It is estimated that there are more than ten million CKD patients [3], who may progress to ESRD requiring dialysis, and more than 280,000 ESRD patients in Japan [4]. The annual cost of dialysis treatment was more than 130 billion yen in Japan in 2008 [4]. The high morbidity of CKD and high cost of dialysis have promoted interest in developing not only effective but also cost-effective interventions for CKD. Previous studies have suggested that CKD is one of the most important risk factors for CVD among those known: hypertension, diabetes, hyperlipidemia, obesity, smoking, and lifestyle-related diseases [5–8]. Therefore, the early detection of and early initiation of treatment for CKD are important in order to prevent kidney failure as well as cardiovascular complications and death.

To conduct a cost-effective analysis, outcome measurement in terms of quality-adjusted life-years (QALYs) is recommended [9, 10], and is crucial to dealing with QOL-deteriorating diseases including CKD. QALYs are calculated as the sum of the adjusted life-years experienced by a patient, where the adjustment is made by multiplying time by weights linked to the changing health state of the patient. The quality-adjustment weight is a value of between 1 (for perfect health) and 0 (for death), which is a type of health-related quality of life (HRQOL) measurement. The weight, in principle, represents social preference for a certain health state, and so it should be measured in every society. However, there are few reports on such weights in regard to CKD in the literature. Therefore, the first objective of this study was to measure quality-adjustment weights for the health states of CKD patients by stage. Furthermore, Perlman et al. [11] and Leaf et al. [12] identified associations between the HRQOL of CKD patients and clinical indices such as hemoglobin or eGFR. Therefore, we examined the relationship between the measured quality-adjustment weight and clinical indices of CKD patients. The accumulation of comorbidities tends to worsen the patients' HRQOL. We further analyzed the significance of major complications of CKD such as hypertension, diabetes, and history of CVD on the HRQOL of CKD patients.

The results of this study should facilitate the economic evaluation of interventions for CKD, which will contribute to the development of efficient ways to manage the disease. They also inform physicians of how patient HRQOL alters with disease progression, which is helpful for realizing more patient-centered clinical decision-making.

Materials and methods

Instrument for measuring quality-adjustment weights

There are preference-elicitation techniques that can be used when measuring quality-adjustment weights, such as the visual analogue scale (VAS), standard gamble (SG), and time trade-off (TTO) [13]. It is recommended that a representative sample of the community should be recruited when using them [9]. They also require a description of life in a particular state of health that is easy for patients to understand. Describing life at a particular stage of CKD, however, is practically impossible. Therefore, another approach, generic preference-based measures, was employed in this study. Specifically, we used the most widely used instrument, EQ-5D [13], which is standardized and validated for use in Japan [14, 15]. It is administered to representative patients in a particular state of health in Japan, who are asked to grade five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) of their health state as one of three levels ("no problem," "some problems," and "extreme problem"). "No problem" is also referred to as level 1, while "inability or extreme problem" is also referred to as level 3 such that (for example) a health state of 21232 means that the patient has some problems walking, no problem washing and dressing, some problems performing their usual activities, suffers extreme pain or discomfort, and is moderately anxious or depressed. The $3^5 = 243$ possible combinations of responses are converted to weight values according to the Japanese value set [15], and the average is calculated as a quality-adjustment weight for the health state under consideration in Japan. The weight values are based on TTO evaluations. The weight ranges from 1 for perfect health (no problem in any dimension) to 0 for death and -0.111 for severe problems in all dimensions. A positive weight means that the health status is better than dead and a negative weight is worse in EQ-5D.

Study design and subjects

We conducted a cross-sectional outpatient questionnaire survey. All 588 outpatients previously diagnosed with CKD at the Department of Nephrology Tsukuba University Hospital were recruited for this study between November and December 2008. We assumed that they comprised a near-representative sample of CKD patients in Japan to which EQ-5D could be applied, since a lack of knowledge of the descriptive epidemiology of CKD in Japan prevented us from obtaining a representative sample and making appropriate bias corrections during our analyses. The EQ-5D questionnaire was given to them to complete if they signed a written informed consent form when visiting the hospital after receiving an explanation of the purpose of this study. Nineteen patients (3.2%) were not included in this study because they were receiving renal replacement therapy. Thirty-two patients (5.4%) were excluded from the analysis because they did not respond to the questionnaire.

Study variables

From the patient records, sex and age were included in our analysis as demographic baseline characteristics. Creatinine, hemoglobin, and serum albumin on the day of the questionnaire survey were also included as routinely checked clinical indices. GFR was estimated from serum creatinine, age, and sex using the new Japanese equation as follows: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) [16]. The presence of complications was also assessed using the records. Hypertension and diabetes were classified based on clinical records. A history of CVD was regarded as present if stroke, congestive heart disease, or ischemic heart disease was recorded.

