

Transient decrease in B-type natriuretic peptide level after liver transplantation does not ensure favorable post-transplant 30-day outcomes

Hye-Mee Kwon, Jae Hwan Kim, Sa-Jin Kang, and Gyu-Sam Hwang

Department of Anesthesiology and Pain Medicine, Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Received April 13, 2022
Revised December 30, 2022
Accepted January 12, 2023

Background: High B-type natriuretic peptide (BNP) levels within the first 3 postoperative days (postBNP_{POD3}) after liver transplantation (LT) are greatly predictive of the 30-day mortality. We evaluated clinical impact of transient decrease in postBNP_{POD3} compared to pretransplant BNP (preBNP) level on mortality and major adverse cardiac event (MACE) within 30 days after LT.

Methods: We retrospectively evaluated 3,811 LT patients who measured delta BNP (deltaBNP), defined by serial postBNP_{POD3} minus preBNP. Thirty-day all-cause mortality and MACE were estimated in patients with deltaBNP < 0 (n = 594, 15.6%) and > 0 (n = 3,217, 84.4%), respectively. Kaplan-Meier survival and multivariable Cox regression analysis were used.

Results: Within 30 days, 100 (2.6%) of all patients died. Unexpectedly, 30-day mortality rate (6.1% [95% CI: 4.2–8.4%] vs. 2.0% [95% CI: 1.5–2.5%], P < 0.001) and MACE (24.2% [95% CI: 20.4–28.5%] vs. 15.3% [95% CI: 14.0–16.7%], P < 0.001) were higher in patients with deltaBNP < 0 compared to those with deltaBNP > 0, respectively. Patients with deltaBNP < 0 had higher preBNP level (median [interquartile range], 251 [118, 586] vs. 43 [21, 92] pg/ml, P < 0.001) and model for end-stage liver disease score (26 [14, 37] vs. 14 [9, 23], P < 0.001) and more transfused intraoperatively. DeltaBNP < 0 remained significant after adjustments for potential confounders in multivariable analysis of 30-day mortality and MACE.

Conclusions: DeltaBNP < 0 within the first 3 postoperative days is mainly attributed to pre-LT severe liver and cardiac disease status, therefore, transient decrease in BNP level after LT does not ensure favorable post-LT 30-day outcomes.

Keywords: Liver transplantation; Major adverse cardiovascular event; Mortality; Natriuretic peptide, brain.

Corresponding author

Gyu-Sam Hwang, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: 82-2-3010-3868
Fax: 82-2-470-1363
E-mail: kshwang@amc.seoul.kr

INTRODUCTION

Because of high early and late cardiovascular death after liver transplantation (LT) in the modern era, identification of vulnerable heart and severity of cardiac disease are crucial in patients with end-stage liver disease (ESLD) undergoing

LT [1–3]. Recent studies demonstrated the routine monitoring of peri-LT B-type natriuretic peptide (BNP) provides risk stratification for early mortality as a practical and useful biomarker in LT [4]. Specifically, high peak BNP levels > 400 pg/ml within the first 3 postoperative days (postBNP_{POD3}) after LT are highly prevalent in advanced liver disease and are

considered as highly vulnerable to become acute heart failure (HF) or “HF likely” status shortly after LT [4,5].

In this regard, physicians may suppose improved cardiac status with expecting favorable post-LT outcomes if there are decreases in postBNP_{POD3} compared to pre-LT BNP (preBNP) level immediately after LT. However, it is unclear whether preBNP is initially higher from the beginning before LT than postBNP_{POD3} in this clinical situation.

In this study, we evaluated clinical impact of transient decrease in postBNP_{POD3} compared to preBNP level on 30-day mortality and major adverse cardiac event (MACE) within 30 days after LT, after adjusting with revised cardiac risk index (RCRI), the most frequently validated model for perioperative cardiac risk stratification [6].

