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Review

Biochemical role of serum ferritin and d-dimer parameters in COVID 19 diagnosis



Abdullah Farasani*

Biomedical Research Unit, Medical Research Center, Jazan University, Jazan 45142, Saudi Arabia

Department of Medical Laboratory Technology, College of Applied Medical Sciences, Jazan University, Jazan 45142, Saudi Arabia

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ABSTRACT

One and one only most unforgettable pandemic is coronavirus 2019 (COVID 19) which is the most memorable pandemic of the twenty-first century. The diagnosis of COVID19 is based on purely clinical symptoms and real time reverse transcription polymerase chain reaction (RT-PCR) test. The role of COVID19 during this pandemic was horrible in diagnosing the disease with RT-PCR as this disease was documented to be a symptomatic disease. Serum ferritin and D-dimer tests plays a major role in identifying the infections in the human body specifically, patients diagnosed with COVID19. Serum ferritin levels are important for an immune response mediator that rises in severe COVID-19 instances, and elevated ferritin levels may trigger a cytokine storm by exerting direct immunosuppressive and pro-inflammatory effects. d-dimer is used to identify the clots in the blood. COVID-19 patients were found to be clotting of blood and d-dimer is recommended. The blood of the COVID-19 patients were found to be clotted than the patients were prescribed the anticoagulant Injections are prescribed. d-dimer can be used as a biomarker in the COVID-19 patients by measuring the d-dimer levels and analyse the mortality and severity. Pulmonary complication risk can also be identified. d-dimer is a mandatory and an essential test in the COVID-19. Numerous COVID-19 vaccines have been shown to have great efficacy levels through clinical trials. COVID-19 vaccines are not 100% effective, although the condition is mild or moderate and can be controlled if COVID-19 is affected. In this review, I have only included serum ferritin and d-dimer; however, C-reactive protein, vitamin D levels, and prolactin were also attributed to COVID-19. This review concludes the importance of RT-PCR, serum ferritin, and d-dimer testing in identifying COVID-19 infection in humans.

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* Address: Biomedical Research Unit, Medical Research Center, Jazan University, Jazan 45142, Saudi Arabia.

E-mail address: aofarasani@jazanu.edu.sa

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1. Introduction

Due to the propagation of Coronavirus 2019 (COVID-19 or 2019n-CoV), which began with a cluster of pneumonia of unknown origin, the Wuhan market will be recognized for the rest of life and in the history (Spiteri et al., 2020). In 2003, a similar form of infection caused by severe acute respiratory syndrome (SARS) was discovered in China (Pal et al., 2020). In 2020, the infectious disease known as the new coronavirus, initially named as 2019-nCoV and then revised by the International Committee on Virus Taxonomy as coronavirus SARS-2 (SARS CoV-2) was fully identified as a pandemic year worldwide (Farasani, 2020). COVID-19 has been declared a public health emergency of international significance by the World Health Organization in the first month of the year 2020. The infectious disease spreads swiftly from human to human transmission (Zhou et al., 2020). CoV is wrapped with RNA viruses with a diameter of 60–140 nm with the spike of projections on its surface, giving it a similar crown under the electron microscopic aspect and 4 CoVs namely HKU1, NL63, 229E and OC43 are in circulation in humans (Singhal, 2020). The two most regularly detected highly dangerous viruses are the SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV) causes severe, pneumonia-like symptoms as SARS, and sometimes mortality in adults. The mortality rate was found to be 10% and 34.4%, respectively, and a large outbreak of SARS-CoV arose from China, infecting 29 nations worldwide. MERS-CoV was first imported into China in Middle East in 2012. SARS-CoV has been spread on wet markets to people from exotic animals, while MERS-CoV is transferred from camels to humans (Ahmed, 2020). SARSCoV-2 is zoonotic based on the history of both SARS-CoV and MERS-CoV, the most plausible source being Chinese horseshoe bats and Pangolins, the most probably intermediary host. While the main source of transmission was the patients with symptomatic COVID-19, subsequent evidence indicated that asymptomatic patients and patients also carry SARS-CoV-2 throughout their incubation period. The epidemiology of COVID-19 has made its management very problematic, since these patients are not identifiable and quarantined in time, which may lead to SARS-CoV-2 buildup in populations (Meng et al., 2020) Table 1.

