

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

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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. *Shinshu Med J 68 : 131-138, 2020*

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Key words : hemodialysis, critical limb ischemia, ambulatory status, prognosis

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I Introduction

The number of end-stage renal disease (ESRD) patients on hemodialysis (HD) due to diabetic ne-

phropathy (DN) is increasing worldwide, with over 350,000 patients currently receiving HD therapy in Japan and approximately 30,000 individuals starting HD treatment every year¹. 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 aspects¹⁰. 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

A 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.

B Patient population

The patient flowchart for this study is presented in **Fig. 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.

C 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 scale¹³. 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.

D Study endpoints

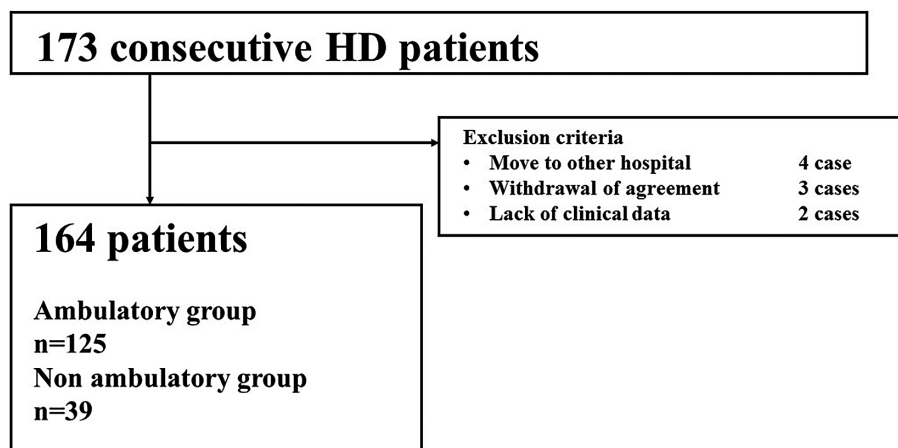


Fig. 1 Patient flow chart

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

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.

E 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

Table 1 Patient 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
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

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

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 inde-

pendent 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 Japan¹⁾. The main causes of death in this study were cardiac death (22.2 %), stroke (18.5

