Data given as mean ± SD or n (%). *P<0.05 (unpaired t-test or Mann-Whitney test as appropriate); †P<0.05 (Chi-squared test or Fisher's exact test as appropriate).
ACEI, angiotensin-converting enzyme inhibitor; ACHD, adult congenital heart disease; AR, aortic regurgitation; ARB angiotensin receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CI, cardiac index; CRT-D, cardiac resynchronization therapy with defibrillator; CVP, central venous pressure; DCM, dilated cardiomyopathy; dHCM, dilated phase of hypertrophic cardiomyopathy; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ICM, ischemic cardiomyopathy; IVSD, interventricular septum diameter; LDH, lactate dehydrogenase; LV left ventricle; LVMI, left ventricular mass index; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; mRAP, mean right atrial pressure; NSVT, non-sustained ventricular tachycardia; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; PWD, posterior wall diameter; RCM, restrictive cardiomyopathy; RVSWI, right ventricular stroke work index; SBP, systolic blood pressure; TR, tricuspid regurgitation; VAD, ventricular assist device.

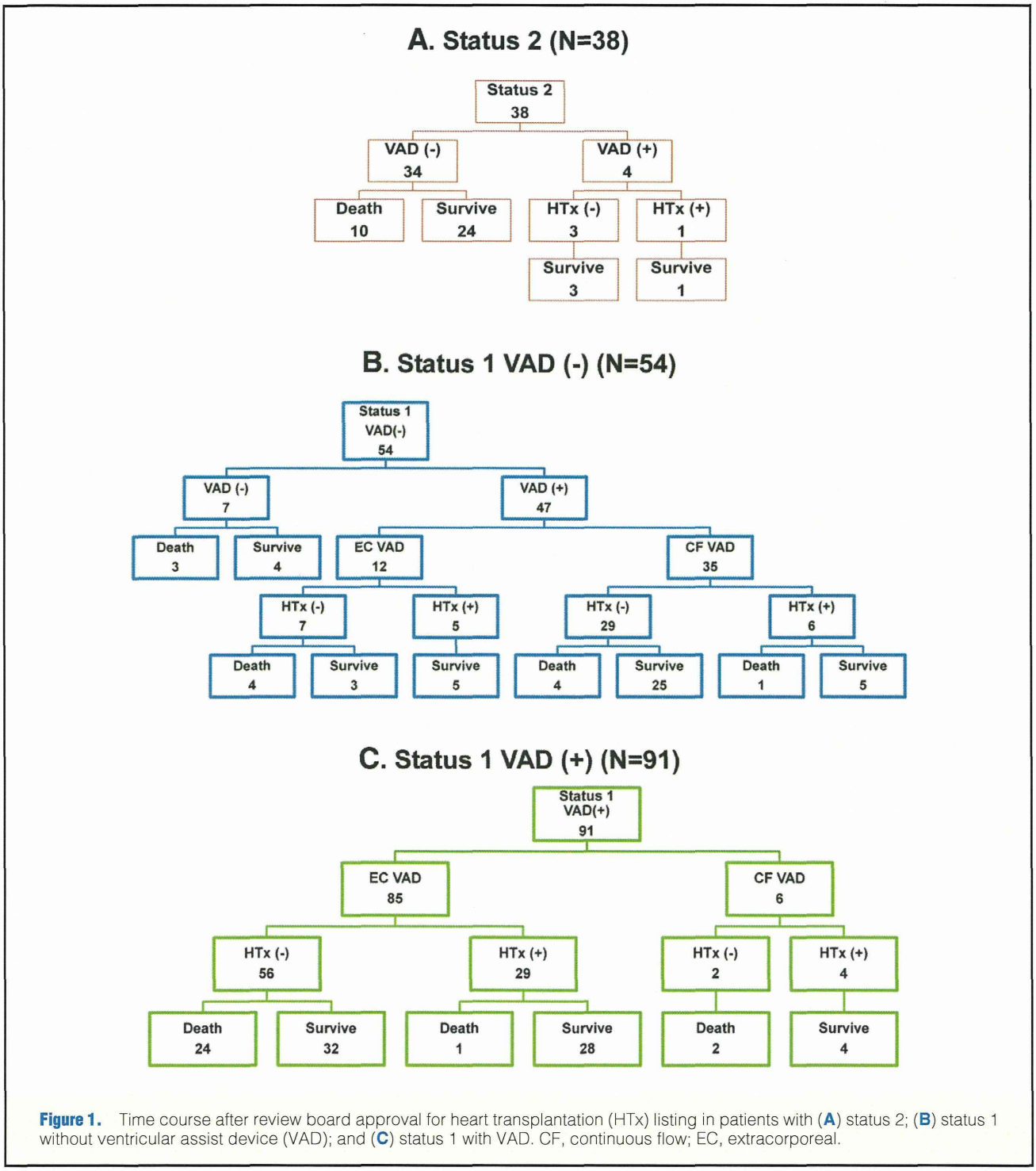

Figure 1. Time course after review board approval for heart transplantation (HTx) listing in patients with (**A**) status 2; (**B**) status 1 without ventricular assist device (VAD); and (**C**) status 1 with VAD. CF, continuous flow; EC, extracorporeal.

