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ORIGINAL ARTICLE

High brain-natriuretic peptide level predicts cirrhotic cardiomyopathy in liver transplant patients

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Summary

Cirrhotic cardiomyopathy may appear following liver transplantation. Brain-natriuretic peptide (BNP) values exceeding 391 pg/ml or 567 pg/ml may partially reflect ventricular stress because of cardiac dysfunction or indicate cirrhotic cardiomyopathy, respectively. The aim of the study was to assess cardiac dysfunction in liver transplant patients and its correlation with BNP as a biomarker. From 1/2008 to 7/2009, 157 adult liver transplant recipients with proven cirrhosis were recruited for the study. BNP and liver enzymes were recorded upon admission, on the first postoperative day (POD) and 1 week after transplantation. Patients with ischemic heart attacks were excluded from the study. We identified two groups of patients. Group 1 was characterized by a BNP <391 pg/ml and Group 2 by a BNP >391 pg/ml. Group 2 had a significantly higher model of end-stage liver disease score than Group 1 (median 30, range 10–40 versus median 22, range 10–40, respectively; $P = 0.003$), required significantly more dialysis treatments and had a significantly higher mortality rate. Postoperative echocardiography in patients with a BNP >391 pg/ml indicated diastolic dysfunction in all of the patients and systolic dysfunction in 10 of the patients. Increased serum-BNP was associated with an overall higher mortality rate.

Introduction

Haemodynamic changes in cirrhotic patients have been well described since 1953 [1–3]. However, the effect of a liver transplantation (LT) on the cardiac function of patients with cirrhosis has not been systematically evaluated in a prospective study.

The presence of cirrhotic cardiomyopathy (CCM) may be revealed by different treatment interventions, including LT, surgical portosystemic shunt, and transjugular intrahepatic portosystemic shunt (TIPSS) [4]. Rayes *et al.* found that 7.3% of deaths following LT were associated with congestive heart failure [5], whereas several case reports have demonstrated heart failure following TIPSS or surgical treatment in patients with unremarkable preoperative cardiac profiles [6,7].

Cardiac dysfunction in cirrhotic patients is characterized by a blunted responsiveness to stress and an altered diastolic relaxation [8]. Many patients with cirrhosis exhibit various degrees of diastolic dysfunction, which affects ventricular filling. Diastolic dysfunction occurs before systolic dysfunction and may progress to systolic dysfunction [9,10].

Determinations of diastolic dysfunction on echocardiography are a decreased E/A ratio (early to late atrial phases of ventricular filling) and a delayed early diastolic

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transmittal filling with prolonged deceleration; systolic dysfunction can be assessed by a left ventricular ejection fraction (ER) that is <50% [11]. However, the limitations of this technique suggest the need for other objective measures of diastolic and systolic dysfunction [12].

Brain-natriuretic peptide (BNP) is a cardiac hormone that is secreted from the ventricle in response to pressure or volume overload [13]. BNP levels correlate with left ventricular dysfunction and prognosis [14]. Maisel *et al.* indicated that a BNP level between 391 and 567 pg/ml reflects diastolic dysfunction, whereas a BNP level >567 pg/ml indicates systolic dysfunction [15]. Elevated circulating BNP levels in cirrhotic patients reflect cardiac dysfunction [16] and correlate with the severity of the cirrhosis [17].

The aim of our study was to assess the level of cardiac dysfunction in liver transplant patients and to evaluate BNP as a biomarker for CCM following LT.

Patients and methods

After approval of the study protocol by the local ethics committee, 157 patients (97 men) with cirrhosis who received transplants in our department from 1/2008 to 7/2009 were enrolled in the study. Patients who experienced acute liver failure, retransplantation within 30 days, or a perioperative major cardiovascular event (pulmonary embolism or myocardial infarction) were excluded from the study. Ischemia was defined by changes in the ST-segment of an electrocardiogram, particularly ST-segment elevation combined with troponin I elevation (>0.5 μg/l), and by clinical signs of myocardial infarction.

