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CLINICAL STUDY

The ability of D-dimer, albumin, and D-Dimer/albumin ratio to predict in-hospital mortality and intensive care unit admission in COVID-19 patients admitted to the emergency department

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ABSTRACT

OBJECTIVES: COVID-19 can also cause multi-organ failure or severe pneumonia. Therefore, new biomarkers are being investigated for rapid diagnosis, early treatment and reduced mortality rates. In this study, D-dimer and albumin were looked at from a different perspective.

BACKGROUND: We think that D-dimer/Albumin ratio (DAR), D-dimer and albumin may be parameters that can be used to predict in-hospital mortality and intensive care unit admission in COVID-19 patients.

METHODS: The patients included in the study were divided into 2 groups according to their hospitalization status in the service and intensive care unit. These two groups were compared in terms of DAR, other laboratory data and in-hospital mortality.

RESULTS: The primary findings we obtained are as follows: (1) DAR and D-dimer values are higher in patients who died in-hospital, and albumin values are lower than those who survived; (2) D-dimer and DAR median values are significantly higher in the intensive care group than in the service group. Albumin was significantly lower in the intensive care group; (3) D-dimer, albumin and DAR predicting in-hospital mortality, respectively: D-Dimer's sensitivity 56 % and specificity 57 %, albumin's sensitivity 70 % and specificity 53 %, DAR's sensitivity 56 %, specificity is 58 %; (4) The parameter with the highest predictive power for intensive care admission is albumin.

CONCLUSION: Although albumin had the highest sensitivity values in determining mortality or predicting intensive care admission in our study, we think that D-dimer and DAR may be other parameters to be used to predict intensive care admission and in-hospital mortality *(Tab. 5, Fig. 2, Ref. 19)*. Text in PDF *www.elis.sk*

KEY WORDS**:** COVID-19, albumin, D-dimer, mortality, D-dimer/albumin.

Introductıon

COVID-19, defined by the World Health Organization as Coronavirus Disease 2019 (COVID-19) in February 2020, is a pandemic associated with a high risk of morbidity and mortality (1). COVID-19 may be asymptomatic or cause multi-organ failure or severe pneumonia (2). Therefore, there is a need for methods that can be applied quickly and easily to predict the prognosis of COVID-19 patients in emergency services. In this context, D-dimer/Albumin ratio, D-dimer, and albumin may be parameters that should be investigated.

Albumin is an acute phase reactant with antioxidant properties. A study demonstrated low albumin levels in 75.8 % of COVID-19 patients admitted to the emergency department (3). Under normal physiological conditions, albumin provides an abundant source of free thiols that can scavenge reactive oxidant species (ROS). Under oxidative stress conditions, the only free thiol (Cys34) in albumin can undergo oxidation. In this case, the antioxidant characteristic of albumin is impaired, resulting in irreversible cell and tissue damage (4).

COVID-19 causes hypercoagulation by causing endothelial damage (5). Although hypercoagulation is associated with a poor prognosis in the course of COVID-19, one of the most significant markers of hypercoagulation is D-dimer levels. Studies have revealed that D-dimer levels are a strong marker in determining mortality (6). Besides, many studies have indicated that high D-dimer, lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), and procalcitonin (PCT) levels are an indicator of a more severe clinic (7, 8). Since the disease has many unknown aspects, there are difficulties in its control. Therefore, new biomarkers are constantly being sought for rapid diagnosis, early treatment, reduced mortality rates, and economic gains. For all these reasons, D-dimer and albumin, examined in routine laboratories, were considered from a different perspective in this study.

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Methods

Study design and settings

In this retrospective study, 588 patients admitted to the emergency department and hospitalized between March 2020 and January 2022 were included. Local Ethics Committee approval (Decree No 2022/08-93) was obtained from Erzurum Regional Training and Research Hospital for the study, and the study was performed per the ethical standards specified in the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived as the data used in the study were anonymous. The criteria for inclusion in the study were to be diagnosed with COVID-19 by PCR test and to be older than 18 years of age. Pregnant women, pre-arrest cases, those younger than 18, and those with missing baseline data were excluded. A demographic information form was created for each patient, which was recorded by the physician responsible for the patient.