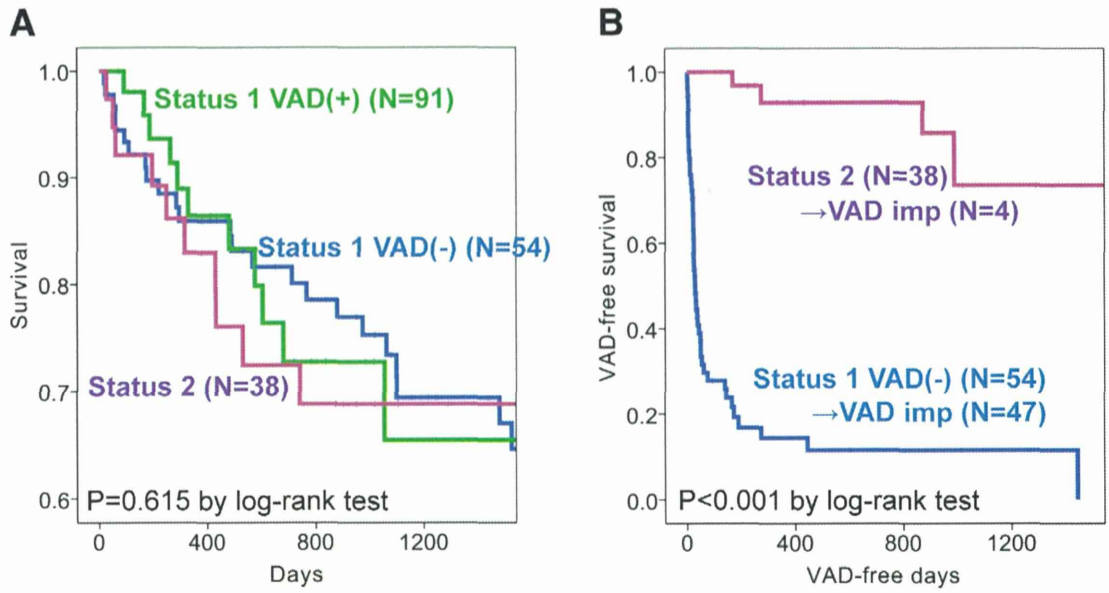

Figure 2. (**A**) Four-year survival among the 3 groups; and (**B**) ventricular assist device (VAD)-free survival in status 2 patients and in status 1 without VAD over 4 years. imp, implantation.

status code 1A and 1B; or (2) "status 2" for patients with New York Heart Association (NYHA) IV symptom but free from continuous inotrope infusion or mechanical circulatory support (MCS), equivalent to INTERMACS profile 4–6 or UNOS status code status 2.[5–7]

Considering its cost, adverse events, and quality of life during VAD treatment,[8] all listed patients are not necessarily considered as candidates for VAD therapy. Thus far, MCS as a tool for BTT has been indicated mostly for patients with status 1, and a number of authors including us have reported preoperative survival risk factors for optimal selection among them.[3,9–16] The indication for MCS in patients with status 2, however, has not been well described. Patients with status 2 are basically outpatients, and it may be difficult for health-care providers to respond to acute hemodynamic deterioration. On the one hand, many people consider that MCS indication is too early for status 2 patients, but, on the other hand, we should not be too late. Therefore, we compared patient prognosis between status 1 and 2 with or without MCS, and identified a therapeutic borderline between medical and MCS therapy in status 2 patients.

Methods

Patient Selection

We retrospectively analyzed 183 consecutive patients with stage D HF who were evaluated by the review board for HTx listing in the University of Tokyo Hospital and then listed for HTx on JOT Network between January 2003 and August 2013. All patients had been treated with guideline-directed medical therapy consisting of β-blockers, ACEI or angiotensin II receptor blockers (ARB), and aldosterone antagonists unless contraindicated. CRT-D was introduced if indicated. Before evaluation by the board, all patients received full examination to confirm eligibility for HTx.[6] In patients assigned to status 2, peak oxygen consumption (peak $\dot{V}O_2$) $\leq 14\,ml \cdot kg^{-1} \cdot min^{-1}$ on cardiopulmonary exercise test was an indispensable eligibility for HTx listing.

EC VAD was implanted as BTT or bridge to decision in patients with acute decline of hemodynamics with or without the approval of the review board. A small number of CF VAD was also implanted in patients under the clinical trials before review board approval for HTx. After confirming eligibility for HTx, they were listed as status 1.

Written informed consent was obtained at admission from the patients and/or their family members in all cases. The study protocol was approved by the Ethics Committee of Graduate School of Medicine, University of Tokyo (application number 779 [1]).

Variables Evaluated

Patients were enrolled at the time of approval by the institutional review board for HTx. All patients enrolled were listed on JOT Network later. Patient demographic, laboratory, echocardiographic, and hemodynamic parameters obtained <1 month before review board approval were analyzed in this study. In patients with VAD, postoperative data were used. History of non-sustained ventricular tachycardia (NSVT) was confirmed on 24-h Holter electrocardiogram. To evaluate effects of different types of β-blocker, the dose of bisoprolol was normalized to the approximately equivalent dose of carvedilol according to efficacy. For example, we regarded 5 mg of bisoprolol as 20 mg of carvedilol.[17] In the same manner, the doses of ACEI/ARB were normalized to the approximately equivalent dose of enalapril. For example, 4 mg of candesartan was regarded as 5 mg of enalapril.[18]