All patients were recruited at the same Intensive Care Unit (ICU). Written informed consent was obtained from each patient before surgery. All of the operations were performed using standard surgical techniques by the same surgical team and a standardized anesthesia protocol was applied to all patients. LT was performed on all recipients without a veno-venous bypass. Patients received standard immunosuppression with tacrolimus (with the trough level adjusted to 8–10 ng/ml), mycophenolate mofetil (MMF), and corticosteroids.

The BNP, aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, and creatinine levels were recorded upon admission, on the first postoperative day (POD) and on the 7th POD. Haemodynamic data were obtained from a right-heart catheter evaluation. Patients with a BNP >391 pg/ml on the 1st POD were regarded as exhibiting CCM [15] and were scheduled for a postoperative echocardiography on the same day. A BNP <391 pg/ml indicated normal heart function. Echocardiography was performed in these patients, if congestive heart failure was suspected or evident.

Systemic haemodynamics

Mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) were recorded using standard disposable pressure transducers (Medex Medical, Klein-Winternheim, Germany), and leads II and V_5 of the electrocardiogram were used to detect the heart rate (Sirecust 1281 Siemens, Germany). Cardiac output was measured using a thermodilution method and the Stewart-Hamilton equation [18]. The CI was calculated by dividing the cardiac output by the body surface area (BSA).

Cirrhosis associated definition of diastolic dysfunction

The following transmitral Doppler velocity recordings from three consecutive cardiac cycles were used to evaluate the measurements: (i) early (E-wave) and late (atrial A-wave) velocities were recorded as the peak values of ventricular inflow, being reached in early diastole and after atrial contraction and (ii) deceleration time (DT), which was defined as the interval from E-wave peak to the decline of the velocity to baseline. In accordance with the current guidelines [19], diastolic dysfunction was classified into three categories based on these measurements:

Impaired diastolic relaxation (*level I*), E/A ≤1 and DT ≥240 ms;

Pseudonormal diastolic relaxation (*level II*), E/A = 1−1.5 and DT ≥240 ms;

Restrictive diastolic relaxation (*level III*), E/A <1 and DT <160 ms.

Cirrhosis associated definition of systolic dysfunction

Systolic dysfunction was defined as an ejection fraction <50% or one of the following: global hypokinesis or discrete wall motion abnormalities. Ejection fraction was measured using the quantitative biplane Simpson method.

Statistical analysis

Categorical variables were analyzed by the chi-square test with Yates' correction for continuity. Continuous variables were analyzed by the *t*-test, in cases where a normal distribution was apparent. Non-normally distributed continuous variables were analyzed by the Kruskal–Wallis one-way analysis of variance on ranks.

The Mann–Whitney rank sum test was performed when the equal variance test failed. $P < 0.05$ was considered statistically significant. Data are presented as mean ± SD.

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Results

One hundred and fifty-seven patients (60 women, 97 men) were recruited for the study. The most common diagnoses that led to the need for a LT were alcohol-induced cirrhosis and hepatitis B- and C-related cirrhoses. For the remaining diagnoses, see Table 1.

Correlation of model of end-stage liver disease and BNP

We found a significant correlation between model of end-stage liver disease (MELD) scores and BNP, with a Pearson correlation coefficient of $r = 0.237$ ($P = 0.003$) (Fig. 1).

The BNP increased from 58 pg/ml (range: 3–169 pg/ml, normal level: ≤100 pg/ml) upon admission to 126 pg/ml (range: 5–4249 pg/ml, $P < 0.001$) on POD 1 and returned to within the regular range on POD 7; however, it remained significantly higher than the baseline level (85 pg/ml, range: 4–309 pg/ml, $P < 0.002$) in all of the patients. Troponin I was <1 μg/l in all of the patients.

On POD 1, we identified two groups: Group 1 ($n = 132$ patients) with normal cardiac function (BNP ≤391 pg/ml) and Group 2 with CCM (BNP >391 pg/ml, $n = 25$ patients) (Table 2).