MATERIALS AND METHODS

Patients and data collection

A total of 3,811 consecutive, prospectively registered patients who underwent living-donor LT or deceased-donor LT from 2010 to 2020 were enrolled after excluding patients with less than 18 years old, re-transplantation, history of open-heart surgery, and incomplete data without measuring serial preBNP and postBNP_{POD3}.

Patient demographics, medical history, model for end-stage liver disease score (MELDs), and laboratory and intraoperative variables were obtained automatically using a fully computerized data extraction software (ABLE). Mortality data were extracted from patients' electronic medical records and the updated record of the institution's LT registry. This study was approved from the Institutional Review Boards of Asan Medical Center (protocol number: 2022-0436).

BNP measurement

Serial BNP levels were measured pre- and post-operatively (the ADVIA Centaur CP Immunoassay System) as a part of our institution's routine cardiac workup since 2008 regardless of the symptoms or signs of acute or chronic HF. BNP levels measured more than once within 3 postoperative days after LT and their peak value (postBNP_{POD3}) was chosen for the analysis, and those who did not measure either preBNP or postBNP_{POD3} were excluded.

PreBNP was selected with the most proximate to the date of LT within 7 pre-LT days, when multiple measurements

were done preoperatively.

Delta BNP (deltaBNP) was defined as the difference with serial preBNP and postBNP_{POD3} (deltaBNP = postBNP_{POD3} - preBNP).

RCRI and post-reperfusion syndrome (PRS)

The traditional RCRI was evaluated for the multivariable analysis. The RCRI is the most frequently validated model for perioperative cardiac risk stratification and is recommended by many guideline committees [6]. Scoring system and variables included in the RCRI are as follows (worth 1 point each): history of ischemic heart disease, congestive heart failure, cerebrovascular disease, high-risk surgery (i.e., liver transplant), preoperative insulin use, and preoperative creatinine level > 2 mg/dl.

PRS was defined as a severe hemodynamic perturbation more than 1 min within the first 5 min after graft reperfusion during LT [2].

Outcomes

The primary endpoint was 30-day all-cause mortality rate after LT and MACE. MACE was defined as the composite of postoperative cardiovascular mortality, atrial fibrillation, ventricular arrhythmias, ST-T wave changes with chest tightness, myocardial infarction, pulmonary embolism, and stroke within 30 days after LT.

Statistics

Data were expressed as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables. In univariate statistical comparisons for the patients with deltaBNP > 0 and < 0, the chi-square test or Fisher's exact test was used for categorical variables, Student's *t*-test and Mann-Whitney test for continuous variables, as appropriate. The Kaplan-Meier survival curve was used to depict the risk of within 30 days all-cause mortality.

To evaluate the relationship between clinical, biochemical parameters, liver disease severity, cardiac risk index and mortality events, multivariate or a Cox proportional multiple regression model was built. With MACE as outcome, multivariable logistic regression model was performed. To obtain adjusted hazard ratios (HR) for mortality or odds ratio for MACE from a multivariable or a Cox regression model, co-

variates included were age, sex, RCRI, MELD score, intraoperative red blood cell (RBC) transfusion amount, PRS and patients with deltaBNP < 0, respectively. The proportional hazards assumption of deltaBNP can be checked using scaled Schoenfeld residuals ($P = 0.430$). Statistical analyses were conducted in R (Version 4.1.2, R Foundation for Statistical Computing), with packages of 'moonBook [7]', autoReg [8], "survminer [9]" "survival [10]" and a two-sided significance level of 0.05.

