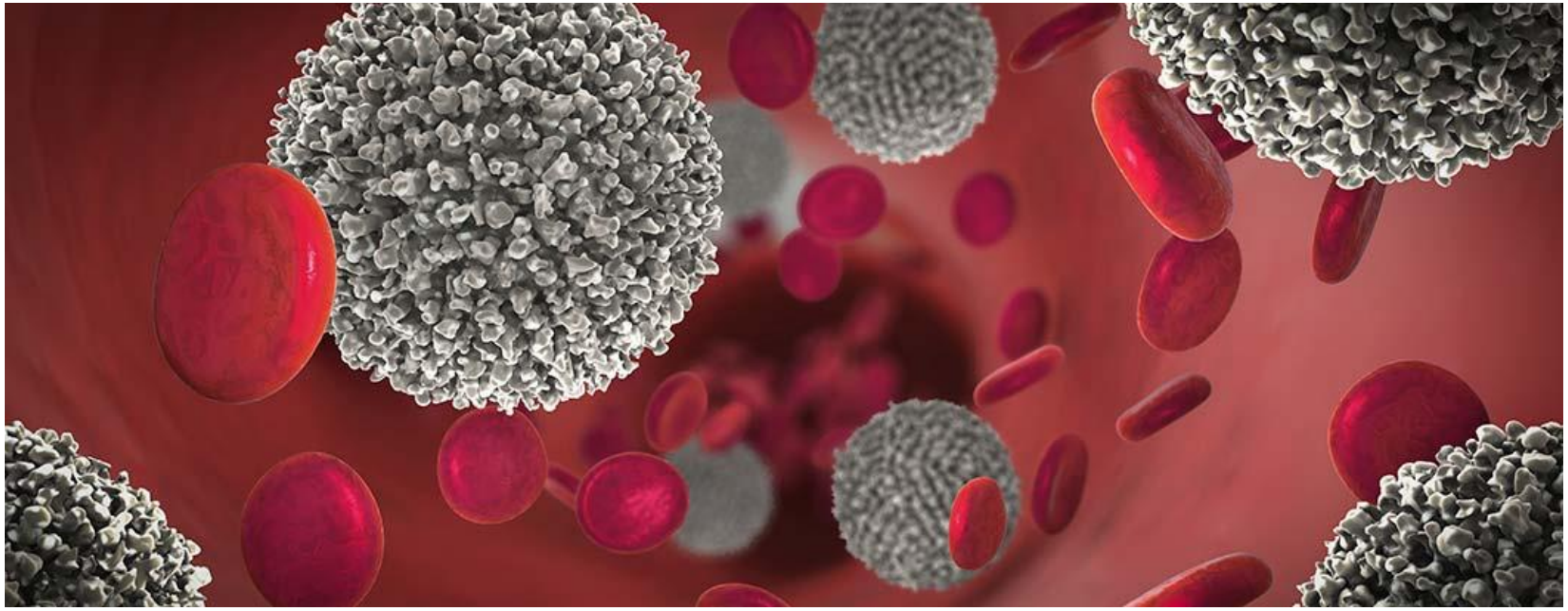
Hematological Abnormalities in COVID-19



By:

