



## Haematological manifestations of COVID 19 and their prognostic significance- A Cross-Sectional Study

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### ABSTRACT

SARS-CoV2 started as pneumonia of unknown aetiology in Wuhan, China. Considered a respiratory pathogen primarily initially, COVID 19 is now identified as a systemic infection with significant effects on the hematopoietic system. Lymphopenia, peak platelet/ lymphocyte ratio and neutrophil/lymphocyte ratio are some of the parameters that could be considered as prognostic markers of the disease. Disseminated intravascular coagulation, along with elevated D-dimer levels, are commonly encountered and are usually associated with a worsening clinical picture. IL-6, C reactive protein and Lactate Dehydrogenase with high serum prolactin and serum ferritin levels project a dismal outcome. Venous thromboembolism occurs in both ambulatory and bedridden patients making thromboprophylaxis with LMWH popular. To correlate haematological parameters like lymphopenia, deranged coagulation profile and elevated d- dimer levels with the outcome (recovery or death) of the patients infected with SARS-CoV-2. In this prospective cross-sectional study, data will be gathered from patients found to be positive for COVID 19 with the duration of the study being four months. Lymphopenia, elevated D-dimer levels and deranged coagulation profile are expected in patients with COVID-19. Haematological parameter like lymphopenia raised D-dimer levels, and deranged coagulation profile are associated with poor prognosis in COVID 19.



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### INTRODUCTION

COVID 19 is a disease entity caused by SARS- CoV2 that started in Wuhan, the capital of Hubei province in China initially unrecognized as a cluster of pneumonia cases of unknown aetiology (Zhu *et al.*, 2020). Initially spreading to other areas in China and Asia, it has now come to dominate the world, causing significant morbidity and mortality along its way. It is transmitted from one person to another via droplets and direct human-to-human contact. On entering the host, it binds to specific receptors like angiotensin-converting enzyme-2 receptor (for which it has high affinity) and an alternate receptor CD209L. ACE 2 receptors are mainly present on the epithelium of trachea, bronchi, alveoli and

macrophages. The virus enters the cells and begins to replicate, following which mature virions are released. These, in turn, infect other cells causing initiation of a wide array of symptoms as the cycle continues (Chan *et al.*, 2020; Xu *et al.*, 2020). Chiefly thought of as a respiratory pathogen, emerging data has now come to suggest that COVID 19 is a systemic disease involving the gastrointestinal, cardiovascular, neurological, immune and hematopoietic systems as well (Driggin *et al.*, 2020; Bangash *et al.*, 2020; Mehta *et al.*, 2020).

Disseminated intravascular coagulation, lymphopenia, elevated D-dimer levels are some of the parameters usually associated with a worsening clinical picture. Lactate Dehydrogenase, high serum prolactin, serum ferritin levels and IL-6 may also be considered as prognostic markers in the disease.

Research indicates that mortality is significantly higher in older individuals with comorbidities, but younger individuals may also succumb if they present with lethal complications like DIC and myocarditis (Tang *et al.*, 2020b; Madjid *et al.*, 2020).

### Aim and objectives

To study the haematological parameters in COVID 19 disease. To correlate haematological parameters like lymphopenia, deranged coagulation profile and elevated d- dimer levels with the outcome of the patients infected with SARS-CoV-2.

### Outcome

The outcomes will be categorized as; recovery and death.

## MATERIALS AND METHODS

### Settings

This cross-sectional study will be conducted in Datta Meghe Institute of medical sciences, J.N. Medical College, Sawangi, Wardha; a rural tertiary care medical teaching institute in central India. The hospital is a designated treatment centre for COVID-19 in Wardha district. Duration of the study will be four months. The study will be conducted after approval from the institutional ethical committee.

### Study participants

Consecutive subjects aged more than 16 years who will present to the hospital with symptoms and signs of COVID 19, which will be confirmed after positive throat/nasal swab will form the study group. Written informed consent (by signature or thumbprint) will be obtained from all participants.

### Exclusion Criteria

1. Haematological malignancies

2. Coagulation disorders
3. Postoperative patients
4. Age less than 16 years of age will be excluded from the study.

A detailed history will be taken, and the examination will be done fulfilling all the proposed guidelines. The swab will be sent to check for infection with SARS-Cov 2. All routine investigations will be sent including CBC, coagulation profile and D-dimer levels.

### Sample size

Patients found positive for COVID 19 will be included in the study. The study will be done for four months.

## DISCUSSION

### Blood Counts and Biochemistry Findings

In the initial phase of the disease patients presents with non-specific symptoms and a picture suggestive of hyperactivity followed by depletion of CD8 and T cells (Zheng *et al.*, 2020; Qin *et al.*, 2020).