The Demographic Information Form contains various information about the individuals who participated in the study. In these forms, parameters such as participants' age, gender, length of hospital stay, comorbid diseases (diabetes, hypertension, pulmonary diseases, coronary artery disease, and other diseases), peripheral blood parameters (CRP, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase) (ALT), D-dimer, albumin), and mortality within 28 days were included. The D-dimer/albumin ratio (DAR) was obtained by dividing the D-dimer level by the albumin level. The study's primary aim was to estimate in-hospital mortality using DAR and determine whether DAR was a more accurate parameter than D-dimer and albumin levels. Besides, the patients were divided into two groups according to their hospitalization status in the ward and intensive care unit. These two groups were compared regarding DAR, other laboratory data, and in-hospital mortality.

Data acquisition

Demographic data, comorbid diseases, and laboratory tests of the patients were recorded by scanning the system data. All the recorded data of the patients belong to the examinations performed on the day the patients were admitted to the ward or intensive care unit and the next day. Different observers checked the data. Before analyzing the data, a definitive outcome (discharge, ongoing treatment, or death) was determined for all patients.

Statistical analysis

SPSS 22.00 package program was used in the analysis of the study data. Before analyzing the data, the assumptions necessary to run the parametric tests were checked.

Tab. 1. Demographic data.

Participants	588 (100%)
Age	71 (61–78)
Sex	
Male	335 (57)
Female	253 (43)
Laboratory findings	
CRP (mg/L)	62 (21.75–131)
D–dimer (ng/mL)	1070 (534–3202)
BUN (mg/dl)	25 (17–42)
Creatinine (mg/dl)	1.1 (0.82–1.60)
ALT (U/L)	29.5 (20–50)
AST (U/L)	44.50 (29–67.50)
Albumin (g/L)	38 (35–42)
Comorbid diseases	
DM	194 (33)
HT	315 (53.6)
PD	109 (18.5)
CAD	131 (22.3)
Others	79 (13.4)
HLS (day)	12 (8–21)
Place of hospitalization	
ICU	480 (81.6)
S	108 (18.4)
In-Hospital Death	
Surviving	309 (52.6)
Non-Surviving	279 (47.4)

CRP – C-reactive protein, BUN – blood urea nitrogen, ALT – alanine amino transferase, AST – aspartate amino transferase, DM – diabetes mellitus, HT – hypertension, PD – pulmonary disease, CAD – coronary artery disease, HLS – Hospital length of stay, ICU – intensive care unit, S – service

Tab. 2. Analysis of Data According to In-Hospital Death.

	Non-Surviving (279)	Surviving (309)	p
Sex[a]			
Female, n (%)	111 (39.8)	142 (46)	0.07
Male, n (%)	168 (60.2)	167 (54)	
Place of hospitalizationa			
ICU, n (%)	276 (98.9)	204 (66)	<0.00
S, n (%)	3 (1.1)	105 (34)	
Age[b]	76 (68–82)	66 (57–75)	<0.00
HLS[b] (day)	11 (9–23)	14 (6–18)	<0.00
DM[a], n (%)	104 (33.3)	90 (29.1)	0.02
HT[a], n (%)	161 (57.7)	154 (49.8)	0.03
PD[a], n (%)	52 (18.6)	57 (18.4)	0.51
CAD[a], n (%)	75 (26.9)	56 (18.1)	<0.00
Others[a], n (%)	49 (17.6)	30 (9.7)	<0.00
CRP[b] (mg/L)	81 (33.80–146)	46 (12.41–107,50)	<0.00
D-dimer[b] (ng/mL)	1226 (650–3410)	841 (470–2744)	<0.00
BUNb (mg/dl)	32 (22–51)	21 (16–31)	<0.00
Creatinine[b] (mg/dl)	0.93 (1–1.97)	1.30 (0.80–1.30)	<0.00
ALT[b] (U/L)	29 (20–51)	30 (20.50–50)	0.81
AST[b] (U/L)	48 (32–79)	41 (28–60)	<0.00
Albumin[b] (g/L)	37 (32–40)	40 (36–43)	<0.00
DAR	35.93 (16.87–96.42)	21.81 (10.86–69.42)	<0.00

