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RESEARCH ARTICLE

New Prognostic Markers İn Acute Cholangitis Patients With COVID-19

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Abstract

Introduction: COVID-19 is the cause of a pandemic with high mortality rates that affect the entire world. In the present study, the importance of blood parameters was investigated in predicting the severity of the disease in patients diagnosed with both covid19 and acute cholangitis simultaneously. **Methods:** A total of 37 patient groups (n=37) who were diagnosed with both COVID-19 and acute cholangitis, a total of 38 patients in the control group (n=38) infected with Covid 19 and with no comorbidity, and 68 completely healthy control group (n) =68) were included in the study retrospectively and simultaneously. Those who had positive RT-PCR (Real-Time Polymerized Chain Reaction) test results were included in the study. The results of routine biochemistry, serology, hormone, and blood gas tests of the patients were compared with those of the control group. The Tokyo 2018 Criteria (TG18) were used in the diagnosis of acute cholangitis and disease severity grading. **Results:** The WBC(white blood cell), CRP(c-reactive protein), N/L Ratio(-neutrophile/lynfosite ratio), AST(Aspartat Aminotransferaz), ALT(Alanin Aminotransferaz), LDH(Laktate dehidrogenaz), GGT(Gama glutamil transferaz), ALP(alkalen fosfataz) total bilirubin, and direct bilirubin levels were higher in the patient group at statistically significant levels than in the control group ($p<0.001$). The albumin levels were lower than in the control group ($p<0.001$). Total bilirubin/lymphocyte, GGT/lymphocyte, ALP/lymphocyte ratios, and D-dimer parameters had the highest AUC (Area Under the Curve) values in ROC analysis (0.984, 0.924, 0.923, and 0.897, respectively). **Conclusion:** Total bilirubin/lymphocyte, GGT/lymphocyte, and ALP/lymphocyte ratios may be useful in predicting the severity of the disease in acute cholangitis cases developing with COVID-19 simultaneously.

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Introduction

The COVID-19 disease pandemic started to appear in China/Wuhan at the end of 2019 (COVID-19). Many people died since then [1]. With its high contagiousness, people had to be hospitalized and live in long-term quarantine. The virus still continues its disease-causing effects by undergoing various mutations. It was also given in many studies that COVID-19 and its variants cause high morbidity and mortality.[2-4] Studies are reporting the co-existence of COVID-19 and acute cholangitis.[5-6]

The symptoms of COVID-19 involve respiratory symptoms such as cough, fever, and shortness of breath. Many studies examined the effects of COVID-19 on other organs. Gastrointestinal symptoms such as diarrhea, vomiting, and hepatobiliary abnormalities were noted in patients with COVID-19.[7] The number of studies in which acute cholangitis accompanied by jaundice and COVID-19 coexistence is low.

In the present study, the purpose was to analyze and examine the effects of the development of acute cholangitis with the co-existence of COVID-19 on the clinical course of the disease, mortality, clinical classification scores, and biochemical parameters in the pandemic in which the virus, which is the causative agent of COVID-19, played a role in its etiology.

Materials and methods:

Study design and participants

The present study was designed retrospectively and approved by Ankara City Hospital/Turkey Ethics Committee.[2021-2047] The cases that were diagnosed with simultaneous COVID-19 and acute cholangitis in Ankara City Hospital between April 1, 2020, and September 01, 2021, were included in the study.

The demographic, clinical, laboratory data and radiological findings of the patients were obtained from the electronic medical records and hospital computer case record forms. The COVID-19 and concurrent cholangitis cases (n=37) were evaluated according to TG18(1) as mild, moderate, and severe. Also, the patients were divided into 3 groups as those who were infected with COVID-19 but without any comorbidity (n=38), the control group, and the completely healthy (n=68) control group. The baseline values of the patients at the time of admission were recorded by using the computer follow-up program, and intergroup comparisons were made. The albumin, total protein, glucose, urea, creatinine, ferritin, ALT, AST, ALP, GGT, LDH, total bilirubin, conjugated bilirubin, amylase, lipase, CK (creatinine kinase), CRP, procalcitonin, D-dimer, troponin, complete blood count, and N/L ratios were analyzed in all groups.

