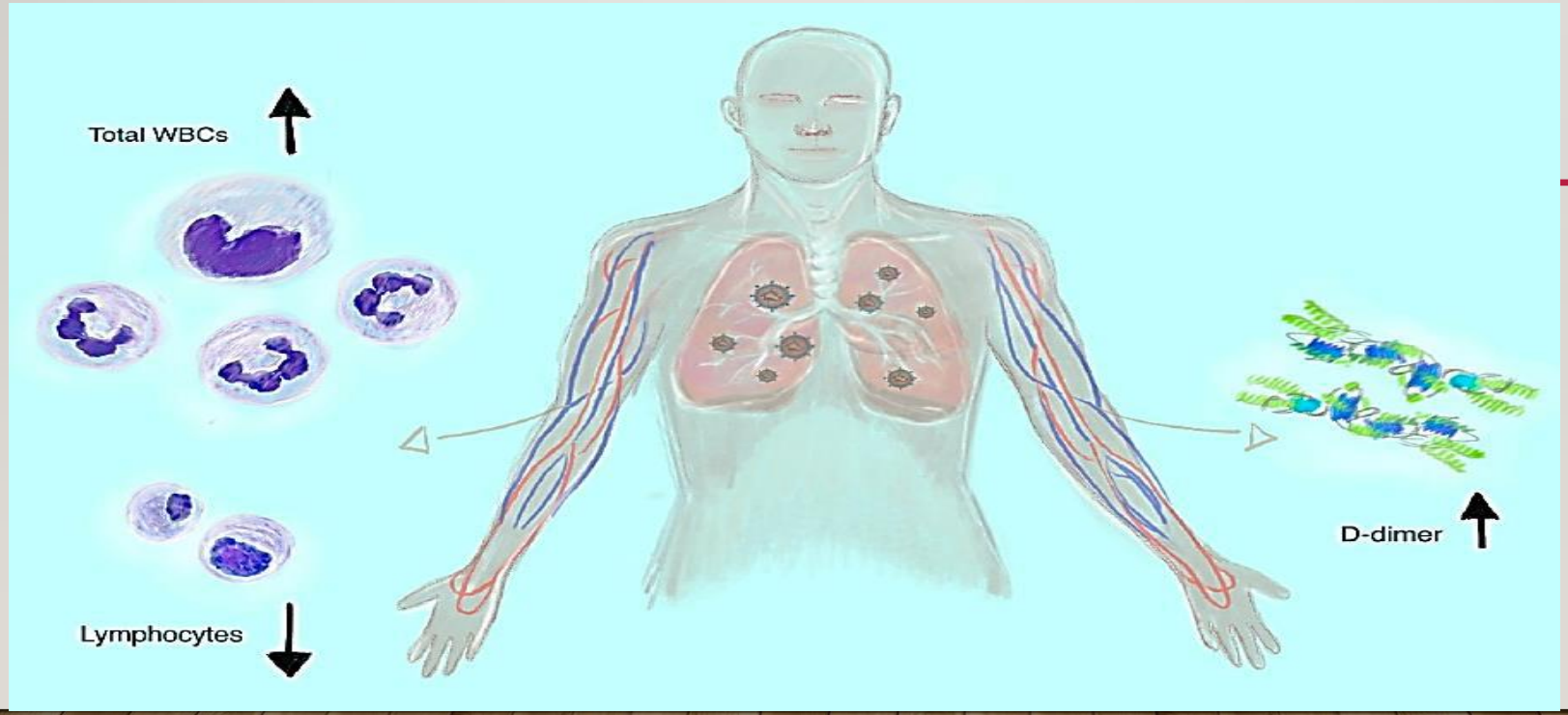
THIQAR UNIVERSITY
COLLEGE OF MEDICINE
MEDICINE DEPARTMENT
2021-2020

HEMATOLOGICAL PROBLEMS IN PATIENTS WITH COVID 2019



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INTRODUCTION

The initial evidence for the existence of what is today known as Coronavirus Disease 19 (COVID-19) emerged on 8 December 2019, Very rapidly the infectious cause was defined and the pathogen isolated on 7 January 2020 as a novel virus named '2019 novel coronavirus' (2019-nCoV) or 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2)'.

The SARS-CoV-2 is a single-stranded RNA virus that is highly infectious and easily transmittable from human to human. Interestingly, bats have been identified as the potential main reservoir in China and there is evidence that SARS related coronaviruses in bats can use the ACE2 receptor, the main receptor for cellular entry by SARS-CoV-2.

