Effects of surgical and medical treatment on quality of life for patients with chronic thromboembolic pulmonary hypertension

（慢性血栓塞栓性肺高血圧症における外科的および内科的治療の QOL に与える効果についての検討）

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Abstract

Background: This study aimed to investigate the predictors of quality of life (QOL) in patients with chronic thromboembolic pulmonary hypertension (CTEPH), changes in QOL after surgical and medical treatments, and the relationship between baseline QOL and survival.

Methods and Results: QOL was measured in 128 patients with CTEPH (male/female: 42/86, age: 56 ± 12 yr, surgical/medical: 65/63) using the Short Form 36 (SF-36). Multiple regression analysis showed pulmonary vascular resistance (PVR) and 6-min walking distance (6MWD) were associated with physical functioning (PF) ($p < 0.01$) and physical component summary (PCS) ($p < 0.01$). Seven subscales and two summary scores improved significantly in the surgical group and six subscales and mental component summary in the medical group, although the change in QOL was greater in the surgical group. The patients in the conventional therapy group with higher PF had significantly better survival compared with those with lower PF (5-yr survival: 89.5% vs. 50.8%, $p = 0.002$). This difference in survival was not observed in the group receiving pulmonary arterial hypertension (PAH)-specific therapy (100% vs. 100%, $p = 0.746$).

Conclusions: PVR and 6MWD were associated with PF or PCS in CTEPH patients. QOL improved after surgical or medical therapies, with a greater change in the surgical group. PAH-specific therapy improved survival in patients with lower PF at diagnosis.

Key Words; chronic thromboembolic pulmonary hypertension; quality of life; pulmonary endarterectomy; pulmonary vasodilator

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension caused by non-resolving thromboembolisms of the pulmonary arteries and pulmonary vascular remodeling, associated with the development of right heart failure without effective treatment and a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg.[1] The optimal treatment is lifelong anticoagulants, and pulmonary endarterectomy (PEA) if the thrombi are surgically accessible. Patient symptoms, walking distance, resting hemodynamics, quality of life (QOL), and WHO functional class have all been reported to improve after successful PEA.[2-4]

On the other hand, the prognosis of CTEPH in medically-treated patients is considered to be poor, with 3-yr survival as low as 40% in patients with a mPAP >30 mmHg.[5] Previously, management of these patients was supportive. However, the use of pulmonary arterial hypertension (PAH)-specific therapy, including endothelin receptor antagonists (ERA) and phosphodiesterase-5 inhibitors (PDE-5I), has improved therapeutic outcomes in patients with inoperable CTEPH.[6-8] Recently, the soluble guanylate cyclase stimulator, riociguat, has been approved for inoperable CTEPH or persistent or recurrent pulmonary hypertension after PEA.[9] Our group has reported previously that PAH-specific therapy was a predictor of survival in medically-treated CTEPH patients.[10, 11]

Various treatments have had favorable outcomes in CTEPH patients and therefore it is important to evaluate QOL as a therapeutic endpoint. QOL represents a broad spectrum of human experiences related to one's overall well being, including nonmedical factors.[12] Changes in physiological measures may not always translate into benefits that can be perceived by the patient.[13] Some studies on patients with pulmonary hypertension have provided controversial results and have questioned whether improvement in QOL is associated with improvements in laboratory data, hemodynamics, exercise capacity, and survival.[14] Therefore, health-related quality of life (HRQOL)

is often measured as an additional endpoint.[15]

Although therapeutic outcomes may be ameliorated, the effect on QOL in patients with CTEPH is not fully understood. The aims of this study were: 1) to determine the predictors of QOL in patients with CTEPH, 2) to examine how QOL changed following therapeutic intervention, and 3) to investigate the relationship between baseline QOL and patient survival.

Methods

Subjects

Between April 1999 and November 2011, a total of 155 patients were diagnosed with CTEPH at Chiba University Hospital, and of this group, 128 completed a QOL questionnaire at their first admission for diagnostic tests. CTEPH was defined as a mPAP $\geq$ 25 mmHg with a normal wedge pressure in patients with dyspnea on exertion for > 6 months.[16] Lung perfusion scans were also required to demonstrate segmental or larger defects concomitant with normal ventilation scans. Helical computed tomography (CT) angiography was used to confirm the diagnosis. Chronic thromboembolic findings were confirmed on pulmonary angiography. Of the128 patients, 65 underwent PEA, while 63 patients were treated medically (Figure 1).

