JKMU
Journal of
Kerman University of Medical Sciences
https://jkmu.kmu.ac.ir
10.34172/jkmu.2024.17
Vol. 31, No. 2, 2024, 98-103

Original Article

Among Aspartate Aminotransferase, Alanine Transaminase, and Alkaline Phosphatase, Which Can Predict Poor Outcomes in COVID-19? A Retrospective Cohort Study

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Abstract

Background: The coronavirus disease 2019 (COVID-19) caused a recent pandemic that killed thousands of people by causing mild and severe systemic organ involvement. Researchers are still trying to find a suitable diagnostic tool for the disease. We investigated the effect of aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) enzyme levels on long-term outcomes.

Methods: The data in this retrospective cohort study were collected from the records of patients with COVID-19 referred to Rouhani hospital in Mazandaran, northern Iran. Patients were followed up to determine the cut-off points for predicting mortality.

Results: The data of the 320 eligible patients showed that AST levels, unlike ALT and ALP levels, were significantly associated with mortality ($P<0.001$) and disease severity ($P=0.016$). Unlike the levels of other tests, AST levels on admission had a significant association with mortality ($P<0.001$, 95% CI = 2.433 to 20.463, MD = 7.056) and the intensive care unit (ICU) length of stay ($P=0.012$, 95% CI = 1.291 to 7.907, MD = 3.195). None of the tests (AST, ALT, or ALP) could predict long-term mortality in patients.

Conclusion: Unlike ALP and ALT levels, AST levels showed an excellent ability to predict mortality and disease severity at admission. However, AST, ALT, and ALP could not predict long-term adverse outcomes.

Keywords: COVID-19, Aspartate aminotransferase, Alkaline phosphatase, Alanine transaminase

Citation: Ebrahimi P, Nasiri-Valikboni A, Sadeghi Haddad Zavareh M, Shirafkan H, Abedi SH. Among aspartate aminotransferase, alanine transaminase, and alkaline phosphatase, which can predict poor outcomes in COVID-19? A retrospective cohort study. *Journal of Kerman University of Medical Sciences*. 2024;31(2):98–103. doi: 10.34172/jkmu.2024.17

Received: September 1, 2023, **Accepted:** January 7, 2024, **ePublished:** April 29, 2024

Introduction

Coronaviruses are a large family of viruses that infect both people and animals. A novel virus that caused pneumonia was identified in December 2019 in Wuhan, and the World Health Organization (WHO) named it coronavirus disease 2019 (COVID-19) (1). In February 2020, the virus was formally designated as severe acute respiratory syndrome coronavirus or SARS-CoV-2, and the resulting sickness was designated as COVID-19 (2). The symptoms of COVID-19 range from asymptomatic to moderate, severe, and fatal. Cough, fever, and shortness of breath are prevalent symptoms (3). Twenty percent of patients advance to severe lung illness, and the total death rate is 2.3%. However, most patients experience mild to moderate symptoms (4). The reverse transcription-polymerase chain reaction (RT-PCR) test is the principal diagnostic method for identifying SARS-CoV-2 infection. Rapid antigen testing and antibody measurement are also used as monitoring diagnostics (5,6). With bilateral lung involvement in 75% and multi-lobe involvement in 71% of patients, abnormalities in imaging may also aid in diagnosing the resulting pneumonia (7). Remdesivir, eculizumab, steroids, immunoglobulins, and monoclonal antibodies have demonstrated possible effectiveness on hospital stay and death (8). According to the WHO data, 74 vaccines have been developed or are under research for COVID-19, and some have completed the third phase of clinical trials and are in use (9).

Aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) levels are measured to assess the function of and injuries to the liver. ALT is more specific to the liver than the other two enzymes, making it more critical for screening or monitoring liver disease. These enzymes are generated by organs other than the liver as well: AST by the brain and cardiac cells, ALT by the kidney, and ALP by bones (10-12). Liver dysfunction is common in COVID-19, and 14%–53% of COVID-19 patients suffer from varying degrees of liver injury (13). It has been found that mortality and the need for intensive care are more significant among those with severe liver disease (14-16).

Although the diagnostic and treatment approaches for patients with COVID-19 are effective and the invention of vaccinations has allowed us to prevent the illness to some extent, we are still unaware of the long-term outcome of patients, and we must establish tests to determine the long-term outcome of patients. As we need a diagnostic factor that can predict the long-term state of these individuals, we assessed the influence of these three diagnostic tests on long-term results.