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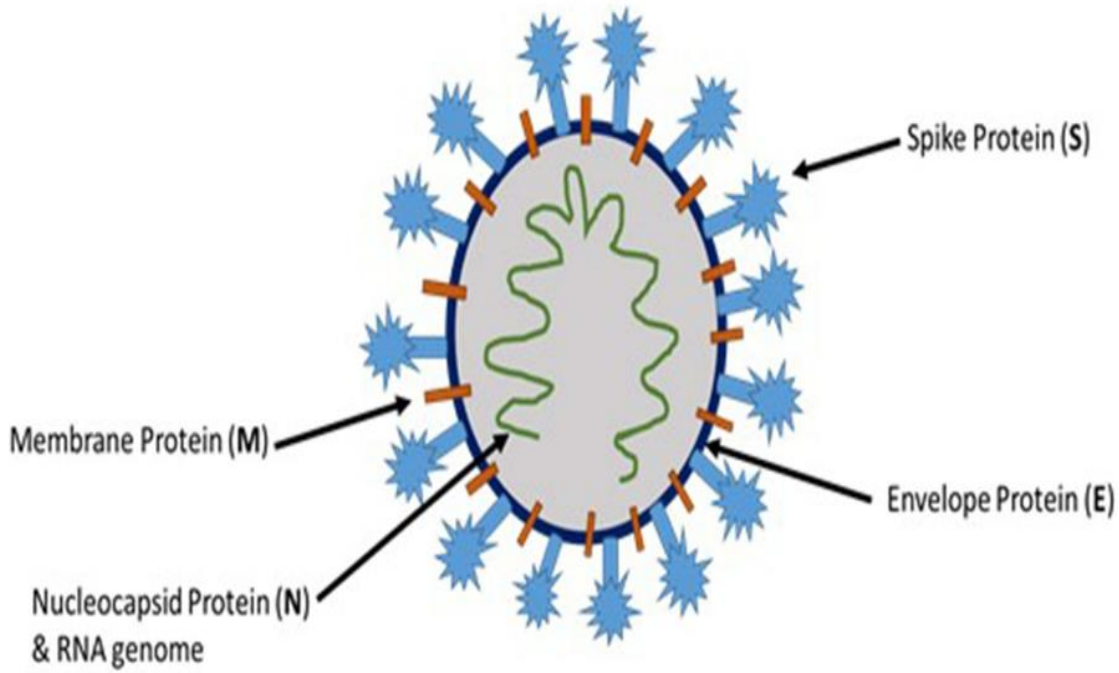
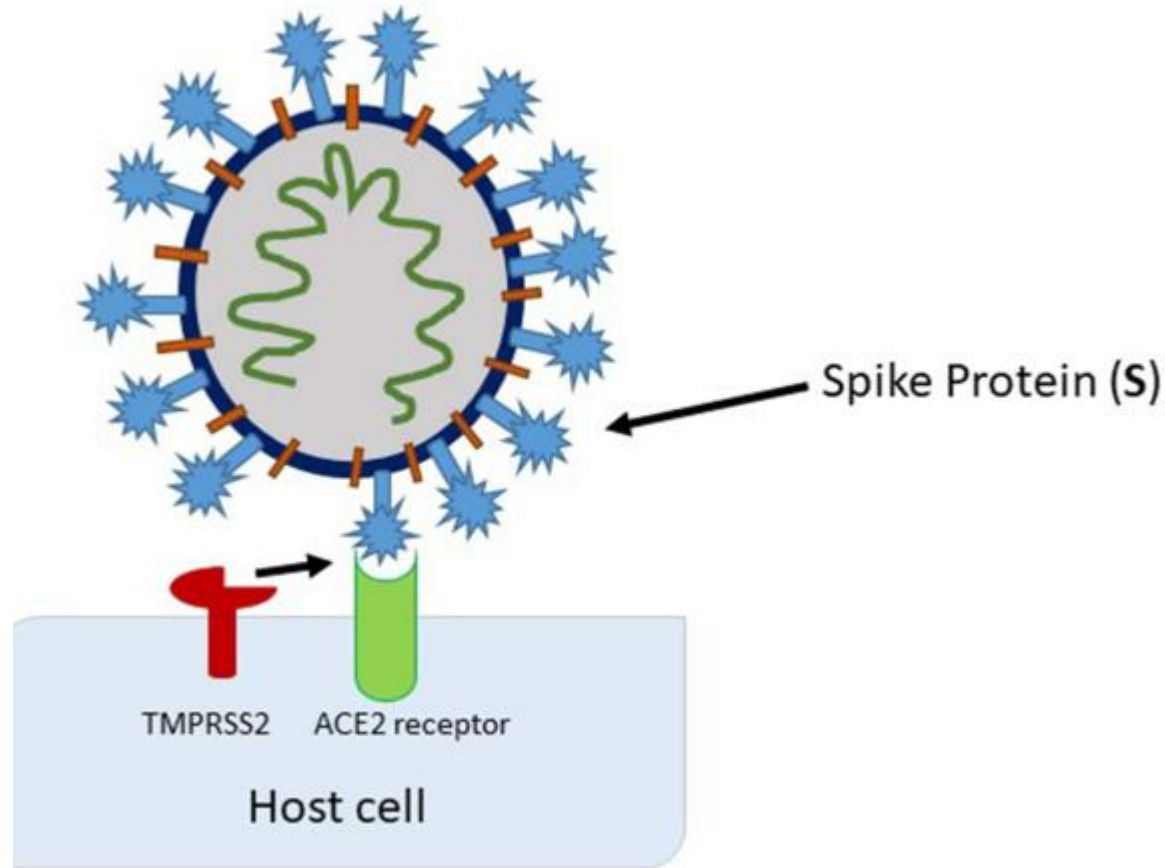
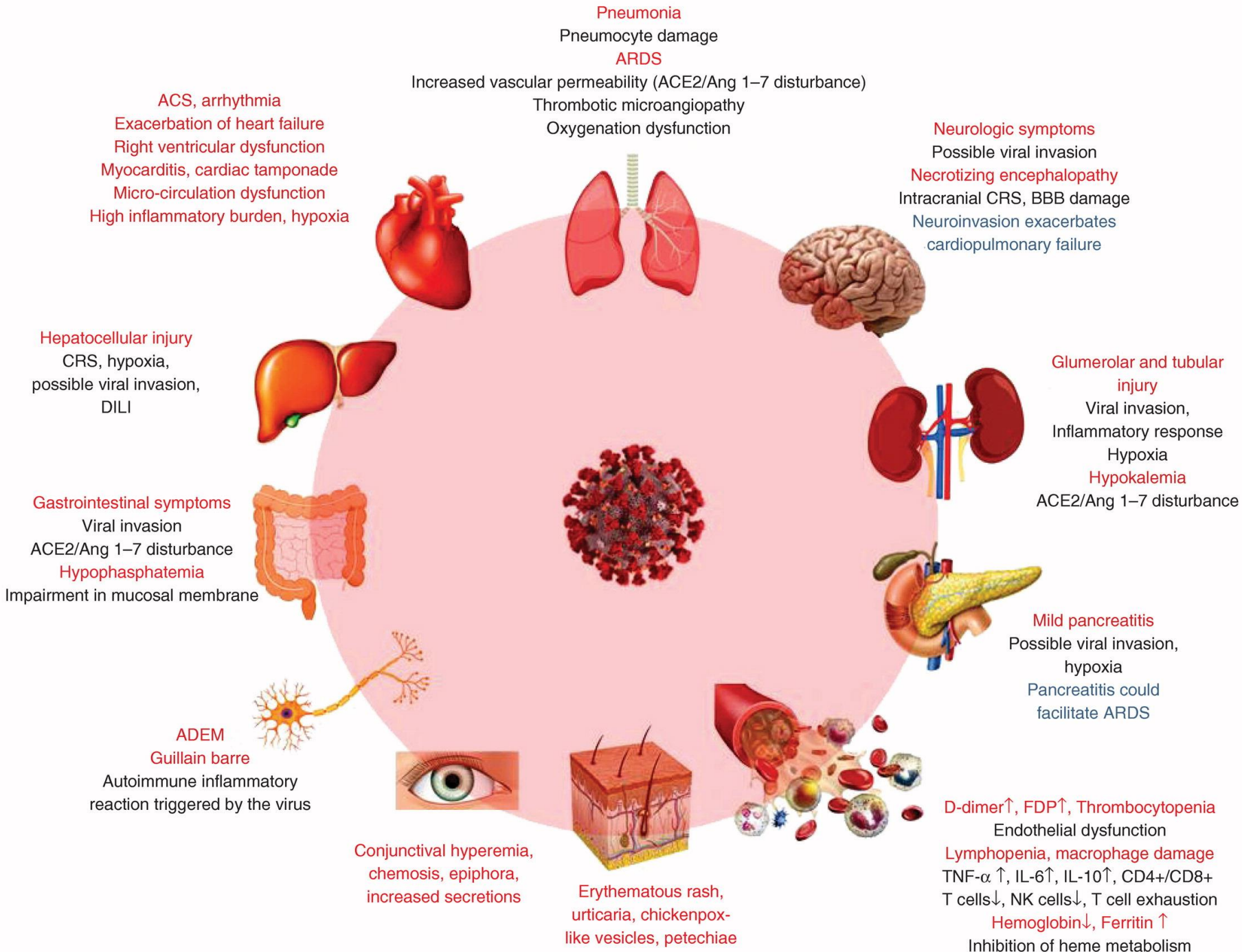
- In December 2019, the Chinese Center for Disease Control and Prevention identified the presence of a novel coronavirus in throat swab samples from a series of pneumonia cases of unknown etiology, that presented with dry cough, dyspnea, and fever.
- March 2020, the World Health Organization declared a global pandemic
- The novel coronavirus, SARS-CoV-2, belongs to the coronaviridae family, which are positive-sense single-stranded enveloped RNA viruses
- SARS-CoV-2 and coronaviruses in general have four essential structural proteins , namely spike (S) glycoprotein, envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein
- S glycoprotein aids in the viral attachment and fusion to the host cell membrane
- viral spike protein binds to host's angiotensin-converting enzyme 2 (ACE2) receptor, which is differentially expressed on various tissues, including respiratory tract cells, gastrointestinal tract cells, cardiac muscle cells, and endothelial cells
- A successful binding of the spike protein to ACE2 and the internalization of the virus requires the presence of the specific protease transmembrane serine protease 2 (TMPRSS2) that cleaves and activates ACE2.[9] With the successful viral entry into the cells, host replication machinery is used, and viral progenies are produced