Assessment of central thrombi

Central arteries were defined as vessels proximal to segmental branches and were divided into four portions.[17] The central disease (CD) score was calculated as the number of abnormal central portions, with a maximal score of 4 (Figure 1). The score was determined using helical CT.

Assessment of QOL

We used the Medical Outcome Study Short Form 36 (SF-36) version 1, a generic measure used to evaluate QOL.[18] SF-36 is a self-administered questionnaire comprised of eight subscales, physical functioning (PF), role physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role emotional (RE), mental health (MH), and two summary scores (physical component summary (PCS) and mental component summary (MCS)). The PCS and MCS were calculated from the eight subscales. Each score ranges from 0 to 100, with a higher score indicating better QOL. The patients were requested to complete the SF-36 within 2 wk of baseline right heart catheterization. We also sent follow-up questionnaires to both medically- or surgically-treated patients between 1 and 37 months after the date of diagnosis. Follow-up QOL scores were obtained from 46 (71%) surgically-treated patients and 34 (54%) medically-treated patients (Figure 1). The study was approved by the ethics committee of Chiba University (approval number 826), with written informed consent being obtained from all patients before catheterization.

Surgical treatment

The selection criteria for PEA were modified slightly by Moser and colleagus.[19] The criteria used in our study were: (1) mPAP of ≥ 30 mmHg, resulting in a calculated PVR of ≥ 300 dyn.s.cm^{-5}, even after oral anticoagulant therapy for > 6 months; (2) WHO functional class of ≥ 2; (3) thrombi defined as accessible to current surgical technique (i.e. in main, lobular, or segmental arteries); and (4) absence of severe associated disease[20]. A median sternotomy under cardiopulmonary bypass with deep hypothermia and circulatory arrest technique was performed in 65 of the 128 patients in the study. The major reasons for exclusion for surgery at that time were mild disease (mPAP < 30 mmHg or PVR < 300 dyn.s.cm^{-5} (3.75 Wood unit [WU]) (n = 10), WHO class II with mild symptoms (n = 1), relatively peripheral type (n = 46), severe comorbidities (n = 2), and age > 70 yr or unwillingness to undergo surgery (n = 4).

Medical treatment

A total of 63 patients were treated medically in this study. Warfarin was prescribed for all 63 patients to obtain a target international normalized ratio prothrombin time of 2 ~ 3 and long-term oxygen therapy (LTOT) of 92% in the group. In Japan, the oral prostanoid, beraprost, has been available as off-label use since 1999. We defined warfarin, LTOT, and oral beraprost as conventional therapy. Although bosentan and sildenafil are off-label use for CTEPH, we have used them since 2005, and define them as PAH-specific therapy in accordance with our previous report.[10]

Survival analysis in medically-treated patients

At December 2011, 51 patients in the medically-treated group had survived, while 12 had died. Survival time was calculated from the date of diagnosis by right heart catheterization. We divided the 63 medically-treated patients into two groups: conventional therapy group (n = 33) and PAH-specific therapy group (n = 30). Of the 34 patients with follow-up SF-36 scores available, 23 had received conventional therapy and 11 PAH-specific therapy (Figure 1).

The patients were also stratified into two groups using the median PF value at diagnosis of 55. The resulting 4 groups were defined as follows: group 1, conventional/PF $\geq$ 55 (n = 19); group 2, conventional/PF < 55 (n = 13); group 3, PAH-specific/PF $\geq$ 55 (n = 13) and group 4, PAH-specific/PF < 55 (n = 17). One patient was excluded because the PF value was not available. The baseline characteristics of the patients, hemodynamics, and survival were compared between the four groups (Table 2).

