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Original Article

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Baseline aspartate aminotransferase activity is closely related to COVID-19 mortality: A bidirectional cohort study

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Abstract

***Background & Aims*:** The coronavirus disease 2019 (COVID-19) outbreak has become a global public health pandemic, and many deaths occurred in a short period. It is possible for coronaviruses to cause hepatic injury, and the dying patient may complain about it. Aim of this study was to compare the liver function parameters, and demographic, clinical, and laboratory results between survivors and non-survivors of COVID-19.

***Materials & Methods*:** This was a retrospective-prospective cohort study conducted at Universal Hospital in Sudan. The Study included 80 cases of coronaviruse infected patients, of them 43 (53.7%) were female and 37 (46.3%) were male. A structured questionnaire was used to collect demographic, clinical, and results of liver function tests on the first day of admission. Patients were divided into survivors (treated and discharged) and non-survivors (died) groups, according to their outcomes. The analysis of the questionnaire was done using SPSS version 25.

***Results*:** Out of the 80 coronaviruse infected patients, 35 (43.8%) were survivors while the remaining 45 (56.2%) were non-survivors. The results revealed a significant increase in the mean levels of AST (p. value= 0.001), ALT (p. value= 0.047), and decreased levels of Albumin (p. value= 0.009) in the Non-survivor group compared to the survivors' group. The regression analysis demonstrated a significant correlation between AST (p value =0.04) and albumin (p value=0.02) with COVID-19 death. In the Receiver Operation Curve (ROC) analysis, the Area Under the Curve (AUC) value of the AST was 0.70 (p=0.002) with sensitivity and specificity of 73% and 66%, respectively.

***Conclusion*:** The Study concluded that baseline AST level was significantly correlated with the mortality of COVID-19 patients.

***Keywords*:** Aspartate Aminotransferase, Coronavirus, COVID-19, Liver Function

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Introduction

The coronavirus 2019 (COVID-19) disease due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was begun in Wuhan-China in December 2019 as a cluster of pneumonia cases of unknown etiology (1, 2). This outbreak was stated as a

pandemic by World Health Organization (WHO) on March 2020 (3). Sudan is the second-biggest African country, with a total population of 45.66 (4). In Sudan, The first coronavirus-infected case was confirmed on 13 March 2020, and then the number of cases increased rapidly. Most approved COVID-19 cases resided in the Khartoum State and had a new history of travel to affected countries or contact with a person from countries with confirmed cases (5). To the date of writing this paper; January 8, 2022, the number of diagnosed COVID-19 cases in Sudan was 63,702 with 58,747 cases recovered and 4,955 deaths (6). The severe acute respiratory syndrome coronavirus 2 employs the angiotensin-converting enzyme 2 (ACE2) as its receptor for entry into host cells (7). Due to broad receptor distribution throughout the body, SARS-CoV-2 may invade hepatocytes, causing liver cell damage (8, 9). The risk factors for death in the patients with this disease stand to be investigated, so this study was conducted to determine the relationship between liver function parameters to COVID-19 mortality.

Materials & Methods

This was a retrospective-prospective (bidirectional) cohort study conducted in Khartoum state at the Universal hospital, Sudan during the period from January to March 2021. Eighty Sudanese patients aged between (25-82 years) clinically diagnosed with COVID-19 were selected for this study. The inclusion criteria include the patients diagnosed with COVID-19 by polymerase chain reaction (PCR) from the nasopharyngeal swab, with complete medical records and voluntarily accepted to participate in this study. Patients who refused to participate in this study in addition to the patients suffering from alcoholism, liver disease, and pregnancy were excluded.

Data Collection:

The demographic, clinical, and laboratory findings of liver function parameters were recovered from individual records and documented in an excel sheet. The patients were followed until discharge or death. The rules for discharge were no fever for at least three days and negative PCR Results.

Ethical Statement:

Approval to conduct the study was granted by the ethics committee of Al Neelain University and complained with the declaration of Helsinki. Verbal informed consent was taken from relatives of each patient for participation at the beginning of the study.

