



Liver Biomarkers Assay in COVID-19 Cases: A Comparison Study between Alive and Dead Patients

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Abstract

Background: Identifying effective biomarkers plays a critical role on screening; rapid diagnosis; proper managements and therapeutic options, which is helpful in preventing serious complications. The present study aimed to compare the liver laboratory tests between alive and dead hospitalized cases for prediction and proper management of the patients.

Methods: This retrospective, cross sectional study consists of all deceased patients admitted in one center in Shiraz, Iran during 19 Feb 2020 to 22 Aug 2021. For further comparison, we selected a 1:2 ratios alive group randomly.

Results: Overall, 875 hospitalized cases died due to COVID-19. We selected 1750 alive group randomly. The median age was significantly higher in died group (65.96 vs 51.20). Regarding the laboratory findings during the hospitalization ALT, AST, Bili.D were significantly higher in non-survivors than survivors but Albumin was less in deceased patients. It was revealed elevated levels of Albumin, AST, Bili.T and Bili.D were associated with increasing the risk of in hospital death. Moreover, the predictive effect of ALP and Bili.D had significantly more than others with high sensitivity and specificity.

Conclusion: We found patients with COVID-19 have reduced serum albumin level, and increase ALT and AST. The current results revealed abnormal liver chemistries is associated with poor outcome, which highlighted the importance of monitoring these patients more carefully and should be given more caution.

Keywords: COVID-19; Liver; Biomarkers; Death; Alive

Introduction

Spreading coronavirus disease all over the world, create a major challenge and effect on all aspect of life. Virtually population all over the globe are susceptible to SARS-CoV-2 infection; since there

is no certain treatment and drug yet (1, 2). Due to the heterogeneity extension in the COVID-19 pattern and its different symptoms, prediction of the disease has become complicated. Although



COVID-19 is known as respiratory disease, but due to different degrees of disease severity, a broad spectrum of clinical manifestations from asymptomatic to acute phases has been reported. Exacerbate in symptoms especially acute respiratory distress syndrome (ARDS); cytokine storm and hyper inflammation causes multi-organ failure and create an increasing death rate (3-5).

Preliminary studies describe about development of disease, which is strongly associated with an excessive change in level of biochemical biomarkers (6). Due to rapid spreading and high transmission; and lack of proper treatment, the mortality rate is in increasing. Therefore, then early prediction and identification are crucial. In this crisis, scientific and medical community needs to be linked to identify reliable biomarkers related to COVID-19 and its progression (7, 8).

Categorizing patients into various risk groups can assist about optimal treatment. Identifying effective biomarkers plays a critical role on screening; rapid diagnosis; proper managements and therapeutic options which is helpful in preventing serious complications (9, 10). Moreover, it was seen some biomarkers are associated with COVID-19 severity. Therefore, identifying efficacious biomarkers for prediction of disease progression and preventive strategies and so decreasing the fatality would be beneficial.

The present study aimed to compare the liver laboratory tests between alive and dead hospitalized cases for prediction and proper management of the patients.

Methods

Study Design and participants

This retrospective cross-sectional study consists of 875 died cases during 19 Feb 2020 to 22 Aug 2021. This study was conducted in Ali Asghar Hospital as the main referral COVID-19 center in Shiraz, Iran affiliated with Shiraz University of Medical Sciences (SUMS). According to the main aim of study, introduced dead cases were compared with a survive control group. In order to compare these cases, we selected a 1:2 ratios alive

group randomly as a control. Patients were hospitalized based on clinical COVID-19 diagnosis criteria (i.e. Fever, respiratory symptoms, Chest pain and etc.). Cases with COVID-19 Real-Time PCR positive results were confirmed and included in the study. The primary endpoint was defined as mortality in hospital at least within 48 h after admission.

This study was approved by Shiraz University of Medical Sciences ethics committee (Ethical code: IR.SUMS.REC.1399.028).

Data Collection

All the information was extracted from the SUMS approval electronic medical registry, which consist demographic characteristics, sign and symptoms of disease and laboratory data (11). On the aims of the study, liver biomarkers included Alanine transaminase (ALT), Aspartate transaminase (AST), Albumin, Alkaline Phosphatase (ALP), Direct Bilirubin. (Bili.D) and Bilirubin Total (Bili.T) were

Statistical analysis

All the data were summarized and described by appropriate descriptive statistics. In order to compare the differences between survivors and non-survivors the Mann-Whitney or *t*-test was used where applicable. Cox regression analysis was performed to evaluate the risk of death from different factors. Receiving operating characteristic curve (ROC curve) was used to evaluate the accuracy of biomarkers for predicting death. All statistical analysis was performed by SPSS ver.18 (Chicago, IL, USA) and *P*-value less than 0.05 was considered as level of significance.