Statistical analysis

All statistical analyses were performed using SAS. Quality-adjustment weights were calculated as the mean of a group of patients' weight values according to the Japanese value set for EQ-5D, and 95% confidence intervals were computed. The weight differences among CKD stages were tested by ANOVA. Correlation analyses were performed between weights and clinical indices. Multiple regression analysis was also applied to identify indices that determine weights. Nonparametric regression analysis was further applied in order to detect inflection points in the curves of quality adjustment weight versus identified indices. The level of significance was set at $P < 0.05$.

Results

The baseline characteristics of respondents are shown in Table 1. The respondents comprised 282 males (52.5%) and 255 females (47.5%). The overall mean age was 55.2 years old. Mean creatinine was 1.7 mg/dl; mean hemoglobin 12.7 g/dl; mean serum albumin 4.1 g/dl; and mean eGFR 56.1 ml/min/1.73 m^2. Regarding complications, 388 (72.2%) patients had hypertension; 146 (27.0%) patients had diabetes, with a mean HbA1c of 6.0%; and 38 (7.0%) patients had a history of CVD. Proportions of patients at various CKD stages were 15.5, 28.5, 29.4, 13.4 and 13.2% for stages 1–5, respectively. Patients at stages 1 and 2 were relatively young compared to those at stages 3–5.

The EQ-5D questionnaire responses are shown in Table 2. The proportions of the patients who responded "no problem" were 82.8% for mobility, 94.0% for self care, 79.3% for usual activities, 72.8% for pain/discomfort, and 82.1% for anxiety/depression. The frequency of "some problems" was significantly higher for mobility (4.8% in CKD 1 and 36.6% in CKD 5) and usual activities (9.6% in CKD 1 and 39.4% in CKD 5) with progression of the CKD stage. Fewer than 3% of the patients answered "extreme problem" for all dimensions.

Table 1 Baseline characteristics (total $n = 537$)

	Values	SD or %
Male, *n* (%)	282	52.5
Mean age (year), SD	55.2	16.0
Mean creatinine (mg/dl), SD	1.7	1.2
Mean hemoglobin (g/dl), SD	12.7	2.1
Mean albumin (g/dl), SD	4.1	0.6
Mean estimated GFR (ml/min/1.73 m^2), SD	56.1	34.1
Hypertension, *n* (%)	388	72.2
Diabetes, *n* (%)	146	27.0
History of cardiovascular disease, *n* (%)	38	7.0

CKD stage	*n*	%	Mean age	Age range
1 (GFR ≥ 90)	83	15.5	35.6	15–70
2 (60 ≤ GFR < 90)	153	28.5	54.1	27–85
3 (30 ≤ GFR < 60)	158	29.4	60.9	26–87
4 (15 ≤ GFR < 30)	72	13.4	62.1	30–94
5 (GFR < 15)	71	13.2	61.0	28–83

Table 3 shows measured quality-adjustment weights by stage: 0.940 (95% CI 0.915–0.965), 0.918 (0.896–0.940), 0.883 (0.857–0.909), 0.839 (0.794–0.884), and 0.798 (0.757–0.839) for stages 1–5, respectively. Figure 1 illustrates these in a box plot with a mark showing the mean. The decrease in weight was significant by ANOVA ($P = 0.000$), and the weight for all stages was 0.885 (0.871–0.898).

Squares of Pearson's correlation coefficient (R^2) were computed between weights and clinical indices and the patients' age. The age was included in the analysis as a controlling variable because years pass during the progression of the disease. R^2 values were relatively high for hemoglobin 0.1393 ($P = 0.000$), age 0.0737 ($P = 0.000$) and serum albumin 0.0892 ($P = 0.000$), and low for eGFR 0.0527 ($P = 0.000$) and creatinine 0.0406 ($P = 0.000$). Hemoglobin and serum albumin were positively correlated to weights, whereas age was negatively correlated. All correlations were significant upon tests of independence. Table 4 shows the results of multiple linear regression analysis aimed at identifying determinants of the weights. According to forced entry regression, hemoglobin, age, and serum albumin were found to be significant, and were selected as explanatory variables by stepwise regression. Figures 2 and 3 show the relationships between weights and hemoglobin/serum albumin based on nonparametric regression analysis, locally weighted regression, and smoothing scatterplots (LOWESS) [17]. Whereas correlations are

