Ministry of Higher Education

And Scientific Research

University of Diyala

College of Medicine

A Review Article in:

The role of biomarkers in COVID-19

Submitted to the Council of the College of Medicine, Diyala University, in Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

Submitted by:

Eman Hussein Jaleel

Supervised by:

Dr. Yasmine Sami Nasir

2021-2022

بسم الله الرحمن الرحيم

(أَمَّنْ هُوَ قَانِتٌ آنَاءَ اللَّيْلِ سَاجِدًا وَقَائِمًا يَحْذَرُ الْآخِرَةَ وَيَرْجُو رَحْمَةَ رَبِّهِ ۗ قُلْ هَلْ
يَسْتَوِي الَّذِينَ يَعْلَمُونَ وَالَّذِينَ لَا يَعْلَمُونَ ۗ إِنَّمَا يَتَذَكَّرُ أُولُو الْأَلْبَابِ)

صدق الله العلي العظيم

من سورة الزمر الآية 9

Abstract

The coronavirus disease pandemic of 2019 (COVID-19) is wreaking havoc on worldwide public health. COVID-19 is caused by infection with the severe acute respiratory syndrome coronavirus-2 (SARSCoV-2). Patients infected with SARS-CoV-2 frequently have dry cough or, less frequently, dyspnea in the lower respiratory tract. To some extent, these symptoms indicate lung inflammation. Inflammation is a 'byproduct' of the immune system's response. Due to the high prevalence of COVID-19 cases around the world because of its highly contagious nature, various studies have been published on the predictors of illness severity in COVID-19 patients. In this short article, we reviewed literature about the significance of biomarkers in COVID-19 infection and their role in diagnosis.

Keywords: COVID-19, biomarkers

Introduction

In December 2019, a novel coronavirus, caused a series of acute atypical respiratory diseases in Wuhan, Hubei Province, China. The disease caused by this virus was termed COVID-19 (1). COVID-19 is caused by infection with the severe acute respiratory syndrome coronavirus-2 (SARSCoV-2), which shares 79.5 percent of the SARS-CoV sequence. SARS-strong CoV-2's transmission capability, as indicated by a basic reproductive number R0 of 2.0 - 3.77, resulted in the virus's rapid spread from a city to the entire world in just three months (2). SARS-CoV-2 infects cells by using angiotensin-converting enzyme 2 (ACE2) as a receptor (3). The lung is a vulnerable target organ because the ACE2 distribution is concentrated in human alveolar epithelial cells. Patients infected with SARS-CoV-2 frequently have dry cough or, less frequently, dyspnea in the lower respiratory tract. To some extent, these symptoms

indicate lung inflammation. Inflammation is a 'byproduct' of the immune system's response (4).

Researchers from all over the world have been looking for predictors of COVID-19 illness severity in order to identify and stratify them for medical care. Insights into disease pathophysiology are developing, as are ways to quickly detect and assess COVID-19 infection. Biomarkers in the lab are less expensive, faster, and easier to get. As a result, they have been the favored method of monitoring and predicting illness outcomes and prognosis (5). Due to the high prevalence of COVID-19 cases around the world as a result of its highly contagious nature, various studies have been published on the predictors of illness severity in COVID-19 patients. When compared to milder cases in which survival is the outcome, studies have shown that severe or fatal cases of COVID-19 disease are associated with an elevated white cell count, blood urea nitrogen, creatinine, markers of liver and kidney function, C reactive protein (CRP), interleukin-6 (IL-6), lower lymphocyte (1000/L) and platelet counts (100x109/L), as well as albumin levels (6-7). In this short review we will highlight the role, importance, efficacy, availability and usage of the laboratory biomarkers in the management of COVID 19 pandemic.

A biomarker is defined as a “characteristic that can be objectively measured and evaluated as an indicator of normal biological and pathological processes, or pharmacological responses to a therapeutic intervention” (8). Early suspicion of disease, confirmation and classification of disease severity, framing hospital admission criteria, framing ICU admission criteria, rationalizing therapies, assessing response to therapies, and framing criteria for discharge from the ICU and/or the hospital are all things that biomarkers in COVID 19 can help with (9). The

biomarkers evaluated in COVID 19 were divided into many groups, which we will explain in the following lines.