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COVID-19 is the **constellation of clinical symptoms** caused by the SARS-CoV-2 virus which range from mild respiratory symptoms to a severe and life-threatening form of pneumonia. The severity of the illness is heavily dependent on age and associated comorbidities.

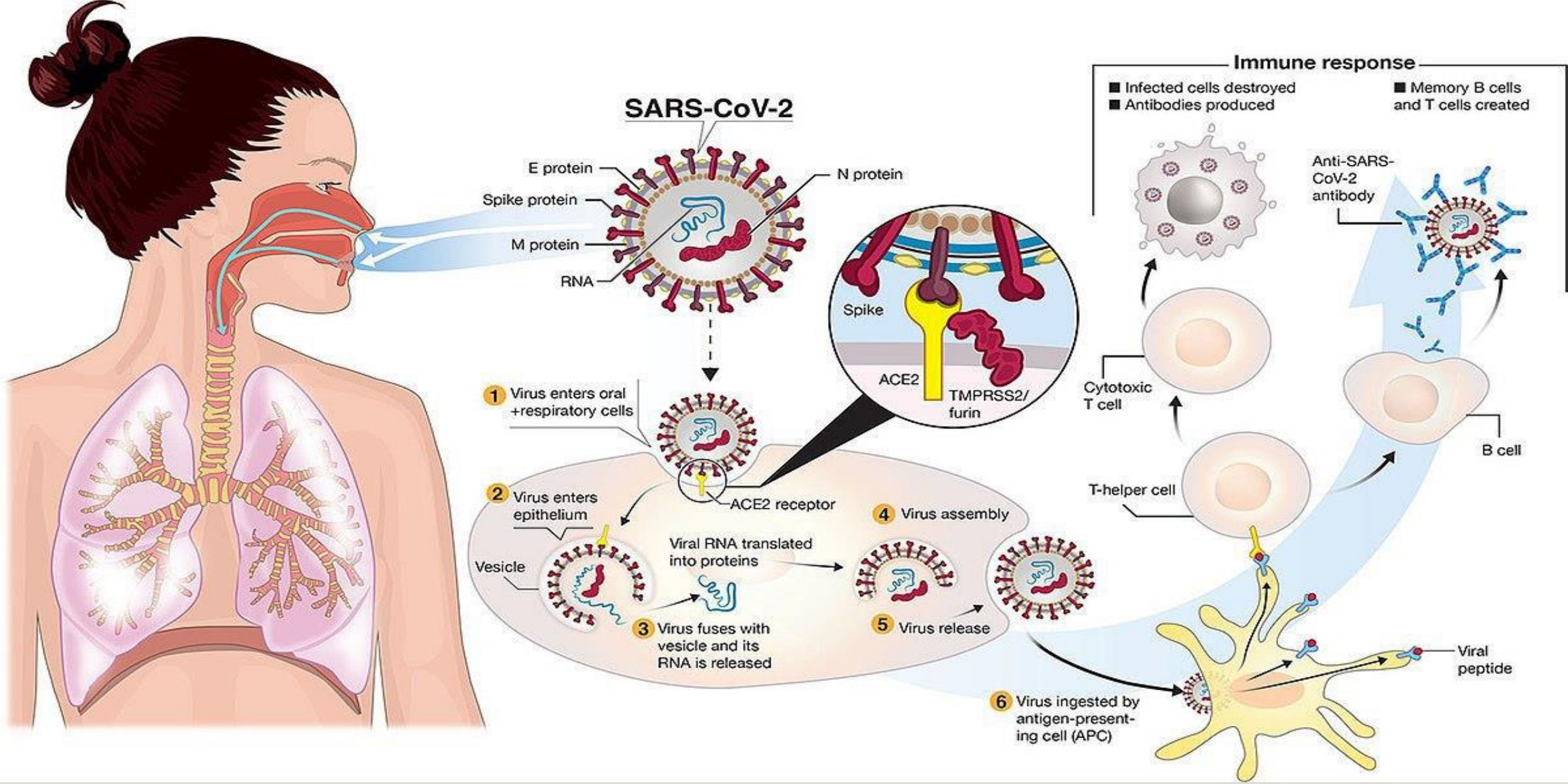
In a summary of 72,314 cases from the Chinese center for disease control and prevention, mortality rates reached 8% in the 70–79 age group and up to approximately 15% in patients older than 80. Overall mortality was 2.3%, but 10.5%, 7.3% and 5.6% in patients with cardiovascular diseases, diabetes and cancer respectively. Emerging evidence from studies in New York City suggest an ever higher death rate in patients with cancer, patients with hematological malignancies.