Methods

Study design and setting

COVID-19 patients were included in this cohort-based retrospective analysis. Patients were randomly selected between February 20, 2020, and February 19, 2021, at Rouhani hospital in Babol, Mazandaran, northern Iran. After being discharged alive, individuals were monitored for mortality until December 6, 2021.

Participants

The inclusion criteria were (I) patients above 18 for whom molecular or clinical and paraclinical results were confirmed and (II) were hospitalized during the specified time frame. The exclusion criteria included (I) patients whose cause for referral could affect the test results used in the study; these included metabolic syndrome, hepatitis, cirrhosis, hemochromatosis, celiac disease, fatty liver disease, and other liver illnesses; (II) people receiving acetaminophen, statins, and remdesivir, as well as patients using antibiotics such as erythromycin, sulfamethoxazole, clindamycin, sulfonamides, tetracycline, amoxicillin, or trovafloxacin; (III) patients who did not have a confirmed diagnosis of COVID, had been treated as outpatients at a hospital, or did not have at least two of the necessary tests before referral; (IV) patients whose hospitalization lasted less than four days or patients who could not be followed up. Patients were monitored until death or December 6, 2021, whichever occurred first.

Variables

The variables examined in this study include age, sex, hospitalization and follow-up mortality status, length of hospital stay, underlying diseases including renal disease, cardiovascular disease (CVD), pulmonary diseases, diabetes mellitus (DM), hypertension (HTN), cancer, and hyperlipidemia (HLP). The use or non-use of interferon, intensive unit care (ICU) admission, AST, ALT, and ALP enzyme levels, and severity were also evaluated. We used the National Early Warning Score 2 (NEWS2) rating system to measure the severity of disease among the referred patients in this study (17).

Statistical techniques

The data were analyzed using SPSS software. Qualitative data were reported in percentage and frequency, and quantitative data were reported as mean and standard deviation. The chi-square test was used to analyze the association between qualitative factors and mortality and severity, and the t-test or analysis of variance (ANOVA) was employed to analyze the relationship between quantitative variables and mortality and severity. It should be emphasized that depending on whether the variances were equal, the Bonferroni or Games-Howell post hoc test was applied if appropriate. AST, ALT, and ALP levels were assessed for normality, and due to their non-normality, they were converted using LG10 (X) and reported in their retransformed form. Then, we used three Cox regression models with the backward stepwise method to identify the effect of independent variables (demographic and paraclinical findings) on the dependent variables (mortality during hospitalization, mortality during follow-up, and ICU admission). In this study, P values < 0.05 were considered significant.

Results

Basic evaluation of variables

In this study, 320 COVID-19 patients met the inclusion and exclusion criteria and were monitored to determine the influence of three diagnostic tests, AST, ALT, and ALP, on their mortality due to COVID-19.

The age of the patients ranged from 21 to 95 years, with a mean and standard deviation of 59.78 ± 16.09 years. In this study, gender distribution was nearly equal, and the majority of patients had diabetes (39.69%) and hypertension (39.06%). In terms of intensity, they mostly fell into two categories: severe (29.7%) and mild (29.1%). The duration of hospitalization was 9.11 ± 5.20 days whereas the length of ICU stay was 7.51 ± 3.68 days; of the patients, 38 expired during hospitalization, and 23 patients expired during follow-up, with a mean and standard deviation of 189.00 ± 286.78 days (Table 1).

Relationship of study variables with mortality

Table 1 demonstrates a statistically significant difference of age between the living and expired groups ($P = 0.013$, 95% CI = 1.490–12.332, MD = 6.911). The approximately 30-unit mean difference in AST levels between the living and expired patients was statistically significant ($P < 0.001$,

Table 1. Baseline data of demographic features and their relationships with in-hospital mortality