Statistical analysis

The results were expressed as mean ± SD for continuous variables and analyzed using Student's t-test. Multiple regression analysis was used to identify the factors associated with PF and

PCS in the CTEPH patients. Survival curves were analyzed by the Kaplan-Meier method using the log-rank test to compare survival. *P* values < 0.05 were considered statistically significant. The statistical analyses were performed using JMP version 9.0 (SAS Institute).

Results

Patient characteristics

The baseline characteristics of all the patients are summarized in Table 1. The age at diagnosis ranged between 18 to 78 yr, with a mean of 56 ± 12 yr. The study population contained more female patients (n = 86) than male patients (n = 42). Baseline mPAP, cardiac index (CI), PVR, and arterial oxygen tension (PaO_2) were 45 ± 12 mmHg, 2.6 ± 0.7 L/min/m^2, 10.0 ± 4.5 WU, and 58 ± 10 Torr, respectively. The 6MWD was 349 ± 94 m.

Comparison of SF-36 and clinical variables

Univariate analysis showed significant correlation between PvO_2 (r = 0.49, $p < 0.0001$; r = 0.30, $p = 0.0009$), right atrial pressure (RAP) (r = -0.29, $p = 0.0013$; r = -0.24, $p = 0.0084$), CI (r = 0.41, $p < 0.0001$; r = 0.24, $p= 0.0087$), PVR (r = -0.46, $p < 0.0001$; r = -0.40, $p < 0.0001$), 6MWD (r = 0.54, $p < 0.0001$; r = 0.46, $p < 0.0001$), serum BNP (r = -0.41, $p < 0.0001$; r = -0.30, $p = 0.0008$) and PF or PCS, respectively (Table S1). Multiple regression analysis demonstrated that higher 6MWD and lower PVR were associated with a higher PF or higher PCS (Table 3).

Association of SF-36 score and operative mortality

Of the 65 surgically-treated patients, 6 patients died within 90 days after the operation. There was no significant difference in all subscales of the SF-36 between patients who died and those who survived.

Improvement of QOL by therapeutic intervention

SF-36 was reassessed at follow-up in 46 of the 65 surgically-treated patients and 34 of the 63 medically-treated patients. The observation time was 14.0 ± 10.1 and 15.3 ± 9.7 months, respectively. In the surgically-treated group, all the SF-36 scores except for BP improved significantly (Table 4), whereas in the medically-treated group, PF, RP, VT, SF, RE, MH, and MCS improved significantly (Table 5). RP, VT, RE, MH, and MCS improved significantly in the conventional therapy group, while PF, VT, SF, RE, and MCS improved significantly in the PAH-specific therapy group (Tables S2 and S3). We compared the change in SF-36 scores between the surgically- and medically-treated groups and showed ΔPF, ΔRP, ΔGH, and ΔPCS were significantly lower in the medically-treated group (Table 6).

Survival analysis in the medically-treated group

The 5-yr survival rate from the date of diagnosis in the medically-treated group was 84.7%. Ten patients in the conventional therapy group died in the conventional therapy group, compared with only two deaths in the PAH-specific therapy group. Figure 2 shows the survival curves of the four groups described above with 5-yr survival in group 1 (conventional/PF ≥ 55) of 89.5%, group 2 (conventional/PF < 55) of 50.8%, group 3 (PAH-specific/PF ≥ 55) of 100%, and group 4 (PAH-specific/PF < 55) of 100%.

In the conventional therapy group, group 1 (PF ≥ 55) had better survival than group 2 (PF < 55). On the other hand, in the PAH-specific therapy group there was no difference in survival between group 3 (PF ≥ 55) and group 4 (PF < 55) (p = 0.746). In patients with lower PF (PF < 55), the PAH-specific therapy group (group 4) had better survival than the conventional therapy group (group 2) (p = 0.019), although 6MWD in group 4 was lower than that measured in group 2 at baseline.

Discussion

This study in patients with CTEPH showed a significant association of higher PVR and lower 6MWD with lower PF and PCS. Most of the SF-36 subscales improved in both the surgically- and medically-treated groups; however, the improvements in PF, RP, GH and PCS in the medically-treated group were smaller than those in the surgically-treated group. In the medically-treated group, PAH-specific therapy improved survival in patients with a lower PF (PF < 55) at baseline. This is the largest study to investigate QOL determinants in CTEPH and the influence of QOL on survival in medically-treated CTEPH. We found initially that PVR was associated with PF and PCS in CTEPH, and that lower PF was associated with poor survival in patients treated with conventional therapy, while it was not associated with survival in patients receiving PAH-specific therapy.

