Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(3): 693-698
doi: 10.52142/omujecm.39.3.19

Comparison of liver biomarkers with N/L ratio, CRP, d-dimer in Covid 19 pneumonia and its effect on mortality

Fadime Güllü HAYDAR[1]*, Yavuz OTAL[2], Gamze AVCIOĞLU[3]

[1] Department of General Surgery, Ankara City Hospital, Ankara, Turkey
[2] Department of Emergency Medicine, Ankara City Hospital, Ankara, Turkey
[3] Department of Medical Biochemistry, Karadeniz Ereğli State Hospital, Zonguldak, Turkey

Received: 18.01.20212 • **Accepted/Published Online:** 14.08.2022 • **Final Version:** 30.08.2022

Abstract

Background: Coronavirus Disease-2019 (Covid-19) is the cause of a pandemic that has high mortality and global effects. The liver damage in Covid-19 cases in mechanical ventilation was investigated in this study. A total of 60 patients (the Study Group) who were diagnosed with Covid-19 pneumonia, and 65 individuals (the Control Group) were included prospectively in the study. The cases were divided into 3 groups as those who were intubated (severe), those who were not intubated (mild), and the healthy Control Group. The lung tomography results of those who were diagnosed with Covid-19 were examined in the study. The cases with positive RT-PCR (Real Time Polymerized Chain Reaction) test results were recorded from the system. The liver tests of the patients were compared with those of the Control Group. The two groups with and without intubation were also compared. The results were evaluated and analyzed statistically. When all the data were evaluated, it was found that LDH, GGT, AST, and aPTT levels were significantly higher in the mild and severe patient group compared to the Control Group, and the T. Protein and albumin levels were low ($p<0.01$). The N/L Ratio, and the CRP levels, which are the other acute phase reactants, were significantly higher ($p<0.05$). No statistically significant differences were detected when all parameters of the groups with and without intubation were compared ($p>0.05$). Increased D-dimer, GGT, D. Bil, LDH, NLR, and AST levels in Covid-19 patients in invasive mechanical ventilation are associated with mortality.

Keywords: Covid-19, Liver Function, mortality, Invasive Mechanical Ventilation, d-dimer

1. Introduction

Coronavirus Disease 2019 (COVID-19) pandemic stems from a novel coronavirus infection called Severe Acute Respiratory Syndrome covid - 19 (1). The infection spread rapidly worldwide and was declared a pandemic by the World Health Organization. As of April 30, 2021, there were 150.110.310 documented cases worldwide and it was reported that 3.158.792 patients died (2). Since there is currently no special treatment or medication against the new virus, it is vital to determine the risk factors for mortality.

Lung involvement in severe infection is a serious complication that requires hospitalization in Intensive Care Units. The lungs are usually affected bilaterally. The severe respiratory failure caused may require mechanical ventilation. There are no specific drugs for the treatment of these patients, and supportive treatment is administered. The blood results of these patients may vary, and since there are comorbidities in COVID-19, examining them is guiding in severe pneumonia in terms of prognosis and treatment.

The total protein, albumin, AST, ALT, GGT, LDH, PT, PTT, T. Bilirubin, D. Bilirubin results, which show liver functions, may vary in patients in invasive mechanical ventilation. Furthermore, levels of acute-phase reactants, WBC (White Blood Cell), N/L (Neutrophil/Lymphocyte Ratio), and CRP (C-Reactive Protein), are guiding in demonstrating the severity of the disease.

The mechanism of the liver injury in COVID-19 patients is still not precise. It may stem from direct virus infection, immune damage, drug-related liver damage, systemic inflammatory response, ischemia, hypoxia, or relapse or exacerbation of the underlying liver disease.

This study investigated the relations between liver functions and other acute-phase reactants in COVID-19 patients in invasive mechanical ventilation and their effects on mortality.

2. Material and Methods

After obtaining the approval of the Ethics Committee of Ankara City Hospital (29/12/2021-2046), we took the blood samples from 60 COVID-19 patients and examined 65

*Correspondence: dryotal@gmail.com

healthy volunteers on the computer in the laboratory.

