


ORIGINAL PAPER

Gastroenterology

Gamma-glutamyl-transferase may predict COVID-19 outcomes in hospitalised patients

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Funding information

None.

Abstract

Aim: In this study, we aimed to define the predictive role of liver function tests at admission to the hospital in outcomes of hospitalised patients with COVID-19.

Material and Method: In this multicentric retrospective study, a total of 269 adult patients (≥ 18 years of age) with confirmed COVID-19 who were hospitalised for the treatment were enrolled. Demographic features, complete medical history and laboratory findings of the study participants at admission were obtained from the medical records. Patients were grouped regarding their intensive care unit (ICU) requirements during their hospitalisation periods.

Results: Among all 269 participants, 106 were hospitalised in the ICU and 66 died. The patients hospitalised in ICU were older than patients hospitalised in wards ($P = .001$) and expired patients were older than alive patients ($P = .001$). Age, elevated serum D-dimer, creatinine and gamma-glutamyl transferase (GGT) levels at admission were independent factors predicting ICU hospitalisation and mortality in COVID-19 patients.

Conclusion: In conclusion, in hospitalised patients with COVID-19, laboratory data on admission, including serum, creatinine, GGT and d-dimer levels have an important predictive role for the ICU requirement and mortality. Since these tests are readily available in all hospitals and inexpensive, some predictive formulas may be calculated with these parameters at admission, to define the patients requiring intensive care.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{1,2} Since the patients can suddenly get worsen requiring intensive care unit (ICU), early identification and timely intervention of patients with a tendency to become severe is essential to improve outcomes.¹ Up to now, August 2021, approximately 225 million COVID-19 confirmed cases and 4.5 million associated deaths were reported worldwide; while 6.5 million confirmed cases and 59 thousand deaths associated with this disease were reported in our country.³

The clinical findings of the patients may vary according to the age and sex. However, the most commonly reported symptoms include headache, loss of smell, nasal obstruction, cough, asthenia, myalgia, rhinorrhea and sore throat. In approximately half of the patients, fever was present at admission.⁴ The severity of the disease was associated with some comorbidities such as hypertension, bilateral lung involvement, older age, high C-reactive protein levels and decreased lymphocyte count.^{4,5}

Liver function tests (LFTs) including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and bilirubin levels were studied in COVID-19 in some previous studies.^{6,7} As with many

viral infections, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is also shown to be associated with abnormal liver function tests.⁸

In hospitalised patients, older age, male sex, comorbidity, and signs of dyspnea were reported as higher risk factors for severe disease.⁹⁻¹¹ Angiotensin-converting enzyme 2 (ACE2) is known to be the host cell receptor for SARS-CoV-2. It has been shown that there is a significant enrichment of ACE2 expression in a major portion of the cholangiocyte clusters. GGT is a diagnostic biomarker for cholangiocyte injury and thus may be suggested as a marker of cholangiocyte involvement in COVID-19.^{12,13} Patients with elevated liver function tests were related to more severe disease in COVID-19.^{14,15}

In this study, we aimed to define the predictive role of liver function tests at admission to the hospital in outcomes of hospitalised patients with Covid-19. In this way, we aimed to define an effective tool for the early clinical detection of severe cases in the COVID-19 outbreak.

2 | MATERIAL AND METHODS

In this multicentric retrospective study, adult patients (≥ 18 years of age) with confirmed COVID-19 who were hospitalised for the treatment were enrolled.

2.1 | Case definition for COVID-19

Diagnosis of COVID-19 was assessed by using nasopharyngeal swab reverse transcriptase-polymerase chain reaction (Real-Time PCR) according to WHO guideline.¹⁶ Patients were treated in line with the recommendations of Turkey's Health Ministry COVID-19 adult patient treatment guidelines.¹⁷

2.2 | Data collection and participants

Demographic features, complete medical history, and laboratory findings of the study participants at admission are obtained from the hospital records. The laboratory data including haemoglobin level, white blood cell count, neutrophil and lymphocyte counts, ALT, AST, GGT, and ALP levels, serum creatinine level, concentrations of D-dimer and C-reactive protein (CRP) levels were recorded. All data were obtained at the admission of the patients before treatment.

