphocytes and release various chemical mediators of inflammation which directly or indirectly influence the increased formation of blood clot at multiple sites. They play a vital role in inflammation and cross react with cell surface receptors, pathogen pattern recognition receptors, or immunoglobulin Fc receptors and complement receptors.[16,18] Usually, majority of the Covid-19 patients will have normal or mild increase in PT. In asymptomatic cases, mild or influenza like illness presentation, there can also be a normal or shortened activated partial thromboplastin time (aPTT). Careful follow up of these values like platelet count, PT and D-Dimer can have impact on nature of the disease process.[19] At the time of patient admission, significant increase in D-Dimer and fibrinogen degradation products (FDP) values, decreased levels of fibrinogen and antithrombin III are having very bad prognosis and such patients have higher mortality and pay attention for needful treatment. Our study also revealed that abnormal significant increase in values for D-Dimer in critical cases.

Disseminated intravascular coagulation (DIC) of Covid-19 infection and septicaemia can be differentiated by laboratory findings. DIC resulting from septicaemia, reveal thrombocytopenia and prolongation of PT as more profound. In Covid-19 infection, D-Dimer values are very high. Whereas, in septicaemia, D-Dimer values are not very high when compared to that of Covid-19 infection. Decrease in platelet count and an increase in PT is proportionate to the severity of sepsis and hence death rate. Several fold increase in D-Dimer, increased PT with decreased platelet count and normal fibrinogen are usually seen in Covid-19 patients who died.

In critical cases of Covid-19 infection, organ failure can occur due to low-grade DIC and formation of blood clot in smaller blood vessels locally in lungs. In such cases, at the time of admission, a D-Dimer cut-off value of ≥ 2 µg / mL can suggest patient death with a sensitivity of 92.3 % and a specificity of 83.3 %. Increased PT, thrombocytopenia and increase in values of D-Dimer especially during initial presentation carry a very bad prognosis and need ICU monitoring and proper management. Such critical cases can have very serious conditions and can result in death.[20] To support these things, few autopsy published pathologic reports have justified that in Covid-19 infected pulmonary tissues showed that there were presence of large number of micro blood vessels filled with blood clot causing luminal obstruction and also microscopic observations showed supporting features of acute respiratory distress syndrome (ARDS).[21]

During critical cases of Covid-19 infection, various chemical mediators of inflammation that are released causes

cytokine storm by activated WBCs, endothelial cells and thrombocytes result in increased procoagulant status and decreased anticoagulant status. This altered environment will result in the formation of blood clot in smaller and bigger vessels.[22] Cytopathic effects by virus, decreased content of oxygen in the blood, causing obstruction of blood vessels, activation of protein C, deranged coagulation with imbalances in plasminogen activator inhibitor (PAI-1) and tissue factor pathway inhibitor are the mechanisms for micro and macrovascular obstruction by thrombus formation.[23]

There are reports showing that, polymorphonuclear leukocytes also have role in the formation of blood clot in the blood vessels. Autopsy reports of Covid-19 patients have revealed that there is a possible role of these cells. In smaller blood vessels with presence of blood clot had plenty of neutrophils. Some cases had partially degenerated polymorphonuclear leukocytes.[24]

Blood vessel constriction, formation of thrombus in the blood vessels and activation of platelets is due to increased release of reactive oxidant species like super oxide anion, hydrogen peroxide and hydroxyl ions by hyper activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-2 enzyme by neutrophils. Coagulation pathways are initiated by neutrophil extracellular traps (NETs) via expression of tissue factor, factor XII activation and platelet activation, which are trapped in the blood clot.[25]

Thus, our study with the help of laboratory investigations was able to find out the critical cases of Covid-19 patients who needed ICU admission and careful management with supervision as most cases were highly susceptible for blood clot formation. Severe thrombocytopenia, elevated D-Dimer and prolonged PT values have strong association with blood clot formation and may result in critical condition of the patient and later if patients are not treated properly, they may die. Many other viral infections also can result in same findings. In coronavirus infections, severe respiratory illness is linked to fibrin clot generation inside the alveoli and blood vessels. This is mainly due to abnormal regulation of cascade of coagulation pathway.

CONCLUSIONS

Treatment of rapidly spreading Covid-19 infection throughout the world has resulted in increased stress and strain on health care provider and health system. Covid-19, DIC coagulopathy can be differentiated from that of septicaemia induced DIC by laboratory values pertaining to coagulation. Coagulopathy of Covid-19 infection is due to abnormal regulation of haemostasis. During admission, and treatment of critically ill Covid-19 patients, this knowledge may be important to the treating physician to diagnose these cases early by noticing the laboratory parameters.

Modalities for diagnosis and appropriate treatment of venous thromboembolism (VTE) with the help of newer drugs acting in coagulation cascade are badly needed in the present scenario of Covid-19 infection for better prognosis and also for minimising death rates. Always, physicians should be extra careful in VTE cases of Covid-19 infections. Prophylactic drugs against formation of blood clot can be implemented in managing critically ill Covid-19 patients to prevent mortality of patients.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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