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Haematological Manifestation in Covid_19

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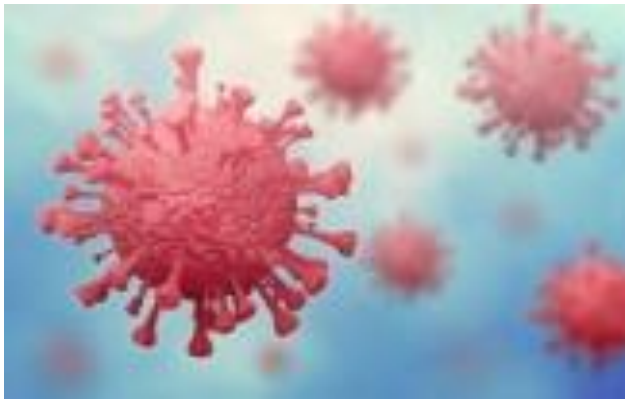


ABSTRACT:

The first evidence for the existence of what is today known as Coronavirus Disease 19 (COVID-19) emerged on 8 December 2019, when many cases of an acute respiratory illness – caused by an unknown at the time pathogen- were reported in the city of Wuhan.

After this very rapidly the cause was defined and the pathogen was isolated on 7 January 2020 as a virus named '2019 novel coronavirus' (2019-nCoV) or as 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2).

The emergence of the Coronavirus Disease 19 (COVID-19) pandemic, has had a significant global influence that resulted in substantial morbidity and mortality across the globe.

Although involvement of the lower respiratory track is what we see for most of the morbidity and mortality cases , the virus also involves several organ systems and the syndrome shows clinical diversity with a wide range of symptoms and manifestations.

The involvement of the hematopoietic system in severe cases is associated with poor outcomes and mortality and they are :

Lymphopenia, leukopenia, thrombocytopenia, disseminated intravascular coagulation, and a prothrombotic state are common manifestations of COVID-19 .

The better understanding of the mechanisms of the pathophysiology of COVID-19- induced hematological manifestations may result in better ways to treat and to decrease the associated morbidity and mortality.

Introduction:

Corona viruses is a flu_like illness that is spread by breathing , eye and faeco_oral route .Most people recover with no or minimal symptoms(70-90%) , however it is very unpredictable _many fit and young people have had very severe illness and even died, bur the majority who had severe course were mostly the eldery people with comorbidities or immunodeficient people.

The virus enter the host cell via TMPRSS2 and ACE2 receptors .

The cells frequently affected are bronchial epithelial cells, type2 alveolar pneumocyes and capillary endothelial cells and an inflammatory response occurs usually TNF , IL_6,IL_1 that are activated by lymphocytes, neutrophils. macrophages and monocytes.This continued inflammatory response results in alveolar interstitial thickening with increased vascular permability and edema.

Along with the symptoms the virus is detected with PT_PCR or the Reverse transcription polymerase chain reaction, though current data say that it is only 30_70% effective for acute infection and this may be due to incorrect use of the kits or not enough virus especially in the early stage of the illness .

Other investigation may also be done like collecting upper respiratory specimen using a nasopharyngeal and in the setting of a productive cough , a sputum can be collected for investigation.

On the othere hand , imaging techniques might also be useful like a chest X ray or CT with the later being more sensitive .

Ultrasound is also emerging as a valuable diagnostic measue.

Review of literature:

Covid (Corona virus disease of 2019) is a virus that belongs to a family of viruses called the "Coronaviridae " , positive _strand and enveloped viruses which are composed of :(47).

