JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Relationship of angiopoietin-2 level with the prognosis of the COVID-19 disease

Olgun Keskin[1], Işılay Kalan Sari[2], Aysegul Seremet Keskin[3], Hamit Yaşar Ellidağ[4], Orbay Harmandar[5]

[1] Department of Chest Disease, University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey
[2] Department of Endocrinology and Metabolic Disorders, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[3] Department of Infectious Disease and Clinical Microbiology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[4] Department of Clinic of Biochemistry, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[5] Department of Internal Medicine, Intensive Care Unit, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey

Abstract

Introduction: COVID-19 infection is associated with coagulopathy. There is increased expression of markers such as E-selectin or angiopoietin-2 upon the activation of endothelin. The aim of this study was to determine whether there was a difference in angiopoietin-2 levels among patients with a diagnosis of COVID-19 who need to be hospitalized in the intensive care units (ICUs) or service.

Methodology: COVID-19 infected patients admitted in the hospital were included in this study. In addition to the routine biochemical parameters of patients in ICUs and services, 5 cc blood samples were collected and angiopoietin-2 was analyzed. Demographic data of the patients, biochemical parameters at the time of hospitalization, places and durations of hospitalization as well as their ways of being discharged from hospital were recorded.

Results: 180 patients who presented to our hospital's emergency service and were hospitalized with a diagnosis of COVID-19 were included in our study. 137 patients (76.1%) were hospitalized in the service and 43 (23.9%) were hospitalized in ICU. The angiopoietin-2 level was determined to be significantly high in the patients hospitalized in ICUs ($p = 0.018$). When the cut-off value of angiopoetin-2 in predicting the ICU hospitalization was assumed as 64.5 ng/L, its sensitivity was determined to be 59% and its specificity was found to be 42%.

Conclusions: We concluded that angiopoietin-2 level in COVID-19 patients upon their presentation to the hospital might be an important parameter in predicting and ascertaining their place of hospitalization.

Key words: angiopoietin-2; COVID-19; prognosis.

J Infect Dev Ctries 2023; 17(10):1394-1400. doi:10.3855/jidc.17297

(Received 26 August 2022 – Accepted 28 February 2023)

Introduction

Coronavirus disease 2019 (COVID-19) disease is a health problem affecting the entire world and there are ongoing studies regarding its pathology, clinical symptoms, laboratory parameters, treatment, and vaccine side effects. Respiratory failure ranks as one of the top causes of mortality from the disease. Much of the pathophysiology of the disease is unclear, and it has been demonstrated that COVID-19 infection is correlated with coagulopathy. High levels of coagulation parameters such as fibrinogen, D-dimer etc. could be detected in the course of the disease [1]. It is known that during the progression of the disease the virus enters into the endothelial cells and as a result, a clinical picture called endotheliitis develops [2]. It is thought that this endotheliitis, which develops during the progression of the disease, may be underlying the microembolism and impaired microcirculation observed in the lungs. There is an increase in the markers such as E-selectin or angiopoietin-2 upon the activation of endothelin. The said markers are involved in hemostasis, thrombo-inflammatory events or sepsis. A study conducted on COVID-19 patients showed that angiopoietin-2 level was a predictive factor for direct hospitalization in intensive care units (ICUs) and suggested that endothelial activation might be related to poor prognosis [2]. Even though the relationship of the parameters such as C-reactive protein (CRP), D-dimer,

ferritin, etc. with the prognosis of COVID-19 is known, it has not yet been established clearly how the angiopoietin-2 level, one of the endothelial markers, relates to the disease prognosis, severity of pulmonary damage, and morbidities in this disease. Therefore, our study's objective was to measure levels of soluble angiopoietin-2 among COVID-19 patients complying with the hospitalization criteria during their presentation to emergency service and to observe whether there is any difference between patients who need to be hospitalized in intensive care units or service and determine the angiopoietin-2 level that is associated with the prognosis of the disease.