2.3 | Inclusion and exclusion criteria

Patients with missing data, having any known chronic hepatobiliary diseases, non-alcoholic fatty liver disease, patients with alcohol abuse, hepatobiliary malignancies and receiving drugs known to have cholestatic effects other than those used in COVID-19 management, end-stage renal disease and patients on haemodialysis were

What's known

- Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

What's new

- GGT, creatine, and d-dimer levels have an important predictive role for the ICU requirement and mortality.

excluded from the study. 483 patients were evaluated and it was decided to include 269 patients because of strict exclusion criteria.

Patients were grouped regarding their ICU requirements during their hospitalisation periods. Moreover, the outcomes of the patients at the end of the treatment were also recorded. Patients whose treatment or hospitalisation periods were continuing during the data collection were not included in the study.

2.4 | Statistical analysis

Statistical analyses were performed using SPSS 20.0 software. Categorical variables were described as frequency rates and percentages, and continuous variables were described using mean values. Mean values for continuous variables were compared using independent group t-tests when the data were normally distributed. Multivariate logistic regression analysis was performed to calculate adjusted odds ratios (OR) with its 95% confidence interval (CI) for ICU hospitalisation and mortality in COVID-19 patients. ROC curves were obtained for the parameters that were significantly affecting mortality. $P < .05$ was considered statistically significant.

2.5 | Ethics statement

The study was approved by the local ethics committee of Lokman Hekim University with the number of 2021/065. Informed consent was obtained from all of the patients.

3 | RESULTS

Totally 269 patients (95 female and 174 male) hospitalised for COVID-19 were included in the study. Among participants, 106 were hospitalised in the intensive care unit and 66 of them died. Thorax tomography images of two patients hospitalised in ICU are shown in Figures 1 and 2. Demographic features of study participants are summarised in Table 1. There was no significant difference between hospitalised patients in ICU or wards and alive or death patients regarding gender. However, patients hospitalised in ICU were older

FIGURE 1 Thorax tomography image of a 79-year-old female patient with Covid pneumonia

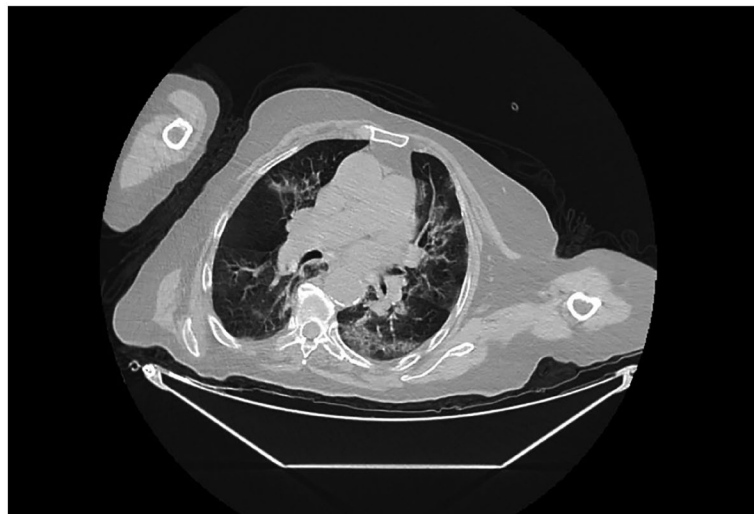


FIGURE 2 Thorax tomography image of a 73-year-old male patient with Covid pneumonia



TABLE 1 Demographic features of study participants

	Hospitalisation in ICU			Outcomes		
	Hospitalised in Wards (n: 163)	Hospitalised in ICU (n: 106)	<i>P</i> ^a	Alive (n: 203)	Death (n: 66)	<i>P</i>
Gender (F/M)	56 /107	39/67	.69	68/135	27/39	.30
Age (y)	49.18 ± 20.72	68.30 ± 14.98	.001	52.08 ± 20.72	70.95 ± 13.66	.001

Abbreviations: F, female; ICU, intensive care unit; M, male.