There were several issues that needed to be considered when we interpreted our results. PF and PCS are the physical components of the SF-36, with our results showing that higher PVR and lower 6MWD were associated significantly with the physical components of QOL. In an observational study of 22 medically-treated CTEPH patients in Switzerland, the physical subscore of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was associated moderately with the New York Heart Association (NYHA) functional class, 6MWD, Borg scale, cardiac index, and mixed venous oxygen saturation ($r = 0.40 \sim 0.59$), whereas hemodynamics, right ventricular systolic pressure and mPAP were only weakly correlated ($r = 0.20 \sim 0.39$).[21] In a multivariate analysis of 63 patients with pulmonary hypertension including 15 CTEPH patients, 6MWD, peak oxygen uptake and mental disorders were associated with PF of the SF-36.[22] In addition, in PAH patients, 6MWD and the baseline dyspnea index (BDI) correlated strongly with PCS, whereas none of the

hemodynamic parameters correlated with PCS.[23] In contrast to these reports, our results showed that PVR correlated with PF and PCS, although the degree of correlation of PVR with PF or PCS was only moderate (r = -0.46 and -0.40). Several possible explanations may account for this inconsistency. First, we investigated only CTEPH, with PVR being a more important determinant of PF and PCS in CTEPH than in PAH. Second, PAH includes more heterogeneous patients, and it is possible that QOL in PAH patients with collagen vascular disease may be related to right ventricular function and other systemic organ impairment. Third, we investigated a larger number of patients with CTEPH than previous reports, and therefore our results could be more reliable.

Improvement of QOL in the medically-treated group was significant, although this change was lower than that observed in the surgically-treated group. However, some of SF-36 subscales improved significantly even in the conventional therapy group as well as in the PAH-specific therapy group (Tables S2 and S3). In the conventional therapy group, 17 of the 23 patients received oral beraprost. Although beraprost has not been approved for CTEPH, Ono et al. reported that it improved NYHA functional class in 50% of patients and significantly decreased total pulmonary resistance in CTEPH.[24] It is therefore possible that oral beraprost may have contributed to an improvement in QOL in the conventional therapy group. On the other hand, our results did not show an obvious advantage of PAH-specific therapy in terms of improvement in QOL compared with the conventional therapy group. Possible explanations for this finding are the relatively small samples used to detect the difference, and that PDE-5 inhibitors and ERA may not be sufficient to provide better QOL compared with beraprost and conventional therapies in patients with CTEPH.

There are some reports that have shown a correlation between QOL and survival of patients with pulmonary hypertension. In a study of 22 CTEPH patients and 26 PAH patients, Cenedese et al. reported that patients with a MLHFQ score < 40 had a higher mortality rate compared with patients

with a score ≥ 40.[21] Fernandes et al. also reported a recent study in 56 patients with PAH that showed those with a baseline PCS > 32 in the SF-36 had better survival than those with a PCS < 32.[25] Our results are similar to these reports in that we observed an association between low QOL and poor survival. In addition, we demonstrated that PAH-specific therapy improved survival even in patients with a lower PF at baseline. On the other hand, in the conventional therapy group, patients with a PF ≥ 55 had better survival compared with patients with a PF < 55. This indicates that PF could be a prognostic factor in patients with CTEPH treated by conventional therapy.

There were some limitations in our study. First, it was a retrospective, small-sized study, especially when evaluating the effectiveness of PAH-specific therapy. Prospective, larger studies are therefore needed to clarify the different effects of treatment on QOL in CTEPH. Second, SF-36 scores are not disease-specific QOL measures and may be less sensitive to changes in QOL in CTEPH. In general, generic measures, including SF-36, represent health status that is comparable even with the healthy population. In contrast, disease-specific measures are more sensitive to treatment. It may therefore be reasonable to use disease-specific measures when evaluating the effects of treatment in terms of sensitivity.