Spike Protein (S)
Membrane Protein (M)
Envelope Protein (E)
Nucleocapsid Protein (N)
& RNA genome

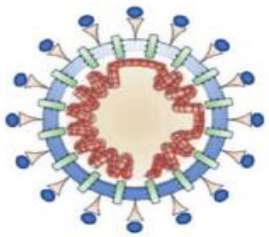

Spike Protein (S)
TMPRSS2
ACE2 receptor
Host cell

- The majority of infected individuals are asymptomatic or experience mild symptoms.
- Observational studies have reported that older adults and those with underlying respiratory and cardiovascular disease are at risk of a severe form of the disease
- Genome sequencing of SARSCoV-2 shows 96.2% homology to a bat coronavirus.

- Although similar to SARS-CoV, SARS-CoV-2 has a higher affinity for the human angiotensin-converting enzyme 2 receptor (ACE-2) and faster transmission than SARS-CoV


Pneumonia
Pneumocyte damage
ARDS
Increased vascular permeability (ACE2/Ang 1–7 disturbance)
Thrombotic microangiopathy
Oxygenation dysfunction
ACS, arrhythmia
Exacerbation of heart failure
Right ventricular dysfunction
Myocarditis, cardiac tamponade
Micro-circulation dysfunction
High inflammatory burden, hypoxia
Neurologic symptoms
Possible viral invasion
Necrotizing encephalopathy
Intracranial CRS, BBB damage
Neuroinvasion exacerbates
cardiopulmonary failure
Hepatocellular injury
CRS, hypoxia,
possible viral invasion,
DILI
Glumerolar and tubular
injury
Viral invasion,
Inflammatory response
Hypoxia
Hypokalemia
ACE2/Ang 1–7 disturbance
Gastrointestinal symptoms
Viral invasion
ACE2/Ang 1–7 disturbance
Hypophasphatemia
Impairment in mucosal membrane
Mild pancreatitis
Possible viral invasion,
hypoxia
Pancreatitis could
facilitate ARDS
ADEM
Guillain barre
Autoimmune inflammatory
reaction triggered by the virus
D-dimer↑, FDP↑, Thrombocytopenia
Endothelial dysfunction
Lymphopenia, macrophage damage
TNF-α ↑, IL-6↑, IL-10↑, CD4+/CD8+
T cells↓, NK cells↓, T cell exhaustion
Hemoglobin↓, Ferritin ↑
Inhibition of heme metabolism
Conjunctival hyperemia,
chemosis, epiphora,
increased secretions
Erythematous rash,
urticaria, chickenpox-
like vesicles, petechiae

Hematologic manifestations of coronavirus



Host risk factors
- Older age
- Co-morbidities like liver disease, CKD, COPD, heart failure

Infects cells via ACE-2 receptors

- Macrophage activation
- Cytokine storm
- Endothelial cell activation
- Tissue factor expression
- Activation of coagulation pathway
- Platelet activation
- Deranged fibrinolysis
- Thrombosis formation

→

- Lymphopenia
- Thrombocytopenia
- Elevated D-dimer, PT and aPTT
- Elevated LDH
- Elevated Ferritin
- Elevated IL-6, C-reactive protein

→

- Venous thromboembolism
- Pulmonary microthrombi
- Myocardial injury, increased troponin
- Arterial thrombosis – myocardial infarction, limb ischemia
- Disseminated intravascular coagulation (DIC)

Hematologic manifestations of coronavirus

- Lymphopenia (69.6–100%) and thrombocytopenia (20–55%) have been reported in patients with SARS-CoV-1 infections
- 45% of SARS-CoV-1 patients had elevated D-dimer levels

THROMBOCYTOPENIA IN COVID-19

- Thrombocytopenia has been reported in 5–21% of COVID-19 patients
- higher risk of mortality in patients with thrombocytopenia
- platelet count < 200 × 10_9/L at admission was associated with three times higher mortality
- elevated platelet– lymphocyte ratio (PLR) to be a prognostic marker in COVID-19
- PLR to be elevated in severe compared with non-severe COVID-19 patients
- idiopathic thrombocytopenia purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) following SARS-CoV-2 infection

MECHANISMS OF THROMBOCYTOPENIA IN COVID-19

- direct effect of SARS-CoV-2 on platelet production, autoimmune destruction of platelets, or increased platelet consumption
- Microthrombi formation is common in COVID-19 and may lead to platelet consumption
- potential immunemediated platelet destruction needs to be considered in the light of reports of post-COVID ITP and TTP
- The likely mechanism in this case is molecular mimicry between the antigens of SARS-CoV-2 and platelet glycoproteins

MANAGEMENT OF THROMBOCYTOPENIA

- severe thrombocytopenia is not common in COVID-19 patients
- treatment of this aspect is usually not needed.
- There are some case reports of patients with COVID- 19, who developed ITP or TTP, and all of them had favorable outcomes.