Hematological Parameters

Anemia and impaired iron homeostasis were prevalent in hospitalized COVID-19 patients, according to a retrospective research. Anemia was linked to a higher risk of death, and a higher ferritin/transferrin ratio predicted the requirement for ICU admission and mechanical ventilation (10). In early disease, when symptoms are non-specific, peripheral blood leukocyte and lymphocyte counts are normal or slightly reduced. Significant lymphopenia appears 7 to 14 days after the onset of symptoms, along with poor clinical status, a rise in inflammatory mediators, and a "cytokine storm." Lympocytopenia is linked to the severity of the disease and death. Lympopenia on admission (defined as a lymphocyte count of less than 1,100 cells/l) is linked to a three-fold increased risk of poor outcome in younger patients when compared to older individuals (11). The absolute number of circulating CD4+ cells, CD8+ cells, B cells, and natural killer (NK) cells is significantly reduced in severe illness; plasma cells are significantly increased (12). There has been thrombocytopenia as well as thrombocytosis. Severe thrombocytopenia and hemorrhage, on the other hand, are unusual. Thrombocytopenia has been linked to other coagulation factors as well as an increased risk of death (13).

Immunological and inflammatory biomarkers

A regulated synthesis of inflammatory mediators occurs during a normal immune response to pathogenic stimuli to promote successful pathogen elimination. After the offending stimuli has been removed, the immune system returns to its normal state. This mechanism entails a coordinated interplay of proinflammatory and anti-inflammatory cytokines

to both localize and extinguish the immune response as needed. A cytokine storm, or the abnormal and excessive release of proinflammatory cytokines, is a systemic inflammatory response that can be produced by a variety of factors, including microorganisms, iatrogenic therapies like CAR-T therapy, and some autoimmune/ autoinflammatory disorders (14).

The cytokine storm has been linked to severe respiratory virus infections, with increased production of proinflammatory cytokines such as TNF-, IL-6, IL-1, and MCP-1. Increased vascular permeability, pulmonary edema, acute respiratory distress syndrome, and various organ failure have all been linked to the release of these cytokines (15). The cytokine storm, on the other hand, plays a crucial role in the etiology of severe COVID-19. As a result, cytokine storm biomarkers may provide early warning of severe disease in COVID-19 patients and motivate more aggressive therapy targeting specific biomolecular targets. Higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP-10, MCP-1, MIP-1A, and TNF- were linked to acute respiratory distress syndrome, heart damage, and subsequent infections, necessitating ICU hospitalization in a study of COVID-19 pneumonia patients (16).

Studies looking at the role of cytokines in SARS and MERS have discovered a link between CRS and the severity of the disease. In severe forms of COVID-19, levels of IL-6, the most prevalent kind of cytokine generated by activated macrophages, have been found to rise dramatically. However, because the majority of research to date have been observational, it's impossible to say whether the rise is big enough to cause the severe signs described (17). During severe CRS circumstances, the immunological protein IL-6 alone can cause cardiomyopathy. Capillary injury, low blood pressure, and coagulopathy may result from a large concentration of activated endothelial cells. These incidents, individually

or in combination, have catastrophic consequences or even result in death (18). According to a new study on inflammatory biomarkers, geriatrics with high IL-6 baseline levels and high overtime IL-6 increment scale levels are more susceptible to numerous systemic disorders than those with low overtime IL-6 increment and high baseline IL-6 titers (19).

Non-survivors' serum ferritin levels are significantly higher than survivors' (WMD: 4.6 pg/mL and 760.2 ng/mL, respectively) and severe vs. non-severe disease (WMD: 1.7 pg/mL and 408.3 ng/mL, respectively) (20). C reactive protein (CRP) is a plasma protein generated by the liver that is triggered by inflammatory mediators like IL-6. Despite its lack of specificity, this acute phase reactant is utilized therapeutically as a biomarker for a variety of inflammatory disorders; an increase in CRP levels is linked to a worsening of illness severity (21). A retrospective singlecenter study in Wuhan, China, highlighted the use of CRP in COVID-19, finding that the majority of patients in the severe cohort had much higher levels than the non-severe cohort (57.9 mg/L vs 33.2 mg/L) (22). Patients with CRP levels more than 41.8mg/L had a higher risk of advancing to severe COVID-19 disease, according to a second retrospective cohort analysis. CRP levels appear to be a robust indication of the presence and severity of COVID-19 infection in both investigations (23).