Yang *et al.* studied 52 critically ill patients and found that about 85% had lymphopenia (Yang *et al.*, 2020). A similar blood picture was seen in the ICU patients studied in Singapore ( $p < 0.0001$ ) (Fan *et al.*, 2020). Lymphopenia was more severe in patients who ultimately succumbed to the disease (Wang *et al.*, 2020). This was also apparent in studies conducted in The United States of America (Arentz *et al.*, 2020; Bhatraju *et al.*, 2020). Qin *et al.* (2020); Deng *et al.* (2020) reported decreased lymphocyte/WBC ratio in those with severe disease. High leukocytes, low platelets and low lymphocytes are found in patients with myocardial injury (Shi *et al.*, 2020; Guo *et al.*, 2020). In Wuhan, 187 patients were evaluated and were found to have high troponin T levels associated with leukocytosis, lymphopenia and increased neutrophil counts (Guo *et al.*, 2020). Based on a meta-analysis involving nine studies, thrombocytopenia is directly associated with the severity of SARS- CoV2 infection (Lippi *et al.*, 2020). A peak in platelet count during the disease was linked with a worse outcome. Cytokine storm causes platelet activation, which in turn results in a high platelet to lymphocyte ratio now considered a prognostic marker (Qu *et al.*, 2020).

Following a study conducted in China raised CRP, Procalcitonin and LDH were found in 60.7%, 5.5% and 41% of the cases, respectively (Guan *et al.*, 2020). Zhou *et al.* studied 191 patients and found higher levels of LDH, IL-6 and serum ferritin in those

that succumbed (Zhou *et al.*, 2020). Elevated LDH levels were indicative of the need for ICU support, imminent ARDS and a higher risk of death (Yang *et al.*, 2020; Fan *et al.*, 2020; Wu *et al.*, 2019). Raised CRP levels are also linked with the same, in addition to raised Troponin T levels and myocardial injury (Deng *et al.*, 2020; Shi *et al.*, 2020; Wu *et al.*, 2019).

A positive correlation was found between serum ferritin levels, the risk of development of ARDS and probable death (Zhou *et al.*, 2020; Wu *et al.*, 2019). IL-6 levels were found to demonstrate a similar likelihood.

### Coagulation complications

Elevated D-dimer levels were found in around 36% of the total number of cases assessed in a study in China (Chen *et al.*, 2020b). Those with High prothrombin time and D dimer levels on admission were more likely to require ICU support during their hospital stay (Huang *et al.*, 2020). Wang *et al.* (2020) demonstrated the same in his analysis.

Those with cardiac disorders are more likely to develop coagulation disorders as compared to those without cardiac involvement (Shi *et al.*, 2020). Raised D-dimer, Troponin T and a deranged coagulation profile were associated with increased risk of death and ARDS (Zhou *et al.*, 2020; Wu *et al.*, 2019; Guo *et al.*, 2020). Sequential rise in D-dimer raised fibrin degradation products, APTT and PT were apparent among non-survivors (Tang *et al.*, 2020b; Zhou *et al.*, 2020). Therefore disseminated intravascular coagulation and D-dimer elevation are seen with severe SARS-CoV2 infection (Lippi and Favaloro, 2020). Endothelial dysfunction and immune deregulation play a part in the pathophysiology of the disease (Lillicrap, 2020). In acutely ill hospitalized patients, the rate of symptomatic VTE is up to 10% (Kahn *et al.*, 2012). The risk of VTE goes up in the presence of cardiovascular risk factors and diseases, acute inflammatory states, prolonged immobilization, classical genetic thrombophilia and history of VTE. Increase in blood viscosity occurs as a result of the release of certain hormones, immunoglobulins and inflammatory mediators in acutely ill patients: mechanical ventilation, surgery and central venous catheterization cause Vascular endothelial damage. A combination of these results in DVT and could lead to pulmonary embolism. Thromboprophylaxis is hence important and can be used prophylactically in these patients (Witt *et al.*, 2018). Early diagnosis and treatment are important in patients who develop PE to prevent morbidity and mortality. D- dimer, USG venous Doppler, bedside echo etc. can be used in patients with PE/DVT. CT

pulmonary angiography confirmed cases of PE had higher D-dimer levels as compared to those without PE (Chen *et al.*, 2020a). Unfractionated heparin or low molecular weight heparin are preferred over direct oral anticoagulants due to drug-drug interaction with concomitant antiviral and antibacterial treatment (Thachil *et al.*, 2020). The antithrombotic effect may be reduced, or bleeding risk may increase if treatments interfere with CYP3A4 and P-gp pathways. Tang *et al.* demonstrated the efficacy of LMWH in patients with markedly elevated D-dimer levels or those meeting the criteria for DIC (Tang *et al.*, 2020a; Huang *et al.*, 2020). Heparin-induced thrombocytopenia must be looked for in patients treated with heparin using 4T score (thrombocytopenia, the timing of fall in platelet count, thrombosis and other causes of thrombocytopenia). The incidence has not been looked into, but there is increased risk given immune dis-regulation, neutrophil extracellular traps, platelet factor 4 release and inflammatory syndrome.

### CONCLUSION

Haematological parameters like lymphopenia, deranged coagulation profile and elevated D dimer levels are associated with poor prognosis in patients infected with SARS-CoV-2. NLR (neutrophil-lymphocyte ratio) >3.13 is indicative of severe disease. Platelet counts also have a significant effect on the overall outcome of the patients. An increase in the platelet counts is associated with a decrease in mortality.

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### Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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