Statistical Analysis

All statistical analysis was done using PASW Statistics 18 (SPSS, Chicago, IL, USA) or JMP9 (SAS Institute, Cary, NC, USA). Categorical variables were summarized as frequencies and percentages, and compared using Chi-squared test or

Table 2. Predictors of Survival in Patients Without VAD at the Time of Review Board Approval

	Death (n=22)	Survival (n=70)	P-value	Hazard ratio	95% confidence interval
Demographic parameters					
Age (years)	39.6±18.5	40.0±14.7	0.631	0.993	0.966–1.021
Male	17 (77.3)	55 (78.6)	0.952	1.030	0.384–2.763
Body surface area (m^2)	1.57±0.26	1.47±0.46	0.147	0.434	0.141–1.340
Etiology of ischemia	2 (9.1)	7 (10.0)	0.815	0.840	0.195–3.613
Systolic blood pressure (mmHg)	88.2±10.5	86.2±8.3	0.391	1.018	0.977–1.061
Heart rate (beats/min)	83.0±14.6	85.4±20.2	0.681	1.005	0.980–1.031
History of NSVT	9 (40.9)	31 (44.3)	0.907	0.952	0.418–2.167
Concomitant treatment					
Furosemide (mg daily)	62.7±46.7	52.0±30.7	0.508	1.004	0.993–1.015
Spironolactone (mg daily)	33.5±25.4	33.8±20.1	0.906	1.001	0.983–1.020
β-blocker (mg daily)	8.0±7.2	9.0±6.4	0.732	0.989	0.927–1.054
ACEI/ARB (mg daily)	3.7±4.7	3.3±2.2	0.301	1.066	0.944–1.203
CRT-D	11 (50.0)	45 (64.3)	0.397	0.699	0.305–1.602
Laboratory parameters					
White blood cells ($\times10^3/\mu l$)	6.1±1.8	6.2±1.4	0.639	0.964	0.934–1.074
Hemoglobin (g/dl)	12.5±2.0	12.5±2.1	0.287	1.108	0.917–1.338
Platelets ($\times10^3/\mu l$)	23.7±10.7	21.2±7.0	0.336	1.023	0.977–1.071
Serum sodium (mEq/L)	134.0±6.4	135.4±4.0	0.694	0.984	0.906–1.068
Serum potassium (mEq/L)	4.3±0.4	4.2±0.4	0.394	1.514	0.583–3.935
Serum BUN (mg/dl)	25.0±7.4	24.1±4.5	0.406	1.032	0.958–1.112
Serum creatinine (mg/dl)	1.0±0.5	1.0±0.4	0.987	0.991	0.348–2.823
Serum albumin (g/dl)	3.7±0.4	4.0±0.6	0.124	0.604	0.318–1.148
Serum GOT (IU/L)	33.3±13.1	26.2±11.6	0.076	1.033	0.974–1.063
Serum GPT (IU/L)	31.0±23.1	26.8±17.6	0.475	1.008	0.987–1.029
Serum LDH (IU/L)	301.3±200.2	255.4±77.6	0.243	1.006	0.988–1.034
Serum total bilirubin (mg/dl)	1.2±0.7	1.2±0.8	0.821	1.072	0.587–1.959
Plasma BNP (log_{10}pg/ml)	3.01±2.88	2.98±3.18	0.324	0.976	0.923–1.084
Echocardiographic parameters					
LV diastolic diameter (mm)	67.1±19.4	69.4±14.5	0.749	0.996	0.971–1.022
LV systolic diameter (mm)	58.4±20.0	62.7±14.7	0.575	0.993	0.969–1.017
IVS (mm)	7.9±2.5	7.7±1.7	0.867	1.018	0.824–1.258
PW (mm)	8.1±2.1	7.9±1.7	0.976	1.003	0.809–1.244
LVMI (g/m^2)	182.2±76.5	172.5±67.8	0.664	1.001	0.996–1.006
Ejection fraction (%)	26.2±15.0	21.1±9.8	0.268	1.017	0.987–1.048
AR (grade)	0.2±0.7	0.2±0.4	0.465	1.354	0.601–3.052
MR (grade)	1.4±0.9	1.5±0.8	0.628	0.997	0.546–1.441
TR (grade)	1.2±0.8	1.2±0.7	0.945	1.022	0.552–1.893
Hemodynamic parameters					
mRAP (mmHg)	9.2±3.3	7.4±4.4	0.087	1.112	0.978–1.228
mPAP (mmHg)	29.9±7.5	27.4±10.6	0.219	1.028	0.983–1.075
PCWP (mmHg)	22.2±6.4	20.0±8.9	0.179	1.037	0.984–1.093
CI ($L\cdot min^{-1}\cdot m^{-2}$)	2.0±0.5	2.1±0.5	0.403	0.64	0.225–1.819
PVR (WU)	2.3±0.9	2.4±1.3	0.889	0.974	0.668–1.419
RVSWI (g/m^2)	7.2±2.8	6.9±3.3	0.730	1.025	0.890–1.180
CVP/PCWP	0.4±0.2	0.4±0.3	0.272	3.531	0.371–33.58

Data given as mean±SD or n (%). *P<0.05 (Cox regression analysis).
Abbreviations as in Table 1.

