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An overview on COVID-19 and vaccines: findings and learnings from the pandemic

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Abstract. – The coronavirus-2019 (COVID-19) pandemic continues to create global impact and continues to stand divided on the mask mandate, the vaccine passport, and the continuous testing process. The focus of this review is to highlight the hematological findings in COVID-19, complications, as well as impact of vaccinations. A detailed literature review has been conducted using keywords including "coronavirus disease", "COVID-19", "COVID-19 vaccinations", "COVID-19 hematological complications" to list a few. The findings highlight mutations in the non-structural proteins NSP2 and NSP3 to be crucial. With over fifty potential vaccine candidates in trial, prevention and symptom management continue to be the primary clinical challenge. Clinical studies have detailed the hematological complications of COVID-19, including coagulopathy, lymphopenia, and changes in levels of platelet, blood cells, and hemoglobin, to state a few. Further, we also discuss the impact of vaccination on hemolysis, on multiple myeloma patients, as well as thrombocytopenia.

Key Words:
Blood cells, Coagulation, COVID-19, Hematology, Multiple myeloma, Platelets.

Background

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) that initiated the coronavirus disease 2019 (COVID-19) pandemic from China, continues to challenge the clinical and geo-political aspects worldwide. As the scientific community across the globe are fighting for evidence around disease emergence, emerging variants, and impact of existing vaccinations, the COVID-19 virus continues to infect different populations irrespective of ethnicity. The SARS-CoV-2 belonging to the true RNA virus family, continues to undergo genetic evolution with time while adapting to different kind of hosts; and as of 2021-year end, five variants of concern (VOCs) have been identified. These include B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), and the latest B.1.1.529 (Omicron)[1]. The Alpha variant reported from UK was documented to be 43-82% more transmissible with increased disease severity and mortality [hazard ratio (HR)=1.61, 95% CI 1.42 - 1.82)][2-4]. The Beta variant from South Africa with increased transmissibility, and Gamma variant from Brazil exhibited neutralization by post-vaccination sera, as well as monoclonal antibody therapy[5-7]. The Delta variant from India was found to harbor ten mutations in spike protein, while the latest Omicron variant from South Africa was found to exhibit over 30 mutations in the spike protein and a 13-fold increased infectivity[8-11]. The Omicron variant has been reported by over 140 countries as of January 2022, with the highest number of COVID-19 infections found in the USA followed by Brazil, and India. Studies[12] also indicate the change in the tropism of Omicron towards the upper respiratory tract, a shift from the wild type that impacts the lower respiratory tract. Further, Omicron also exhibits a high growth advantage, greater secondary attacks and reproduction number.

The impact of COVID-19 infection has been associated majorly with the respiratory and the vascular system. The early stage involves virus-mediated tissue damage, while the late stage is characterized by immune response recruitment of T lymphocytes, which further in cases of severe infection proceeds to the stage of cytokine storm leading to local and systemic inflammatory response[13]. Apart from the principal target of the respiratory system, the other extrapulmonary organ systems, which have been documented[14] to be impacted, include the gastrointestinal tract, cardiovascular, renal, hemostatic system, and the central nervous system. Acute coronary syndrome has been documented[15,16] to be a cardiac impact of COVID-19, possibly due to the release of pro-inflammatory cytokines including IL-6 linked to

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vascular inflammation, and myocarditis. In terms of hematological impact of COVID-19, leukocytosis has been documented[17] to be the most common observation. Another uncommon aspect reported[14] has been thrombocytopenia and neutrophilia which are considered hallmark of severe illness. Hypercoagulability in COVID-19 has been postulated to be caused due to virus-induced vascular endothelium injury causing activation of platelets, monocytes, macrophages, along with increased expression of multiple clotting factors, leading to formation of the fibrin clot[18]. The focus of this review article is to detail the hematological findings and impact of COVID-19 on the hematopoietic system apart from the impact of vaccination on the blood cells. This is crucial as the role of hematologists becomes significant as the risk of severe COVID-19 endangers lives of many patients with blood-borne disorders, and immune dysfunction.

