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The Relationship Between Changes in Liver Enzymes and Mortality of Patients Admitted to a Surgical Intensive Care Unit

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Abstract

Background: Increased levels of alanine transaminase (ALT) and alkaline phosphatase in the liver are associated with an increased risk of mortality in hospitalized patients. This study aimed to survey the relationship between changes in liver enzymes and mortality of patients admitted to a surgical intensive care unit (ICU).
Methods: This cross sectional study was based on the electronic and clinical records of patients, hospitalized in the ICU of Rasool Akram hospital from 2012 to 2015. The information of 199 alive and 140 deceased patients was studied. The laboratory parameters, clinical information, acute physiology and chronic health evaluation (APACHE-II) scores, and sequential organ failure assessment (SOFA) scores were determined upon admission, and length of ICU stay was measured.
Results: There was a significant difference in the aspartate aminotransferase (AST) level upon admission in alive and deceased groups (42.01 ± 46.65 and 58.54 ± 80.95 mg/dL, respectively) ($P < 0.05$). However, there was no significant difference in the level of AST at discharge between the groups (39.05 ± 36.69 and 67.95 ± 21.7mg/dL, respectively) ($P > 0.05$). There was a significant difference in the level of ALT upon admission between the groups (34.21 ± 58.13 and 41.32 ± 66.77 mg/dL, respectively) ($P > 0.05$). However, there was no significant difference in ALT level at discharge between the groups (38.44 ± 48.69 and 42.94 ± 76.47 mg/dL, respectively) ($P > 0.05$). Based on the multivariate logistic regression model, the predictive factors for mortality included use of inotropes, alkaline phosphatase, and reduced platelet count, potassium level, and heart rate.
Conclusions: Measurement of serum liver enzymes has inadequate predictive value for mortality in ICU patients.

Keywords: Liver Enzyme, Mortality, Intensive Care Units

1. Background

Liver plays a key role in the synthesis and metabolism of proteins, toxins, and drugs and is involved in the regulation of immune system (1). Acute liver failure or sudden liver damage is associated with acute liver function failure and can result in brain malfunctions, such as encephalopathy (2). In liver damage, hepatocellular permeability increases, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) secrete from the internal part of the cell to the plasma.

The time it takes for liver enzymes to increase in level depends on the intensity of enzyme production in the liver, as well as enzyme half-life, ranging from 17 hours for AST to 50 hours for ALT (3). In case of liver cell malfunction, variations are predictable in the plasma level of several markers. Bilirubin is associated with liver function and is largely used in scoring systems of organic functional disorders, such as sequential organ failure assessment (SOFA) in intensive care units (ICUs). However, this index is a delayed marker of liver function disorder, and serum bilirubin level may remain low in the primary stages of disorder (4-8).

However, serum albumin level cannot be a specific test for liver function in some patients (9, 10). Similarly, the international normalized ratio (INR) is not a specific test for liver function disorder in ICU patients (11, 12). Several factors have been mentioned for liver function disorder in patients hospitalized in ICUs, including hypoxic hepatitis,

sepsis, drugs, and vein feeding (13-26). Most drugs used for patients are metabolized in the liver, and consequently, proper hepatic function is important from this point of view.

Evaluation of liver function is normally based on monitoring liver enzymes, such as ALT, AST, alkaline phosphatase (ALP), and bilirubin. In many critical ICU patients, there is an increase in mortality with abnormal biochemical and functional liver tests, and liver enzymes cannot identify organ insufficiency or liver cell function disorder; however, they can show a spectrum of liver damages in critical patients (7, 8). Overall, functional liver tests are simple and available in clinics. Although the increase in liver enzymes can occur before patient hospitalization, it can be a result of other conditions, such as sepsis, right-sided heart failure, cardiogenic shock, hypoxia, ischemic hepatitis, drug-related damages, sclerosing cholangitis, or parental feeding in critical patients (15, 20, 23, 25).