RESULTS

Of 3,811 LT recipients included, their age was median 54 (48, 59) years and men were 2,769 (72.7%). The MELDs were median 15 (10, 26) and total bilirubin was median 2.2 (1.0, 10.5) mg/dl. The primary causes of liver disease were hepatitis B or C virus-related liver cirrhosis (60.9%), alcoholic liv-

er disease (24.7%) and others (14.4%) (Table 1). Prevalence of RCRI category 1, 2, and 3 were 66.2%, 26.5%, and 7.3%, respectively (Table 1)

Characteristics in patients with deltaBNP < 0

Patients with deltaBNP < 0 had higher MELD score compared to those with deltaBNP > 0 (26 [14, 37] vs. 14 [9, 23], $P < 0.001$). They also showed higher risk of RCRI preoperatively and suffered from more transfusion intraoperatively. However, the rate of intraoperative postreperfusion syndrome were similar (Table 1). Fig. 1 shows individual changes in BNP, demonstrating that patients with deltaBNP < 0 ($n=594$, 15.6%) had higher preBNP level compared to those with deltaBNP > 0 (251 [118, 586] vs. 43 [21, 92] pg/ml, $P < 0.001$).

Table 1. Descriptive Statistics Between DeltaBNP > 0 and DeltaBNP < 0

Variable	DeltaBNP > 0 (n = 3,217)	DeltaBNP < 0 (n = 594)	Total (n = 3,811)	P value
Age (yr)	54.0 (49.0, 59.0)	54.0 (47.0, 60.0)	54.0 (48.0, 59.0)	0.139
Male	2,368 (73.6)	401 (67.5)	2,769 (72.7)	0.003*
MELD score	14 (9, 23)	26 (14, 37)	15 (10, 26)	< 0.001*
Viral liver disease	2,050 (63.7)	269 (45.3)	2,319 (60.9)	< 0.001*
Alcoholic liver disease	655 (20.4)	178 (30.0)	833 (21.9)	< 0.001*
Diabetes	810 (25.2)	133 (22.4)	943 (24.7)	0.163
Hypertension	592 (18.4)	120 (20.2)	712 (18.7)	0.329
RCRI				< 0.001*
1	2,225 (69.2)	299 (50.3)	2,524 (66.2)	
2	789 (24.5)	220 (37.0)	1,009 (26.5)	
3	203 (6.3)	75 (12.6)	278 (7.3)	
Intractable ascites	991 (30.8)	257 (43.3)	1,248 (32.7)	< 0.001*
Orthotopic LT	446 (13.9)	231 (38.9)	677 (17.8)	< 0.001*
Hydrothorax	438 (13.6)	99 (16.7)	537 (14.1)	0.057*
Creatinine (mg/dl)	0.8 (0.6, 1.0)	1.0 (0.7, 1.8)	0.8 (0.6, 1.1)	< 0.001*
INR	1.4 (1.2, 1.8)	1.7 (1.4, 2.3)	1.4 (1.2, 1.9)	< 0.001*
Total bilirubin (mg/dl)	2.0 (1.0, 6.9)	9.2 (1.9, 25.1)	2.2 (1.0, 10.5)	< 0.001*
pRBC (units)	8.0 (3.0, 16.0)	12.0 (6.0, 20.5)	8.0 (3.0, 16.0)	< 0.001*
PRS	1,940 (60.3)	377 (63.5)	2,317 (60.8)	0.160
BNP (pg/ml)	43 (21, 92)	251 (118, 586)	54 (24, 130)	< 0.001*
postBNP _{POD3} (pg/ml)	197 (95, 423)	132 (73, 287)	183 (90, 405)	< 0.001*
DeltaBNP (pg/ml)	130 (52, 330)	-76 (-241, -24)	95 (24, 273)	< 0.001*
MACE	493 (15.3)	144 (24.2)	637 (16.7)	< 0.001*
30-day mortality	64 (2.0)	36 (6.1)	100 (2.6)	< 0.001*

Values are presented as median (1Q, 3Q) or number (%). BNP: B-type natriuretic peptide, MELD: model for end-stage liver disease, RCRI: revised cardiac risk index, LT: liver transplantation, INR: international normalized ratio, pRBC: packed red blood cells transfused, PRS: post-reperfusion syndrome, postBNP_{POD3}: peak BNP levels within the first 3 postoperative days, MACE: major adverse cardiovascular events. * $P < 0.05$ was considered statistically significant.