Group 2 had significantly higher MELD scores than Group 1 (median 30, range: 10–40 versus median 22, range: 10–40, $P = 0.003$) and required significantly more dialysis treatments (11 of 25 (44%) for Group 2, 25 of 132 (19%) for Group 1, $P = 0.03$). The hospital mortality rate of Group 2 was significantly higher than that of Group 1 (52% vs. 15%, $P = 0.0001$).

Table 1. Diagnoses leading to transplantation.

	Group 1	Group 2
Diagnosis	Number of patients	
Alcoholic related cirrhosis	36	11
Hepatitis B	16	1
Hepatitis C	29	6
Cryptogenic	15	0
Autoimmune	4	1
Amyloidosis	1	1
Wilson disease	4	1
NASH	7	1
Primary biliary cirrhosis	4	2
Primary sclerosing cholangitis	8	0
Secondary sclerosing cholangitis	4	0
Secondary biliary cirrhosis	3	1
Antitrypsin 1 deficiency	1	0
Total	132	25

NASH, nonalcoholic-steato-hepatitis.

Postoperative echocardiography and diastolic versus systolic dysfunction

All of the patients underwent a preoperative cardiac workup, which included standardized transthoracic echocardiography and clinical cardiologic assessment.

In Group 1, the preoperative echocardiogram indicated diastolic dysfunction (E/A = 1, DT = 250 ms) in two patients, whereas in Group 2, the preoperative echocardiogram indicated five patients with diastolic dysfunction (E/A in all patients was <1, DT >240 ms).

The patients in Group I did not exhibit any signs of congestive heart failure and passed the postoperative period without echocardiography. Every patient in Group 2 was scheduled for a postoperative echocardiogram because the cardiologist was unaware of the study protocol. Impaired relaxation (E/A <1 and DT >240 ms) was observed in all 25 patients.

Group 2 was further stratified into patients, for which 391 pg/ml < BNP < 567 pg/ml (Group 2a) and patients, for which BNP > 567 pg/ml (Group 2b). In 10 patients of Group 2b, EF <50% was observed. Two of these 10 patients suffered from cardiogenic shock with EF <20% and died within 3 days after transplantation.

The first of these two patients suffered from alcohol-related cirrhosis with a MELD score of 40 at the time of transplantation. The transplantation itself was uneventful. On admission to the ICU, the patient required high-dosage catecholamine support. On admission, the BNP was 475 pg/ml and increased to 4004 pg/ml 6 hours

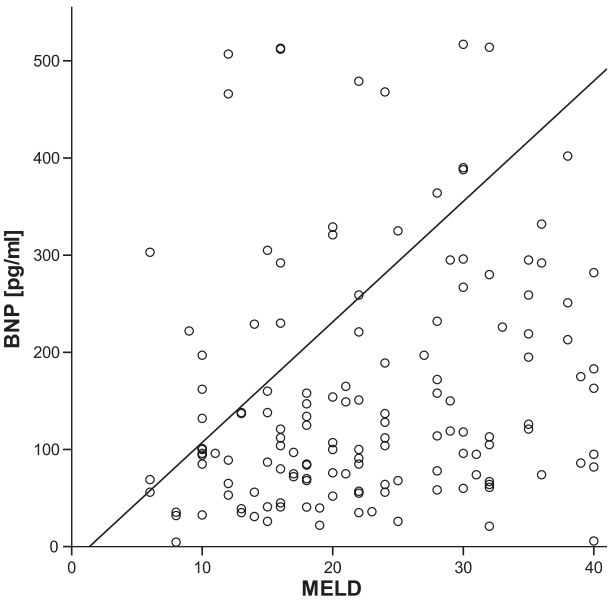

Figure 1 Correlation between brain-natriuretic peptide (BNP) level and model of end-stage liver disease (MELD) Score.

