ORIGINAL ARTICLE

Post-operative N-terminal pro-brain natriuretic peptide predicts in-hospital mortality after living donor liver transplantation

Canlı vericili karaciğer nakli cerrahisi sonrası N-terminal pro-beyin natriüretik peptit düzeyleri hastane içi mortaliteyi öngördürmektedir

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ABSTRACT

Objective: The post-operative serum level of N-terminal pro-brain natriuretic peptide (NT-proBNP) has been found to be associated with post-operative cardiovascular complications and mortality in high-risk surgeries. The usefulness of the post-operative NT-proBNP level as a predictor of mortality after liver transplantation (LT) is unknown.

Methods: The records of patients at a single, tertiary university hospital who had undergone adult living donor liver transplantation (LDLT) with data of post-operative NT-proBNP level values were retrospectively analyzed for in-hospital mortality. The highest post-operative NT-proBNP level from the first 3 days after surgery was included in the study. Receiver operating characteristic curve analysis was performed to assess the best cut-off value of post-operative NT-proBNP, and Cox regression analysis was performed to investigate the effect of NT-proBNP on mortality.

Results: A total of 114 LT recipients with a mean Model for End-Stage Liver Disease score of 15.8 were included in the study. In-hospital mortality occurred in 11 (9.6%) of the patients. A history of diabetes mellitus and the post-operative NT-proBNP level were found to be associated with mortality (p=0.011 for diabetes mellitus and p<0.001 for NT-proBNP). The best cut-off value of post-operative NT-proBNP was 1009 ng/L. Cox regression analysis indicated that the NT-proBNP level was a strong predictor of in-hospital mortality (hazard ratio: 24.467, 95% confidence interval: 3.120–191.750; p=0.002).

Conclusion: The post-operative NT-proBNP serum level independently predicted in-hospital mortality in patients who underwent LDLT. Post-operative NT-proBNP-guided management of LT recipients should be pursued.

ÖZET

Amaç: Yüksek riskli cerrahilerde operasyon sonrası bakılan N-terminal pro-beyin natriüretik peptit (NT-proBNP) serum düzeyleri kardiyovasküler komplikasyonları ve mortaliteyi öngördürücü olarak saptanmıştır. Karaciğer nakli sonrası bakılan NT-proBNP serum düzeyleri ile mortalite arasındaki ilişki henüz bilinmemektedir.

Yöntemler: Tek merkezli bu çalışmada, ameliyat sonrası NT-proBNP değerine sahip canlı vericili karaciğer nakli uygulanan hastalar hastane içi mortalite açısından retrospektif olarak incelendi. Operasyon sonrası ilk 72 saatte, günlük olarak bakılan nt-proBNP değerlerinden en yüksek değer analize alındı. Postoperatif nt-proBNP'ye ait en iyi kestirim değerini belirlemek için ROC eğrisi analizi yapıldı ve ameliyat sonrası NT-proBNP'nin bağımsız öngördürücülüğünü değerlendirmek için Cox regresyon analizi uygulandı.

Bulgular: Karaciğer nakli uygulanmış, ortalama MELD skoru 15.8 olan 114 hasta çalışmaya dahil edildi. Hastane içi mortalite 11 (9.6%) hastada gerçekleşti. Diabetes mellitus ve postoperatif NT-proBNP değerleri hastane içi mortalite ile istatistiksel olarak anlamlı idi (diabetes mellitus için p=0.011 ve NT-proBNP için p<0.001). Ameliyat sonrası NT-proBNP için en iyi kestirim değeri 1009 ng/L idi. Cox regresyon analizinde NT-proBNP hastane içi mortalitenin kuvvetli bir öngördürücüsü olarak saptandı [HR (95% CI): 24.467, (3.120–191.750), p=0.002].

Sonuç: Canlı vericili karaciğer nakli uygulanan hastalarda, ameliyat sonrası NT-proBNP hastane içi mortalitenin bağımsız bir öngördürücüsüdür. Ameliyat sonrası NT-proBNP kılavuzluğunda karaciğer nakli alıcısının yönetimi açısından çalışmalar gerekmektedir.

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Developments in both technical aspects and medical therapies used after liver transplantation (LT) have resulted in an important increase in short- and long-term survival. However, morbidity after LT is still high, and cardiovascular complications are a leading cause.[1,2] Multiple risk indices have been developed to predict cardiovascular morbidity and mortality, but the accuracy is still uncertain.[3,4]

B-type natriuretic peptide (BNP), and its inactive form, N-terminal pro-BNP (NT-proBNP), are neuroendocrine peptides released from the myocardium. It most often occurs secondary to myocardial stretch, but it may also be in response to ischemic, inflammatory, and other neuroendocrine stimuli.[5] Preoperative natriuretic peptide (NP) levels have been found to be an independent predictor of mortality and cardiovascular morbidity after non-cardiac surgery.[6,7] The data regarding the predictive role of the postoperative NP level on mortality and cardiovascular morbidity are limited.[8] The aim of this study was to assess the relationship between postoperative NT-proBNP levels and mortality after LT.