Any changes during hospitalization, such as mechanical ventilation in the first 48 hours of hospitalization, can result in an increase in ALT during the first 3 days. Increased levels of abnormal enzymes, such as ALT and liver ALP, can cause an increase in the risk of mortality and morbidity during the 30 first days of hospitalization (16). However, further analysis is required to reach a proper treatment plan for ICU patients with abnormal liver tests (24). The importance of such plans lies in the evaluation of the relationship between changes in liver tests and mortality to confirm the necessity of regular liver test monitoring in ICU patients.

2. Methods

This cross sectional study was based on the electronic and clinical records of patients (available in the hospital archive), hospitalized in the ICU of Rasool Akram hospital from 2012 to 2015. The study was performed in accordance with an inquiry, which included information such as age, sex, type of surgery (elective or emergency), length of ICU stay, complications during hospitalization (eg, loss of consciousness, need for dialysis, and mechanical ventilation), and Acute Physiology and Chronic Health Evaluation (APACHE II) and SOFA scores upon admission.

Changes in the scores were registered and liver indices were measured upon admission, during hospitalization, after the complications, and upon discharge from ICU (due to improvements in the clinical condition or death). The patients with the following conditions were excluded from the study: 1) infants or patients younger than 16 years; 2) history of congenital, metabolic, or genetic diseases; 3) known liver and icteric problems; 4) malignancies, immunodeficiency, and chronic diseases; 5) high levels of liver enzymes (twice the normal level); and 6) incomplete information for registration in the clinical records.

Liver function indices, including bilirubin (total/direct), ALP, AST, and ALT levels upon admission, during hospitalization, and upon discharge from ICU (due to reasons such as improvement in the clinical condition or death) were registered in the patients' files. Cases of mortality during the ICU stay and the correlation between changes in liver enzymes were determined. In this study, increased enzyme levels were at least twice higher than the limit on liver tests.

Data were analyzed using SPSS version 22. First, normal distribution of quantitative variables was assessed using Kolmogorov-Smirnov test. To compare quantitative variables, independent sample t test or Mann-Whitney U test was used, while to compare qualitative variables, Chi square test was applied. P value less than 0.05 was considered statistically significant. To predict mortality, multivariate logistic regression analysis was used. To determine the predictive value of quantitative variables, multiple regression analysis was performed. Moreover, to determine the correlation between quantitative variables, Pearson's or Spearman's correlation coefficient tests were used.

3. Results

In total, 199 patients from the alive group and 140 patients from the deceased group were evaluated. There was a significant difference in terms of age, type of surgery, and glasgow coma scale (GCS) score at admission between the groups ($P < 0.05$). However, there was no significant difference regarding sex, ischemic heart disease, diabetes, and hypertension between the groups ($P > 0.05$) (Table 1).

There was a significant difference in total bilirubin at discharge, direct bilirubin at discharge, creatinine at admission, creatinine at discharge, AST at admission, ALP at discharge, blood urea nitrogen (BUN) at admission, BUN at discharge, platelet count at admission, platelet count at discharge, potassium level at discharge, and sodium level at discharge between the groups ($P < 0.05$). However, there was no significant difference in total bilirubin at admission, direct bilirubin at admission, AST at discharge, ALT at admission, ALT at discharge, ALP at admission, potassium at admission, sodium at admission, white blood cell (WBC) count at admission, WBC at discharge, hematocrit at admission, and hematocrit at discharge between the groups ($P > 0.05$) (Table 2).

There was a significant difference between the groups in terms of systolic blood pressure (SBP) at admission, SBP

Table 1. Comparison of Age, Gender, Type of Surgery, Ischemic Heart Disease, Hypertension, Diabetes, Inotrope Administration, and GCS Score at Admission Between the Groups[a]

Variables	Groups		P Value
	Alive	Deceased	
Age, y	51.63 ± 22.61	58.96 ± 20.19	0.002
Sex			0.672
Male	122 (61.3)	89 (63.6)	
Female	77 (38.7)	51 (36.4)	
Surgery			0.001
Elective	47 (23.6)	0 (0)	
Emergency	152 (76.4)	140 (100)	
Ischemic heart disease			0.12
Yes	12 (6)	2 (1.4)	
No	187 (94)	138 (98.6)	
Diabetes			0.278
Yes	14 (7)	14 (10)	
No	185 (93)	126 (90)	
Hypertension			0.466
Yes	29 (14.6)	25 (17.8)	
No	170 (85.4)	115 (82.2)	
Admission GCS	13.05 ± 3.08	7.24 ± 3.57	0.001