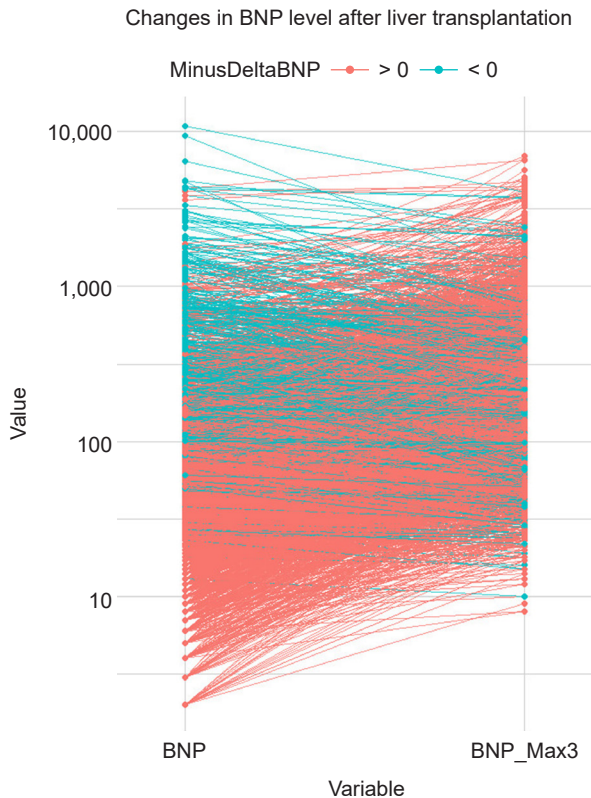


Fig. 1. Line plots depicting individual value preoperative B-type natriuretic peptide (BNP) and BNP_Max3 liver transplantation. Line shows the change of preoperative BNP value to the BNP_Max3. BNP: B-type natriuretic peptide, BNP_Max3: high BNP levels within the first 3 postoperative days, DeltaBNP: difference between BNP_Max3 and preoperative BNP.

Thirty-day mortality and MACE

Within 30 days, 100 (2.6%) of all patients died. However, unexpectedly, 30-day mortality rate (6.1% [95% confidence interval, 95% CI: 4.2–8.4%] vs. 2.0% [95% CI: 1.5–2.5%], $P < 0.001$) and MACE (24.2% [20.4–28.5%] vs. 15.3% [14.0–16.7%], $P < 0.001$) were higher in patients with deltaBNP < 0 compared to those with deltaBNP > 0 , respectively (Table 1). Fig. 2 shows the Kaplan-Meier survival curve of the risk of within 30 days all-cause mortality.

In Cox proportional HR analysis for 30-day mortality, sex, MELD score, transfusion amount, and deltaBNP < 0 remained as significant variables, whereas, age, RCRI, transfusion amount, MELD score, deltaBNP < 0 was remained in the multivariable analysis of MACE (Figs. 3, 4).

DISCUSSION

In the current study, we hypothesized that transient decreases in postBNP_{POD3} compared to pre-LT BNP (preBNP) level immediately after LT, i.e. deltaBNP < 0 , favorable post-LT outcomes might be expected if the decrease in postBNP_{POD3} could imply the improvement of cardiac status after LT. However, patients with deltaBNP < 0 after LT showed higher rates of 30-day mortality and MACE. We considered that these are attributed mainly to high preBNP level and high MELD score in patients with deltaBNP < 0 . These results