[a] – chi-square test, data are given as frequency and percentage in parentheses; [b] – Mann-Whitney U Test, data are given as median and in parentheses with a range of 25 % to 75 %

HLS – Hospital length of stay, DM – diabetes mellitus; HT – hypertension; PD – pulmonary disease, CAD – coronary artery disease, CRP – C-reactive protein, BUN – blood urea nitrogen, ALT – alanine amino transferase, AST – aspartate amino transferase, DAR – D-dimer albumin ratio

Kolmogorov-Smirnov test was used in addition to histograms and standardized Skewness and Kurtosis values to test the normality of the data. As a result of the normality analysis, nonparametric tests were applied since the data did not show normal distribution in the groups, and the data were presented with median and 25–75 % quartiles. Inter-group differences were investigated using the Mann-Whitney U test. Intra-group comparisons of categorical variables were made using the Chi-Square, Fisher's exact test.

Tab. 3. Analysis of data according to hospital stay.

	ICU (480)	S (108)	p
Sex[a]			
Female, n (%)	196 (40.8)	57 (52.8)	0.03
Male, n (%)	284 (59.2)	51 (47.2)	
Age[b]	72 (63–79)	66 (58–72)	<0.00
HLS[b] (day)	12 (7–21)	13 (9–20)	0.74
DM[a], n (%)	169 (35.2)	25 (23.1)	0.01
HT[a], n (%)	259 (54)	56 (51.5)	0.74
PD[a], n (%)	84 (17.5)	25 (23.1)	0.17
CAD[a], n (%)	116 (24.2)	15 (13.9)	0.02
Others[a], n (%)	74 (15.4)	5 (4,6)	<0.00
CRP[b] (mg/L)	74,50 (23–140)	40 (11–83)	<0.00
D-dimer[b] (ng/mL)	1135 (571.50–3284)	756 (471–2693)	0.01
BUN[b] (mg/dl)	28 (19.45)	17 (15–27)	<0.00
Creatinine[b] (mg/dl)	1,17 (0.9 –1.71)	0,90 (0.7–1.1)	<0.00
ALT[b] (U/L)	29 (20–53)	30 (21–45)	0.38
AST[b] (U/L)	46.50 (31–74)	34 (25–51)	<0.00
Albumin[b] (g/L)	38 (34–41)	41 (37–44)	<0.00
DAR	29.82 (14.46)	17.01 (89.56)	<0.00

HLS – Hospital length of stay, DM – diabetes mellitus, HT – hypertension, PD – pulmonary disease, CAD – coronary artery disease, CRP – C-reactive protein, BUN – blood urea nitrogen, ALT –alanine amino transferase, AST – aspartate amino transferase, DAR – D-dimer albumin ratio, ICU – intensive care unit, S–service

Tab. 4. Diagnostic value of D-dimer, albumin, and DAR in predicting in-hospital death.

		D-Dimer (ng/mL)	Albumin (g/L)	DAR
In-Hospital Death	AUC (95% CI)	0.578 (0.532–0.625)	0,658 (0.614–0.702)	0,593 (0.547–0.639)
	p	0.001	0.000	0.000
	Cut-off level	>1072.50	<39.50	>27.83
	Sensitivity	56%	70%	56%
	Specificity	57%	53%	58%
	PPV	54%	57%	55%
	NPV	58%	66%	60%

CI – Confidence interval, AUC – Area under the curve, PPV – Positive predictive value, NPV – Negative predictive value

Tab. 5. Diagnostic value of D-dimer, albumin and DAR in predicting intensive care admission.

		D-Dimer	Albumin	DAR
Intensive care admission	AUC (95% CI)	0.572 (0.510–0.635)	0.677 (0.612–0.723)	0.589 (0.527–0.651)
	p	0.02	<0.00	<0.00
	Cut-off level	>923	<39.50	>23.87
	Sensitivity	50%	62%	50%
	Specificity	60%	60%	60%
	PPV	84%	87%	84%
	NPV	21%	26%	21%

CI – Confidence interval, AUC – Area under the curve, PPV – Positive predictive value, NPV – Negative predictive value

ROC analysis was performed to determine the most appropriate cut-off point for D-Dimer, Albumin, and DAR values in in-hospital mortality and additionally to calculate sensitivity, specificity, and negative and positive predictive values. Youden's index (sensitivity + 1-specificity) was used for optimum threshold levels of biochemical parameters. The statistical significance level was determined as $p < 0.05$.