In conclusion, we demonstrated that PVR and 6MWD were associated with PF and PCS in patients with CTEPH. QOL improved after surgical or medical therapies, with a greater change in QOL being observed in the surgical group. In the medically-treated group, PAH-specific therapy improved survival in patients with a low PF at diagnosis.

Disclosures

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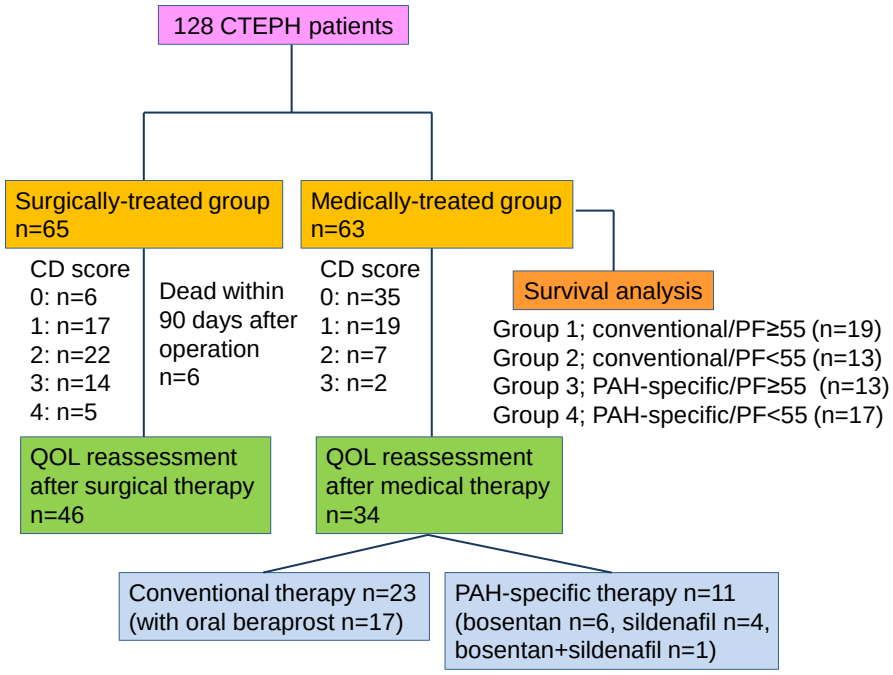
Figures and Tables

Figure 1. Algorithm of management and course for chronic thromboembolic pulmonary hypertension (CTEPH)



CD score, central disease score; QOL, quality of life; PAH, pulmonary arterial hypertension; PF, physical function (a SF-36 subscale); PAH, pulmonary arterial hypertension

The CD score of one patient was not available in the surgically-treated group. Conventional therapy includes warfarin, long-term oxygen therapy and oral beraprost. PAH-specific therapy includes bosentan and sildenafil. The median value for PF was 55. In the survival analysis, one patient was excluded because the PF value was not available.

Table 1. Baseline patient characteristics

Parameters	All patients (n=128)	Surgically-treated group (n=65)	Medically-treated group (n=63)
Age (yr)	56 ± 12	55 ± 11	57 ± 14
Sex (male/female)	42 / 86	29 / 36	13 / 50
mPAP (mmHg)	45 ± 12	47 ± 11	43 ± 12
RAP (mmHg)	6 ± 4	7 ± 5	5 ± 4
CI (L/min/m^2)	2.6 ± 0.7	2.6 ± 0.7	2.7 ± 0.6
PVR (Wood unit)	10.0 ± 4.5	10.9 ± 4.3	9.1 ± 4.5
6MWD (m)	349 ± 94	347 ± 89	351 ± 98
PaO_2 (torr)	58 ± 10	58 ± 9	58 ± 11
PvO_2 (torr)	32 ± 4	32 ± 4	33 ± 4
Serum BNP (pg/ml)	232 ± 307	239 ± 259	225 ± 351
WHO class			
I	2	0	2
II	34	12	22
III	88	49	39
IV	4	4	0

Data are expressed as mean ± SD or number. mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; 6MWD, 6 min walking distance; PaO_2, arterial oxygen tension; PvO_2, mixed venous oxygen tension; BNP, brain natriuretic peptide; WHO, World Health Organization.