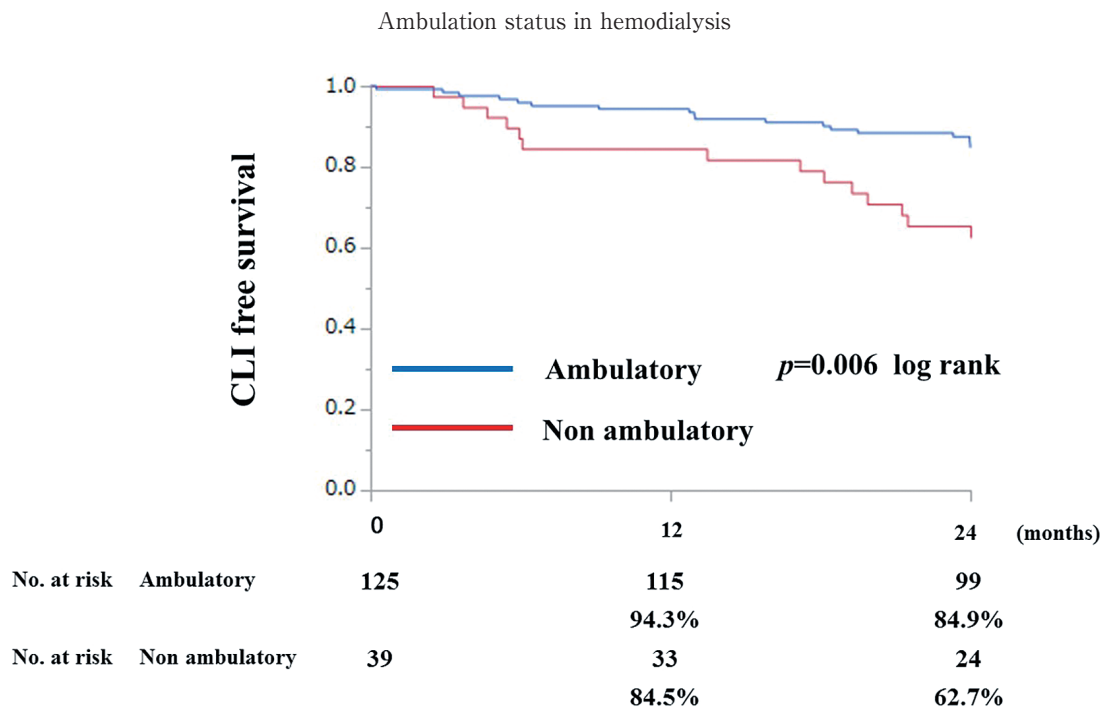


Fig. 2 CLI-free survival at 2 years in HD patients

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

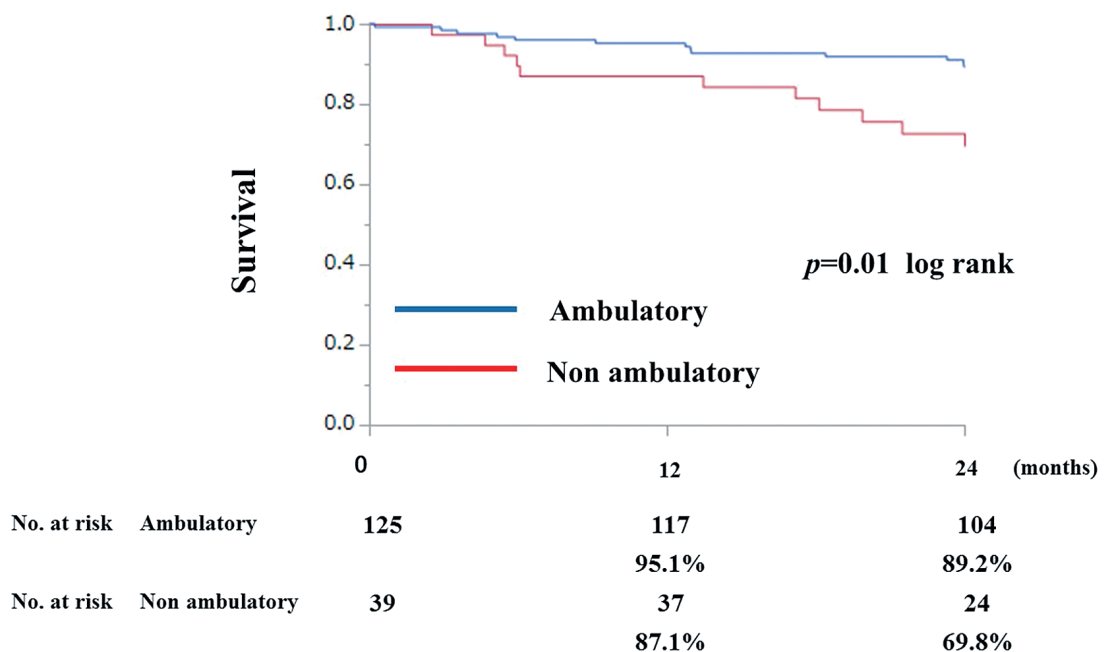


Fig. 3 Survival at 2 years in HD patients

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

%), malignant tumor (14.8 %), and infection (33.3 %), which were similar to previous reports from Japan¹⁾. 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 death¹⁾. Chao reported that frailty

score based on fatigue, resistance as measured by stair climbing, ambulation, and illness-related weight loss were significantly associated with mortality¹⁴⁾. We observed contradictions in the results of ABI and PSV in this study, possibly due to calcification change of the vessels.

