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COVID-19: A REVIEW OF THE IMPACTS AND IMPLICATIONS ON HAEMATOLOGY AND HAEMATOLOGICAL PARAMETERS[1]

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ABSTRACT: *Background: Coronavirus disease is a viral disease which originated from China in late 2019 and has spread to the entire surface of the earth. The clinical symptoms are usually due to the effect on the respiratory system which is the main target of the infection. This review is to find out the effect of the disease on Haematology and haematological parameters. Materials and methods: A review based on theoretical and empirical literature was done through internet search engines such as Google, Pubmed, Medline, Journals and books. The literature search spans 2003-2020. Results: A total of 103 publications were reviewed. Most of them were international articles. The review revealed that not much has been published on the effect of covid-19 on Haematology in general and the haematological parameters in particular. The main findings include lymphopenia, increased neutrohil lymphocyte ratio and thrombocytopenia. The Anti-thrombin (AT) levels were found to be lower in covid-19 patients compared to their healthy controls. D-dimer and FDP were elevated and found to be especially predictive of disease progression. Transfusion of convalescent plasma has shown improvement of clinical symptoms and laboratory parameters within few days after the transfusion. Conclusion: There is quite some level of impact of covid-19 on Haematology and haematological parameters, just as it also affects other systems, and specialties/sub-specialties. However, there is room for more research in determining more extensive involvement of the disease on haematological parameters.*

KEYWORDS: Covid-19, Impacts, Implications, Haematology, Haematological Parameters

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) is a disease caused by a new strain of coronavirus that has not been previously identified in humans.[1] It is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The disease was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the ongoing 2019–20 coronavirus pandemic.[3,4]. The symptomatology of Covid-19 is yet to be fully understood as it is still evolving. However, the incubation period for COVID-19 is typically five to six days but may range from two to 14 days.[5,6] About 97.5% of people who develop symptoms will do so within 11.5 days of infection.[7]

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Epidemiology

Covid-19 began in Wuhan in China in December 2019, the virus has now spread throughout the entire world, with sub-saharan African countries bearing considerable brunt. Till date (June 24, 2020) about 9,377,609 cases of Covid-19 have been reported world-wide, with 480,242 reported deaths, representing a case fatality rate (CFR) of 5.12% globally. However, there are countries that has recorded very high CFR on account of covid-19 such as Spain and Italy with CFR of up to 10.4% and 13.3%, respectively.[1] African countries, by contrast, have recorded much lower CFR. For example, Nigeria has reported 22,020 cases with 542 deaths and CFR of 2.46%. Even within the African continent, the virus appears to be predominant in some of the most prosperous countries that are the destinations for tourists from outside the continent. Countries such as South Africa has recorded highest rates of infections and related deaths in the continent.[1] The Covid-19 has emerged as one of the most traumatic pandemics in contemporary times with implications not only for morbidity and mortality of humans, but for the overall economic survival of the entire planet.

Signs & Symptoms

Those infected with the virus may be asymptomatic or develop flu-like symptoms, including fever, cough, fatigue and shortness of breath.[8,9-10] Emergency symptoms include difficulty in breathing, persistent chest pain or pressure, confusion, difficulty waking and bluish face or lips; immediate medical attention is advised if these symptoms are present.[11] Less commonly, upper respiratory symptoms, such as sneezing, runny nose or sore throat may be seen. Symptoms such as nausea, vomiting, and diarrhoea have been observed in varying percentages.[12,13-14] Some cases in China initially presented only with chest tightness and palpitations.[15] In March 2020 there were reports indicating that loss of the sense of smell (anosmia) may be a common symptom among those who have mild disease.[16,17] In some, the disease may progress to pneumonia, multi-organ failure and death.[3,18] In those who develop severe symptoms, time from symptom onset to needing mechanical ventilation is typically eight days.[19]