RED CELL AND HEMOGLOBIN ABNORMALITIES IN COVID-19

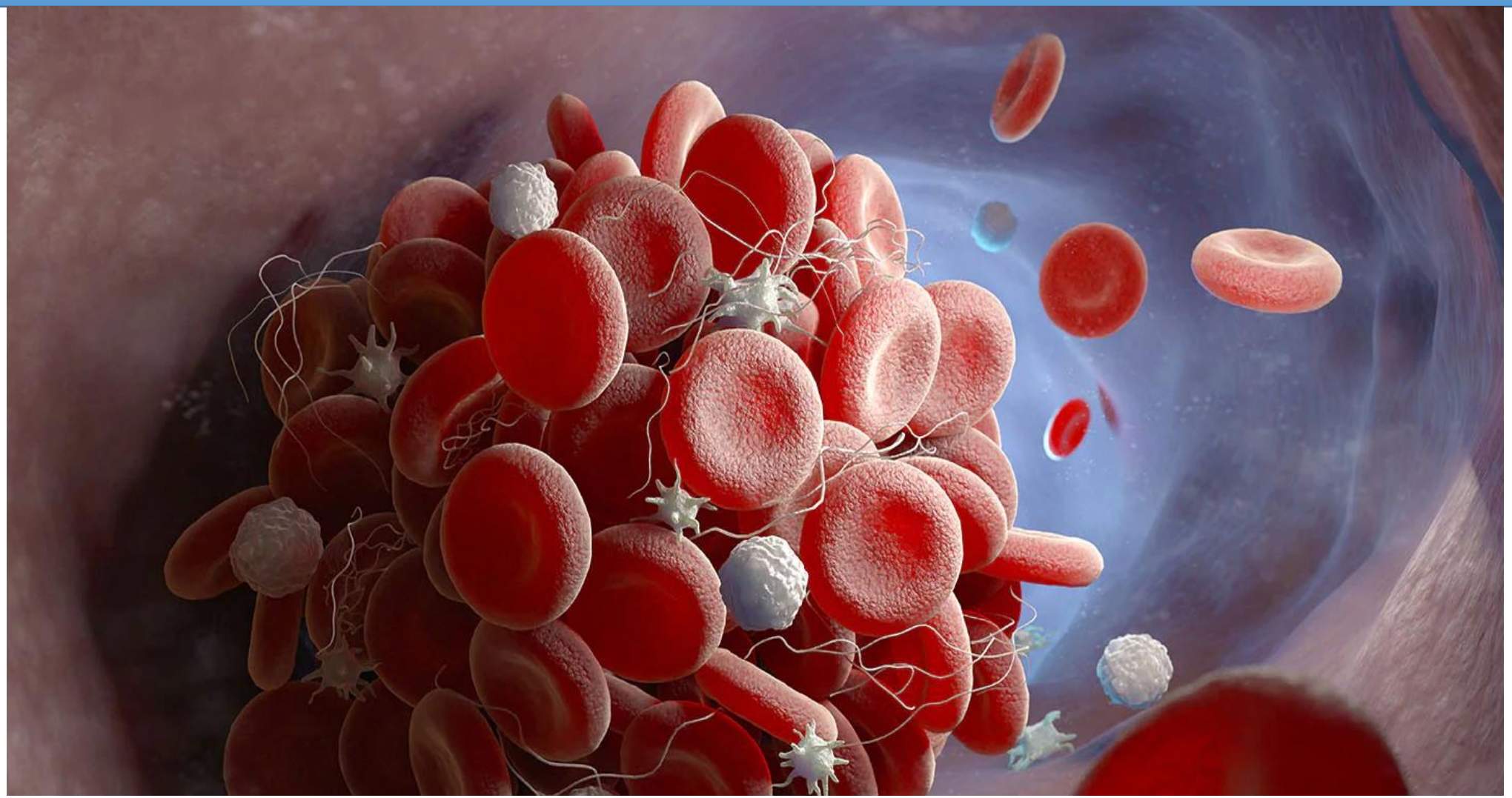
- hemoglobin concentrations to be lower in severe disease than in mild infections
- No significant effects on red blood cell (RBC) counts have been found, but structural changes have been noted
- Red blood cells of COVID-19 patients had increased oxidation of structural proteins and altered lipid metabolism

MECHANISMS OF Anemia IN COVID-19

- SARS-CoV-2 proteins may attack the beta chain of hemoglobin, thus reducing its level.
- A reduction in hemoglobin (and thus oxygen content) may explain some of the symptoms of respiratory distress

- no studies have shown transfusion support for this indication alone, to improve outcomes.
- Patients with hemoglobinopathies and COVID-19 should continue to receive transfusions and chelation therapy as needed