Methodology

Patients ≥ 18 years of age, who presented to the emergency service between March 2021 and November 2021 with suspected COVID-19 infection and a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test result, with COVID pneumonia determined at the first thoracic tomography upon presentation, and who were indicated for hospitalization (based on COVID-19 diagnosis and treatment guides of the Ministry of Health) were included in the study. The criteria for severe pneumonia were patients with fever and respiratory tract infection findings, respiratory rate ≥ 30/min and/or severe respiratory distress (dyspnea, use of accessory respiratory muscles and/or oxygen saturation ≤ 90% in room air (PaO_2/FiO_2 < 300 in patients receiving oxygen). Characteristic thoracic computerized tomography (CT) findings of COVID-19 pneumonia were defined as the presence of bilateral lobular, peripherally located, diffuse patchy ground-glass opacities on the thorax CT. The participants were asked for their consent and after receipt thereof, they were included in the study [3]. 5 cc blood was collected into a gel separator biochemistry test tube from the patients during hospitalization, in addition to the routine blood samples for testing biological parameters (haemogram, C-Reactive Protein CRP, D-Dimer, ferritin, fibrinogen, procalcitonin) that were tested for all pandemic patients in ICUs. The blood samples were centrifuged and stored at -80 °C. Later on, the blood samples were thawed and analyzed using the human angiopoietin (AFG Bioscience Illionis, USA) commercial enzyme-linked immunosorbent assay (ELISA) kits (intraassay < 8%, intraassay < 10%, detection range: 3-150 ng/L, sensitivity: 0.6% ng/L). Demographic data of the patients, laboratory parameters at the time of hospitalization, places and durations of hospitalization, and condition of discharge from the hospital were recorded and statistically analyzed.

Statistical analysis

The data was analyzed using the statistical package for the social sciences (SPSS) 23.0 program. Conformity of the variables to normal distribution was analyzed by visual (histograms and probability graphics) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyses were provided for normally distributed variables by using mean values and standard deviations. Based on hospitalization of patients in the service and intensive care units, mean and standard deviation of age and biochemical data were given and intergroup difference was established by using the Student's t-test. Health information, disease symptoms and difference in percentages between the genders, which are categorical variables of the patients hospitalized in services and intensive care units, were evaluated by applying Chi Square test. Based on the poor prognosis of the patients, Student's t-test and Mann-Whitney U test were used for evaluating the biochemical data according to whether or not the parameters were distributed normally. Statistical significance level was determined at $p < 0.05$. Logistic regression analysis was conducted and the effects of biochemical findings of the patients on the disease prognosis were evaluated. Attributes of angiopoietin levels of the patients in predicting the transfer of patients from the service to the ICU were analyzed using the receiver operating characteristics (ROC) curve. Sensitivity and specificity values for the significant limit value were calculated. During the evaluation of the area under the curve, the cases where type-1 error level was below 5% were considered significant.

Results

Demographic data of the patients

The 180 patients who presented to our hospital's emergency service and were scheduled to be hospitalized with a diagnosis of COVID-19 were included in our study. 137 of the patients (76.1%) were hospitalized in the service and 43 (23.9%) were hospitalized in ICU. However, 58 (43.9%) of the 137 patients who had been initially hospitalized in service later needed to be transferred to the ICU. Among the patients included in the study 114 were male and 52 were female. The mean age was 62.5 ± 14.55 years.

In the beginning, the patients were divided into 2 groups: those hospitalized in ICU and those in service. Patients with severe pneumonia criteria were admitted

to the ICU. The difference between the mean ages of the patients hospitalized in service and those hospitalized in ICU was statistically significant. The mean age (65.0 ± 15.56 years) of the patients hospitalized in the ICU was significantly higher (p = 0.045). There was no difference between the groups regarding underlying diseases. Considering the presentation symptoms, it was found that the complaints of fever, muscle and joint pain, and cough were more common among the patients hospitalized in the service (p values: 0.014, 0.041, and 0.001 respectively). As expected, SpO_2 values were determined to be lower (87 ± 11.96) in the patients hospitalized in the ICU at the time of presentation to the hospital (p = 0.000). It was observed that hospitalization duration was longer with a time period of 17.6 ± 18.78 days (p = 0.023). Patients' demographic data were provided in Table 1.

Laboratory data at the first presentation to the hospital

Laboratory findings were analyzed based on the patients' place of hospitalization. Urea, D-dimer and fibrinogen levels were significantly higher in patients hospitalized in the ICUs (p values were 0.003, 0.034, and 0.007 respectively). Angiopoietin-2 level was also determined to be significantly high in the patients hospitalized in ICUs (p = 0.018). The laboratory values are provided in Table 2.