We divided the cases into three groups: 1) the healthy Control Group, 2) the intubated, and 3) the non–intubated patients. We then examined the lung tomography results of the cases diagnosed with COVID-19. We recorded the PCR results from the system, entering the total protein, albumin, AST, ALT, GGT, LDH, PT, PTT, T. Bilirubin, and D. Bilirubin test results separately into the statistics program.

We excluded those under 18 years of age, trauma patients and pregnant women from the study.

2.1. Statistical analysis

We used the Statistical Package for Social Sciences for Windows, Version 22 (IBM, Armonk, NY, USA) for the statistical analyses; the Kolmogorov-Smirnov test for the normality of the variables; Mean±Standard Deviation (SD) for the parameters with normal distribution; median (interquartile range) (IQR) for the parameters not consistent with the normal distribution; and the One-Way ANOVA Test for the parameters normally distributed. We evaluated those without normal distribution with the Kruskal-Wallis Test and compared categorical variables using the Chi-Square Test or the Fisher's Exact Test. We used the Receiver Operation Characteristic (ROC) curve to analyze the efficiency of the COVID-19 severity and calculated the optimal cut-off values of the AST, GGT, procalcitonin, direct bilirubin, LDH, and NLR. A p-value <0.05 was considered to be statistically significant.

3. Results

Table 1 shows the demographic data of the COVID-19-related pneumonia cases and the control group. We found no significant differences between the cases regarding age and gender. The intubated 52 patients were under mechanical ventilation. The RT-PCR test results of all patients were positive. We examined the tomography results of all patients and entered the findings into the system.

We calculated the p-value for each parameter comparing the groups in the statistical analysis and divided the cases into three groups: 1) the healthy Control Group, 2) intubated (severe), and 3) not intubated patients (mild). As in Table 1, the data of the three groups evinced that the total protein and albumin levels were significantly lower in the serum ($p<0.01$). The LDH, GGT, AST, and ALT levels were higher at statistically significant levels in the mild and severe patient groups ($p<0.05$). The statistical analysis conducted between the severe and mild patient groups without including the Control Group indicated no significant changes in all these parameters. Fig. 1 shows the analysis in detail.

Table 2 includes the analysis of the cases who recovered from COVID-19 and who died. The serum T. protein and albumin levels were close to normal limits in fully recovering cases but lower in those who died ($p<0.01$). The LDH and GGT values were significantly higher in those who died ($p<0.01$). Comparing the two groups excluding the Control Group, we found significantly higher LDH levels ($p<0.01$).

Fig. 2 shows the event analysis of the blood routine parameters (i.e. the ROC curves) in estimating critical COVID-19 patients. We designated the COVID-19 Group with mortality as the positive and the Control Group as the negative group. We used the ROC curve to analyze the effectiveness of various blood routine parameters in diagnosing severe COVID-19 at admission and analyzed the optimal cut-off values calculated with the ROC Analysis. The D-dimer, NLR, AST, GGT, D. Bil, and LDH values had the highest AUC in the ROC analysis. Table 3 shows the laboratory parameters' EAA, optimal cut-off, and sensitivity and specificity values.

Table 1. Blood parameter characteristics of patient groups according to the intubated group

Characteristics	Control group (n=65)	Non-intubated group (n=68)	Intubated group (n=52)	p Value*	p Value**
Age, Median(IQR), range, years	58.2 ± 17.1, 18-75	66.3 ± 14.2, 23-80	69.8 ± 10.9, 23-80	0.272	0.683
Gender, male/female	34/31	36/32	29/23	0.861	0.848
Laboratory analysis					
PLT, (×109 / L)	259.9 ± 75.0	263.5 ± 136.9	241.1 ± 120.5	0.584	0.570
Albumin, (g/L)	46.5 ± 4.4	33.9 ± 6.2	33.1 ± 6.5	<0.001	0.789
T.protein, (g/L)	71.0 ± 4.1	58.9 ± 9.1	59.9 ± 77.4	<0.001	0.778
ALT, (U/L)	27.8 ± 17.0	51.3 ± 94.1	125.8 ± 61.1	0.034	0.102
AST, (U/L)	21.7 ± 12.9	58.1 ± 88.6	63.6 ± 106.1	0.008	0.927
LDH, U/L	206.8 ± 45.2	377.2 ± 212.7	469.0 ± 149.1	0.002	0.419
GGT, (U/L)	27.4 ± 18.0	63.2 ± 59.3	77.8 ± 117.4	0.001	0.514
D-dimer, mg/L	0.5 ± 0.6	2.3 ± 3.2	11.6 ± 12.6	<0.001	<0.001
T.bilirubin, (mg/dL)	0.8 ± 1.3	1.5 ± 5.1	0.8 ± 0.9	0.412	0.560
D.bilirubin, (mg/dL)	0.2 ± 0.2	0.4 ± 0.6	0.5 ± 0.7	0.022	0.753
PT, sec	13.3 ± 13.1	15.6 ± 13.8	13.9 ± 3.0	0.721	0.757
aPTT, sec	24.3 ± 3.5	29.9 ± 16.1	28.0 ± 8.0	0.019	0.691