The demographic data of the patients, as well as clinical, laboratory, and radiological findings were evaluated to evaluate the acute cholangitis criteria. The severity of cholangitis, length of hospital stay, and mortality rates were examined in each category. The PCR+ test requirement was sought for COVID-19 contamination, and white blood test results were obtained for these patients. The TG18 was used for the diagnosis of cholangitis and grading of disease severity.

Diagnostic criteria:

Oro/nasopharyngeal swab samples for RT-PCR and routine blood tests were obtained from the patients for the diagnosis of COVID-19. Those with fever and respiratory symptoms according to the WHO (World Health Organization)Interim Guideline for the diagnosis of COVID-19, pneumonia findings on Thoracic CT, or clinical signs according to positive COVID-19 PCR results were also included.

The diagnosis of acute cholangitis was confirmed with the TG18 Criteria. For the diagnosis of the disease; *PART-A:* Systemic inflammation (fever; >38oCelsius, or WBC<4 or >10x1.000/ml and/or CRP>=1 mg/dL with laboratory data of inflammatory response). *PART-B:* Total bilirubin >=2 mg/dL. As abnormal liver enzyme values; ALP, GGT, AST, and ALT values of 1.5xSTD were accepted for the evaluation of cholestasis. PART-C: Biliary dilatation (abdominal CT, ERCP, MRCP, USG results) and biliary dilatation etiology (stenosis, stone, stent, carcinoma) were evaluated in the imaging evaluation.

Cardiovascular dyspnea, hypotension, dopamine 5 microgram/kg or any dose, noradrenali-

ne use), neurological dysfunction (blurring of consciousness), respiratory dysfunction (PaO2/FiO2 <300), renal dysfunction (creatinine>2.0mg/dL), hepatic dysfunction (PT-INR>1.5), hematological dysfunction (PLT<100.000/mm3) abnormal WBC (>12.000/mm3 or<4000mm3, high fever(>=39oCelsius), age (>=75) parameters were used for the grading of the severity of acute cholangitis disease.

Among the diagnostic criteria of the disease, in the criteria of systemic inflammation response (PART A), only other systemic inflammation responses without using fever>38oCelsius criteria, WBC, and/or CRP counts were used. Those who could be diagnosed with acute cholangitis without using fever criteria at the beginning were included in this study. Also, fever criteria were not used in the grading.

Statistical Analyses

The Statistical Package for Social Sciences for Windows, Version 22 (IBM, Armonk, NY, USA) was used in the statistical analyses of the study data. The Shapiro-Wilk test was used for the normality analysis of the variables. Descriptive statistical analysis was made by using the mean ± SD for normally distributed variables and median (interquartile range (IQR)) for non-normally distributed variables. The demographic and laboratory data were compared among the groups by using the Student's t-test for parametric variables and the Mann-Whitney U-test for non-parametric variables. The comparisons for categorical variables were made by using the Chi-Square test or Fisher's Exact test. Receiver Operation Characteristic (ROC) was constructed to analyze the effectiveness of disease severity. The optimal cut-off values of the D-dimer, Total bilirubin/Lymphocyte, GGT/ Lymphocyte, ALP/ Lymphocyte, WBC, and CRP were calculated by using the ROC Analysis. Statistical significance was taken as $p < 0.05$.

Results

The study included 37 hospitalized patients who were diagnosed with COVID-19 according to the WHO Criteria and also diagnosed with acute cholangitis, 38 patients who were infected with COVID-19 but without comorbidities, and a healthy control group of 68 participants. The demographic data of all cases that were included in the study, comorbidities, complaints of admission to the emergency department, and the degree of acute cholangitis according to Tokyo 2018 Criteria are given in Table 1.

Abdominal pain was the most common symptom in the acute cholangitis group at 3 different severities at admission to the hospital (p=0.686) along with jaundice (p=0.225). The data of the patients with comorbidities are given in Table 1. The most common comorbidities were cancer, systemic hypertension, and diabetes mellitus, respectively.

The hemogram and biochemical parameters and statistical analysis of the groups are given in Table 2. The WBC, CRP, N/L ratio, albumin, AST, ALT, LDH, GGT, ALP, total bilirubin, and direct bilirubin levels were higher in the patient group at statistically significant levels than in the control group (p<0.001). The albumin levels were found to be low (p<0.001) (Figure 1).

