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Original Article

Evaluation of Elevated Liver Enzymes and their Association with Increased Risk of Perioperative Mortality in Heart Transplant Patients

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Abstract

Background: Cardiovascular disease, which itself can lead to liver disorders, is known as the most common cause of death in many countries, including Iran. Elevated liver enzymes can increase mortality risk after transplantation in most heart surgeries. This study aimed to investigate the effect of elevated liver enzymes before and after transplantation on the risk of perioperative mortality in heart transplant patients.

Methods: The information of this historical cohort study was prepared using patients' hospital records from 2014 to 2019. The data belonged to demographic information, medical history, and laboratory data of 203 patients admitted to Dr. Masih Daneshvari Hospital. More than three times normal institutional ranges defined elevated liver enzymes. Also, the number of deaths within 30 days after transplantation was considered to determine perioperative mortality. The Chi-square test and regression method were used to analyze the data using SPSS software.

Results: Mortality of patients with elevated liver enzymes before and on the first, second, and third days after heart transplantation was 4.08, 3.95, 3.75, and 4.89 times higher than those with normal liver enzymes, respectively. Increasing the Model for End-Stage Liver Disease (MELD) score was associated with a significantly increased risk of death ($p<0.001$).

Conclusion: Elevated liver enzymes before or three days after heart transplantation are significantly associated with perioperative transplant death. Optimization of liver function before transplantation can play an important role in preventing mortality.

Keywords: Heart transplant surgery, Liver disorders, Liver enzymes, Perioperative mortality

Introduction

Currently, cardiovascular disorders are the most common causes of death in many countries of the world, including Iran (1). One approach to deal with the increase in mortality due to heart disorders is heart transplant surgery (2). On the other hand, cardiac transplant surgery has always been associated with some risks; these risks may threaten the patients' life both during and after the transplant (3,4).

After heart transplantation, changes in various blood factors increase the risk of death (5,6). Enzymatic factors and liver function indices are such factors that increase the risk of death in patients undergoing heart transplant surgery (7). In most heart surgeries, the phenomenon of hyperbilirubinemia is a usual phenomenon. This problem may increase the risk of death from heart surgery by up to 25% (8,9). All these results and similar studies have led to the approach of paying attention to liver function factors before and after heart transplantation on the agenda of many treatment groups worldwide (10,11).

Increased liver enzymes are very important in clinical evaluation and can help predict subsequent heart disease events. In this way, monitoring liver enzymes may prevent the death of some patients. Elevated liver enzymes such as Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and Alkaline Phosphatase (ALP) are commonly found in these patients. Heart disease can be one of the predisposing factors for liver disorders, affecting heart transplantation patients' mortality rate. Therefore, timely and accurate clinical diagnosis can play an important role in recovery from cardiovascular disease (12).

Given the above content and since more studies are still needed in this field in Iran, we decided to conduct a study to investigate the trend of elevated liver enzymes and its effect on perioperative mortality of patients, to help 1) prevent mortality after heart transplantation, 2) accelerate the healing process or prevent possible exacerbations of the disease.

Materials and Methods

The present study was a historical cohort study using available hospital records. The study population was patients undergoing heart transplant surgery, 203 heart transplant patients who were admitted to Dr. Masih Daneshvari Teaching, Research and Treatment Hospital for Tuberculosis and Lung Diseases in Tehran (the capital of Iran) from the beginning of 2014 to the end of 2019.

Inclusion criteria included the following items: 1) patients with heart failure who have undergone a heart transplant, and 2) patients who were 18 years old or above. Exclusion criteria comprised the following items: 1) alcohol consumers, 2) patients with viral hepatitis or with liver failure in the field of infiltrative diseases.