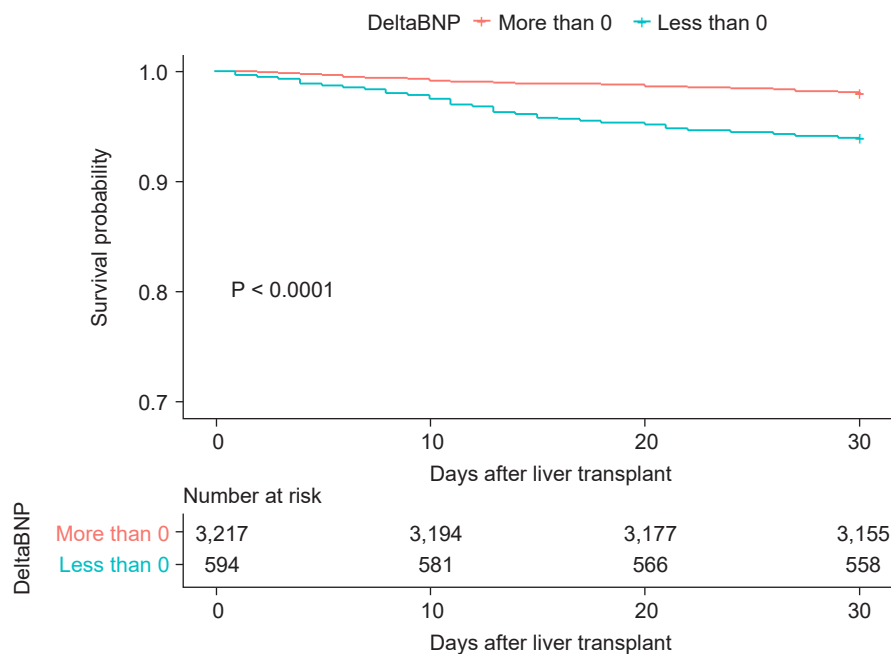


Fig. 2. Kaplan-Meier plot within 30 days after liver transplantation. BNP: B-type natriuretic peptide.

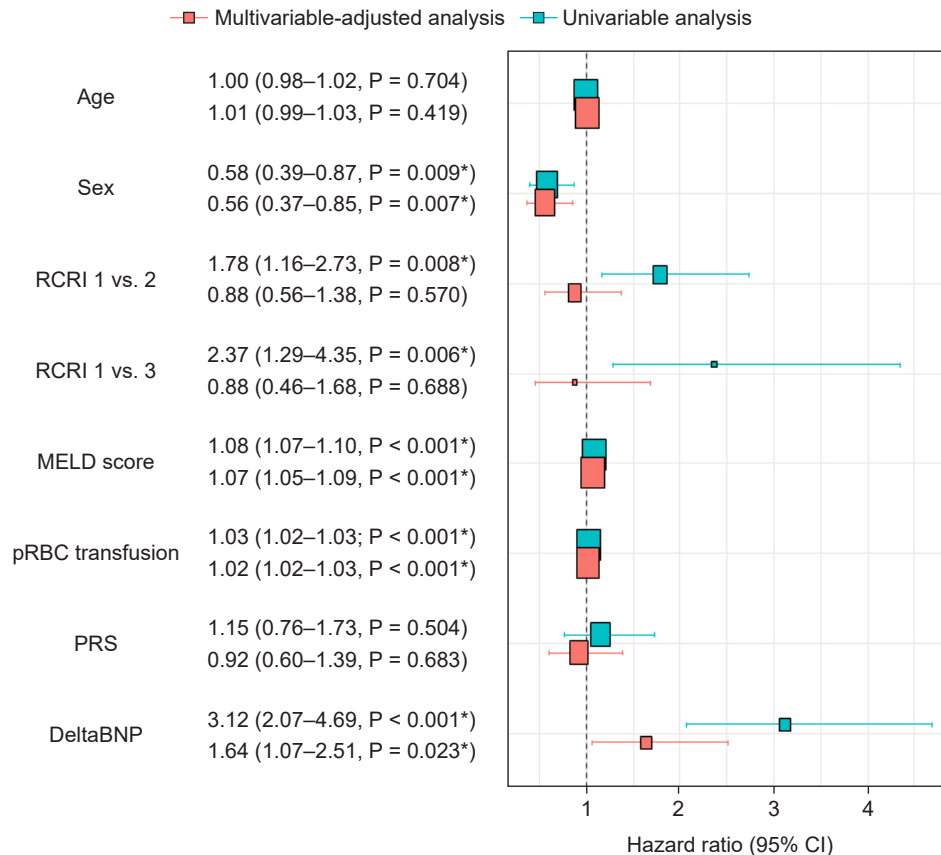


Fig. 3. Hazard ratios of univariable and multivariable analysis for 30-day mortality. RCRI: revised cardiac risk index, MELD: model for end-stage liver disease, pRBC: packed red blood cells transfused, PRS: post-reperfusion syndrome, BNP: B-type natriuretic peptide, CI: confidence interval. *P < 0.05 was considered statistically significant.