The ROC analysis of the routine blood parameters in predicting the prognosis in patients diagnosed with CoVID-19 and acute cholangitis:

The ROC Curve Analysis was used to determine the efficacy of various parameters in predicting the prognosis in the group diagnosed with COVID-19 and acute cholangitis (Figure 2). COVID-19 and acute cholangitis group was defined as positive, and the COVID-19 positive group without comorbidity wasdefined as the negative group. Total bilirubin/lymphocyte, GGT/lymphocyte, ALP/lymphocyte ratio, and D-dimer parameters in ROC analysis had the highest AUC (Area Under the Curve) values (0.984, 0.924, 0.923, and 0.897, respectively (p<0.001)). Albumin, on the other hand, had a low AUC value and was statistically not significant (p>0.05). AUC, optimal cut-off, sensitivity, and specificity values of the laboratory parameters are given in Table 3.

Table 1 Characteristics of the colangitis and control group

Variables	Total colangitis group (n=37)	Grade 1 (n=8)	Grade 2 (n=8)	Grade 3 (n=21)	p Value
Baseline characteristics					
Age, median (IQR),range, years	65 (50-78), 31-97	63 (53-78), 47-89	55 (38-72), 33-77	74 (52-84), 31-97	0.107
Gender, female/male	17/20	3/5	4/4	10/11	0.858
Outcome characteristics					
Mortality, (%)	16 (43.2%)	0	0	16 (76.2%)	-
Intubation	16 (43.2%)	0	0	16 (76.2%)	-
Comorbidities, (%)	31 (83.8%)	6 (75%)	8 (87.5%)	18 (85.7%)	0.359
Systemic hypertension, (%)	8 (21.6%)	1 (12.5%)	2 (25%)	5 (23.8%)	0.791
Diabetes mellitus, (%)	6 (16.2%)	1 (12.5%)	2 (25%)	3 (14.3%)	0.760
Cardiovascular or gan failure, (%)	3 (8.1%)	0	0	3 (14.3%)	-
Bile duct stones, (%)	4 (10.8%)	2 (25%)	1 (12.5%)	1 (4.8%)	0.306
Cancer, (%)	10 (27%)	2 (25%)	2 (25%)	6 (28.6%)	0.973
Symptoms at admission, (%)					
Fever	13 (35.1 %)	0	3 (37.5%)	10 (47.6%)	-
Jaundice	10 (27%)	1 (12.5%)	4 (50%)	5 (23.8%)	0.225
Dyspnea	5 (13.5%)	0	1 (12.5%)	4 (19%)	-
Vomiting/nausea	7 (18.9%)	2 (25%)	1 (12.5%)	4 (19%)	0.828
Tremor	5 (13.5%)	0	0	5 (23.8%)	-
Abdominal pain	17 (45.9%)	3 (37.5%)	3 (37.5%)	11 (52.4%)	0.686

Discussion

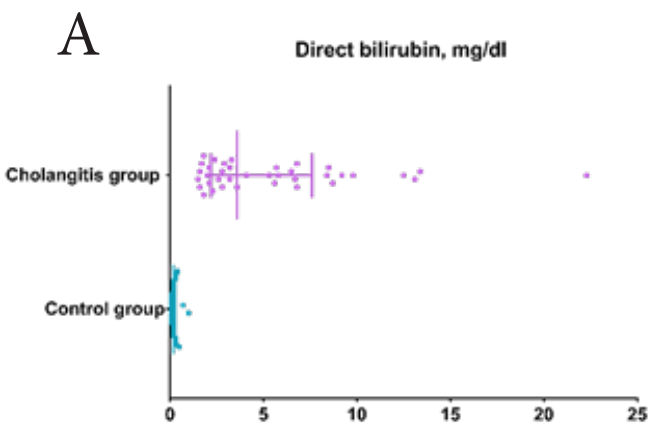
The COVID-19 pandemic continues to affect the entire world with different variations. Intra-abdominal organ involvement can be detected in COVID-19 cases, especially when it involves the lungs and multi-organ involvement. The present study, in which the data of COVID-19 patients who were PCR+ and also diagnosed with acute cholangitis were evaluated, was conducted in one single center. Few studies are reporting that acute cholangitis can develop in COVID-19 cases and affect the prognosis.[5-6] The present study is an example of detailed analysis in terms of providing a new alternative in the prognosis of cases that are diagnosed with COVID-19 and simultaneously with acute cholangitis.