Procalcitonin (PCT) is a glycoprotein that is the pro-peptide of calcitonin but lacks hormonal function. It is created in the C-cells of the thyroid gland under normal conditions. PCT levels in healthy persons are undetectable (0.1 ng/mL). PCT levels can rise to beyond 100 ng/mL after severe infection (bacterial, parasitic, and fungal) with systemic symptoms, with extra-thyroid tissue producing the majority of it. The sequence homologies between PCT and other human cytokines, such as TNF-a

family, IL-6, and others, support the concept that PCT is a mediator of inflammation, despite the fact that its biological function is mostly unknown (24). When it came to COVID-19 patients, the more severe cases had a higher PCT than the non-severe instances (25). A small increase in PCT levels (less than 0.5 ng/mL) is a useful diagnostic for distinguishing between SARS-CoV-2-positive and SARS-CoV-2-negative individuals (26).

In patients with uncomplicated SARS-CoV-2 infection, the PCT value remains within reference limits; any significant increase indicates bacterial coinfection, the development of a severe form of sickness, and a more complicated clinical picture (27). Although the first PCT result can assist determine the severity of an infection, it is not always a useful prognostic indication. PCT readings may be high because they are impacted by prior comorbid diseases including CKD and congestive heart failure. PCT, on the other hand, can provide vital information when used in a clinical setting (28).

Cardiovascular and thrombotic biomarkers

Patients with COVID-19 who are at risk of acute illness and ICU admission are typically older and have similar comorbidities, such as heart failure, hypertension, and coronary artery disease. Cardiac troponins are a family of cardiac regulatory proteins that regulate muscle contraction and may be used as a marker for heart muscle injury. The sole established biomarker for detecting acute myocardial infarction is cardiac troponin. An high level of cardiac troponin indicates the onset of myocardial infarction (29). Cardiac troponin I (cTnI) levels were observed to be somewhat higher in mildly severe COVID-19 patients and considerably higher in severely ill patients. A significantly elevated cTnI level was also found in COVID-19 patients who had sustained cardiac damageFurthermore, one out of

every five COVID-19 patients admitted to the hospital had significantly high cardiac troponin levels, making them more likely to need invasive or noninvasive ventilation (30).

Lactate dehydrogenase (LDH) is an intracellular glycolytic enzyme that is involved in the conversion of lactate to pyruvate and is found in larger concentrations in practically every cell of the body. It's also been proposed as a biomarker for cardiovascular events such as myocardial ischemia, and a new study reveals a link to coronary artery disease (31). Increased serum LDH levels have been linked to increased disease severity and a higher risk of COVID-19 mortality in the hospital setting. In patients with high levels of LDH, a recent pooled analysis found a >sixfold increase in the risk of severe COVID-19 infection outcomes and a >16-fold increase in the risk of mortality (32). The high release of LDH could be due to cytokine-mediated lung tissue destruction, which is a common symptom of severe SARS-CoV-2 infection. The higher levels of LDH generated in the bloodstream as a result of the severe form of interstitial pneumonia could lead to ARDS, which is a significant symptom of COVID-19 infection (33).

D-dimer, which comprises two D fragments of the fibrin, is formed by the activation of the plasmin enzyme. This suggests that a degraded fibrin is present in the bloodstream. The activity of the coagulation and fibrinolysis systems is represented by the D-dimer. Technically, the amount of D-dimer in the body is measured using a monoclonal antibody and several commercial kits on the market. In clinical practice, the D-dimer test is typically used to rule out deep vein thrombosis (DVT) and pulmonary embolism (PE) and confirm the diagnosis of disseminated intravascular coagulation (DIC) (34). D-dimer levels appear to be elevated often in COVID-19 patients (36–43 percent) and may be linked to serious

consequences and death. However, the interpretation of D-dimer during illness monitoring is currently ambiguous, as it may or may not be directly connected to the severity of the disease. Troponins may have certain similarities (35).

D-dimer levels more than 1.0 g/ml were related with increased mortality among COVID-19 patients, according to a retrospective cohort study of 191 patients. Furthermore, they discovered that COVID-19 levels of 2.0 g/ml or above on admission were the best predictors of in-hospital death (36). The researchers discovered that ICU patients had higher median D-dimer levels than non-ICU patients (2.4 mg/L vs. 0.5 mg/L). This, combined with a prior study, suggests that D-dimer levels can be used as a prognostic marker, allowing clinicians to keep track of patients who are more likely to worsen (37).