Transmission

The World Health Organisation (WHO) and Centre for Disease Control (CDC) say it is primarily spread during close contact and by small droplets produced when people cough, sneeze or talk;[20,21] with close contact being within 1–3 metres.[20] A study in Singapore found that an uncovered coughing can lead to droplets travelling up to 4.5 meters.[22,23] It advised that droplets can travel around 7 - 8 metres.[24] Respiratory droplets may also be produced during breathing out, including when talking. Though the virus is not generally airborne[4,25] the National Academy of Science has suggested that bioaerosol transmission may be possible and air collectors positioned in the hallway outside of people's rooms yielded samples positive for viral RNA.[26] The droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs.[27] Some medical procedures such as intubation and cardiopulmonary resuscitation (CPR) may cause respiratory secretions to be aerosolised and thus result in airborne spread.[25] It may also spread when one touches a contaminated surface, known as fomite transmission, and then touches their eyes, nose or mouth.[20] While there are concerns it may spread by faeces, this risk is believed to be low.[20,21]

The virus is most contagious when people are symptomatic; while spread may be possible before symptoms appear, this risk is low[20,21] The European Centre for Disease Prevention and Control (ECDC) says while it is not entirely clear how easily the disease spreads, one person generally infects two to three others.[28]

The virus survives for hours to days on surfaces,[20,28] specifically, the virus was found to be detectable for one day on cardboard, for up to three days on plastic and stainless steel and for up to four hours on copper.[29] This, however, varies based on the humidity and temperature.[30,31] Surfaces may be decontaminated with a number of solutions (within one minute of exposure to the disinfectant for a stainless steel surface), including 62–71% ethanol (alcohol used in methylated spirits), 50–100% isopropanol (isopropyl alcohol), 0.1% sodium hypochlorite (bleach), 0.5% hydrogen peroxide and 0.2–7.5% povidone-iodine. Other solutions, such as benzalkonium chloride and chlorhexidine gluconate (a surgical disinfectant), are less effective.[32]

Laboratory diagnosis of Covid-19

Viral culture of novel coronavirus (2019-nCoV), the causative agent of Covid19, is not recommended.[33] However, the diagnostic method preferred and recommended for diagnosis of Covid-19 is the RT-PCR (Real Time Polymerase Chain Reaction).[34-36] This is same diagnostic method developed in respect of SARS-CoV1.[37,38]

Pre-Analytical Phase

Five to six days of the onset of clinical symptoms, COVID-19 patients have shown high viral loads in their upper and lower respiratory tracts,[39-42] hence for the screening and diagnosis of early infection a nasopharyngeal (NP) swab and/or an oropharyngeal (OP) swab are usually recommended.[37,40,43]

It is preferable to use a single NP swab because it is better tolerated by the patient and is safer to the operator. Again, NP often reaches the correct area to be tested in the nasal cavity. During the COVID-19 outbreak in China, Wang et al, have just reported that OP swabs were used much more frequently than NP but the SARS-CoV-2 RNA was detected in only 32% of OP swabs, which was significantly lower than the level seen in nasal swabs (63%).[44]

Again, another advantage to limit testing with NP swabs is to prolong supplies of flocked swabs and/or transport media. However, there are few exceptions where the OP swab would be far better, for example, patients with pharyngitis as a dominant initial presenting symptom could better be sampled via the OP route.[33]

Proper collection of NP swab is a very important aspect of the pre-analytical phase. In order to properly collect an NP swab specimen, the swab must be inserted deeply into the nasal cavity. Patients may likely wince, which indicates the swab has hit the target. Swabs should be kept in place for 10 seconds while being twirled three times. Swabs should have flocked nontoxic synthetic fibers, such as polyester, as well as synthetic nylon handles. 45 Collecting an NP/OP swab specimen may carry a theoretical risk of transmitting SARS-CoV-2, particularly if airborne transmission is demonstrated as the investigation of the COVID-19 outbreak continues.[46] If personal protective equipment (PPE) cannot be used due to scarcity, other means of collecting upper respiratory tract specimens will be needed. 46 One alternative option for collecting an upper respiratory tract specimen to evaluate patients with

suspected COVID-19 pneumonia is a self-collected saliva specimen.[47-50] After collection, swabs should be placed in viral (universal) transport medium for rapid transportation to the clinical microbiology laboratory under refrigerated conditions.[45]