▪ Helical capsid; enveloped (outer lipid membrane)

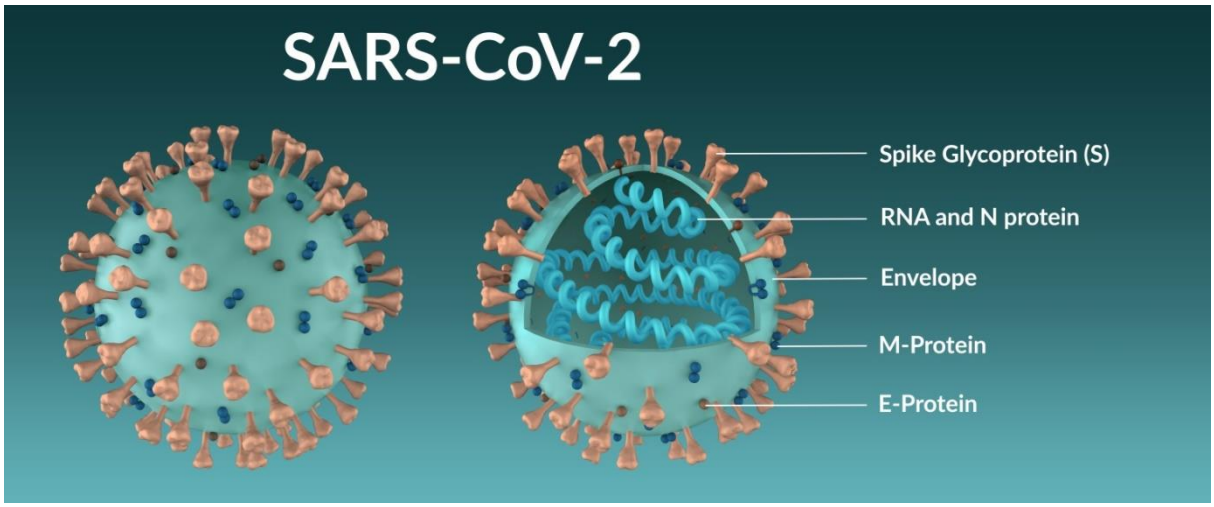
▪ Structural proteins are:

1.Small envelope protein (E)

2.Membrane protein (M).

3.Nucleocapsid protein (N)

4.Spike protein (S) that binds, fuses with host cell membrane.



Taxonomy: (47)

Corona means crown and was named after the spiked appearance seen in electron microscopy.

Those viruses were identified since the mid1960s but before SARS_CoV they were known to cause only mild and self_limiting illness in humen which we call as "cold" .

Recently it was confirmed that a mutation happened in some of these viruses in their non_humen hosts especially bats and then they find their way to infect humen beings.

SARS-CoV-2 is approximately 80% similar to SARS-CoV, and invades host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor

It invades the cell of the host through the 4 steps mechanism(46):

