Impact of Ambulation Status in Patients with End-stage Renal Disease on Hemodialysis due to Diabetic Nephropathy: The PREDICT Study

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Abstract

Background: Hemodialysis (HD) patients often have severe morbidity and mortality, with critical limb ischemia (CLI) being a cause of major amputation and death. In the clinical setting, the predictive ability of patient ambulatory status on outcome in patients on HD due to diabetic nephropathy (DN) is not well known.

Aim: To investigate the association of ambulatory status with clinical outcome in end-stage renal disease patients on HD and its predictive ability for CLI-free survival.

Methods: In the multi-center, observational Prospective REgistry with the DIalysis patient due to diabetes to prevent CriTical limb ischemia (PREDICT) study, 173 patients on HD due to DN were enrolled between April 2012 and August 2013 from 9 institutions. We investigated ambulatory status, ankle-brachial index, lower limb artery lesions by duplex ultrasound, and laboratory findings every 6 months for 2 years. The primary endpoint was CLI-free survival at 2 years.

Results: Complete follow-up was possible for 164 patients (94.2%) at 2 years. Average age was 68 (range: 58-74) years and average HD duration was 49.4 (range: 23.5-90.5) months. The CLI-free survival rate of ambulatory patients was significantly higher than that of non-ambulatory patients (84.9% vs. 62.7%, p=0.0006). Survival rate was also significantly higher in the ambulatory group (89.2% vs. 69.8%, p=0.01). Cox regression analysis revealed a significant association between ambulatory status and CLI or death (hazard ratio 6.06, 95% confidence interval 1.34-732.3; p=0.02).

Conclusion: This study revealed that ambulatory status might predict mid-term CLI-free survival in HD patients with DN.

背景　透析患者は予後が悪く、合併症が多い。また重症下肢虚血は下肢大切断や死亡の要因の一つになる。糖尿病性腎症による透析患者の歩行状態と臨床成績についての関連はよくわかっていない。

目的　本研究の目的は透析患者における歩行状態と重症下肢虚血回避生存の関連を調査することである。

方法　本研究は前向き、多施設、観察研究　の PREDICT 研究の結果である。173 名の糖尿病腎症による透析患者を 2012 年 4 月から 2013 年 8 月まで 9 透析センターから登録した。我々は歩行状態、ankle-brachial index (ABI)、下肢血管エコーといくつかの血液検査を 6 か月毎に 2 年間追跡した。本研究の主要エンドポイントは 2 年間の重症下肢虚血回避生存とした。

結果　2年間の追跡は164患者でフォローアップ率は94.2%だった。患者の平均年齢は68歳(23.5-90.5歳)で透析期間は 49.4 か月(23.5-90.5 か月)だった。2 年間の歩行患者の重症下肢虚血回避生存率は歩行不能患者よりも有意に高かった(84.9% vs 62.7%, *p*=0.0006)。生存率についても歩行患者の方が歩行不能患者より有意に高かった(89.2% vs 69.8%, *p*=0.01)。コックスレグレッション解析にて歩行可能状態は重症下肢虚血回避生存の強い予測因子であることが明らかにされた(ハザード比 6.06, 95%信頼区間 1.34-732.3; *p*=0.02)

結語　透析患者の歩行状態は中期間の重症下肢虚血回避生存を予測することができる

Keywords: Hemodialysis, Critical limb ischemia, Ambulatory status, Prognosis

244 words

Ⅰ. Introduction

The number of end-stage renal disease (ESRD) patients on hemodialysis (HD) due to diabetic nephropathy (DN) is increasing worldwide, with over 350,000 patients currently receiving HD therapy in Japan and approximately 30,000 individuals starting HD treatment every year[1]. Mortality among ESRD patients remains high, 30-50% of which is caused by cardiovascular disease[2-5]. Critical limb ischemia (CLI) is a cause of major amputation and death in peripheral artery disease (PAD)[6]. Major amputation of lower limbs reduces quality of life, decreases activities of daily living, and may raise treatment costs. HD patients constitute roughly a quarter of PAD patients in daily clinical practice. Although endovascular treatment (EVT) is a less invasive therapy for PAD, patients receiving EVT may still experience heavy calcification in target lesions and extended arteriosclerosis. Earlier PAD detection and intervention are therefore needed.