Table 2. Comparison of patient characteristics of the medically-treated grouped according to therapeutic agent (conventional or PAH-specific) and PF value.

	Group 1 (n=19)	Group 2 (n=13)	Group 3 (n=13)	Group 4 (n=17)
Age (yr)	58.1 ± 11.2	60.8 ± 13.3	50.7 ± 15.0	57.9 ± 13.2
Sex (male/female)	4 / 15	3 / 10	1 / 12	4 / 13
mPAP (mmHg)	36.8 ± 12.6	43.2 ± 12.0	45.8 ± 12.7	46.6 ± 9.6
CI (L/min/m^2)	2.99 ± 0.57	2.48 ± 0.55 *	2.60 ± 0.46 *	2.46 ± 0.56
PVR (Wood unit)	6.54 ± 2.44	10.49 ± 6.09 *	9.81 ± 4.26 $	10.77 ± 3.72
6MWD (m)	398.7 ± 47.9	311.1 ± 120.9 $	375.3 ± 72.0	292.6 ± 109.6 †
PaO_2 (torr)	60.7 ± 11.5	52.2 ± 8.9 ††	61.0 ± 13.6	56.4 ± 9.2

*: $p<0.05$ compared with group 1
$: $p<0.01$ compared with group 1
†: $p<0.05$ compared with group 3
††: $p<0.05$ compared with group 1 and 3

Data are expressed as mean ± SD or number. Abbreviations as in Figure 1 and Table 1. Group 1, conventional/PF ≥ 55 (n=19); Group 2, conventional/PF < 55 (n=13); Group 3, PAH-specific/PF ≥ 55 (n=13) and Group 4, PAH-specific/PF < 55 (n=17). One patient was excluded because of no PF value.

Table 3. Multiple regression analysis of factors associated with QOL in CTEPH patients

Variables	PF (n=126)		PCS (n=121)	
	β	*p* value	β	*p* value
6MWD (m)	0.10	<0.0001	0.03	0.0012
PVR (Wood unit)	-1.32	0.0072	-0.58	0.0041
R^2		0.34		0.27
Adjusted R^2		0.33		0.26

PF, Physical functioning; PCS, Physical component summary; 6MWD, 6 min walking distance; PVR, pulmonary vascular resistance

Table 4. QOL at diagnosis and after surgical therapy in the surgically-treated group

SF-36	n	At diagnosis	After surgical therapy	
PF	46	44.7 ± 24.2	69.9 ± 22.1	$
RP	46	20.7 ± 32.2	62.3 ± 43.7	$
BP	46	71.5 ± 27.9	72.1 ± 25.7	
GH	45	35.2 ± 19.4	55.6 ± 18.2	$
VT	44	45.9 ± 22.6	63.4 ± 21.7	$
SF	46	47.6 ± 29.7	64.2 ± 31.5	$
RE	46	42.7 ± 46.4	62.3 ± 45.3	*
MH	45	56.7 ± 20.2	67.1 ± 20.5	$
PCS	44	37.0 ± 8.0	45.1 ± 7.5	$
MCS	44	46.0 ± 8.5	49.4 ± 8.5	*

*: $p<0.05$

$: $p<0.01$

Data expressed as the mean ± SD. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality, SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary

Table 5. QOL at diagnosis and after medical therapy in the medically-treated group

SF-36	n	At diagnosis	After medical therapy	
PF	33	51.1 ± 22.2	60.9 ± 20.5	$
RP	33	26.5 ± 35.3	45.7 ± 40.1	*
BP	33	70.1 ± 24.9	72.2 ± 27.4	
GH	33	45.2 ± 18.6	46.5 ± 15.3	
VT	31	44.7 ± 23.8	61.5 ± 18.2	$
SF	34	48.5 ± 24.4	62.9 ± 24.7	$
RE	33	45.5 ± 46.3	73.7 ± 42.3	$
MH	31	58.5 ± 25.4	73.2 ± 17.6	$
PCS	30	38.6 ± 9.1	38.1 ± 10.2	
MCS	30	45.5 ± 10.4	51.2 ± 8.5	$

*: $p<0.05$

$: $p<0.01$

Data expressed as the mean ± SD. Abbreviations as in Table 4.