METHODS

In this single-center, tertiary hospital study, the records of patients who had undergone adult living donor liver transplantation (LDLT) were retrospectively analyzed for in-hospital mortality as the index procedure. The exclusion criteria were 1) patients without postoperative NT-proBNP level data, 2) patients with known heart failure or structural heart disease, 3) patients with atrial fibrillation, and 4) patients with renal failure. NT-proBNP evaluation with an electrochemiluminescence immunoassay (Elecsys NT-proBNP; Roche Diagnostics, Basel, Switzerland) was performed every 24 hours for the first 3 days after transplantation. The highest serum NT-proBNP serum level value was used for the analysis.

This study was conducted in compliance with the regulations and ethical guidelines for retrospective research.

Statistical analysis

Analyses of descriptive statistics were presented using the mean, SD, median, first quartile, third quartile, frequency, and percentage for the variables. Normal distribution of quantitative variables was assessed with the Shapiro-Wilk test. Quantitative variables with normal distribution were compared using an independent samples t-test. The Mann-Whitney U test was used when the variables did not display normal distribution. Categorical variables were compared with the Fisher's exact test due to low expected cell counts. Receiver operator characteristic (ROC) curve analysis was used to analyze the discriminatory performance of NT-proBNP to predict mortality. The possible factors identified in univariate analysis were entered into Cox regression analysis with backward selection to determine independent predictors of survival. A two-sided p value of <0.05 was considered statistically significant. All of the statistical analyses were performed using NCSS 2007 software (NCSS LLC, Kaysville, UT, USA).

Abbreviations:

ACC	*American College of Cardiology*
BNP	*B-type natriuretic peptide*
ESC	*European Society of Cardiology*
LDLT	*Living donor liver transplantation*
LT	*Liver transplantation*
MELD	*Model for End-Stage Liver Disease*
NP	*Natriuretic peptide*
NT-proBNP	*N-terminal pro-BNP*
RCRI	*Revised Cardiac Risk Index*
ROC	*Receiver operating characteristic*

RESULTS

Patients with atrial fibrillation (n=2), patients with dual liver-kidney transplantation (n=3), patients with cadaveric transplantation (n=37), pediatric patients (n=39), and patients without a recorded postoperative NT-proBNP level (n=147) were excluded from an initial group of 342 patients, and 114 patients remained for analysis. Patients included in the study had a mean

Table 1. Baseline characteristics of the patients

Characteristic	n=114
Gender (female), n (%)	30 (26.3)
Age (years), mean±SD	51.46±5.24
Diabetes mellitus, n (%)	17 (14.9)
Hypertension, n (%)	9 (7)
Creatinine (mg/dL), median (range)	0.8 (0.36–2.6)
CAD, n (%)	5 (4.4)
Tobacco use, n (%)	30 (26.3)
MELD score, mean±SD	15.87±5.24
LVEF, mean±SD	59.30±3.29
ePAPs, mean±SD	30.22±7.67

CAD: Coronary artery disease; DM: Diabetes mellitus; ePABs: Estimated systolic pulmonary artery pressure; HT: Hypertension; LVEF: Left ventricular ejection fraction; MELD: Model for End-Stage Liver Disease.; SD: Standard deviation.

Table 2. Demographic and clinical characteristics of the patients according to mortality

Characteristic	Non-survivor (n=11)	Survivor (n=103)	*p*
Gender (female), n (%)	3 (30)	27 (26)	0.519
Age (years), mean±SD	53.5±9.33	51.27±11.34	0.622
Diabetes mellitus, n (%)	5 (45.4)	13 (12.6)	0.011
Hypertension, n (%)	1 (10)	7 (6.7)	0.532
Creatinine (mg /dL), median	0.9	0.7	0.486
CAD, n (%)	0 (0)	5 (4.8)	0.626
Tobacco use, n (%)	2 (18.1)	28 (27.1)	0.167
MELD score, mean±SD	17.1±6.17	15.75±5.16	0.518
Nt-proBNP (ng/L), median (Q1,Q3)	1890 (1069,13656)	470 (284,862)	0.0001
LVEF, mean±SD	59.44±3.16	58.00±4.29	0.169
ePAPs, mean±SD	30.15±7.88	30.91±5.65	0.755

CAD: Coronary artery disease; DM: Diabetes mellitus; ePABs: Estimated systolic pulmonary artery pressure; HT: Hypertension; LVEF: Left ventricular ejection fraction; MELD: Model for End-Stage Liver Disease; Q1: First quartile; Q3: Third quartile; SD: Standard deviation.

age of 51.4 years and a mean Model for End-Stage Liver Disease (MELD) score of 15.8. Baseline characteristics of the entire group are provided in Table 1. The records of these patients were analyzed according to in-hospital mortality.

