Review Article

Haematological abnormalities and pharmacotherapy in severe acute respiratory syndrome corona virus 2

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ABSTRACT

The first case of SARS-CoV-2 (severe acute respiratory syndrome corona virus 2) was reported in Wuhan, China at the end of year 2019. It shows flu-like symptoms, but anosmia, fatigue, persistent cough and loss of appetite, that collectively might spot individuals with COVID-19. The aim of writing this review was to gather the information about blood abnormalities and pharmacotherapy for COVID-19 as a resource for healthcare professionals. A blood workup as well as continuous tracking hematological changes could divulge the risks of disease progression. The indirect indicators such as C-reactive protein (CRP), D-dimer, albumin, ferritin and LDH levels which are used as markers to estimate the severity of COVID-19 infection and prognosis. The most common hematological findings include lymphocytopenia, neutrophilia, eosinopenia, mild thrombocytopenia and less frequently, thrombocytosis. Clinical management includes prophylactic and therapeutic measures. Supportive care including supplemental oxygen and mechanical ventilatory support as and when indicated. Several class of drugs like anti-malarial, anti-viral, anti-inflammatory drugs are being used for the treatment and prevention of COVID-19. The target for development of most of the vaccine for COVID-19 is S protein of the corona virus. Various vaccines available for use across the globe are COVAX, Covishield, Moderna, Johnson and Johnson, Sputnik V, Novavax, Sinopharm, SinoVac. Serial monitoring of hematological manifestations is recommended and the treating doctor should stay vigilant and consider proper screening. The therapeutic intention is to decrease viral load and pharmacological thrombo-prophylaxis in high risk patients.

Keywords: COVID-19, Lymphocytopenia, Neutrophilia, 2-DG, COVAX

INTRODUCTION

The first case of SARS-CoV-2 was reported in Wuhan, China at the end of year 2019. Soon it spread to all over the world and it became a global pandemic. The number of cases in India has increased rapidly and exceeded 12.8 million at the end of March 2021. Though the fatality of COVID-19 is less in India, its infectivity is very high. It shows flu-like symptoms, but anosmia, fatigue, persistent cough and loss of appetite, that collectively might spot individuals with COVID-19.[1] The severity of illness range from mild respiratory symptoms to a severe and life-threatening form of pneumonia and is dependent on age and associated comorbidities.[2] A blood workup as well as continuous tracking hematological changes could divulge the risks of disease progression. Reported studies showed the onset of inflammatory cytokine storms in COVID-19 led to progress to severe lung injury, respiratory distress, and multiple organ failure. Literature analysis shows that COVID-19 is subject to cause hematological changes.[3]

Serological tests are being accessed for diagnosis of COVID-19 and their use is more suitable for epi-

demiological purpose. Indirect indicators of COVID-19 such as CRP, D-dimer, albumin, ferritin and LDH levels are used to estimate the severity of infection.[4] Hematological changes are useful for checking the status of SARS-CoV-2 infection, since the hematopoietic system and hemostasis suffer significant impacts during the evolution of COVID-19.[5] The most common hematological findings include lymphocytopenia, neutrophilia, eosinopenia, mild thrombocytopenia and less frequently, thrombocytosis.[6]

Presently, United States food and drug administration (USFDA) have approved very few drugs or other therapeutics to prevent or treat COVID-19. Clinical management incorporates infection prevention, control measures and supportive care including supplemental oxygen and mechanical ventilatory support when indicated. Several drugs like anti-malarial, anti-viral, anti-inflammatory drugs are being used for the treatment and prevention of COVID-19.

The aim of writing this review was to gather the information about blood abnormalities and pharmacotherapy for COVID-19 as a resource for healthcare professionals.