Results

A total of 641 patients admitted to the emergency department suspected of COVID-19 and whose PCR test was positive were determined for the study. 8 of 641 patients were excluded since they wanted to be discharged from the hospital against medical advice, 11 because they were referred to another hospital, and 34 because at least one of the baseline parameters was missing. The remaining 588 patients were enrolled. Of the 588 patients included in the study, 335 (57 %) were male, and 253 (43 %) were female. Details of the participants, such as age, duration of hospital stay, laboratory findings, comorbidities, hospitalization in the service or intensive care unit, and in-hospital mortality, are presented in Table 1.

A Chi-square test was performed to determine the association between in-hospital mortality status with gender and hospitalization in the intensive care unit or service. As a result of the analysis, a statistically significant relationship was determined between the variables ($p = 0.07$ and $p < 0.00$, respectively). The median values of D-dimer, BUN, AST, and DAR of the patients in the deceased group were statistically significantly higher than those in the surviving group. Detailed intra-group comparisons according to in-hospital mortality are summarized in Table 2.

When the data were evaluated according to the hospital stay, the median D-dimer value was significantly higher in the intensive care group (ICU) than in the ward (W) group (ICU: 1135 (571.50–3284); W: 756 (471–2693); $p = 0.01$). A similar condition was valid for BUN ($p < 0.00$), creatinine ($p < 0.00$), AST ($p < 0.00$), and DAR ($p < 0.00$), and these variables were significantly higher in the ICU group. Albumin median values were significantly lower in the ICU group (ICU: 38 (34–-41); W: 41 (37–44); $p = 0.01$). Other intra-group comparisons are detailed in Table 3.

ROC analysis was performed to determine the predictive power of D-dimer, albumin, and DAR for in-hospital mortality. As a result of the analysis, the AUC value of D-Dimer was 0.578, the sensitivity value was 56 %, and the specificity value was 57 %. The AUC of albumin was 0.658, the sensitivity was 70 %, and the specificity was 53 %. Finally, the AUC of DAR was 0.593, and when the cut-off value of

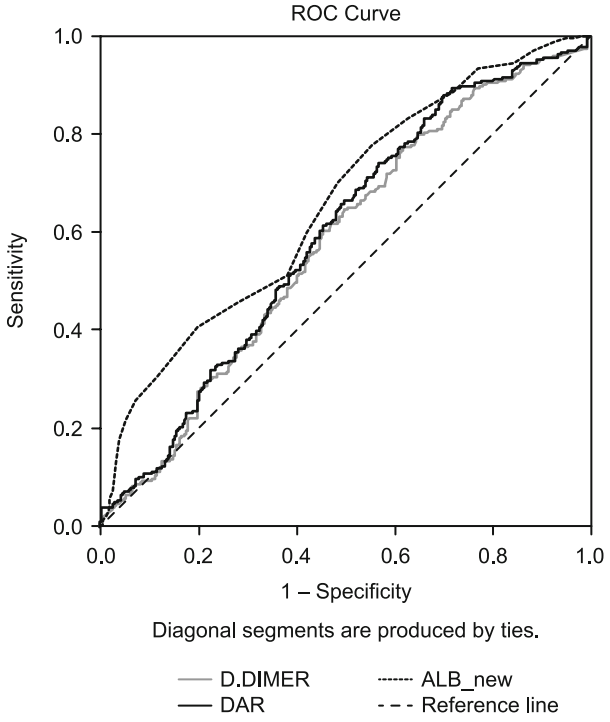

Fig. 1. ROC analysis to determine the predictive power of D-dimer, Albumin, and DAR for in-hospital mortality.

