Nat. Volatiles & Essent. Oils, 2022; 9(1): 1086-1101

NVEO
Natural Volatiles &
Essential Oils

Relationship Between Serum Levels Of Procalcitonin, Vitamin B12, Vitamin D In Patients With COVID-19

Nesreen Ahmed Nasser[1] , Rayah Sulaiman Baban[2]

[1]Department . Of Medical Lab.Techonology, Mazaya University College.

[2]Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, Baghdad, Iraq.

Abstract :

COVID-19 is a new infectious disease, for which there is currently no treatment. It is therefore necessary to explore biomarkers to determine the extent of lung lesions and disease severity**.**

Objective. The study aimed to assess the usefulness of procalcitonin levels in the COVID-19 and to correlate them with other biomarkers .

Methods. the collected the data, prospectively, all COVID-19 cases admitted in lab private (30) cases with COVID-19 pneumonia and (30) control . patients had Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive. laboratory analysis of inflammatory indices and organ function was accomplished for the sum total of cases and controls measured procalcitonin, CRP,B 12,LDH . Result. – procalcitonin , CRP, LDH, D-dimer levels in patients groups the higher than those in the controls highly significant

..Conclusion. – In the early stage of COVID-19 procalcitonin levels were positively correlated with CRP,D-dimer , ferritin, LDH and negative correlated with B12 .

Introduction :

Coronaviruses are a vast viral family that can cause a variety of infections, ranging from the common cold to more serious infectious disorders. In humans, many coronavirus subtypes that are easily transferred from person to person have been found. In humans, those subspecies are largely responsible for common colds. Furthermore, many coronavirus subtypes have been identified in animals, with animal-to-human transmission causing serious disease in humans [1,2 ,3,4]

The plasmin cleavage product D-dimer is a breakdown product of cross-linked fibrin. During systemic fibrinolysis after alpha2 depletion, plasmin may destroy fibrin monomers, cross-linked fibrin polymers, and perhaps fibrinogen. Fibrin degradation products refers to all of these fragments (FDPs). The name D-dimer comes from two adjacent fibrin 'D' domains (ends) that are cross-linked and discharged as a complete fragment. D-dimer assays are divided into

two categories, each reporting distinct D-dimer units. The Fibrinogen Equivalent Unit (FEU) calculates D-dimer levels using fibrinogen's molecular weight (340kDa), whereas the D-Dimer Unit (DDU) uses its own molecular weight (195kDa), which is nearly half that of fibrinogen. **(5)**

Thrombotic consequences and coagulopathies, such as disseminated intravascular coagulopathy, are prevalent in COVID-19, most likely because to viremia or cytokine storm activating the coagulation cascade, or potentially related to superinfection and organ dysfunction. [6]

D-dimer is a fibrin breakdown product that is commonly utilized as a thrombotic biomarker. A D-dimer level of less than 0.5 g/mL is considered normal, and levels rise with age and during pregnancy. The level of D-dimer increases as the severity of community-acquired pneumonia increases [7]. Following the advent of the COVID-19 pandemic, D-dimer was established as a possible predictor of COVID-19 patient prognosis. Multiple studies have indicated that the admission day D-dimer can predict illness severity. [8–9]

Lactate dehydrogenase (LDH) is one such biomarker of relevance, particularly because higher LDH levels have previously been linked to poorer outcomes in patients with other viral infections [10]. Early evidence in COVID-19 patients suggests that there are significant disparities in LDH levels between patients with severe illness and those who do not. As a result, we conducted a pooled analysis of the published literature to look into the potential link between elevated LDH levels and disease severity and mortality in COVID-19 patients[11].

CRP is an inflammatory marker that is measured in the acute phase of plasma. In the early stages of infection, the CRP marker was found to be considerably elevated in the COVID-19 patient

C-reactive protein (CRP) levels can be used to detect pneumonia early, and patients with severe pneumonia had high CRP levels. To give a reference for clinical treatment, researchers looked at the relationship between CRP levels, lung lesions, and disease severity [12].

Vitamin B12 is a water soluble vitamin, which means it can't be stored by the body. It's also a necessary vitamin that your body can't produce on its own. B12 must be ingested on a daily basis. B12 is essential for most physiological processes, as it aids in the formation of proper blood cells and the health of nerve cells. B12 is also important for brain and heart function. Anemia can be caused by a lack of vitamin B12, which causes fatigue, lightheadedness, and pale complexion. A shortage of vitamin B-12 in the diet can also result in a lengthy number of symptoms. Loss of appetite, tingling or numbness in the hands, mental disorientation, sadness, panic attacks, sleeplessness, and issues with balance and walking are some of the symptoms (13).

Vitamins are thought to boost resistance to COVID-19. Vitamin B12 (cobalamin) is a cellular immuno-modulator that supports the hematological, neurological, and immune systems. The elderly may have the highest cobalamin deficiency because they have trouble absorbing this vitamin from food due to a loss of stomach acid or the intrinsic factor required for active B12 absorption(14) .

Serum ferritin is a spherical protein structure made up of 24 Hand L-subunits that is found in a variety of tissues and cell types, as well as blood plasma and serum. Iron status can vary as

a result of inflammation, and ferritin levels might rise, acting as a signal. During the pandemic, investigations indicated that an increase in serum ferritin levels was linked to COVID-19 infection (15).

High ferritin levels can lead to immunosuppression and pro inflammatory changes. Ferritin levels were observed to be greater in diabetic SARSCoV2 patients who were critically ill (16,17). A multicenter study of SARS-CoV-2 infection reported a higher incidence of acute respiratory distress syndrome (ARDS), and increased morbidity was associated with higher hyperferritinemia (18).

Material and method : the collected the data, prospectively, all COVID-19 cases admitted in lab private during the study period between February2021 and July 2021. During the six months , (30) cases with COVID-19 pneumonia and (30) control . patients had Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive. laboratory analysis of inflammatory indices and organ function was accomplished for the sum total of cases and controls.

Study population: the study participants incorporates an admitted patients in the medical ward From a private lab in Baghdad city, the diagnosis relied on any attainable investigations in the case documents of patients, entire number of the patients comprised in the analysis was (60) patients, with (30) cases proved to be COVID-19 pneumonia and (30) controls . Inclusion criteria: Every patient with clinical and radiological properties denotes to pneumonia and proved by positive polymerase chain reaction for either cases(COVID-19) or controls **Sampling size:** was suitable ,confined by accessibility of patients and time extents of the analysis, but sampling job for control, systematic random sampling technique was achieved to assemble the control. Ethical issue: an ethical agreement was attained from a private lab in Baghdad directorate. A knowledgeable permissions was gained from all candidates. Vital signs comprising respiratory rate measurement were undertaken for all participants, oxygen saturation was tested by pulse oximetry for all participants up on reception. The participators were categorized into hypoxic and non-hypoxic.Spo2 less than 93% was regarded as hypoxic . polymerase chain reaction conducted on nasopharyngeal swab specimen was accomplished upon reaching to medical ward. All candidates undergone laboratory assessment laboratory indices of inflammatory markers were performed in form of ferritin, C-reactive protein titer, lactate dehydrogenase, D-dimer and procalcitonin .