Table 2 Responses to the five dimensions of EQ-5D by CKD stage and complications

	n	Mobility			Self-care			Usual activities			Pain/discomfort			Anxiety/depression		
		No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)
CKD stage																
1	83	95.2	4.8	–	97.6	2.4	–	89.2	9.6	1.2	89.2	10.8	–	89.2	10.8	–
2	153	91.5	8.5	–	98.0	2.0	–	87.6	11.8	0.7	82.4	15.7	2.0	86.3	13.7	–
3	158	81.7	17.7	0.6	94.3	5.1	0.6	82.3	17.1	0.6	77.9	21.5	0.6	76.6	22.8	0.6
4	72	72.2	25.0	2.8	88.9	8.3	2.8	66.7	27.8	5.6	75.0	25.0	–	84.7	15.3	–
5	71	63.4	36.6	–	85.9	14.1	–	56.3	39.4	4.2	60.6	38.0	1.4	74.7	25.4	–
All stages	537	82.8	16.6	0.6	94.0	5.4	0.6	79.3	18.8	1.9	78.2	20.9	0.9	82.1	17.7	0.2
Presence of HT																
CKD stage																
1	37	97.3	2.7	–	100.0	–	–	89.2	10.8	–	83.8	16.2	–	86.5	13.5	–
2	99	89.9	10.1	–	98.0	2.0	–	87.9	11.1	1.0	78.8	19.2	2.0	84.8	15.2	–
3	122	83.6	16.4	–	94.3	4.9	0.8	82.8	16.4	0.8	79.5	19.7	0.8	78.7	20.5	0.8
4	66	72.7	25.8	1.5	89.4	9.1	1.5	69.7	25.8	4.5	75.8	24.2	–	86.4	13.6	–
5	64	60.9	39.1	–	84.4	15.6	–	53.1	42.2	4.7	57.8	40.6	1.6	73.4	26.6	–
All stages	388	80.9	18.8	0.3	93.3	6.2	0.5	77.6	20.4	0.5	75.5	23.5	1.0	81.4	18.3	0.3
Absence of HT																
CKD stage																
1	45	93.3	6.7	–	95.6	4.4	–	88.9	8.9	2.2	93.3	6.7	–	91.1	8.9	–
2	54	94.4	5.6	–	98.1	1.9	–	87.0	13.0	–	88.9	9.3	1.9	88.9	11.1	–
3	36	75.0	22.2	2.8	94.4	5.6	–	80.6	19.4	–	72.2	27.8	–	69.4	30.6	–
4	6	66.7	16.7	16.7	83.3	–	16.7	33.3	50.0	16.7	66.7	33.3	–	66.7	33.3	–
5	7	85.7	14.3	–	100.0	–	–	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–
All stages	148	87.8	10.8	1.4	95.9	3.4	0.7	83.8	14.9	1.4	85.1	14.2	0.7	83.8	16.2	–
Presence of DM																
CKD stage																
1	14	85.7	14.3	–	92.9	7.1	–	71.4	28.6	–	78.6	21.4	–	92.9	7.1	–
2	35	91.4	8.6	–	97.1	2.9	–	88.6	11.4	–	77.1	20.0	2.9	88.6	11.4	–
3	38	68.4	31.6	–	89.5	7.9	2.6	71.1	26.3	2.6	65.8	34.2	–	65.8	34.2	–
4	25	72.0	24.0	4.0	92.0	8.0	–	68.0	28.0	4.0	80.0	20.0	–	92.0	8.0	–
5	34	55.9	44.1	–	85.3	14.7	–	52.9	38.2	8.8	50.0	50.0	–	64.7	35.3	–

Table 2 continued

	n	Mobility			Self-care			Usual activities			Pain/discomfort			Anxiety/depression		
		No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)
All stages	146	87.8	10.8	1.4	95.9	3.4	0.7	83.8	14.9	1.4	85.1	14.2	0.7	83.8	16.2	–
Absence of DM																
CKD stage																
1	69	97.1	3.0	–	98.6	1.4	–	92.8	5.8	1.4	91.3	8.7	–	88.4	11.6	–
2	118	91.5	8.4	–	98.3	1.7	–	87.3	11.9	0.8	83.9	14.4	1.7	85.6	14.4	–
3	120	85.8	13.3	0.8	95.8	4.2	–	85.8	14.2	–	81.7	17.5	0.8	80.0	19.2	0.8
4	47	72.3	25.5	2.0	87.2	8.5	4.3	66.0	27.7	6.4	72.3	27.7	–	80.9	19.1	–
5	37	70.2	29.7	–	86.5	13.5	–	59.5	40.5	–	70.3	27.0	2.7	83.8	16.2	–
All stages	391	86.4	13.0	0.5	95.1	4.3	0.5	82.6	16.1	1.3	81.8	17.1	1.0	83.6	16.1	0.3
Presence of CVD																
CKD stage																
1	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	7	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–
3	11	54.5	45.5	–	81.8	9.1	9.1	54.5	36.4	9.1	63.6	18.2	9.1	54.5	45.5	–
4	6	66.7	33.3	–	100	–	–	33.3	50	16.7	83.3	16.7	–	100	–	–
5	14	50	50	–	78.6	21.4	–	42.9	50	7.1	35.7	64.3	–	42.9	57.1	–
All stages	38	60.5	39.5	–	84.2	13.2	2.6	52.6	39.5	7.9	60.5	36.8	2.6	63.2	36.8	–
Absence of CVD																
CKD stage																
1	83	95.2	4.8	–	97.6	2.4	–	89.2	9.6	1.2	89.2	10.8	–	89.2	10.8	–
2	146	91.8	8.2	–	98.6	1.4	–	87.7	11.6	0.7	82.2	15.8	2.1	86.3	13.7	–
3	147	83.7	15.6	0.7	95.2	4.8	–	84.4	15.6	–	78.9	21.1	–	78.2	21.1	0.7
4	66	72.7	24.2	3	87.9	9.1	3	69.7	25.8	4.5	74.2	25.8	–	83.3	16.7	–
5	57	66.7	33.3	–	87.7	12.3	–	59.6	36.8	3.5	66.7	31.6	1.8	82.5	17.5	–
All stages	499	84.6	14.8	0.6	94.8	4.8	0.4	81.4	17.2	1.4	79.6	19.6	0.8	83.6	16.2	0.2

