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Original Research Paper

Pathology

HAEMATOLOGICAL CHANGES IN RT-PCR POSITIVE COVID-19 PATIENTS: A STUDY OF 35 PATIENTS

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ABSTRACT

BACKGROUND: Corona viruses have been a major pandemic. SARS-CoV-2 is the third known coronavirus that causes fatal respiratory diseases in humans. The initial clinical features of SARS-CoV-2 infection are nonspecific flu-like symptoms and therefore initial diagnosis is challenging. The coronavirus disease 2019 (COVID-19) has multi-systemic involvement, including the hematopoietic system. The haematological manifestations of COVID-19 include blood count anomalies notably lymphopenia and neutrophilia which are of prognostic significance. Hyperferritinemia and elevated lactate dehydrogenase and IL-6 have also been associated with increased mortality. **MATERIALS AND METHODS:** This observational cohort study done in 35 RT-PCR proven COVID-19 patients for haematological and immunological abnormalities in tertiary health centres during period 1st April 2021 to 31st August 2021. The present study included hospitalized and outdoor COVID-19 patients with complication due to corona infection. Inclusion criteria were COVID-19 patients with a confirmed RT-PCR diagnosis. Exclusion criteria of this study were those who are taking medicine for reducing lymphocyte, leukocytes, or white blood cells count, and patients previously diagnosed with any haematological disorders. **RESULT:** WBC and neutrophils levels were positively correlated with each other ($r = 0.333$; $p<0.001$), whereas, WBC levels were negatively correlated with lymphocyte ($r = 0.400$; $p<0.001$) and monocyte levels ($r = 0.330$; $p<0.001$). Moreover, neutrophils levels were negatively correlated with Lymphocyte ($r = -0.530$; $p<0.001$) and monocyte ($r = -0.354$; $p<0.001$) levels. Leucocytosis with neutrophilia and lymphopenia was seen in 18 patients (51%) ,highest TLC count was 67x 10 ^ 3/μL, mild to moderate variable anaemia was found in 13 patients (37%) and mild thrombocytopenia was found in 4 patients(11%) . CRP, Ferritin and IL-6 were positively connected with each other ($r = 0.330$; $p<0.001$).The most common and maximum value of Ferritin was >1650.00 ng/ml. CRP was initial inflammatory marker. **CONCLUSION:** There is paramount importance of haematological and immunological parameters such as inflammatory markers, D-dimer level and absolute lymphocyte count in defining prognostic groups and monitoring response to therapy in COVID-19. The emphasis on the increased thrombotic risk and the importance of anticoagulation in COVID-19 is of specific relevance to clinicians. Hematological changes in COVID-19 patients have diagnostic and prognostic significance

KEYWORDS : COVID-19, RT-PCR, lymphopenia, SARS-CoV-2, Ferritin IL-6, D-Dimer, CRP

INTRODUCTION:

COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-C oV-2), a betacoronavirus which is transmitted mainly via droplets and contaminated surfaces. [1, 2,3] it is known that SARS-CoV-2, binds to host cells via its receptor, angiotensin converting enzyme 2 (ACE2), which is expressed across a wide range of human cell types including lung type II pneumocytes and the endothelium of blood vessels . [4,5]The clinical spectrum of COVID-19 ranges from asymptomatic to severe pneumonia or acute respiratory distress syndrome resulting in respiratory failure and death. [6,7] While COVID-19 is considered to be primarily a respiratory infection, there is increasing evidence of multi-systemic complications of the disease. Haematological manifestations of COVID-19 include lymphopenia, neutrophilia, mild thrombocytopenia, monocytopenia, elevated LDH, reactive and plasmacytoid lymphoid cells on peripheral blood film, and elevated ferritin, LDH and IL-6 in serum. The COVID-19 associated coagulopathy has elevated D-dimer, prolonged PT, APTT and fibrinogen. The most commonly reported blood count abnormality is lymphopenia which occurs in 35%-83% of patients. [8, 9, 10, 13] Lymphopenia is also more frequent and the absolute lymphocyte count (ALC) much lower in severe cases of COVID-19. [14,15]. Mild thrombocytopenia (100-150 $\times$ 10^9/L) has been reported in up to 20%-36% of COVID-19 cases [16], however, severe thrombocytopenia (<50 $\times$ 10^9/L) is unusual. The bone marrow hemophagocytosis can be a feature of severe COVID-19. Observations from the clinical, biochemical and serological manifestations of COVID-19 strongly support an immunological basis for the severe manifestations of the disease. (17, 18, 19] The marked elevation of pro-inflammatory markers such as IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ frequently seen in severe COVID-19[20,21,22] due to disordered and exaggerated immune response to SARS-CoV-2 infection, referred to as the "cytokine storm". Several complex pathways have been implicated in the pathogenesis of COVID-19 cytokine storm including the Renin-Angiotensin-Aldosterone system (RAAS), JAK/STAT and Complement activation pathways.[22,23,24] CRS, thought to be due to T-cell activation, is characterised by marked elevation of inflammatory markers and cytokines notably IL-6, fever, hypotension and respiratory insufficiency following the infusion of CAR T cells or other immune therapies .[23.24.25] Similarly, HLH is characterised by uncontrolled activation of cytotoxic T lymphocytes, natural killer (NK) cells and macrophages resulting in hypercytokinemia and immune-mediated organ damage.[35] Given the pivotal role of IL-6 signalling in CRS and its prognostic significance in COVID-19,[40] there has been considerable interest in the therapeutic potential of the IL-6 receptor antagonist, tocilizumab. Two separate case reports of the use of tocilizumab in acute chest syndrome of Sickle cell disease precipitated by COVID-19 reported rapid responses in an adult and a teenager. [41,42].