Disorders of hemostasis



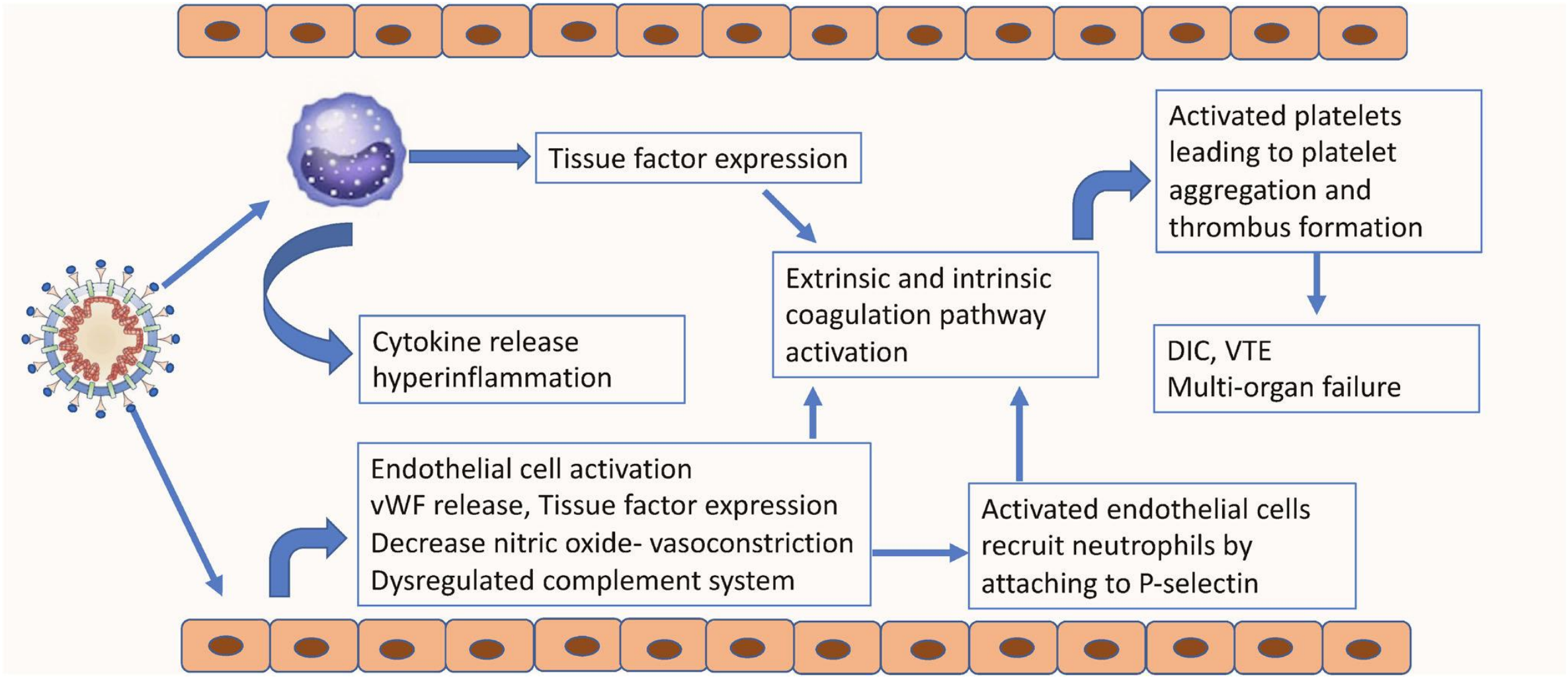
Disorders of hemostasis: thrombosis, disseminated intravascular coagulation, and thrombocytopenia

- Critically ill patients are at an increased risk of venous thromboembolism (VTE) due to immobilization, systemic inflammation induced by a critical illness such as sepsis or acute pancreatitis, dehydration, endothelial dysfunction, and stasis
- The presence of metabolic syndrome (hypertension, diabetes, obesity), coronary artery disease, peripheral artery disease, a previous history of VTE, and hereditary thrombophilia are some of the patient-related risk factors which predispose to VTE formation
- Infections in critically ill patients are known to cause disseminated intravascular coagulation (DIC) via endothelial damage, neutrophil activation, and activation of intravascular coagulation
- Elevated D-dimer levels (> 1,000 $ng \times mL_{-1}$) and increased prothrombin times were seen in COVID-19 patients

Incidence

- Exact incidence of thrombotic complications is unknown
- Cui and colleagues from China reported VTE in 20 out of 81 patients (25%)
- In a retrospective cohort study of 388 patients from Italy,The cumulative rate of thromboembolic events was 21%
- Dutch study evaluating 184 intensive care unit (ICU) patients with COVID-19, the cumulative incidence of thromboembolic events was 31%. Pulmonary embolism (PE) was the most frequent thrombotic complication (81%)
- In an autopsy study of 12 patients by Wichmann and colleagues, 58% had deep venous thrombosis (DVT). Four patients (33%) had PE, but microthrombi were regularly seen within small lung arteries

Pathogenesis



Pathogenesis

- SARS-CoV-2 activates endothelial cells by ACE-2 receptors.
- Activated endothelial cells release chemoattractants like CCL2, CCL7, and a delayed type 1 interferon response leading to sustained recruitment of blood monocytes, which differentiate into proinflammatory macrophages.
- Activated natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) further promote recruitment and activation of monocyte-derived macrophages through the production of granulocyte-macrophage colonystimulating factor (GM-CSF), tumor necrosis factor (TNF), and interferon-γ (IFN-γ)

Pathogenesis

- These activated monocyte-derived macrophages produce the characteristic COVID-19 cytokine storm, releasing massive amounts of pro-inflammatory cytokines including IL-6, TNF, IL-8, IL- 10, and IL-1RA
- This surge in inflammatory cytokines predisposes to thrombosis in both arterial and venous circulation
- In severe cases, the result is hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome (HPS)
- activation of endothelial cells causes reduced production of nitric oxide (NO) and von Willebrand factor (vWF) release
- Major endogenous anticoagulant pathways, including tissue factor pathway inhibitor (TFPI), antithrombin, and protein C, are downregulated
- hypo-fibrinolysis caused by the plasminogen activator inhibitor 1 (PAI 1) release stimulated by increased angiotensin II from SARS-CoV-2-induced ACE-2 blockade

Laboratory findings and prognostic implication

- normal or slightly prolonged PT and aPTT in mild disease, to marked prolongation of PT and aPTT in severe disease
- Platelet counts can be normal to slightly increased in mild illness and markedly reduced in severe disease
- Mild to marked elevations in D-dimer and fibrinogen relate to milder and severe form of the disease
- A meta-analysis of nine studies included 1779 COVID-19 patients. It showed that platelet count was significantly lower in those with severe disease. A low platelet count was associated with an over fivefold enhanced risk of severe COVID-19

Clinical manifestations

- sudden increase in the partial pressure of arterial carbon dioxide ($PaCO_2$) may indicate an increase in dead-space ventilation due to pulmonary embolism
- Diagnosis requires a high index of suspicion and sequential coagulation panels to follow changes in PT, aPTT, D-dimer, platelet count, and fibrinogen
- A study involving 3334 consecutive hospitalized patients with COVID-19 from New York showed that VTE was associated with an increased mortality rate
- Arterial thrombotic events, including stroke (reported in 1.6%) and myocardial infarction (reported in 8.9%), were associated with increased mortality
- Bleeding is less common than clotting in COVID-19.