Frailty has been defined as a progressive syndrome or state of increased vulnerability to stressful situations resulting from aging-associated decline that is characterized by a reduction in biological functional reserves. Frailty increases the risk of poor outcomes, such as disease progression, disability, hospitalization, and death[7-9]. Both frailty and sarcopenia are important concepts in the quest to prevent physical dependence as the field of geriatrics shifts towards indications of the early stages of disability. Although their definitions are still developing, these notions clearly overlap in many physical aspects[10]. Approximately one third of patients on HD are frail and thus at increased risk of mortality[11,12]. The present study aimed to clarify the association of ambulatory status with clinical outcome in HD patients with DN.

Ⅱ. Methods

1) Study design

The Prospective REgistry with the DIalysis patient due to diabetes to prevent CriTical limb ischemia (PREDICT) study was a prospective, observational, multi-center investigation that included a total of 13 institutions in and around the city of Matsumoto, Japan. Recruited subjects were consecutive patients receiving HD treatment due to DN between April 2012 and August 2013. We investigated symptoms, ambulatory status, ankle-brachial index (ABI), lower limb artery lesions by duplex ultrasound, and hematological findings every 6 months for 2 years. This study was approved by the Shinshu University School of Medicine Institutional Review Board (no. 2366) and by the ethics committee of each participating institution. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant.

2) Patient population

The patient flowchart for this study is presented in Figure 1. A total of 173 patients without CLI receiving HD due to DN between April 2012 and August 2013 were initially enrolled. There were no non-ambulatory subjects due to PAD since CLI patients were excluded from the study. Nine patients were excluded due to transfer to another hospital (4 patients), withdrawal of consent (3 patients), or lack of clinical data (2 patients). Ultimately, 164 patients were followed for 2 years.

3) Definitions

Amputation-free survival was defined as freedom from major amputation, revascularization, or all-cause death. Ambulatory status was defined as the ability to walk unassisted in daily life and, in the case of medical examinations, enter the consultation room without the need of a wheelchair or stretcher. Ambulatory status was judged by HD medical attendants using a frailty scale[18]. Limb arterial stenosis was defined as peak systolic velocity ≥200 mm/sec, peak systolic velocity ratio >2.4, or duplex ultrasound findings. The indication for revascularization was based on symptomatic and duplex arterial stenosis criteria. CLI was defined as gangrene, non-healing ischemic ulcer, or ischemic rest pain. CLI-free survival was defined as freedom from the composite of all-cause death and the onset of CLI. Revascularization was performed for clinical symptoms of ≥50% restenosis on duplex ultrasound or angiography. Major adverse limb events (MALEs) included all-cause death, major amputation, and lower limb revascularization.

4) Study endpoints

The primary endpoint in this study was CLI-free survival at 2 years. The secondary endpoints were survival and MALE at 2 years. Multivariate analysis was employed to determine the predictors of death and CLI in the HD population.

5) Statistical analysis

Normal variables are expressed as numbers and percentages. Continuous variables are expressed as the mean ± standard deviation for non-skewed data and median (interquartile range) for skewed data. Categorical variables were reported as frequencies and compared with the chi-square test. Comparisons of the means between groups were performed using analysis of variance (ANOVA) and either the Bonferroni test or the non-parametric test. Survival curves were constructed for time-event variables with Kaplan–Meier estimates and compared using the log-rank test. Cox regression analysis was used to identify independent predictors of CLI-free survival and all-cause death. A *p*-value of <0.05 was considered statistically significant. Data were analyzed with JMP 13 software (SAS Institute, Cary, North Carolina, U.S.A.).

Ⅲ. Results

The baseline patient characteristics are shown in Table 1. CLI-free survival patients were significantly younger than CLI or death patients (65 [range: 34-91] vs. 71 [range: 38-88] years, p=0.003). A history of PAD was significantly less frequent in the CLI-free survival group than in the CLI or death group (11.2% vs. 20.5%, *p*=0.03). Ambulatory patients were significantly more frequently observed in the CLI-free survival group than in the CLI or death group (84% vs. 48.7%, *p*=0.003). ABI was significantly more frequent in the CLI-free survival group than in the CLI or death group (1.1 [range: 0.49-1.47]vs. 0.9 [range: 0.26-1.36] *p*=0.005), as was PSV (71 [range: 31-251]vs. 60 [range: 13-103] mm/sec *p*=0.01). The CLI-free survival group had significantly higher albumin level (3.8 [range: 3.6-3.9] vs. 3.4 [range: 3.0-3.7] g/dL, *p*=0.0003), hemoglobin level (10.7 [range: 10.1-11.4] vs. 10.2 [range: 9.6-10.8] g/dL, *p*=0.008), and HDL level (41.3 [range: 3-52] vs. 36.7 [range: 29-40] mg/dL, *p*=0.03) and lower CRP level (0.1 [range: 0.05-0.2] vs. 0.15 [range: 0.06-0.46] mg/L, *p*=0.03) and BNP level (177.1 [range: 71.4-389.1] vs. 280.6 [range: 133.6-695.4] pg/mL, *p*=0.04).