Blood abnormalities in SARS-CoV-2

The severity of the disease and clinical outcome are indicated by the most apparent abnormalities which are the decrease in lymphocytes and the increase in neutrophil-lymphocyte ratio (NLR) ratio. The lower count of eosinophils and its delay in rising can also be the signs of poor outcome of COVID-19. Thus, dynamic monitoring of the parameters of peripheral blood as a routine has important reference value for judging the progression and prognosis of COVID-19.[6]

The disease progression of COVID-19 is demonstrated by abnormal coagulation function. One of the most consistent abnormal haemostatic laboratory markers in COVID-19 is raised D-dimers. It is an early and helpful marker to improve management of COVID-19 patients. This occurs due to activation of broncho-alveolar hemostasis in response to SARS-CoV-2. In healthy individuals, the coagulation-fibrinolysis balance of the broncho-alveolar haemostasis is shifted towards fibrinolysis. This high fibrinolytic activity clears fibrin deposited in alveolar compartment and allows uninterrupted gas exchange.[7] However, in patients who develop acute lung injury secondary to COVID-19, this balance shifts towards pro-coagulant side, with the purpose of creating pulmonary thrombi possibly to limit viral invasion and the breakdown of these thrombi would cause an increase in D-dimers.[8] Patients with severe COVID-19 have a higher level of D-dimer than those with non-severe disease and D-dimer greater than 0.5 µg/ml is associated with severe infection in patients with COVID-19.

The other laboratory abnormalities noted were hypoalbuminemia, lymphopenia, neutrophilia, elevated CRP, LDH and decreased CD8 count. Severe disease can develop in COVID-19 patients with raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[9] In a study conducted by Burugu et al it has been observed that the serum ferritin was elevated among the COVID-19 patients who could not survive the treatment as compared to the recovered patients. The serum concentrations of ferritin could be used as a prognostic marker in the management of COVID-19 patients.[10] It has been reported in literature that hypo-albuminemia is a potent, dose-dependent predictor of poor outcome.[11] Therefore, albumin therapy might be a potential remedy for NCP.

A genomic sequence study reveals that the new coronavirus shared the ACE2 receptor of SARS-CoV which is a critical enzyme in the renin angiotensin system (RAS).[12] RAS plays important roles in maintaining blood pressure homeostasis and salt and fluid balance. ACE and ACE2 play different roles in RAS; ACE generates angiotensin II, whereas ACE2 is a negative regulator of the system, decreasing angiotensin II. The abnormal increase of angiotensin II was reported mostly associated with hypertension and heart failures and sometimes also lung and renal dysfunctions.[13] The plasma levels of angiotensin II from COVID-19 patients were considerably higher than that of healthy individuals and it was strongly associated with viral load and lung injury, suggesting that the imbalanced RAS in patients was caused by SARS-CoV-2 and drugs of angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) balancing RAS may be used repurposing on SARS-CoV-2 infected patients.[14] The other common finding in COVID-19 patients are elevated CRP, decreased lymphocyte count, as well as increased LDH. In a study conducted by Deng et al showed that the CRP, ALT, AST and creatinine levels were higher in the death group compared to the recovered group at the time of admission and the CRP levels remained high during the progression of the disease.[15] Raised CRP might be an early marker to anticipate hazard for seriousness of COVID-19. A meta-analysis of four published studies showed that increased pro-calcitonin values were associated with a nearly 5-fold higher risk of severe infection.[16] Higher serum ferritin and increased IL-6 levels have been associated with increased risk of death in COVID-19 patients.[17]

The main pathophysiology of SARS-CoV-2 infection in severe cases could be hypercytokinemia related to traumas. A hyperinflammatory syndrome called secondary hemophagocytic lymphohistiocytosis (sHLH), is usually activated by viral infections.[18] A cytokine profile, similar to sHLH, is related to the patients with severe COVID-19, as demonstrated by enhanced TNF-α, IL-7, IL-2, granulocyte-colony stimulating factor (GCSF), monocyte chemoattractant protein 1 and macrophage inflammatory protein 1-α.[19]

Lymphopenia

Several studies confirmed that the raised pro-inflammatory cytokines play a vital role in the induction of lymphopenia. Accordingly, hypercytokinemia impacts the lymphopenia and hence is incapable to guard against SARS-CoV-2 infection.[18] Various mechanisms might work together to cause lymphopenia. SARS-CoV-2 might directly attack the lymphocytes or destroy lymphoid organs. Lymphopenia could be due to elevated blood lactic acid levels in patients with severe phenotype of COVID-19.[20] In a study conducted by Bhandari et al 52.38% patients were presented with lymphopenia and it was more common in male patients as compared to female patients.[21] Lymphopenia was observed in 80% of symptomatic patients when compared to 11.5% of asymptomatic patients in the study conducted by Sharma et al.[22] Prevalence of lymphopenia was 83.20% in a study conducted by Guan et al.[23]