In a study comparing coagulation parameters in hospitalised COVID-19 patients, 15 (71.4%) of non-survivors met the International Society on Thrombosis and Haemostasis (ISTH) criteria for overt disseminated intravascular coagulation (DIC) compared with 1 (0.6%) of survivors.

[43, 44] Therefore, the ISTH DIC scoring system which includes platelet count, fibrinogen, and D-dimer and prothrombin time (Table 1) is likely to be a useful prognostic tool for COVID-19-associated CAC. The CAC of COVID-19 appears to be distinct from DIC due to other causes in elevated fibrinogen, modest prolongation of the APTT and the absence of schistocytes on the blood film. Interestingly, despite the derangements in coagulation tests, abnormal bleeding is unusual. [45, 46, 47]

Table 1. Isth Criteria For Overt Dic Has Prognostic Significance In Covid-19-related Coagulopathy

Parameters	Score
Platelet count	
>100	0
50-100	1
<50	2
Elevated fibrin-related marker D-Dimer	
Not elevated	0
Moderate increase (1-10x ULN)	1
Severe increase	2
Prolonged PT	
<3s ULN	0
>3 to <6 s above ULN	1
>3 to <6 s above ULN	2
Fibrinogen level	
<1 g/L	0
>1 g/L	1
Total score of ≥5: compatible with overt DIC	

MATERIALS AND METHODS:

This retrospective observational cohort study of 35 COVID-19 patients was done for clinical, haematological, immunological and laboratory parameters during period 1st April ,2021 to 31st August 2021 in tertiary health centres. The present study included hospitalized and outdoor COVID-19 patients with complication due to corona infection. Inclusion criteria were COVID-19 patients with a confirmed RT-PCR diagnosis. Exclusion criteria of this study were those who are taking medicine for reducing lymphocyte, leukocytes, or white blood cells count, and patients previously diagnosed with any haematological disorders.

Nasal and throat swab sample were taken in viral transport medium containing vacutainers for RT-PCR and processed in Microbiology Department and 2 millilitres of blood samples of all patients were collected using an ethylenediaminetetraacetic acid (EDTA)-containing vacutainers tube for analysis of haematological parameters in haematology section of Pathology Departments. Citrated blood sample and plain vacutainers were used respectively for coagulation and immunological parameters. The immunoassay parameters including IL-6 was performed on Siemens ADVIA Centaur XP immunoassay system and Dimension Expand plus used to measure CRP, Ferritin and other biochemical parameters. STA COMPACT MAX Stago coagulometer was used to measure coagulation parameters like PT, APTT, Fibrinogen and D-dimer. The Sysmex 1800i was used for CBC. PBS was made from each sample for manual platelet count, atypical lymphocytes, toxic granules in neutrophils etc.

RESULT

The descriptive statistics for all the COVID-19 patients are summarized and presented in Table 1 & 2. Among the participants, male female ratio was 4:1 and average age was 59.45. The oldest patient was 85-year male and youngest was 29-year male. Most of the participants were between 29–60 years old.