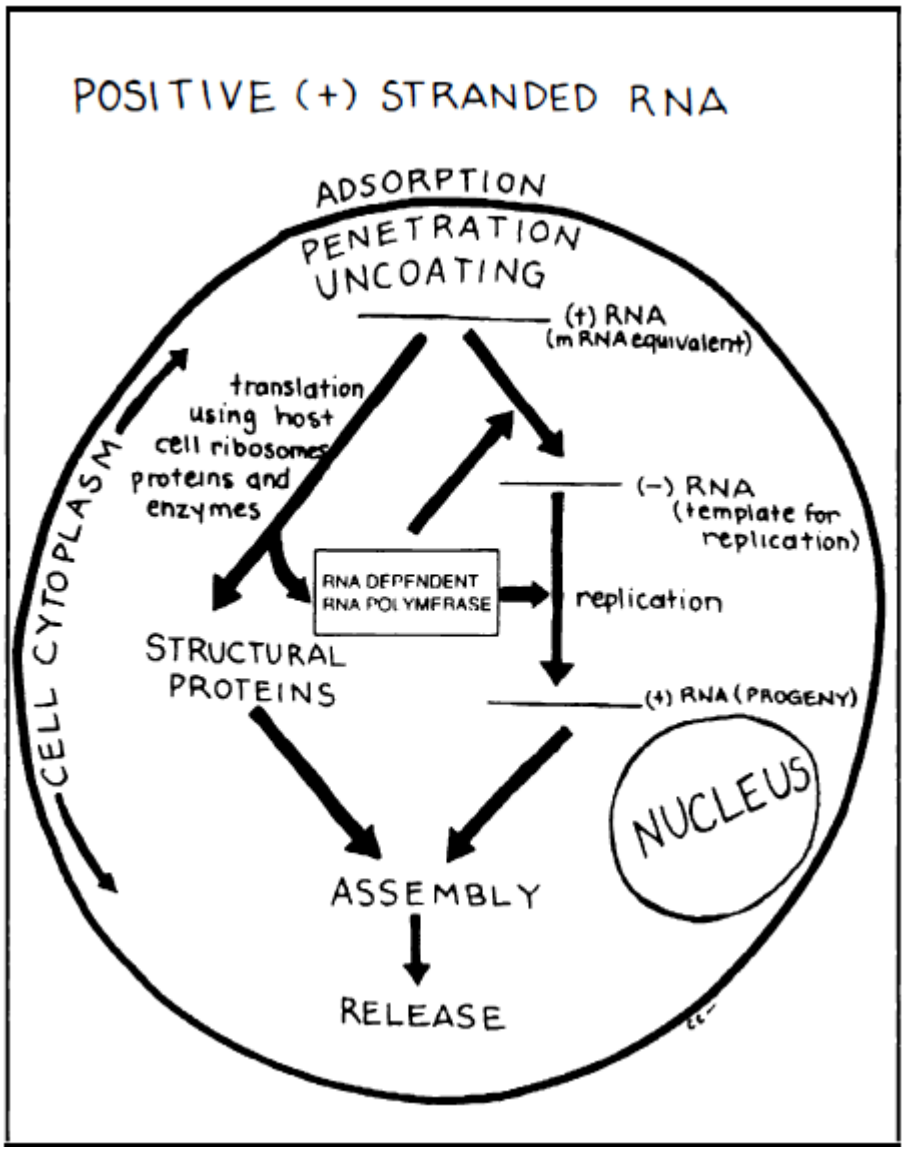
1) Adsorption and penetration.

2) Uncoating of the virus.

3) Synthesis and assembly of viral products

4) Release of virions from the host cell .

The first step " the absorption " happens by that the viral particle is attached to the cell membrane of the host.



Unlike other coronaviruses, SARS-CoV-2 possess a furin-like cleavage site in the S-protein domain that is located between the S1 and S2 subunits (41, 42). Furin-like proteases are expressed, albeit at low levels, indicating that S-protein priming at this cleavage site could contribute to the wide cell tropism and transmissibility of SARS-CoV-2 (43).

But whether furin-like protease-mediated cleavage is essential for SARS-CoV-2 host entry has yet to be determined.

Inhibiting these processing enzymes may serve as a potential antiviral target (44). SARS-CoV-2 has developed a unique S1/S2 cleavage site in its S protein,

characterized by a four-amino acid insertion, that seems to be absent in other coronaviruses (45).

COVID-19 is the constellation of clinical symptoms caused by the SARS-CoV-2 virus which range from aymptomatic to Acute respiratory distress syndrome.

With the percentages of symptoms being :

Headache 70.3% .