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Table 2. Laboratory, haemodynamic and perioperative data for Group 1 and Group 2 on the 1st postoperative day.

	Group 1	Group 2
Age (years)	50.9 ± 11.5	56.54 ± 8.5
BMI (kg/m^2)	27.1 ± 4.8	26.7 ± 4.7
MELD	22 (10–40)	30 (10–40)*
CIT (min)	438 ± 149	397 ± 131
WIT (min)	32 ± 11	32 ± 9
Bilirubin (mg/dl)	2.9 (0.3–21)	4.2 (0.9–13.7)
AST (U/l)	562 (88–6747)	535 (88–5582)
ALT (U/l)	518 (58–6941)	584 (134–5582)
CRP (mg/dl)	9.7 (0.3–23.4)	9.8 (2.1–20.8)
PCT (ng/ml)	23 (0.3–416)	31.3 (8–500)
INR	1.3 (0.9–2.5)	1.5 (0.9–2.4)
Creatinine	1.5 (0.6–7)	2 (0.9–4.3)
CI (l × m^2 × min^{-1})	4,3 ± 1.7	4.5 ± 1.2
MAP (mmHg)	85 ± 10	84 ± 9
MPAP (mmHg)	20 ± 7	25 ± 7*
PVR (dyn × sec × cm^{-5})	103 (24–556)	119 (42–480)
PCWP (mmHg)	10 ± 4	15 ± 6**
CVP (mmHg)	8 ± 3	8 ± 4
Norepinephrine (μg/kg/min)	0.05 (0–8)	0.1 (0–7)
RPC (transfused numbers)	4 (0–38)	4 (0–20)
FFP (transfused numbers)	0 (0–26)	0 (0–26)
PLT (transfused numbers)	0 (0–24)	0 (0–4)
Ventilation time (h)	12 (0–1538)	48 (0–1104)
ICU stay (days)	7.7 (0.5–94.5)	5 (1–46)

CRP, C-reactive protein; CI, cardiac index; CVP, central venous pressure; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; AST, asparagine transaminase; ALT, alanine transaminase; PCT, procalcitonin; INR, international normalized ratio; RPC, red packed cells; FFP, fresh frozen plasma; PLT, platelets; ICU, Intensive Care Unit; CIT, cold ischemia time; WIT, warm ischemia time; MELD, model of end-stage liver disease; BMI, body-mass-index; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.
*P = 0.003; **P = 0.005.

before death, with troponin I at 0.5 ng/ml. The echocardiogram indicated an ejection fraction that was less than 20%. Despite adequate pharmacological treatment, the CI remained at 0.9 l/min/m^2, and the patient died from cardiogenic shock (PCWP = 29 mmHg, CVP = 19 mmHg), systemic vascular resistance (SVR) = 2187 dyn × sec × cm^{-5} (the evaluation was 6 h before death). A postmortem autopsy indicated an intact liver anastomosis. Pulmonary embolism and myocardial infarction were excluded. The histologic workup of the heart indicated subepicardial macrophages and granulocytes, netted myocardial fibrosis, and myocyte edema.

The second of these two patients, who also had alcoholic cirrhosis and a MELD score of 38 at the time of transplantation, had an uneventful transplantation. The liver graft exhibited a regular clinical course. Three days after transplantation, the patient developed cardiogenic shock, which was verified by evaluation with the right-heart catheter (CI = 1.3 l/min/m^2, PCWP = 26 mmHg, CVP = 19 mmHg, SVR = 1887 dyn × sec × cm^{-5}). The echocardiogram indicated an ejection fraction of <10%. The BNP was >6000 pg/ml on the 3rd POD, and troponin I was 0.3 ng/ml.