Fisher's exact test as appropriate. Continuous variables are represented as mean±SD unless otherwise specified, and compared using unpaired t-test or Mann-Whitney test as appropriate. Variables of status 1 and 2 with/without VAD were compared using ad-hoc Tukey test when analysis of variance confirmed significance. Kaplan-Meier analysis was done with log-rank test for survival over 4 years. Cox regression analysis was used to examine significant factors for survival. Receiver operating characteristic (ROC) analysis was used to calculate a cut-off value of plasma B-type natriuretic peptide (BNP) for survival in the status 2 group. All hypothesis tests reported are 2-tailed, and P<0.05 was set as significant.

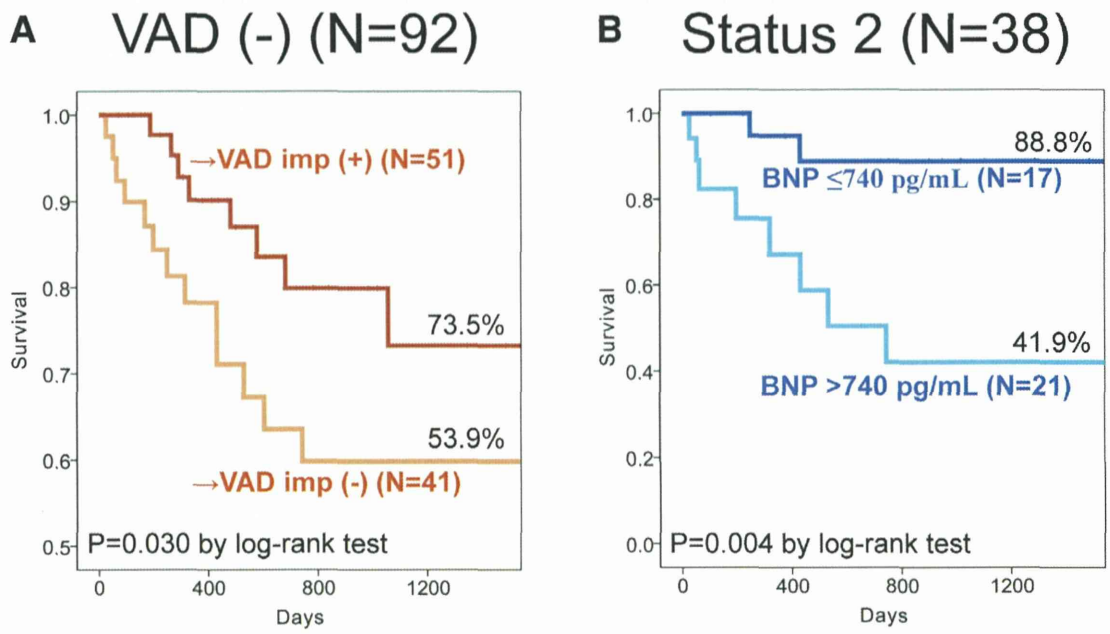

Figure 3. Four-year survival in (**A**) patients without ventricular assist device (VAD) stratified by eventual VAD implantation (imp); and (**B**) status 2 patients stratified according to plasma B-type natriuretic peptide (BNP) level.

Results

Patient Baseline Characteristics

Dilated cardiomyopathy and ischemic cardiomyopathy were the dominant etiologies of HF in all 3 groups (**Table 1**). Dilated phase of hypertrophic cardiomyopathy was another major etiology of HF in the status 2 and the status 1 without VAD groups. Fulminant myocarditis was the third major etiology of HF in the status 1 with VAD group.

There were no statistical differences in demographic, laboratory, echocardiographic, and hemodynamic parameters between the status 2 and the status 1 without VAD groups except for higher prevalence of previous NSVT in the latter group (34.2% vs. 50.0%, P=0.026). The status 1 with VAD group had a higher prevalence of improved hemodynamics along with unloaded left ventricle regardless of lower dose of diuretics (all P<0.05 compared with status 2).

Clinical Course Over 4 Years at Time of Review Board Approval

In the status 2 group (n=38), only 4 patients (10.5%) received VAD treatment eventually, and all of them survived during the study period (**Figure 1A**). Peak $\dot{V}O_2$ averaged 12.0±3.6 ml·kg^{-1}·min^{-1}, and all patients were assigned INTERMACS profile 4–6 at the time of enrollment (profile 4, 12 patients, 31.6%; profile 5, 21 patients, 55.3%; profile 6, 5 patients, 13.2%). Of the patients without VAD treatment, 10 patients (29.4%) died (6 due to acute hemodynamic compromise and 4 due to ventricular fibrillation [Vf]). Of the 4 patients who died due to Vf, 2 patients had received CRT-D previously.

In the status 1 without VAD group (n=54), 47 patients (87.0%) received VAD treatment eventually (CF, 35 patients, 74.5%; EC, 12 patients, 25.5%; **Figure 1B**). All patients were assigned INTERMACS profile 2 or 3 at the time of enrollment (profile 2, 23 patients, 42.6%; profile 3, 31 patients, 57.4%). Eleven patients (20.3%) received HTx eventually and, of them, only 1 patient died. Five patients (14.3%) died during CF VAD support, whereas 4 patients (33.3%) died during EC VAD support. Cause of death was multiple organ failure or stroke after VAD implantation.