COVID-19 has three escalating severity levels. Symptoms such as the flu may appear at an early stage, primarily as a result of viral infection and viral pneumonia, and patients may be hospitalized for an extended period of time or placed on a ventilator. Pulmonary inflammation and coagulopathy, which can occur consecutively

but are commonly overlapping, are also characterized during the second stage. In addition, the development of acute respiratory distress syndrome and a poor clinical course involve increased levels of inflammatory biomarkers, such as C-reactive Protein (CRP), ferritin, IL-6, IL-1, and d-dimer. Finally, fibrosis is the third stage of the disease. Two respiratory phenotypes; low and the high elastance type can be distinguished in patients who require mechanical ventilation. The higher lung edema in the H-type results in elevated pulmonary weight and reduced lung compliance (Polak et al., 2020). In suspected COVID-19 cases, chest CT is strongly indicated for both initial assessment as well as follow-up in the predominant involvement of the respiratory system. Chest x-rays have a low diagnostic value in early stages, although CT results can occur before the onset of the symptoms. In addition, CT results in few instances have proven to be diagnostic with an initial false-negative result with real-time reverse-transcriptase polymerase chain reaction (RT-PCR) (Salehi et al., 2020). Reliable laboratory diagnosis is one of the main concerns for facilitating public health actions. RT-PCR is used routinely to detect causal viruses from respiratory secretions in acute respiratory infections (Corman et al., 2020).

2. Prevalence of COVID19

As of July 10th 2021, there were 187,185,828 infected cases and 4,040,978 death cases were recorded internationally. The ten highest number of infected cases were recorded in USA (n = 34,723,159), followed by India (n = 30,836,231), Brazil (n = 19,069,003), France (n = 5,808,383), Russia (n = 5,758,300), Turkey (n = 5,470,764), UK (n = 5,089,893), Argentina (n = 4,627,537), Columbia (n = 4,471,622) and Italy (n = 4,269,885) (Fig. 1). Overall, 222 countries were infected globally and the highest number of cases were recorded in the USA with 34,723,159 and lowest number of cases were recorded in Micronesia with one infected person. However, MS Zaandam (n = 09), Vanuatu and Marshall Islands (n = 04), Samoa (n = 03), Saint Helena (n = 02) and Micronesia (n = 01) were recorded with the single digit number. However, Falkland Islands (n = 63), Macao (n = 55), Greenland (n = 51), Vatican City (n = 28), Saint Pierre Miquelon (n = 27), Montserrat and Solomon Islands (n = 20) and Western Sahara (n = 10) were recorded with the double-digit cases.

Till now, 4,040,978 COVID-19 deaths were recorded globally and again USA (n = 622,803) were recorded top and remaining 9

Table 1

List of SARS-CoV-2 identified variants of concerns and variants of Interest.

Types of Variants	WHO label	Pango Lineage	GISAID Clade/Lineage	Next strain clade	Earliest documented samples	Date of designation
Variants of Concern	Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I (V1)	United Kingdom, Sep-2020	18-Dec-2020
Variants of Concern	Beta	B.1.351	GH/501Y.V2	20H (V2)	South Africa, May-2020	18-Dec-2020
Variants of Concern	Gamma	P.1	GR/501Y.V3	20J (V3)	Brazil, Nov-2020	11-Jan-2021
Variants of Concern	Delta	B.1.617.2	G/478 K.V1	21A	India, Oct-2020	11-May-2021
Variants of Interest	Delta	B.1.617.2	G/478 K.V1	21A	India, Oct-2020	04-Apr-2021
Variants of Interest	Epsilon	B.1.427/B.1.429	GH/452R.V1	21C	United States of America, Mar-2020	05-Mar-2021
Variants of Interest	Zeta	P.2	GR/484 K.V2	20B/S.484K	Brazil, Apr-2020	17-Mar-2021
Variants of Interest	Eta	B.1.525	G/484 K.V3	21D	Multiple countries, Dec-2020	17-Mar-2021
Variants of Interest	Theta	P.3	GR/1092 K.V1	21E	Philippines, Jan-2021	24-Mar-2021
Variants of Interest	Lota	B.1.526	GH/253G.V1	21F	United States of America, Nov-2020	24-Mar-2021
Variants of Interest	Kappa	B.1.617.1	G/452R.V3	21B	India, Oct-2020	04-Apr-2021
Variants of Interest	Lambda	C.37	GR/452Q.V1	20D	Peru, Dec-2020	14-Jun-2021