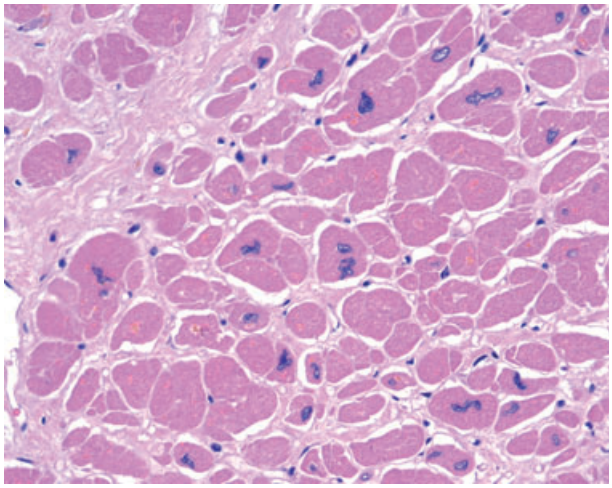

Figure 2 A 57-year-old female with cirrhotic cardiomyopathy after liver transplantation. Section (HE ×400) of the left ventricle, showing hypertrophy, diffuse fibrosis and cardiomyocytes of varied diameters, irregularly shaped nuclei and unusual pigmentation.

The postmortem autopsy again excluded a myocardial infarction. The histologic workup of the heart indicated myocytes edema, myocyte hypertrophy, and unusual pigmentation (Fig. 2).

Both patients had working liver grafts. The highest AST was 1200 U/l with subsequently declining transaminases. The highest international normalized ratio (INR) after transplantation was 1.8. In both patients, an alcoholic cardiomyopathy was ruled out preoperatively. The death of these two patients was related to cardiac failure and was not associated with the transplanted graft.

Liver function and haemodynamics

We did not find any differences in bilirubin, AST, ALT or INR between the groups. Systemic inflammation, expressed as C-reactive protein (CRP) and procalcitonin (PCT), did not differ between the groups.

Haemodynamic data, such as CI, MAP, CVP and transfusion requirements, were comparable between the groups. PCWP was significantly higher in Group 2.

Ventilation time and ICU stay was not influenced by diastolic dysfunction (Table 3). In patients with systolic dysfunction, however, we recorded significantly higher PCWP compared with patients with diastolic dysfunction (17 vs. 11 mmHg, P = 0.04), whereas CVP and cardiac index did not differ in patients with systolic and diastolic

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Table 3. Laboratory, haemodynamic and perioperative data for Group 2a and Group 2b on the 1st postoperative day.

	Group 2a	Group 2b
BNP (pg/ml)	509 (402–560)	1658 (596–4249)*
CIT (min)	396 ± 98	403 ± 157
WIT (min)	31 ± 9	32 ± 13
Bilirubin (mg/dl)	3.3 ± 2.3	5.9 ± 3.9
AST (U/l)	511 (177–4756)	535 (88–5582)
ALT (U/l)	480 (166–1563)	569 (134–3321)
CRP (mg/dl)	12.3 ± 5.4	8.6 ± 3.8
PCT (ng/ml)	31.3 (8–500)	33.5 (9–262)
INR	1.7 (0.9–2)	1.4 (1.1–2.4)
Creatinine	1.8 (0.9–3.3)	2.5 (1.3–4.3)
CI ($l \times m^2 \times min^{-1}$)	4,2 ± 1.2	4.1 ± 1.1
MAP (mmHg)	82 ± 6	84 ± 12
MPAP (mmHg)	20 ± 5	28 ± 7**
PVR (mmHg)	100 (42–176)	149 (58–480)
PCWP (mmHg)	11 ± 4	17 ± 6 ***
CVP (mmHg)	8 ± 5	9 ± 3
Norepinephrine (μg/kg/min)	0.08 (0–1.2)	0.3 (0–7)
RPC (transfused numbers)	4 (0–38)	4 (0–20)
FFP (transfused numbers)	0 (0–26)	0 (0–26)
PLT (transfused numbers)	0 (0–24)	0 (0–4)
Ventilation time (h)	14 (8–55)	60 (0–1104)
ICU stay (days)	4.5 (1–16)	6.5 (2–46)