Result :

Among the 60 included subject , 30 patients belong to covie-19 and 30 were controls groups The basic characteristics of the patients affected by -CoV-19 are shown in Table 1. the levels CRP (mean±SE: 563.43+16.49, 117.86+10.20) D-dimer (mean±SE: 4.59+0.24, 0.24+0.019) PCT(mean±SE: 1.069+0.081, 0.23+0.017) LDH(mean±SE: 345.37+ 14.41, 172.73+ 4.95) respectively was highly significantly and ferritin (mean±SE: 396.73+19.96, 112.57+ 10.38) not significant between patients and controls groups. B12(mean±SE: 223.96+11.33, 289.33+18.42) levels B12 is significant between each groups .

Table 1: Demographics and clinical characteristics of COVID-19 patients and controls . The mean values of the laboratory test results and corresponding standard error values are shown by the patient groups and controls .

	Patients Mean + SE	Controls Mean + SE	P VALUE
CRP	563.43+16.49	117.86+10.20	**0.000**
D-dimer	4.59+0.24	0.24+0.019	**0.000**
PCT	1.069+0.081	0.23+0.017	**0.000**
Ferritin	396.73+19.96	112.57+ 10.38	**0.03**
B12	223.96+11.33	289.33+18.42	**0.003**
LDH	345.37+ 14.41	172.73+ 4.95	**0.000**

To better detect the critical illness, the ROC curve of level CRP was administrated and listed in (Table 2, figure 1) (AUC=1.000, P =0.000). The best cut-off point of age was 1.75 with a specificity of 100% and a sensitivity of 100 %. The ROC curve d-dimer level was (AUC =1.000, P= 0.000) in critical group cut-off point of age was 1.9 with a specificity of 100% and a sensitivity of 100 %. The ROC curve PCT level was (AUC =0.967, P= 0.000) in critical group cut-off point of age was 0.9 with a specificity of 100% and a sensitivity of 100 %. The ROC curve Ferritin level was (AUC =0.969, P= 0.000) in critical group cut-off point of age was 22.0 with a specificity of 100% and a sensitivity of 100 %. The ROC curve B12 level was (AUC =0.288, P= 0.005) in critical group cut-off point of age was 156 with a specificity of 96 % and a sensitivity of 100 %. The ROC curve LDH level was (AUC =0.967, P= 0.000) in critical group cut-off point of age was 121 with a specificity of 100% and a sensitivity of 100 %.

Table 2 : The area under the curve (AUC) values for the serum levels of C-reactive protein (CRP) , D-dimer , Procalcitonin(PCT), ferritin ,B12 and lactate dehydrogenase (LDH).

Test Result Variable(s)	AUC	p value	Cut-off value	Sensitivity	1 - Specificity
CRP	1.000	0.000	1.75	100 %	100 %
D-dime	1.000	0.000	1.9	100 %	100 %
PCT	0.967	0.000	0.9	100 %	100 %
Ferritin	0.969	0.000	22.0	100 %	100 %
B12	0.288	0.005	156	96 %	100 %
LDH	0.967	0.000	121	100 %	100 %

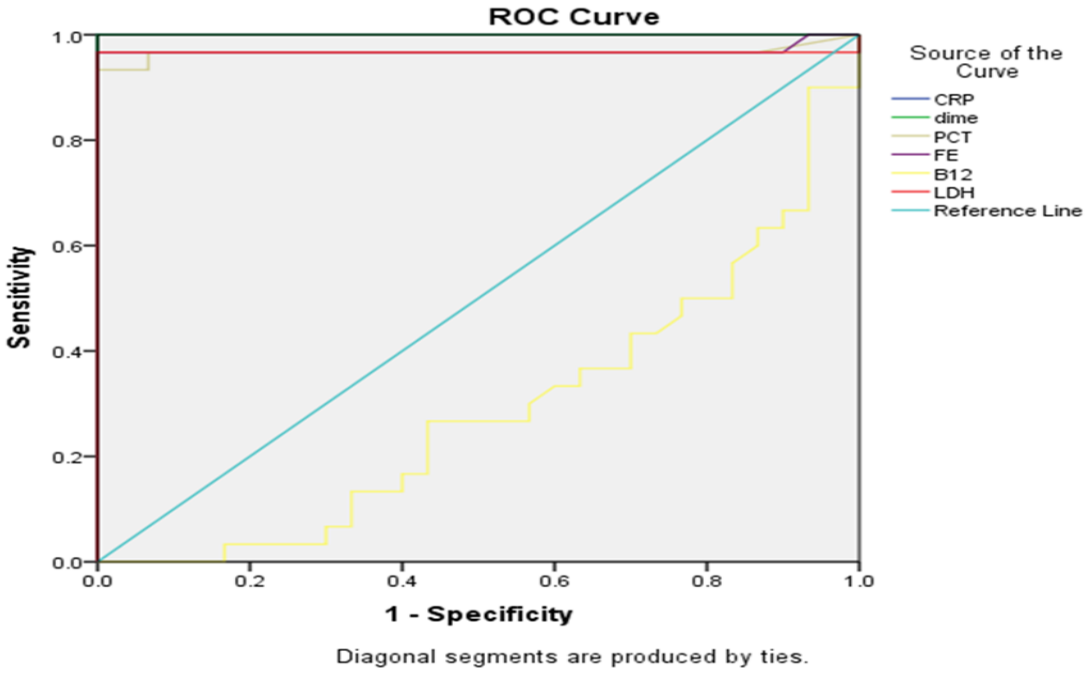

Figure 1 : The ROC curve for serum CRP, D-dimer ,PCT, ferritin, B12 LDH levels for determining disease severity on admission.