Thrombocytopenia

It is also one of the most important hematological findings in COVID-19 patients.[24] The proposed mechanisms for thrombocytopenia are inhibition of platelet synthesis by direct infection of bone marrow cells by the virus, cytokine storm destroys bone marrow progenitor cells and leads to the decrease of platelet production following virus infection, lung injury indirectly results in reduction of platelet synthesis; destruction of platelets by the immune system; aggregation of platelets in the lungs forming microthrombi and platelet consumption.[25]

Thrombocytopenia was seen in 23.81% patients in a study conducted by Bhandari et al and 40% symptomatic patients and 6% asymptomatic patients in a study conducted by Sharma et al.[21,22] While in a study of Guan et al 36.20% patients showed thrombocytopenia.[23] Procalcitonin (PCT) has arisen as a promising prognostic biomarker in COVID-19. Various studies have upheld the view that PCT levels are below the optimal cut-off in COVID-19 and any considerable increase from baseline reflects the development of a critical state.[26] The increased PCT and hypersensitivity C-reactive protein (hs-CRP) are strongly suggestive of secondary bacterial infection, as bacteria attack the already fragile immune system. In multivariable regression analysis, it has been shown that patients had poor prognosis when hs-CRP greater than 86.7 mg/l.[27]

Pharmacotherapy in SARS-CoV-2

The definitive therapy does not exist for COVID-19. The aim of therapeutic intervention is to reverse hypoxaemia and provide adequate organ support and also to reduce viral load and thus halt disease progression.

Anti-malarials

In-vitro studies have revealed that chloroquine and hydroxychloroquine causes alkalinisation of the intracellular phagolysosome, which prevents virion fusion, uncoating and viral spread thus inhibiting SARS-CoV-2 transmission.[28] Chloroquine has been found to have immunomodulatory effects through the suppression of TNF-α and IL-6 release, which can prevent the cytokine storm that leads to rapid deterioration of patients with COVID-19.[29] In a study conducted by Gao et al chloroquine and hydroxychloroquine was found to be superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion and shortening the disease course.[30]

Anti-virals

Remdesivir is a nucleotide analogue which gets fused into the viral RNA chain resulting in premature chain termination.[31] Remdesivir may be considered in patients with severe disease and respiratory failure. It cannot be used in conjunction with hydroxychloroquine due to an increased risk of QT prolongation and fatal dysrhythmias.[32] A study showed more clinical improvement in severe COVID-19 hospitalized patients who were treated with remdesivir.[33] It is not currently FDA-approved to treat or prevent any diseases, including COVID-19. Under the revised emergency use authorization (EUA), remdesivir is authorized for emergency use by healthcare providers for the treatment of suspected or laboratory-confirmed COVID-19 in all hospitalized adult and pediatric patients, irrespective of their severity of disease.[34]

A nucleoside analog favipiravir acts by inhibiting viral RNA polymerase and was initially used for the treatment of RNA viruses such as ebola and influenza.[35] The most common adverse effects are hyperuricemia, abnormal transaminases, psychiatric symptoms and gastrointestinal discomfort like diarrhea, nausea and vomiting.[36] In a public notice dated 21 June 2020 issued by CDSCO states "considering the emergency and unmet medical need for COVID-19 disease", CDSCO has approved restricted emergency use of remdesivir injectable formulations for treatment of patients with severe COVID-19 infection and favipiravir tablets for mild to moderate COVID-19 infection subject to various conditions and restrictions.[37] An open-label, non-randomized trial of 80 patients with COVID-19 in China identified a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared with historical controls treated with lopinavir-ritonavir.[38]

Anti-parasitics

Ivermectin is an FDA-approved broad spectrum anti-parasitic agent that have demonstrated to have anti-viral activity against a broad range of viruses in vitro.[39] Ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses capture to augment infection by suppressing the host's antiviral response and it also interfere with the attachment of SARS-