Statistical Analysis:

Categorical variables were expressed as frequency and percentages; continuous variables given expressed as means ± SD or median and interquartile range (IQR). The differences between groups were compared using an independent Student's t-test for continuous variables and a chi-square test for categorical variables. Receiver Operating Characteristics (ROC) curve analysis was done to evaluate ideal cut-off values, sensitivity, and specificity in order to determine the best indicator of COVID-19 mortality. P-values below 0.05 were considered to be statistically significant.

Results

Eighty COVID-19 patients were included in the study, 35 (43.7%) of them were discharged alive, whereas the remaining 45 (56.3%) died. Table 1 explains the values of variables at the time of admission and compares them between survivors and non-survivors. Compared with survivors, non-survivors were older in age, had a higher prevalence of comorbidities, and required more ICU and respiratory support. Gender was not significantly different between the two groups ($P > 0.05$).

Table 1. Comparison of Demographic and Clinical Data of the Patients on Admission

Variables	Total	Survivors	Non-survivors	P value
Number	80	35	45	
Age	60.98 ± 11	55.26 ± 11	65.42 ± 7.1	0.000
Sex				0.59

Variables	Total	Survivors	Non-survivors	P value
Male (%)	37 (46.3%)	15 (18.8%)	22 (27.5%)	
Female (%)	43 (53.7%)	20 (25%)	23 (28.7%)	
Initial symptoms				
Fever (%)	77 (96.3%)	32 (40%)	45 (56.3%)	
Cough (%)	75 (93.8%)	33 (41.3%)	42 (52.5%)	
Disease Severity				
Severe-critical (%)	43 (53.7%)	17 (21.3%)	26 (32.4%)	
Mild-moderate (%)	37 (46.3%)	18 (22.5%)	19 (23.8%)	
Comorbidity				
Hypertension (%)	50 (62,5%)	19 (23.8%)	31 (38.7%)	
Diabetes Mellitus (%)	49 (61.3%)	19 (23.8%)	30 (37.5%)	
Need for ICU (%)	40 (50%)	16 (20%)	24 (30%)	
Need for Respiratory Support (%)	67 (83.8%)	30 (37.5%)	37 (46.3%)	

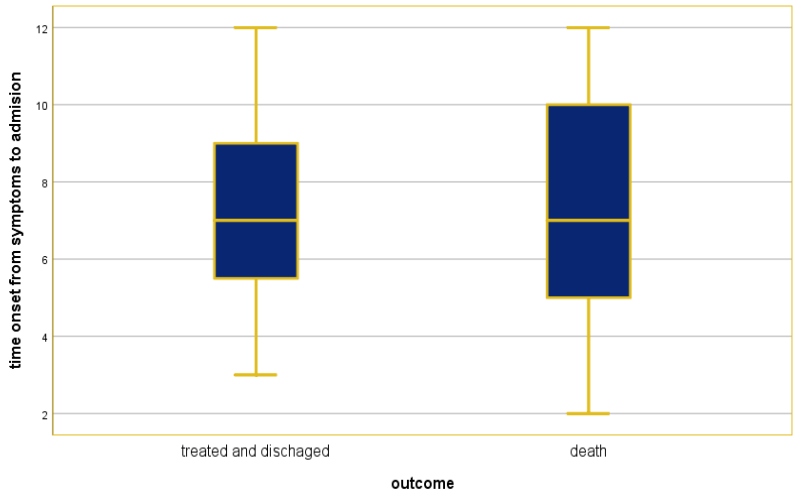

Fig. 1. shows the median time onset from symptoms to admission

Comparison of baseline laboratory findings between survivors and non-survivors:

Table 2 illustrates the laboratory findings of liver function parameters on admission to the hospital. The laboratory examination revealed that non-survivor patients had significantly higher levels of AST, ALT, and lower levels of Albumin compared to survivors.