All values are presented as Mean±SD. *Comparison of three groups, **Comparison of the intubated and non-intubated groups. p-values less than .05 were considered significant and highlighted in bold.

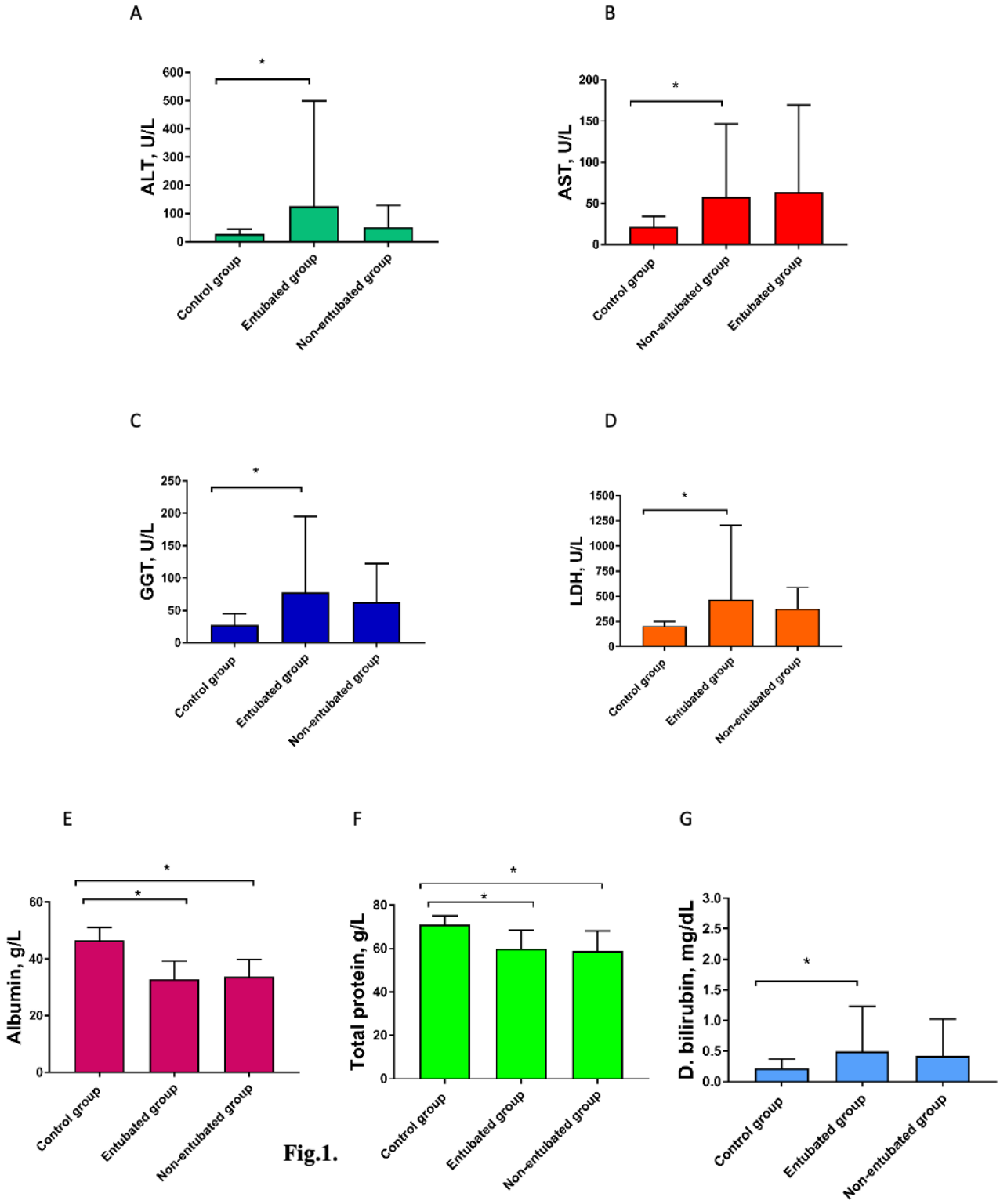

Fig.1.