[a]Values are expressed as mean ± SD or No. (%).

at discharge, diastolic blood pressure (DBP) at admission, DBP at discharge, respiratory rate (RR) at discharge, heart rate (HR) at admission, HR at discharge, oxygen saturation (O_2Sat) at discharge, bicarbonate (HCO_3) at admission, HCO_3 at discharge, and pH at discharge ($P < 0.05$). However, there was no significant difference in RR at admission, O2Sat at admission, and pH at admission between the groups ($P > 0.05$) (Table 3).

The coefficients of predictive variables in the multivariate logistic regression analysis showed the significance of ALP, platelet count, potassium level, and HR ($P < 0.05$). In fact, these variables were significant factors in categorizing patients and predicting mortality in ICU patients (Table 4).

The coefficients of predictive variables in the multivariate regression analysis showed the significance of age, GCS score at admission, ischemic heart disease (IHD), RR, and pH ($P < 0.05$). In fact, these factors were significant predictors of APACHE II score at admission in ICU patients (Table 5).

The coefficients of predictive variables in the multivariate regression analysis showed the significance of age and GCS score at admission ($P < 0.05$). In fact, these factors were significant predictors of SOFA score at admission in ICU patients (Table 6).

The coefficients of predictive variables in the multivariate regression analysis showed the significance of hypertension and HCO3 ($P < 0.05$). In fact, these factors were significant predictors of the length of stay in ICU (Table 7).

There was no significant correlation between ALT and AST levels and APACHE II score in ICU patients ($P > 0.05$). There was also no significant correlation between ALT and AST levels and SOFA score in ICU patients ($P > 0.05$) (Table 8).

4. Discussion

In recent years, few studies have indicated a correlation between increased levels of transaminase enzymes in the liver and prognosis of patients in ICUs. By determining the serum level of AST and ALT enzymes upon ICU admission, it is possible to predict mortality in patients. However, in this study, the role of AST and ALT enzymes in predicting the consequences of ICU patients was not confirmed, and no significant correlation was found between these enzymes and mortality. This result was in contrast with some studies, while similar to some findings on the predictive value of liver enzymes in mortality.

In a study by Sy et al. there was no significant difference in survival based on cirrhosis etiology and severity of liver engagement (considering the level of liver enzymes). However, among indices of engagement intensity, CLIF-SOFA showed the greatest value in predicting survival (27). Moreover, in a study by Ambrosy et al. ALT level was directly

Table 2. Comparison of Laboratory Data Between the Groups[a]

Variables	Groups		P Value
	Alive	Deceased	
Total bilirubin at admission	1.16 ± 0.91	1.37 ± 1.85	0.185
Total bilirubin at discharge	0.97 ± 1.39	1.48 ± 1.87	0.022
Direct bilirubin at admission	0.42 ± 0.52	0.57 ± 1.22	0.147
Direct bilirubin at discharge	0.38 ± 0.69	0.68 ± 1.17	0.014
Creatinine at admission	1.38 ± 1.08	1.82 ± 1.34	0.002
Creatinine at discharge	1.26 ± 0.98	2.07 ± 1.69	0.001
AST at admission	42.01 ± 46.65	58.54 ± 80.95	0.02
AST at discharge	39.05 ± 36.69	67.95 ± 21.7	0.107
ALT at admission	34.21 ± 58.13	41.32 ± 66.77	0.308
ALT at discharge	38.44 ± 48.69	42.94 ± 76.47	0.566
ALP at admission	205.94 ± 128.92	223.22 ± 130.86	0.241
ALP at discharge	226.92 ± 85.41	273.44 ± 179.09	0.007
BUN at admission	20.59 ± 15.71	32.05 ± 23.68	0.001
BUN at discharge	17.7 ± 17.86	38.17± 28.78	0.001
Platelet count (*1000) at admission	218.01 ± 98.49	198.16 ± 95.93	0.047
Platelet count (*1000) at discharge	244.55 ± 120	170.73 ± 118.4	0.001
Potassium at admission	4.13 ± 0.59	4.21 ± 0.78	0.343
Potassium at discharge	3.99 ± 0.56	4.23 ± 0.82	0.003
Sodium at admission	140.82 ± 5.74	141.01 ± 7.02	0.878
Sodium at discharge	138.8 ± 5.24	140.69 ± 7.15	0.011
WBC at admission	15.15 ± 0.49	13.15 ± 0.65	0.637
WBC at discharge	10.26 ± 0.49	11.69 ± 4.72	0.222
Hematocrit at admission	33.96 ± 6.28	34.65 ± 21.44	0.668
Hematocrit at discharge	30.96 ± 4.9	30.39 ± 10.64	0.326