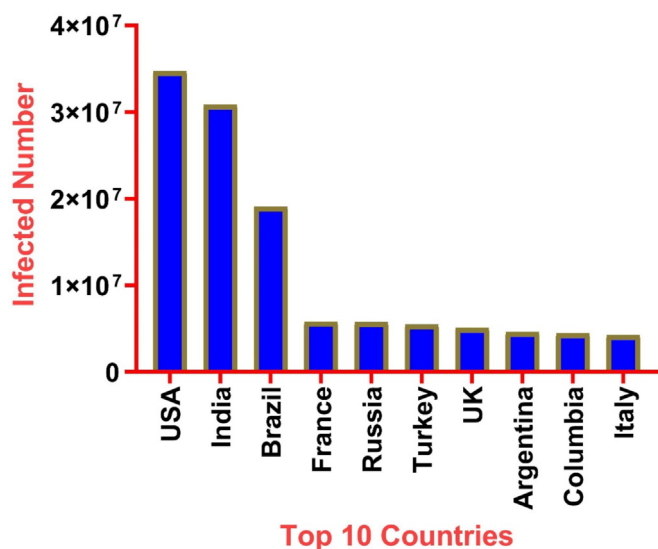


Fig. 1. List of top ten countries infected with COVID-19.

countries were Brazil (n = 532,893), India (n = 408,072), Mexico (n = 234,675), Peru (n = 194,084), Russia (n = 142,253), UK (n = 128,399), Italy (n = 127,768), Columbia (n = 111,731) and France (n = 111,321). However, Burundi (n = 08), Wallis and Futuna (n = 07), Laos, British Virgin Islands, Saint Kitts and Nevis and Brunei (n = 03), Cayman Islands and MS Zaandam (n = 02) and Bhutan, St. Barth, Faeroe Islands, Grenada, Montserrat, Western Sahara and Vanuatu (n = 01) were recorded with the single digit cases. Some of the countries such as Dominica, New Caledonia, Anguilla, Falkland Islands, Macao, Greenland, Vatican City, Saint Pierre Miquelon, Solomon Islands, Marshall Islands, Samoa, Saint Helena and Micronesia have not recorded any COVID-19 deaths until now (Covid).

3. Clinical symptoms

It is well known that the condition might be asymptomatic or that the symptoms may be mild to extremely severe. Cough, Anosmia, Sore throat, Ageusia, Nasal congestion, Runny nose, Postnasal discharge, Hoarseness, and other otolaryngological symptoms Otagia, Tinnitus, Gingivitis, Bell's palsy, and Sudden Hearing Loss (Elibol, 2021). The symptoms may occur from 2 to 14 days after exposure and from 4 to 7 days after incubation, which is likely to be asymptomatic and contaminating to any infected patient. During numerous COVID-19 patients, the anti-proliferation antibodies and independent immune activity have asymptomatic and/or healthy neutralization and cell-mediated tolerance (Kaye et al., 2020, Farasani, 2020). The most prevalent symptoms, such as fever, dry cough and fatigue, differ in age categories for persons. Fatigue, muscle or body aches, headache, new taste or smell loss, sober throat, congestion or nose, nausea or sprouting diarrhea have also been added for other clinical symptoms. COVID-19 causes significant consequences such as shortness of breath, chest pain, and loss of speech mobility (Rahmani and Mirmahaleh, 2020).

4. RT-PCR analysis

Accurate laboratory testing is crucial in the diagnosis of new infectious diseases and their management. The following infection symptoms are non-specific and case confirmation is based on nucleic acid amplification assays that detect RT-PCR viral ribonucleic acid sequences. Various RT-PCR assays, including the N gene

coding for the virus nucleocapsid have been proposed. The E gene for the virus envelope, the S gene for the spike protein and the Hel gene for the RNA polymerase gene are other possible targets. Molecular diagnostic criteria on COVID-19 in vitro are varied; two or more SARS-CoV-2 genes are typically detected (Arevalo-Rodriguez et al., 2020). Application of quantitative PCR (qPCR) is preceded, routinely, by (1) collection and purification of total sample RNA, (2) elution and potential concentration of the material, and (3) by a reverse Transcription Response of purified RNA resulting from the template RNA used for qPCR reactions (Smyrlaki et al., 2020).