Blood Cells, Immunity, and COVID-19

The immune system includes the bone marrow, wherein from the progenitor or the hematopoietic stem cells originate. Blood cells then migrate through the lymphatic system to protect the peripheral tissues. The three key cellular entities in blood include the red blood cells (RBCs), the platelets, and the white blood cells (WBCs). The pluripotent hematopoietic stem cells differentiate to form the lymphoid and myeloid progenitor cells; the former further becomes either B cells or T cells, while the later differentiates to form the granulocyte progenitor (granulocytes) and the megakaryocytes and erythroblasts that finally form the platelets and the erythrocytes[19]. The lymphocytes including the B and the T mature in the bone marrow and the thymus, from wherein they enter the lymph node and the spleen, awaiting activation post antigen challenge. The first line of defense involves the innate immune system followed by the adaptive immune system which involves clonal expansion of the lymphocytes ultimately resulting in long-lasting, and highly specific response sustained by the memory cells[20]. Studies[21] around clinical COVID-19 cases of differing severity, and recovery stages have also characterized the physical changes on blood cells that lead to hematological complications including mechanical features of RBCs, lymphocytes (WBCs), neutrophils, eosinophils, and monocytes. Study found significant changes in lymphocyte stiffness, heterogeneity in RBCs deformation and size, monocyte size, as well as neutrophil size and deformability[17]. Further, many of the changes have also been documented[21] to be long-lasting post hospitalization discharge in COVID-19. Many recent studies[22] have also highlighted the mechanism behind RBC function alteration by the SARS-CoV-2 because of their ability to damage membrane RBC; more specifically the oxidation process of band 3 that lowers ATP release ability, lowering vasodilation, and supply of oxygen to tissues; causing severe hypoxia seen in cases of severe COVID-19.

Hematological Findings and Complications in COVID-19

Studies have indicated the impact of COVID-19 disease to range beyond the respiratory system to include many peripheral organ systems, and immunity[23]. The cytokine storm has been documented[24] to cause increasing disease severity, and substantial activation of the same has been found to cause lymphoid organ atrophy, including that of the spleen, further causing impairment of lymphocyte turnover. A study[25] from early 2020 in China involving over 500 hospitals identified lymphocytopenia in 83.2% patients on admission. Another study involving 191 patients identified with high D-dimer levels to be associated with higher odds of death [odds ratio (OR)=18.42, 95% CI, 2.64-128.55][26]. Studies in literature[27] have also highlighted clonal hematopoiesis (CH) to be stable among COVID-19 patients, and not linked to aggravated clinical course. Clonal hematopoiesis is the imprint inflammation of myeloid cells that perpetuates acute and chronic inflammatory response. It has also been associated with comorbidities that increase risk for severe COVID-19 disease[27]. However, a recent study[28] involving 160 patients were subjected to sequencing analysis for CH variants, and 19.4% of the study patients exhibited the variants. Further, this study highlighted the presence of CH variants to not be associated with disease severity[28]. Studies[29] also highlighted the risk of COVID-19 fatality to be higher among patients with hematological malignancies.

Erythrocytes, Lymphocytes, COVID-19, and Therapeutics

In quantitative hematologic analysis, atypical reactive lymphocytes have also been occasionally

reported[30-33]; a few of them were found to be lymphoplasmacytoid, apart from the most common ones which include lymphocytopenia, neutrophilia, thrombocytopenia, and eosinopenia. Hematological parameters comparison between intensive care unit (ICU) patients, and non-ICU identified lymphopenia to be common among the ICU-group [median nadir absolute lymphocyte count (ALC) of $0.4x10^9$/L] indicating monitoring of blood cells to be crucial to identify need for ICU care. This study also found ICU patients to have significantly lower CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts[33]. Several studies[34] have also assessed the morphological changes in blood cells through blood film microscopic analysis among COVID-19 patients before initiation of anti-viral or anti-inflammatory agents. Hyperchromatic platelets have been noted with peripheral areas of different size, occurring among both thrombocytosis, and thrombocytopenia patients. Further, at the time of the hospital admission, elevated neutrophil counts have been noted, with morphological abnormalities including nuclear and cytoplasmic granulation. Presence of dark toxic granules have been recorded apart from the presence of apoptotic cells. Changes in blood cell morphology post treatment, indicated the disappearance of morphological changes in the neutrophil, and wide heterogeneity occurring in the lymphocyte population with large, atypical lymphocytes, lymphoplasmacytoid cells, and increased population of granular lymphocytes. This shift indicates profound lymphocyte activation post-treatment. These studies[34-36] highlight the involvement of myelopoiesis in the pathogenesis of COVID-19. Peripheral hematological studies[37] which have compared characteristics of WBCs among survivors and non-survivors have documented levels of eosinophils, lymphocytes, and basophils to be significantly lower among non-survivors, indicating lymphopenia, and eosinopenia to be predictors of poor prognosis in COVID-19. A published case report[38] involving a 59-year-old male with no medical history and severe COVID-19 documented the presence of multi-organ failure with deranged liver function tests, high inflammatory markers, acute kidney injury, as well as lymphopenia. The blood film analysis also detected presence of reactive atypical lymphocytes including lymphoplasmacytoid lymphocytes with eccentric nucleus, basophilic cytoplasm, and prominent paranuclear hof[38].