Patient information was collected by referring to hospital records. In the present study, demographic information, medical history and laboratory data and also some characteristics of patients, including age, sex, history of diabetes, Hypertension (HTN), Myocardial Infarction (MI), Cerebral Vascular Accident (CVA), liver and kidney dysfunction before transplantation, blood transfusion, smoking, opium, duration of anesthesia, duration of surgery, duration of pump and duration of ischemia were recorded. The patients' laboratory tests, previously performed before and three days after surgery, including AST, ALT, ALP, total Bilirubin, Albumin, Prothrombin Time and International Normalized Ratio (PT/INR), were recorded. The normal upper range limits for AST, ALT, and total bilirubin was 33 *IU/L*, 34 *IU/L* and 1.5 *mg/dL*, respectively. The used lower limit of the normal range for Albumin was 3.5 g/dL. And the normal upper limit for ALP was 267 *IU/L*. Also, values that were more than "three times of upper limits of normal ranges" were used to define elevated liver enzymes. The values were bigger than 100 *IU/L* for AST and ALT and more than 800 *IU/L* for ALP. Finally, MELD scores were calculated. MELD score is a scoring system used to assess the severity of liver disease and predict patient survival. Serum bilirubin, serum creatinine and the patient's INR are utilized to obtain the MELD score. This index is calculated according to the following formula:

$$MELD = 3.78 \times \ln[\text{serum bilirubin } (mg/dL)] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine } (mg/dL)] + 6.43$$

The MELD scores number is located in one of three groups: less than 14, 14 to 20 and more than 20.

Also, the number of deaths within 30 days after transplantation was considered to determine perioperative mortality.

For data analysis, SPSS 21 software was used. The mean (median), standard deviation, number and percentage indexes were used to describe the demographic variables. The Chi-square test and logistic regression were used to analyze the relationship between mortality and elevated liver enzymes (as the independent variables) during the first month after heart transplantation. In this study, data were analyzed at a significance level of 0.05.

Results

The general characteristics of the study population showed that the average age of patients was 40.15 years, with a standard deviation of 12.95. Also, the majority of the patients (76.8%) were male, with the remainder (23.2%) being female. And the mean ejection fraction of the patients' hearts before surgery was 12.29%, with a standard deviation of 4.56. 33% of the patients had a history of kidney disease, and 6.89% and 13.30% of the patients had liver dysfunction and diabetes, respectively. Additionally, 17.24% of the patients had a history of HTN, and 17.73% and 2.95% had a history of MI and CVA, respectively. Furthermore, 40.3% of the patients had a MELD score of 14 or less, 29.6% had a score of 14 to 20, and 24.1% had a score greater than 20. Patients receiving inotrope and intra-aortic balloon pump (IABP) were 12.3% and 3%, respectively, before transplantation, and 87.2% and 23.6%, respectively, after transplantation. Moreover, 20.2% of the patients required extracorporeal membrane oxygenation (ECMO) after transplantation.

The results of descriptive enzyme statistics before transplantation demonstrated that the number of patients with ALT and AST enzymes more than 100 *IU/L* was 16 (7.9%) and 21 (10.3%), respectively. Also, the number of patients with ALP of more than 800 *IU/L* was 3 (1%). The results on the first day after transplantation indicated that the number of patients with ALT and AST enzymes more than 100 *IU/L* was 31 (15.3%) and 72 (35.5%), respectively. Also, the number of patients with ALP of more than 800 *IU/L* was 1 (0.5%). On the second day, the results showed that the number of patients with ALT and AST enzymes of more than 100 *IU/L* was 50 (24.6%) and 77 (37.9%), respectively. Also, the number of patients with ALP of more than 800 *IU/L* was 3 (1.5%). On the third day after transplantation, the number of patients with ALT and AST enzymes of more than 100 *IU/L* was 47 (23.2%) and 58 (28.6%), respectively. Also, the number of patients with ALP of more than 800 *IU/L* was 2 (1%).

The logistic regression model investigated the relationship between increased liver enzyme levels and mortality. Additionally, confounding factors such as duration of surgery, duration of ischemia, duration of mechanical ventilation, duration of hospitalization, duration of hospitalization in an Intensive Care Unit (ICU), IABP, ECMO, and renal dysfunction were also matched in two target and control groups (with and without increased liver enzymes). In general, patients who had an increase in enzyme before transplantation were 4.08 times [Confidence Interval (CI)=1.28-12.96] more mortality rate than patients with a normal enzyme. Similarly, the results of the study on the first, second and third days after transplantation showed that patients with elevated enzymes have 3.95 times (CI=1.407-11.127) and 3.75 times (CI=1.047-13.44) and 4.89 times (CI=1.26-18.98) higher mortality rate than patients with normal enzymes, respectively. Finally, the chance of death in patients with an overall increase in the enzyme is 4.02 (CI=1.12-14.46) times higher than the other patients (details are comparable in table 1).