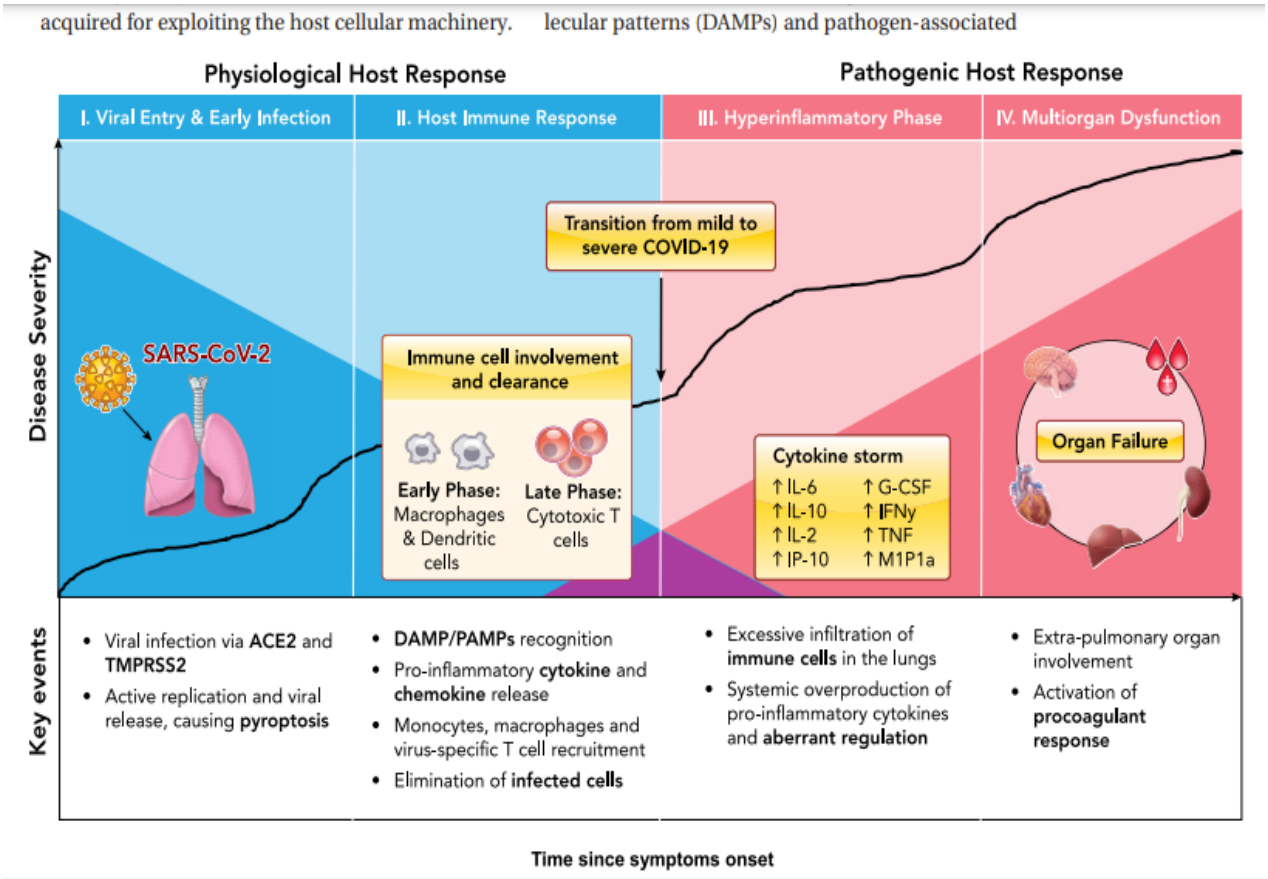
Loss of smell 70.2%

Dry cough 63.2%

Gustatory dysfunction 54.2%

Sore throat 52.9%

Diarrhea 1_10% (5 to 6 days).



Haematological manifestations : are the followings : (34)

Lymphocytopenia
Thrombocytopenia
Coagulopathy

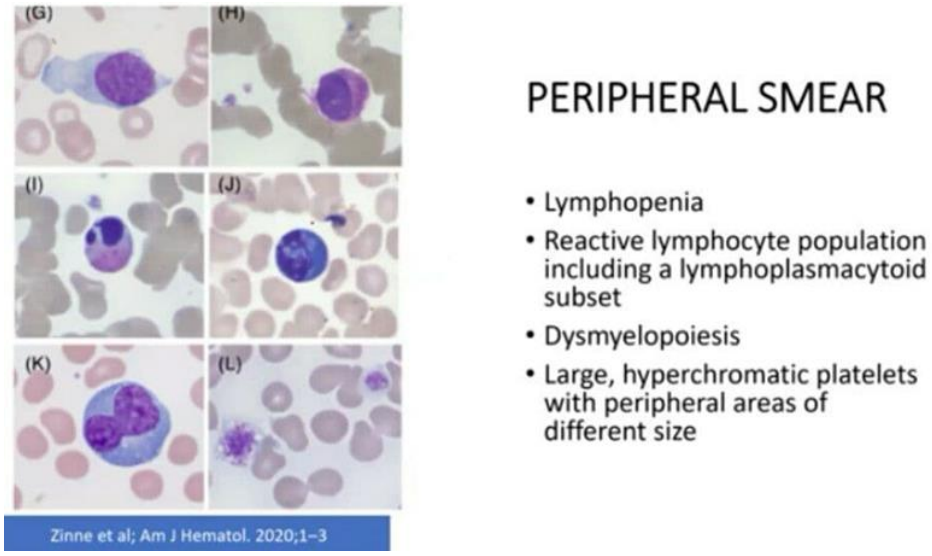
1.Lymphocytopenia :

Lymphocytes have ACE2 receptors found on their surface hence can be infected by COVID.