Table 3 Quality-adjustment weights by CKD stage

	n	Mean	95% CI	*P* value
CKD stage				
1	83	0.940	0.915–0.965	<0.0001
2	153	0.918	0.896–0.940	
3	158	0.883	0.857–0.909	
4	72	0.839	0.794–0.884	
5	71	0.798	0.757–0.839	
All stages	537	0.885	0.871–0.898	

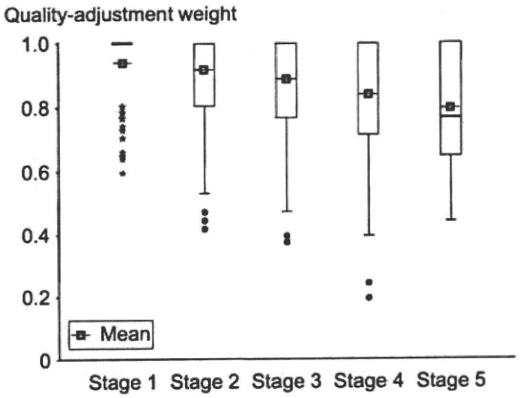

Fig. 1 Box and whisker plots of quality-adjustment weights by CKD stage. Quality-adjustment weights decrease with progression of CKD stage. Quality-adjustment weights at CKD stages 4 and 5 are significantly lower than those at CKD stages 1–3

not very clear when plots of cases are studied, smoothing curves reveal nonlinear relationships. The curves are stable regardless of the chosen bandwidth. Notable inflections in the weight against hemoglobin are seen at around 10.0 and 13.0 g/dl in Fig. 2. Similarly, inflections against serum albumin are seen at around 3.2 and 4.2 g/dl in Fig. 3.

The results from an analysis of the effect of comorbidity on HRQOL are shown in Table 5. The presence of hypertension lowers the weight from 0.910 (0.885–0.936) to 0.874 (0.858–0.891), diabetes from 0.901 (0.886–0.917) to 0.840 (0.811–0.869), and CVD from 0.892 (0.878–0.906) to 0.783 (0.718–0.848). There was a significant relationship between quality-adjustment weights and the presence of complications.

Discussion

We measured the HRQOL in terms of quality-adjustment weight using EQ-5D in patients with CKD. Measured weights by stage were: 0.94 for stage 1, 0.918 for stage 2, 0.883 for stage 3, 0.839 for stage 4, 0.798 for stage 5, and 0.885 for all stages. This is the first report on such weights using EQ-5D, and it can be used in cost-effectiveness analysis with a preferred outcome measure, QALYs, of interventions for CKD. The weights illustrate that CKD patient HRQOL lowers according to the progression of the disease, as expected. We consider that these results show the health-related quality of CKD patients' lives to a certain extent.

Although it is known that a direct international comparison of quality-adjustment weights is not possible, and that the measurement is sensitive to the technique/instrument used, Gorodetskaya et al. [18] report such weights by stage of CKD with TTO and Health Utility Index Mark 3 (HUI3); that is, a generic preference-based measures instrument [19]. TTO yields 0.90 for stages 1 and 2, 0.87 for stage 3, 0.85 for stage 4, 0.85 for stage 4, 0.85 for stage 5, and 0.72 for stage 5D; HUI3 yields 0.67 for stages 1 and 2, 0.67 for stage 3, 0.55 for stage 4, 0.54 for stage 4, 0.54 for stage 5, and 0.72 for stage 5D. The weight decreases along with progression of the stage, which is similar to our results. Gorodetskaya's weights, however, are lower than ours, which may be due to differences in social preferences between Japan and the United States, in the characteristics of the technique/instrument used, or in other factors including measurement errors. A well-designed international comparative study is needed in order to explore the causes of these differences.

