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Original Article

Evaluation of primary biochemical parameters and vitamin D in Covid-19

Covid 19'da öne çıkan biyokimyasal parametrelerin ve D vitamininin değerlendirilmesi

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Abstract

Aim: We aimed to evaluate potential coagulation and inflammatory biomarkers. The recently discussed vitamin D levels predict the course ef the disease and determine the patients to be admitted to the intensive care unit in advance.

Materials and Methods: This retrospective case-control study was conducted on 121 patients diagnosed and treated with COVID-19 disease, from March 2020 to June 2020 at the Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkey. D-dimer, Fibrinogen, Ferritin, and 25-OH Vitamin D levels that could be associated with COVID-19 infections were evaluated. The patients were divided into three groups: only Polymerase Chain Reaction positivity (PCR+), only Computerized Tomography positivity (CT+) and both PCR+ and CT+ among COVID-19 cases.

Results: 121 patients with at mean age of 53 were investigated (52% male). Only CT+ cases were significantly older than other patients, $p<0.001$. D-dimer, Ferritin, and Fibrinogen levels were considerably higher in CT+ patients among all subjects, $p =0.001$, $p =0.001$, and $p<0.001$, respectively. There were no apparent differences in vitamin D levels between PCR+ and CT+ and others, CT+ and, PCR+ and others, $p=0.277$, $p=0.350$, $p=0.397$. However, we found that vitamin D levels were deficient in all groups.

Conclusion: Since coagulopathy may accompany COVID-19, D-dimer and fibrinogen levels are predictive during admission. Serum ferritin demonstrates a potential risk factor for poor prognosis in COVID-19 patients.

Keywords: covid-19; d-dimer; ferritin; fibrinogen; vitamin d

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Öz

Amaç: Bu çalışmada hastalığın seyrini tahmin etmek ve yoğun bakım ünitesine yatırılacak hastaları önceden belirlemek için potansiyel koagülasyon ve inflamasyon biyobelirteçlerini ve son dönemde sıkça vurgulanan D vitaminini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu retrospektif vaka-kontrol çalışması, Mart 2020'den Haziran 2020'ye kadar Amasya Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesi'nde COVİD-19 tanısı alıp tedavi edilen 121 hasta üzerinde yapıldı. COVİD-19 ile ilişkili olabilecek D-dimer, fibrinojen, ferritin ve 25-OH Vitamin D'yi değerlendirdik. Hastalar, sadece polimeraz zincir reaksiyon pozitifliği (PCR +), sadece bilgisayarlı tomografi pozitifliği (CT +) ve hem PCR + hem de CT + olmak üzere üç gruba ayrıldı.

Bulgular: Yaş ortalaması 53 olan 121 hasta incelendi (% 52 erkek). Sadece CT + hastalar diğer hastalardan daha yaşlıydı ($p < 0.001$). D-dimer, ferritin ve fibrinojen seviyeleri tüm hastalar arasında CT + olan grupta oldukça yüksekti (sırasıyla $p = 0.001$, $p = 0.001$ ve $p < 0.001$). Hem PCR + hem de CT + olanlar ve diğerleri, CT + olanlar ve diğerleri, PCR + olanlar ve diğerleri karşılaştırıldığında D vitamini düzeyleri arasında anlamlı fark bulunamadı ($p = 0.277$, $p = 0.350$, $p = 0.397$). Bununla beraber tüm gruplarda D vitamini düzeylerinin yetersiz olduğu tespit edildi.

Sonuç: COVİD-19'a koagülopati eşlik edebileceğinden başvuru esnasındaki D-dimer ve fibrinojen seviyeleri öngörü sağlamaktadır. Serum ferritini ise, COVİD-19 hastalarında kötü prognoz için potansiyel risk faktörü göstergesidir.