CLI-free survival was assessed at 12 and 24 months using Kaplan–Meier testing. The CLI-free survival rate of the ambulatory group was significantly higher than that of the non-ambulatory group (94.3% vs. 84.5% at 12 months and 84.9% vs. 62.7% at 24 months [*p*=0.006], respectively) (Fig. 2). The survival rate of the ambulatory group was also significantly higher than that of the non-ambulatory group (95.1% vs. 87.1% at 12 months and 89.2% vs. 69.8% at 24 months [*p*=0.01], respectively) (Fig. 3). MALE avoidance rates in the ambulatory and non-ambulatory groups were 92.7% and 81.7% at 12 months and 81.6% and 58.6% at 24 months, respectively, and were significantly higher in the ambulatory group at 24 months (*p*=0.006) (Fig. 4).

Death occurred in 27 patients during the study period due to heart failure (2 patients), arrhythmia (4 patients), stroke (5 patients), pneumonia (5 patients), sepsis from CLI (4 patients), malignant tumor (4 patients), or other

(3 patients) (Table 2). Cardiac death accounted for 22% of deaths. Univariate analysis revealed age (hazard ratio [HR] 13.7, 95% confidence interval [CI] 1.94-117.6; *p*=0.002), past history of coronary artery disease (HR 2.89, 95% CI 1.09-7.35; *p*=0.03), ambulatory status (HR 0.29, 95% CI 0.13-0.65; *p*=0.003), and albumin (HR 0.07, 95% CI 0.08-0.74; *p*=0.017) to be significantly associated with CLI or death (Table 3). Ambulatory status was an independent predictor of CLI or death in multivariate analysis (HR 0.32, 95% CI 0.11-0.87; *p*=0.03) (Table 4).

Ⅳ. Discussion

The present study clarified the 2-year clinical outcome of patients receiving HD due to DN. CLI-free survival was significantly associated with younger age and ambulation status. The ambulatory group also had longer amputation-free survival, survival, and freedom from MALE. Moreover, ambulatory status was a strong independent predictor of CLI-free survival in the HD population.

The crude death rate of dialysis patients in 2011 was 10.2% in Japan[1]. The main causes of death in this study were cardiac death (22.2%), stroke (18.5%), malignant tumor (14.8%), and infection (33.3%), which were similar to previous reports from Japan[1]. Nakai et al. observed cardiac death (25%), cerebrovascular disorder (5.4%), malignant tumor (11.6%), infection (24.5%), and cardiac infarction (3.6%) as factors related to death[1]. Chao reported that frailty score based on fatigue, resistance as measured by stair climbing, ambulation, and illness-related weight loss were significantly associated with mortality[13]. We observed contradictions in the results of ABI and PSV in this study, possibly due to calcification change of the vessels.

Several studies have analyzed the risk factors for mortality in HD patients. Age, low body mass index (BMI), low albumin, low hemoglobin, and high CRP were susceptibility factors for all-cause mortality in an HD population[14], while Ishi et al. associated age, diabetes, low BMI, cardiac artery disease history, low hemoglobin, and low albumin with all-cause death and cardiac death[15]. Frailty was also identified as a risk factor in HD patients[16]. However, the components of frailty varied in each study and included such parameters as weight loss, exhaustion, low physical activity, slow gait speed, and weak grip strength[16] in addition to physician subjectivity[17]. In this study, the patients were divided into two groups by ambulatory status, which we believed to be a very clear cutoff line. Our results indicated that ambulation was strongly related to clinical outcomes. Thus, the maintenance of ambulation may represent a concrete goal in patient care and rehabilitation.

The convalescence of HD patients may be improved by appropriate nourishment and exercise, such as walking[19]. As is the case for sarcopenia, it will be necessary to examine the precise merits of diet, aerobic exercise, and rehabilitation in the future. The present study indicated that maintaining an ambulatory status was important for a more favorable outcome in patients.