Variable			In-hospital mortality		*P* value
			Survived	Died	
Age (Mean ± SD)		16.09 ± 59.78	58.96 ± 16.09	65.87 ± 14.80	0.013*
Gender, No. (%)	Female	156 (48.8)	138 (88.8)	18 (11.5)	0.856
	Male	154 (51.3)	144 (87.7)	20 (12.2)	
Renal diseases, No. (%)	No	303 (94.7)	266 (87.8)	37 (12.2)	0.432
	Yes	17 (5.3)	16 (94.1)	1 (5.9)	
Pulmonary disease, No. (%)	No	302 (94.4)	265 (87.7)	37 (12.3)	0.394
	Yes	18 (5.6)	17 (94.4)	1 (5.6)	
Cardiovascular diseases, No. (%)	No	207 (64.7)	185 (89.4)	22 (10.6)	0.351
	Yes	113 (35.3)	97 (85.8)	16 (14.2)	
HTN, No. (%)	No	195 (60.9)	175 (89.7)	20 (10.3)	0.264
	Yes	125 (39.1)	105 (85.6)	18 (14.4)	
DM, No. (%)	No	193 (60.3)	174 (90.2)	19 (9.8)	0.166
	Yes	127 (39.7)	108 (85)	19 (15)	
Cancer, No. (%)	No	311 (97.2)	273 (87.8)	38 (12.2)	0.264
	Yes	9 (2.8)	9 (100)	0 (0)	
Severity (NEWS2), No. (%)	Mild	93 (29.1)	91 (97.8)	2 (2.2)	<0.001*
	Mild-moderate	43 (13.4)	42 (97.7)	1 (2.3)	
	Moderate	87 (27.2)	76 (87.4)	11 (12.6)	
	Severe	95 (29.7)	71 (74.7)	24 (25.3)	
Interferon, No. (%)	No	185 (60.7)	163 (88.1)	22 (11.9)	0.710
	Yes	120 (33.3)	104 (86.7)	16 (13.3)	
ICU need, No. (%)	No	260 (81.3)	248 (95.4)	12 (4.6)	<0.001*
	Yes	60 (18.7)	34 (56.4)	26 (43.3)	
AST (mean ± SD)		50.26 ± 45.63	46.71 ± 38.12	77.66 ± 78.13	<0.001*
ALT (mean ± SD)		39.88 ± 41.40	38.32 ± 38.91	51.50 ± 55.87	0.117
ALP (mean ± SD)		216.22 ± 189.09	209.48 ± 169.31	264.84 ± 293.71	0.052

SD: standard deviation; DM: diabetes mellitus; HTN: hypertension; NEWS2: national early warning score 2; ICU: intensive care unit; AST: aspartate aminotransferase; ALT: alanine transaminase, ALP: alkaline phosphatase.
* Statistically significant (*P*-value < 0.05)

95% CI = 0.269–0.098, MD = 0.183). Considering the variance of around 13 units in ALT levels and 55 units in ALP levels, there was no significant association between these factors in the surviving and expired patients ($P > 0.05$ in both instances). Despite the absence of a correlation between hospitalization time until ICU admission and mortality during hospitalization, a significant relationship was found between hospitalization duration and mortality, with a mean hospitalization period of 12.13 ± 8.24 days in the deceased patients and 8.71 ± 4.5 days in the surviving patients ($P < 0.001$, 95% CI = 1.694 to 0.880, MD = 3.426).

Relationship of study variables with severity

In assessing the relationship between the variables and disease severity, we found that the factors that substantially increased disease severity were diabetes ($P = 0.04$), hypertension ($P = 0.012$), and cardiac disease ($P = 0.004$). There was no significant correlation between other underlying disorders and gender or even interferon usage ($P > 0.05$ for all). In addition to the correlation between ICU admission and patient death, there was a strong correlation ($P < 0.001$) between severity and ICU admission. The ANOVA test revealed a significant relationship between age and disease severity ($P < 0.001$, $F = 35.512$). The post hoc test showed the relationship between age and mild to mild-moderate ($P < 0.001$, 95% CI = -4.20 to -17.79), mild to moderate ($P < 0.001$, 95% CI = -8.96 to -19.65), mild to severe ($P < 0.001$, 95% CI = -15.87 to -25.30, mild-moderate to severe ($P = 0.004$, 95% CI = -2.38 to -16.71), and moderate-severe ($P = 0.032$, 95% CI = -0.39 to -12.17) severities. Unlike the relationship between duration of hospitalization and ICU admission ($P = 0.206$, $F = 1.531$), the duration of hospitalization was significantly associated with an increase in disease severity ($P = 0.002$, $F = 5.090$). This relationship existed with mild to moderate severity ($P = 0.001$, 95% CI = -0.76 to -3.66) and mild to severe

severity ($P=0.002$, 95% CI = -0.73 to -4.55). In terms of test levels, in contrast to ALT and ALP levels, which were not significantly associated with increasing severity (ALT: $P=0.990$, $F=0.038$; ALP: $P=0.401$, $F=0.984$), AST level had a significant correlation with increased severity ($P=0.016$, $F=3.506$); this relationship was observed with mild and severe severities ($P=0.009$, 95% CI = -0.1717 to -0.217).