Hepatic biomarkers

Previous research on COVID 19 have found that the frequency of aberrant alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in COVID 19 patients ranged from 14 percent to 53 percent. Despite the fact that liver dysfunction is more likely in COVID 19 individuals with severe symptoms (38). In COVID-19 individuals, serum levels of various clinical indicators, such as liver enzymes (e.g., ALT and AST), are increased. Furthermore, new data reveal that the concentration of lactate dehydrogenase (LDH) increases in COVID-19 individuals and is considerably higher in patients with elevated ALT compared to patients with normal ALT (39).

The SAA protein, which is largely produced by the liver, is involved in the body's inflammatory reactions and lipid metabolism. Amyloid A is also known for its role in the central nervous system, and it has been linked

to a variety of neurodegenerative diseases (40). SAA has been shown to be an independent COVID-19 prognostic biomarker in several investigations. It has been discovered that a higher level of SAA is linked to the severity of COVID-19 infection. The expression of SAA was much higher in acute phase infection compared to convalescent phase infection in severe patients, although the precise mechanism for the heightened release of this acute-phase protein is still unknown., but could be influenced by the increase in production and secretion of inflammatory mediators, a characteristic phenomenon of SARS-CoV-2 infection (41).

Renal biomarkers

In several laboratory-confirmed COVID-19 patients, the incidence and clinical features of acute kidney damage (AKI) have been described among the secondary organs. A recent research of 116 patients indicated that 18.1 percent of the patients had AKI, and the majority of them were in critical condition, with a greater prevalence of mixed shock. The incidence of combined shock was much lower in non-AKI patients, with just a fourth of them being critical (42). COVID-19 patients have been found to have varying degrees of renal impairment, as measured by blood urea nitrogen (BUN) and serum creatinine levels. According to one study, 27% of COVID-19 patients had elevated BUN levels, with two-thirds of those who had elevated BUN levels and serum creatinine levels exceeding 200 mol/l dying (43).

Novel biomarkers

Adrenomedullin (ADM) and its surrogate, Mid regional-pro-ADM, are organ damage biomarkers whose predictive values have primarily been examined in infected patients for identifying individuals at risk of sepsis. In addition, regardless of the reason for ICU admission, MR-pro-ADM is

thought to be a strong predictive biomarker for predicting mortality in ICU patients (44).

The monocyte distribution width (MDW) is a new sepsis biomarker that has recently been highlighted for its predictive significance. MDW is a good analyte for predicting positivity in SARS-CoV-2 molecular diagnostic testing, according to a study. Patients who required ICU admission had a higher median MDW level than those who did not. However, the predictive value was determined utilizing a small sample size (23 ICU vs. 8 non-ICU patients) (45).

Krebs von den Lungen-6 (KL-6) is a high-molecular-weight glycoprotein found in the blood of patients with ILDs such as idiopathic pulmonary fibrosis and hypersensitivity pneumonitis. Damaged or regenerated alveolar type II pneumocytes create the majority of it (46). KL-6 serum concentrations were exclusively higher in patients with extensive pulmonary involvement, suggesting a predictive value and confirming the potential utility of KL-6 measurement to evaluate COVID-19 patients' prognosis, according to a new study (47).

Conclusion

The biomarkers have become irreplaceable tool in medical practice during the COVID-19 pandemic and may be more accurate than PCR. Nevertheless, there're number of difficulties in their use including the cost, availability and staff experience which can lead to wrong values and misdiagnoses. There are some novel COVID-19 specific biomarkers, which can give the physicians a huge advantage in the diagnosis of the infection. We recommend more research about the role of biomarkers specially KL-6 and SAA protein because of their predictive prognostic value and to conduct more studies about the efficacy of the other

biomarkers in order to write a frank obvious guidelines for future challenges.