Table 3: correlation procalcitonin with CRP, D-dimer , ferritin , B12, LDH

		CRP	dime	PCT	FE	B12	LDH
CRP	Pearson Correlation		.901**	.775**	.848**	-.348-**	.807**
	Sig. (2-tailed)		.000	.000	.000	.006	.000
dime	Pearson Correlation	.901**		.843**	.833**	-.383-**	.870**
	Sig. (2-tailed)	.000		.000	.000	.003	.000
PCT	Pearson Correlation	.775**	.843**	1	.779**	-.292-*	.815**
	Sig. (2-tailed)	.000	.000		.000	.024	.000
FE	Pearson Correlation	.848**	.833**	.779**	1	-.312-*	.844**
	Sig. (2-tailed)	.000	.000	.000		.015	.000
B12	Pearson Correlation	-.348-**	-.383-**	-.292-*	-.312-*	1	-.292-*
	Sig. (2-tailed)	.006	.003	.024	.015		.024
LDH	Pearson Correlation	.807**	.870**	.815**	.844**	-.292-*	1
	Sig. (2-tailed)	.000	.000	.000	.000	.024	
**. Correlation is significant at the 0.01 level (2-tailed).							
*. Correlation is significant at the 0.05 level (2-tailed).							
c. Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples							

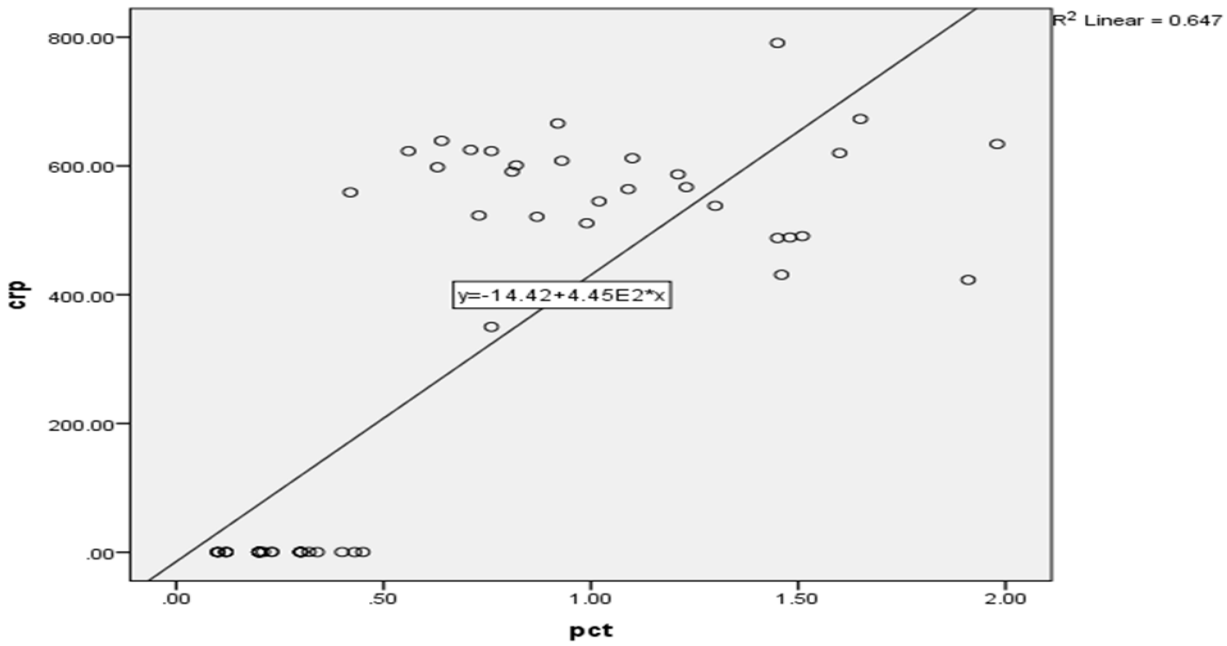

Fig 2: correlation between CRP with PCT

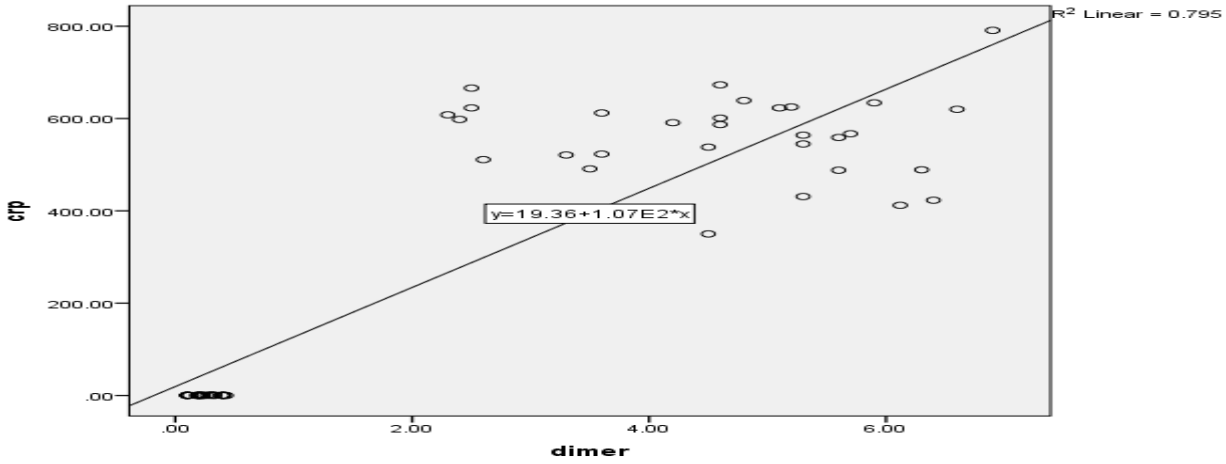

Fig 3: correlation between CRP with dimer

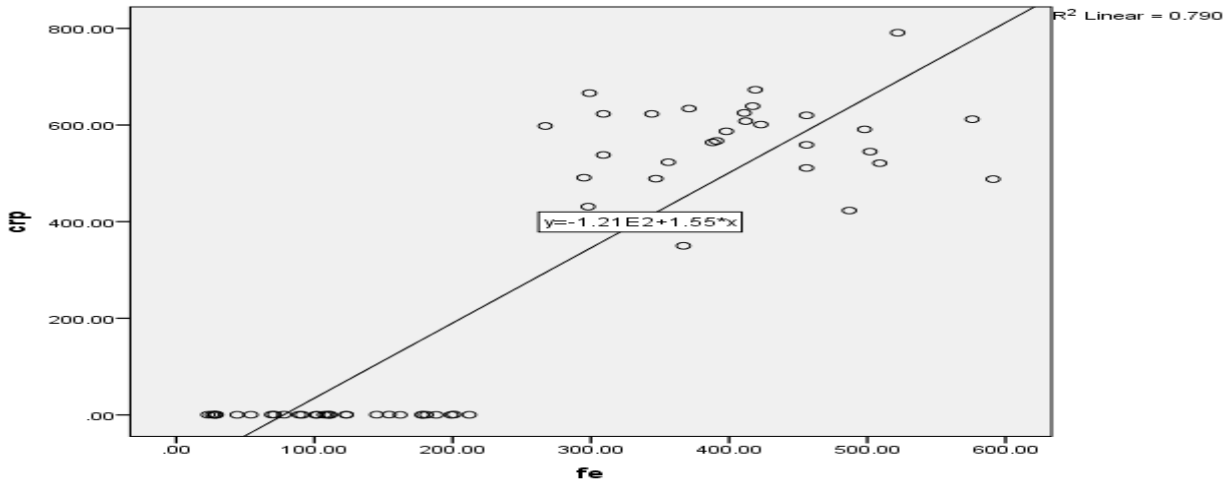

Fig 4 : correlation between CRP with ferritin

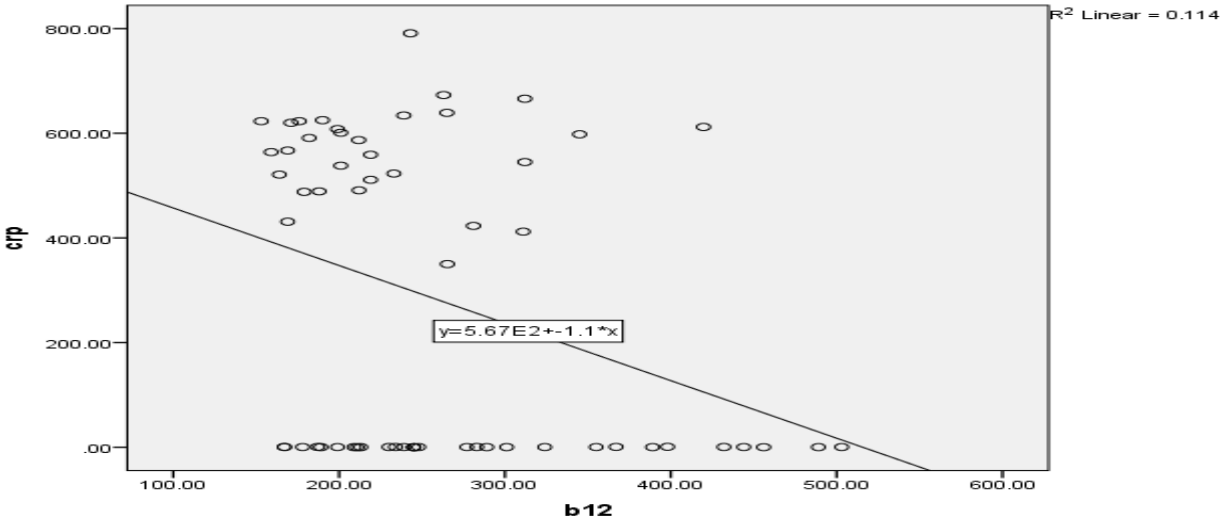

Fig 5 : correlation between CRP with B12

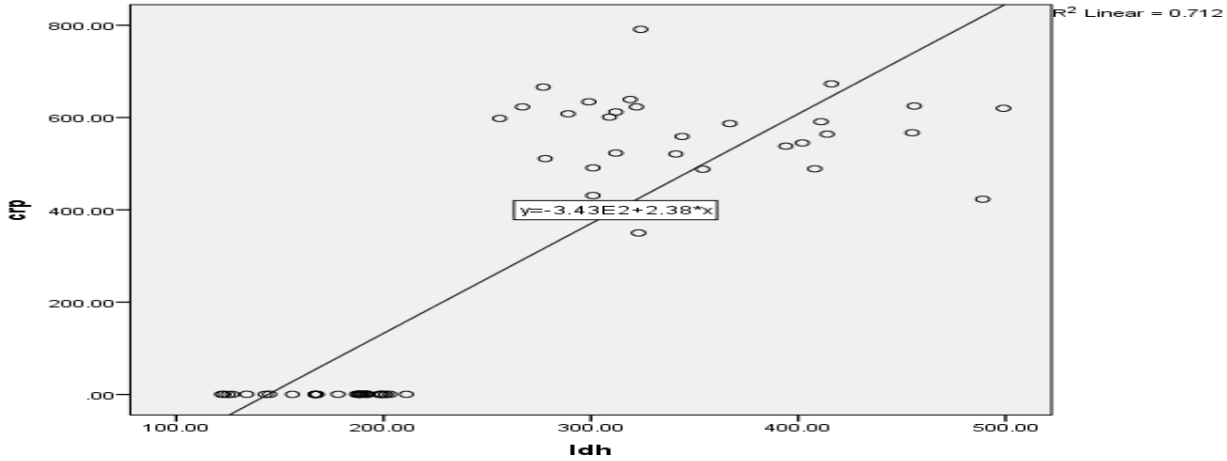

Fig 6 : correlation between CRP with LDH