Results

Of all hospitalized cases during the study time, 875 confirmed patients were died with COVID-19 in this center. Selected control group consist of 1750 alive confirmed patients. The median age was significantly higher in died group (65.96 vs 51.20). Males accounted for 530 (60.57%) and 927 (52.97%) of the death and survivor group

respectively. The proportion of underlying disease between two studies groups was found significantly higher in died group. However, in aspect of signs and clinical symptoms, no significant differences were seen between survivor and

deceased patients except muscle pain. Regarding the laboratory findings during the hospitalization; ALT, AST, Bili.D were significantly higher in non-survivors than survivors were but Albumin was in less level in deceased patients (Table 1).

Table 1: Characteristics of COVID-19 patients

<i>Variables</i>	<i>Died (875)</i>	<i>Survivor (1750)</i>	<i>P-value</i>
Age (yr)	65.96 (59 – 78)	51.20 (39 – 64)	<i>P</i> < 0.001
Sex(Male: Female)	(530:382)	(927:886)	0.36
Albumin	3.30 (2.90 – 3.70)	4.26 (3.95 – 4.60)	<i>P</i> < 0.001
Alkaline Phosphatase	189.50 (147-277)	161 (134 -206)	0.402
Alanine transaminase	41(30-60)	29(21-47)	<i>P</i> < 0.001
Aspartate transaminase	45(30-70)	37(26-60)	<i>P</i> < 0.001
Direct Bilirubin	0.37(0.26-0.49)	0.28(0.20-0.40)	<i>P</i> < 0.001
Bilirubin Total	0.80(0.56-1.06)	0.67(0.41-0.90)	0.38
Headache	63(7.20)	359 (20.51)	0.507
Fever	211(24.11)	890 (50.85)	0.304
Chills	370 (42.28)	360 (20.57)	0.713
Chest Pain	57 (6.51)	166 (9.48)	0.89
Cough	370 (42.285)	1023 (58.45)	0.23
Diarrhea	13 (1.48)	297 (16.97)	0.99
Muscle pain	258 (29.48)	923 (52.74)	0.002
Sore through	57 (6.51)	183 (10.45)	0.12
Short breath	723 (82.62)	902 (51.54)	0.079
Smell disorder	120 (13.71)	170 (9.71)	0.082
Taste Disorder	98 (11.2)	53 (3.02)	0.55
Hypertension	302 (34.51)	688 (39.31)	0.003
Diabetes	251 (28.68)	642 (36.68)	0.01
Cardiovascular Disease	356 (40.68)	1101 (62.91)	<i>P</i> <0.001
Liver disease	27 (3.08)	63 (3.6)	0.12
Renal disease	3 (0.34)	10 (0.57)	0.10
Asthma	35 (4)	210 (12)	0.803
HIV	2 (0.225)	8 (0.45)	0.61
Cancer	23 (2.62)	184 (10.51)	0.32
Hospital stay (days)	8 (3 – 15)	5 (2 -7)	<i>P</i> <0.001

Data are presented as Median (Inter Quartile Range) or Frequency (%). *P*-value less than 0.05 was considered as level of significance

Based on the univariate cox regression analysis, it was revealed elevated levels of Albumin, AST,

Bili.T and Bili.D, which were associated with increasing the death (Table 2).

Table 2: Cox regression analysis for the association liver biomarkers with risk of mortality in COVID-19 patients

<i>Biomarkers</i>	<i>HR (95% CI)</i>	<i>P-value</i>
Albumin	0.49 (0.27 – 0.46)	0.01
Alanine transaminase	1.005 (1.00 – 1.001)	0.057
Aspartate transaminase	1.23 (1.03 – 1.53)	0.03
Alkaline Phosphatase	0.997 (0.99 – 1.001)	0.15
Bilirubin Total	1.17(0.65 – 2.10)	0.001
Direct Bilirubin	1.56 (0.99 – 1.83)	0.02

Furthermore, the predictive ability of biomarkers was evaluated by ROC curve and the results are provided in Table 3. The area under ROC curve was 0.64 and 0.60 for Bili.D and ALP respective-

ly (Fig 1). The predictive effect of ALP and Bili.D had significantly more than others with high sensitivity and specificity.

Table 3: Receiver operating characteristic curves for in-hospital mortality

<i>Variables</i>	<i>AUC (95%CI)</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>P-value</i>
Albumin	0.36 (0.26 – 0.46)	0.84	0.73	0.057
Alkaline Phosphatase	0.601 (0.49-0.71)	0.87	0.74	0.03
Alanine transaminase	0.56 (0.45 – 0.67)	0.75	0.68	0.23
Aspartate transaminase	0.59 (0.49 – 0.68)	0.84	0.61	0.087
Direct Bilirubin	0.64 (0.54 – 0.74)	0.81	0.69	0.008
Bilirubin Total	0.55 (0.45 -0.63)	0.75	0.66	0.27