There are more reports of weights for ESRD from several countries obtained with various techniques/instruments, although we have not assessed them. The weights for the ESRD range from 0.39 up to 0.93 using TTO, SG, or EQ-5D [20]. Limiting the instrument to EQ-5D, the reported weights were 0.66–0.81 for hemodialysis and 0.71–0.81 for peritoneal dialysis from the Netherlands [21], 0.76 for dialysis from Germany [22], 0.62 for hemodialysis and 0.55 for peritoneal dialysis from Canada [23], and 0.44 for hemodialysis and 0.65 for peritoneal dialysis from Sweden [24]. These values do not raise any concerns over our measurement of 0.798 for stage 5, although no straightforward comparison can be made.

The measured quality-adjustment weights were correlated with routinely checked clinical indices such as hemoglobin, serum albumin, eGFR, and creatinine. Additionally, they significantly depend on hemoglobin and serum albumin after controlling for age. The significance of hemoglobin as a determinant of the HRQOL of CKD patients is consistent with the findings of previous studies, which measured HRQOL along with other measurements, such as SF-36 [11, 12]. The significance of serum albumin has also been pointed out [11]. These results suggest that a patient's HRQOL more closely depends on a general secondary state such as anemia or undernutrition than the primary pathology of CKD, i.e., a low GFR. A notable inflection in the weight at around a hemoglobin level of 10.0 g/dl is also noted in the relationship between the

Table 4 Multiple linear regression analysis of clinical determinants of HRQOL

Variable	Coefficient	SE	*t* Value	*P* value
Forced entry regression[a]				
Alb	0.0465	0.013	3.497	0.001
Hb	0.0148	0.004	3.434	0.001
sCre	−0.0065	0.006	−1.124	0.261
eGFR	−0.0002	0.000	−0.732	0.465
Age	−0.0021	0.001	−4.069	0.000
Sex dummy ("0" for male; "1" for female)	−0.0323	0.015	−2.219	0.027
Constant	0.6607	0.085	7.427	0.000

Step	Variable added	Coefficient	SE	*F* value	Adjusted R^2
Stepwise regression[b]					
1	Hb	0.0165	0.004	79.896	0.133
2	Age	−0.0019	0.000	49.961	0.160
3	Alb	0.0458	0.013	37.584	0.176
4	Sex dummy ("0" for male; "1" for female)	−0.0280	0.014	29.402	0.181

[a] $n = 537$, $R^2 = 0.189$, adjusted $R^2 = 0.180$, $F = 19.785$, $P = 0.000$

[b] Forward selection method, critical $F_{in} = 0.05/F_{out} = 0.1$, other variables considered: sCre, eGFR

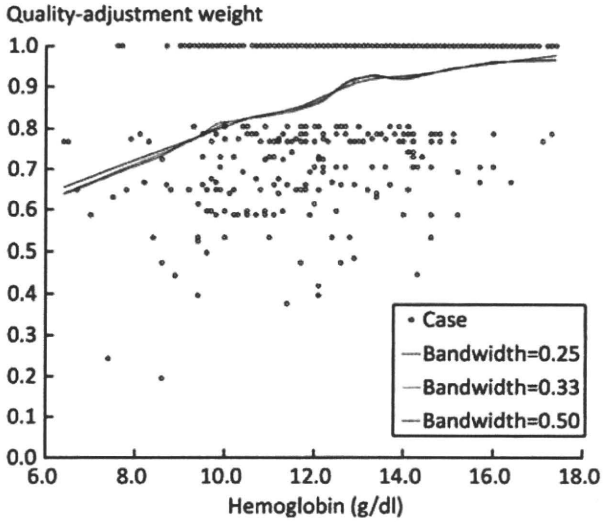

Fig. 2 Smoothing scatterplots of quality-adjustment weight and hemoglobin. Bandwidth is a smoothing parameter that specifies the weighting between the central point and points further away in local linear regressions. The greater the bandwidth, the greater the smoothing. Smoothing curves are stable irrespective of the bandwidth. Inflections in the weight against hemoglobin can be seen at around 10.0 and 13.0 g/dl