Fig. 1. Comparison levels of ALT (A), AST (B), GGT (C), LDH (D), albumin €, total protein (F) and direct bilirubin (G) of control, entubated and non-entubated groups, p values less than. 001 were considered significant highlighted in asterisk

Table 2. Blood parameter characteristics of patient groups according to ex and recovery groups

Characteristics	Control group (n=65)	ex group (n=46)	recovery group (n=76)	p Value*	p Value**
Age, Median(IQR), range, years	63.2 ± 17.1, 18-75	67.4 ± 13.5, 42-90	72.7 ± 14.6, 43-88	0.324	0.149
Gender, male/female	34/31	30/16	44/32	0.637	0.474
Laboratory analysis					
PLT, (×109 / L)	259.9 ± 75.0	239.1 ± 137.7	265.9 ± 127.3	0.453	0.431
Albumin, (g/L)	46.5 ± 4.4	33.1 ± 6.4	33.6 ± 6.1	<0.001	0.906
T.protein, (g/L)	71.0 ± 4.1	56.2 ± 10.2	61.1 ± 7.6	<0.001	0.002
ALT, (U/L)	30.9 ± 22.0	62.9 ± 105.6	50.9 ± 68.2	0.058	0.631
AST, (U/L)	21.7 ± 12.9	64.0 ± 107.9	57.4 ± 85.7	0.008	0.893
LDH, U/L	206.8 ± 45.2	693.2 ± 96.4	299.1 ± 123.3	<0.001	<0.001
GGT, (U/L)	27.4 ± 18.0	77.4 ± 88.2	62.5 ± 80.6	0.001	0.483
T.bilirubin, (mg/dL)	0.8 ± 1.3	0.9 ± 1.0	0.8 ± 0.7	0.668	0.779
D.bilirubin, (mg/dL)	0.2 ± 0.2	0.5 ± 0.7	0.4 ± 0.6	0.020	0.685
PT, sec	13.3 ± 13.1	15.3 ± 3.6	14.8 ± 14.2	0.905	0.972
aPTT, sec	24.3 ± 3.5	35.1 ± 20.1	25.6 ± 5.3	<0.001	<0.001
D-dimer, mg/L	0.5 ± 0.6	10.7 ± 11.9	1.8 ± 2.1	<0.001	<0.001

All values are presented as Mean±SD. *Comparison of three groups, **Comparison of ex and recovery groups. p-values less than .05 were considered significant and highlighted in bold.