Next, we looked at how underlying diseases, gender, and ICU admission affected AST, ALT, and ALP levels in patients with COVID-19. The mean ALP level was significantly linked to kidney disease ($P=0.007$), cardiac disease ($P=0.012$, 95% CI = 0.108 to 0.013, MD = 0.061), and cancer ($P=0.009$, 95% CI = 0.318 to 0.013, MD = 0.061). ALT level was strongly associated with the male gender ($P=0.046$, 95% CI = 0.135 to 0.001, MD = 0.068) (38.65 ± 36.09 vs. 43.67 ± 43.49). AST and ALT levels were significantly associated with ICU admission (AST: $P=0.002$, 95% CI = 0.184 to 0.040, MD = 0.112, 43.53 ± 47.35 vs. 52.35 ± 62.90; ALT:

$P=0.029$, 95% CI = 0.181 to 0.009, MD = 0.095, 36.13 ± 37.40 vs. 58.25 ± 50.67).

The models shown in Table 2 provide an overview of the final results of the Cox regression. AST level at the time of referral, unlike ALT and ALP levels at that time, affected mortality during hospitalization and ICU admission, which shows the superiority of this test to other tests, none of which (AST, ALT, and ALP) were able to predict mortality in the long term accurately. Among the underlying conditions, diabetes affects hospitalization mortality, and hypertension affects long-term mortality, and, unlike diabetes, also has a substantial influence on blood pressure.

Table 2. Risk factors affecting death or severity by COX regression model analysis

Models**	Variable		HR	95% CI		*P value*
				Lower	Upper	
Model 1	DM		1.829	0.938	3.566	0.076
	AST		7.056	2.433	20.463	<0.001*
	Severity	Mild-moderate	0.443	0.039	4.989	0.510
		Moderate	2.207	0.477	10.218	0.311
		Severe	3.968	0.900	17.499	0.069
Model 2	Age		0.985	0.969	1.002	0.090
	AST		3.195	1.291	7.907	0.012*
	Severity	Mild-moderate	2.121	0.632	7.120	0.224
		Moderate	4.303	1.576	11.747	0.004*
		Severe	5.557	1.988	15.453	0.001*
Model 3	HTN		1.858	1.074	3.214	0.027*
	ICU need		4.415	2.520	7.734	<0.001*
	Severity	Mild-moderate	0.879	0.218	3.541	0.856
		Moderate	2.136	0.825	5.529	0.118
		Severe	3.451	1.400	8.508	0.007*

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; AST, aspartate aminotransferase;
* statistically significant (P value < 0.05)
** Event 1: in-hospital death ($N=38$), Time 1: length of stay in the hospital; covariates used in Model 1: age, sex, history of lung disease, heart disease, kidney disease, DM, HTN, HLP, AST, ALP, severity (censored = 273). Event 2: ICU need, Time 2: duration between hospital and ICU admission ($N=58$); covariates used in Model 2: age, sex, history of lung disease, heart disease, DM, cancer, HLP, AST, ALT, ALP, severity (censored = 253). Event 3: in long-term follow-up death ($N=56$), Time 3: duration between admission to the endpoint; covariates used in Model 3: age, sex, history of lung disease, kidney disease, heart disease, DM, HTN, cancer, HLP, ICU need, interferon, length of stay in the hospital, AST, ALP, severity (censored = 240).

Discussion

The mean age of patients in this research was 59.78 years, and there was a strong relationship between age and death at the time of discharge and illness severity. In a meta-analysis by Kang et al. (18), increasing age was associated with higher mortality and morbidity. Hundt et al and Cen et al reported increased disease severity with rising age (19,20).