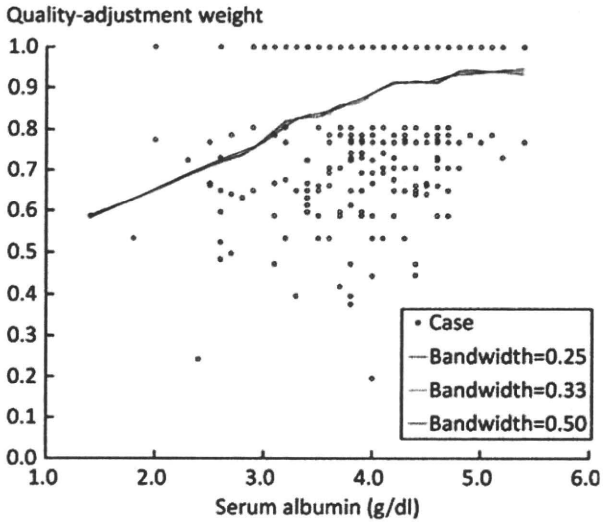

Fig. 3 Smoothing scatterplots of the quality-adjustment weight and serum albumin. Bandwidth is a smoothing parameter that specifies the weighting between the central point and points further away in local linear regressions. The greater the bandwidth, the greater the smoothing. Smoothing curves are stable irrespective of the bandwidth. Inflections in the weight against serum albumin can be seen at around 3.2 and 4.2 g/dl

weight and hemoglobin. This finding corresponds to what Lefebvre et al. [25] reported in an intervention study to improve HRQOL measured by Kidney Disease Questionnaire (KDQ) on the administration of erythropoietin, whereby the maximal gain in HRQL occurred between hemoglobin values of 10 and 12 g/dl. This could be an additional rationale from the viewpoint of HRQOL supporting a target hemoglobin level of 10–12 g/dl for CKD patients as recommended in the CKD Clinical Practice Guideline in Japan of 2007 [26].

The presence of comorbidities such as hypertension, diabetes, or a history of CVD is found to lower quality-adjustment weights, i.e., the HRQOL, of CKD patients, as anticipated. HRQOL deterioration is most severe in the

Table 5 Quality-adjustment weights by CKD stage and complications

	Presence of hypertension				Absence of hypertension			
	n	Mean	95% CI	*P* value	*n*	Mean	95% CI	*P* value
CKD stage								
1	37	0.935	0.896–0.974	0.0000	45	0.942	0.909–0.975	0.0017
2	99	0.909	0.880–0.938		54	0.935	0.901–0.969	
3	122	0.889	0.861–0.917		36	0.862	0.800–0.924	
4	66	0.851	0.807–0.895		6	0.708	0.470–0.946	
5	64	0.782	0.740–0.824		7	0.941	0.825–1.057	
All stages	388	0.874	0.858–0.891	0.0229*	148	0.910	0.885–0.936	
	Presence of diabetes				Absence of diabetes			
	n	Mean	95% CI	*P* value	*n*	Mean	95% CI	*P* value
CKD stage								
1	14	0.867	0.818–0.976	0.0041	69	0.948	0.923–0.973	0.0001
2	35	0.911	0.862–0.960		118	0.920	0.895–0.945	
3	38	0.826	0.767–0.885		120	0.901	0.873–0.929	
4	25	0.843	0.770–0.916		47	0.837	0.780–0.894	
5	34	0.757	0.700–0.814		37	0.836	0.779–0.893	
All stages	146	0.840	0.811–0.869	0.0001*	391	0.901	0.886–0.917	
	Presence of CVD				Absence of CVD			
	n	Mean	95% CI	*P* value	*n*	Mean	95% CI	*P* value
CKD stage								
1	0	–	–		83	0.940	0.915–0.965	0.0000
2	7	0.912	0.793–1.031	0.1731	146	0.918	0.895–0.941	
3	11	0.773	0.633–0.913		147	0.891	0.866–0.916	
4	6	0.816	0.695–0.937		66	0.841	0.793–0.889	
5	14	0.713	0.620–0.806		57	0.819	0.774–0.899	
All stages	38	0.783	0.718–0.848	0.0018*	499	0.892	0.878–0.906	

* *P* value, presence vs. absence of complication at all stages

presence of a history of CVD, and least in the presence of hypertension.

In regard to the presence of diabetes, Sakamaki et al. [27] reported the HRQOL of type 2 diabetes mellitus Japanese patients using EQ-5D. Nephropathy was classified as present with an early-stage urinary albumin/creatinine ratio of >20 mg/g. The quality-adjustment weights of patients with nephropathy were 0.81 (95% CI 0.72–0.90) and 0.87 (0.85–0.89) in those without nephropathy ($P = 0.193$) [27]. In our study, the weights of CKD patients with diabetes were 0.840 (0.811–0.869) and 0.901 (0.886–0.917) in those without diabetes ($P = 0.0001$). We noted slightly higher weights than Sakamaki et al. This may be due to a difference in the age of respondents according to our analysis of weight determinants. The mean age of respondents in our study, 55.2 years old, was younger than that in the report by Sakamaki et al., at 63.3 years old.