During the incubation period 1_14 days when there are non_specific symptoms lymphocyte counts are normal or slightly reduced.

Approximately 7 to 14 days from the onset of the intial symptoms there will be a surge in the clinical manifestation (cytokine storm) and associated with significant lymphopenia.

Cytokine storm: mark increase levels of interleukins
IL_6 ,IL_2 ,IL_7,granulocyte colony stimulating factor, interferon_gamma, MCP_1,MCP_1aand tumor necrosis factor _alpha which may promote lymphocyte apoptosis,and could also cause atrophy of lymphoid organs like spleen.



In cancer patients who have metabolic disorders like the coexisting lactic acid acidosis could also inhibit lymphocyte proliferation.

2.Thrombocytopenia:

In most cases , the platelet count did not decrease to a level at which bleeding occurs , because megakaryocytes are still being formed keeping platelet at normal levels.

Thrombocytopenia occur due to many mechanisms , include:

Cytokine strom destroys the platelet progenitors in the bone marrow .

Increase in autoantibodies and immune complexes which means that the platelets are cleared by the immune system .

Lung injury which causes platelet activation and their consumption.

At admission ,patients with thrombocytopenia had lower white blood cells,neutrophil and lymphocyte count and higher levels of procalcitonin and C_reactive protein compared with those without thrombocytopenia.

Lower levels of plateletcrit (PCT) which is the volume occupied by platelets in the blood and higher mean platelet volume MPV+platelet large cell ratio P_LCR which is >12ft circulating platelets.

Blood smear will show large cells .

Patients who had platelet count less than 200 at admission were considered the wrosr prognosis that if it was going to be even lower the survival rate decreased as well,

3.Coagulopathy : high incidence of thrombosis and the most common caiuse of death , this includes:

1.Increased prothrombin
2.Increased or normal activated partial thromboplastin time
3.Increased fibrinogen
4.Increased FDP
5.Increased D dimer
6.Mild decrease in platelet

Generally prothrombin is more increased than activated partial thromboplastin because of factor8 that is an acute phase reactant which helps normalizing aPTT.

Fibrinogen is an acute phase reactant so its level is increased.

Inflammation_induced endothelial cell injury could result in massive release of plasminogen activators _ Fibrin degradation products and D dimer- usually in sever cases of COVID.

The major difference between COVID_19 associated coagulopathy and disseminated intravascular coagulation (DIC) are the elevation of fibrinogen and marked elevation of D_dimer levels _in DIC there ai decreased level of

fibrinogen and less elevation of D_dimer _and from other differences is that thrombocytopenia is very elevated in DIC while mild in COVID associated coagulopathy and also prothrombin time is more than partial thromboplastin time while microangiopathy is not present.

We can say that a combination of low_grade DIC and a localized pulmonary thombotic microangiopathy is what we call as (COVID _19 associated coagulopathy.

Plasma exchange can be helpful because it was found to replenishing ADAMTS and removing inflammatory mediators.

Generally a diagnostic approach is consisting of the measurements of D_dimer , prothrombin time and platelets counts that should be repeated every 2_3 days.

We should also keep in mind that every COVID associated coagulopathy can be progressed to DIC .

4.Inflammatory biomarkers:

Erythrocyte sedimentation rate , C_reactive protein , serum ferritin levels all elevated and correlate with cytokine storm.

Study :(1- 30)

A study result of subjects in seven centers of five hospitals of Union Hospital (Central Hospital, Union West Hospital, and Union Tumor Hospital), Wuhan Central Hospital, General Hospital of Central Theater Command, PLA, Wuhan Third Hospital, and Wuhan Jin-Yin-Tan Hospital between January 20, and April 4, 2020.