Anahtar Kelimeler: covid-19; d-dimer; ferritin; fibrinojen; vitamin d

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease (COVID-19), which primarily affects the lower respiratory section and leads to severe acute respiratory syndrome (SARS). COVID-19 became a pandemic in a short length of a lifetime and seriously threatens human health. Common symptoms are fever, cough, fatigue, shortness of breath, and loss of smell and taste. The known incubation period is two to fourteen days. Although most people have mild symptoms, some could develop acute respiratory distress syndrome (ARDS) caused by cytokine storm, multi-organ failure, septic shock, and blood clots. There is no curative medicine, and all we can do is maintain social distance, use a mask, and follow hygiene rules [1]. Most COVID-19 patients (80%) who develop symptoms have a mild disease or are clinically asymptomatic. Severe or life-threatening clinical findings may develop in 13.8% and 6.1% of patients, respectively [2]. Asymptomatic cases and the long incubation period require us to understand more about the fatal disease. Clinicians use numerous biochemical and radiological tests to diagnose patients in the early stage. Patients who would be hospitalized and taken to the intensive care unit must be carefully selected so that healthcare workers could not get tired. The burden on health systems could not increase, and the resources could be used ideally without exhaustion. Laboratory parameters may be crucial for predicting the disease's course and determining the patients to be admitted to the intensive care unit in advance. Ferritin, D-dimer, fibrinogen, and recently 25-OH vitamin D have come to the fore in this field.

Scientists found significant differences interleukin-6 (IL-6), D-Dimer, glucose (GLU), thrombin time (TT), fibrinogen (FIB), and C-reactive protein (CRP) levels between severe COVID-19 patients and mild ones [3]. Hyper coagulation condition such as pulmonary microthrombosis and disseminated intravascular coagulation (DIC) are often complications of severe COVID-19. Mechanisms that cause coagulation problems include dysfunction of endothelial cells due to infection, which causes increased thrombin production and decreased fibrinolysis [4]. In severe COVID-19 patients, an increase in D-dimer and fibrin/fibrinogen degradation products (FDP) levels were detected due to changes in the coagulation system [5]. Likewise, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) measurements during the transition from the hipper coagulating state into fibrinolysis were found interrelated with severe illness [6]. The prominent clinical finding in COVID-19 coagulopathy is often an abnormal increase in D-dimer levels. High d-dimer measurements indicate a poor prognosis in COVID-19 patients. The authors stated that it would be beneficial to perform PT, fibrinogen, D-dimer, and platelet tests

every 48 hours to monitor thrombotic risk continuously and determine venous thrombotic events at an early stage [7]. The first study of COVID-19 coagulopathy indicates an increased D-dimer level above 0.5 mg/L in 46.4% of the patients during the initial presentation [8]. Regular monitoring of D-dimer, prothrombin, and fibrinogen is essential in COVID-19. Because in survivors, a significant increase in D-dimer and prothrombin was detected with a decrease in fibrinogen, and an increased D-dimer level was identified as a vital independent risk factor in this vulnerable population.

Hyperferritinemia caused by excessive inflammation resulting from infection is associated with intensive care unit admission and high mortality rates and is a marker to identify high-risk patients to alleviate inflammation and guide treatment. As a result of hemophagocytic lymphohistiocytosis, a complication that may develop due to viral infections, serum levels of increased ferritin are closely related to the poor prognosis of COVID-19 patients, and ferritin levels are higher in patients with lung involvement [9]. Serum ferritin demonstrates potential risk factors for poor prognosis in COVID-19 patients.