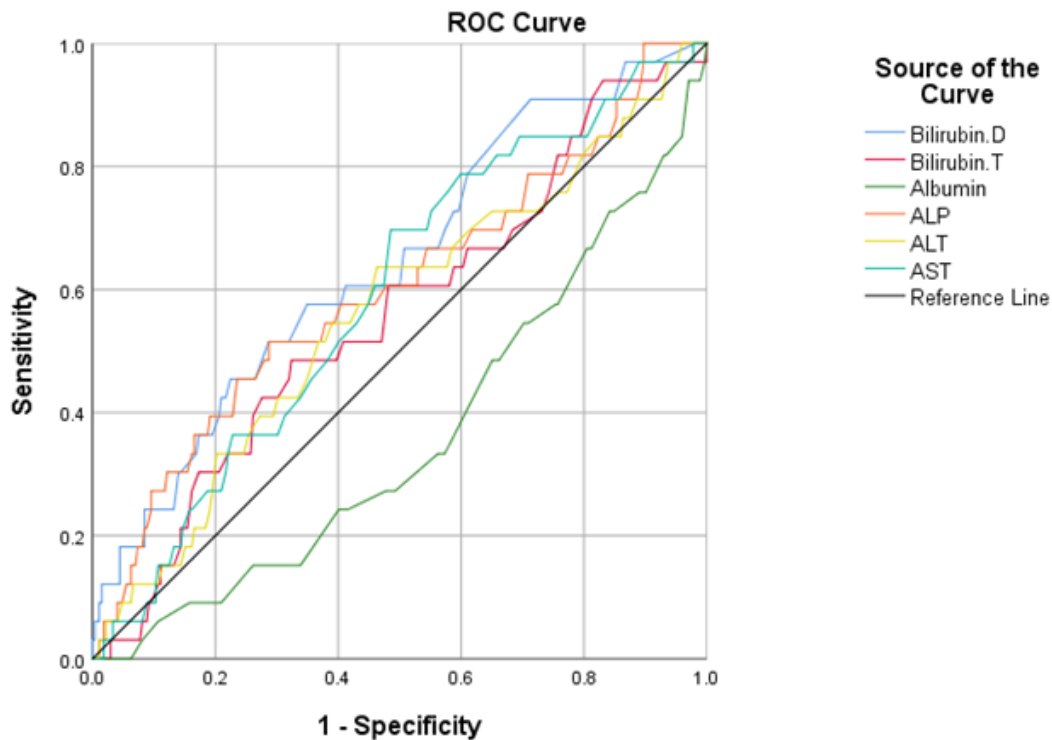


Fig.1: Receiver operating characteristic curves for in-hospital mortality

Discussion

Rapid spreading of SARS-CoV-2 infection all over the world creates a global burden on health care staff and medical facilities. Several biomarkers are useful in evaluating reflection of diseases pathological development. Biomarkers would be a good index for clinicians in starting treatment, monitoring and screening the patient's condition (12, 13).

Although various studies are conducted about different biomarkers, in this study specifically the liver indexes were assessed in non-survivor COVID-19 patients and compared with survivor cases. Based on the current findings; Albumin, ALT, AST and direct Bilirubin were different significantly between two studied groups. Moreover, it was seen except Albumin which had lower value, other biomarkers were significantly high in died cases. Furthermore, ROC curve analysis had shown ALP and Bilirubin.D were predictive factors for in hospital mortality. Abnormalities in Albumin, AST and Bilirubin.D were identified as hazardous biomarkers which increase the rate of mortality. Several studies have investigated serum markers with severity of COVID-19, however, organ failure due to COVID-19 should be considered as a fact which needs more evaluation. Therefore, it is crucial to know the beneficial biomarkers to predict and prevent in these patients so far (14).

Changes in biomarkers may potentially be important in severity of the disease, organ failure and finally death. The changes of liver biomarker between died and discharge patients is similar to that between severe and non-severe groups (15). Moreover high level of ALT and AST in died cases were seen in other studies which is along with current results (16). Furthermore lower level of Albumin was seen either in died cases of other studies (17). Related explanations may be due to Albumin's role in protecting organs from hurts and incidence of cytokines storm in infected patients (18). This means SARS-CoV-2 infection creates an increasing trend on ALT, AST,

Bilirubin.D, and Bilirubin.T and make patients' more severe and worsen outcomes.

Since synthesizing all coagulation factors are happening in the liver, liver dysfunction in deceased patients was exacerbated due to inflammation storm and hypoxemia. Based on the recent analysis it was found liver chemistry abnormalities are worse in dead patients than those who discharge (19). As SARS-CoV-2 infection is novel and creates a new disease, identifying the complications is very important. Based on the published reports; the acute liver injury was seen in 9% of dead patients and only 2% in recovered cases (20).

Following the use of high-dose corticosteroids, anti-virals and anti-bacterials may result in acute/chronic liver failure or lead to underlying liver diseases and become susceptible to re-infection after recovery. On the whole, monitoring is necessary for these patients during hospitalization. Clinicians must be aware of the risk of death or progression of disease and liver failure to prevent further deterioration of the patient's condition. This means the importance of liver biomarkers for diagnostic and preventive processes and early warning against potential death.

Conclusion

We found patients with COVID-19 have reduced serum albumin level, and increase ALT and AST. The current results revealed abnormal liver chemistries is associated with poor outcome, which highlighted the importance of monitoring these patients more carefully and should be given more caution.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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