^aChi Square and Independent Sample *T* test.

Statistically significant *P* values are indicated in bold.

than patients hospitalised in wards (*P*: .001); and expired patients were older than alive patients (*P*: .001).

Laboratory data of study participants are summarised in Table 2. Haemoglobin, white blood cell count, liver and renal function tests, D-dimer and CRP levels of study participants are summarised in Table 2. While AST, GGT, white blood cell count, creatinine, D-Dimer and CRP levels were significantly higher in patients hospitalised in

intensive care units than in patients hospitalised in wards, Hb levels were significantly lower. These laboratory parameters showed similar changes in expired patients compared with survivors.

Risk factors associated with the ICU hospitalisation and mortality in COVID-19 patients were analysed with the logistic regression analysis (Table 3). Regarding these findings, age (>65) (*P*: .001, OR: 4.05), elevated serum d-dimer (>500) (*P*: .001, OR: 4.046), creatinine (>1,1) (*P*:

TABLE 2 Laboratory data of study participants

	Hospitalisation in ICU			Outcomes		
	Hospitalised in Wards (n: 163)	Hospitalised in ICU (n: 106)	P ^a	Alive (n: 203)	Death (n: 66)	P ^a
Haemoglobin	13.38 ± 1.99	11.96 ± 2.66	.001	13.10 ± 2.27	11.95 ± 2.53	.001
WBC count (×10 ⁹ /L)	6.71 ± 2.04	1.01 ± 5.57	.001	7.17 ± 3.48	1.09 ± 6.04	.001
Neutrophil (×10 ⁹ /L)	4.66 ± 2.81	8.11 ± 5.38	.001	5.19 ± 2.56	8.57 ± 5.48	.001
Lymphocyte (×10 ⁹ /L)	1.48 ± 0.78	1.42 ± 1.00	.65	1.47 ± 0.90	1.40 ± 0.93	.62
ALT (U/L)	30.68 ± 31.04	46.22 ± 38.28	.061	31.47 ± 22.62	53.20 ± 40.72	.021
AST(U/L)	26.63 ± 17.81	81.52 ± 40.11	.023	30.10 ± 27.766	104.12 ± 80.51	.001
GGT(U/L)	23.62 ± 14.98	43.27 ± 37.075	.001	26.02 ± 16.431	47.85 ± 34.24	.001
ALP(U/L)	70.63 ± 23.97	74.68 ± 27.42	.15	72.16 ± 25.6	79.45 ± 29.44	.12
Creatinine (mg/dl)	0.95 ± 0.22	1.30 ± 0.98	.001	0.97 ± 0.32	1.45 ± 1.14	.001
D-dimer (ng/mL)	1823.33 ± 1020.73	3722.52 ± 1236.17	.001	1762.41 ± 975.53	4943.288 ± 1191.26	.001
CRP(mg/L)	44.22 ± 31.77	110.589 ± 88.50	.001	51.95 ± 43.43	127.03 ± 98.45	.001

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl-transferase; ICU, intensive care unit; WBC, white blood cell.

^aIndependent sample *T* test.

Statistically significant *P* values are indicated in bold.