The hematologic complications of the SARS-CoV-2 virus, including

lymphopenia,

thrombocytopenia and

disruption in the coagulation cascade leading to laboratory abnormalities and coagulopathy.


SARS-CoV-2
E protein
Spike protein
M protein
RNA
N protein
Spike
ACE2
TMPRSS2/
furin
1 Virus enters oral
+respiratory cells
ACE2 receptor
2 Virus enters
epithelium
Vesicle
Viral RNA translated
into proteins
3 Virus fuses with
vesicle and its
RNA is released
4 Virus assembly
5 Virus release
6 Virus ingested by
antigen-present-
ing cell (APC)
Immune response
Infected cells destroyed
Antibodies produced
Memory B cells
and T cells created
Anti-SARS-
CoV-2
antibody
Cytotoxic
T cell
T-helper cell
B cell
Viral
peptide

HEMATOLOGICAL FINDINGS AND COMPLICATION

In patients with COVID-19, the most prevalent hematological findings observed in a complete blood count (CBC) include lymphopenia (83.2%), thrombocytopenia (36.2%), leukocytopenia (33.7%), and neutrophilia (34.5%). Of note, other significant laboratory findings representing inflammatory markers are elevations in erythrocyte sedimentation rate (ESR) (93.8%), serum ferritin (78.5), C-reactive protein (CRP) (60.7%), and procalcitonin (5.5%). Median hemoglobin levels have been found to be lower in patients with severe COVID-19 disease, such as those who are admitted to an intensive care unit (ICU), who require mechanical ventilation, or who succumb to death.

Laboratory Finding	% With Finding
Lymphopenia	83%
Thrombocytopenia	36%
Leukopenia	34%
C-reactive protein ≥10 mg/L	61%
Elevated AST and ALT	20%-39% (higher with severe disease)
Procalcitonin	Typically normal on admission

Coinfections:

- Sporadic viral coinfections reported (eg, influenza, parainfluenza)
- Community-acquired secondary bacterial infection not reported in published case series (blood cultures: negative)

Among the various hematological manifestations of COVID-19, coagulopathic abnormalities have recently emerged as important markers of negative prognosis, such as elevated D-dimer (23.3%), prolonged PT (2.1%), prolonged aPTT (9.7%). Another retrospective cohort study showed an increase in hospital mortality among patients with a D-dimer level > 1 μg/dl. These coagulopathic factor elevations suggest a procoagulant state in COVID-19, which often manifests as both venous and arterial thrombosis, and in severe cases can progress to DIC.

Lupus anticoagulant has been detected with an incidence as high as 90%, further supporting the presence of a hypercoagulable state. Furthermore, the presence of antiphospholipid antibodies in affected patients may contribute to coagulopathy via secondary antiphospholipid syndrome. The thrombotic complications that have been observed in patients with COVID-19 include deep vein thrombosis (DVT), pulmonary embolism (PE), I.V. catheter–associated thrombosis, acute myocardial infarction (MI), limb ischemia, and cerebrovascular thrombosis.(2)

CYTOPENIA'S AND PROGNOSIS IN COVID-19

Lymphopenia

COVID-19 associated lymphopenia is a common finding in affected patients and has a significant adverse prognostic value.

Hematologic abnormalities were more prominent in patients with severe disease when compared to non-severe presentations.