Table 2. laboratory findings of liver function parameters on admission to hospital

Variables	Non-survivors	Survivors	P value
AST	69.93 ± 15.5	56.06 ± 19.7	0.001
ALT	71.96 ± 15.5	63.60 ± 21.3	0.047
Albumin	3 ± 0.6	3.5 ± 0.8	0.009

Association of Age and liver function parameters with the Patient outcome:

Patients' age and LFTs showed a correlation with the outcome. Out of 28 middle-aged patients (25-56 years), 18 were treated and 10 died. Fifty-two patients were from the old age group (>56 years of age) and out of these, 17 were treated and 35 died. Advancing age increases the risk of death (p-value= 0.02 and Odds ratio 2.9) (Table 3).

Six patients with normal AST levels were treated and one patient died whereas out of 73 patients having high AST levels (>40 U/L), 29 were treated and 44 died. P-value 0.04 and Odds ratio 9 show more elevations of AST in the non-survivor group.

ALT was found to be normal in 7 patients, of them 5 were treated and 2 died, whereas from 73 patients having high ALT levels, 43 were non-survivors, showing an association of increased ALT levels with the death of COVID-19, p-value 0.14, and the odd ratio calculated was 3.5. Out of 35 patients having normal albumin levels 24 were treated and 11 died whereas out of 45 hypoalbuminemia patients 11 were treated and 34 died (OR 1.37 and p-value 0.02). Therefore, liver function parameters abnormality increases the risk of death in COVID-19 patients (Table 4).

Table 3. Association of age with outcome in COVID-19 patients

Variables		Survivors	Non-survivors	P value	Odd ratio for death
Age Years	Middle Age	18	10	0.02	2.9
	Old Age	17	35		

Table 4. Association of liver function parameters with outcome in COVID-19 patients

Variables		Survivors	Non-survivors	P value	Odd ratio for death
AST U/L	Normal	6	1	0.04	9
	Increase	29	44		
ALT U/L	Normal	5	2	0.14	3.5
	Increase	30	43		
	Increase	17	32		
Albumin (g/dl)	Normal	24	11	0.02	1.37
	Decrease	11	34		

AST could predict the mortality of COVID-19 patients:

To detect the cut-off values of AST and albumin to predict COVID-19 mortality, the ROC curve was administrated and listed in table 5 and Figure 2. In ROC curve analysis, the AUC value of AST (AUC=0.709, p value= 0.002) was significantly higher than the AUC values of albumin (AUC= 0.66, 95% CI 0.53-0.79) and showed higher sensitivity (73%) and specificity (66%) values with a cut-off point of 57 IU. Moreover, patients with AST ≥ 57 on admission had significantly poor survival when compared to those with AST < 57 (P = 0.002) and therefore high AST level on admission could be considered an independent risk factor for COVID-19 mortality.

Table 5. Receiver Operating Characteristics (ROC) curves of ast and albumin

	AUC	CI	P value	Cut-off	Sensitivity	Specificity
AST	0.70	0.58-0.82	0.002	57 U/L	73%	66%
Albumin	0.66	0.53-0.79	0.016	3.1 g/dl	69%	69%