CRP, C-reactive protein; BNP, brain-natriuretic peptide; CI, cardiac index; CVP, central venous pressure; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; AST, asparagine transaminase; ALT, alanine transaminase; PCT, procalcitonin; INR, international normalized ratio; RPC, red packed cells; FFP, fresh frozen plasma; PLT, platelets; ICU, Intensive Care Unit; CIT, cold ischemia time; WIT, warm ischemia time; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.
*P = 0.002, **P = 0.01, ***P = 0.003.

dysfunction (Table 3). Upon further analysis of the haemodynamic data, we discovered that the MPAP was significantly higher in Group 2 compared with Group 1 (Tables 2 and 3).

Discussion

Literature about cardiac dysfunction after transplantation is sparse. Our data indicate altered cardiac function in some recipients after LT. The levels of BNP increased significantly on POD 1 and returned to regular values after 1 week. Patients with CCM had significantly higher MELD scores compared with patients without it. Patients with CCM required significantly more dialysis treatments compared with patients without it, although liver function, systemic inflammation and haemodynamic parameters were not different between the groups.

Furthermore, the MELD scores and the BNP levels exhibited a significant correlation. Indeed, Maisel *et al.* [15] also evaluated BNP levels as a screening tool for cardiac dysfunction. Patients were referred for echocardiography to evaluate the presence or absence of left ventricular dysfunction. They observed in 105 patients (whose ventricular function was subsequently determined to be normal by echocardiography) BNP levels that averaged 37 ± 6 pg/ml. This average was significantly less than the values observed for patients with diastolic dysfunction (BNP 391 ± 89 pg/ml; $P < 0.001$) or systolic dysfunction (BNP 567 ± 115 pg/ml; $P < 0.001$).

Following Maisel *et al.*, we stratified a group of patients with a BNP >391 on POD 1 who were scheduled for echocardiography to confirm diastolic and systolic dysfunction.

Brain-natriuretic peptide is a hormone that is primarily secreted by the cardiac ventricles. Its secretion is associated with ventricular volume or pressure overload [20].

Therapondos *et al.* [21] demonstrated cardiac dysfunction during the first 3 months after transplantation. In their study, the BNP baseline levels were similar to our data. However, in contrast to our study (in which BNP increased on POD 1 and returned to regular limits after 1 week), their data indicated an increase in BNP after the first week. The BNP levels for patients who received cyclosporine returned to normal limits after 2 weeks, whereas the BNP levels for patients who received tacrolimus returned to baseline after 8 weeks. These results are in contrast to our data, where BNP returned to the normal range after 1 week. Our study design might have been responsible for this discordance. Patients with acute liver failure, retransplantation within 30 days, perioperative major cardiovascular events (pulmonary embolism and myocardial infarction), or troponin I levels ≥1 ng/ml were excluded from the study.

Our data were supported by Fukazawa *et al.* [22], who described a recovery of diastolic dysfunction soon after reperfusion. The authors suggested that the rapid recovery of diastolic dysfunction in cirrhotic patients indicates a metabolically mediated cause and argues against structural changes.

Yildiz *et al.* [17] found higher BNP levels with more advanced cirrhoses in nonalcoholic cirrhotic patients. Higher BNP levels correlated with diastolic dysfunction, which was confirmed by echocardiography.

These findings were supported by Henriksen *et al.* [16], who observed that patients suffering from cirrhosis with CHILD C had significantly higher BNP levels compared with patients with CHILD A cirrhosis.

Our data also indicate a significant correlation between the MELD score and the BNP level. Patients with CCM had significantly higher MELD scores compared with patients without it.

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Cirrhotic cardiomyopathy has been described as an asymptomatic condition that may become symptomatic as a result of volume or pressure overload [11]. Liver transplantation itself induces severe stress on the cardiovascular system [23] and, in some selected cases, hypotension at the time of graft reperfusion [24]. In our study, the transplant procedure caused serious haemodynamic deterioration in two patients, despite an uneventful operation without major blood loss. These patients died from cardiac failure. The histologic workup of the hearts of these patients confirmed cirrhotic cardiomyopathies.