Examining the link between tests and mortality and severity revealed that, unlike the other two enzymes, higher AST levels were associated with greater severity and mortality in patients. This result is comparable to that of Ding and colleagues' research, which revealed higher AST levels related to mortality of COVID-19 patients (21). In Hu's study, identifying the cut-off criteria for AST as > 35 or < 13 revealed a substantial correlation between AST levels and mortality and severity (22). The research by Clark et al. identified a systemic inflammatory reaction as the source of liver injury in COVID-19 patients (23). Lei et al discovered that ALT and AST levels affected severity; however, there was no correlation between ALP levels and severity (24). As indicated, differing classifications of illness severity have resulted in discrepancies in identified risk factors; however, there is consensus about the impact of AST levels on disease severity. In research by Mertoglu et al, correlations were discovered between the AST levels of patients who were admitted to the ICU and those who were not; however, no correlations were found for other liver enzymes (25). A study conducted by Pott-Junior et al suggested that a mild to severe elevation of AST and ALT levels correlates with severe conditions based on NEWS2 (26). Given that the inclusion criteria for patients with liver illness were missing and that ALT levels are more specific than AST for the liver, we anticipate that AST levels will be greater than ALT due to the systemic involvement of COVID disease and can better predict mortality and severity.

Unlike the ALT and ALP tests, AST level is an influential factor in both mortality during hospitalization and ICU admission, such that a rise in its level raises the risk ratio by 7.05 for mortality and by 3.19 for ICU admission. Notably, a rise in the level of any of the tests

over time cannot predict mortality; thus, the AST level should only be used to identify the severity and mortality during hospitalization in COVID-19 patients and not for an extended period. In HU's study, a logistic regression model was employed to examine the influence of factors on disease severity. Age was one of the eight variables that remained in the model as an independent risk factor (22). Although diabetes was related to a 1.82-fold increase in mortality at the time of admission in our analysis, this result was not statistically significant. Patients with hypertension had a considerably higher risk ratio of 1.85 for mortality in the long term, highlighting the need for shorter follow-ups in patients with COVID-19 and a history of hypertension. Using logistic regression, Escalera-Antezana et al found that only hypertension and age affected mortality in patients with COVID-19 (27). A comparable study employed Cox regression in a one-month follow-up of patients to examine the influence of different factors on mortality in two models. In the first model in this investigation, after entering twelve variables, ultimately, the variables of age above 65, male gender, history of diabetes, coronary heart disease, hypertension, and COPD were identified as mortality risk factors. The second model of this investigation, which incorporated laboratory variables and age and gender, age above 65, procalcitonin, nitrogen urea, and alpha-hydroxybutyrate dehydrogenase, remained in the model. The ineffectiveness of the AST level in this investigation, which contrasts our results, may be due to the qualitative assessment of this variable, as a 40 U/L level or higher of this enzyme was considered significant (19). Using the Cox regression model, Lv et al found that cardiac disease, hypertension, and age above 50 significantly influenced disease severity (28). In an investigation done by Kim et al, using a regression model, age at various time intervals, diabetes, obesity, and male gender were demonstrated to influence ICU admission (29), comparable to our results regarding the impact of diabetes on ICU admission.

This study had the following limitations: lack of adequate follow-up of patients for readmission of patients, the probability of patients developing new diseases or taking drugs affecting the tests, and the lack of accurate information regarding the underlying diseases that could influence the results.

One of the features of the study is that we picked the definition of intensity based on the NEWS2 scoring system, which few studies have employed, and we demonstrated the usefulness of this system in predicting mortality during hospitalization and the duration of hospitalization before admission to the ICU.

Conclusion

AST level not only has a good ability to predict mortality during hospitalization of patients with COVID-19 but is also associated with disease severity according to NEWS2 and is recognized as an influential factor in predicting patient survival in terms of mortality during hospitalization and ICU admission. To determine the prognosis and risk ratio of COVID-19 patients, we advise evaluating the levels of this enzyme. Additionally, we advise testing the levels of ALP and ALT to assess further deterioration. It should be highlighted that monitoring the levels of these three enzymes cannot be used to forecast the long-term outcomes of patients.

Acknowledgements

The authors would like to express their gratitude to the Clinical Research Development Unit of Rouhani Hospital in Babol, Iran.

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Competing Interests

None.

Ethical Approval

This study was approved by the Ethics Committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRI.REC.1400.081.

Funding

None.

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