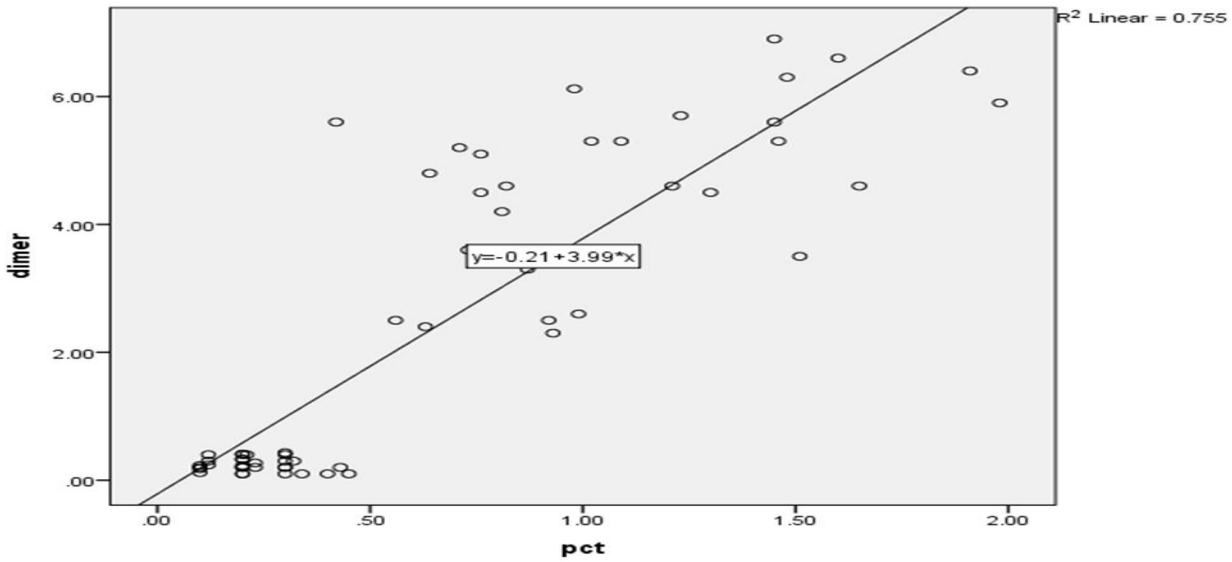

Fig 7: correlation between D-dimer with PCT

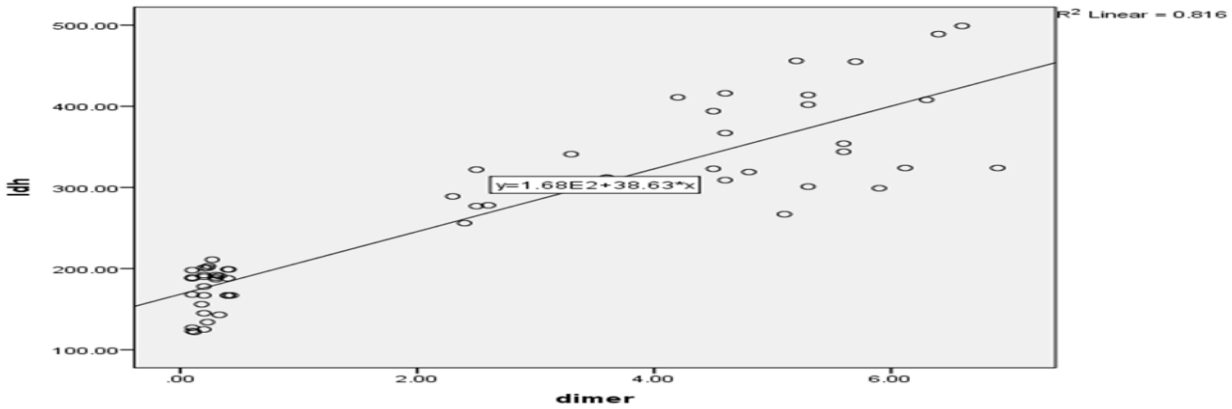

Fig 8: correlation between D-dimer with LDH

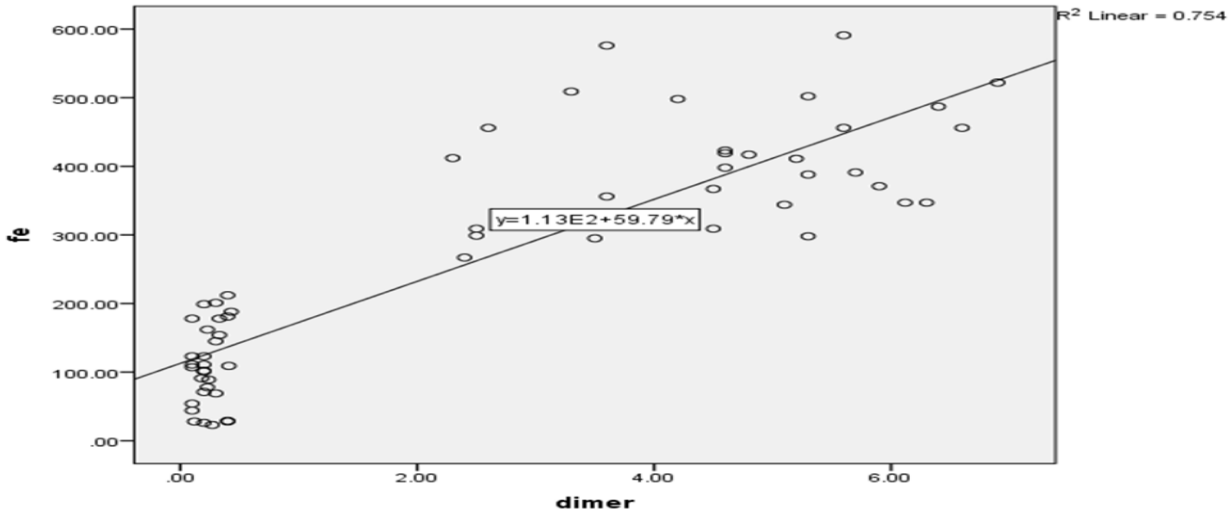

Fig 9: correlation between D-dimer with ferritin

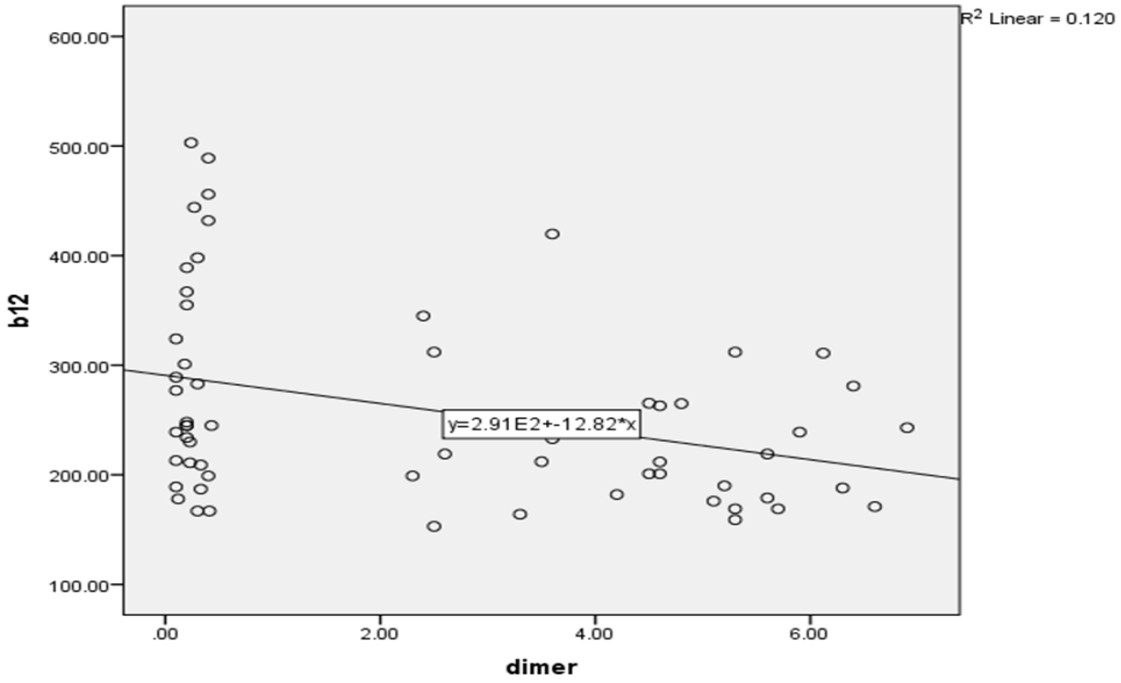

Fig 10: correlation between D-dimer with b12

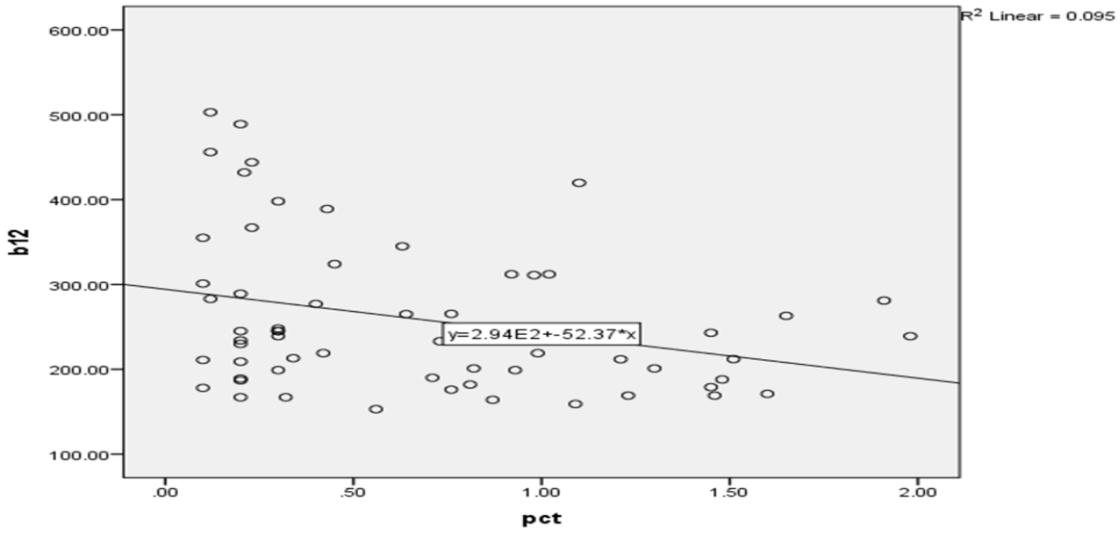

Fig 11: correlation between pct with b12

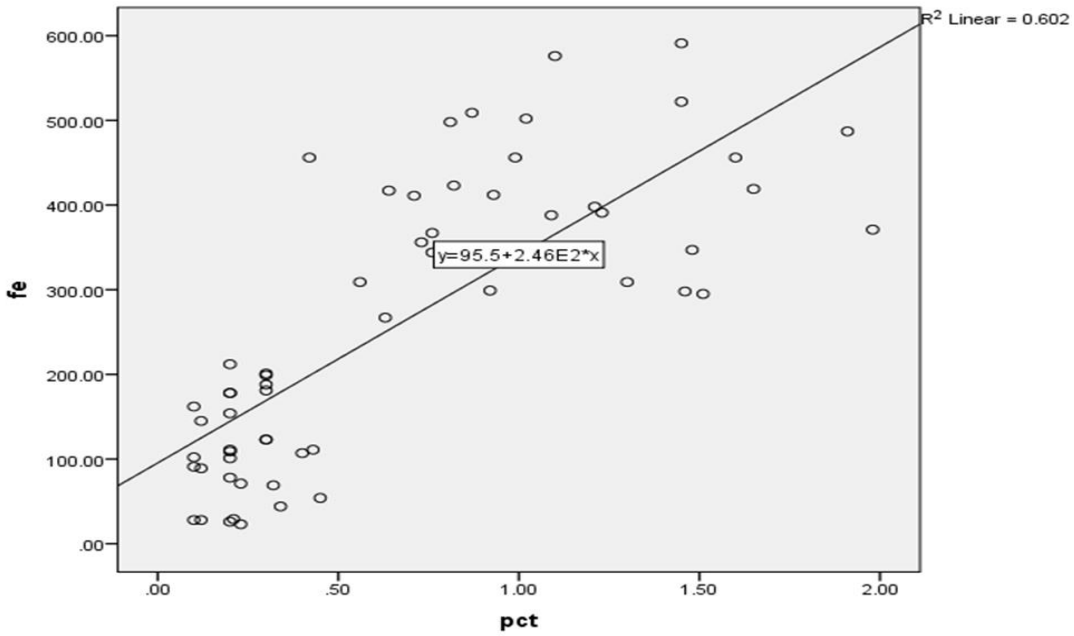

Fig 12: correlation between PCT with ferritin

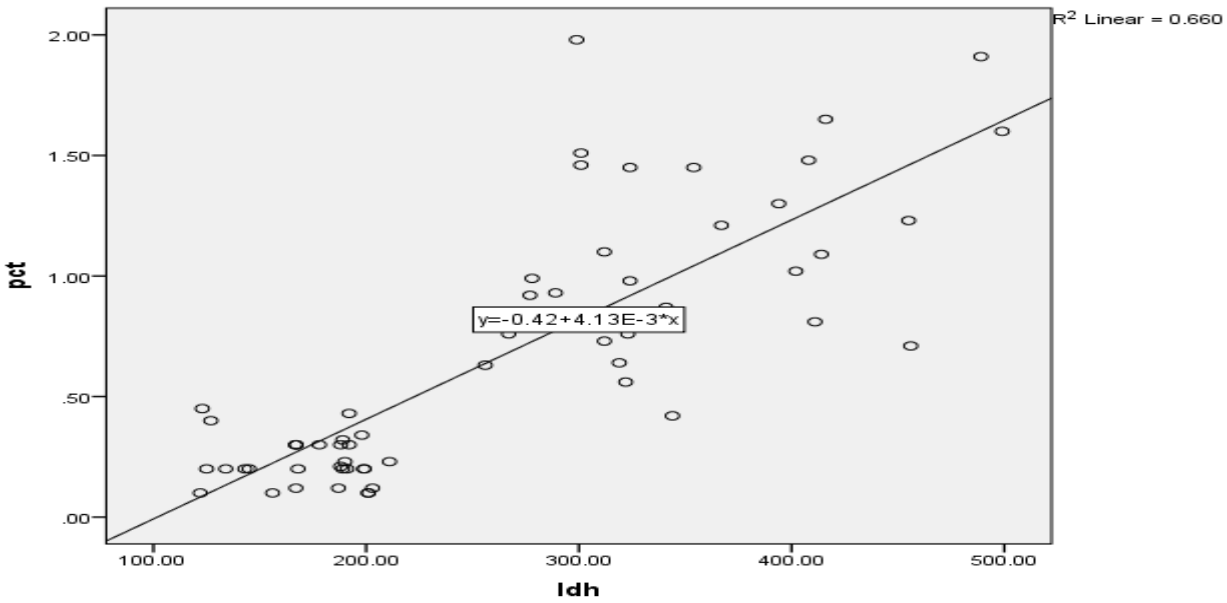

Fig 13: correlation between PCT with LDH

Discussion :

CRP levels are connected to the severity of inflammation, and their concentration is unaffected by age, gender, or physical condition. CRP levels can activate complement and increase phagocytosis, ridding the body of harmful germs (19)

Patients with severe pneumonia had elevated CRP levels, which can be used to diagnose pneumonia early. It's a crucial metric for diagnosing and assessing severe lung infectious illnesses. The value of CRP levels in severe pneumonia was also demonstrated in Matsumoto's study (20)

This study showed that CRP levels highly significant in patient group . CRP levels were positively correlated with d-dimer, LDH , ferritin, PCT . CRP levels could reflect lung lesions and disease severity.