In our cohort, the median MPAP in patients with CCM was 25 mmHg in Group 2 as a whole and 27 mmHg in Group 2b. These data may indicate the presence of portopulmonary hypertension (PPH), which is considered to begin at 25 mmHg [25]. An MPAP of 25–34 mmHg is categorized as mild pulmonary hypertension. Patients with mild PPH are accepted for LT [26] assuming that right heart function is well. In addition to a MPAP ≥25 mmHg, another essential criterion for PPH is an increased pulmonary vascular resistance (PVR) ($\geq$240 dyn × sec × cm^{-5}) [26]. In all the patients in our study, however, PVR was <240 dyn × sec × cm^{-5}. This finding may indicate that the increased MPAP was not associated with PPH but rather with CCM.

Moreover, patients with CCM required significantly more dialysis treatments, which was associated with a significantly higher mortality rate. It is well known that dialysis in patients with acute renal failure is an indicator for increased mortality [27].

As renal dysfunction has been shown to affect the BNP levels in some studies, the diagnostic value of BNP levels in conjunction with kidney failure has been questioned [28,29]. However, Tagore *et al.* [30] evaluated the influence of the glomerular filtration rate (GFR) on BNP in 142 patients. The authors found that the level of BNP was independent of the GFR. Suresh *et al.* [31] evaluated the influence of kidney failure on BNP levels. In the dialysis population, BNP correlates significantly with cardiac function and may act as a prognosticator for risk stratification among dialysis patients.

Brain-natriuretic peptide is metabolized by specific natriuretic peptide receptors found in the kidney, lung, liver and along the vascular endothelium [32]. It is thought that BNP is metabolized in organs other than the kidneys during kidney failure.

Although we cannot be sure that BNP levels were not influenced by kidney function in our study, the echocardiography results verified diastolic dysfunction in all of the patients with BNP > 391 pg/ml.

In both groups, the volume challenge, haemodynamic data, liver function, and severity of inflammation were comparable. CCM was associated with the severity of cirrhosis before transplantation.

Troponin I has been shown to be specific for myocardial ischemia [33]. Pateron *et al.* evaluated the levels of troponin I in patients with cirrhosis [34]. They found that 31% of the patients exhibited slightly increased troponin I (<1 μg/l). These data were supported by our study, in which troponin I was <1 μg/l for all of the patients, including the two who died from cardiogenic shock.

As with any clinical trial, our study has some limitations. First, we obtained typical cardiac histologic specimens only for those patients who died. Postoperative echocardiography was performed only in patients with BNP levels >391 pg/ml. We are unable to make any statements concerning echocardiography in the patients who had BNP levels <391 pg/ml. Moreover, preoperative BNP levels, even for patients with severe CCM, were lacking.

However, all of the patients underwent a cardiac workup preoperatively, which consisted of echocardiography and cardiologic assessment. None of the patients presented with clinical signs of cardiac decompensation preoperatively. Our data support the position that a liver transplant procedure, even without surgical complications, will unmask CCM. From our data, we may conclude that a BNP ≥391 pg/ml indicates CCM.

The clinical significance of CCM is an important topic for future research, and the initiation of new randomized studies of potential methods for earlier diagnosis and treatment of these complications is needed.

In conclusion, patients are at risk of cardiac failure following a LT. The BNP level seems to be a useful and noninvasive biomarker for detecting cardiac dysfunction in liver transplant recipients when cardiac failure is not evident clinically. Volume challenge must be performed carefully to prevent cardiac deterioration. Future studies should address the early detection of CCM.

Authorship

FS: designed the study, collected the data, and wrote the manuscript. JT, TN and AC: collected the data and participated in research design. MH and KG: participated in data analysis. SB, SB and VC: participated in data analysis and helped write the manuscript. AP: participated in research design and data analysis.

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