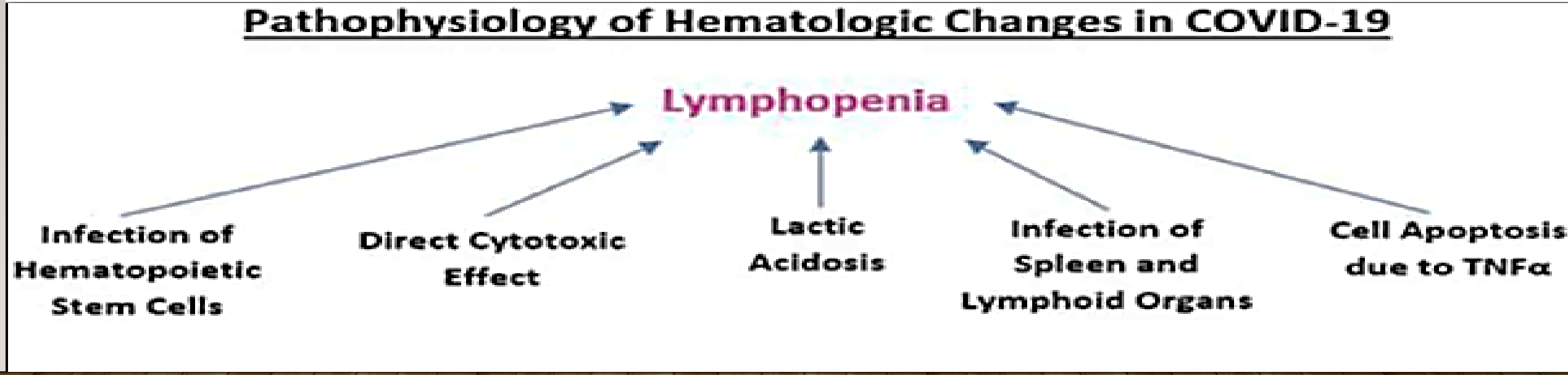
Decreased lymphocyte counts were associated with more severe outcomes and an increased risk of **ARDS**. hematologic factors linked to ARDS development (but not death) included **lymphocyte count, CD3, CD4 and CD8 T-cells**. There is an association between higher CD3 and CD4 T-cell counts and protection against ARDS as well as higher CD8 T-cell counts and survival. The authors hypothesized that the ability of patients to recover from the SARS-CoV-2 infection may depend on the gradual increase in lymphocyte counts and the ability of the immune system to recover.

The pathophysiology of the association between lymphopenia and clinical course and prognosis is multifactorial include :

1. **i**t is possible that during the initial incubation phase of the virus, lymphocyte counts are normal, even as viremia is in full effect, and clinical manifestations such as fatigue, fever, diarrhea and other nonspecific symptoms ensue. As virus spreads and concentrates in tissues expressing the angiotensin-converting enzyme 2 (ACE2) such as lungs, heart and gastrointestinal tract, symptoms worsen and radiographic findings such as chest lesions on CT scans become much more pronounced. **At this point both T- and B-cell lymphocyte counts decrease in conjunction with a significant rise in inflammatory markers**. This accelerated increase in cytokines and other components of the inflammatory response has been described as a '**cytokine storm'** and is characterized by a spike in the levels of several interleukins such as IL-2, IL-6, IL-7, tumor necrosis factor (TNF)-alpha and granulocyte colony stimulating factor, promoting lymphocyte apoptosis.

2- the expression of the ACE2 receptor on the surface of lymphocytes.
Thus, it is possible that one mechanism of the observed lymphopenia involves direct cytotoxic effects of the virus and cell membrane lysis.

3- metabolic derangements observed in critically ill patients such as **lactic acidemia** have been associated with inhibitory effects of lymphocytes. (1)



the degree of lymphocyte suppression correlated with poorer outcomes and a higher likelihood of ICU admission. In fact, when stratified by lymphocyte count, patients with >1100/μL were significantly less likely to have a severe illness than those in the 0–500/μL and 500–1100/μL ranges. Their findings also suggested that the drop in lymphocyte counts persisted until death and was accompanied by multiorgan failure including myocardial injury, kidney injury, hepatic injury, and coagulation.