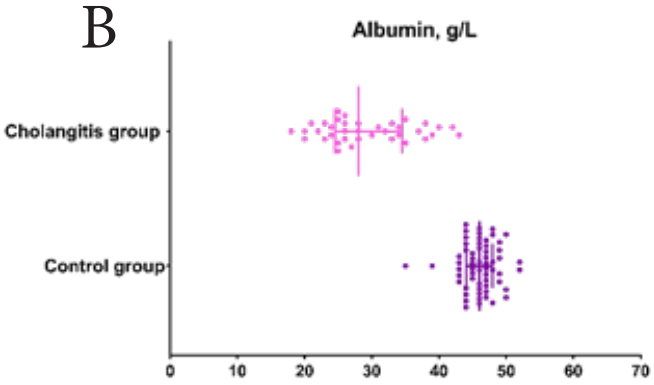
Table 2 Demographic characteristics of COVID-19 without comorbidity group, Cholangitis and control groups.

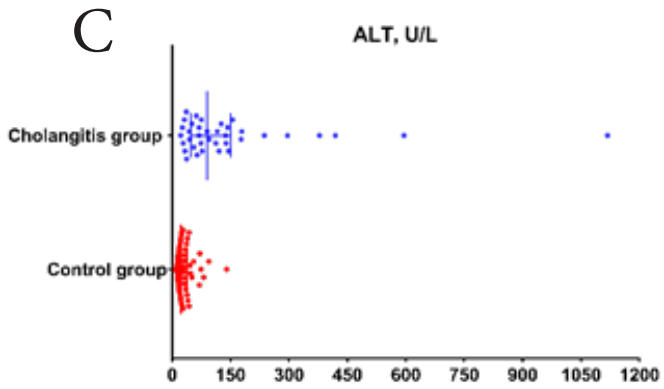
Parameters	Control group (n=68)	COVID-19 without comorbidity group (n=37)	Cholangitis group (n=37)	p Value
Age, years, range	40 (29-54), 18-79	44 (37-56), 25-73	69 (50-78), 31-97	<0.001
Gender, female/male	1/37	14/23	17/20	0.686
Amylase, U/L	59 (51.5-83)	65 (52-85)	40 (27-107)	0.101
Lipase, U/L	30 (25-37)	38 (31-45)	40 (21-111)	0.008
CRP, g/L	0.004 (0.002-0.007)	0.02 (0.006-0.08)	0.11 (0.022-0.156)	<0.001*
PCT, µg/L	0.03 (0.03-0.07)	0.03 (0.03-0.09)	0.44 (0.20-3.71)	<0.001*
WBC, 10^9/L	7.7 (6.8-9.2)	6.9 (4.5-8.8)	13.1 (10.2-16.9)	<0.001*
Neutrophil, 10^9/L	4.8 (3.1-7.7)	4.4 (2.8-7.0)	10.4 (6.3-15.6)	<0.001*
Lymphocyte, 10^9/L	2.1 (1.5-2.7)	1.3 (0.9-1.7)	0.9 (0.5-1.5)	<0.001*
N/L	2.1 (1.4-5.4)	2.9 (1.7-6.7)	8.3 (3.5-28.1)	<0.001*
PLT, 10^9/L	252 (203.5-308)	209 (162.5-256)	233 (113-355.5)	0.022
Hemoglobin, g/dL	13.8 (12.7-14.5)	14.5 (14-15.7)	10.5 (8.9-11.4)	<0.001*
Albumin, g/L,	46 (44-48)	44.5 (42-46)	28 (24.5-34.5)	<0.001*
Total protein, g/L	71 (68.5-73)	67 (65-70)	57.5 (46-62.5)	<0.001*
ALP, U/L	65 (60-76)	71.5 (58-83)	273 (183-520)	<0.001
AST, U/L	17 (14-23.5)	28 (19.5-38.3)	118 (72-267)	<0.001*
ALT, U/L	23 (16.5-37.5)	27 (21-47)	90 (48-150)	<0.001*
LDH, U/L	201 (174.5-244)	279 (216-338)	374 (244.5-722.5)	<0.001
GGT, U/L	20 (15-33.5)	25.5 (18.8-50.3)	256 (155.5-498.5)	<0.001*
D-dimer, mg/L	0.37 (0.22-0.49)	0.38 (0.27-0.67)	2.99 (1.3-7.3)	<0.001*
T.Bilirubin, mg/dL	0.6 (0.4-0.9)	0.5 (0.4-0.7)	4.8 (2.8-10.1)	<0.001*
D.Bilirubin, mg/dL	0.2 (0.1-0.3)	0.2 (0.1-0.2)	3.6 (2.2-7.6)	<0.001*
Urea, mg/dL	29 (22-39)	28 (24-38)	43 (24-75)	0.013*
Creatinin, mg/dL	0.74 (0.65-0.89)	0.85 (0.69-0.91)	0.77 (0.56-1.47)	0.402
Total bilirubin/LYM	0.4 (0.2-0.6)	0.4 (0.3-0.7)	7.4 (3.1-13.7)	<0.001*
GGT/LYM	10.5 (7.2-19.4	21.5 (11.3-63.7)	290.9 (139.2-692.7)	<0.001*
ALP/LYM	31.1 (23.1-46.9)	53.8 (34-87.8)	257.5 (164.8- 1063.6)	<0.001*