Hospitalization duration of non-ICU inpatients and grouping based on the disease endpoint

Inpatients included in the study were divided into two groups: those with a length of stay less than 10 days and those with a hospitalization period of more than 10 days. The number of inpatients with a length of stay of < 10 days was 78 whereas there were 102 inpatients with hospitalization duration of > 10 days. For a variety of reasons, 58 of the 137 non-ICU inpatients needed to be shifted to the ICU during their stay.

The patients were also grouped based on the disease outcome: patients who died and patients who were discharged. It was determined that 131 patients had been discharged while 49 had died.

Table 1. General demographic and clinical characteristics of patients.

	Service (n: 137)	**ICU (n: 43)**	***p***
Gender (n: %)			
Male	85 (62.0)	29 (67.4)	χ^2: 0.411; p: 0.589
Female	52 (38.0)	14 (32.6)	
Age (years) **(x ± SD)**	60.0 ± 13.67	65.0 ± 15.56	**0.045***
Underlying disease (n %)	80 (58.4)	29 (67.4)	χ^2: 1.122; p: 0.190
Diabetes mellitus	40 (29.2)	14 (32.6)	χ^2: 0.176; p: 0.405
Hypertension	53 (38.7)	17 (39.5)	χ^2: 0.010; p: 0.529
Chronic kidney failure	2 (1.5)	1 (2.3)	χ^2: 0.145; p: 0.564
Hyperlipidemia	3 (2.2)	2 (4.7)	χ^2: 0.734; p: 0.343
Coronary artery disease	8 (5.9)	5 (11.6)	χ^2: 1.601; p: 0.174
Cerebrovascular event	5 (3.6)	4 (9.3)	χ^2: 2.202; p: 0.140
Rheumatological disease	4 (2.9)	1 (2.3)	χ^2: 0.043; p: 0.657
Symptoms (n: %)			
Fever	48 (35.0)	7 (16.3)	**χ^2: 5.427; p: 0.014***
Cough	72 (52.6)	10 (23.3)	**χ^2: 11.327; p: 0.001***
Dyspnea	82 (59.9)	26 (60.5)	χ^2: 0.005; p: 0.545
Muscle joint pain	17 (12.4)	1 (5.6)	**χ^2: 3.697; p: 0.041***
Nausea, vomiting	26 (19.0)	4 (9.3)	χ^2: 2.206; p: 0.102
Diarrhea	7 (5.1)	-	χ^2: 2.286; p: 0.142
Loss of taste and smell	2 (1.5)	2 (4.7)	χ^2: 1.534; p: 0.242
Chest pain	5 (3.6)	3 (7.0)	χ^2: 0.853; p: 0.292
Backache	5 (3.6)	1 (2.3)	χ^2: 0.178; p: 0.559
Phlegm	10 (7.3)	5 (11.6)	χ^2: 0.803; p: 0.271
SpO2 % **(**x ± SD)	92 ± 4.58	87 ± 11.96	**0.000***
Fever ^{0}C (x ± SD)	37.0 ± 0.77	36.8 ± 0.46	0.271
Duration of hospitalization (x ± SD)	15.3 ± 11.33	17.6 ± 18.78	**0.023***

ICU: intensive care unit; x: mean; SD: Standard deviation; p: statistical significance value. *: indicates statistically significant value.

Table 2. Laboratory values according to place of hospitalization.

	Service (n: 137) (x ± SD)	**ICU (n: 43) (x ± SD)**	***p***
Urea (mg/dL)	22.6 ± 15.02	31.3 ± 20.35	**0.003***
Creatinine (mg/dL)	1.4 ± 5.08	1.2 ± 0.87	0.765
Albumin (g/dL)	3.6 ± 2.77	3.2 ± 1.52	0.429
Alanine aminotransferase (U/L)	48.9 ± 54.42	44.8 ± 35.41	0.646
Aspartate aminotransferase (U/L)	47.2 ± 40.62	43.1 ± 22.12	0.553
Gamma glutamyl transferase (U/L)	52.5 ± 65.21	59.0 ± 51.28	0.584
Lactate dehydrogenase (U/L)	400.1 ± 218.97	448.5 ± 220.60	0.231
Cholesterol (mg/dL)	162.6 ± 45.10	154.6 ± 58.26	0.608
HDL (mg/dL)	39.2 ± 11.27	37.1 ± 12.43	0.554
LDL (mg/dL)	87.4 ± 31.49	86.8 ± 44.34	0.959
Triglycerides (mg/dL)	175.0 ± 96,12	144.6 ± 74.92	0.122
C-Reactive Protein (mg/L)	82.3 ± 78.96	98.5 ± 66.97	0.230
Leukocytes (10^3/mm^3)	11.3 ± 21.81	12.5 ± 16.60	0.740
Hemoglobin (g/dL)	12.6 ± 2.15	11.9 ± 2.00	0.056
Platelet (10^3/mm^3)	248.8 ± 132.25	253.0 ± 124.74	0.855
Lymphocyte (%)	13.4 ± 12.78	10.6 ± 8.74	0.185
Neutrophil/Lymphocyte ratio	14.6 ± 32.56	15.8 ± 14.74	0.821
Ferritin (µg/L)	638.8 ± 1218.43	908.3 ± 1632.40	0.298
D-dimer (µg/L)	1067.1 ± 2022.38	2199.6 ± 3173.92	**0.034***
Fibrinogen	500.8 ± 194.36	522.2 ± 213.45	**0.007***
Angiopoietin- 2	63.2 ± 17.37	71.3 ± 25.24	**0.018***