Nutrition, muscular strength, quantity of muscle, anemia, and other factors are known to influence the prognosis of HD patients[13,19,20]. By including ambulation, more precise convalescence predictions will be possible by examining prediction factors compositely. Meanwhile, the goal of ambulation for treatment and rehabilitation remains a simple and easily understood endpoint that can be coordinated smoothly among medical staff. Whether a patient can walk or not may have real-world implications on PAD treatment decisions, with intervention for non-ambulatory patients having a diminished prognosis requiring more careful attention.

Ⅴ. Limitations

This study had several limitations that may have affected clinical outcomes. First, the sample size and study period were limited and need validation in larger and longer trials. Second, there may have been selection bias by attending physicians in that patients with co-morbities or unfavorable conditions may have been avoided during recruitment. Lastly, specific details were unavailable for HD and CLI treatment.

Ⅵ. Conclusion

This study revealed an association between ambulatory status and mid-term CLI-free survival in HD patients with DN. As ambulatory status is a strong predictor of CLI-free survival in DN patients, careful attention is required and early fragility intervention is advised for non-ambulatory patients.

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Figure 1

Patient flow chart

Figure legend

A total of 173 patients were enrolled. After the exclusion of 9 patients, 164 patients were followed for 2 years.

Figure 2

CLI-free survival at 2 years in HD patients

Figure legend

The CLI-free survival rate of the ambulatory group was significantly higher than that of the non-ambulatory group.

Figure 3

Survival at 2 years in HD patients

Figure legend

The survival rate of the ambulatory group was significantly higher than that of the non-ambulatory group.

Figure 4

Freedom from MALE at 2 years in HD patients

Figure legend

The freedom from MALE rate of the ambulatory group was significantly higher than that of the non-ambulatory group.

Table 1 Patient characteristics

CAD: coronary artery disease, CVD: cerebral vascular disease, PAD: peripheral artery disease, ABI: ankle brachial index, PSV: peak systolic velocity, LVEF: left ventricle ejection fraction, Alb: albumin, Hb: hemoglobin, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, CRP: C-reactive protein, BNP: brain natriuretic peptide

Table 2 Causes of death

VF: ventricular fibrillation

Table 3 Univariate analysis for factors associated CLI or death

CAD: coronary artery disease, CVD: cerebral vascular disease

Table 4 Multivariate analysis for factors associated with CLI or death

CAD: coronary artery disease

Table 1 Baseline characteristics continued

	CLI free survival n=125	CLI or death n=39	p value
ABI	1.1 (0.49-1.47)	0.9 (0.26-1.36)	0.005
PSV (mm/sec)	71 (31-251)	60 (13-103)	0.01
LVEF (%)	64.1 (38-77)	66.2 (22-78)	0.38
Laboratory			
Alb (g/dl)	3.8 (3.6-3.9)	3.4 (3-3.7)	0.0003
Hb (g/dl)	10.7 (10.1-11.4)	10.2 (9.6-10.8)	0.008
HbA1c (%)	6.6 ± 1.1	6.7 ± 1.2	0.53
LDL (mg/dl)	82.5 (68.3-104)	96 (70-106)	0.42
HDL (mg/dl)	41.3 (33-52)	36.7 (29-40)	0.03
CRP (mg/L)	0.1 (0.05-0.2)	0.15 (0.06-0.46)	0.03
BNP (pg/ml)	177.1 (71.4-389.1)	280.6 (133.6-695.4)	0.04

Table 1 Baseline characteristics

	CLI free survival n=125	CLI or death n=39	p value
Age (year)	65 (34-91)	71 (38-88)	0.003
Male (%)	94 (75.2)	27 (69.2)	0.98
BMI	22.8 (15.2-30.2)	22.9 (14.7-29.6)	0.4
HD duration (months)	46.7 (1-291)	73.6 (5-190)	0.09
Hypertension (%)	112 (89.6)	30 (76.9)	0.68
Dyslipidemia (%)	34 (27.2)	11 (28.2)	0.91
Insulin user (%)	61 (48.8)	29 (74.4)	0.79
Smoking (%)	73 (58.4)	13 (33.3)	0.08
CAD (%)	17 (13.6)	11 (28.2)	0.08
CVD (%)	13 (10.4)	5 (12.8)	0.84
PAD (%)	14 (11.2)	8 (20.5)	0.03
History of heart failure (%)	49 (39.2)	19 (48.7)	0.19
Ambulatory (%)	105 (84)	19 (48.7)	0.003