Among the diagnosis of COVID-19 infection, quick rapid test was recommended initially and the results were found to be not satisfactory. To detect COVID-19 infections in humans, RT-PCR has been commonly applied around the world. Basic characteristics, such as sensitivity, specificity, and the likelihood of becoming infected with COVID-19, remain mostly unknown. Sensitivity is particularly important in understanding the likelihood of false negative testing. There are consequential false-negative findings. Persons with these results may relax physical distance and other personal measures aimed at reducing the virus' transmission to others. For clinicians, they might be sent to the frontlines and mistakenly transmitted to patients and colleagues and the tenuous ability of the health system to respond to the pandemic could be further stressed (Furukawa et al., 2008, West et al., 2020). RT-PCR detects fluorogenic primers/probes and thermal cycling stages for viral ribonucleic acid. The SARS-CoV-2 genome was first submitted to the Global Initiative on Sharing all Influenza Data by the Chinese Disease Control and Prevention Centers and then received a Food and Drug Administration emergency user permit for the first RT-PCR in the USA. It is more sensitive, safe, and cost-effective than viral culture approaches, but it has drawbacks. Serology has also gained popularity due to specific benefits, such as estimating Sero-prevalence, asymptomatic viruses, contact tracking, and vaccine effectiveness (Shyu et al., 2020).

5. Importance of biochemical parameters in COVID19

Several pro-inflammatory cytokines and chemokines were observed in the bloodstream and target tissue of COVID-19 patients. Ferritin is widely known as an acute phase reactant and as a mediator for severe COVID-19 immunological dysfunction. Ferritin may therefore be an active agent not only in a cytokine storm but also a signal of the inflammatory environment. COVID-19. Complex feedback loops may exist between ferritin and cytokines, as cytokines may increase the expression of ferritin, but ferritin can induce the expression of pro and ant inflammatory cytokines. In this sense the range of hyperferritinemic syndrome could cover COVID-19 with pulmonary involvement (Alunno et al., 2020, Gandini et al., 2020, Kappert et al., 2020). Ferritin is the intracellular reserve of iron, and iron insufficiency is well known. Anemia is distinguished by low ferritin levels. High levels of iron storage imply the presence of several viruses or bacteria in the human body. This can be accomplished by measuring ferritin levels even in the presence of a transient presence of COVID-19. According to research, high ferritin levels indicate the severity of COVID-19, as COVID patients with particularly high ferritin levels died in 50% of cases. A series of physiological and metabolic changes start immediately after tissue injury are the active phase reaction of an inflammatory process. The fluctuation in the concentration of certain plasma proteins called acute phase proteins is one of the many systemic symptoms of this acute phase reaction. Most commonly used among them is C-reactive protein, amyloid serum A, haptoglobin, fibrinogen, and ferritin. Serum Ferritin has been extensively investigated as a measure of iron metabolism,

however, it has recently shown a great importance in the context of COVID-19 progression as proven by past studies. Ferritin is an acute phase reactant, and, as such, is typically raised in any inflammatory response. To assess for the most typically seen cytokine storm syndromes laboratory findings include a complete blood count, serum ferritin levels, and liver function tests. Most medical facilities provide these testing (Lino et al., 2021). Tang *et al* studies found that higher fibrin-relevant (d-dimer and fibrin degradation product) levels were significantly associated with non-surviving COVID-19 patients when compared to survivors, as was the use of low molecular heparin in severe SARS-CoV-2 infected patients with elevated d-dimer or sepsis-induced disseminated intravascular coagulation. Increased d-dimer levels may be a good predictor of COVID-19 severe and fatal cases in hospital admission (Tang et al., 2020). Similar study has shown that d-dimer has a discriminatory capacity in patients with and without serious COVID-19 forms but does not have mortality data (Henry et al., 2020). Several studies have shown that ferritin in hospitalized patients has a considerable elevation, but typically not a particular marker for hemophagocytic lymphohistiocytosis. Ferritin is an acute protein that increases in response to a wide range of inflammatory conditions, including malignancies, overload of iron, and liver or kidney diseases (Melo et al., 2021). Global studies aimed to better understand the pathophysiology of the disease and to analyze how specific laboratory markers help in the COVID-19 process. Recent results revealed that patients with COVID-19 had lower hemoglobin levels and higher levels of ferritin. USA: A study done revealed that ferritin levels were pathologically high in 5700 individuals hospitalized for COVID-19. Anemia accompanies hyperferritinemia, no matter what underlying diseases are present. When ferritin levels begin to rise, a time bomb of inflammation is likely to be present. Patients with COVID-19 have reported that inflammatory processes also produce high levels of ferritin. In severe cases serum ferritin levels were substantially higher (Bozkurt et al., 2021). A recent meta-analysis of patients with poor composite result showed that ferritin was higher in non-survivor groups and subgroup findings showed a higher ferritin level.