CRP levels and the diameter of the greatest lung lesion rose as the disease advanced, according to this study. CRP levels were found to be linked to lung lesions and the severity of the disease. This shows that CRP levels may reflect lung lesions and disease severity in the early stages of COVID-19 (21)

The impact of PCT levels on the prognosis of COVID-19 patients Model analysis revealed that elevated PCT level was substantially related with a higher risk of overall mortality among COVID-19 patients, with the elevated PCT group having a higher risk of critical disease than the normal PCT group.

PCT is a non-hormonal glycoprotein that is the precursor to calcitonin. Patients with viral pneumonia, particularly SARS pneumonia, have been demonstrated in previous clinical investigations to have PCT. Given that COVID-19 and SARS have comparable clinical symptoms, it is suspected whether PCT can likewise predict COVID-19 prognosis (22)

Similar to our study, recent studies in patients with COVID-19 have also reported that the increase of PCT may be related to the severity of the disease [23, 24].

Fever, most of which is high fever in a few days and cannot be cured by traditional anti-infective medications, cough, headache, and muscle discomfort or weariness are the main first symptoms of COVID-19 [25].

Serum ferritin was discovered to be a reliable predictor of severe SARSCoV2 infection. Ferritin levels were observed to be considerably higher in SARSCoV2 patients with cytokine storm. The ferritin levels of SARS-CoV 2 patients were found to be greater in several autopsies. Patients with raised ferritin levels in the elderly who had SARS CoV2 had a greater mortality rate than those with lower ferritin levels.

Zhou et al. also reported increased mortality in SARS-CoV-2 patients with higher levels of serum ferritin.(26) Elevated ferritin levels can be utilized as a biomarker to differentiate high-risk from low-risk patients, which could aid in the early detection and treatment of SARSCoV2 patients (27) Critically ill and discharged SARSCoV2 patients had higher rates of hyperferritinemia than stable hospitalized patients (28)

LDH is an intracellular enzyme that catalyzes the conversion of pyruvate and lactate, as well as the conversion of NADH and NAD+, in practically all organ systems [29]. The enzyme is made up of two primary subunits (A and B), and there are five different isozymes in humans (LDH-1 in cardiomyocytes, LDH-2 in reticuloendothelial system, LDH-3 in pneumocytes, LDH-4 in kidneys and pancreas, and LDH-5 in liver and striated muscle). Although LDH has been used as a diagnostic of heart damage since the 1960s, aberrant readings can be caused by various organ injury and reduced oxygenation when the glycolytic pathway is upregulated. Metalloproteases are activated and macrophage-mediated angiogenesis is enhanced when the extracellular pH is acidic due to increased lactate from infection and tissue injury [30].

Severe infections may result in tissue damage mediated by cytokines and the release of LDH [31]. Because LDH is present in lung tissue (isozyme 3), patients with severe COVID-19 infections can expect to release more LDH into the circulation, as the condition is characterized by a severe form of interstitial pneumonia that typically progresses to acute respiratory distress syndrome. The contribution of distinct LDH isoenzymes to the LDH rise seen in COVID-19, however, has yet to be identified. In thrombotic microangiopathy, which is linked to renal failure and cardiac damage, LDH levels are also high [32]. In individuals with severe COVID-19, elevated d-dimer values and thrombocytopenia have also been documented, suggesting that a hypercoagulable state may be contributing to the severity of illness and mortality [33,34].

Multiple organ injury and failure appear to play a more important role in this pathophysiology in impacting clinical outcomes in COVID-19 individuals with elevated LDH

levels. Increased LDH levels were linked to a 6-fold increase in the risk of severe COVID-19 illness.

Inflammation and cell damage play an important role in the pathological processes of pulmonary tissues (35). COVID-19 patients had higher LDH levels than individuals with SARS-CoV-2 negative confirmed pneumonia (36). Yuan et al. found that COVID-19 mRNA clearance ratio was highly associated with LDH levels (37).

A higher D-dimer value on admission to the hospital was found to be substantially linked with in-hospital mortality in COVID-19 patients in this study. The principal application of D-dimer, a fibrin breakdown product, is in the diagnosis and therapy of thrombotic diseases. Despite some evidence to the contrary, D-dimer was not considered a reliable biomarker for bacterial or viral pneumonia prior to the 2019 COVID-19 pandemic[38]. However, increased D-dimer levels and thrombotic problems have been extensively reported in COVID-19 patients since then Guan et al [38]. The relationship between initial D-dimer readings and illness severity and outcome has been studied in several research[39].

Another study in China discovered that a D-dimer value of more than 2 g/ml at the time of admission was linked to an increased risk of mortality [40].

According to a comparable study conducted in India, the ideal cutoff value for admission D-dimer to predict hospital death is 1.44 g/ml, while the optimal value for maximum D-dimer measurement during hospital stay to predict hospital mortality is 2.01 g/ml [41]. COVID-19 patients with high D-dimer values had a higher risk of severe disease and mortality, according to a systematic analysis published in August 2020, which also stated that no consistent cutoff value had been determined to predict adverse events [42].

References:

1-Republic of Turkey Ministry of Health General Directorate of Public Health (2020) COVID-19 general information. Available: https://covid19.saglik.gov.tr/Eklenti/38597/0/covid-19rehberigenelbilgilerepidemiyolojivetanipdf.pdf. Accessed 1 September 2020 [Article in Turkish]

2. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R (2020) Features, evaluation and treatment coronavirus (COVID-19) In: Statpearls [internet]. Stat Pearls Publishing.

3. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, Penzar D (2020) Severe acute respiratory syndrome-related coronavirus: The species and its viruses–a statement of the Coronavirus Study Group. Preprints 20200211.

4. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky AM (2020) The role of biomarkers in diagnosis of COVID-19–A systematic review. Life Sci 254: 117788

5. Arch Pathol Lab Med. 2013;137:1030–1038; doi: 10.5858/arpa.2012-0296-CP

6-Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology.