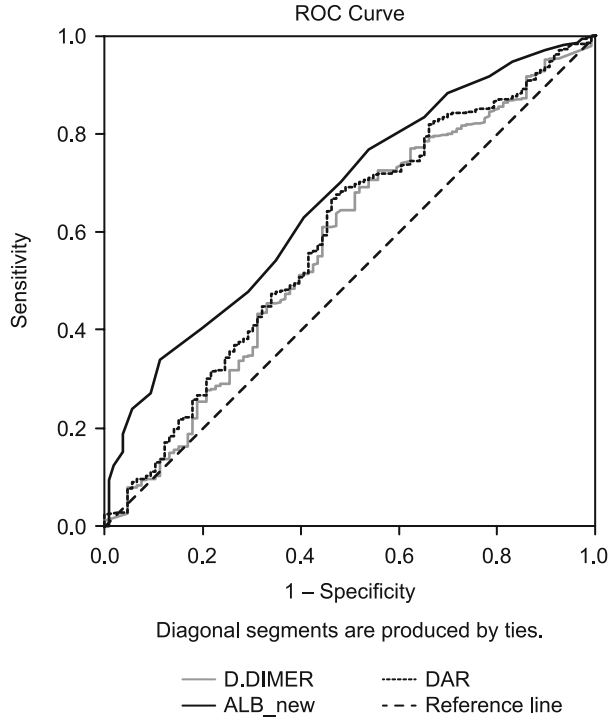

Fig. 2. ROC analysis to determine the predictive power of D-dimer, Albumin, and DAR for ICU admission.

27.83 was determined, 56 % sensitivity and 58 % specificity were achieved. Detailed results of ROC analysis are presented in Table 4 and Figure 1.

Finally, the predictive power of D-dimer, Albumin, and DAR for ICU admission was examined. As a result of the analysis, albumin had the highest predictive power for ICU admission among these three parameters (Tab. 5, Fig. 2).

Discussion

The present study investigated the ability of D-dimer, albumin, and DAR to predict in-hospital mortality and ICU admission in COVID 19 patients.

As a result of the analyzes we performed in the study, it is thought that D-dimer is a parameter that can be used to predict intensive care admission and in-hospital mortality. D-Dimer is a fibrin degradation product, which is considered a hypercoagulant marker (9). Studies investigating the relationship between D-dimer levels and mortality in COVID-19 patients have reported that high D-dimer levels are common and associated with mortality (10, 11). There are some possible reasons for the association between increased mortality and high D-dimer in COVID-19. COVID-19 causes hypercoagulation (12), and hypercoagulation is one of the main risk factors for intensive care therapy, mechanical ventilation, and death in critically ill COVID-19 patients. In a study, vascular occlusion and pulmonary intravascular coagulation were reported as common findings in autopsies of patients who died due to COVID-19 (13). The same study also demonstrated that COVID-19 leads to an increased risk of arterial thromboses such as myocardial infarction and ischemic stroke. D-dimer levels are also increased in hypercoagulable states (14). Also, the risk of microthrombus formation increases in COVID-19 patients due to hypercoagulation, exposure to more invasive procedures, more comorbid diseases, and more inactivity (11). Because of all these conditions, high D-dimer levels in COVID-19 patients may be associated with high mortality and intensive care treatment.

Another parameter examined in our study was albumin. Our study indicates that albumin, like D-dimer, can be used to predict ICU admission and in-hospital mortality. When the reasons for the inverse correlation between hypoalbuminemia and increased mortality are examined, the first one is that albumin (4), which has antioxidant and anti-inflammatory properties, may protect against the cytokine storm and subsequent organ failure seen in COVID-19. In this context, low albumin levels may be associated with increased mortality. The second reason is that albumin inhibits platelet activation and coagulation (15). Therefore, hypoalbuminemia causes hypercoagulation. The negative effect of hypoalbuminemia on coagulation activation may explain the poor survival. The literature indicates that hypoalbuminemia is associated with increased arterial and venous thrombosis risk in different clinical situations (16, 17). Besides, a recent study has demonstrated that albumin infusion can be used to improve hemodynamics and decrease D-dimer plasma level, which is the main marker of thromboembolism, in critically ill COVID-19 patients (18).