Eleven (9.6%) patients died while in the hospital for the index surgery. The cause of mortality was infection in 4 patients, graft failure in 4 patients, bleeding in 2 patients, and renal failure in 1 patient. None of the patients died due to cardiovascular complications. Table 2 illustrates a comparison of the clinical characteristics of the study patients according to in-hospital mortality. There was a significantly higher percentage of diabetes mellitus in non-survivors (p=0.011).

The patients who died during the index hospitalization had a higher postoperative NT-proBNP level (median: 470 ng/L for survivors vs 1890 ng/L for non-survivors; p<0.001). ROC curve analysis was performed to find the best cut-off value for in-hospital mortality (Table 3). It was determined that the best cut-off value for the postoperative NT-proBNP value was 1009 ng/L (Fig. 1). Cox regression analysis indicated that a postoperative NT-proBNP level >1009 ng/L was independently associated with in-hospital mortality (hazard ratio: 24.467, 95% confidence interval: 3.120–191.750; p=0.002) (Table 4).

Table 3. Results of receiver operating characteristic curve analysis for postoperative NT-proBNP

AuROC (95% CI)	0.869 (0.793, 0.925)
p	<0.001
Sensitivity (95% CI)	90.91 (58.7, 99.8)
Specificity (95% CI)	76.7 (67.3, 84.5)
PPV (95% CI)	29.4 (15.1, 47.5)
NPV (95% CI)	98.7 (93.2, 100)

AuROC: Area under the receiver operating characteristic curve; NPV: Negative predictive value; NT-proBNP: N-terminal pro-brain natriuretic peptide; PPV: Positive predictive value; ROC: Receiver operator characteristic; CI: Confidence interval.

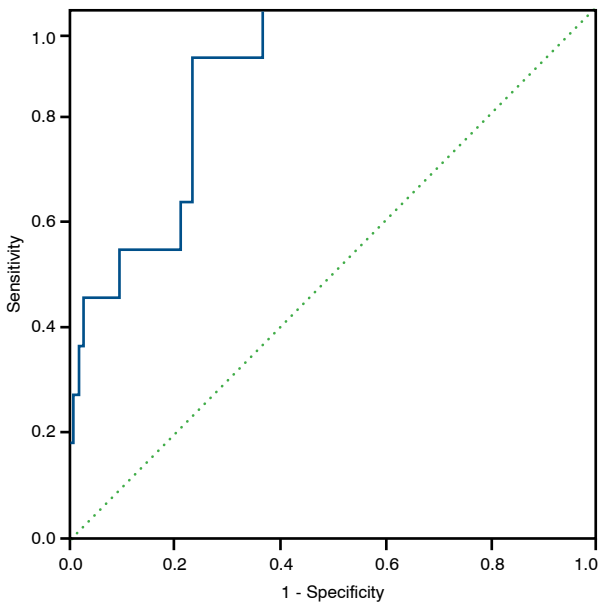

Figure 1. ROC curve analysis for in-hospital mortality in patients with NT-proBNP ≤1009 and >1009 ng/L. NT-proBNP: N-terminal pro-brain natriuretic peptide; ROC: Receiver operating characteristic.

Table 4. Multivariate regression analysis of predictors of in-hospital mortality

	Odds ratio	95% Confidence interval	*p*
Diabetes mellitus	1.424	1.261–13.668	0.019
Nt-ProBNP	3.197	3.120–191.750	0.002

NT-proBNP: N-terminal pro-brain natriurectic peptide.

Patients with a postoperative NT-proBNP serum level >1009 ng/L had a significantly longer intensive care unit stay, a longer need for inotropic infusion, and a greater need for red blood cell and fresh frozen plasma replacement (Table 5).

DISCUSSION

In this retrospective study, we investigated a predictive role of the postoperative NT-proBNP level to identify mortality after LDLT. The postoperative NT-proBNP level was found to independently predict in-hospital mortality with a best cut-off value of 1009 ng/L. Only 1 in-hospital death occurred among 80 LT recipients with an NT-proBNP value <1009 ng/L.