2021; 88: 15–27. https://doi.org/10.1159/000512007 PMID: 33049751

7. Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, et al. Plasma ddimer

levels correlate with outcomes in patients with community-acquired pneumonia. Chest. 2004; 126: 1087–1092. https://doi.org/10.1378/chest.126.4.1087 PMID: 15486368

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients
with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3 PMID: 32171076
9- Soni M, Gopalakrishnan R, Vaishya R, Prabu P. D-dimer level is a useful predictor for mortality in
patients with COVID-19: Analysis of 483 cases. Diabetes Metab Syndr Clin Res Rev. 2020; 14: 2245–
2249. https://doi.org/10.1016/j.dsx.2020.11.007 PMID: 33395786

10-Tao RJ, Luo XL, Xu W, et al. Viral infection in community acquired pneumonia patients with fever: a prospective observational study. J Thorac Dis. 2018;10(7):
4387–95.
[11] Henry B, De Olivera MHS, S. B, M. P, G. L Hematologic, biochemical and immune marker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID 19): a meta-analysis. Clin Chem Lab Med. 2020
12- Warusevitane A, Karunatilake D, Sim J, Smith C, Roffe C. Early diag-nosis of pneumonia in severe stroke: clinical features and thediagnostic role of C-reactive protein. PloS one 2016;11(3):e0150269,http://dx.doi.org/10.1371/journal.pone.0150269.
13- Alan Carter, Pharm.D. — Written by Adam Felman on November 28, 2017.
14- Shakoor H, Feehan J, Mikkelsen K, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, Stojanovska L, Apostolopoulos V. Be well: A potential role for vitamin B in COVID-19. Maturitas. 2021 Feb;144:108-111. doi: 10.1016/j.maturitas.2020.08.007. Epub 2020 Aug 15. PMID: 32829981; PMCID: PMC7428453.
15- Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: Past, present and future. Biochim Biophys Acta. 2010 Aug;1800(8):760-9. doi: 10.1016/j.bbagen.2010.03.011. Epub 2010 Mar 19. PMID: 20304033; PMCID: PMC2893236.
16- Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. Diabetes Res Clin Pract. 2020;164:
108214.
17. Ma A, Jia R, Ma X, Sun Y, Zhang H, Ma Y. Iron storage in women is positively correlated with aging and BMI values. Energy Nutr Metab. 2016;30(S1):377-382.
18. Wu J, Liu J, Zhao X, et al. Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu Province: a multicenter descriptive study. Clin Infect Dis. 2020;
71(15):706-712.

19- Bilgir O, Bilgir F, Calan M. Comparison of pre-and post-levothyroxine high-sensitivity C-reactive protein and fetuin-A levels in subclinical hypothyroidism. Clinics 2015;70(2):97–101, http://dx.doi.org/10.6061/clinics/2015(02)05.
20- Chalmers S, Khawaja A, Wieruszewski PM, Gajic O, Odeyemi Y. Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: therole of inflammatory biomarkers. World J Crit Care Med 2019;8(5):59–71,http://dx.doi.org/10.5492/wjccm.v8.i5.59.

21- Matsumoto H, Kasai T, Sato A, Ishiwata S, Yatsu S, Shitara J, et al. Associa-tion between C-reactive protein levels at hospital admission and long-termmortality in patients with acute decompensated heart failure. Heart Vessels2019;34(12):1961–8, http://dx.doi.org/10.1007/s00380-019-01435-9.
22- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.
23- Xu G, Yang Y, Du Y, Peng F, Hu P, Wang R, et al. Clinical Pathway for Early Diagnosis of COVID-19: Updates from Experience to Evidence-Based Practice. Clin Rev Allergy Immunol. 2020.
24- Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020.
25- Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020; 133: 1025-31.

26- Sun L, Shen L, Fan J, et al. Clinical features of patients with

coronavirus disease 2019 from a designated hospital in Beijing,

China. J Med Virol. 2020;395(10223):497-506.

27- Cecconi M, Piovani D, Brunetta E, et al. Early predictors of

clinical deterioration in a cohort of 239 patients hospitalized

for Covid-19 infection in Lombardy, Italy. J Clin Med. 2020;

9(8):2429.

28- Hou H, Zhang B, Huang H, et al. Using IL-2R/lymphocytes for

predicting the clinical progression of patients with COVID-19.

Clin Exp Immunol. 2020;201:76-84.

29- Hsu PP, Sabatini DM. Cancer cell metabolism: Warburg and beyond. Cell. 2008;134(5):703–7.

[30] Martinez-Outschoorn UE, Prisco M, Ertel A, et al. 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; 10(8):1271–86.

31 - Kaplan B, Meier-Kriesche HU. Death after graft loss: an important late study endpoint in kidney transplantation. Am J Transplant. 2002;2(10):970–4.

[32] Zhang T, Chen H, Liang S, et al. A non-invasive laboratory panel as a diagnostic andprognostic biomarker for thrombotic microangiopathy: development and application in a Chinese cohort study. PLoS One. 2014;9(11):e111992.

[33] Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. Thromb Haemost. May 2020;120(5):876–8.

[34] Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145–8.

35-Drent M, Cobben NA, Henderson RF, et al. Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. Eur Respir J 1996;9:1736-42.

36. Zhao D, Yao F, Wang L, et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clin Infect Dis 2020;71:756-61.

37. Yuan J, Zou R, Zeng L, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflamm Res 2020;69:599-606.

38. Yap JKY, Moriyama M, Iwasaki A. Inflammasomes and Pyroptosis as Therapeutic Targets for COVID-19. J Immunol 2020;205:307-12.

39- Querol-Ribelles JM, Tenias JM, Grau E, Querol-Borras JM, Climent JL, Gomez E, et al. Plasma ddimer levels correlate with outcomes in patients with community-acquired pneumonia. Chest. 2004; 126: 1087–1092. https://doi.org/10.1378/chest.126.4.1087 PMID: 15486368

40- Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382: 1708–1720. https://doi.org/10.1056/NEJMoa2002032 PMID: 32109013

41- Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality

in patients with Covid-19. J Thromb Haemost. 2020; 18: 1324–1329. https://doi.org/10.1111/jth.

14859 PMID: 32306492

42- Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020; 8: 49. https://doi.org/10.1186/ s40560-020-00466-z PMID: 32665858

43- Soni M, Gopalakrishnan R, Vaishya R, Prabu P. D-dimer level is a useful predictor for mortality in patients with COVID-19: Analysis of 483 cases. Diabetes Metab Syndr Clin Res Rev. 2020; 14: 2245– 2249. https://doi.org/10.1016/j.dsx.2020.11.007 PMID: 33395786

44- Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, et al. Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: a systematic review and meta-analysis. Cardiol Rev. 2020. https://doi.org/10.1097/CRD.0000000000000330 PMID: 33017364