	ICU hospitalisation		Mortality	
	OR (95% CI)	P ^a	OR (95% CI)	P ^a
Age (>65)	3.27 (1.64-6.61)	.001	4.050 (1.918-8.551)	.001
Haemoglobin (<12)	0.867 (0.434-1.729)	.685	1.089 (0.539-2.199)	.813
WBC count (>9 × 10 ⁹ /L)	0.82 (0.68-1.29)	.207	2.280 (1.156-4.496)	.017
AST(>35 U/L)	0.641 (0.297-1.383)	.257	1.036 (0.478-2.248)	.928
GGT(>40 U/L)	2.731 (1.26-5.90)	.011	2.374 (1.23-4.48)	.015
Creatinine (mg/dL) (>1.1)	2.19 (1.11-4.29)	.022	2.165 (1.115-4.206)	.023
D-dimer (ng/mL) (>500)	3.84 (1.94-7.57)	.001	4.046 (1.821-8.989)	.001
CRP (mg/L) (>10)	3.95 (1.52-10.17)	.004	1.273 (0.690-2.645)	.205

Abbreviations: AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl-transferase; ICU, Intensive Care Unit; OR, odds-ratio; WBC, white blood cell.

^aMultivariate logistic regression analysis.

Statistically significant *P* values are indicated in bold.

TABLE 3 Risk factors associated with the ICU hospitalisation and mortality in COVID-19

.023, OR: 2.165) and GGT levels (>40) (*P*: .015, OR: 2.374) at admission were independent factors predicting mortality in COVID-19 patients.

In ROC curve analysis, the areas under the curve were calculated for these variables and summarised in Table 4, Figure 3.

Since the AUC was the highest for GGT, we calculated some GGT values to predict the mortality in ROC curve with different sensitivity and specificity values. Regarding these results, 30.5 U/L has the best sensitivity (76.3%) and specificity (69.7%) combination.

4 | DISCUSSION

In this study, we analysed the factors affecting ICU hospitalisation and mortality in patients with Covid-19 and we determined that

age older than 65 years, higher serum D-dimer, creatinine, and GGT levels than the upper limits of the laboratory at admission were independent factors predicting ICU hospitalisation and mortality in COVID-19 patients. Moreover, in ROC analysis, we determined that GGT values higher than 30 U/L at admission should be regarded as a risk factor for mortality and these patients should be evaluated more intensely.

Since an early identification and timely intervention of patients with a tendency to become severe is essential to improve outcomes in COVID-19 patients, there are many studies in previous literature evaluating the predictive factors of outcomes. Jinrui et al reported that the higher level of CRP and ALT levels and chronic comorbidities were the risk factors for the progression into severe pneumonia in COVID-19 patients.¹⁸ Ullah et al defined elevated CRP and

TABLE 4 The results of ROC curve analyses

	AUC	Asymptotic 95% confidence interval	
		Lower bound	Upper bound
Age	0.728	0.703	0.807
GGT	0.759	0.69	0.827
Creatinine	0.698	0.615	0.782
CRP	0.758	0.692	0.824

Abbreviations: CRP, C-reactive protein; GGT, gamma-glutamyl-transferase.

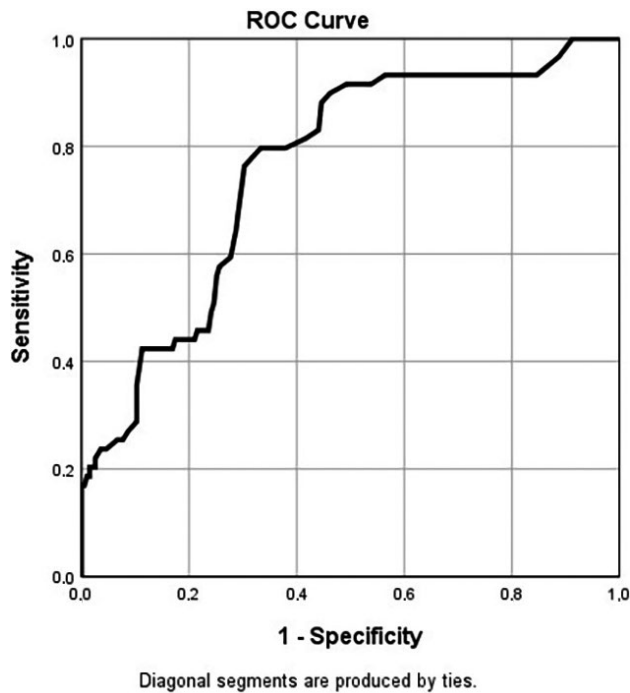


FIGURE 3 ROC curve for GGT in prediction of mortality

D-dimer levels as independent predictors of in-hospital mortality.¹⁹ Supporting our results, in a meta-analysis, age, and CRP levels were also defined as the main risk factors in predicting severe COVID-19 outcomes.²⁰ Unlike this study, in our study, it was determined that GGT is important in predicting the outcome. Our strict exclusion criteria and the fact that the study was conducted in a larger population may explain this difference between these two studies.