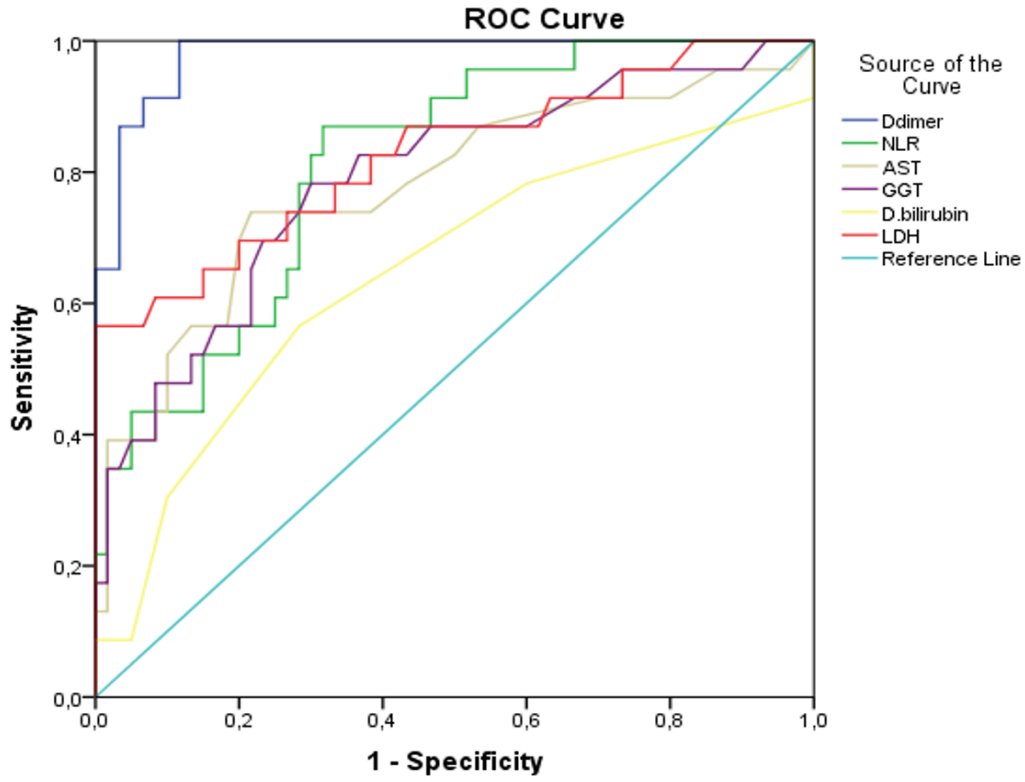

Fig. 2. The ROC curves of NLR, AST, GGT, D. bilirubin, LDH and D-dimer in predicting severity of COVID-19 infection on admission. NLR: Neutrophils-to-lymphocytes ratio

Table 3. Blood parameters in the diagnosis of ex patients with intubated COVID-19

Variables	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	p-value
AST	>22.5	0.779 (0.686 - 0.871)	76.1	73.3	<0.001
GGT	>28.5	0.770 (0.679 - 0.862)	73.9	66.7	<0.001
D. bilirubin	>0.25	0.642 (0.531 - 0.754)	52.2	71.7	0.012
NLR	>3.875	0.799 (0.716 - 0.881)	76.1	70.0	<0.001
LDH	>204.5	0.749 (0.651 - 0.846)	80.4	55.5	<0.001
D-dimer	>0.985	0.980 (0.957 - 1.00)	95.7	88.3	<0.001

AUC: Area under the curve; NLR: Neutrophils-to-lymphocytes ratio. A p-value less than 0.05 were considered significant.

4. Discussion

SARS-COV-2 infection causes a wide clinical spectrum ranging from an asymptomatic state to severe pneumonia. Mechanical ventilation is inevitable in the treatment of cases with severe respiratory failure. The intensive care duration and improvement period increase in these cases (3). Evaluating the prognostic factors in this process is essential for prioritizing patients who need intensive care more. COVID-19 has no specific treatment except for infection control and support treatment. Multi-organ support treatment is the basis in the treatment of COVID-19 critical patients. Therefore, identifying the prognostic severity criteria is paramount in providing early intervention to patients who might require ICU support (3, 4).

Increasing numbers of liver damage have been reported since the Covid-19 pandemic began; however, the mechanism of the liver damage caused by COVID-19 is not yet precise. All genome sequencing results showed us that SARS-COV-2 is similar to SARS-COV with 82% genome sequence and the Middle East Respiratory Syndrome Coronavirus (MERS-COV), sharing 50% genome sequence homology (5). SARS-COV, MERS-COV, and SARS-COV- 2 are known coronaviruses causing severe respiratory symptoms. Previous studies reported liver damage in 60% of patients infected with SARS-COV and in some infected with MERS-COV (6, 7).

A study conducted in Wuhan with COVID-19 infected cases reported that abnormal Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) levels were observed in 43 of 99 patients (8). At least 12 clinical studies conducted with a single or multicenter design reported that approximately 14.8%-53% of COVID-19 patients had liver damage. These studies showed that liver damage is relatively common in COVID-19 patients (9).

Liver damage manifests with increased ALT, GGT, LDH, AST and TBIL levels, decreased albumin (ALB) levels, and as abnormal liver biochemical indicators in COVID-19 patients (9-12). We found in our study that the AST, ALT, T. Bil, and LDH have increased at significant levels in both groups of intubated and non-intubated patients. The T. protein and albumin levels were low. Our findings were in line with the literature data. Detecting that these biomarkers have increased abnormally suggests that they could be used as criteria in treating COVID-19. Clinicians should follow the changes in the liver biochemical indicators in COVID-19 treatment, detect the patients with liver damage in the early period, and initiate the transfer to Intensive Care Units.