Late Detection and Monitoring of Patients with Severe COVID-19 Pneumonia

Ideally, sputum sampling or bronchoalveolar lavage should be used for collecting lower respiratory tract specimens as they have yielded the highest viral loads for the diagnosis of COVID-19.[46,51] Samples of bronchoalveolar lavage (BAL) fluid, according to a recent study, yielded the highest SARS-CoV-2 RNA rate, but this study did not compare results from NP swabs.[44] Patients who present with severe pneumonia and acute respiratory distress syndrome may need emergent intubation as well as respiratory isolation in a negative-pressure room. If possible, a lower respiratory tract sputum specimen should be collected during the intubation procedure. Alternatively, sputum and/or bronchoalveolar lavage fluid specimens can be collected after intubation. [37, 39]

In contrast, high viral RNA loads of SARS-CoV-2 has been shown in faecal material [52,53] in some patients with covid-19. Enteric involvement previously has been seen in patients with severe novel coronavirus infections.[39,54-60] Therefore, aside from direct respiratory sampling, the preferred method for detecting SARS-CoV-2 in advanced COVID-19 cases may be a rectal swab and real-time RT-PCR.[37,54-56, 58-62]

Safety Measures for Specimen Processing for PCR Processing and Testing

Processing of respiratory specimens should be done in a class II biological safety cabinet [34,37,38], For nucleic acid extraction before real-time RT-PCR is performed, the specimen should be transferred to lysis buffer under this BSL-2 cabinet. The lysis buffer should contain a guanidinium-based inactivating agent as well as a nondenaturing detergent. The clinical specimens/swabs should not be heated to 56°C for 30 min as evidence suggests that this process may also degrade the coronavirus RNA even as it inactivates viable coronavirus. [37,63,64] Once the clinical specimen in viral transport medium is transferred into a cartridge in a class II biosafety cabinet, the cartridge is sealed. Many of these random-access sealed devices are suitable for point-of-care testing for local hospitals and clinics without biosafety cabinets. In this situation, the specimen collector in appropriate protective gear (splash guard/goggles, mask, gloves, and disposable laboratory coat) could directly transfer the specimen into detection cartridges at bedside or in a location without a class II biosafety cabinet, and the closed cartridge could be safely placed on an instrument for testing. However, spills of transport solution during transfer to these cartridge-based tests should be avoided, and if they occur, decontamination should be performed as appropriate.

Management and Medications

People are managed with supportive care, which may include fluid, oxygen support and supporting other affected vital organs.[65-67] The CDC recommends that those who suspect they carry the virus wear a simple face mask.[68] Extracorporeal membrane oxygenation (ECMO) has been used to address the issue of respiratory failure, but its benefits are still under consideration[69,70] Some medical professionals recommend paracetamol (acetaminophen) over ibuprofen for first-line use[71,72] The WHO does not oppose the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen for symptoms[73] and the FDA says currently there is no evidence that NSAIDs worsen COVID-19 symptoms.[74]

Experimental Treatment

No medications are approved to treat the disease by the WHO although some are recommended by individual national medical authorities[75-77] Research into potential treatments started in January 2020,[78] and several antiviral drugs are in clinical trials.[79,80] Although new medications may take until 2021 to develop,[81] several of the medications being tested are already approved for other uses or are already in advanced testing.[80] Antiviral medication may be tried in people with severe disease.[65] The WHO recommended volunteers take part in trials of the effectiveness and safety of potential treatments.[82]

On 17 March 2020, the Italian Pharmaceutical Agency included chloroquine and hydroxychloroquine in the list of drugs with positive preliminary results for treatment of COVID-19.[83] Korean and Chinese Health Authorities recommend the use of chloroquine.[84,85]. However, the Wuhan Institute of Virology, while recommending a daily dose of one gram, notes that twice that dose is highly dangerous and could be lethal. On 28 March 2020, the FDA issued an emergency use authorisation for hydroxychloroquine and chloroquine at the discretion of physicians treating people with COVID-19.[86,87]

Haematological Findings, Manifestations and Effects

Even though much knowledge has been gained on clinical features of covid-19, not much has been published on the effect of Coronavirus-2 on haematology and haematological parameters. However, the causative agent of COVID-19, a novel coronavirus causes haematological changes which arise from abnormal haematopoiesis. Haematology therefore plays an indispensable role in COVID-19 diagnosis and prognosis. Common haematological manifestations include thrombocytopenia, lymphopenia and leukopenia.[88,89]