6. d-dimer

d-dimer is the main fibrin disintegration fragment and is used in the synthesis and degradation of fiber as a biomarker. Healthy people have modest levels of d-dimer in circulation while high levels are detected in thrombosis-related diseases. For the diagnosis, surveillance and treatment of venous thromboembolism, for which d-dimer is commonly employed, extensively investigated. Many studies have demonstrated that D-dimer is a good marker for coagulation and fibrinolysis activation. Berger *et al* investigation found that abnormal d-dimer levels were often detected with COVID-19 admission and were associated with an increased risk of critical disease, thrombotic events, acute renal injury, and death (Berger et al., 2020). d-dimer comes from cross-linked fibrin synthesis and lysis and is responsible for coagulation activation and fibrinolysis. COVID-19 has been reported to be connected with hemostatic anomalies, and significantly high amounts of d-dimer in non-survivors have been recorded (Zhang et al., 2020). d-dimer is one method to spot thrombotic-state. After the creation of the clot, the fibrinolytic system breaks down the mesh. By activating the plasmin enzyme, the D-dimer consists of two D fragmentations of the fibrin. This shows that the bloodstream has demolished fibrin. d-dimer is a coagulation and fibrinolysis activation system. The d-dimer test is commonly used in clinical practice to rule out deep vein thrombosis and pulmonary embolism and to confirm the diagnosis of disseminated intravascular coagulation. d-dimer level is one step in thrombosis detection used in patients. In

early stage of COVID-19 disease studies have shown an increase in d-dimer and fibrinogen levels. The increase of d-dimer levels by 3 to 4 times is related to poor forecasts. Increasing d-dimer levels in COVID-19 individuals could also be triggered by underlying conditions such as diabetes, cancer, stroke, and pregnancy. In the control and management of COVID-19 the measurement of d-dimer and coagulation parameters at an early stage of the disease can also be important (Rostami and Mansouritorghabeh, 2020). patients with COVID-19 were reported to have a hypercoagulable state, with 71% of patients who died from COVID-19 having satisfied the DIC criteria. In this context, this means that a total of 71% of patients who died from COVID-19 met the DIC threshold, with the remaining 29% falling short. Furthermore, venous thromboembolism occurred in 25% of patients with severe COVID-19, and in 30% of those patients, pulmonary embolism was identified. COVID-19 individuals with ischemic stroke have also raised D-dimer levels in their blood (He et al., 2021).

Huang *et al* found from 11 previous studies that an increased d-dimer was related with an increase in composite poor outcome [RR 2.93 (2.14–4.01), $p < 0.001$]. Furthermore, subgroup analysis revealed that an elevated D-dimer was linked to an increased risk of mortality. This review focused on a few biochemical parameters, such as serum ferritin and d-dimer. Furthermore, documented studies have revealed that CRP, vitamin D levels, and prolactin play a role in detecting COVID-19 in humans.

7. Conclusion

This review concludes as COVID-19 infectious disease plays a major role in Serum ferritin and d-dimer tests apart from RT-PCR test. The severity of the disease might be efficiently determined with early ferritin levels analysis in patients with COVID-19. d-dimer can be used as a biomarker in the COVID-19 patients by measuring the d-dimer levels and analyse the mortality and severity. Serum ferritin and d-dimer tests should be included in the future studies to predict the severity in the patients diagnosed with COVID-19 disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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