Subjects were studied on admission for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infection by quantitative realtime reverse transcriptase-polymerase chain reaction **(qRTPCR)** of nasal and pharyngeal

swabs and/or blood test for anti-SARS-CoV-2 IgG/IgM antibodies using a colloidalgold- based 2019-nCoV IgG/IgM Detection Kit

Analyzed data from 3559 consecutive subjects were taken:

1700 were excluded because of missing data of SARS-CoV-2 qRT-PCR or anti-SARS-CoV-2 IgG/ IgM, 410 with co-morbidities and/or receiving drugs that would potentially affect bone marrow function . The resulting study cohort was only 1449 subjects.

733 subjects **(51%) were male**. Median age was 57 years (IQR, 42–66 years), 576(40%) were 60–79 years and 66 (5%), ≥80 years.

Common signs and symptoms on admission included:

1. dry cough (485; 43%)

2.productive cough (551; 38%),

3. fatigue (531; 37%)

4.shortness of breath (520; 37%).

5.hematological manifestations.

1327(92%) were alive at time of the study while 122(8%) died.

First the comparison was between hematological co-variates between

survivors and non-survivors.

White blood cells and platelets:

As we see that white blood cells are more in subjects who died while platelets were less in the following table:

Table 2 Blood hematological co-variates of survivors and non-survivors with COVID-19.

	N	Total	Alive	Died	*P* value
Hemoglobin, g/L (115–150)					
Baseline	1437	129 (119–139)	128 (119–139)	131 (122–143)	0.068
Max	1101	132 (122–142)	131 (126–146)	136 (122–142)	0.049
Min	1101	119 (108–131)	120 (110–131)	105 (78–126)	<0.001
White blood cell, ×10E + 9/L (3.5–10)					
Baseline	1420	5 (4–7)	5 (4–7)	8 (6–11)	<0.001
Max	1421	7 (5–9)	7 (5–8)	16 (12–21)	<0.001
Min	1421	5 (4–6)	5 (4–6)	6 (4–9)	<0.001
Neutrophil, ×10E + 9/L (1.8–6.3)					
Baseline	1417	3 (2–5)	3 (2–4)	7 (5–10)	<0.001
Max	1421	5 (3–7)	4 (3–6)	14 (11–20)	<0.001
Min	1421	3 (2–4)	3 (2–4)	5 (3–8)	<0.001
Lymphocyte, ×10E + 9/L (1.1–3.2)					
Baseline	1440	1.2 (0.8–1.6)	1.2 (0.9–1.7)	0.5 (0.4–0.8)	<0.001
Min	1411	1.0 (0.7–1.4)	1.1 (0.8–1.5)	0.3 (0.2–0.5)	<0.001
Monocyte, ×10E + 9/L (0.1–0.6)					
Baseline	1408	0.4 (0.3–0.53)	0.4 (0.3–0.5)	0.3 (0.2–0.5)	<0.001
Max	1419	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.8)	0.305
Min	1419	0.3 (0.2–0.4)	0.3 (0.3–0.4)	0.2 (0.1–0.3)	<0.001
Platelet, $\times 10^9$ E + 9/L (125–350)					
Baseline	1415	206 (159–264)	208 (164–268)	166 (109–223)	<0.001
Max	1420	258 (204–325)	263 (208–331)	190 (134–255)	<0.001
Min	1420	176 (135–224)	180 (143–226)	80 (39–147)	<0.001

Data are presented as medians (interquartile ranges, IQR). *p* values were calculated by Mann–Whitney *U* test, χ^2 test, or Fisher's exact test, as appropriate

Blood lymphocyte subset :the baseline blood lymphocyte subsets between subjects who died and survivors (Table 3).