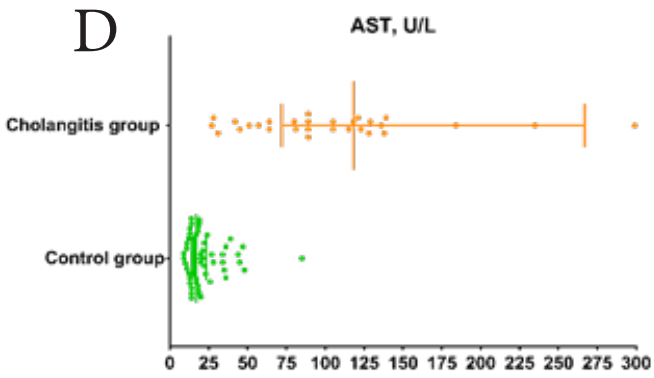
Data are expressed as median (IQR) for continuous variables. LYM: Lymphocytes. The comparison of COVID-19 without comorbidity and cholangitis groups highlighted with asterisk and significant according to Kruskal Wallis analysis.

*:p values less than .001 were considered significant highlighted in bold.


A
Direct bilirubin, mg/dl
Cholangitis group
Control group
0
5
10
15
20
25


B
Albumin, g/L
Cholangitis group
Control group
0
10
20
30
40
50
60
70


C
ALT, U/L
Cholangitis group
Control group
0
150
300
450
600
750
900
1050
1200


D
AST, U/L
Cholangitis group
Control group
0
25
50
75
100
125
150
175
200
225
250
275
300

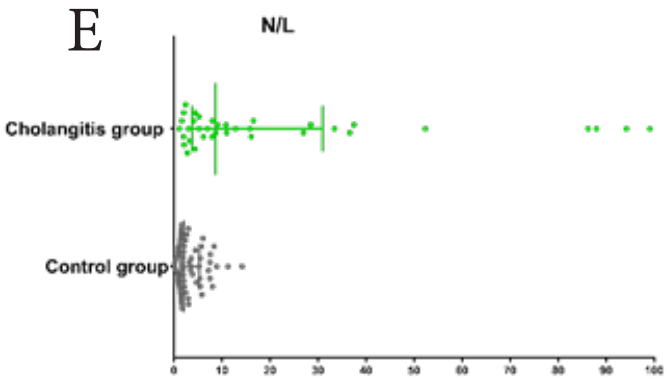

E
N/L
Cholangitis group
Control group

Table 3 The blood routine parameters in diagnosis of patients with COVID-19 with cholangitis on admission.

Variables	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	p value
D-dimer	≥ 0.725	0.897 (0.803-0.992)	86.7	75.8	<0.001
Total bilirubin/LYM	≥ 1.748	0.984 (0.962-1.000)	93.3	90.9	<0.001 GGT/
LYM	≥ 73.6	0.924 (0.857-0.992)	86.7	87.9	<0.001
ALP/LYM	≥ 105.2	0.923 (0.854-0.992)	86.7	90.9	<0.001
WBC	≥ 10.05	0.727 (0.579-0.874)	73.3	84.8	0.002
CRP	≥ 0.062	0.726 (0.599-0.854)	66.7	72.7	0.002

AUC: Area Under The Curve; LYM: Lymphocytes. Asymptotic Significance Less Than 0.05 Were Considered Significant.