Studies have defined the main driver of COVID-19 mortality to be the hyperinflammatory response like the one during hemophagocytic lymphohistiocytosis (HLH) that promotes ARDS. Blockage of the cytokine storm has been discussed to be the treatment rationale and the redundant and pleiotropic characteristics of certain cytokines pose challenge when therapeutics against single cytokines are involved. The Janus family kinase (JAK) inhibition has hence been recommended as an alternate strategy as major cytokines converge in the JAK/signal transducer and activator of transcription (STAT) pathway. Few of the JAK inhibitors in clinical trial used for treating COVID-19 include ruxolitinib, tofacitinib, pacritinib, and baricitinib; and the immunologic similarities between HLH and severe COVID-19 constitute supportive evidence for the ongoing JAN inhibitors trial[39]. Studies[40] have also documented the risk and occurrence of vaso-occlusive crisis triggered by COVID-19 among sickle cell disease (SCD) patients and ensuing complications in clinical management. Among SCD, COVID-19 has the potential to cause severe pulmonary complications through pneumonia or to trigger vaso-occlusive crisis, both of which can occur without patients exhibiting flu-like symptoms. The study[40] which describes the relation discusses two cases involving SCD patients who presented with vaso-occlusive crisis and no flu-like symptoms. While patient 1 presented with negative COVID-19 PCR, a diagnosis of acute chest syndrome was done, and a second test was subsequently found to be positive. In case of patient 2, the test was positive for COVID-19 upon admission for vaso-occlusive crisis but exhibited no respiratory of gastrointestinal complaints. Only a dip in oxygen saturation led to suspicion, testing and treatment. These case studies[40] indicate the need to test for COVID-19 among SCD patients who present with vaso-occlusive crisis irrespective of respiratory symptoms. Case studies presentation around the hematologic findings among COVID-19 hospitalized patients is heterogenous with another one discussing evidence of leuko-erythroblastosis which is noted usually in cases of bone marrow fibrosis including myelofibrosis, and other myeloproliferative disorders. The case report by Mitra et al[36] describes a 46-year-old healthy female with no travel history to China who presented severe-flu like symptoms and chest X-ray findings of lobular pneumonia, with worsening symptoms needing intubation and ventilation. Upon arrival, the complete blood count (CBC) test indicated lymphopenia, and further on the patient developed leukocytosis with a left-shifted population of

neutrophilic cells. The peripheral blood film analysis identified leukoerythroblastosis with normocytic anemia (occasional nucleated red blood cells), mild anisocytosis, and rare dacrocytes.