The active form of 25-OH vitamin D affects innate and adaptive immune responses that may alter many infectious diseases. Recent studies point to a diverse and elusive interaction between viral infections and 25-OH vitamin D, including enhancement of anti-viral capacity, functional immunoregulatory properties, interaction with cellular and viral factors, autophagy and apoptosis stimulation, and genetic and epigenetic changes. While the interaction between 25-OH vitamin D and intracellular signaling pathways may have a regulatory impact on viral gene transcription, the organization of the immune system effect of 25-OH vitamin D against viral infections appears to be short-lived [10]. Respiratory monocytes/macrophages and epithelial cells fundamentally manifest the 25-OH vitamin D receptor. Via this receptor, 25-OH vitamin D could protect the human body against respiratory infections. Several studies showed that low 25-OH vitamin D levels are associated with the severity of infectious respiratory diseases, such as pharyngotonsillitis, bronchiolitis, pneumonia, influenza, and even an intracellular pathogen, mycobacterium tuberculosis. 25-OH Vitamin D supplementation has been claimed to reduce the incidence of viral infections and has been shown in clinical trials to prevent poor prognosis in patients. Besides, 25-OH vitamin D is associated with COVID-19 risk factors, and 25-OH vitamin D supplementation is considered to diminish the risk of developing the disease and prevent severe illness [11]. Munshi et al. found that patients with a poor prognosis had inadequate 25-OH vitamin D levels than patients with a good prognosis [12]. An Israeli population study on both COVID-19 positive and negative patients declared that 25-OH vitamin D deficiency was associated with the incidence and severity of COVID-19 [13]. Conversely, a UK biobank evaluation survey showed no correlation between 25-OH vitamin D levels and disease severity [14]. However, the 25-OH vitamin D values considered in the study were based on old dates, so it would be more beneficial to check the current 25-OH vitamin D levels when evaluating patients and healthy controls. Considering data from 12 European countries, similar data was found on the relationship between average 25-OH vitamin D levels and COVID-19 mortality rates [15]. While no effective medications for the treatment of COVID-19 have yet been found, 25-OH vitamin D supplementation may protect healthy people or reduce the disease's severity.

Based on these findings and discussions, we aimed to evaluate potential coagulation and inflammatory biomarkers and recently discussed 25-OH vitamin D levels in COVID-19 patients.

Materıal and Methods

This retrospective case-control study includes 121 patients, 52% male and 48% female, with a mean age of 53, from March 2020 to June 2020, at the Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital, Amasya, Turkey. COVID-19 cases were determined according to the Turkish Ministry of Health guidelines. The study was performed after obtaining the agreement of the Afyon Medical Sciences University Clinical Research Ethical Committee, Turkey (No:2021-63). All participants in this study obtained consent. The study was done following the Declaration of Helsinki. Positive SARS-CoV-2 RNA Polymerase Chain Reaction (PCR) with throat swab samples or positive pulmonary evidence via Computerized Tomography (CT) confirmed all subjects. Demographic, laboratorian, and radiological variables were provided from medical records. We worked on potential confounding variables, including D-dimer, fibrinogen, ferritin, and 25-OH vitamin D, which could be associated with COVID-19 infections. D-dimer was immuno-

turbidimetric, and fibrinogen was measured by clotting method on STA Compact (Diagnostica Stago, Gennevilliers, France). Ferritin (two-site sandwich immunoassay) and 25-OH vitamin D (competitive immunoassay) were performed using a Siemens Advia Centaur (Tarrytown, NY, USA). We evaluated 25-OH vitamin D levels like this; >30 ng/mL sufficient, 20-30 ng/mL insufficient, <20 ng/mL deficient. Standard distribution variables were calculated using the Mann-Whitney U test. We analyzed our data mean ± standard error (SE), mean ± standard deviation (SD), and interquartile range (IQR). Multivariate analysis was managed via an unconditional logistic regression model. All measured risk factors included independent variables and the dependent variable as PCR positivity (PCR+), CT positivity (CT+), or both (PCR+ and CT+) among COVID-19 cases. Statistical analyses were assessed using JASP 0.14 statistical software (JASP team, Amsterdam, Netherlands). We compared our data between sets of two groups (PCR+ and CT+ and others, only CT+ and others, only PCR+ and others). P-values below 0.05 were considered significant. Descriptive statistics of patients in 3 groups are shown in Table 1, Table 2, and Table 3.