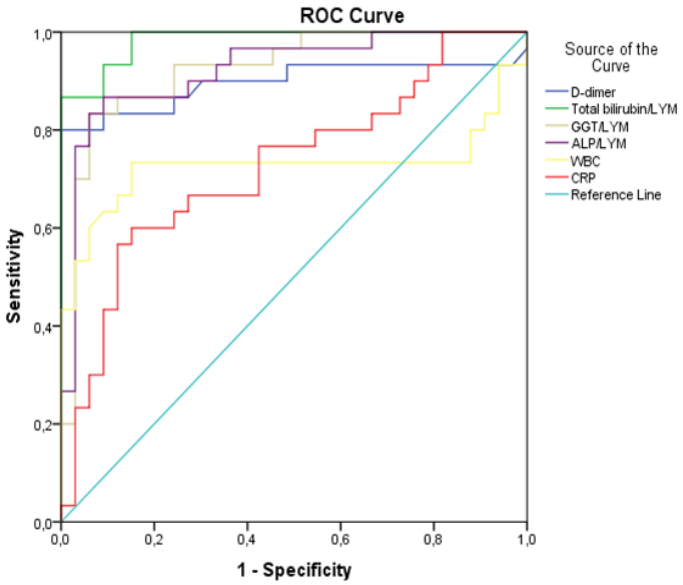


Fig. 2. The ROC curves of D-dimer, Total bilirubin/LYM, GGT/LYM, ALP/LYM, WBC and CRP in predicting COVID-19 with cholangitis on admission.

The release of TNF-alpha, IL-1, or IL-6, the pro-inflammatory cytokines common in patients with COVID-19 infection, especially in intensive care patients, causes hyperviscosity, hypercoagulopathy, thromboembolic event, which may deteriorate the condition of patients.[8] Proinflammatory cytokines also alter the function of hepato-biliary transporters along with the function of protective tissues in the bile ducts. The defect of the guard cells causes bile toxicity and may be a risk factor for chronic cholangitis.[9] The morbidity and mortality rate of cholangiopathy cases detected in COVID-19 cases can be reduced with early treatment.

Cholangiopathy is manifested by increased ALT, AST, GGT, LDH, T.Bil levels, and decreased albumin (ALB) levels in COVID-19 patients.[10-12] In the present study, AST, ALT, T.Bil, LDH levels were significantly higher in the COVID-19 + acute cholangitis group and the total protein and albumin levels were low. The findings were found to be compatible with the literature data. The abnormal detection of these biomarkers suggests that they can be used as the criteria for patients who may need intensive care in the treatment of COVID-19. Clinicians who treat COVID-19 should monitor the changes in liver biochemical indicators and detect patients with liver damage in the early period and initiate their transfer to Intensive Care Units. Increased D-dimer levels and lymphopenia were associated with higher mortality in COVID-19 patients.[13-14] In the study, D-dimer levels were found to be higher in the COVID-19 + cholangitis group. WBC, Neutrophil, lymphocyte, and NLR values were also significantly higher. WBC and NLR were shown to play roles in predicting the prognosis of chronic and acute inflammatory processes.[15] The presence of elevated WBC and NLR values in the coexistence of COVID-19 + and cholangiopathy may predict that the prognosis may be severe. In publications released on cholangiopathy, which may develop after COVID-19, it was associated with elevated liver enzymes such as ALT, AST, ALP, and GGT (16-17). These biomarkers have an important place in the diagnosis and follow-up. In a previous study, elevated liver enzymes, ALP, and GGT values were found in a case who developed liver failure (18). There was no case of hepatic failure in our cases.

Publications are reporting the optimum cut-off value of some serum biochemical parameters as the prognosis indicators in COVID-19 by using the severe disease ROC curve (19, 20). In the present study, in predicting the severity of the disease in COVID-19 + acute cholangitis patients in the ROC curve analysis, total bilirubin/lymphocyte, GGT/lymphocyte, ALP/lymphocyte rat ios, and D-dimer parameters had the highest AUC values (0.984, 0.924, 0.923 and 0.897, respectively ($p<0.001$)). Especially T.bil/lymphocyte, GGT/lymphocyte, and ALP/lymphocyte ratios can be useful in estimating the mortality and prognosis.

Conclusion

Elevated T.bil/lymphocyte, GGT/lymphocyte, and ALP/lymphocyte ratios may be useful in showing the severity of the disease in patients diagnosed with COVID-19 and acute cholangitis.

The authors declare that there is no conflict of interest between them.

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