Thrombotic Complications in COVID-19

Studies[41] have identified several mechanisms of hypercoagulability to be upregulated in COVID-19 including immune-mediated thrombotic mechanisms, macrophage and complement activation, antiphospholipid antibodies, and dysregulation of the renin-angiotensin system. Studies[42-44] have identified micro- and macrovascular thromboembolic events and complications in the vasculature of the lungs, spleen, brain, and the gut. The most common thrombotic events recorded at a frequency of 20-30% among critically ill COVID-19 cases are pulmonary embolism (PE) and deep vein thrombosis (DVT). Studies[43,45,46] have recorded the frequency of occurrence of thrombotic events to be 49% in a Dutch cohort despite involving universal thromboprophylaxis (HR=5.4; 95% CI 2.4 - 12), and 21% in an Italian cohort. Another study[42] involving autopsy cases of COVID-19 deaths from Germany identified venous thromboembolism in 7 of the 12 deaths. Another multicenter study[47] studied the incidence and mortality of PE among COVID-19 hospitalized and identified the incidence to be 25% among the hospitalized, 29% among ICU patients, and 24% among non-ICU cases. Further, the study[47] also identified D-dimer levels over 1,600 ng/mL to help predict PE with 100% sensitivity and 62% specificity. Extrapulmonary embolism involving cardiac events have also been recorded[48] in COVID-19 with exacerbation of existing atherosclerotic disease, with many patients suffering acute ischemic stroke. Thrombotic complications can impact multiple cardiac events including instent thrombosis, myocardial infarction, many of which have been identified among hospitalized patients; one such documented the incidence of cardiac injury with a much higher risk of death (51.2% mortality with cardiac injury *vs.* 4.5% without, $p<0.001$)[49]. Studies[42,44] have also documented occurrence of microthrombi in many extrapulmonary organs including the spleen, prostate and testicular vein. Studies[50] around feasibility to use fibrinolytic therapy to treat systemic thrombotic events in COVID-19 have been discussed, albeit the risk for major hemorrhagic events does increase. Another study[50] evaluated prothrombin fragment 1.2 (PF 1.2) in COVID-19 patients in synchrony with D-dimer measurement. This study found moderate positive correlation between the markers, and the median PF 1.2 was found to be higher among thrombosis patients. PF 1.2 exhibited increased specificity and a higher positive likelihood ratio in identifying patients with thrombosis than D-dimer (PF1.2 threshold of >523 pmol/L: 69.2% sensitivity, 67.7% specificity; >924 pmol/L: 37.9% sensitivity, 87.8% specificity)[50]. Coagulopathy studies[51] in COVID-19 have identified elevated levels of factor V activity and patients with COVID-19 and factor V activity >150 IU/dL were documented to exhibit significantly higher rates of DVT/PE.

Other Complications in COVID-19

Apart from hypoxia and respiratory failure, very few studies[52] have also highlighted the incidence of acute kidney injury (AKI) in COVID-19, wherein kidney histology autopsy analysis revealed presence of prominent acute proximal tubular injury, peritubular erythrocyte aggregation, and glomerular fibrin thrombi with ischemic collapse. Clinically the incidence of AKI has been reported to vary between 0.9% to 29% across different institutions. This study[52] also documented presence of significant acute tubule injury, occlusion of microvascular lumens by erythrocytes with ensuing endothelial damage, as well as glomerular and vascular changes indicative of underlying diabetic or hypertensive disease. Ethnicity-related studies[53] have identified expression of ACE2 and kidney disease-related genes to be high among occidental donors relative to Asian donors, indicating possible susceptibility to kidney injury from COVID-19 to be higher among individuals of occidental rather than Asian descent. Combination of multiple pathological events in COVID-19 have been linked to cause AKI including dysregulation of the complement system, cytokine storm, AngII pathway, and hypercoagulation[54]. Further, studies[55] have also reported mortality rates (>60% in hospital) to be higher among COVID-19 patients with AKI than among those lacking kidney involvement.

Vaccinations and COVID-19

COVID-19 vaccines emerged as a scientific boon to overcome the severity of the disease of multiple VOCs across the world, as they aid in

reducing disease severity and need for hospitalization to a great extent. The main categories of vaccine include the most popular messenger RNA (mRNA)-based that involves the use of genetically engineered mRNA, that aids in the development of the S protein found on the surface of COVID-19 virus. The muscle cells synthesize the S protein through the mRNA vaccine, which triggers the immune system to develop antibodies against the same. The next category includes the vector vaccines involving use of genetic material from the virus placed inside a viral vector. Once delivered, the human cells synthesize and display the S protein on the surface, thereby triggering host immune response. The last category involves the protein subunit vaccine that includes the harmless S proteins that trigger the immune system[56]. The side effects of almost all the vaccines have been documented to be mild and hence approved for use in general population. However, certain segment of patients with pre-existing conditions showed certain vaccine side-effects.