The relationship between mortality and increased liver enzymes before transplantation using a logistic regression model demonstrated that the risk of death in patients with elevated ALT enzyme was 4.54 (CI=1.23-16.70) times higher than the patients with a normal enzyme. Patients with elevated AST were 6.71 times (CI=1.87-24) more likely to die than patients with normal enzymes. An increase in INR was associated with a 3.78-fold (CI=1.43-9.98) increase in the risk of death. Increasing the MELD score was associated with an increased risk of death (compared to the MELD score >20, the risk was about 12-fold for the score <14 and about 9-fold for the score=14-20) (Table 2).

Also, examining the relationship between mortality and an increase in liver enzymes on the first day after transplantation using a logistic regression model showed that the risk of death in patients with elevated ALT enzyme was 6.345 (CI=2.123-18.966) times higher than the patients with a normal

Table 1. Regression model for evaluating the relationship between enzyme increase and mortality before and three days after transplantation

	Expired	95%CI* for expire		p-value
		Lower	Upper	
Before transplantation	4.084	1.286	12.968	0.017
The first day after transplantation	3.956	1.407	11.127	0.009
The second day after transplantation	3.753	1.047	13.445	0.042
The third day after transplantation	4.894	1.261	18.986	0.022
Overall increase	4.025	1.120	14.469	0.033

* Confidence Interval

Table 2. Regression model for investigating the relationship between mortality and increased liver enzymes before and three days after transplantation

Model	Variable	Expired	p-value	95% CI* for expire	
				Lower	Upper
Before	ALT >100 *IU/L*	4.541	0.023	1.234	16.702
	AST >100 *IU/L*	6.717	0.003	1.879	24.006
	ALP >800 *IU/L*	3.207	0.372	0.248	41.528
	Alb >=3.5 *g/dL*	1.067	0.898	0.396	2.871
	INR >=1.5	3.787	0.007	1.437	9.980
	Bili >=2 *mg/dL*	1.849	0.200	0.722	4.734
	MELD Score>20	1			
	MELD Score<14	11.778	<.001	3.261	42.533
	MELD Score 14-20	8.704	0.002	2.283	33.191
First day	ALT >100 *IU/L*	6.345	0.001	2.123	18.966
	AST >100 *IU/L*	3.715	0.012	1.337	10.324
	ALP >800 *IU/L*	3.101	0.354	0.234	40.365
Second day	ALT >100 *IU/L*	6.262	0.004	1.799	21.794
	AST >100 *IU/L*	5.467	0.010	1.488	20.083
	ALP >800 *IU/L*	2.945	0.425	0.207	41.931
Third day	ALT >100 *IU/L*	6.279	0.008	1.618	24.366
	AST >100 *IU/L*	2.803	0.123	0.757	10.374
	ALP >800 *IU/L*	5.699	0.243	0.307	105.917

* Confidence Interval.

enzyme. Patients with elevated AST were 3.715 times (CI=1.337-10.324) more likely to die than patients with normal enzymes.

Additionally, the results on the second day after transplantation demonstrated that the risk of death in patients with increased ALT and AST were 6.262 (CI=1.79-21.79), 5.467 (CI=1.48-20.08) times higher than those with normal enzymes, respectively. Also, the results on the third day after transplantation showed that the risk of death in patients with increased ALT was 6.279 (CI=1.61-24.36) times higher than those with normal enzymes (Table 2).

Discussion

This study aimed to determine the effect of liver enzyme changes on patients' mortality after heart transplantation from 2014 to 2019. According to the findings, the following results were obtained: there is a statistically significant relationship between liver enzyme levels (before or three days after transplantation) and death probability. The logistic regression model suggested that patients with elevated enzymes were 4.08 times more likely to die than patients with a normal enzyme.