Table 2. Inflammatory And Immunological Markers In Corona Patients

CASE NO	AGE	SEX	CRP	FERRITIN	D -DIMER	IL-6
1	85	M	18.6	>1650	3241	100.50
2	62	M	0.2	400.0	876	67.40
3	77	M	16.4	551.2	876	100.10
4	75	M	8.5	411.0	876	27.30
5	39	M	35.0	> 1650.0	3241	19.90
6	62	F		402		3.8
7	65	M	9.6		781	17.40
8	55	F	30.5	> 1650.0	341	57.70
9	46	M	28.50	1,551.0	3200	18.70
10	78	M	9.0	781	806	171.80
11	36	M	27.00	> 1650.0		660.70
12	75	M		205.0	776	29.6
13	57	M	12.4	>1650	4041	3,747.60
14	48	M	20.6	>1650.0	4243	135.20
15	65	M	16.2	> 1650.0	975	86.90
16	58	M	29.0	685		32.00
17	72	F	12.2	> 1650.0	886	56.60
18	73	M	10.50	422	1210	181.70
19	38	M		> 1650.0	2241	205.00
20	79	M	9.2	1,239	2141	199.90
21	71	M	30.1	> 1650.0	970	11.70
22	62	F	15.2	289.9	586	11.7
23	75	M	20.0	822	676	18.10
24	50	F	22.2	1,429	1441	83.50
25	65	M	25.3	> 1650.0	2941	0.5
26	39	M	7.9	> 1650.0	1201	4.2
27	29	M	29.2	1000.00	2241	10.10
28	53	M	33.0	558.9	564	0.80
29	50	F	55.0	1,063	380	4.80
30	66	M	34.4	361.8	495	2,490.90
31	60	F	7.9	86	563	2,163.00
32	57	M	6.4	1005	579	216
33	69	M	23.0	1206.6	488	68.00
34	41	M	21,6	1316.8	1281	174.5
35	49	M		> 1650.0	4141	10.5

FERRITIN: 22-322 ng/ml, IL-6: up to 4.4 pg/ml, EDTA Plasma, CRP: < 1 mg/dL, D-DIMR <250ngFEU/ml

Table 3. Inperpretation Of Cbc Reports In Corona Patients

CASE	AGE	GENDER	TLC	N	L	HB	PLT
1	85	M	2.9	68	27	14.3	180
2	62	M	12.69	85	12	13.0	165
3	77	M	16.24	91	07	11.0	160
4	75	M	9.49	69	26	13.2	160
5	39	M	9.50	63	28	12.0	155
6	62	F	6.85	58	30	13.6	188
7	65	M	7.70	66	30	12.90	198
8	55	F	5.99	67	28	11.00	155
9	46	M	10.00	59	32	14.00	198
10	78	M	9.50	68	30	12.00	200
11	36	M	15.80	80	15	11.0	167
12	75	M	11.60	76	20	13.0	100
13	57	M	5.80	65	30	12.90	159
14	48	M	9.0	77	20	14.0	198
15	65	M	10.20	75	21	13.40	200
16	58	M	8.36	70	26	11.90	188
17	72	F	35.50	90	08	9.00	100
18	73	M	8.00	64	30	11.80	188
19	38	M	15.80	80	15	13.00	95
20	79	M	9.30	75	30	11.00	166
21	71	M	5.50	55	40	11.60	155
22	62	F	6.60	48	38	14.00	200

23	75	M	13.50	81	16	12.00	105
24	50	F	16.60	78	18	10.50	155
25	65	M	10.00	68	20	8.00	150
26	39	M	9.80	70	22	12.00	155
27	29	M	15.40	68	25	11.00	190
28	53	M	25.00	90	8	10.00	100
29	50	F	12.69	85	10	13.3	165
30	66	M	15.00	88	08	12.00	205
31	60	F	8.90	78	20	11.80	200
32	57	M	9.90	75	21	13.00	188
33	69	M	14.0	76	18	11.90	120
34	41	M	25.00	88	11	10.80	168
35	49	M	9.0	49	35	13.50	198