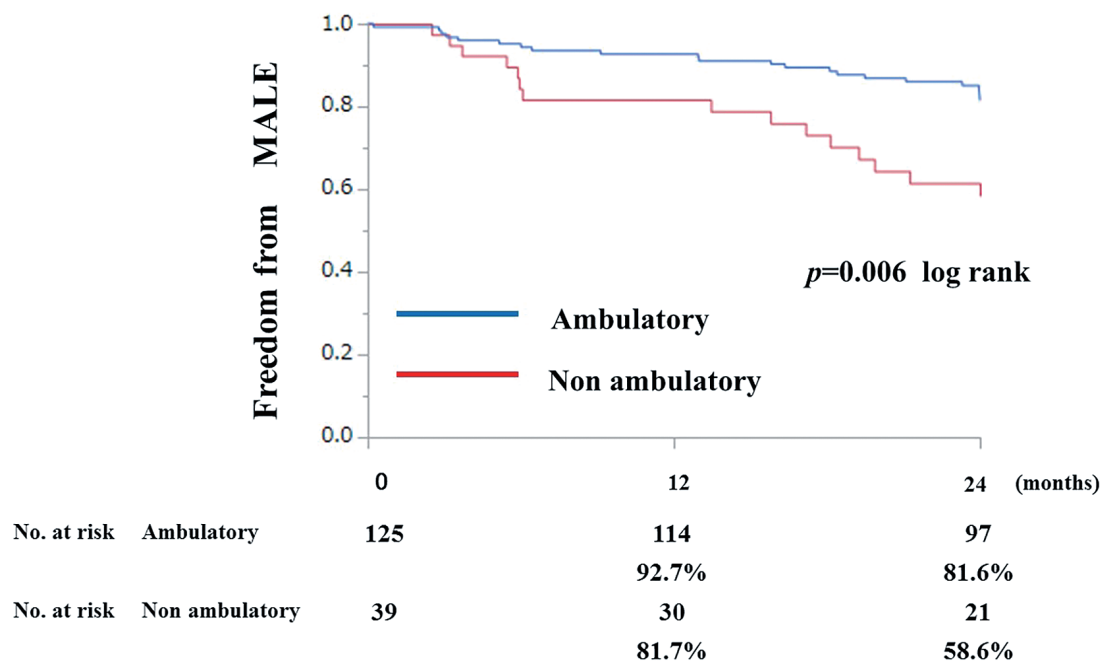


Fig. 4 Freedom from MALE at 2 years in HD patients

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

Table 2 Causes 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

VF : ventricular fibrillation

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 population¹⁵⁾, while Ishi et al. associated age, diabetes, low BMI, cardiac artery disease history, low hemoglobin, and low albumin with all-cause death and cardiac death¹⁶⁾. Frailty was also identified as a risk factor in HD patients¹⁷⁾. However, the components of frailty varied in each study and included such parameters as weight loss, exhaustion, low

Table 3 Univariate analysis for factors associated 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

CAD : coronary artery disease, CVD : cerebral vascular disease

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

CAD: coronary artery disease

physical activity, slow gait speed, and weak grip strength¹⁷⁾ in addition to physician subjectivity¹⁸⁾. 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 walking¹⁹⁾. 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 patients¹⁴⁾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-morbidities 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.

References

- 1) Nakai S, Watanabe Y, Masakane I: Overview of regular dialysis treatment in Japan. *Ther Apher Dial* 17: 567–611, 2013
- 2) Foley RN, Parfery PS, Sarnak M: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32 (5 Suppl. 3): s112–119, 1998
- 3) Tonelli M, Wiebe N, Culleton B, et al: Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 17: 2034–2047, 2006
- 4) Parfrey PS, Foley RN: The clinical epidemiology of cardiac disease in chronic uremia. *J Am Soc Nephrol* 10: 1606–1615, 1999
- 5) Schiffirin EL, Lipman ML, Mann JF: Chronic kidney disease: effects on the cardiovascular system. *Circulation* 116: 34–39, 2007

- 6) Mustapha JA, Katzen BT, Neville RF, et al : Determinants of long-term outcomes and costs in the management of critical limb ischemia : a population-based cohort study. *J Am Heart Assoc* 7 : e009724, 2018
- 7) Clegg A, Young J, Iliffe S, et al : Frailty in elderly people. *Lancet* 381 : 752-762, 2013
- 8) Hogan DB, MacKnight C, Bergman H : Models, definitions and criteria of frailty. *Aging Clin Exp Res* 15 : 1-29, 2003
- 9) Vermeiren S, Vella-Azzopardi R, Beckwee D : Frailty and the prediction of negative health outcome : a meta-analysis. *J Am Med Dir Assoc* 17 : 1163e17, 2016
- 10) Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC : Nutrition, frailty and sarcopenia : *Aging Clin Exp Res* 29 : 43-48, 2017
- 11) Johansen KL, Dalrymple LS, Delgado C, et al : Association between body composition and frailty among prevalent hemodialysis patients : a US Renal Data System special study. *J Am Soc Nephrol* 25 : 381-389, 2014
- 12) Anand S, Johansen KL, Kurella Tamura M : Aging and chronic kidney disease : the impact on physical function and condition. *J Gerontol Med Sci* 69 : 315-322, 2014
- 13) Rockwood K, Song X, MacKnight C, et al : A global clinical measure of fitness and frailty in elderly people. *CMAJ* 173 : 489-495, 2005
- 14) Chao CT, Wang J, Huang JW, et al : Frailty predicts an increased risk of end-stage renal disease with risk competition by mortality among 165461 diabetic kidney disease patients. *Aging and Disease* 10 : 1270-1281, 2019
- 15) Ma L, Zhao S : Risk factors for mortality in patients undergoing hemodialysis : A systemic review and meta-analysis. *Int J Cardiol* 238 : 151-158, 2017
- 16) Ishii J, Takahashi H, Kitagawa F et al : Multimarker-approach to risk stratification for long-term mortality in patients on chronic hemodialysis. *Circ J* 79 : 656-663, 2015
- 17) Johansen KL, Delgado C, Kaysen GA et al : Frailty among patients receiving hemodialysis : Evolution of components and associations with mortality. *J Gerontol A Biol Sci Med Sci* 74 : 380-386, 2019
- 18) Takeji Y, Yamaji K, Tomi Y, et al : Impact of Frailty on Clinical Outcomes in Patients with Critical Limb Ischemia. *Circ Cardiovasc Interv* 11 : e006778, 2018
- 19) Johansen KL, Delgado C, Kaysen GA, et al : Frailty among patients receiving hemodialysis : evolution of components and associations with mortality. *J Gerontol A Biol Sci Med Sci* 74 : 380-386, 2019
- 20) Rao M, Sharma M, Juneja R, Jacob S, Jacob CK : Calculated nitrogen balance in hemodialysis patients : influence of protein intake. *Kidney Int* 58 : 336-345, 2000

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