THROMBOCYTOPENIA

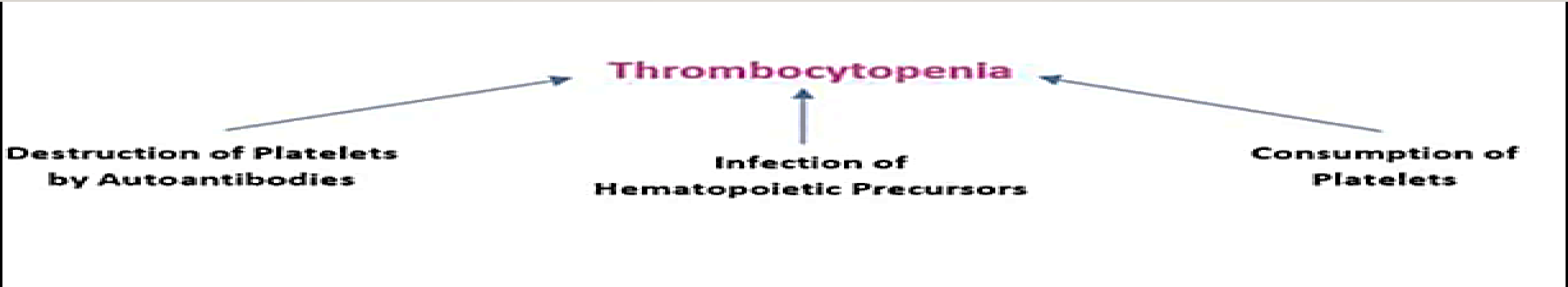
Thrombocytopenia is frequently seen in COVID-19 patients and **the platelet count appears to be independently linked to poor clinical outcomes**. thrombocytopenia at admission was linked to a **three-fold increase in mortality** compared to patients with normal platelet counts. In most instances, SARS-Cov-2 did not cause a decrease in platelet count that was significant enough to cause bleeding complications. But given the prevalence of thrombocytopenia among COVID-19 patients and its prognostic implications, there is increasing interest in understanding its pathophysiology. This would hopefully help understand how the coronavirus disrupts the entirety of the hematopoietic system.

Mechanisms of Thrombocytopenia :

1-the virus binds to bone marrow cells, such as granulocytes, monocytes and platelets, through the CD13 receptor and leads to **aberrant growth and apoptosis in the bone marrow.**

2- increased platelet destruction through formation **of autoimmune antibodies** in a similar fashion to the immune-mediated thrombocytopenia phenomenon. Viral epitopes circulating in the bloodstream would mimic antigens present on platelet surfaces and lead to formation of antibodies and the platelet-antibody complexes would be destroyed through a complement independent immune-mediated response.

3-**Endothelial damage triggered by a systemic inflammatory response and mechanical ventilation leads to hyperactivation of platelets and thrombosis causing disseminated platelet consumption**.(1)



COAGULATION DISORDERS IN COVID-19

COVID-19 associated coagulopathy

Evidence of a disruption in the coagulation cascade is a common finding through most accounts of patients with COVID-19, particularly those with severe disease.

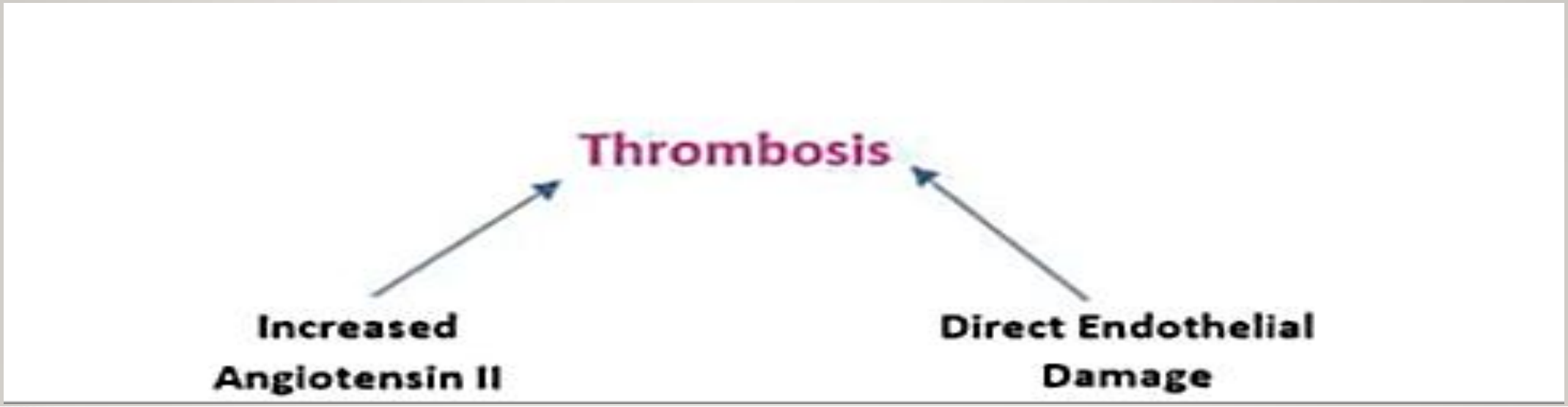
Almost all emerging data confirms that d-dimer elevation is a frequent occurrence in infected patients and suggests a correlation with disease severity.