Table 1. Descriptive Statistics of both PCR and CT positive (1) and only one of them is positive (0).

	AGE		D- dimer		Fibrinogen		Ferritin		25-OH Vitamin D	
Group	0	1	0	1	0	1	0	1	0	1
Mean	53.27	54.72	2.039	1.23	495.6	506.63	473.957	294.506	14.687	15.739
Std. Error of Mean	2.577	2.309	0.308	0.19	24.86	30.929	87.262	66.587	1.595	1.641
Std. Deviation	23.75	13.85	2.841	1.16	222.4	185.57	785.362	393.936	9.568	8.369
IQR	42.00	19.00	1.210	0.88	287.0	217.75	479.900	343.700	11.762	9.138
Minimum	1.000	25.00	0.130	0.47	50.20	36.000	4.700	5.800	3.000	3.000
Maximum	87.00	86.00	20.00	6.00	1150	1013	4630	1458	45.400	36.810
5th percentile	17.40	33.00	0.464	0.47	202	280	10.400	10.590	3.933	6.445
95th percentile	86.00	78.00	6.902	3.09	935.6	776.50	2182	1285.40	30.817	30.008

Table 2. Descriptive Statistics of only CT positive (1) and others (0).

	AGE		D- dimer		Fibrinogen		Ferritin		25-OH Vitamin D	
Group	0	1	0	1	0	1	0	1	0	1
Mean	33.621	60.033	1.054	2.033	343.593	546.182	204.489	485.135	14.827	15.224
Std. Error of Mean	3.734	1.812	0.281	0.280	24.455	22.163	70.870	80.099	2.729	1.255
Std. Deviation	20.106	17.380	1.515	2.685	127.074	209.083	368.254	755.655	10.570	8.605
IQR	26.000	30.250	0.480	1.718	108.500	256.000	114.000	458.000	10.845	9.695
Minimum	1.000	23.000	0.130	0.470	145.000	36.000	4.700	5.800	3.000	3.000
Maximum	82.000	87.000	7.800	20.000	793.000	1.150.000	1.343.000	4.630.000	45.400	39.900
5th percentile	4.400	31.100	0.264	0.510	189.000	259.400	7.730	19.480	4.694	4.018
95th percentile	63.400	86.000	3.264	6.505	535.100	953.200	1.079.100	2.052.800	30.896	30.007

Table 3. Descriptive Statistics of only PCR positive (1) and others (0).

	AGE		D- dimer		Fibrinogen		Ferritin		25-OH Vitamin D	
	0	1	0	1	0	1	0	1	0	1
Mean	64.018	45.106	2.586	1.143	579.119	433.953	618.592	252.584	14.588	15.405
Std. Error of Mean	2.468	2.431	0.437	0.162	30.366	22.642	124.321	47.880	1.976	1.423
Std. Deviation	18.307	19.753	3.239	1.316	218.971	181.138	905.073	380.038	9.055	9.115
IQR	30.000	28.750	3.510	0.573	283.250	211.750	550.000	179.500	10.800	9.570
Minimum	23.000	1.000	0.510	0.130	50.200	36.000	10.000	4.700	3.910	3.000
Maximum	87.000	86.000	20.000	7.800	1.150.000	1.013.000	4.630.000	1.458.000	39.900	45.400
5th percentile	31.100	8.750	0.587	0.445	272.900	206.600	22.000	7.560	3.940	5.420
95th percentile	86.300	76.500	7.072	3.450	1.004.250	749.300	2.388.200	1.263.000	27.790	30.010