HDL: high density lipoprotein; LDL: low density lipoprotein; SD: standard deviation; x: mean; *p*: statistical significance value. *: indicates statistically significant value.

Table 3. Hospitalization duration of non-ICU inpatients and the fact that it becomes necessary to hospitalize them in ICU while they are non-ICU inpatients and their laboratory data according to the disease endpoint.

Biochemical Findings	**Died (n: 49)**	**Discharged (n: 131)**	**p**	**Duration of hospitalization < 10 Days (n: 78)**	**Duration of hospitalization ≥ 10 Days (n: 102)**	***p***	**Patients continuing to stay in non-ICU unit (n: 79)**	**Inpatients transferred from non-ICU unit to ICU (n: 58)**	***p***
Urea (mg/dL)	32.4 ± 20.06	21.8 ± 14.47	**0.001***	22.3 ± 14.92	26.5 ± 18.00	0.097	21.5 ± 14.82	24.0 ± 15.29	0.332
Creatinine (mg/dL)	1.1 ± 0.61	1.4 ± 5.20	0.652	1.7 ± 6.69	1.1 ± 0.72	0.320	1.7 ± 6.66	1.0 ± 0.44	0.444
Albumin (gr/dL)	2.9 ± 0.55	3.7 ± 2.89	0.060	4.0 ± 3.65	3.1 ± 0.61	**0.019***	3.4 ± 0.64	3.8 ± 4.16	0.348
ALT (U/L)	45.2 ± 35.39	48.9 ± 55.16	0.658	53.4 ± 65.58	43.7 ± 34.50	0.205	49.8 ± 63.17	47.6 ± 39.96	0.813
AST (U/L)	44.6 ± 23.13	46.8 ± 40.93	0.734	48.8 ± 48.47	44.2 ± 25.04	0.472	43.4 ± 41.29	52.5 ± 39.42	0.220
GGT (U/L)	44.1 ± 33.08	57.3 ± 69.27	0.249	61.2 ± 81.58	48.3 ± 41.32	0.233	59.8 ± 78.41	41.7 ± 36.82	0.131
LDH (U/L)	512.4 ± 215.90	376.8 ± 210.75	**0.000***	347.9 ± 226.00	461.0 ± 202.41	**0.001***	371.6 ± 188.20	440.9 ± 253.11	0.083
Cholesterol (mg/dL)	157.5 ± 47.54	159.4 ± 54.16	0.910	171.3 ± 51.19	153.6 ± 51.55	0.305	177.0 ± 46.42	147.0 ± 39.88	0.114
HDL (mg/dL)	41.6 ± 13.54	36.5 ± 10.67	0.170	39.3 ± 9.50	37.7 ± 12.76	0.669	39.8 ± 11.59	38.6 ± 11.45	0.806
LDL (mg/dL)	87.5 ± 38.63	86.9 ± 38.13	0.963	90.9 ± 29.60	85.8 ± 40.63	0.708	94.9 ± 35.94	80.0 ± 25.85	0.277
Triglycerides (mg/dL)	158.5 ± 84.05	162.1 ± 90.85	0.857	175.7 ± 112. 96	154.4 ± 75.21	0.329	186.0 ± 100.91	164.9 ± 92.76	0.484
CRP (mg/L)	122.0 ± 73.28	73.2 ± 73.62	**0.000***	68.8 ± 78.95	99.6 ± 71.96	**0.008***	78.0 ± 80.34	88.1 ± 77.34	0.464
Leukocyte (10^3/ mm3)	15.7 ± 35.85	10.0 ± 10.16	0.273	9.3 ± 5.17	13.3 ± 26.99	0.204	12.6 ± 28.42	9.4 ± 4.85	0.386
Hemoglobin (g/dL)	11.9 ± 2.55	12.7 ± 1.91	**0.026***	12.4 ± 1.90	12.5 ± 2.30	0.748	12.4 ± 2.27	12.8 ± 1.96	0.287
Platelet (10^3/mm^3)	234.4 ± 146.31	255.5 ± 123.70	0.333	251.4 ± 126.64	248.5 ± 133.41	0.882	253.9 ± 132.85	241.8 ± 132.27	0.599
Lymphocyte (%)	10.2 ± 12.05	13.6 ± 11.86	0.090	15.4 ± 13.00	10.7 ± 10.76	**0.009***	12.6 ± 10.58	14.4 ± 15.32	0.396
N/L ratio	23.8 ± 52.71	11.6 ± 10.64	**0.013***	10.8 ± 11.54	18.0 ± 37.34	0.103	12.3 ± 10.52	17.8 ± 48.59	0.329
Ferritin (µg/L)	1007.3 ± 17958	602.2 ± 1120.66	0.117	440.4 ± 436.08	910.6 ± 1704.56	**0.021***	606.5 ± 1457.24	679.8 ± 835.92	0.767
D-Dimer (µg/L)	2324.7 ± 31868	985.4 ± 1926.43	**0.001***	1081.8 ± 2216	1546.1 ± 25178	0.208	1158.4 ± 22444	938.6 ± 1672.61	0.544
Fibrinogen	542.7 ± 191.31	492.7 ± 200.70	0.154	474.1 ± 191.03	530.4 ± 202.24	0.072	490.5 ± 211.12	516.3 ± 167.20	0.475
Angiopoetin-2	66.4 ± 18.89	64.6 ± 20.14	0.588	65.0 ± 22.37	65.2 ± 17.64	0.943	59.8 ± 17.01	67.7 ± 16.93	**0.008***