Based on the admission data, in elderly patients, serum albumin and D-dimer levels and onset to hospitalisation time were reported as significant predictors for the severity of COVID-19.²¹ In another meta-analysis performed to identify the predictors associated with poor clinical outcomes in patients with COVID-19, severe COVID-19 was associated with lower levels of lymphocytes and haemoglobin; elevated levels of ALT, AST, creatinine, high-sensitivity CRP, D-dimer, ferritin and LDH levels.²² Our results were supporting these previous findings and we also determined that older age and elevated serum d-dimer, creatinine, and GGT levels at admission were independent factors predicting ICU hospitalisation and mortality in

COVID-19 patients. Admission serum CRP levels were associated with the ICU hospitalisation but not with the mortality in our study. This may be associated with the late elevation of CRP levels requiring time for the synthesis during the hospitalisation of patients.

In previous literature, patients with elevated liver function tests were related to more severe disease in COVID-19.^{14,15} However, Ramachandran et al reported that elevated AST or ALT levels among hospitalised COVID-19 patients were associated with higher rates of mechanical ventilation but were not a significant independent predictor of more severe disease.²³ In a recent study from Turkey, elevated serum ALT, AST levels and AST/ALT ratio >1 were associated with the more severe course and increased mortality in COVID-19.²⁴ However, Ponziani et al reported that baseline liver test abnormalities were associated with the increased risk of ICU admission but not the outcomes.²⁵ Similarly, Monterde et al reported that abnormalities in liver function tests on admission were not associated with survival but with respiratory complications at admission. However, an increase during hospitalisation in GGT, and ALP levels was associated with reduced survival.²⁶ Zhang et al did not determine any role of ALT, AST or GGT levels in predicting severe COVID-19 infection.²⁷

In a clinical epidemiological study, Shao et al reported that elevated GGT and CRP levels were associated with a longer length of hospital stay.²⁸ Very recently, abnormal liver biochemical tests at admission were reported to be closely related to the severity and prognosis of COVID-19 patients, supporting our findings.²⁹ In this study, we determined that elevated serum GGT levels, but not aminotransferases, at admission were associated with the increased risk for ICU hospitalisation and mortality.

There are some limitations to this study that should be mentioned. First, this is a retrospective study carrying some bias of this type of investigation. Second, we did not analyse the effects of comorbidities in this group of patients, which may also affect the outcomes. Although we could not exclude all factors that may cause GGT elevation in participants, multicentered design of study and using same treatment algorithms were the strong ways of this current research.

In conclusion, in hospitalised patients with COVID-19, laboratory data on admission, including serum GGT, creatine and d-dimer levels have an important predictive role for the ICU requirement and mortality. Since these tests are readily available in all hospitals and inexpensive, some predictive formulas may be calculated with these parameters at admission, to define the patients requiring more intense treatments.

DISCLOSURES

Authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

B.K and MK contributed to study design. A.Y, A.T, G.C and YSS contributed to data collection. B.K, A.Y, A.T, G.C and YSS contributed to data analysis. B.K, A.Y and MK contributed to manuscript preparation.

GUARANTOR OF THE ARTICLE

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How to cite this article: Kasapoglu B, Yozgat A, Tanoglu A, Can G, Sakin YS, Kekilli M. Gamma-glutamyl-transferase may predict COVID-19 outcomes in hospitalised patients. *Int J Clin Pract.* 2021;75:e14933. doi:10.1111/ijcp.14933