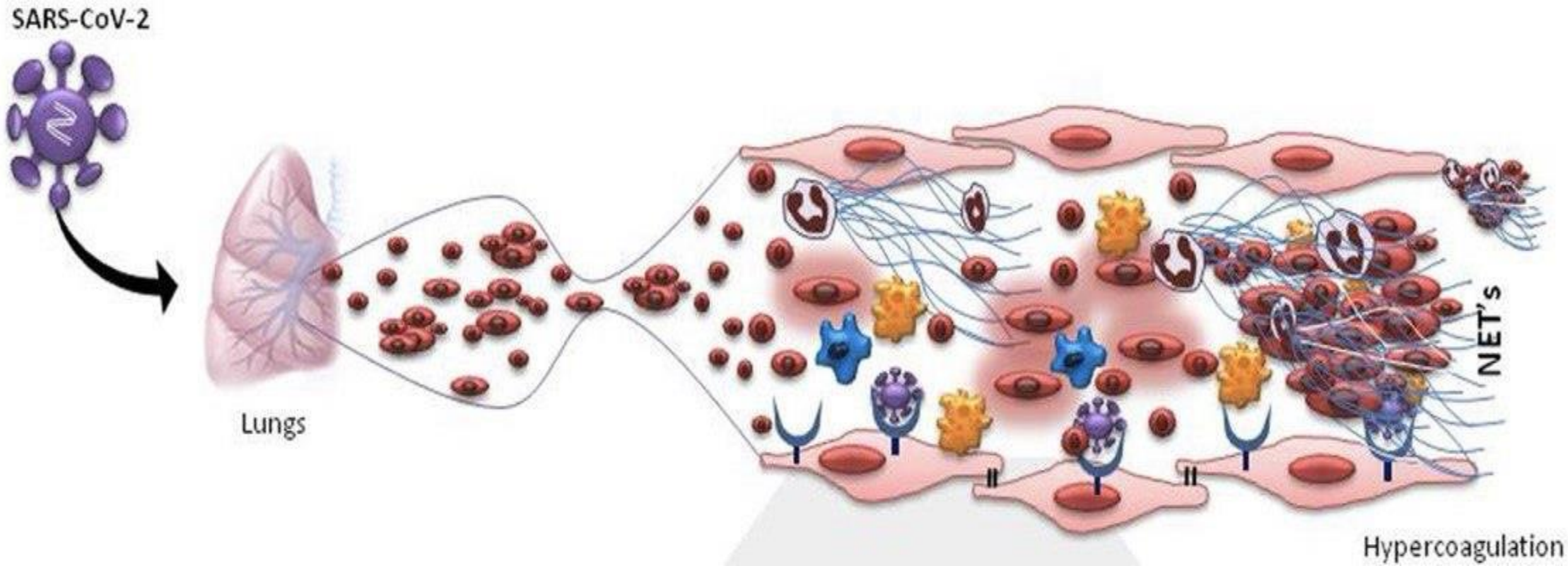
the major associated clinical presentation involves thrombosis,

COVID-19 positive patients with new onset CVD were significantly older and more likely to have predisposing risk factors such as elevated blood pressure, diabetes mellitus and prior CVD events. In addition, they also had higher rates of elevated markers of inflammation and hypercoagulability such as C-reactive protein and d-dimer

There have also been numerous accounts of autopsies of patients who have died from COVID-19 associated hypoxic respiratory failure demonstrating **microvascular thromboses** that have been linked to either **hypercoagulability, complement hyperactivation** or **direct endothelial damage.**

In fact, one specific mechanism of the SARS-CoV-2 virus is through its ACE2 receptor found to be expressed in endothelial cells, They hypothesized that the virus uses the ACE2 receptor to directly infect the endothelium and recruit immune cells**. Inflammation of the endothelium or 'Endotheliitis' ensues and leads to microvascular dysfunction, vasoconstriction, organ ischemia, and a hypercoagulable state.**


Thrombosis
Increased Angiotensin II
Direct Endothelial Damage


SARS-CoV-2
Lungs
NET's
Hypercoagulation

Disseminated intravascular coagulation

its association with mortality extends beyond the well-known hyperactive cytokine response leading to local and systemic inflammation, hemodynamic changes, and coagulopathy. Elevated PT, APTT and d-dimer have been shown to accompany an elevation in troponin-T underlining an association between systemic inflammatory response, coagulation disorders and cardiac injury.

the difference in d-dimer levels between surviving patients and patients who died was more pronounced than that between the ARDS and non-ARDS groups, reflecting additional undefined pathophysiological elements leading to death independent of ARDS, but likely related to the development of DIC .