References

1. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, Chen Y, Zhang Y. COVID-19: immunopathogenesis and Immunotherapeutics. Signal transduction and targeted therapy. 2020 Jul 25;5(1):1-8.
2. Wu JT, Leung K, Bushman M, Kishore N, Niehus R, de Salazar PM, Cowling BJ, Lipsitch M, Leung GM. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nature medicine. 2020 Apr;26(4):506-10.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N. H., Nitsche A., Müller MA, Drosten C., Pöhlmann S. Cell. 2020;181:271.
4. Deng HJ, Long QX, Liu BZ, Ren JH, Liao P, Qiu JF, Tang XJ, Zhang Y, Tang N, Xu YY, Mo Z. Cytokine biomarkers of COVID-19. medRxiv. 2020 Jun 1.
5. Aronson JK, Ferner RE. Biomarkers—a general review. Current protocols in pharmacology. 2017 Mar;76(1):9-23.
6. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion Jr TR, Nahid M, Ringel JB, Hoffman KL. Clinical characteristics of Covid-19 in New York city. New England Journal of Medicine. 2020 Jun 11;382(24):2372-4.
7. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine. 2020 May;46(5):846-8
8. Dhanalakshmi K, Venkataraman A, Balasubramanian S, Madhusudan M, Amperayani S, Putilibai S, Sadasivam K, Ramachandran B, Ramanan AV. Epidemiological and clinical profile of pediatric inflammatory multisystem syndrome—temporally associated with SARS-CoV-2 (PIMS-TS) in Indian children. Indian pediatrics. 2020 Nov;57(11):1010-4.
9. Samprathi M, Jayashree M. Biomarkers in COVID-19: an up-to-date review. Frontiers in pediatrics. 2021:972.
10. Bellmann-Weiler R, Lanser L, Barket R, Rangger L, Schapfl A, Schaber M, Fritsche G, Wöll E, Weiss G. Prevalence and predictive value of anemia and dysregulated iron homeostasis in patients with COVID-19 infection. Journal of clinical medicine. 2020 Aug;9(8):2429.
11. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G, Dimopoulos MA. Hematological findings and complications of COVID-19. American journal of hematology. 2020 Jul;95(7):834-47.
12. Liu R, Wang Y, Li J, Han H, Xia Z, Liu F, Wu K, Yang L, Liu X, Zhu C. Decreased T cell populations contribute to the increased severity of COVID-19. Clinica chimica acta. 2020 Sep 1;508:110-4.
13. Amgalan A, Othman M. Hemostatic laboratory derangements in COVID-19 with a focus on platelet count. Platelets. 2020 Aug 17;31(6):740-5.
14. Teijaro JR. Cytokine storms in infectious diseases. InSeminars in immunopathology 2017 Jul (Vol. 39, No. 5, pp. 501-503). Springer Berlin Heidelberg.
15. Wang S, Le TQ, Kurihara N, Chida J, Cisse Y, Yano M, Kido H. Influenza Virus—cytokine-protease cycle in the pathogenesis of vascular hyperpermeability in severe influenza. The Journal of infectious diseases. 2010 Oct 1;202(7):991-1001.

16. Pinto BG, Oliveira AE, Singh Y, Jimenez L, Gonçalves AN, Ogava RL, Creighton R, Schatzmann Peron JP, Nakaya HI. ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. The Journal of infectious diseases. 2020 Jul 23;222(4):556-63.
17. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.
18. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baildon MS. Cytokine release syndrome. Journal for immunotherapy of cancer. 2018 Dec;6(1):1-4.
19. Fajgenbaum DC, June CH. Cytokine storm. New England Journal of Medicine. 2020 Dec 3;383(23):2255-73.
20. Henry BM, De Oliveira MH, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM). 2020 Jul 1;58(7):1021-8.
21. Gong J, Dong H, Xia SQ, Huang YZ, Wang D, Zhao Y, et al. Correlation Analysis Between Disease Severity and Inflammation-related Parameters in Patients with COVID-19 Pneumonia. medRxiv. 2020 Feb 27;2020.02.25.20025643.
22. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020 Mar 12;
23. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, Creactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020 Apr 14;127:104370.
24. Karzai W, Oberhoffer M, Meier-Hellmann A, et al. Procalcitonin—a new indicator of the systemic response to severe infections. Infection. 1997;25(6): 329–334.
25. Sun D, Li H, Lu X-X, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr. 2020.
26. Chen X, Yang Y, Huang M, Liu L, Zhang X, Xu J, Geng S, Han B, Xiao J, Wan Y. Differences between COVID-19 and suspected then confirmed SARS-CoV-2-negative pneumonia: A retrospective study from a single center. Journal of medical virology. 2020 Sep;92(9):1572-9.
27. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a metaanalysis. Clin Chim Acta. 2020;505:190–191
28. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Critical reviews in clinical laboratory sciences. 2020 Aug 17;57(6):389-99.
29. Hochholzer W, Morrow DA, Giugliano RP. Novel biomarkers in cardiovascular disease: update 2010. American heart journal. 2010 Oct 1;160(4):583-94.
30. Nie SF, Yu M, Xie T, Yang F, Wang HB, Wang ZH, Li M, Gao XL, Lv BJ, Wang SJ, Zhang XB. Cardiac troponin I is an independent predictor for mortality in hospitalized patients with COVID-19. Circulation. 2020 Aug 11;142(6):608-10.
31. Kopel E, Kivity S, Morag-Koren N, Segev S, Sidi Y. Relation of serum lactate dehydrogenase to coronary artery disease. The American journal of cardiology. 2012 Dec 15;110(12):1717-22.
32. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, Lippi G. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. The American journal of emergency medicine. 2020 Sep 1;38(9):1722-6.