CoV-2 spike protein with human cell membrane.[40] Ivermectin in the dose of 12 mg BD alone or in combination with other therapy for 5 to 7 days may be considered as safe therapeutic option for mild, moderate or severe cases of COVID-19 infection. It is cost effective especially when the other drugs are very costly and not easily available.[41] An observational propensity-matched case-controlled study conducted by Patel et al showed an association of ivermectin use with lower in-hospital mortality.[42]

Corticosteroids

Methylprednisolone and dexamethasone have potent anti-inflamatory activity. They bind to cytoplasmic receptors to change the transcription of mRNA and reduce production of inflammatory mediators. Dexamethasone reduces mortality by one-third in mechanically ventilated patients hospitalized with severe COVID-19 and by one-fifth in patients requiring oxygen without mechanical ventilation. The drug did not improve survival in patients not requiring respiratory support.[43]

Anti-coagulants

Severe COVID-19 is commonly complicated with coagulopathy and disseminated intravascular coagulation (DIC) may exist in the majority of deaths. Anticoagulants may not benefit the unselected patients, instead, only the patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer may benefit from anticoagulant therapy mainly with low molecular weight heparin.[44]

Fibrinolytics

COVID-19 has caused thrombotic coagulopathy and respiratory failure in extraordinary numbers and pulmonary microvascular thrombosis is particularly prominent in COVID-19 respiratory failure. t-PA fibrinolytic therapy shown to be effective in decompensating patients and such approach could be rapidly widened globally due to t-PA's availability at most medical centers.[4]

Statin therapy

Guideline-directed continuation of statin therapy among COVID-19 patients with a history of atherosclerotic cardiovascular disease or diabetes should be recommended. But de novo initiation of statin therapy for management of COVID-19 episode can be done only as a clinical trial, not routinely.[46]

Non steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs act by inhibiting cyclooxygenase 1 and 2, thus, blocking production of prostaglandins, which are important mediators of fever and inflammation. The WHO declared that there is no evidence of severe adverse events, acute health care utilization, long-term survival or quality of life in patients with COVID-19 with the use of NSAIDs.[47]

Pegylated interferon alfa-2b

Recently this drug has received restricted emergency use approval from drug controller general of India (DCGI) for the treatment of moderate COVID-19 infection in adults. It has direct inhibitory effects on viral replication and it supports an immune response to clear viral infection. In the multi-center, randomized, open-label clinical trial, it had shown lesser need for supplemental oxygen, indicating that it was able to control respiratory distress and failure which has been one of the major challenges in treating COVID-19.[48]

2-deoxy-D-glucose (2-DG)

This new anti-COVID oral drug has been developed by the defence research and development organisation's leading laboratory, institute of nuclear medicine and allied sciences in alliance with Dr Reddy's laboratories. The 2-DG drug was recently granted emergency use approval by the DCGI as an adjunct therapy in moderate cases of COVID-19. Like glucose, this drug spreads through the body, reaches the virus infected cells and prevents virus growth by stopping viral synthesis and destroys the protein's energy production. The drug also acts on virus spread into lungs which helps to reduce patients dependability on oxygen.[49]

Monoclonal antibody

Tocilizumab is a recombinant monoclonal antibody against IL-6 receptors and IL-6 is implicated in immunologic response in patients with cytokine-release syndromes (CRS). Increased levels of IL-6 have been associated with hyperinflammatory states and CRS in severe COVID-19 cases and can potentially lead to increased rates of mortality.[50] Patients who develop evidence of COVID-19 associated CRS may be treated using this agent. In a recent study it has been found that acute phase reactant levels were decreased and the patients were getting to a stable condition reflected by a later gradual decrease of IL-6 after tocilizumab administration.[51]

Passive immunity

Convalescent plasma, donated by persons who have recovered from COVID-19, is the acellular component of blood that contains antibodies, including those that specifically recognize SARS-CoV-2. These antibodies when transfused into COVID-19 patients exert an antiviral effect by suppressing virus replication before patients have

raised their own humoral immune responses. The US FDA has approved the use of plasma from recovered patients to treat people who are critically ill with COVID-19.[52]