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gama glutamyl transferase; LDH: lactate dehydrogenase; ICU: intensive care unit; *p*: statistical significance value. *: indicates statistically significant value.

Table 4. Values of some biochemical parameters and angiopoietin-2 in predicting place/unit of hospitalization of the patients considering their first place of hospitalization

	B	SE	*p*	OR	Lower	Upper
Lactate dehydrogenase (U/L)	-0.001	0.001	0.635	0.999	0.997	1.002
C-Reaktive protein (mg/L)	0.000	0.003	0.991	1.000	0.994	1.006
Lymphocyte (%)	-0.023	0.030	0.455	0.978	0.922	1.037
Neutrohıl/Lymphocyte ratio	-0.002	0.010	0.821	0.998	0.978	1.018
D-dimer (µg/L)	0.000	0.000	0.357	1.000	1.000	1.000
Angiopoetin-2	0.028	0.012	**0.018***	**1.029**	1.005	1.053

SE: standard error; B: unstandardized beta; OR: odds ratio; *p*: statistical significance value. *: indicates statistically significant value.

Having a length of stay of more than 10 days, requiring hospitalization in ICU during non-ICU hospitalization and death as an endpoint was considered a poor prognosis for the patients. No difference was spotted between patient groups comprising the patients who died or were discharged and the patients with more than and less than 10 days of hospitalization in terms of angiopoietin-2 level. The level of angiopoietin-2 was significantly higher among the inpatients who later required to be shifted to the ICU ($p = 0.008$). Laboratory values of the groups of patients are presented in Table 3.

Role of biochemical parameters and angiopoietin-2 in predicting hospitalization unit

Parameters such as lactate dehydrogenase (LDH), CRP, lymphocyte value, neutrophil/lymphocyte ratio (N/L), and D-dimer level that are known to be important in determining the diagnosis and prognosis of COVID-19, were compared with angiopoietin-2. A logistic regression analysis was performed. Each increase of one unit in angiopoietin-2 value was observed to have increased the risk of ICU hospitalization. However, the other parameters had no impact on distinguishing between non-ICU unit hospitalization and ICU hospitalization at the time of hospitalization (Table 4).

When the cut-off value of angiopoietin-2 in predicting ICU hospitalization was considered as 64.5 ng/L, its sensitivity was determined to be 59% and its specificity was found to be 42% (Table 5). The ROC curve is presented in Figure 1.