suggest that pre-LT high BNP level and severe liver disease status might be main determinant of poor 30-day outcomes irrespective of transient decrease of post-LT BNP level.

There are several potential explanations for these findings. One possibility is that there was more blood loss during LT in association with more severe liver disease, which implies greater loss of intravascular volume loss during LT. In fact, transfusion amount and MELD score were higher in those with deltaBNP < 0 in the current study.

Several studies demonstrated that the BNP increase after LT was markedly prevalent in advanced liver disease and was associated with increased risk of 30-day mortality and worse outcomes [4,11–13].

Kwon et al. [4] showed that strong correlates of preBNP > 400 pg/ml were MELD score, kidney failure, respiratory failure, and congestive HF. In contrast, the strongest correlate of postBNP_{POD3} > 400 pg/mL increase was preBNP level, hyponatremia, MELD score, massive intraoperative transfusion, and intractable ascites. They specifically emphasized that

patients with preBNP of 1,000–2,000 pg/ml and BNP > 2,000 pg/ml showed 14.8% and 25% 30-day post-LT mortalities.

In the current study showed that patients with deltaBNP < 0 had also higher preBNP level, therefore, patients with unusually high preBNP should examine their cardiac status again and modifiable risk factors thoroughly reevaluated before LT and should receive the optimal medical treatment.

One important point that deserves emphasis is that serial measurement of BNP is recommended for the risk stratification of mortality after LT regardless of our study results [12,14]. Rodseth et al. [12] also demonstrated that additional postoperative BNP measurement enhanced risk stratification for the composite outcomes of death or nonfatal myocardial infarction at 30 days and more than 180 days after noncardiac surgery compared with a preoperative BNP measurement alone.

The RCRI, which is recommended by many guideline committees, one of the most frequently validated models for perioperative cardiac risk stratification [5,15]. We adjusted