In the VAD group (n=91), 85 patients (93.4%) had already received EC VAD, and 6 patients (6.6%) had CF VAD under the clinical trials (**Figure 1C**). All patients were assigned INTERMACS profile 1 or 2 before VAD implantation (profile 1, 50 patients, 54.9%; profile 2, 41 patients, 45.1%). Thirty-three patients (36.3%) received HTx eventually and, of them, only 1 patient died. While waiting for HTx, 26 patients (44.8%) died under VAD treatment.

There were no significant differences in overall survival among the 3 groups over 4 years (status 2, 68.8%; status 1 without VAD, 65.5%; and status 1 with VAD, 64.6%, P=0.615; **Figure 2A**). Patients assigned status 1 without VAD had markedly lower VAD-free survival than those of status 2 over 4 years (11.5% vs. 73.5%, P<0.001; **Figure 2B**).

Risk Analysis for Survival in Patients Without VAD at Time of Review Board Approval

On Cox regression analysis there were no significant predictors for 4-year survival in patients without VAD treatment (including both status 1 and 2) at the time of review board approval (n=92; **Table 2**), whereas more than half of the patients (n=51, 55%) eventually received VAD therapy as shown in **Figure 2B**, and clinical course was affected by MCS. Consistently, eventual VAD implantation significantly stratified 4-year survival in patients without VAD treatment according to Kaplan-Meier analysis (P=0.030, log-rank test; **Figure 3A**).

In contrast, Cox regression analysis showed that higher plasma BNP was the only significant predictor of 4-year mortality in status 2 patients (P=0.024, hazard ratio [HR], 8.267; **Table 3**). On ROC analysis the cut-off level of plasma BNP was 740 pg/ml (area under the curve, 0.704; sensitivity, 0.800;

Table 3. Predictors of Survival in Status 2 Patients at the Time of Review Board Approval

Total n=38	Death (n=10)	Survive (n=28)	P-value	Hazard ratio	95% confidence interval
Demographic parameters					
Age (years)	32.9±17.1	41.0±17.6	0.163	0.977	0.945–1.010
Male	6 (60.0)	20 (71.4)	0.363	0.556	0.156–1.973
Body surface area (m^2)	1.31±0.51	1.48±0.32	0.217	0.420	0.106–1.662
Etiology of ischemia	0 (0)	4 (14.3)	0.495	0.042	0.001–372.6
Systolic blood pressure (mmHg)	86.2±12.0	88.1±9.0	0.596	0.983	0.921–1.048
Heart rate (beats/min)	90.0±16.8	80.1±13.0	0.068	1.043	0.998–1.090
History of NSVT	5 (50.0)	9 (32.1)	0.972	1.022	0.297–3.515
Peak $\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	10.9±3.3	11.9±3.8	0.708	1.033	0.873–1.221
Concomitant treatment					
Furosemide (mg daily)	46.0±40.9	47.9±29.1	0.718	0.996	0.975–1.018
Spironolactone (mg daily)	37.5±27.0	37.1±22.4	0.850	1.002	0.977–1.028
β-blocker (mg daily)	9.1±8.2	11.3±6.7	0.451	0.962	0.870–1.064
ACEI/ARB (mg daily)	3.1±4.3	3.6±2.6	0.802	1.032	0.806–1.322
CRT-D	4 (40.0)	18 (64.3)	0.181	0.420	0.118–1.496
Laboratory parameters					
White blood cells ($\times 10^3/\mu l$)	5.4±1.4	6.1±1.5	0.087	0.596	0.37–1.023
Hemoglobin (g/dl)	13.3±1.6	12.8±2.0	0.273	1.203	0.865–1.672
Platelets ($\times 10^3/\mu l$)	19.3±5.0	22.2±7.6	0.361	0.951	0.854–1.059
Serum sodium (mEq/L)	135.4±8.0	136.2±4.1	0.868	1.010	0.902–1.130
Serum potassium (mEq/L)	4.2±0.4	4.2±0.3	0.573	0.652	0.147–2.885
Serum BUN (mg/dl)	22.5±6.3	23.3±3.4	0.672	0.972	0.851–1.109
Serum creatinine (mg/dl)	0.9±0.4	0.9±0.5	0.432	0.521	0.102–2.653
Serum albumin (g/dl)	3.8±0.5	4.1±0.6	0.355	0.669	0.285–1.568
Serum GOT (IU/L)	33.3±14.6	27.6±11.3	0.151	1.031	0.989–1.076
Serum GPT (IU/L)	28.6±18.9	26.8±18.1	0.664	1.008	0.974–1.042
Serum LDH (IU/L)	336.4±282.5	269.6±63.8	0.223	1.005	0.997–1.014
Serum total bilirubin (mg/dl)	1.2±0.7	1.0±0.6	0.504	1.391	0.529–3.62
Plasma BNP (log_{10}pg/ml)	2.96±0.35	2.70±0.34	0.024*	8.267	1.041–65.66
Plasma BNP >740 pg/ml	8 (80.0)	9 (32.1)	0.014*	7.037	1.487–33.29
Echocardiographic parameters					
LV diastolic diameter (mm)	64.6±21.4	65.6±13.3	0.829	0.995	0.954–1.038
LV systolic diameter (mm)	54.7±21.3	58.6±13.8	0.545	0.988	0.952–1.026
IVS (mm)	7.4±2.5	7.7±1.6	0.636	0.916	0.636–1.318
PW (mm)	7.8±2.5	7.9±1.3	0.800	0.947	0.621–1.444
LVMI (g/m^2)	177.1±82.9	169.6±64.3	0.813	1.001	0.992–1.010
Ejection fraction (%)	30.8±18.3	23.6±11.8	0.314	1.018	0.983–1.055
AR (grade)	0.3±0.9	0.1±0.4	0.394	1.461	0.611–3.497
MR (grade)	1.5±0.9	1.3±0.6	0.253	1.774	0.665–4.734
TR (grade)	1.1±0.9	1.1±0.6	0.681	0.824	0.328–2.072
Hemodynamic parameters					
mRAP (mmHg)	7.8±3.8	6.7±4.2	0.513	1.051	0.905–1.221
mPAP (mmHg)	27.8±8.7	24.1±8.6	0.263	1.043	0.969–1.123
PCWP (mmHg)	21.0±6.1	17.7±8.3	0.331	1.039	0.961–1.124
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.2±0.6	2.2±0.5	0.991	0.993	0.304–3.246
PVR (WU)	1.8±0.8	2.2±1.4	0.918	0.974	0.594–1.597
RVSWI (g/m^2)	6.7±2.7	6.3±2.6	0.574	1.069	0.848–1.347
CVP/PCWP	0.4±0.2	0.4±0.2	0.892	0.786	0.024–25.88