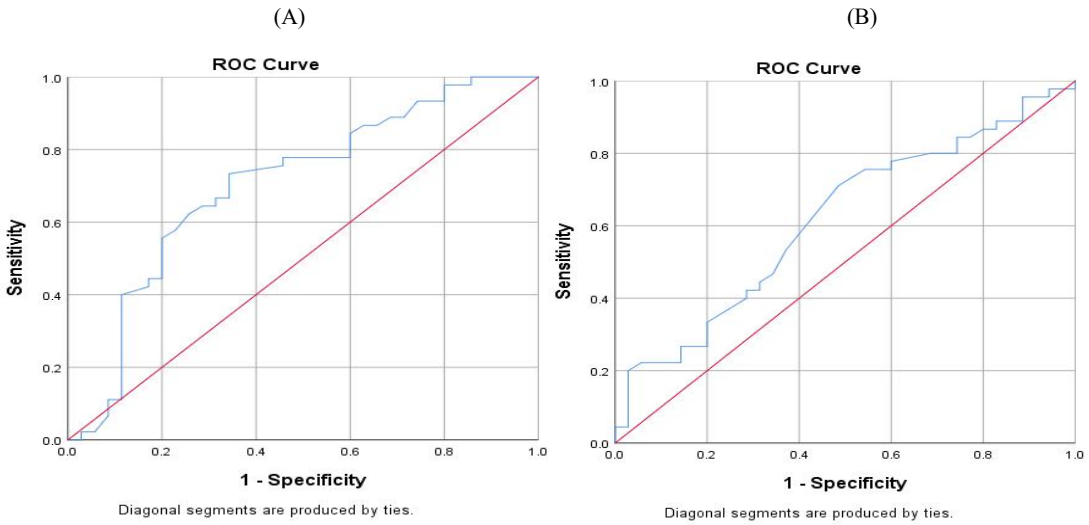

Figure 2. ROC curve of indicators. (A) AST; (B) Albumin

Discussion

In the present study, the mean age of the non-survivor group (65.4 years) was significant (p value=0.000) higher than that of the survivors' group (55.2 years), and the most common comorbidities were hypertension (38.5%) and diabetes mellitus (37.5%). These findings were quite similar to the findings of Chen et al., 2020 (10) and Wang et al., 2020 (11), who found that age and comorbidity may be risk factors for bad outcomes. Furthermore, 96.3% and 93.6 of the patients presented with fever and cough, respectively. In accordance with the studies done by Vahey et al. 2020 (12) and Wang et al., 2020 (13) who experienced fever and cough as significant signs of coronaviruses infection worldwide. This study showed that the levels of AST and ALT had significantly increased in both groups, indicating that liver injury was frequent in coronavirus-infected patients. This phenomenon was agreed with studies conducted by Huang C. et al., 2020 (14) and Guan WJ et al., 2020 (9). The potential causes of liver injury are immune-facilitated damage due to the inflammatory action following viral infection and anoxia (15). However, it cannot be excluded that antiviral drugs used for treatment may be accountable for liver injury in coronavirus patients. It needs to be said that in this study, liver function parameters were taken on the first day of admission before antiviral drugs were taken.

On the other hand, the mean level of albumin was significantly (p value= 0.009) decreased in non-survivors compared to survivors. This result is constant with the findings reported by Huang et al., 2020 (14) and Li et al., 2020 (16) who found considerable differences in albumin with lower levels seen in non-survivor groups. Albumin is produced by the liver and the half-time was 21 days. Furthermore, the median time from the start of the disease to admission was only 7 days, far shorter than the half-time of albumin, implying that hypoalbuminemia was less likely to be due to decreased synthesis of albumin and may be due to the COVID-19 inflammation, which causes the escape of albumin into interstitial space (17).

The present study found a significant correlation between age, AST, and albumin with COVID-19 prognosis; these finding is quite similar to the results of research conducted by Aziz et al., 2020 (18) and Li et al., 2020 (16) who found that poor outcome in COVID-19 is significantly associated with old age and abnormal liver test results at admission or during hospitalization. Older patients are believed to have superseded adaptive immunity and dysfunctional innate immune response.

In ROC curve analysis, the AST on admission was able to significantly differentiate between survivors and non-survivors (AUC=0.7, p value= 0.002) at 57 UL with a sensitivity of 73% and specificity of 66%. This finding agrees with a previous study done by Qin, C et al., 2020 who found that AST was an independent risk factor for COVID death -19 (AUC= 0.68, P vale= 0.001). AST is generally allocated in the mitochondria and cytoplasm of the liver cells, which gives back injury to organelle if the levels of the enzyme are increased (19). Additionally, the level of AST in the heart was higher than that in liver cells (20). Based on the above, we suppose that coronavirus may cause injury to tissue cells by hindering mitochondrial function.

Conclusion

This study concludes that elevated AST on Admission was independently associated with in-hospital mortality in SARS-CoV-2 disease. There are potential limitations of this study, of its small sample size and the study being single centered which did not reduce the generalization of the results. So, further studies with large sample sizes and from multicenter are recommended to confirm the capacity of AST to independently predict mortality and to further evaluate whether the AST may represent a useful tool for risk stratification in hospitalized COVID-19 patients.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there was no conflict of interest.

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Authors' Contributions

All the authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

There is no conflict of interest among the authors in this study.

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