COVID-19 infection may deteriorate blood coagulation functions. COVID-19 studies reporting liver damage also reported Prolonged PT, aPTT, elevated D-dimer, and thrombocytopenia (13-15). The clinical reflection of COVID-19-related coagulopathy is basically the dysfunction of organs, and hemorrhagic events are less frequent. The changes in hemostatic biomarkers represented by increased D-dimer and fibrin/fibrinogen destruction products show massive fibrin formation in the etiopathogenesis of coagulopathy (14).

Currently, the mechanisms of coagulopathy in COVID-19 have not yet been elucidated. Inflammatory cytokines, lymphocyte cell death, hypoxia, and irregular immune responses caused by endothelial damage may play roles in this respect. The bleeding tendency is rare even in cases with prolonged coagulation tests (14, 15). Certain studies found D-dimer levels to be associated with increased mortality. These studies recommended heparin at low molecular weight to prevent thromboembolic complications (16, 17). We found in our research that the PT and APTT values were slightly prolonged, and the platelet values did not show any significant changes. Moreover, the finding of high D-dimer levels is compatible with the literature data. The ROC curve shows that D-dimer is associated with mortality as a biomarker in COVID-19 patients in invasive mechanical ventilation.

Certain publications reported the optimum cut-off value of some serum biochemical parameters as the indication of prognosis in COVID-19 by using the severe disease ROC curve (4, 18). D-dimer, GGT, D. Bil, LDH, NLR and AST had the highest AUC in the ROC Analysis. The AUC values of the AST, GGT, D. Bilirubin, and LDH, which show the liver functions, are crucial in revealing the severity of COVID-19 infection. These tests are significant compared to the ROC Analysis in showing the prognosis.

Elevated D-dimer, GGT, D. Bil, LDH, NLR and AST levels are associated with mortality in COVID-19 patients in invasive mechanical ventilation.

Conflict of interest

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

References

1. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol, 2020. 5(4): p. 536-544.
2. https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
3. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S,et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care, 2020. 24(1): p. 188.
4. Bastug A, Bodur H, Erdogan S, Gokcinar D, Kazancioglu S, Kosovali BD, et al. Clinical and laboratory features of COVID-19: Predictors of severe prognosis. Int Immunopharmacol, 2020. 88: p. 106950.
5. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med, 2020. 382(8): p. 727-733.
6. Alsaad KO, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, et al. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection -

clinicopathological and ultrastructural study. Histopathology, 2018. 72(3): p. 516-524.

7. Chau TN, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology, 2004. 39(2): p. 302-10.

8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y,et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020. 395(10223): p. 507-513.

9. Tian D,Q. Ye. Hepatic complications of COVID-19 and its treatment. J Med Virol, 2020. 92(10): p. 1818-1824.

10. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. Hepatology, 2020. 72(4): p. 1169-1176.

11. X Xu W, Huang C, Fei L, Li Q, Chen L. Dynamic Changes in Liver Function Tests and Their Correlation with Illness Severity and Mortality in Patients with COVID-19: A Retrospective Cohort Study. Clin Interv Aging, 2021. 16: p. 675-685.

12. Wang Q, Zhao H, Liu LG, Wang YB, Zhang T, Li MH , et al. Pattern of liver injury in adult patients with COVID-19: a retrospective analysis of 105 patients. Mil Med Res, 2020. 7(1): p. 28.

13. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res, 2020. 191: p. 145-147.

14. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost, 2020. 18(9): p. 2103-2109.

15. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol, 2020. 127: p. 104362.

16. Di Micco P, Russo V, Carannante N, Imparato M, Rodolfi S, Cardillo G, et al. Clotting Factors in COVID-19: Epidemiological Association and Prognostic Values in Different Clinical Presentations in an Italian Cohort. J Clin Med, 2020. 9(5).

17. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost, 2020. 18(5): p. 1094-1099.

18. Sun S, Cai X, Wang H, He G, Lin Y, Lu B, et al.Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta, 2020. 507: p. 174-180.