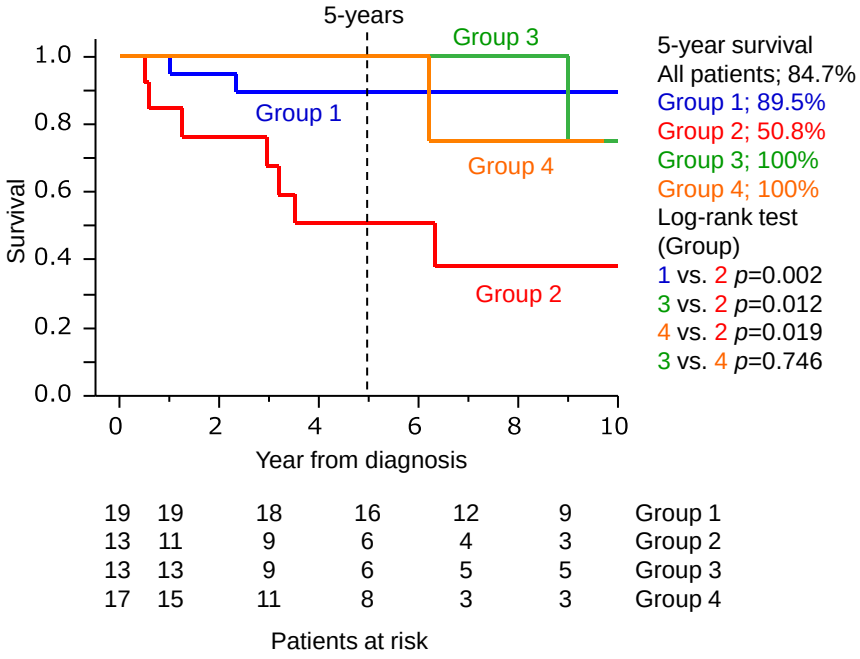
Table 6. Comparison of the change in QOL following therapeutic intervention between the surgically- and medically-treated group

SF-36	Surgical group (n)			Medical group (n)			
ΔPF	25.2	± 23.4	(46)	9.7	± 19.3	(33)	$
ΔRP	41.7	± 47.0	(46)	19.2	± 44.3	(33)	*
ΔBP	0.7	± 32.0	(46)	2.1	± 32.5	(33)	
ΔGH	20.4	± 23.5	(45)	1.3	± 16.3	(33)	$
ΔVT	17.5	± 21.3	(44)	16.8	± 22.2	(31)	
ΔSF	16.6	± 31.3	(46)	14.3	± 25.2	(34)	
ΔRE	19.6	± 52.9	(46)	28.3	± 45.7	(33)	
ΔMH	10.4	± 22.5	(45)	14.7	± 20.0	(31)	
ΔPCS	8.0	± 10.0	(44)	-0.6	± 7.8	(30)	$
ΔMCS	3.4	± 8.5	(44)	5.7	± 7.3	(30)	

*: $p<0.05$
$: $p<0.01$

'Δ' refers to the finite differences between SF-36 scores at diagnosis and at follow-up. The extent of improvement of physical function (PF), role physical (RP), general health (GH) and, physical component summary (PCS) in the surgically-treated group was significantly greater than that in the medically-treated group. Abbreviations as in Table 4.

Figure 2. Survival curves of patients with medically-treated chronic thromboembolic pulmonary hypertension



Patients were classified into four groups according to the therapeutic agent (conventional therapy or PAH-specific therapy) and PF value. The median value for PF was 55. Patients with PF < 55 had poorer survival than those with PF ≥ 55 under conventional therapy (group 1 vs. 2, p = 0.002). In contrast, patients treated with PAH-specific therapy had no difference in survival regardless of PF at diagnosis (group 3 vs. 4, p = 0.746).