Table2 Cause of death

	Death n=27
Heart failure	2
VF/Sudden death	4
Stroke	5
Pneumoniae	5
Sepsis from CLI	4
Malignant Tumor	4
Others	3

Table 3 Univariate analysis for factors associated with CLI or Death

Risk factor	Hazard ratio	95% confidence interval	p value
Age	13.7	1.94-117.6	0.002
Male	1.10	0.85-2.7	0.81
Dyslipidemia	1.47	0.59-3.1	0.41
Hypertension	0.62	0.10-9.47	0.38
HD duration	2.55	0.17-62.1	0.34
Smoking	0.80	0.30-1.98	0.64
Insulin	1.42	0.23-0.62	0.35
CAD	2.89	1.09-7.35	0.03
CVD	1.41	0.04-8.93	0.51
Past history of heart failure	1.91	0.43-7.52	0.09
Ambulatory	0.29	0.13-0.65	0.003
Albumin	0.07	0.08-0.74	0.017

Table 4 Multivariate analysis for factors associated with CLI or death

Risk factor	Hazard ratio	95% confidence interval	p value
Age	7.2	0.73-85.3	0.09
CAD	2.85	0.68 - 8.61	0.06
Ambulatory	0.32	0.11 – 0.87	0.03
Albumin	0.41	0.03-5.48	0.50

Fig1 Patients flow chart

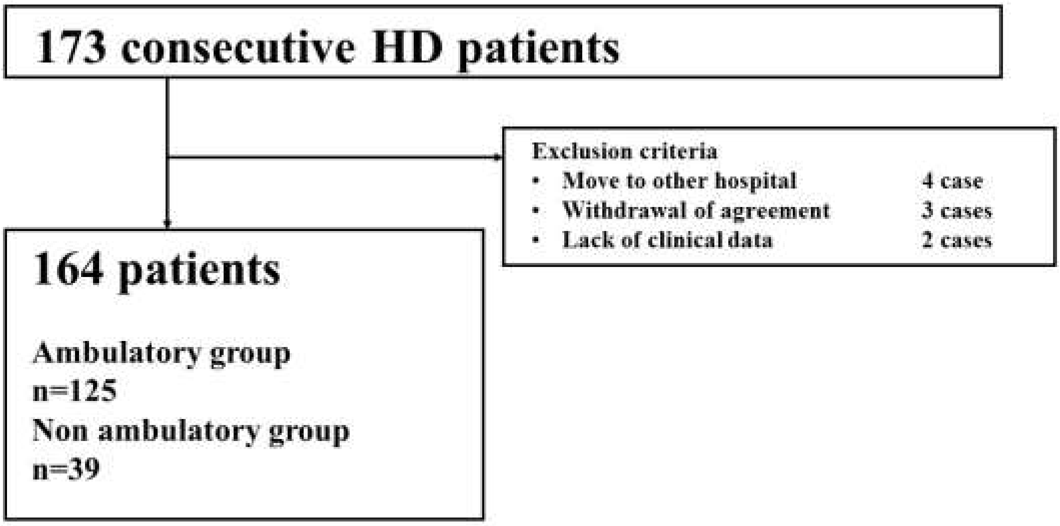
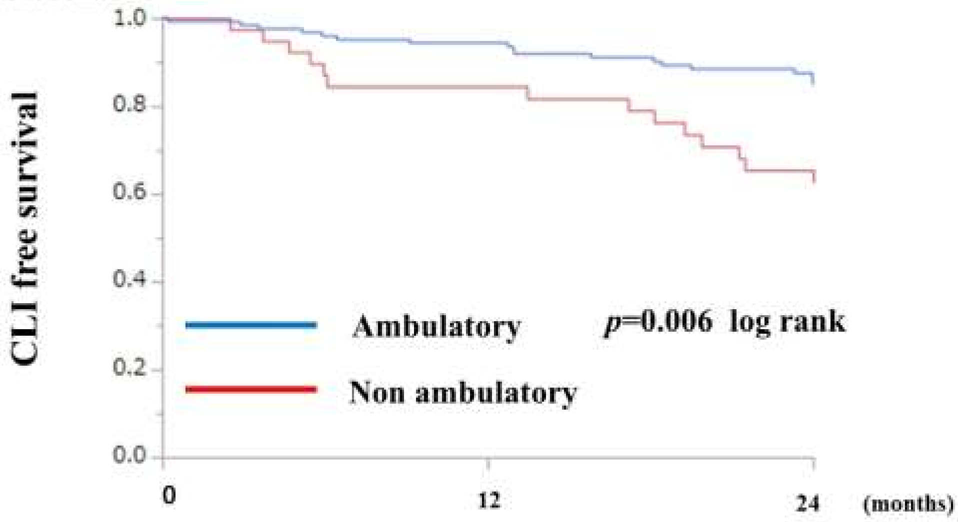
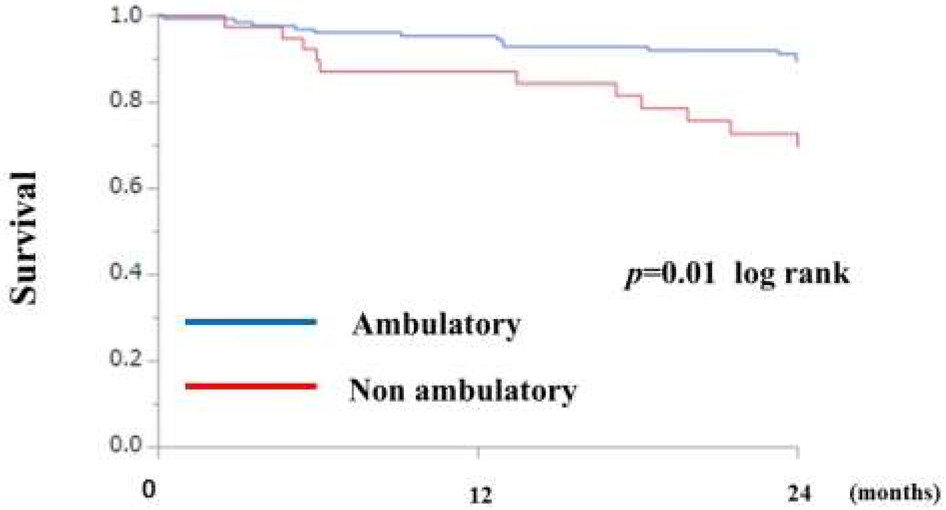