Vaccination and RBCs

Several studies[57] have reported different impact of COVID-19 vaccinations on RBCs including induction of severe hemolysis. General reaction to vaccines, that have been recorded, have been mild, though few cases of increased complement activation leading to severe effects in diseases like paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by lack of complement regulatory proteins, have been noted[57]. Case studies[57] have recorded severe adverse impact of mRNA vaccine in patients with PNH including abdominal pain, needing emergency hospital evaluation and treatment with complement inhibitor due to suspicion of small bowel microvascular thrombosis. Another case[57] presented with fever, severe fatigue, myalgia, headache, and hemoglobinuria. These observations led to the understanding that strong complement amplification is a by-product of inflammatory response responsible for clinically observed hemolysis[58]. Certain studies[59] have also highlighted occurrence of autoimmune disorders post vaccination including aplastic anemia (AA) which is a bone marrow failure syndrome. A case study by Tabata et al[59] reported the development of AA in a 56-year-old male patient post-vaccination with mRNA vaccine which was treated with allogeneic hematopoietic stem cell transplantation (HSCT). The patient was admitted due to progressive pancytopenia and had no history of COVID-19 disease. Post replacement, significant improvement in AA was noted, despite the presence of anti-SARS-CoV-2 antibodies. Other case reports[60,61] on vaccine-induced autoimmune conditions have also documented occurrence of immune thrombocytopenia and acquired hemophilia. Another case study by Okuno et al[62] reported the occurrence of autoimmune hemolytic anemia in a 75-year-old woman post COVID-19 mRNA vaccination. The patient had a history of postoperative chemotherapy for lung adenocarcinoma, Helicobacter pylori eradication for idiopathic thrombocytopenic purpura (ITP), and was admitted for the treatment of anemia, two weeks after mRNA COVID-19 vaccination. This report reiterates the need for hematologists to be vigilant towards development of autoimmune hemolytic anemia, post mRNA vaccination.

Vaccination and WBCs

Studies[63] have also demonstrated the impact of COVID-19 disease on patients with hematological malignancies, as well as myeloproliferative neoplasm (MPN). The mortality rates by COVID-19 in both groups of patients have been documented to be 34%, and 48% respectively[64,65]. The JAK inhibitor ruxolitinib has been approved for the use in myelofibrosis (MF) patients, and the use of the same has a potent impact in lowering inflammatory cytokine production[66]. This impact has hence been linked to increased risk of infection among MPN patients in ruxolitinib treatment, abrupt withdrawal of which has also been linked with incidence of mortality; survival probabilities at 60 days from COVID-19 diagnosis were found to be 75%, 68%, and 11% among the no ruxolitinib group, the ruxolitinib continued group, and the discontinued group[65]. The immunomodulatory properties of the JAK inhibitor have also been implicated to impact vaccine efficacy among patients. A study[67] which evaluated the serological response rate to mRNA vaccines between healthy controls and MPN patients with no clinical suspicion of COVID-19 identified vaccine seropositivity to be 100% among healthy volunteers, and only 30% in the MPN group. Another study[68] evaluated immune response to vaccine among patients with multiple myeloma (MM) and found evidence for low proportion of patients exhibiting neutralizing antibodies

post 22 days of first dose of vaccine (20.6% *vs*. 32.5%). The response was also not found to improve post second dose. Another reference study[69], an observational cohort study estimated antibody responses who received COVID-19 mRNA vaccine and also diagnosed with lymphoma of which only 40% of those currently being treated had anti-S protein titers above the designated cutoff value in patients with chronic lymphocytic leukemia (CLL). Further, active therapy in the Hodgkin lymphoma (NHL) subgroup was associated with poor vaccine response, with only 21.4% developing anti-S protein titers above the cut-off. Also, CLL and NHL patients treated >24 months with anti-CD20 mAb therapy before vaccination had a response rate of 66.7% and 71.4%, respectively. This study[69] demonstrated commonly used lymphoma therapies to adversely influence the performance of COVID-19 vaccines, with anti-CD20 mAbs having the greatest impact. A study report by Herzog Tzarfati et al[70] documented the serologic response to BNT162b2 COVID-19 vaccine among patients with hematologic malignancies. This study found serologic responses to the vaccine in a lower proportion of patients following vaccination (75%) than in a comparison group (99%; $p<0.001$). Further, CLL patients exhibited lowest seropositivity rate followed by indolent lymphoma, and among those recently treated with chemo-immunotherapy, exhibited significantly less seropositive responses and lower median (IQR) antibody titers.