The use of clinical risk indices is recommended in order to determine and stratify perioperative risk.[9-11] In our previous study, we evaluated the American College of Surgeons National Surgical Quality Improvement Program risk tool and the Revised Cardiac Risk Index (RCRI), which are risk tools recommended by the American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines for perioperative risk stratification in patients undergoing non-cardiac surgery to predict cardiovascular complications and mortality after LDLT. It was observed that these 2 risk tools failed to predict perioperative cardiac complications.[12] A medium-high RCRI score was able to predict in-hospital mortality.

NPs have been investigated as a prognostic biomarker to predict cardiovascular morbidity and mortality after non-cardiac surgery.[13,14] Previous meta-analyses have suggested that a single NP value may predict cardiovascular morbidity more accurately than risk indices.[15,16] Although the current ASC and ESC guidelines favor risk indices over the NP value in risk stratification, the Canadian Cardiovascular Society guidelines recommend a routine, single, preoperative NP level measurement in patients who are ≥65 years old, are 45–64 years old and have cardiovascular disease, or have an RCRI score of ≥1.[17]

NPs have been investigated as a cardiac stress marker in various clinical situations involving cirrhosis. The level of NPs has been found to be associated with disease severity scores (Child-Pugh and MELD scores) and mortality in cirrhotic patients.[18–20] Several studies have examined the role of preoperative NP levels in LT recipients. Kim et al.[21] analyzed 185 patients who underwent LT and found that the preoperative BNP level was independently associated with 1-year mortality. Toussaint et al.[22] investigated the prognostic value of pre-LT BNP and found that a BNP serum level of >155 pg/mL was an independent predictor of post-LT intensive care unit mortality.[22] In addition, a meta-analysis of 7 studies that included 2010 patients also suggested that NPs could be helpful in risk stratification and may predict mortality after LT.[23]

Table 5. Postoperative characteristics of patients according to postoperative NT-proBNP level

	Post-LT NT-proBNP concentration ≤1009 ng/L (n=80)	Post-LT NT-proBNP concentration >1009 ng/L (n=34)	*p*
In-hospital mortality, n (%)	1 (1.2)	10 (29.4)	<0.001
Length of hospital stay (d), mean±SD	21.78±15.72	22.37±12.14	0.489
Length of ICU stay (d), median (IQR)	2 (1.5–3.75)	5 (3.5–8)	0.036
Need for inotropic infusion (d), median (IQR)	0.3 (0.1–1)	1 (0.5–2)	0.003
Red blood cells (units), median (IQR)	2 (1–4)	5 (2–7)	0.002
Fresh frozen plasma (units), median (IQR)	1 (0–2)	3 (1–6)	0.002

d: Days; LT: Liver transplantation; ICU: Intensive care unit; IQR: Interquartile range; NT-proBNP: N-terminal pro-brain natriurectic peptide; SD: Standard deviation.

However, data about the prognostic role of postoperative NP levels are limited. In a meta-analysis, Rodseth et al.[24] demonstrated that adding a postoperative NP measurement to preoperative risk indices led to significantly greater accuracy in predicting perioperative mortality compared with a preoperative NP measurement alone. Saner et al.[25] investigated the role of BNP in the prediction of cirrhotic cardiomyopathy in 157 LT patients. They obtained a BNP measurement on admission and postoperative days 1 and 7. Only an increased BNP level on postoperative day 1 was associated with a higher all-cause mortality rate. In our study, the highest NT-proBNP level from the first 3 postoperative days was included. Our analysis suggests that the NT-proBNP level has a predictive role for mortality after LDLT. To our knowledge, this is the first study in the literature to examine a predictive role of postoperative NT-proBNP values for mortality after LT.

Study limitations

The number of cardiovascular complications (3 patients had cardiac morbidity: 1 patient had an anterior myocardial infarction, 1 patient had an intraoperative cardiac arrest with successful cardiopulmonary resuscitation, and heart failure occurred in 1 patient) limited an analysis of the relationship between postoperative NT-proBNP levels and cardiovascular morbidity. This was a retrospective study and the lack of recorded NT-proBNP data restricts the ability to apply the results to LT patients more broadly. Only patients who underwent LDLT were included in this study; therefore, these findings may not apply to the outcomes of patients who undergo cadaveric LT. The absence of preoperative NT-proBNP data limited a determination of the prognostic role of NT-proBNP trends and a correlation with postoperative outcomes.

In conclusion, the postoperative NT-proBNP level was found to significantly predict mortality after LDLT. Pre- and postoperative NT-proBNP level-guided management of LT recipients should be pursued.

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