The negative effect of hypoalbuminemia on coagulation activation suggests an inverse relationship between D-dimer and albumin levels. Our study observed high D-dimer and low albumin levels in both patient groups who died and patients hospitalized in the intensive care unit. Hence, D-dimer/Albumin ratio was also examined in our study. According to the result of the ROC analysis performed to calculate the power of DAR to predict ICU admission and in-hospital mortality in COVID-19 patients, the AUC value was 0.593, and when the cut-off value of 27.83 was determined, it had 56 % sensitivity, 58 % specificity, 55 % PPD and 60 % NPD. Considering the literature, only one article has investigated the ability of DAR to predict mortality in COVID-19 patients. AUC and Odds ratio values obtained using DAR to predict COVID-19 mortality in that study on DAR were higher than those obtained using any other parameter (D-dimer, albumin, and Fibrinogen/Albumin ratio) (19). In our study, the highest AUC value among D-dimer, albumin, and DAR was determined for albumin. Besides, the highest sensitivity values were observed for albumin in detecting mortality or predicting admission to the intensive care unit.

Conclusion

The present study reports that patients with Covid-19 have decreased serum albumin levels and increased D-dimer levels, which may pave the way for poor survival. Although albumin had the highest sensitivity values in determining mortality or predicting intensive care admission in our study, we think that D-dimer and DAR may be other parameters to be used to predict intensive care admission and in-hospital mortality. In conclusion, no test or method should be used alone to determine the prognosis of patients. It would be more accurate to evaluate patients by considering similar tests and clinical manifestations.

References

1. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med 2020; 382: 102.

2. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395 (10223): 497–506.

3. Cheng MP, Papenburg J, Desjardins M et al. Diagnostic Testing for Severe Acute Respiratory Syndrome–Related Coronavirus 2. Ann Intern Med 2020; 172 (11): 726–734.

4. Violi F, Cangemi R, Romiti GF et al. Is albumin predictor of mortality in COVID-19? Antioxidants & redox signaling 2020.

5. Küçükceran K, Ayrancı MK. The Effect of a Pandemic on Computed Tomography Pulmonary Angiography Results and Utilize in the Emergency Department. Clin Exp Health Sci 2022; 12 (2): 280–284.

6. Saygıdeğer Y, Candevir AU, Özkan H, Kömür S, DEMİR MS. Covid-19 hastalarında Eozinofil/Lenfosit ve D-Dimer/Fibrinojen oranlarının hastalık seyri ile ilişkisi. Mersin Üniversitesi Sağlık Bilimleri Dergisi 2021; 14 (2): 307–319.

7. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta 2020; 510: 475–482.

8. Kavsak PA, de Wit K, Worster A. Emerging key laboratory tests for patients with COVID-19. Clin Biochem 2020; 81: 13–14.

9. Olson JD. D-dimer: an overview of hemostasis and fibrinolysis, assays, and clinical applications. Adv Clin Chem 2015; 69: 1–46.

10. Zhou F, Yu T, Du R 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 (10229): 1054–1062.

11. Zhang L, Yan X, Fan Q et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020; 18 (6): 1324–1329.

12. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. Thromb Haemost 2020; 18 (7): 1559–1561.

13. Gerotziafas GT, Catalano M, Colgan MP et al. Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb Haemost 2020; 120 (12):1 597.

14. Danese E, Montagnana M, Cervellin G, Lippi G. Hypercoagulability, D-dimer and atrial fibrillation: an overview of biological and clinical evidence. Ann Med 2014; 46 (6): 364–71.

15. Basili S, Carnevale R, Nocella C et al. Serum Albumin Is Inversely Associated With Portal Vein Thrombosis in Cirrhosis. Hepatol Commun 2019; 3: 504–512.

16. Chi G, Gibson CM, Liu Y et al. Inverse relationship of serum albumin to the risk of venous thromboembolism among acutely ill hospitalized patients: Analysis from the APEX trial. Am J Hematol 2019; 94: 21–28.

17. Ronit A, Kirkegaard-Klitbo DM, Dohlmann TL et al. Plasma Albumin and Incident Cardiovascular Disease: Results From the CGPS and an Updated Meta-Analysis. Arterioscler Thromb Vasc Biol 2020; 40: 473–482.

18. Ramadori G. Albumin infusion in critically Ill COVID-19 patients: hemodilution and anticoagulation. Internat J Mol Sci 2021; 22 (13): 7126.

19. Küçükceran K, Ayranci MK, Girişgin AS, Koçak S. Predictive value of D-dimer/albumin ratio and fibrinogen/albumin ratio for in-hospital mortality in patients with COVID-19. Internat J Clin Pract 2021; 75 (7): e14263.

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