Fig 2 CLI free survival at 24 months



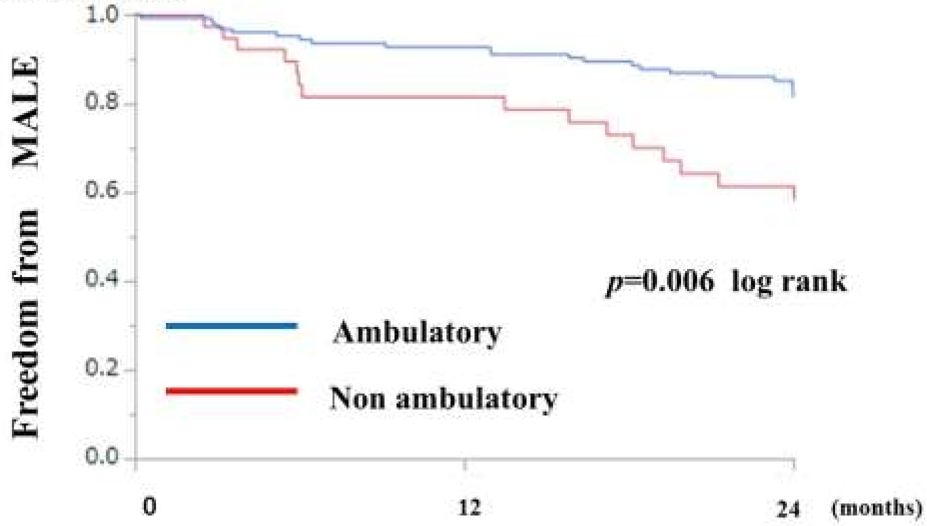
		0	12	24
No. at risk	Ambulatory	125	115	99
			94.3%	84.9%
No. at risk	Non ambulatory	39	33	24
			84.5%	62.7%

Fig 3 Survival at 24 months



No. at risk	Ambulatory	125	117	104
			95.1%	89.2%
No. at risk	Non ambulatory	39	37	24
			87.1%	69.8%

Fig 4 Freedom from MALE at 24 months



No. at risk	Ambulatory	125	114	97
			92.7%	81.6%
No. at risk	Non ambulatory	39	30	21
			81.7%	58.6%