Lymphocyte subset	*N*	Total	Alive	Died	*P* value
CD3+ (%)	579	72 (62–78)	72 (63–78)	59 (50–67)	<0.001
CD3 concentration × 10E + 9/L	246	359 (2–901)	381 (2–918)	140 (75–190)	0.023
CD3+CD4+ (%)	579	41 (33–48)	41 (33–48)	37 (28–48)	0.443
CD3+CD4+ concentration × 10E + 9/L	246	200 (1–481)	227 (1–487)	71 (46–107)	0.036
CD3+CD8+ (%)	579	23 (18–30)	24 (19–30)	14 (10–18)	<0.001
CD3+CD8+ concentration × 10E + 9/L	246	119 (1–302)	141 (1–308)	49 (14–64)	0.023
NK cell (%)	415	10 (6–17)	10 (6–17)	10 (5–12)	0.29
NK cell concentration × 10E + 9/L	246	76 (0.4–185)	77 (0.4–188)	41 (19–102)	0.453
B lymphocyte (%)	415	13 (9–18)	12 (9–17)	16 (10–28)	0.022
B lymphocyte concentration × 10E + 9/L	246	96 (0.3–178)	98 (0.3–188)	55 (22–91)	0.136
CD4+/CD8+ ratio					
Max	577	2 (1.4–2.6)	1.9 (1.4–2.6)	3.0 (1.9–4.5)	<0.001
Min	489	1.6 (1.2–2)	1.57 (1.2–2)	1.6 (1.3–2.3)	0.336

Data are median (IQR), *n* (%), or *n*/*N* (%). Cell count at presentation (cells/ul). *p* values were calculated by Mann–Whitney *U* test, χ^2 test, or Fisher's exact test, as appropriate.

NK cell natural killer cell

Clotting co-variates

Baseline and maximum values of prothrombin time, activated partial thromboplastin time, and also D-dimer concentrations were significantly higher in subjects who died in comparison with the survivors.

In contrast, fibrinogen concentration was higher at baseline in subject who died (median 4.3 g/L versus 3.6 g/L but had lower minimum values 2.6 g/L versus 3.2 g/L).

Generally patients with **fibrinogen albumin ratio** <0.0883_albumin as a negative phase reactant will be low_ and **platelet count** >135 will have a low probability of severe disease.

	N	Total	Alive	Died	P value
PT, s (11–16)					
Baseline	1055	13 (12–13)	13 (12–13)	14 (13–15)	<0.001
Max	1035	13 (12–14)	13 (12–14)	17 (14–20)	<0.001
APTT, s (28–43.5)					
Baseline	1055	34 (30–38)	34 (30–37)	35 (300–40)	0.019
Max	1289	34 (30–38)	34 (30–37)	40 (34–50)	<0.001
D-dimer, mg/L (<0.5)					
Baseline	1239	0.4 (0.2–0.9)	0.4 (0.2–0.8)	3.6 (0.9–8)	<0.001
Max	1262	0.6 (0.2–1.6)	0.5 (0.2–1)	8 (6–8)	<0.001
Fibrinogen, g/L (2–4)					
Baseline	1304	3.7 (2.9–4.6)	3.6 (2.9–4.5)	4.3 (3.2–5.2)	<0.001
Min	976	3.2 (2.5–3.9)	3.2 (2.6–3.9)	2.6 (1.7–3.9)	<0.001

PT prothrombin time, *APTT* activated partial thromboplastin time.

Inflammatory and biochemical co-variates: C_reactive protein and lactic dehydrogenase levels and ferritin as acute phase reactants were high.