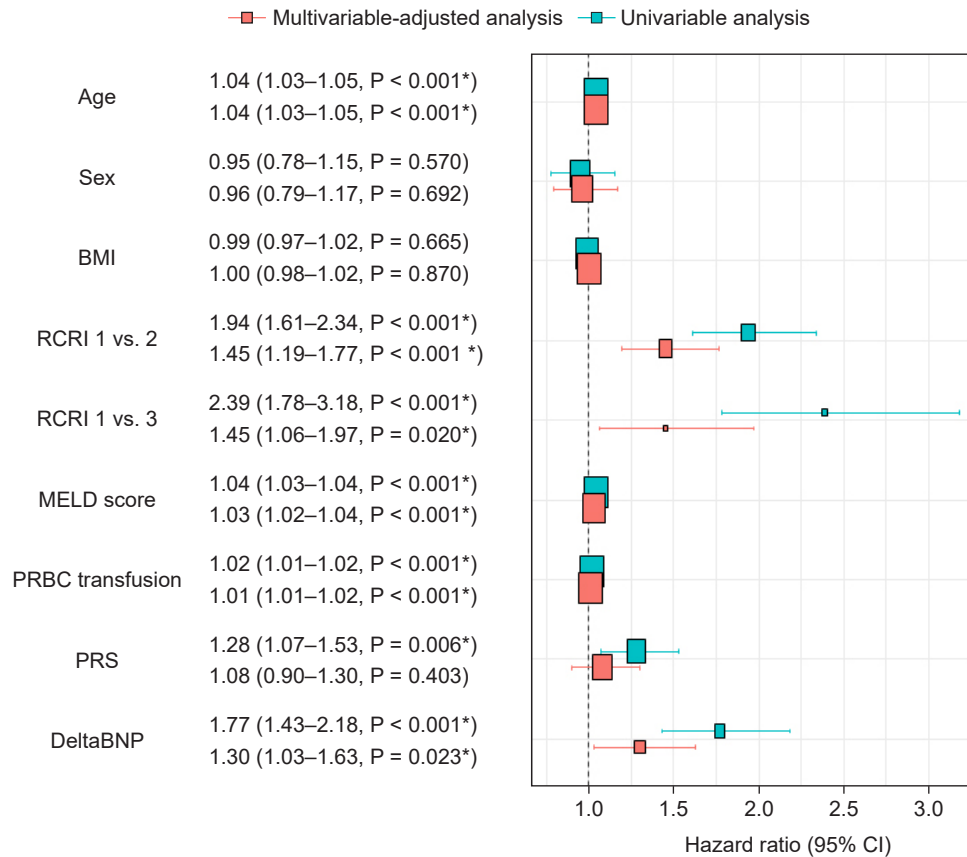


Fig. 4. Odds ratios of univariable and multivariable analysis for major adverse cardiovascular events (MACE). BMI: body mass index, RCRI: revised cardiac risk index, MELD: model for end-stage liver disease, PRBC: packed red blood cells transfused, PRS: post-reperfusion syndrome, BNP: B-type natriuretic peptide, CI: confidence interval. *P < 0.05 was considered statistically significant.

this risk index to evaluate the 30-day mortality risk and MACE and then the $\Delta\text{BNP} < 0$ remained significant. However, previous study showed that the 30-day mortality rates with RCRI of 1, 2, and ≥ 3 were 2.0%, 3.6%, and 4.7% after LT and revealed poor discriminative performance the RCRI in LT (C-statistic = 0.58) [4]. Nonetheless, adding preBNP, postBNP_{POD3}, and both BNP values to the RCRI improved reclassification analysis to 22.5%, 29.5%, and 33.1% of 30-day mortality prediction, respectively [4]. Therefore, the routine monitoring of peri-LT BNP provides risk stratification for early mortality as a useful biomarker in LT [16–19].

Our study has several limitations, first, prospective multi-center study is recommended because our study is retrospective. Secondly, we did not follow the BNP level further in patients with mortality and MACE, therefore further study is needed including serial BNP level monitoring. Thirdly, the patients with high preBNP (i.e., high ΔBNP) may indicate higher possibility of cardiac diseases. Those with higher decrease of BNP levels may show higher mortality compared

to those with normal or slightly increased preoperative BNP. Therefore, the result our study should be interpreted with caution. Further studies investigating the classification of cardiac status or patients with similar levels of preoperative BNP are needed in the near future.

In conclusion, $\Delta\text{BNP} < 0$ within the first 3 postoperative days is mainly attributed to pre-LT severe liver and cardiac disease status, therefore, transient decrease in BNP level after LT does not ensure favorable post-LT 30-day outcomes.

These findings suggest that determinants of mortality and MACE are multiple and cannot reliably be predicted simply from changes in initial improvement of BNP, thereby special attention should also be paid to patients with $\Delta\text{BNP} < 0$.

FUNDING

This research was supported partly by a grant from the Korea Health Technology R&D Project through the Korea

Health Industry Development Institute, which is funded by the Ministry of Health & Welfare of the Republic of Korea (grant number: HI18C2383).

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Data curation: Gyu-Sam Hwang, Hye-Mee Kwon, Jae Hwan Kim, Sa-Jin Kang. Formal analysis: Gyu-Sam Hwang, Hye-Mee Kwon. Methodology: Gyu-Sam Hwang, Jae Hwan Kim, Sa-Jin Kang. Writing - original draft: Hye-Mee Kwon. Writing - review & editing: Gyu-Sam Hwang. Software: Hye-Mee Kwon. Supervision: Gyu-Sam Hwang.