Discussion

COVID-19 leads to various clinical scenarios in patients. It is known that 10-15% of the mild cases become severe cases, and 15-20% of the severe cases require ICU hospitalization over time [4]. When the cases start to rise, hospitals try to accommodate the ever-increasing number of patients with their limited resources. Therefore, developing a clinical decision process for determining which patients should be prioritized for hospitalization and which ones for ICU hospitalization are important. Various studies have been conducted in order to be able to determine the patients who run the risk of progressing to serious diseases or those who might need ICU hospitalization, but no markers have been established so that the patients' hospitalization in non-ICU or ICU would be clearly predicted at the time of their presentation to the emergency service [5]. In our study, we have reached the conclusion that the angiopoietin-2 level in COVID-19 patients upon their presentation to the hospital might

Figure 1. Specificity and sensitivity of angiopoietin-2 in prediction of ICU hospitalization.

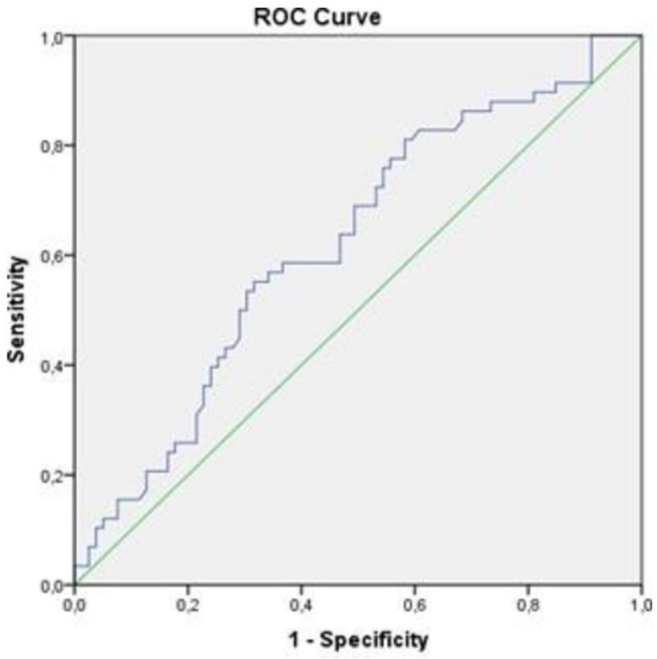

Table 5. Value of Angiopoetin-2 in predicting the ICU hospitalization.

Risk factor	Area Under Curve (AUC) (95%)	Cut-off	*p* value	Sensitivity (%)	Specificity (%)
Angiopoetin-2	0.621(0.526-0.715)	64.5	**0.016***	59.0	42.0

ICU: intensive care unit; *p*: statistical significance value. *: indicates statistically significant value.

be an important parameter in predicting and ascertaining their disease progression.