LYMPHOPENIA: A significant decrease was observed in peripheral CD4+ and CD8+ T lymphocyte subsets. A number of potential mechanisms may be involved. The development of auto-immune antibodies or immune complexes triggered by viral infection may play a major role in inducing lymphopenia.[88] Some authors have reported that apoptosis is the cause of lymphopenia in coronavirus severe acute respiratory syndrome.[89-90] Lymphocyte counts may be useful in predicting the severity and clinical outcomes. Other possible reasons for the lymphopenia may be direct infection of lymphocytes by Coronavirus, lymphocyte sequestration in the lung or cytokine-mediated lymphocyte trafficking. There may also be immune-mediated lymphocyte destruction, bone marrow or thymus suppression, or apoptosis.[91]

EOSINOPHIL CYTOPENIA: Eosinophil cytopenia in addition to leukopenia and lymphopenia are more common in covid-19 patients than those in non-covid 19 patients[92]

THROMBOCYTOPENIA: Low platelet count is associated with increased risk of severe disease and mortality in patients with COVID-19, and thus should serve as clinical indicator of worsening illness during hospitalization.[92] Thrombocytopenia from Immune Thrombocytopenic Purpura due to coronavirus infection has been reported.[93] Apart from immune mediated thrombocytopenia through the development of autoimmune antibodies or immune complexes triggered by the viral infection, coronavirus may also directly infect haematopoietic stem/progenitor cells, megakaryocytes and platelets inducing their growth inhibition and apoptosis.[93] Moreover, the increased consumption of platelets and/or the

decreased production of platelets in the damaged lungs are a potential alternative mechanism that can contribute to thrombocytopenia.[93]

NEUTROPHIL LYMBHOCYTE RATIO (NLR): The trend of changes in Neutrophil (NEU), Lymphocyte (LYM) and Neutrophil Lymphocyte Ratio (NLR), which are derived by repeated blood examinations, contributes to prediction of the outcome of patients with Blood Stream Infection of Covis19.[94]

EFFECT ON HAEMOSTASIS AND COAGULATION: The Anti-thrombin (AT) levels were found to be lower in covid-19 patients compared to their healthy controls. Whereas the values of D-dimer and fibrin degradation product (FDP) and fibrinogen (FIB) values in SARS-CoV-2 patients higher than those in the control group.[95, 96]

Unlike these tests, no differences could be observed in values of Activated Partial Thromboplastin Time(APTT), Prothrombin Time (PT), PT-INR and Thrombin Time (TT) between the two groups.[63] D-dimer and FDP were found to be especially predictive of disease progression; hence, their routine monitoring would appear advisable in patients with COVID-19.[95] Studies have shown there is dysregulated thrombin generation which is further exacerbated by an inhibition of fibrinolysis and the impairment of natural anticoagulant mechanisms. To date, treatment of DIC has been focused on strategies to target the primary pathology[97] but this is limited in the case of Covid-19, until more is learnt about effective antiviral agents for this new pathogen. Otherwise, supportive care to maintain critical organ function is required. Trials of natural anticoagulant infusions have met with variable outcomes[98]

Blood and Blood Products Requirements

As COVID-19 continues to claim lives and a likelihood that many potential blood donors are going to be unwell, consideration should be given to blood conservation protocols with critical, global blood shortages on the horizon. Previous studies have reported the use of convalescent plasma transfusion in the treatment of various infections.[99-102] Preliminary studies in the administration of convalescent plasma containing neutralizing antibody was followed by improvement in the patients' clinical status.[103] However, these observations require evaluation in clinical trials. Another study shows improvement of clinical symptoms and laboratory parameters within 3 days after convalscent plasma transfusion. CP can serve as a promising rescue option for severe COVID-19, while the randomized clinical trial is ongoing.

CONCLUSION

There is quite some level of impact of covid-19 on Haematology and haematological parameters, just as it also affects other systems, and specialties/sub-specialties. However, there is room for more research in determining more extensive involvement of the disease on haematological parameters.

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