[a]Values are expressed as mean ± SD.

Table 3. Comparison of Hemodynamic Changes Between the Groups

Variables	Groups		P Value
	Alive	Deceased	
SBP at admission	126.8 ± 24.96	118.26 ± 27.39	0.004
SBP at discharge	124.65 ± 19.26	119.29 ± 25.5	0.032
DBP at admission	76.65 ± 15.16	69.45 ± 17.85	0.001
DBP at discharge	76.49 ± 14.92	70.94 ± 19.11	0.009
RR at admission	15.92 ± 4.15	17.12 ± 5.55	0.134
RR at discharge	15.72 ± 2.77	18.85 ± 4.39	0.001
HR at admission	89.85 ± 19.12	97.13 ± 22.28	0.002
HR at discharge	88.1 ± 16.51	98.87 ± 20.45	0.001
O_2Sat at admission	77.68 ± 64.24	73.23 ± 67.53	0.522
O_2Sat at discharge	64.28 ± 38.69	51.33 ± 36.58	0.013
HCO_3 at admission	22.17 ± 5.35	30.07 ± 31.81	0.005
HCO_3 at discharge	22.08 ± 5.51	28.92 ± 20.95	0.002
pH at admission	7.38 ± 0.08	7.36 ± 0.11	0.226
pH at discharge	7.38 ± 0.11	7.31 ± 0.15	0.001

associated with the increased level of BUN (> 10 mg/dL), need for hospitalization in ICU, and longer hospitalization. In their study, patients with the highest ALT showed high mortality (28), which is not in accordance with the findings of the present study.

In a study by Yeo et al. there were some differences in the increased level of liver enzymes between the groups of alive and deceased patients. In this study, the increase in liver enzymes played a major role in the prediction of mortality (29), which is not in accordance with the results of the present study. Moreover, in a study by Shteyer et al. increased level of liver enzymes was mostly accompanied by heart insufficiency, such as tetralogy of Fallot. The total mortality was correlated with the increased level of enzymes (30), which confirms the role of liver enzymes in the prediction of mortality in ICU patients, unlike the present study.

In a study by Raurich et al. factors related to the risk of mortality included long INR, need for kidney transplantation, and septic shock (31). However, similar to our study,

Table 4. Predictors of Mortality During ICU Stay Based on the Multivariate Logistic Regression Analysis

Variables	β	SE (β)	P Value	Odds Ratio	95% CI
Age	0.045	0.032	0.167	1.046	0.98 - 1.11
Surgery	-3.679	2.848	0.197	0.025	0 - 6.711
GCS	-0.064	0.213	0.765	0.938	0.61 - 1.42
Total bilirubin	0.498	0.906	0.582	1.64	0.27 - 9.72
Direct bilirubin	-1.046	1.52	0.493	0.351	0.018 - 7.005
Creatinine	0.202	0.505	0.688	0.817	0.304 - 2.19
AST	0.051	0.029	0.082	1.053	0.99 - 1.11
ALT	-0.068	0.044	0.121	0.934	0.85 - 1.01
ALP	0.011	0.005	0.021	1.011	1.002 - 1.02
BUN	0.051	0.046	0.267	1.053	0.96 - 1.15
Platelet	-0.022	0.009	0.019	0.979	0.96 - 1.15
Potassium	2.696	1.19	0.023	14.82	1.43 - 152.72
Sodium	-0.05	0.09	0.576	0.951	0.79 - 1.13
SBP	-0.011	0.04	0.776	0.989	0.91 - 1.069
DBP	-0.02	0.054	0.712	0.98	0.88 - 1.089
RR	0.056	0.112	0.615	1.058	0.85 - 1.317
HR	0.064	0.03	0.034	1.066	1.005 - 1.13
O2Sat	0	0.008	0.99	1	0.98 - 1.015
HCO3	0.083	0.075	0.268	1.087	0.93 - 1.25
pH	-2.59	6.09	0.67	0.075	0 - 11390
Constant	20.79	47.29	0.66	1.07×10 9	-