DIC is frequently associated clinically with bleeding.

Mechanism of DIC

1. It is well known **that infectious pathogens can activate a systemic inflammatory response** that triggers an unimpeded coagulation cascade that no longer functions to maintain hemostasis but **leads to DIC and multi-organ failure**. It is therefore not surprising that sepsis associated with COVID-19 can lead to a coagulopathy through 'thromboinflammation
2. **whereby cytokine release activates endothelial cells and monocytes.** The latter can secrete tissue factor and Von Willebrand factor, resulting in platelet activation and initiation of fibrinolysis.
3. levels of fibrin related markers such as d-dimer and fibrin degradation products are markedly elevated in most COVID-19 deaths, suggesting overly activated inflammatory and coagulation pathways.

Pathogenesis of DIC

Activation of Intravascular Coagulation

Endothelial Damage

Platelet consumption

Coagulation Factors Consumption

Fibrinolysis

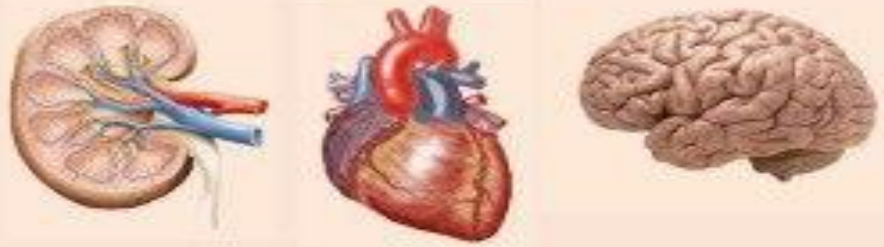
Microvascular thrombosis

↓Platelet

↑ PT
↑ aPTT

↑ D-Dimer

Impaired coagulation and Bleeding



Multi-Organ Ischemia or Failure

CLINICAL OUTCOME

- Hematological laboratory findings can be utilized to determine the severity and prognosis of COVID-19 infection.
- **Thrombocytopenia** has been shown to be associated with an increased risk of severe disease and COVID-19-related mortality**, lymphopenia** was linked to a threefold increase of severe COVID-19 disease , increase in neutrophils was directly linked to adverse outcomes and mortality.

- Abnormalities in coagulation parameters, such as increased prothrombin time (PT) and activated partial thromboplastin time (aPTT), elevated fibrinogen, fibrin degradation products (FDP), and D-dimer levels, have also been shown to be important prognostic factors in patients with COVID-19 pneumonia. Numerous studies focusing on hematologic abnormalities in COVID-19 patients indicate the presence of a co-existing coagulopathy, which may predispose to thrombotic complications, including venous thromboembolism (VTE), PE, arterial thromboembolism, MI, cerebral infarction, and DIC.

	Parameter	Clinical Value
White blood cell (WBC) –related parameters	WBC count	↑ in severe cases
	Lymphocyte count	↓ in severe cases
	$CD3^+$, $CD4^+$, $CD8^+$ T cell count	Early prognosis of severity
	Neutrophil to $CD8^+$ T cell ratio (N8R)	↓ in severe patients
	Neutrophil to lymphocyte ratio (NLR)	↑ in severe cases
	Lymphocyte to C–reactive protein ratio (LCR)	Early prognosis of severity
Red blood cell (RBC) –related parameters	Ferritin levels	↑ in severe cases
	Erythrocyte sedimentation rate (ESR)	↑ in severe cases
	Platelet (PLT) count	Early prognosis of severity
	D–dimer levels	↓ in severe patients
		Early prognosis of severity and mortality
		↑ in severe cases

TREATMENT OF COVID-19 ASSOCIATED COAGULOPATHY

- The American Society of Hematology has recommended the use of **either low molecular weight heparin (LMWH) or fondaparinux for thromboprophylaxis in COVID-19-associated hypercoagulability,** except in cases where the risk of bleeding supersedes thrombosis risk.
- In those with existing contraindications for anticoagulation, **pneumatic compression devices** could be initiated instead. A regulatory agency approved regimen may be used for **thromboprophylaxis after discharge,** such as a first dose of **betrixaban 160 mg,** followed by **80 mg daily for 35–42 days**, or **rivaroxaban 10 mg daily for 31–39 days.**.