Data given as mean±SD or n (%). *P<0.05 (Cox regression analysis).
Abbreviations as in Table 1.

specificity, 0.607), and plasma BNP concentration >740 pg/ml had HR 7.037 on Cox regression analysis (P=0.014). Kaplan-Meier analysis significantly stratified 4-year survival in patients with status 2 according to plasma BNP level (P=0.004, log-rank test; **Figure 3B**).

Discussion

Among 183 consecutive patients with stage D HF who were evaluated by the review board of the University of Tokyo Hospital for HTx listing, the prognosis of status 2 patients was

as poor as those of status 1 with or without VAD treatment over 4 years. Eventual VAD implantation provided significantly better 4-year survival in patients without VAD treatment regardless of any baseline characteristics. On Cox regression analysis plasma BNP >740 pg/ml was the only significant predictor for 4-year mortality among status 2 patients.

Patient Prognosis

The VAD group had the sickest preoperative background because a large proportion of them had had INTERMACS profile 1, and received MCS due to cardiogenic shock. The group of status 1 without VAD, which was equivalent to INTERMACS profile 2 or 3, also had a sicker background, because i.v. inotropes could not be discontinued due to refractory HF. Surprisingly, less sick patients with status 2, equivalent to INTERMCS profile 4–6, had a prognosis as poor as other 2 groups. Nader et al consistently reported that UNOS status 2 patients, equivalent to those with JOT status 2, had a poor prognosis without transplantation (3-year survival with/without HTx, 87% vs. 57%, P<0.01).[19] Patient baseline characteristics including end-organ function and plasma BNP level of the status 1 group were as good as those of status 2 at the time of review board approval. Accordingly, not only MCS but intensive inotropic support could successfully maintain hemodynamics for a certain period. Approximately 90% of inotrope-dependent patients, however, needed VAD therapy within 1 year (cf. **Figure 2B**), and we should remember that inotropes are not as powerful as MCS for support on a month-to-month basis.

VAD Indication in Status 1 and 2

Previously established predictors of survival in HF patients, such as hyponatremia, chronic kidney disease, and high plasma BNP,[20–22] were not risk factors for survival among patients without VAD. Instead, VAD implantation provided significantly better survival. Among patients who are destined to receive MCS, such biomarkers may not simply become good predictors for survival. Consistent with this, Kelsey et al recently reported that previously developed preoperative health status had a limited association with outcome in patients who received HeartMate II VAD.[23]

CF VAD is indicated in patients with status 1, whereas those with status 2 have rarely received VAD treatment thus far in Japan.[9,10,24] INTERMACS similarly reported that not many (18.3%) of less sick patients (ie, profile 4–7) received VAD treatment in the past.[8] Among the status 2 group, 4 patients (10.5%) eventually received VAD treatment via status 1 due to worsening of HF, and all patients remained alive. The other 34 patients (89.5%) did not receive VAD implantation simply because they were assigned the less sick status 2. Boyle et al found that patients assigned INTERMACS profile 4–7, that is, almost equivalent to status 2 in Japan, had better 3-year survival after CF VAD implantation than the group who was more acutely ill.[25] Then, the next question is whether all patients with status 2 should receive VAD implantation.

Selection for VAD in Status 2

Plasma BNP >740 pg/ml was the only significant risk factor for mortality in the status 2 group, and 20 patients (52.6%) had plasma BNP >740 pg/ml. In other words, approximately half of the status 2 patients had been followed as outpatients without MCS, albeit with considerably high plasma BNP. Consistent with this, Kato et al reported that patients with peak $\dot{V}O_2$ 10–14 $ml \cdot min^{-1} \cdot kg^{-1}$ had a worse prognosis when they had plasma BNP ≥506 pg/ml.[26] All 10 deceased patients died due to acute deterioration of hemodynamics or fatal ventricular tachyarrhythmia. Their plasma BNP was already high (1197±943 pg/ml at the time of review board approval. Status 2 patients with higher plasma BNP appear to have high risk for sudden death, and may be good candidates for MCS in terms of survival benefit. Moreover, most of the deceased patients were followed in other hospitals, where VAD treatment could not be carried out. It might be better for such high-risk patients to be followed at an institution where VAD is available. In contrast, 3 of 4 patients with status 2 who eventually received VAD implantation had plasma BNP <740 pg/ml. The exacerbation of HF was relatively gradual among them and LVAD could be successfully implanted after they were inotrope dependent for a certain time period. It is of note that BNP level can stratify different time frames of HF progression.