Table 5. Predictive Factors for APACHE II Score During ICU stay Based on the Multivariate Regression Analysis

Variables	β	SE (β)	P Value
Age	0.054	0.018	0.004
Surgery	-0.258	1.042	0.805
GCS score	-1.23	0.216	< 0.001
IHD	4.31	1.6	0.008
Creatinine	-0.608	0.426	0.155
AST	-0.002	0.005	0.725
BUN	0.022	0.033	0.502
SBP	0.017	0.028	0.537
DBP	-0.027	0.042	0.52
RR	0.195	0.088	0.029
HR	0.028	0.019	0.159
HCO_3	0.008	0.016	0.626
pH	-7.97	3.98	0.048
Constant	70.77	30.38	0.021

Table 6. Predictive Factors for SOFA Score During ICU Stay Based on the Multivariate Regression Analysis

Variables	β	SE (β)	P Value
Age	0.123	0.044	0.012
Surgery	-0.258	1.042	0.826
GCS score	-1.57	0.234	< 0.001
IHD	4.31	1.6	0.124
Creatinine	0.608	0.426	0.235
AST	-0.002	0.005	0.998
BUN	0.022	0.033	0.457
SBP	0.017	0.028	0.482
DBP	-0.027	0.042	0.326
RR	0.195	0.088	0.122
HR	0.028	0.019	0.456
HCO_3	0.008	0.016	0.478
pH	-7.97	3.98	0.447
Constant	72.24	30.38	0.034

Table 7. Predictive Factors for Length of ICU Stay Based on the Multivariate Regression Analysis

Variables	β	SE (β)	P Value
Age	0.029	0.022	0.128
Hypertension	3.06	1.239	0.011
HCO_3	0.044	0.02	0.043
Constant	10.6	2.88	< 0.001

there was no correlation between mortality and increased level of liver enzymes. Finally, in a study by Lazzeri et al. the levels of AST and ALT were correlated with mortality in hospital and ICU patients (32).

Overall, evaluation of recent studies shows that various factors may influence the predictive value of liver enzymes for mortality in ICU patients. It seems that the role of enzymes can be affected by the study plan, method of sample selection, selection of factors, and study power with respect to the number of samples. For instance, in some studies, patients with liver cirrhosis and toxemic hepatitis were excluded, while in some other studies, these criteria were discarded. Moreover, many drugs, which are frequently used in ICUs and affect the level of liver enzymes, are evaluated differently in various studies.

In summary, by removing potential confounding factors, which can influence the level of liver enzymes in ICU

Table 8. The Correlation Coefficient and Linear Relationship Between Liver Enzymes and APACHE II and SOFA Scores in ICU Patients

Scores Enzymes	APACHE II		SOFA	
	Correlation	P Value	Correlation	P Value
ALT	-0.071	0.278	-0.109	0.095
AST	-0.106	0.105	-0.115	0.078

patients, we can obtain more reliable results regarding the relationship between the increased level of liver enzymes and prognosis of patients.

4.1. Conclusions

Measurement of the serum level of liver enzymes has no considerable value in predicting the undesirable outcomes of ICU patients. Therefore, records of risk factors and other laboratory biomarkers can be beneficial in the prediction of mortality. In addition, it seems that design of future studies in this field is essential.

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