Diagnosis and management

- Early diagnosis of VTE is important in COVID-19 patients.
- PE should be considered in COVID-19 patients with sudden deterioration of oxygenation, respiratory distress, tachycardia, unexplained hypotension, or increasing vasopressor requirement.
- Laboratory parameters such as a sudden rise in $PaCO_2$ may indicate increased dead-space ventilation due to a PE.
- A sudden increase in D-dimer should warrant further investigation.

Diagnosis and management

- Computed tomography pulmonary angiogram (CTPA) and DVT ultrasonography
- bedside echocardiography
- All hospitalized patients with COVID-19 must receive pharmacologic thromboprophylaxis with low molecular weight hepari (LMWH), fondaparinux, or unfractionated heparin (UFH).
- Once-daily LMWH and fondaparinux would be preferable, limiting staff contact and preserving personal protective equipment (PPE).
- Recent guidelines recommend against using intermediate or weight-based dosing of LMWH
- Caution is advised when using direct oral anticoagulation (DOAC) for thromboprophylaxis due to hemodynamic instability and high risk of rapid deterioration, and increased incidence of acute kidney injury

Diagnosis and management

- In patients where anticoagulants are contraindicated or are unavailable, mechanical thrombo prophylaxis (e.g., pneumatic compression devices) should be used
- Post discharge thrombo prophylaxis should be considered on a case-by-case basis considering the patient’s severity of illness, VTE risk factors at the time of discharge, such as reduced mobility, bleeding risk, and feasibility
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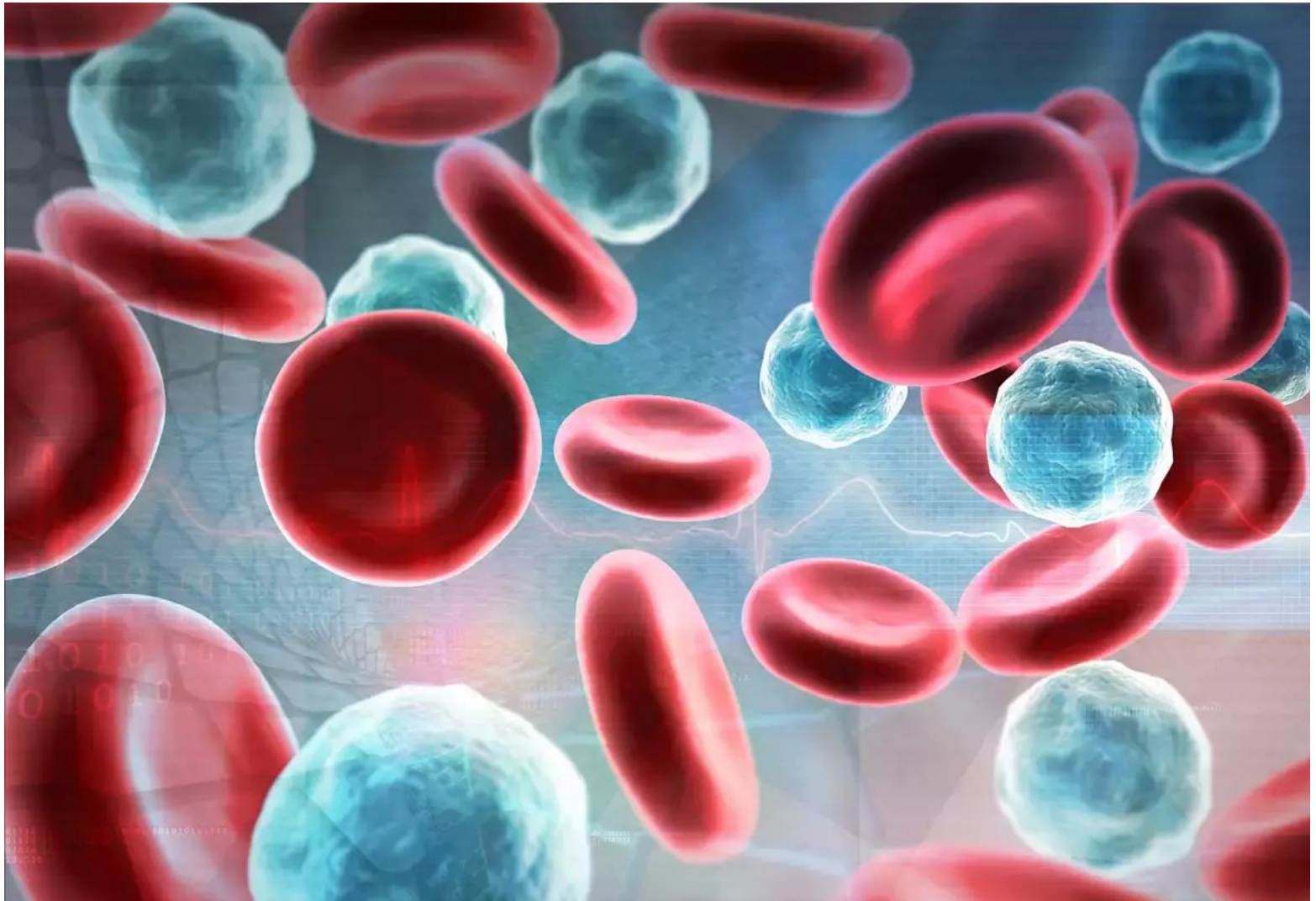
Diagnosis and management

- Therapeutic anticoagulation for VTE can be achieved by the use of LMWH, UFH, or DOACs.
- In patients with pulmonary embolism and hypotension, who are not at high risk of bleeding, systemic thrombolytic therapy is recommended.
- LMWH, fondaparinux, and DOAC, unless contraindicated, may be preferable due to administration ease, limiting staff contact, and absence of need for serial monitoring.
- As they do not require initial parenteral anticoagulation, rivaroxaban and apixaban might be preferred over dabigatran and edoxaban

Diagnosis and management

- Management of DIC is typically focused on the treatment of the underlying condition
- Platelet concentrate should be transfused to maintain a platelet count > 50 × 10_9/L in case of active bleeding and > 20 × 10_9/L in those at high risk of bleeding or requiring invasive procedures.
- Fresh frozen plasma (FFP) and cryoprecipitate should be given to actively bleeding patients with prolonged PT or aPTT and severe hypofibrinogenemia, respectively