	N	Total	Alive	Died	P value
CRP, mg/L (<8)					
Baseline	1046	11 (3, 44)	9 (3, 30)	93 (58, 125)	<0.001
Max	1063	14 (4, 55)	11 (3, 38)	140 (110, 181)	<0.001
Procalcitonin, ng/ml (<0.5)					
Baseline	1273	0.05 (0.05, 0.1)	0.05 (0.04, 0.1)	0.2 (0.12, 0.6)	<0.001
Max	1065	0.07 (0.04, 0.1)	0.06 (0.04, 0.1)	1.2 (0.4, 4)	<0.001
LDH, U/L (109–245)					
Baseline	1338	207 (165, 283)	199 (161, 258)	470 (359, 599)	<0.001
Max	1354	215 (174, 302)	207 (169, 271)	707 (509, 1154)	<0.001
Ferritin, ng/ml (4.6–204)	231	542 (226, 1207)	446 (191, 906)	1584 (1196, 2000)	<0.001
ALT, U/L (5–35)	1429	39 (22, 68)	37 (21, 66)	62 (34, 150)	<0.001
AST, U/L (8–40)	1428	31 (22, 49)	30 (22, 44)	68 (45, 143)	<0.001
Total bilirubin, μmol/L (5.1–19)	1245	14 (10, 19)	13 (10, 17)	25 (16, 39)	<0.001
Creatine kinase, U/L (26–140)	1151	87 (54, 150)	81 (52, 130)	253 (104, 656)	<0.001
BNP, pg/ml (<100)	627	50 (14, 160)	39 (12, 115)	454 (116, 1377)	<0.001
Myoglobin, ng/ml (<140)	718	32 (21, 60)	29 (21, 49)	476 (147, 1200)	<0.001
Troponin I, ng/L (<26.2)	830	3 (1, 10)	2 (0.9, 7)	212 (48, 1011)	<0.001
BUN, mmol/L (2.9–8.2)	1414	5 (4, 6)	5 (4, 6)	14 (8, 23)	<0.001
Scr, μmol/L (44–106)	1414	70 (59, 83)	69 (59, 81)	100 (71, 211)	<0.001
IL-2, pg/ml (0.1–4.1)	344	3 (3, 4)	3 (3, 4)	3 (3, 5)	0.849
IL-4, pg/ml (0.1–3.2)	380	3 (2, 4)	3 (2, 4)	2 (2, 4)	0.804
IL-6, pg/ml (0.1–2.9)	659	10 (4, 37)	9 (4, 30)	71 (29, 442)	<0.001
IL-10, pg/ml (0.1–5)	380	4 (3, 6)	4 (3, 5)	11 (6, 30)	<0.001
TNF α, pg/ml (0.1–23)	380	3 (2, 6)	4 (2, 6)	3 (2, 4)	0.183
IFN γ, pg/ml (0.1–18)	380	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.88

CRP C-reactive protein, *LDH* lactate dehydrogenase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BNP* brain natriuretic peptide, *BUN* blood urea nitrogen, *Scr* serum creatinine, *IL*

Conclusion:

Covid affects the haematological system in many different ways .However, evidence of alarming coagulation abnormalities are the most significant .

The high incidence of thrombotic events in COVID-19 patients that could cause fibrin thrombi in pulmonary small arterial vessels in 87% of fatal cases examined suggests the contribution of coagulation in diffuse alveolar and endothelial damage(35) . These data clearly show a state of hypercoagulability in severe COVID-19.

Although prominent changes in blood coagulation may be a contributing mechanism to COVID-19 mortality, its pathogenesis is estimated to be tightly linked to inflammation and cytokine release.

Complement-mediated pulmonary tissue damage and microvascular injury have been observed in small cohort studies with severe COVID-19 (36).

Procoagulant response is also associated with the inflammatory effects of cytokines in the vascular endothelium and this includes: increased vascular permeability and damage because of the immune-cell infiltration (37).

Presence of neutrophil extracellular traps (NETs) might also be linked to COVID-19 thrombosis and this occur by the activation of intrinsic coagulation (38,39,40). Generally , the predominant mechanism seems that explain SARS-CoV-2-induced endothelial damage fosters monocyte recruitment and activation, and this along with tissue factor exposure, which then in turn activates blood coagulation.

The Recruitment of neutrophils by activated endothelial cells can also synthesize and release many cytokines into the circulation, hence further accelerating this process (48).

Beside the coagulopathy seen in COVID-19, severe bleeding in patients is rare in comparison to other RNA-type viruses with hemorrhagic manifestations (49). However, a recent report in Blood suggested bleeding as a significant cause of morbidity in COVID-19 patients, emphasizing the need for randomized trials on the benefit of prophylaxis (50).

By taking these data into consideration, a close connection among the inflammatory and coagulation response of COVID-19 patients appears to exist, wherein treatment options for both contributing factors should be explored.

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