In a study by Lebray *et al* in France in 2018, was investigated liver injury's effect on complications after heart transplantation in 384 patients. The average age of patients undergoing heart transplantation in that research was 52 years, whereas the average age of patients in our study was 40.15 years. In addition, in their study, 77% of heart transplant patients were male, while 23% were female, but in our analysis, the percentages were 76.8 and 23.2%, respectively. In addition, their research showed an increase in MELD scores related to an increased risk of mortality following heart transplantation. This conclusion was also consistent with our research (13).

In a study conducted by Golitaleb *et al* on 600 patients between 2014 and 2015 (at the Rajai Cardiovascular Research, Medical and Research Center in Tehran, Iran), liver function tests before and after cardiac surgery (on days 1, 3 and 7), indicated hyperbilirubinemia in 150 patients (25%) (14). In the current study, 83 (40.8%) patients had increased bilirubin levels before surgery. On the first day following surgery, 97 patients (49%) showed an increase in bilirubin, 83 patients (43%) on the second day, and 80 patients (43%) on the third day. But, no considerable rise in bilirubin in patients was seen in our study, and no significant association between bilirubin increase and the mortality rate was observed.

In 2013, Kobulnik *et al* conducted a study investigating the effect of elevated liver enzymes on mortality in Canada in the first month after heart transplantation. In 126 organ-receiving patients, the mortality rate in the first month after transplantation was 10.3%. It was concluded that assessing liver enzymes is important in predicting mortality after heart transplantation (15). In our study, the logistic regression model showed that patients who had an increase in the liver enzyme (before transplantation or three days after transplantation) were 4.02 times (CI)=1.12-14.46) more likely to die than patients who had a normal enzyme.

In a 2012 study of liver parameters in patients undergoing heart transplant surgery, Chokshi *et al* examined 617 patients (including 75% male and 25% female) and analyzed ALT and AST enzymes. Then, they observed, for these patients, an 18% increase in AST enzyme and a 29% increase in ALT enzyme and concluded that preoperative liver dysfunction has a significant effect on the risk of death after heart transplantation (2). In our study, 76.8% of the patients were male, while 23.2% were female. Furthermore, liver enzymes were tested three days after the heart transplant, and it was shown that an increase in liver enzymes increased mortality risk by 4.08 times.

A retrospective study by Szyguła-Jurkiewicz *et al* in Netherlands between 2011-2014 aimed to predict the MELD scoring model using the INR one year after orthotopic heart transplantation, the data of 87 consecutive adults who underwent heart transplantation were analyzed, and the mortality rate during the observation period was 18.4%. It was concluded that the preoperative MELD-XI score, sodium serum concentration and highly sensitive C-Reactive Protein (hs-CRP) serum concentration could be used to estimate postoperative risk in heart transplant recipients during one-year follow-up (16), but MELD Score data in our study demonstrated that 46.3% of the patients had a MELD score of less than 14. In addition, 29.6% scored between 14 and 20, while 24.1% scored greater than 20. Furthermore, the logistic regression model showed that increased

MELD scores were associated with increased mortality risk following heart transplantation.

The limitations of this study included the following points: lack of full access to information (due to incomplete registration of follow-ups, outpatient and clinic visits) of patients, lack of access to information due to incomplete registration of patients' medical records in the file and lack of access to outpatient examinations after hospital discharge.

For future studies, it is recommended to investigate the following: 1) The effect of indicators other than liver enzymes on after-heart transplantation prognosis, 2) Possible relationship between the duration of the transplant list and prognosis after heart transplantation, 3) The possible relationship between the presence of various diseases in the donors and the prognosis of the recipients after heart transplantation.

Conclusion

According to our findings, an increase in liver enzymes before and three days after heart transplantation is significantly associated with the risk of mortality after transplantation. Therefore, the mortality rate after heart transplantation would be significantly decreased with preventative approaches or effective therapies for liver problems, as well as accurate follow-up of patients who had elevated liver enzymes before transplantation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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