Lymphopenia



Lymphopenia

- SARS-CoV-2 infection is associated with CD4+ and CD8+ T cell lymphopenia
- SARS-CoV-2 invades human cells by binding to the angiotensin converting enzyme 2 (ACE-2) receptor , expressed on the surface of lymphocytes. Consequently, SARS-CoV-2 may bind directly to these cells and cause lysis.
- production and release of multiple inflammatory cytokines,This potent cytokine activation can promote lymphocyte apoptosis and lead to atrophy of lymphoid organs, thus decreasing lymphocyte regeneration
- CD4+ T cells play an essential role as immune modulators, including downregulation of the inflammatory response. Consequently, lymphopenia may contribute to the hyperinflammation cascade

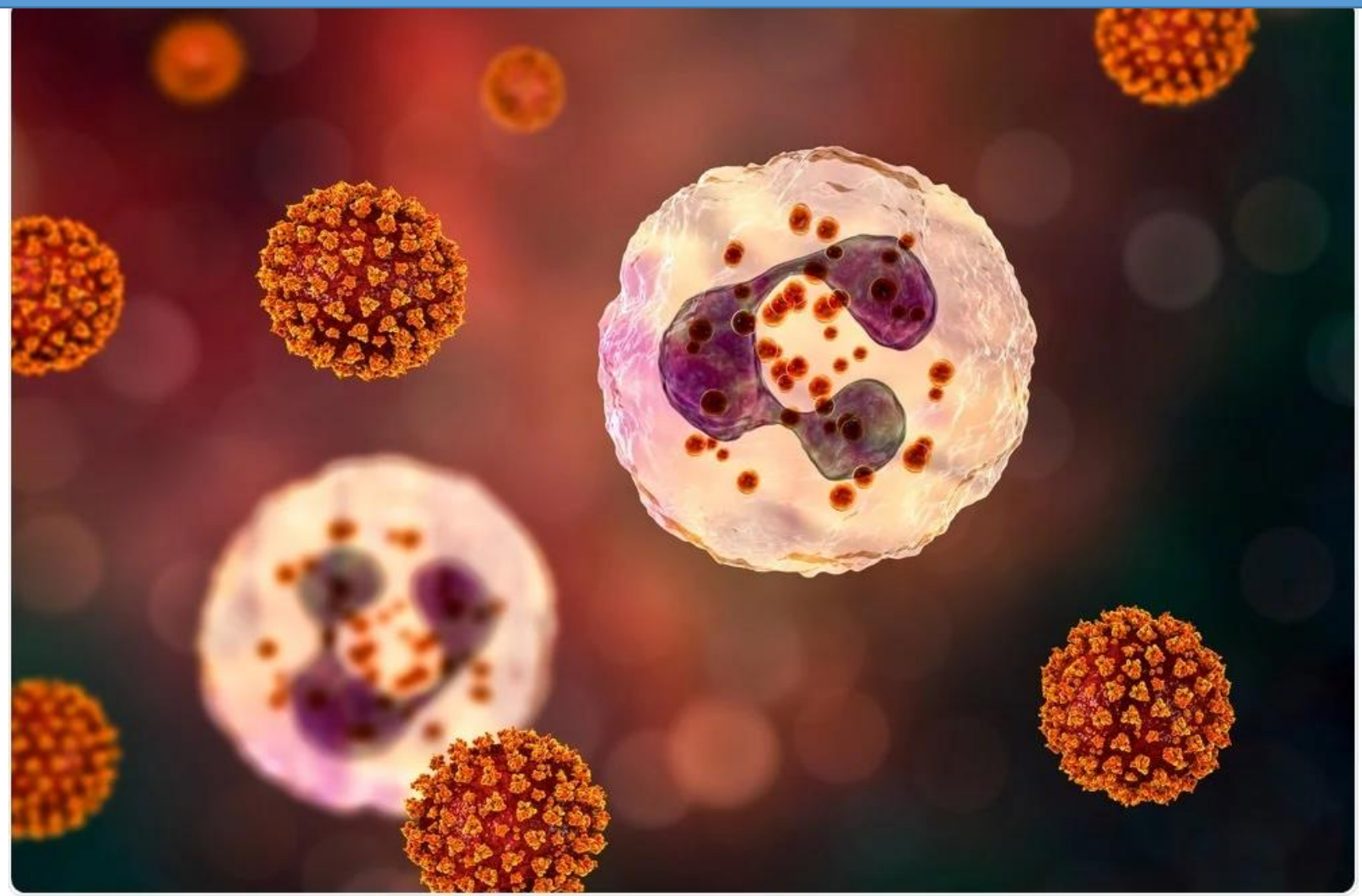
Lymphopenia

- Lymphopenia has been described among a large percentage of COVID-19 patients, especially those with more severe illness

(Lymphopenia (lymphocyte count >1,100 cells/μL) was seen in 30–75% of COVID-19 patients)

- Lower CD+ T cell levels were found to be an independent predictor of mortality
- A meta-analysis, which included 18 studies and almost 3000 COVID-19 patients, showed a decreasing trend in lymphocytes between patients with severe vs. nonsevere disease and non-survival vs. survival