- **Therapeutic anticoagulation** is initiated in patients with confirmed cases of VTE, with patient comorbidities and co-existing conditions dictating the choice of treatment- either low molecular weight heparin, unfractionated heparin, or direct anticoagulants. If necessary, reduced antithrombin III levels can be replenished with fresh frozen plasma. **PE management in COVID-19** patients follows a standardized guideline with hemodynamically stable patients receiving anticoagulation with close monitoring and severe cases receiving fibrinolysis. In unstable patients or if systemic fibrinolysis is contraindicated, catheter-directed therapies can be utilized. Patients with COVID-19-associated coagulopathy should be evaluated with viscoelastic coagulation tests including thromboelastography (TEG) and a coagulation and platelet function analyzer. Patients with prolonged PT or APTT > 1.5 times, TEG R time > 10 min, are candidates for fresh frozen plasma infusion

- **In acute coronary syndrome with plaque rupture,** the use of dual antiplatelet and anticoagulants is recommended in accordance with standard guidelines, unless contraindicated. Differentiation between myocarditis, nonspecific myocardial injury, and plaque rupture is important as the former two conditions do not require intervention. Transthoracic echocardiography (TTE) can be utilized prior to intervention to assess regional wall motion abnormalities.

- In ST-elevation myocardial infarction (STEMI), the risk (of transmission and delay in treatment) benefit ratio must be considered and selected cases may receive fibrinolysis. In STEMI, the decision to proceed to the catheterization laboratory is guided by the severity of STEMI, the severity of COVID-19 in patients, and the risk of transmission. **Heparin is generally avoided in DIC but is recommended in DIC associated with COVID-19.** Unless clinically necessary**, long-acting antiplatelet drugs should be discontinued. In cases with active bleeding,** the transfusion of blood products can be considered, with platelet concentrate administered to maintain counts > 50*109/l and fresh frozen plasma in patients with deranged PT/ APTT ratio or decreased fibrinogen.(2)

CONCLUSION

- As the world was shaken by the COVID-19 pandemic, clinicians and scientists are gathering as much data as possible to help them understand, and perhaps predict, the behavior of this pathogen in order to design strategies that might help improve outcomes and reduce morbidity and mortality .
- the most common complication associated with the SARS-CoV-2 infection has been related to viral pneumonia and ARDS, we now know that COVID-19 affects a host of systems including the cardiovascular and hematopoietic systems.

- This virus acts mainly through hyperactivation of a systemic inflammatory response known as a ‘cytokine storm’ that exhausts the immune system, depletes certain immune cells, decreases production of hematopoietic stem cells and activates the coagulation cascade. Although patients suffering from COVID-19 can develop DIC and have bleeding complications, most present with thrombotic episodes that can be either venous or arterial. Unlike popular belief, COVID-19 does not discriminate against age as an increasing number of ‘young’ patients are presenting with thrombotic complications. In fact a very recent study demonstrated that large vessel stroke can be the initial presenting clinical feature in relatively young patients with COVID-19

- Looking into laboratory parameters will help us predict outcomes and severity of disease, in the hope of designing strategies to manage potential complications such as cytopenia, DIC, VTEs, CVD, cardiac injury
- one strategy should aim at building predictive models that would combine inflammatory and coagulation markers with clinical features and predict life threatening emergencies such as thrombosis and DIC. These models may guide clinical decisions early on such as full versus prophylactic anticoagulation and thresholds for blood product transfusions.(1)

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- 1- Alain Mina, Koen van Besien & Leonidas C. Platanias (2020) Hematological manifestations of COVID-19,Leukemia & Lymphoma, 61:12, 2790-2798, DOI: 10.1080/10428194.2020.1788017 2- Khandait, H., Gandotra, G., Sachdeva, S. *et al.* COVID-19 and Hematology—What Do We Know So Far?. *SN Compr. Clin. Med.* **2,** 2631–2636 (2020). https://doi.org/10.1007/s42399-020-00607-3 **3-** Słomka, A.; Kowalewski, M.; Żekanowska, E. Coronavirus Disease 2019 (COVID–19): A Short Review on Hematological Manifestations. *Pathogens* **2020**, *9*, 493. https://doi.org/10.3390/pathogens9060493