Vaccination and Platelets

Immune thrombocytopenia (ITP) has been reported[71] from multiple centers in response to mRNA vaccine, with mortality being reported due to intracranial hemorrhage. The Centers for Disease Control and Prevention (CDC) data study highlights twenty case reports of thrombocytopenia following vaccination. One of the reports describes the hospitalization of 20 patients post mRNA vaccination exhibiting symptoms of petechiae, bruising or mucosal bleeding. The cases[72] had history of ITP in remission, mild-moderate thrombocytopenia with positive anti-platelet antibodies, inherited thrombocytopenia, autoimmune conditions like hypothyroidism, Crohn's disease, and anti-thyroglobulin antibodies. Another case study by Dhoot et al[73] reported occurrence of thrombocytopenia and splanchnic thrombosis post Ad26.COV2.S vaccination in a 24-year-old healthy male. The case reported the occurrence of symptoms such as severe abdominal pain, nausea, vomiting, and decreased oral intake (11 days post vaccination). Further, the symptoms worsened with drop in hemoglobin levels, and he was admitted to ICU. A computed tomography assessment indicated extensive occlusive thrombosis of the portal, superior mesenteric (SMV), and splenic veins with severe bowel wall thickening concerning for venous ischemia. Treatment was done for vaccine-induced thrombotic thrombocytopenia (VITT) with thrombectomy and transjugular intrahepatic portosystemic shunt (TIPS) for severe VITT involving the splanchnic circulation. Another incidence of VITT classified as a life-threatening syndrome by the European Medicines Agency as thrombotic thrombocytopenic syndrome (TTS) following ChAdOx1 nCoV-19 vaccination was released in March 2021. This condition has been documented[74,75] to cause the formation of pathologic anti-platelet factor 4 (PF4) antibodies leading to thrombocytopenia and thrombosis in the absence of heparin exposure, like "autoimmune" heparin-induced thrombocytopenia (HIT). A case report by Abou-Ismail et al[76] describes the occurrence of confirmed VITT following Ad26.COV2.S vaccination, resulting in acute DVT and bilateral pulmonary emboli (PE), and a post-discharge course complicated by refractory thrombocytopenia. Another case study report by Shah et al[77] describes the case of a 53-year-old male with past medical history of Crohn's disease who was admitted for myalgias and diffuse petechial rash 8 days after receiving second dose of Pfizer-BioNTech COVID-19 vaccine. A laboratory report[77] highlighted thrombocytopenia which was normalized by intravenous immunoglobulin (IVIG) and oral dexamethasone. A second case[77] involved a 67-year-male with past medical history of chronic ITP in remission who was admitted for melena 2 days after receiving his first dose of Pfizer-BioNTech COVID-19 vaccine. Examination indicated thrombocytopenia and generalized petechiae. Treatment involved IVIG and oral dexamethasone. The third case[77] included a 59-year-old female with past medical history of chronic ITP secondary to systemic lupus erythematosus, who was admitted for bloody diarrhea 2 days after receiving her first dose of Johnson and Johnson COVID-19 vaccine, and laboratory diagnosis indicated thrombocytopenia. These numerous published case reports highlight the need to acknowledge and monitor for risk of COVID-19 vaccine induced ITP.

Conclusions

The therapeutic management of COVID-19 involves the use of antivirals, antibodies, anti-inflammatory agents, as well as protein-based agents[78]. Drug repurposing has also been experienced in this pandemic which became crucial to lower disease severity. COVID-19-associated coagulopathy continues to be observed among the hospitalized indicated by elevated levels of D-dimer, fibrinogen, and mild prolongation of prothrombin time (PT). Elevated D-dimer, and markedly increasing D-dimer levels (3- to 4-fold) over have been associated with high mortality, due to coagulation activation, cytokine storm and impending organ failure. Thus, monitoring of platelet count, PT, D-dimer, and fibrinogen has been recommended[79]. The hematological impact of COVID-19 disease, as well as the vaccine, necessitates the need to infer the availability of blood products for clinical management. Blood donation drives have been impacted by ongoing waves, and lockdown stresses the supply chain management of blood products putting critical patients at risk. COVID-19 has prominent impact on the hematopoietic system, and this reinforces the need for careful monitoring of outcomes, both in case of the disease and vaccinations.

Conflict of Interest

Abdulkarim S. Binshaya does not have any conflict of interests.

Authors' Contributions

Abdulkarim S. Binshaya: data analysis, concepts, design, data analysis, statistical analysis, manuscript preparation, manuscript review, guarantor definition of intellectual content, literature search, data acquisition, manuscript editing.

Availability of Data and Materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study. All the generated data are available in this article itself. The raw data that support the findings of this study are available from the corresponding author upon reasonable request.

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