Neutrophilia



Neutrophilia

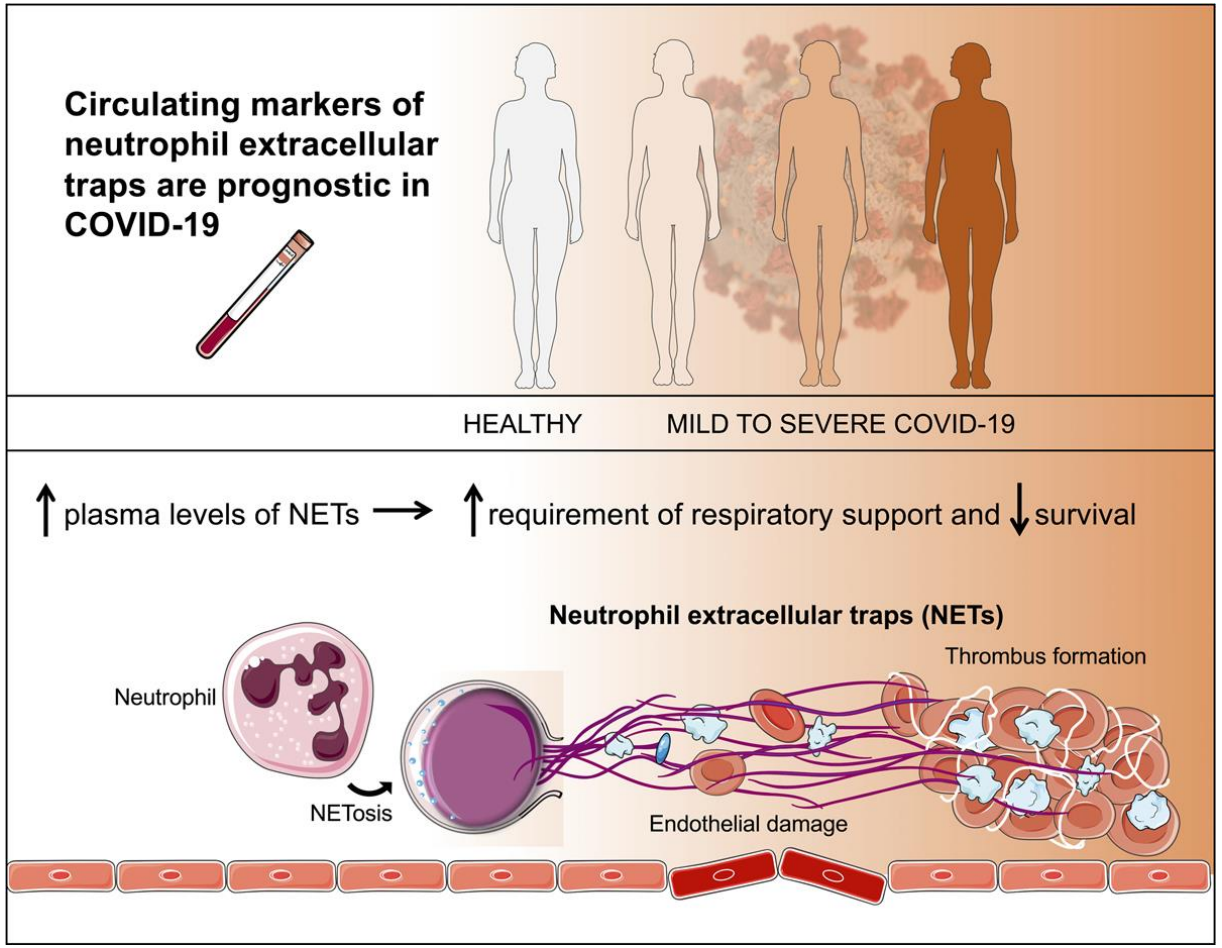
- COVID-19-associated immune dysregulation leads to neutrophil production and lymphocyte apoptosis
- The hyperinflammatory response and subsequent cytokine production of COVID-19 infection drive an exaggerated neutrophil, macrophage, and monocyte infiltration into the lung parenchyma
- Recently, a lesser-known neutrophil function has been proposed as a contributor to SARS-CoV-2 pathogenesis.
- Neutrophil extracellular traps (NETs) are web-like structures of DNA and proteins made by neutrophils and designed to entrap pathogens

NETs are structures made up of intracellular components released by activated neutrophils that discharge DNA, histones and proteins derived from intracellular granules.

Intravascular NETosis in COVID-19 infection could play a role in the vasculature complications, where thrombotic disease can drive organ damage

The excessive NET formation can cause an inflammatory cascade, leading to the destruction of surrounding tissues, microthrombosis, and permanent organ damage involving

the pulmonary, cardiovascular,and renal systems



- Neutrophilia by itself is associated with COVID-19 disease progression, increased risk of acute respiratory distress syndrome (ARDS), and death
- The neutrophilto-lymphocyte ratio (NLR) has been used as a prognostic indicator
- A prospective single-center study from Beijing, China, showed that 50% incidence of critical illness in patients with NLR ≥ 3.13 and aged ≥ 50 years, with the incidence decreasing to 9.1% with an NLR of < 3.13 and age < 50 years
-

Biomarkers

- biomarkers that have emerged as useful indicators of prognosis, or even mortality, include C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and ferritin
- CRP is an acute-phase reactant induced by IL-6, produced by the liver, and is a sensitive biomarker in various inflammatory conditions, such as infection and tissue damage
- reliable indicator of the presence and severity of SARS-CoV-2 infection

Biomarkers

- Lactate dehydrogenase (LDH) is an enzyme expressed in nearly all human cells,Damage to any of the multiple cell types that express LDH results in increased serum LDH levels
- LDH elevation is commonly seen in COVID- 19 patients with critical disease and is believed to indicate poor outcomes
- elevated LDH has been correlated with poor prognosis in COVID-19

Biomarkers

- D-dimer arises from the lysis of cross-linked fibrin and indicates the activation of coagulation and fibrinolysis
- One study found that a Ddimer > 1 μg/mL at admission was associated with increased odds of in-hospital death
- elevated D-dimer level remained a significant determinant with or without underlying disease when data was adjusted for age and gender

Biomarkers

- Ferritin not only has the role of iron storage but is also a well-known acute phase reactant
- Ferritin is composed of subunits H and L, and synthesis is induced by different inflammatory stimuli, including cytokines such as IL-6
- serum ferritin levels of ≥ 500 μg/L on admission, as well as CRP and lymphocyte counts, were independent risk factors for disease severity in COVID-19 patients

Biomarker abnormalities associated with severe disease

Hematologic biomarkers	Lymphopenia (decreased T cell and B cell count) Thrombocytopenia Neutrophilia
Coagulation biomarkers	Elevated prothrombin time and activated plasma thromboplastin time Elevated D-dimer Elevated fibrinogen (decreased in acute DIC)
Inflammatory biomarkers	Elevated erythrocyte sedimentation rate Elevated C-reactive protein Elevated serum ferritin Elevated cytokines (IL-2, IL-8, IL-8, and IL-10)
Biochemical biomarkers	Elevated cardiac enzymes (troponins, creatine kinase) Elevated liver enzymes (aspartate and alanine aminotransferases, total bilirubin) Elevated serum blood urea nitrogen and creatinine

Thanks for your Attention