Results

We included 121 COVID-19 patients who measured their vitamin D levels within three months in our study, with a mean age of 53 and a male ratio of 52%. There were no statistically significant differences in gender between the groups. CT+ cases were significantly older than other patients, p<0.001. D-dimer, ferritin and fibrinogen levels were considerably higher in CT+ patients among all subjects, p =0.001, p =0.001, and p<0.001, respectively. Males had elevated 25-OH vitamin D levels but were not statistically significant, p=0.056. There were no apparent differences in 25-OH vitamin D levels between PCR+ and CT+ and others, CT+ and others, PCR+ and others, p=0.277, p=0.350, p=0.397. However, we found that 25-OH vitamin D levels were deficient in all groups. Mean and SD values were 15.4 ± 9.1, 14.5 ± 9, and 14.6 ± 9.8 ng/mL for each group. For all patients, 25-OH vitamin D mean and SD was 15.1 ± 9.0 ng/mL (Figure 1). Ferritin & D-dimer and ferritin & fibrinogen levels were correlated in CT+ group and in PCR+ group, p <0.001, p <0.001. In the group of both PCR+ and CT+ patients, in addition to previous correlations, fibrinogen and D-dimer levels were correlated, p=0.004. 25-OH vitamin D levels between PCR+ and CT+ and others, CT+ and others, PCR+, and others showed no correlation with other biochemical parameters.

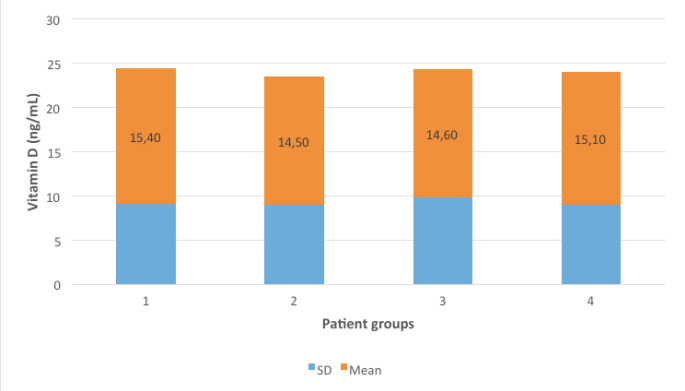

Figure 1. Vitamin levels of groups had no significant difference. Besides, all patients show vitamin D deficiency. 1; PCR+ and CT+, 2;CT+, 3;PCR+, 4;All patients.

Discussion

Severe COVID-19 cases have a high risk for DIC and thromboembolic events due to cytokine storm and sepsis. Increasing proof shows that thromboembolic processes promote disease severity, especially with positive CT findings. Prothrombin forms thrombin in the coagulation cascade, which turns fibrinogen into fibrin to create a fibrin-based clot to stop bleeding. D-dimer is a fibrin degradation product that emerges in the blood after the clot dissolves by fibrinolysis. Sepsis and cytokine storm cause DIC by releasing large amounts of coagulation factors by vigorously activating the coagulation system [2]. Immediate changes in fibrinogen levels are significant in COVID-19 patients. Fibrinogen levels reduce, and fibrin degradation products elevate not only in patients compared to healthy persons but also in severe patients compared to mild patients [16]. Increased D-dimer and decreased fibrinogen levels may support these clinical findings and explain the disease's severity beforehand. Clinical and laboratory findings of COVID-19 are similar to hyperferritinemic syndromes like macrophage activation syndrome (MAS), adult-onset stills disease (AOSD), catastrophic anti-phospholipid syndrome (CAPS), and septic shock. Hyperferritinemic syndromes show high serum ferritin and hyper-inflammation by cytokine storm, which eventually causes multi-organ failure in the end [17].