33. Martinez-Outschoorn UE, Prisco M, Ertel A, Tsirigos A, Lin Z, Pavlides S, Wang C, Flomenberg N, Knudsen ES, Howell A, Pestell RG. Ketones and lactate increase cancer cell "stemness," driving recurrence, metastasis and poor clinical outcome in breast cancer: achieving personalized medicine via Metabolo-Genomics. Cell cycle. 2011 Apr 15;10(8):1271-86.
34. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert review of hematology. 2020 Nov 1;13(11):1265-75.
35. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. Thrombosis and haemostasis. 2020 May;120(05):876-8.
36. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. Journal of thrombosis and haemostasis. 2020 Jun;18(6):1324-9.
37. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19–A systematic review. Life sciences. 2020 Aug 1;254:117788.
38. Li T, Guo Y, Zhuang X, Huang L, Zhang X, Wei F, Yang B. Abnormal liver-related biomarkers in COVID-19 patients and the role of prealbumin. Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association. 2020 Sep;26(5):272.
39. Chang D, Lin M, Wei L, Xie L, Zhu G, Cruz CS, Sharma L. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. Jama. 2020 Mar 17;323(11):1092-3.
40. Tabassum T, Rahman A, Araf Y, Ullah MA, Hosen MJ. Prospective selected biomarkers in COVID-19 diagnosis and treatment. Biomarkers in Medicine. 2021 Oct;15(15):1435-49.
41. Zhang Y, Wang D, Lin M, Sun T, Chen J, Xu J, Zhu H, Zhu G, Lu R, Hong L, Shen B. Serum amyloid A protein as a potential biomarker useful in monitoring the course of COVID-19: a retrospectively studied.
42. Cui X, Yu X, Wu X, Huang L, Tian Y, Huang X, Zhang Z, Cheng Z, Guo Q, Zhang Y, Cai Y. Acute kidney injury in patients with the coronavirus disease 2019: a multicenter study. Kidney and Blood Pressure Research. 2020;45(4):612-22.
43. Li Z, Wu M, Yao J, Guo J, Liao X, Song S, Li J, Duan G, Zhou Y, Wu X, Zhou Z. Caution on kidney dysfunctions of COVID-19 patients.2020
44. Spoto S, Agrò FE, Sambuco F, Travaglino F, Valeriani E, Fogolari M, et al. High value of mid-regional proadrenomedullin in COVID-19: a marker of widespread endothelial damage, disease severity and mortality. J Med Virol 2020;93:2820-7.
45. Ognibene A, Lorubbio M, Magliocca P, Tripodo E, Vaggelli G, Iannelli G, et al. Elevated monocyte distribution width in COVID-19 patients: the contribution of the novel sepsis indicator. Clin Chim Acta 2020;509:22-4.
46. Lee JS, Lee EY, Ha YJ, Kang EH, Lee YJ, Song YW. Serum KL-6 levels reflect the severity of interstitial lung disease associated with connective tissue disease. Arthritis research & therapy. 2019 Dec;21(1):1-8.
47. d'Alessandro M, Cameli P, Refini RM, Bergantini L, Alonzi V, Lanzarone N, Bennett D, Rana GD, Montagnani F, Scolletta S, Franchi F. Serum KL-6 concentrations as a novel biomarker of severe COVID-19. Journal of medical virology. 2020 Oct;92(10):2216-20.