Group 1, conventional/PF ≥ 55; Group 2, conventional/PF < 55; Group 3, PAH-specific/PF ≥ 55; Group 4, PAH-specific/PF < 55.

Table S1. Correlation between SF-36 and the clinical parameters of the patients

	(Physical functioning) PF	(Role physical) RP	(Bodily pain) BP	(General health) GH	(Vitality) VT	(Social functioning) SF	(Role-emotional) RE	(Mental health) MH	PCS	MCS
(n)	(126)	(128)	(127)	(124)	(124)	(128)	(128)	(125)	(121)	(121)
Age	0.03	-0.10	-0.02	0.07	0.06	0.05	-0.21 $	0.00	0.05	0.13
mPAP	-0.23 $	0.03	0.25 $	-0.18 *	0.08	0.03	0.00	0.22 *	-0.24 *	0.17
RAP	-0.29 $	0.02	0.15	-0.24 $	-0.01	0.09	0.06	0.06	-0.24 $	0.05
CI	0.41 $	0.15	0.04	0.29 $	0.25 $	0.12	0.04	0.14	0.24 $	0.13
PVR	-0.46 $	-0.10	0.11	-0.29 $	-0.05	-0.07	0.00	0.08	-0.40 $	0.08
6MWD	0.54 $	0.33 $	0.14	0.08	0.16	0.16	0.17	0.09	0.46 $	-0.10
PaO_2	0.14	0.24 $	0.02	0.16	0.05	0.14	0.29 $	0.06	0.04	-0.01
PvO_2	0.49 $	0.27 $	0.06	0.31 $	0.22 *	0.18 *	0.22 *	0.11	0.30 $	0.04
Serum BNP	-0.41 $	-0.11	0.09	-0.13	-0.10	0.03	-0.09	0.04	-0.30 $	0.08
WHO class	-0.44 $	-0.14	-0.02	-0.32 $	-0.24 $	-0.12	-0.11	-0.15	-0.26 $	-0.12

*: $p<0.05$

$: $p<0.01$

mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; 6MWD, 6 min walking distance; PaO_2, arterial oxygen tension; PvO_2, mixed venous oxygen tension; BNP, brain natriuretic peptide; WHO, World Health Organization; PCS, physical component summary; MCS, mental component summary

Table S2, 3. QOL at diagnosis and after conventional therapy (Table S2) and PAH-specific therapy (Table S3) in medically-treated group

Table S2

SF-36	n	At diagnosis	After conventional therapy	
PF	22	55.9 ± 21.7	62.4 ± 20.4	
RP	22	29.5 ± 35.9	50.0 ± 40.8	*
BP	22	66.2 ± 26.2	71.3 ± 29.0	
GH	23	46.6 ± 17.3	44.9 ± 15.5	
VT	21	45.2 ± 21.9	60.8 ± 18.9	$
SF	23	49.5 ± 27.3	59.8 ± 25.0	
RE	22	51.6 ± 45.7	77.3 ± 40.4	*
MH	21	58.5 ± 22.0	74.3 ± 15.0	$
PCS	20	39.6 ± 9.6	39.5 ± 9.3	
MCS	20	44.5 ± 9.4	49.8 ± 7.2	$

*: $p<0.05$

$: $p<0.01$

Tables S3

SF-36	n	At diagnosis	After PAH-specific therapy	
PF	11	41.6 ± 21.0	57.8 ± 21.2	*
RP	11	20.5 ± 35.0	37.1 ± 39.2	
BP	11	77.9 ± 20.8	73.9 ± 25.2	
GH	10	41.9 ± 21.9	50.0 ± 14.9	
VT	10	43.5 ± 28.5	63.0 ± 17.5	*
SF	11	46.6 ± 17.8	69.3 ± 24.0	$
RE	11	33.3 ± 47.1	66.7 ± 47.1	*
MH	10	58.4 ± 32.7	70.8 ± 22.8	
PCS	10	36.7 ± 8.1	35.2 ± 11.9	
MCS	10	47.4 ± 12.5	54.0 ± 10.4	$

*: $p<0.05$

$: $p<0.01$

Data given as mean ± SD. Abbreviations as in Table 4.

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