COVID-19 is known to be associated with coagulopathy. It has been demonstrated in vivo and in vitro that the SARS-CoV-2 virus binds to angiotensin converting enzyme (ACE-2) receptors, enters the cells and infects the blood vessels [2,6,7]. Thus, a picture of endotheliitis occurs. This picture of endotheliitis is thought to be the reason underlying the microembolisms observed in the lungs. It is known that the markers arising with endothelin activation such as endoglin, E-selectin or angiopoietin-2 play a role in homeostasis, thrombo-inflammatory events or sepsis. In the literature, a study conducted on COVID-19 patients showed that angiopoietin-2 level was a predictive factor for direct hospitalization in intensive care unit and suggested that endothelial activation might be related to poor prognosis. In the same study, angiopoietin-2 threshold value was set as 5000 pg/mL. It was further established that there was a significant correlation between the angiopoeitin-2 level and CRP, creatinine and D-dimer levels for predicting ICU hospitalization [8]. Similarly, in our study, the angiopoietin-2 level was found to be significantly high among ICU inpatients as well as those initially hospitalized in non-ICU units but later needed ICU hospitalization during the follow-up (p: 0.018 and 0.008 respectively). It was observed that every 1 unit of increase in angiopoietin-2 level elevated the risk of ICU hospitalization. When the cut-off value of angiopoietin-2 for predicting ICU hospitalization is set at 64.5 ng/L, its sensitivity was found to be 59% and the specificity was determined to be 42%. Our study suggested that the angiopoietin-2 level controlled at the time of hospitalization might be an important parameter in depicting the patients' need for ICU. Many studies have been conducted regarding various laboratory parameters in order to predict ICU hospitalization or detect high-risk COVID-19 patients. In our study, when the patients hospitalized in non-ICU units and those hospitalized in ICU were reviewed separately and a distinction was made between them, then D-dimer and fibrinogen levels were found to be higher in patients hospitalized in ICU (respective p values: 0.003, 0.034 and 0.007). Even though these results are similar to the results of other studies, in the regression analysis, it was found that no other parameters than angiopoietin-2 level were effective in predicting ICU hospitalization at the first presentation to the hospital [9]. Another study analyzing the correlation of the angiopoietin-2 level with the progression of COVID-19 demonstrates that the angiopoietin-2 level is an early and helpful biomarker in predicting the progression of the COVID-19 [10]. Still another study showed that angiopoietin-2 levels of the critically ill ICU patients measured both at the presentation and at 10-14 days of hospitalization were significantly higher relative to the control group, and additionally, when the patients were divided into two groups with one group comprising the patients who recovered and the other consisting of the patients who did not recover, it was established that angiopoietin-2 levels were high in the group of the patients who did not recover [11]. Contrary to the literature, our study found no difference between the patients who died and those who survived in terms of angiopoietin-2 levels measured at the time of presentation to the hospital. Yet another study conducted in our country, investigated the association of serum surfactant-D and angiopoietin-2 levels for predicting the severity of COVID-19 and concluded that both of these markers were high in severe COVID-19 cases [12].

Values such as the neutrophil/lymphocyte (N/L) ratio [13], presence of lymphopenia [14], high CRP levels [15], high ferritin levels [16] and LDH levels [17] were investigated as prognostic factors in our study. LDH, urea, N/L ratio and hemoglobin levels of the patients who died were relatively higher. Patients with high levels of LDH, CRP and ferritin, and having hypoalbuminemia and lymphopenia were shown to have longer periods of hospitalization. Although these parameters were demonstrated to be helpful in determining the disease prognosis, none of them were found to be effective in the prediction of ICU hospitalization. In the literature, there are studies showing that angiopoietin-2 level can be used as a prognostic factor in the patients with sepsis, acute respiratory distress syndrome (ARDS), preeclampsia, acute pulmonary damage and hypertension [18-22]. Although it has been shown through various studies that angiopoietin-2 level could be used for determining the prognosis of COVID-19, our study suggested that it could be an efficacious parameter in predicting their hospitalization in non-ICU or ICU at the time of presentation to the hospital.

Conclusions

We conclude that the angiopoietin-2 level can be used for determining the place of hospitalization of the COVID-19 patients, predicting the disease prognosis, and determining the thromboembolic complications such as pulmonary embolism. The use of ACE inhibitors and anticoagulants in the early stage of the disease may contribute positively to the prognosis of the disease.

Author contributions

All authors contributed to the design of the study, data collection, statistical analysis and final version of the paper.

Funding sources

This study was supported by the Health Science University Antalya Education and Research Hospital.

Ethical approval

This study was approved by the institutional review board of the Health Science University Antalya Education and Research Hospital ethics committee (079/2021).