This study has several limitations. Firstly, the employment of an established HRQOL measurement tool, EQ-5D [14, 15], improves the reliability of our study and its results. However, its plausibility depends on our sample's representativeness of CKD patients. We made an assumption that outpatients at our department could be considered to comprise a near-representative sample, since a better sampling method such as simple random sampling of CKD patients in the community is not feasible due to the limitations on our epidemiologic knowledge. Therefore, we can neither exclude the possibility of sample selection bias nor implement a bias correction. Further epidemiologic studies are awaited. Secondly, we assessed the effect of the presence or absence of cormobidities (hypertension, diabetes, and CVD) on HRQOL, but not the influence of the severities of these comorbidities on HRQOL.

Finally, the utilization of quality-adjustment weights of CKD patients is a valuable aid when devising an effective

strategy to solve both socioeconomic and public health problems like CKD.

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ORIGINAL ARTICLE
Peripheral Vascular Disease

Characteristics of Revascularization Treatment for Arteriosclerosis Obliterans in Patients With and Without Hemodialysis

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Background: Limb ischemia is a major complication in patients who are receiving hemodialysis (HD). In this study, distinctive features and factors affecting the outcome of HD patients with limb ischemia are identified.

Methods and Results: One hundred and eighty consecutive symptomatic limb ischemic patients who were or were not receiving HD and who successfully underwent surgical bypass grafting (bypass, n=75) or endovascular angioplasty (percutaneous transluminal angioplasty (PTA), n=105) were retrospectively compared at our hospital. The endpoint of this study was amputation of the ischemic leg or death. Median follow up was 2.25 years. The amputation-free survival of HD patients was significantly lower than that of non-HD patients (P<0.0001). In the bypass group, the amputation-free survival of HD patients was significantly lower than that of non-HD patients (P=0.0002), even if the graft was patented or not (P=0.77). In contrast, in the PTA group, the amputation-free survival of HD patients was lower than that of non-HD patients (P=0.03), and with a significantly lower patency rate (P=0.0004). Predictors of amputation-free survival differed between HD and non-HD patients; predictors were diabetes mellitus and gender in HD patients, while they were Fontaine classification and hyperlipidemia in non-HD patients. The infectious death rate was higher in HD patients than in non-HD patients (53% vs 22%, P<0.05).

Conclusions: This study clearly showed a poorer prognosis in HD patients than in non-HD patients especially after bypass surgery, even if the the graft was patented or not. (*Circ J* 2010; **74:** 2426–2433)

Key Words: Angioplasty; Bypass surgery; Hemodialysis outcomes; Peripheral arterial disease

Peripheral artery disease (PAD) is one of the major complications in patients on hemodialysis (HD). The number of patients with PAD is increasing due to increases in the number of patients on HD, the elderly population and patients with diabetic nephropathy. Surgical bypass grafting (bypass) and percutaneous transluminal angioplasty (PTA) are the 2 main interventional treatments for PAD. The advantages of surgery over than PTA were reported to be good long-term anatomical patency and clinical durability.[1–3] In contrast, balloon angioplasty was reported to have the advantages of low procedural morbidity and mortality, and a shortened hospital stay.[4,5] A recent randomized controlled trial that compared the outcomes of bypass and PTA in patients with severe limb ischemia and concluded that their outcomes were similar.[6]

In HD patients, however, several studies described the outcome of dialysis patients with PAD who were treated by bypass surgery.[7–10] The survival at 1 and 2 years was in the range of 50–60% and 40–50%, respectively. The cumulative limb salvage rate and primary patency rate at 1 year were in the range of 50–80% and 50–70%, respectively. Also PTA was considered as feasible and effective in HD patients with severe PAD.[11,12] However, these studies did not directly compare the outcomes of these 2 treatments in patients on HD, and treated years were different between these 2 groups. The primary endpoint of this retrospective study was to compare the outcomes between HD and non-HD patients, and the secondary endpoint of this study was to reveal the characteristics of PAD treatments in HD patients by directly determining the outcome associated with bypass or PTA between

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Table 1. Patients' Characteristics (n=180)

	HD (n=41)	Non HD (n=139)	P value
Gender, F/M	8/33	13/126	0.09
Age	63.3±8.7	68.9±7.9	<0.01
Fontaine, II/III/IV	27 (65.9%)/6/8	121 (87.1%)/8/10	0.01
IHD history	23 (56.1%)	57 (41.0%)	0.09
Hypertension	31 (75.6%)	106 (76.3%)	0.93
Smoking	31 (75.6%)	123 (88.5%)	0.05
Diabetes mellitus	21 (51.2%)	80 (57.6%)	0.47
Hyperlipidemia	10 (24.4%)	5 (38.9%)	0.08
Bypass/PTA	23 (56.1%)/18 (43.9%)	52 (37.4%)/87 (62.6%)	0.03

Data are presented as number (%) unless otherwise stated. Plus-minus values are mean±SD.
P values were calculated with the use of the chi-square test for categorical variables and the t-test for continuous variables.
HD, history of hemodialysis; IHD, history of ischemic heart disease (angina pectoris or myocardial infarction).

patients who were or were not receiving HD.