COVID-19 vaccines

Several approaches to COVID-19 vaccines are currently being evaluated. The vaccine target and platform mainly decides vaccine efficacy. Among all platform technologies, whole-virus such as live-attenuated viral vaccines and killed whole virus vaccines, subunit vaccines, plasmid-based DNA vaccines, RNA replicons and virus-like particle have been developed to induce protective responses to viral infections.[53] The target for development of most of the vaccine for COVID-19 is S protein of the corona virus. Various vaccines available for use across the globe are COVAX, Covishield, Moderna, Johnson and Johnson, Sputnik V, Novavax, Sinopharm, SinoVac (Table 1).[54]

Supplements and immune boosters

Supplements like ascorbic acid, zinc and vitamin D can be used in treatment of COVID-19 patients. The powerful antioxidant ascorbic acid helps to protect against damage induced by oxidative stress. Zinc is a vital component to white blood corpuscles which combat infections. Respiratory infections can be prevented and pulmonary function can be improved when vitamin D-deficient patients are supplemented with vitamin D.[55]

Table 1 : Vaccines available for COVID-19 worldwide.

Vaccines	Mechanism of action	Efficacy (%)	Dosing	Side effects
COVAXIN	Inactivated virus vaccine-SARS-CoV2 is chemically inactivated by beta-propiolactone, so it cannot replicate but all the proteins remain intact, which produces immune response	81	2 doses-4 weeks apart	Injection site pain/swelling/redness/itching, headache, fever, body ache, nausea, vomiting, rashes
Covishield	Viral vector vaccine-dsDNA encoding for the spike protein is protected in a safe virus; the infected cell expresses the spike protein which leads to an immune response.	82	2 doses-6 to 8 weeks apart	Injection site pain/swelling/redness/itching, headache, fever, chills, body ache, nausea, vomiting, rashes
Moderna	Encapsulated mRNA vaccine-mRNA encoding for the spike protein is protected in a lipid nanoparticle; once absorbed, the cell expresses the spike protein resulting in an immune response.	94	2 doses-4 weeks apart	Injection site pain/swelling, fatigue, headache, muscle pain, joint pain, chills, nausea, vomiting, fever
Pfizer-BioNTech	Encapsulated mRNA vaccine-mRNA encoding for the spike protein is protected in a lipid nanoparticle; once absorbed, the cell expresses the spike protein resulting in an immune response.	95	2 doses-3 weeks apart	Injection site pain, tiredness, headache, muscle pain, chills, joint pain, fever
Johnson and Johnson	Viral vector vaccine-dsDNA encoding for the Spike protein is protected in a safe virus; the infected cell expresses the spike protein which leads to an immune response.	72	1 dose	Injection site pain, headache, feeling very tired, muscle aches, nausea, fever
Sputnik V	Viral vector vaccine-dsDNA encoding for the Spike protein is protected in a safe virus; the infected cell expresses the spike protein which leads to an immune response.	91	2 doses-3 weeks apart	Weakness, muscle pain, fever
Novavax	Virus-like particle vaccine-nanoparticles are coated with synthetic spike proteins; an adjuvant Matrix-M is added which allows to boost the immune reaction.	96	2 doses-3 weeks apart	Injection site pain and tenderness, muscle ache, fatigue, headache
Sinopharm	Inactivated virus vaccine-SARS-CoV2 is chemically inactivated by beta-propiolactone, so it cannot replicate but all the proteins remain intact, which produces immune response.	79	2 doses-3 weeks apart	Headache, eye pain, injection site pain/rash/itching, fever, fatigue, diarrhoea

CONCLUSION

The COVID-19 disease has had marked hematological manifestations like lymphopenia, thrombocytopenia, coagulation abnormalities and have been associated with poor outcome. Serial monitoring is recommended and the treating doctor should stay vigilant and consider proper screening. The authorities have permitted for emergency use authorization of some anti-malarials, anti-virals, anti-parasitics, corticosteroids and vaccines. The therapeutic intention is to decrease viral load and pharmacological thrombo-prophylaxis in high risk patients.

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