Among 10 deceased patients, 4 out-hospital patients died suddenly due to Vf. Two patients had already received CRT-D, and they had been assigned "modifier A", the significance of which we previously proposed.[27] Patents with modifier A cannot be rescued only by CRT-D because of the deterioration of hemodynamics during electrical storm. Such patients may also be good candidates for MCS considering its advantage in avoidance of sudden death due to hemodynamic deterioration following fatal ventricular tachyarrhythmia, although sometimes these patients appear too well to receive MCS.

Guidelines state that CRT may be considered for ambulatory NYHA IV patients but not indicated for those who are inotrope dependent.[28] Nevertheless, CRT-D is often indicated for patients with advanced HF before VAD treatment partly because of hesitation in VAD implantation. In agreement with this, 56 patients (60.9%) had received CRT-D before review board approval among those who had not had VAD treatment. CRT-D, however, was not significantly associated with better 4-year survival according to Cox regression analysis. Furthermore, CRT-D was not sufficient to rescue patients with modifier A. Therefore, the evidence-based indication for CRT-D should be more strictly observed in order to minimize the percentage of non-responders as well as to save medical expenses.

Recently, the Medical Arm of INTERMACS (MEDAMACS) and the randomized evaluation of VAD intervention before inotropic therapy (REVIVE-IT) have been conducted in the USA to assess medically treated patients with profile 4–6 who might become candidates for VAD treatment.[8,29] The results would provide a reasonable indication for MCS in less sick patients.

Study Limitations

This study was conducted retrospectively at a single center, and consequently included a limited number of patients. The present institutional review board, however, is one of the major committees in Japan and a number of patients (62 patients; 33.9%) were referred from other institutes. Nevertheless, data from all HTx centers in Japan would definitely strengthen statistical power.

Only 4 VAD implants in the status 2 group were carried out, and we could not analyze the effects of VAD implantation on prognosis. Although the impact of VAD implantation on mortality appears to be clear in the combined group of status 1 and status 2, the survival benefit of VAD implantation in status 2 patients was not able to be demonstrated in this study.

Conclusions

Prognosis in status 2 patients was as poor as those dependent on inotrope infusion or VAD treatment because of out-of-hospital sudden death without MCS. Status 2 patients with high

plasma BNP may be good candidates for CF VAD therapy.

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Analysis of the Hepatic Functional Reserve, Portal Hypertension, and Prognosis of Patients With Human Immunodeficiency Virus/Hepatitis C Virus Coinfection Through Contaminated Blood Products in Japan

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ABSTRACT

Background. As the survival of human immunodeficiency virus (HIV)-infected individuals has improved due to the widespread use of antiretroviral therapy, the mortality rate due to hepatitis C virus (HCV)-related liver disease has increased in HIV/HCV-coinfected patients.

Aim. The aims of this study were to establish the appropriate therapeutic strategy for HIV/HCV-coinfected patients by evaluating the liver function, including the hepatic functional reserve and portal hypertension, and to investigate the prognosis of HIV/HCV-coinfected patients in Japan.

Patients and Methods. In addition to regular liver function tests, the hepatic functional reserve of 41 patients with HIV/HCV coinfection was evaluated using the indocyanine green retention rate and liver galactosyl serum albumin-scintigraphy. The data for 146 patients with HIV/HCV coinfection through blood products were extracted from 4 major HIV centers in Japan. In addition to liver function tests, the platelet counts (PLT) were evaluated as a marker of portal hypertension.

Results. In spite of the relatively preserved general liver function test results, approximately 40% of the HIV/HCV-coinfected patients had an impaired hepatic functional reserve. In addition, while the albumin and bilirubin levels were normal, the PLT was <150,000/μL in 17 patients. Compared with HCV mono-infected patients with a PLT <150,000/μL, the survival of HIV/HCV-coinfected patients was shorter (HCV, 5 years, 97%; 10 years, 86% and HIV/HCV, 5 years, 87%; 10 years, 73%; $P < .05$).

Conclusion. These results must be taken into account to establish an optimal therapeutic strategy, including the appropriate timing of liver transplantation in HIV/HCV-coinfected patients in Japan.

FROM 1970 until the early 1980s, blood products were imported to Japan, and contaminated blood products were unknowingly used to treat patients with hemophilia. It was later revealed that these patients were sometimes infected with both human immunodeficiency virus (HIV) and hepatitis C virus (HCV; HIV/HCV coinfection) [1].

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However, as the survival of HIV-infected people has improved due to the widespread use of antiretroviral therapy, the mortality due to HCV-related liver disease has increased in HIV/HCV-coinfected patients [2,3].

The main aims of this investigation were to investigate the status of portal hypertension and the prognosis in HIV/HCV-coinfected patients, and to establish an appropriate therapeutic strategy for HIV/HCV-coinfected patients, including the timing of liver transplantation, in Japan.