References

1. Akpinar S (2020) COVID-19 related coagulopathy. Namık Kemal Medical Journal 8: 564-569. [Article in Turkish].
2. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Moch H (2020) Endothelial cell infection and endotheliitis in COVID-19. Lancet 395: 1417-1418. doi: 10.1016/S0140-6736(20)30937-5.
3. Turkish Republic Ministry of Health (2021) COVID-19 adult patient treatment guide. Turkish Republic Ministry of Health Public Health Directorate.
4. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. JAMA 323: 1239. doi: 10.1001/jama.2020.2648.
5. Jain V, Yuan JM (2020) Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health 65: 533-546. doi: 10.1007/s00038-020-01390-7.
6. Monteil V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Pozo CHD, Prosper F, Romero JP, Wirnsberger G, Zhang H, Slutsky A, Conder R, Montserrat N, Mirazimi A, Penninger JM (2020) Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 181: 905-913. doi: 10.1016/j.cell.2020.04.004.
7. Qanadli SD, Beigelman-Aubry C, Rotzinger DC (2020) Vascular changes detected with thoracic CT in coronavirus disease (COVID-19) might be significant determinants for accurate diagnosis and optimal patient management. AJR Am J Roentgenol 7: W15. doi: 10.2214/AJR.20.23185.
8. Smadja, DM, Guerin CL, Chocron R, Yatim N, Boussier J, Gendron N, Diehl JL (2020) Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. Angiogenesis 23: 611-620. doi: 10.1007/s10456-020-09730-0.
9. Zeng F, Li L, Zeng J, Deng Y, Huang H, Chen B, Deng G (2020) Can we predict the severity of coronavirus disease 2019 with a routine blood test. Pol Arch Intern Med 130: 400-406. doi: 10.20452/pamw.15331.
10. Villa E, Critelli R, Lasagni S, Melegari A, Curatolo A, Celsa C, Errico A (2021) Dynamic angiopoietin-2 assessment predicts survival and chronic course in hospitalized patients with COVID-19. Blood advances 5: 662-673. doi: 10.1182/bloodadvances.2020003736.
11. Hultström M, Fromell K, Larsson A, Quaggin SE, Betsholtz C, Frithiof R, Jeansson M (2022) Elevated angiopoietin-2 inhibits thrombomodulin-mediated anticoagulation in critically ill COVID-19 patients. Biomedicines 10: 1333. doi: 10.3390/biomedicines10061333.
12. Alay H, Laloglu E (2021) The role of angiopoietin-2 and surfactant protein-D levels in SARS-CoV-2-related lung injury: a prospective, observational, cohort study. J Med Vir 93: 6008-6015. doi: 10.1002/jmv.27184.
13. Jimeno S, Ventura PS, Castellano JM, García-Adasme SI, Miranda M, Touza P, López-Escobar A (2021) Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. Eur J Clin Invest 51: e13404. doi: 10.1111/eci.13404.
14. Ünver T, Demirköse M, Bilek HC (2021) Diagnostic utility and prognostic value of basic laboratory parameters in COVID-19. Klimik Journal 34: 174-181. doi: 10.36519/kd.2021.3666.
15. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z (2020) Plasma CRP level is positively associated with the severity of COVID-19. Annals of Clinical Microbiology and Antimicrobials 19: 1-7. doi: 10.1186/s12941-020-00362-2.
16. Vargas M, Cortés RC (2020) Ferritin levels and COVID-19. Rev Panam Salud Publica 44: e72. doi: 10.26633/RPSP.2020.72.
17. 17. Li C, Ye J, Chen Q, Hu W, Wang L, Fan Y, Lu H (2020) Elevated lactate dehydrogenase (LDH) level as an independent risk factor for the severity and mortality of COVID-19. Aging (Albany NY) 12: 15670. doi: 10.18632/aging.103770.
18. Orfanos SE, Kotanidou A, Glynos C, Athanasiou C, Tsigkos S, Dimopoulou I, Roussos C (2007) Angiopoietin-2 is increased in severe sepsis: correlation with inflammatory mediators. Crit Care Med 35: 199-206. doi: 10.1097/01.CCM.0000251640.77679.D7.
19. Su L, Zhai R, Sheu CC, Gallagher DC, Gong MN, Tejera P, Christiani DC (2009) Genetic variants in the angiopoietin-2 gene are associated with increased risk of ARDS. Intensive Care Med 35: 1024-1030. doi: 10.1007/s00134-009-1413-8.
20. Boztosun A, Deveci K, Atılgan R, Söylemez M, Yanık A, Müderris I (2012) Angiopoietin-related growth factor level in preeclampsia. Cumhuriyet Med J 34: 60-65. doi: 10.7197/1305-0028.1267.
21. Calfee CS, Gallagher D, Abbott J, Thompson BT, Matthay MA, NHLBI ARDS Network (2012) Plasma angiopoietin-2 in clinical acute lung injury: prognostic and pathogenetic significance. Critical Care Med 40: 1731. doi: 10.1097/CCM.0b013e3182451c87.
22. Patel JV, Lim HS, Varughes GI, Hughes EA, Lip GY (2008) Angiopoietin-2 levels as a biomarker of cardiovascular risk in patients with hypertension. Ann Med 40: 215-222. doi: 10.1080/07853890701779586.

Corresponding author

Ayşegül Seremet Keskin, MD
University of Health Sciences Antalya Training and Research Hospital,
Infectious Disease and Clinical Microbiology, Antalya, Turkey.
Tel: +905333147871
Fax: +902422494462
Email: aseremetkeskin@yahoo.com

Conflict of interests: No conflict of interests is declared.