We found the D-dimer levels higher in COVID-19 CT+ patients, consistent with previous studies, but unlike the other authors, fibrinogen levels were not decreased but increased. Contrary to studies our high fibrinogen measurements may reflect the stage before DIC development. The onset of secretion of acute-phase proteins and related mediators in the early phase of the infection may increase the blood's viscosity and further stimulate the liver, thereby increasing fibrinogen levels. D-dimer and fibrinogen levels may help predict the severity of the disease and early treatment. Some other studies demonstrate that non-survivors developed significantly higher D-dimer and fibrinogen amounts, more prolonged PT, and aPTT than survivors at admission [18]. Therefore, the disease's stage and the patient's clinical condition should be considered when evaluating fibrinogen and D-dimer levels. Scientists indicate that COVID-19 coagulopathy is becoming more outstanding in critically ill cases. D-dimer and PT monitoring can help patient triaging and management. The ISTH (International Society on Thrombosis and Haemostasis) released the guidance for COVID-19 coagulopathy and advised routine hemostatic markers testing for all cases [19].

Ferritin could indicate that either patient tends to have the virus

or clinical risk for intensive care unit (ICU) transfer and death in hospitalized COVID-19 patients. Ferritin levels of COVID-19 patients rise in non-survivors and advance with the disease's worsening. PCR+ patients showed no significant difference in these parameters. Perhaps the PCR methods and swab sampling practices used at the epidemic's beginning were insufficient for diagnosis. Maybe the kits used for PCR testing did not have the necessary success in detecting the COVID-19 virus. Applying the correct swab technique and PCR kits may have taken time to achieve success. For this reason, the virus may have settled in the lung before PCR could diagnose it and caused the patients to be diagnosed with computed tomography. The long incubation time may negatively affect the results, depending on when the health worker took the swab.

Whether interpreting all COVID-19 patients or investigating between groups, 25-OH vitamin D levels were insufficient in all cases. Similar results in all groups made it impossible to compare the groups in terms of 25-OH vitamin D. More importantly, 25-OH vitamin D values in the Turkish population are generally insufficient. Scientists commonly accept that 25-OH vitamin D levels are low in the Turkish people, making comparison difficult. 25-OH vitamin D deficiency is endemic in Turkey. In "Turkish Diabetes, Hypertension, Obesity, and Endocrinological Diseases Prevalence Study II" (TURDEP-II), which is one of the most extensive research in Turkey, 9560 adults living in various areas were evaluated, and 93% had serum 25-OH vitamin D levels less than 20 ng/mL [20]. The prevalence of 25-OH vitamin D deficiency observed varied from 24% to 99% in various studies and regions in the Turkish population. Therefore, 25-OH vitamin D deficiency continues to be a severe problem throughout Turkey. 25-OH vitamin D concentrations may affect gender, age, pregnancy, season, and cultural differences. Daily sunlight disclosure acts to prohibit 25-OH vitamin D deficiency. Nevertheless, even in sunny climates, 25-OH vitamin D deficiency is 50-97%, most probably due to wearing clothes that leave little skin exposed to sunlight. Given this information, 25-OH vitamin D deficiency in patients does not significantly conclude than the general population. In healthy Turkish people, 25-OH vitamin D levels are generally low. It is inadequate to distinguish whether low 25-OH vitamin D levels cause COVID-19 or deficiency occurs randomly because of reflecting the general population.

Institute of Medicine (IOM) achieved that 20 ng/mL 25-OH vitamin D and above were sufficient for adequate bone health after reviewing the literature [21]. They reached this conclusion via several observations, including those by Malabanan et al. [22] and Primel et al. [23]. Scientists also determined that at least 30 ng/mL 25-OH vitamin D levels were sufficient based on the bone biopsies. However, studies suggest that 25-OH vitamin D deficiency is about 40% in Europe, and 13% are severely deficient [24]. Therefore, there were questions about this deficiency and the need for supplementation. Besides 25-OH vitamin D deficiency is widespread worldwide, and many laboratory and clinical studies have demonstrated a substantial relationship between chronic diseases and acute conditions [25].