TLC *10 ^ 3/μL, PLT*10 ^ 3/μL , HB gm/dl

WBC and neutrophils levels were positively correlated with each other (r = 0.333; p<0.001), whereas, WBC levels were negatively correlated with lymphocyte (r = 0.400; p<0.001) and monocyte levels (r = 0.330; p<0.001). Moreover, neutrophil levels were negatively correlated with Lymphocyte (r = -0.530; p<0.001) and monocyte (r = -0.354; p<0.001) levels. Leucocytosis with neutrophilia and lymphopenia was seen in 18 patients (51%), highest TLC count was 67x 10 ^ 3/μL, mild to moderate variable anaemia was found in 13 patients (37%) and mild thrombocytopenia was found in 4 patients (11%) CRP, Ferritin and IL-6 were positively connected with each other (r = 0.330; p<0.001).The most common and maximum value of Ferritin was >1650.00 ng/ml. CRP was initial inflammatory marker and positive in 34 patient 97%) and thus only one had normal value. All patients has raised D-Dimer and IL-6 value in this series, maximum IL-6 value was detected 2490.90 pg/ml.

DISCUSSION:

The most commonly reported blood count abnormality is lymphopenia which occurs in 35%-83% of patients. [11, 12, 13] Lymphopenia is also more frequent and the absolute lymphocyte count (ALC) much lower in severe cases of COVID-19. [14,15] In one study of haematological parameters in hospitalised COVID-19 patients in Singapore, the median nadir of the ALC was significantly lower in patients requiring admission to intensive care unit (ICU) (0.4×10^9/L vs 1.2×10^9/L) as was neutrophilia (11.6×10^9/L versus 3.5×10^9/L).[13] Another study from Wuhan revealed a similar pattern with more severe cases having higher neutrophils (4.3×10^9/L versus 3.2×10^9/L; $P < .001$) counts, lower lymphocytes counts (0.8 1.0×10^9/L versus 1.0×10^9/L; $P < .001$), higher neutrophil-to-lymphocyte ratio (5.5 versus 3.2; $P < .001$).Mild thrombocytopenia (100-150 $\times 10^9$/L) has been reported in up to 20%-36% of COVID-19 cases [14,15] however, severe thrombocytopenia ($<50 \times 10^9$/L) is unusual. These haematological findings are also found in our study [Table 2]. COVID-19 patients have an increased thrombotic tendency. Approximately one-third of patients with COVID-19 had CT scan evidence of pulmonary embolism (PE) in a French study [44] Notably, two-thirds of the patients without PE in this cohort also had elevated D-dimer with a higher cut off value of 2660 μg/L being more predictive of PE in this cohort. A retrospective study of COVID-19 patients admitted to ICU identified DVT in 25% with advanced age, lower lymphocyte counts and elevated D-dimers being significant risk factors. [46] The prognostic importance of D-dimer testing was further demonstrated in a prospective study of hospitalised COVID-19 patients which revealed that significantly higher D-dimer and prolonged prothrombin time (PT) were associated with a higher probability of mortality. [47] In a study investigating prolonged activated partial thromboplastin time (APTT) in patients with COVID-19, the lupus anticoagulant was detected in 91% [48 Taken together, these findings strongly support the existence of a syndrome of COVID-19-associated CAC characterised by derangements in clotting tests (PT and APTT), elevated D-dimer and an increased thrombotic tendency. In our resent study D-dimer was raised in all patients [table 3]. The precise mechanism of the development of lymphopenia in COVID-19 is not known but lymphocytes have been shown to express ACE2 and lymphoid cell apoptosis may be a consequence of SARS-CoV-2 infection. [50] Trafficking of lymphocytes away from the peripheral blood to the lungs or other sites of infection may also play a role. The neutrophilia observed in severe cases of COVID-19 is most likely a response to the cytokine storm which has been implicated in the most severe manifestations of the disease. Further more significant elevations of acute-phase markers such as ferritin, CRP and procalcitonin have been associated with mortality from COVID-19 and these biomarkers are positively correlated with increased pro-inflammatory cytokines such as Interleukin-6 and TNF- .[26,28] Therefore, serial monitoring of these markers may facilitate early therapeutic intervention with experimental immunomodulatory agents.

CONCLUSION:

There is paramount importance of haematological and immunological parameters such as inflammatory markers, D-dimer level and absolute lymphocyte count in defining prognostic groups and monitoring response to therapy in COVID-19. The emphasis on the increased thrombotic risk and the importance of anticoagulation in COVID-19 is of specific relevance to clinicians. Hematological changes in COVID-19 patients have diagnostic and prognostic significance.

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