ORCID

Hye-Mee Kwon, <https://orcid.org/0000-0001-7788-9555>

Jae Hwan Kim, <https://orcid.org/0000-0002-0041-3054>

Sa-Jin Kang, <https://orcid.org/0000-0002-6082-2474>

Gyu-Sam Hwang, <https://orcid.org/0000-0002-3627-1107>

REFERENCES

1. Izzy M, VanWagner LB, Lee SS, Altieri M, Angirekula M, Watt KD. Understanding and managing cardiovascular outcomes in liver transplant recipients. *Curr Opin Organ Transplant* 2019; 24: 148-55.
2. Kwon HM, Hwang GS. Cardiovascular dysfunction and liver transplantation. *Korean J Anesthesiol* 2018; 71: 85-91.
3. VanWagner LB, Lapin B, Levitsky J, Wilkins JT, Abecassis MM, Skaro AI, et al. High early cardiovascular mortality after liver transplantation. *Liver Transpl* 2014; 20: 1306-16.
4. Kwon HM, Moon YJ, Kim KS, Shin WJ, Huh IY, Jun IG, et al. Prognostic value of B-type natriuretic peptide in liver transplant patients: implication in posttransplant mortality. *Hepatology* 2021; 74: 336-50.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18: 891-975.
6. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation* 2014; 130: 2215-45.
7. Moon KW. R statistics and graphs for medical papers. Seoul, Hannarae. 2015.
8. Moon KW. Survival analysis with R for medical personnel. Seoul, Hannarae. 2022.
9. Kassambara A, Kosinski M, Biecek P. survminer: survival analysis and visualization. ggsvrplot: drawing survival curves [Internet]. 2021 [2022 Jan 3]. Available from <https://rpkgs.datanova.com/survminer/>.
10. Therneau T. A package for survival analysis in R. Version 3.2-13 [Internet]. 2021 [updated 2023 Jan 9; 2022 Jan 3]. Available from <https://cran.r-project.org/web/packages/survival/index.html>.
11. Kim YK, Shin WJ, Song JG, Kim Y, Kim WJ, Kim SH, et al. Evaluation of intraoperative brain natriuretic peptide as a predictor of 1-year mortality after liver transplantation. *Transplant Proc* 2011; 43: 1684-90.
12. Rodseth RN, Biccadd BM, Le Manach Y, Sessler DI, Lurati Buse GA, Thabane L, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. *J Am Coll Cardiol* 2014; 63: 170-80.
13. Saner FH, Neumann T, Canbay A, Treckmann JW, Hartmann M, Goerlinger K, et al. High brain-natriuretic peptide level predicts cirrhotic cardiomyopathy in liver transplant patients. *Transpl Int* 2011; 24: 425-32.
14. Rodseth RN, Biccadd BM, Chu R, Lurati Buse GA, Thabane L, Bakhai A, et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. *Anesthesiology* 2013; 119: 270-83.
15. Vernooij LM, van Klei WA, Moons KG, Takada T, van Waes J, Damen JA. The comparative and added prognostic value of biomarkers to the Revised Cardiac Risk Index for preoperative

- prediction of major adverse cardiac events and all-cause mortality in patients who undergo noncardiac surgery. *Cochrane Database Syst Rev* 2021; 12: CD013139.
16. Ryding AD, Kumar S, Worthington AM, Burgess D. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology* 2009; 111: 311-9.
17. Møller S, Bendtsen F. Cirrhotic multiorgan syndrome. *Dig Dis Sci* 2015; 60: 3209-25.
18. Møller S, Danielsen KV, Wiese S, Hove JD, Bendtsen F. An update on cirrhotic cardiomyopathy. *Expert Rev Gastroenterol Hepatol* 2019; 13: 497-505.
19. Møller S, Henriksen JH. Cirrhotic cardiomyopathy. *J Hepatol* 2010; 53: 179-90.