We suspect that the low 25-OH vitamin D levels we detected in COVID-19 patients in our study are associated with getting the disease and worsening the prognosis. In a pandemic like COVID-19, 25-OH vitamin D deficiency makes it impossible to compare patients with a healthy population. Also, 25-OH vitamin D levels were not measured at diagnosis in most patients, including in our study. Although it is known that 25-OH vitamin D regulates the immune system and protects against viral respiratory system diseases, the pathophysiology of COVID-19 infection has not been fully resolved, which prevents us from reaching clear information. However, the lack of an effective treatment fort the disease has led clinicians to use different methods to prevent infection and illness severity. In this respect, careful 25-OH vitamin D supplementation may be beneficial, especially in hospitalized patients. Further studies with control groups are essential to understand the subject better and clarify the unknown points.

References

1. Berekaa, M.M., Insights into the COVID-19 pandemic: Origin, pathogenesis, diagnosis, and therapeutic interventions. Front Biosci (Elite Ed), 2021. 13: p. 117-139.
2. Danwang, C., et al., A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res, 2020. 8: p. 37.
3. Mardani, R., et al., Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study. Arch Acad Emerg Med, 2020. 8(1): p. e43.
4. Khourssaji, M., et al., A biological profile for diagnosis and outcome of COVID-19 patients. Clin Chem Lab Med, 2020. 58(12): p. 2141-2150.

5. Luo, H.C., et al., Characteristics of coagulation alteration in patients with COVID-19. Ann Hematol, 2021. 100(1): p. 45-52.
6. Long, H., et al., D-Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. BioMed Research International, 2020. 2020: p. 6159720.
7. Ikewaki, N., et al., Coagulopathy associated with COVID-19 - Perspectives & Preventive strategies using a biological response modifier Glucan. Thromb J, 2020. 18: p. 27.
8. Fu, L., et al., Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect, 2020. 80(6): p. 656-665.
9. Kernan, K.F. and J.A. Carcillo, Hyperferritinemia and inflammation. Int Immunol, 2017. 29(9): p. 401-409.
10. Zdrenghea, M.T., et al., Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol, 2017. 27(1).
11. Panagiotou, G., et al., Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. Clin Endocrinol (Oxf), 2020. 93(4): p. 508-511.
12. Munshi, R., et al., Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. J Med Virol, 2021. 93(2): p. 733-740.
13. Merzon, E., et al., Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. Febs j, 2020. 287(17): p. 3693-3702.
14. Hastie, C.E., et al., Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr, 2020. 14(4): p. 561-565.
15. Laird, E., J. Rhodes, and R.A. Kenny, Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. Ir Med J, 2020. 113(5): p. 81.
16. Hayiroglu, M.I., T. Cinar, and A.I. Tekkesin, Fibrinogen and D-dimer variances and anticoagulation recommendations in Covid-19: current literature review. Rev Assoc Med Bras (1992), 2020. 66(6): p. 842-848.
17. Perricone, C., et al., COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. Immunol Res, 2020. 68(4): p. 213-224.
18. Iba, T., et al., Coagulopathy in COVID-19. J Thromb Haemost, 2020. 18(9): p. 2103-2109.
19. Thachil, J., et al., ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost, 2020. 18(5): p. 1023-1026.
20. Doğan E, S.N., Türkiye'de Batı Karadeniz bölgesindeki çocukların D vitamini düzeyleri. Pamukkale Tıp Dergisi, 2021. 14(1): p. 1-10.
21. in Dietary Reference Intakes for Calcium and Vitamin D, A.C. Ross, et al., Editors. 2011: Washington (DC).
22. Malabanan, A., I.E., Veronikis, and M.F. Holick, Redefining vitamin D insufficiency. Lancet, 1998. 351(9105): p. 805-6.
23. Priemel, M., et al., Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res, 2010. 25(2): p. 305-12.
24. Cashman, K.D., et al., Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr, 2016. 103(4): p. 1033-44.
25. Bouillon, R., et al., Vitamin D and energy homeostasis: of mice and men. Nat Rev Endocrinol, 2014. 10(2): p. 79-87.