PATIENTS AND METHODS

Routine hematology and blood chemistry tests (general liver function), abdominal ultrasonography, and contrast-enhanced computed tomography (CT) were performed for 30 patients with HIV/HCV coinfection at Nagasaki University Hospital. To investigate the hepatic functional reserve, liver GSA-scintigraphy and the indocyamine green retention test at 15 minutes were performed. In addition, upper gastrointestinal tract endoscopy to diagnose gastroesophageal varices was performed.

The data of the 146 patients who had acquired HIV/HCV coinfection through blood products were extracted from 4 major HIV centers in Japan, including the AIDS Clinical Center, Osaka National Hospital, Yokohama Municipal Hospital, and Kyushu Medical Center. In addition to liver function tests, platelet counts (PLT) were evaluated as a marker of portal hypertension. As a control, HCV mono-infected patients from Nagasaki Medical Center were used for comparison.

RESULTS

In spite of the relatively well-maintained general liver functions, approximately 40% of the HIV/HCV-coinfected patients had an impaired hepatic functional reserve (Table 1). In addition, in spite of maintained albumin and bilirubin levels, the PLT was <150,000/μL in 17 coinfected patients, indicating the presence of ongoing portal hypertension.

Even with Child-Pugh A liver function, the HIV/HCV-coinfected patients showed a worse prognosis than the HCV mono-infected patients. The prognosis was especially poor in those with lower PLT than in the patients with a normal PLT (Table 2). When compared with HCV mono-infected patients with a PLT <150,000 μL, the survival of HIV/HCV-coinfected patients was much shorter (HCV, 5 years, 97%; 10 years, 86% and HIV/HCV, 5 years, 87%; 10 years, 73%; $P < .05$).

Table 1. Patient Characteristics

Child-Pugh A/B/C	38 (93%)/1 (2%)/2 (5%)
ICG R15 (%)	
<10/10–20/20–30/30<	24 (59%)/8 (20%)/3 (7%)/6 (14%)
GSA schincigram LHL15	
>0.9/0.8–0.9/0.8>	28 (69%)/6 (15%)/7 (16%)
Liver configuration on CT	
Normal/CH/LC	10 (24%)/17 (42%)/14 (34%)
Splenomegaly	
Yes/no	26 (63%)/15 (37%)
Esophageal varices	
Yes/no	13 (32%)/28 (68%)

CH, chromic hepatitics; LC, liver cirrhosis.

Table 2. Patient Survival after Diagnosis

	5Y OS	10Y OS	
HCV mono-infection (Child-Pugh A)	97%	86%	
HIV/HCV coinfection (Child-Pugh A)			
PLT > 150,000	94%	85%	
PLT < 150,000	87%	73%	$P < .05$ vs HCV mono-infection

5Y OS, 5 year patient survival; 10Y OS, 10 year patient survival.

DISCUSSION

In HIV/HCV-coinfected patients, liver failure due to HCV hepatitis was previously reported to be enhanced by antiretroviral therapy ART-related hepatotoxicity, especially manifesting as noncirrhotic portal hypertension (NCPH) [4,5]. One of the ART drugs, Didanosin (DDI), has been suspected to be related to the serious morbidity observed in coinfected patients [6]. Thus, not only in patients with deteriorated liver function, such as in Child-Pugh B or C cases, but also even in Class A cases, the patients' liver function can easily deteriorate abruptly [7]. The natural course of pure NCPH is unknown because it can be modulated by HCV or other causes, and has only been reported as case series. An important study of "NCPH in HIV Mono-Infected Patients Without HCV" was published in 2012 [8]. All 5 patients had portal hypertensive symptoms, such as ascites or variceal bleeding, after receiving antiretroviral therapy.

Therefore, all HIV/HCV-coinfected patients should be carefully followed up so as not to miss an opportunity for liver transplantation (LT) [9]. The prognosis for HIV/HCV-coinfected patients was reported to be worse than that for HCV mono-infected patients [10]. In the present study, coinfected patients with a PTL <150,000 μL had an especially poor prognosis, with a shorter survival than mono-infected patients. Our results should be taken into account to establish a therapeutic strategy, while also considering the appropriate timing of LT in HIV/HCV-coinfected patients.

In 2013, based on the evidence of rapid progression of the liver cirrhosis and portal hypertension in patients with HIV/HCV coinfection, a rank-up system for the waiting list for deceased donor LT was set up in Japan. Even HIV/HCV-coinfected liver cirrhotic patients with Child-Pugh class A can be listed for LT as "point 3" because of the NCPH (noncirrhotic portal hypertension) nature. Coinfected patients with Child-Pugh class B and C disease can be listed as "point 6" and "point 8," respectively, based on the data collected by the HIV/acquired immunodeficiency syndrome (AIDS) project team of the Ministry of Health, Labor, and Welfare of Japan, and the published literature [11]. This primarily covers victims who received contaminated blood products for hemophilia.

Future perspectives on LT for HIV/HCV coinfection include the following: new anti-HCV agents should be

developed to improve the control against HCV; new ART drugs, such as Raltegravir, should facilitate post-transplantation immunosuppressive therapy; noninvasive tests for portal hypertension, such as the fibroscan, should be performed for hemophilic patients; and the development of guidelines for the management hemophilia in the peri-operative period should facilitate better outcomes.

In conclusion, the present results should be taken into account to establish an optimal therapeutic strategy, including the appropriate timing of LT in HIV/HCV-coinfected patients.

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