Methods

The study population included 231 symptomatic patients with chronic limb ischemia who underwent bypass or PTA at our hospital between 1999 and 2006. Patients who could not achieve clinical success (12 patients in PTA and 1 patient in bypass), who had been treated with in-stent restenosis (10 patients), had a past history (within 3 months) of angioplasty (16 patients), had had a scheduled amputation after the procedure (2 patients in PTA), had symptomatic advanced malignancy (1 patient in PTA), could not be followed up after discharge (4 patients in PTA and 2 patients in bypass), and who were considered inadequate to follow up (2 patients in PTA and 1 patient in bypass) were excluded from this study. As a result, 180 symptomatic patients with chronic limb ischemia who underwent bypass or PTA were included in this study. The primary endpoint of this study was amputation of the ischemic leg or death, and the secondary endpoint was occlusion after treatment. We compared these outcomes between HD and non-HD patients, and then determined outcomes associated with bypass or PTA between them. Whether to perform bypass or PTA was considered according to the Trans Atlantic Inter-Society Consensus (TASC) criteria[13,14] after discussion among cardiovascular specialists.

Clinical success was defined by the absence of residual obstructions after treatment.[12] All subjects were diagnosed with limb ischemia by clinical symptoms, angiographic examinations and the ankle-brachial pressure index (ABI) (form PWV/ABI; Omron Colin, Tokyo, Japan). Patients' previous histories were examined by using clinical records. A history of ischemic heart disease was defined as a history of angina pectoris or myocardial infarction. Renal function of the patients who did not receive hemodialysis was calculated by using an estimated glomerular filtration rate (eGFR) formula by Matsuo et al.[15] Follow up continued until the patients had reached an endpoint (amputation of the ischemic leg or death) or were lost to follow up. To find the prognostic factor differences, we examined patient characteristics, time to death from any cause, time to amputation of the ischemic leg or death (whichever came first) (amputation-free survival), and the primary patency period in both groups. The primary patency period was defined as the time after treatment to occlusion. Occlusion after treatment was defined as angiographic occlusion, loss of distal pulsation after treatment or worsened symptoms requiring another treatment. Hypertension, hyperlipidemia, and diabetes mellitus (DM) were defined as a systolic blood pressure of 140 mmHg or higher, a total cholesterol of 220 mg/dl and/or a LDL cholesterol of 140 mg/dl or higher, and a fasting blood glucose of 126 mg/dl or higher, respectively.

Statistical Analysis

Baseline characteristics of patients were compared using the 2-tailed t-test, or the Mann-Whitney test where appropriate, for continuous data, and the chi-square test for categorical data. Cumulative event rates were estimated with Kaplan-Meier survival curves, and possible statistical differences were evaluated by the log-rank test. Multiple linear regression analysis was used to determine factors affecting survival and amputation-free survival. The Cox proportional hazards model was used to obtain hazard ratios (HR) and 95% confidence intervals (CI) for overall survival and amputation-free survival. Any covariates that were significant on univariate analysis were assessed by multivariate analysis. The considered variables were as follows: age, gender, treatment methods, Fontaine classification, DM, hypertension, hyperlipidemia, smoking history, ischemic heart disease, history of dialysis, and time from dialysis start. Among the explanatory variables, qualitative variables were evaluated by a marginal method, and stepwise analysis was performed by an increasing variable method. A P value <0.05 was considered statistically significant. Data were entered and analyzed using the statistical software, JMP 8.0 (SAS Institute, Cary, NJ, USA).

Results

The baseline characteristics of the patients in each group are shown in Table 1. Over 70% of the patients had a history of hypertension and a smoking history in each group. Approximately half of the patients had a history of DM. The percentage of CLI (Fontaine III+IV) patients was 34.1% in the HD group and 12.9% in the non-HD group, respectively (P=0.01). There were greater numbers of older patients, patients with a history of smoking and who treated by PTA in the non-HD group than in the HD group. The mean duration of HD was 9.9±9.2 years; 9.4±9.9 years in the bypass group, and 10.7±8.5 years in the PTA group (P>0.05). The mean eGFR of non-HD patients was 67.5±25.0 ml/min in the bypass group and 63.0±20.1 ml/min in PTA group (P>0.05). The types of endovascular treatment lesions in patients with HD were: TASC A, 16%; TASC B, 38%; and TASC C, 46%;

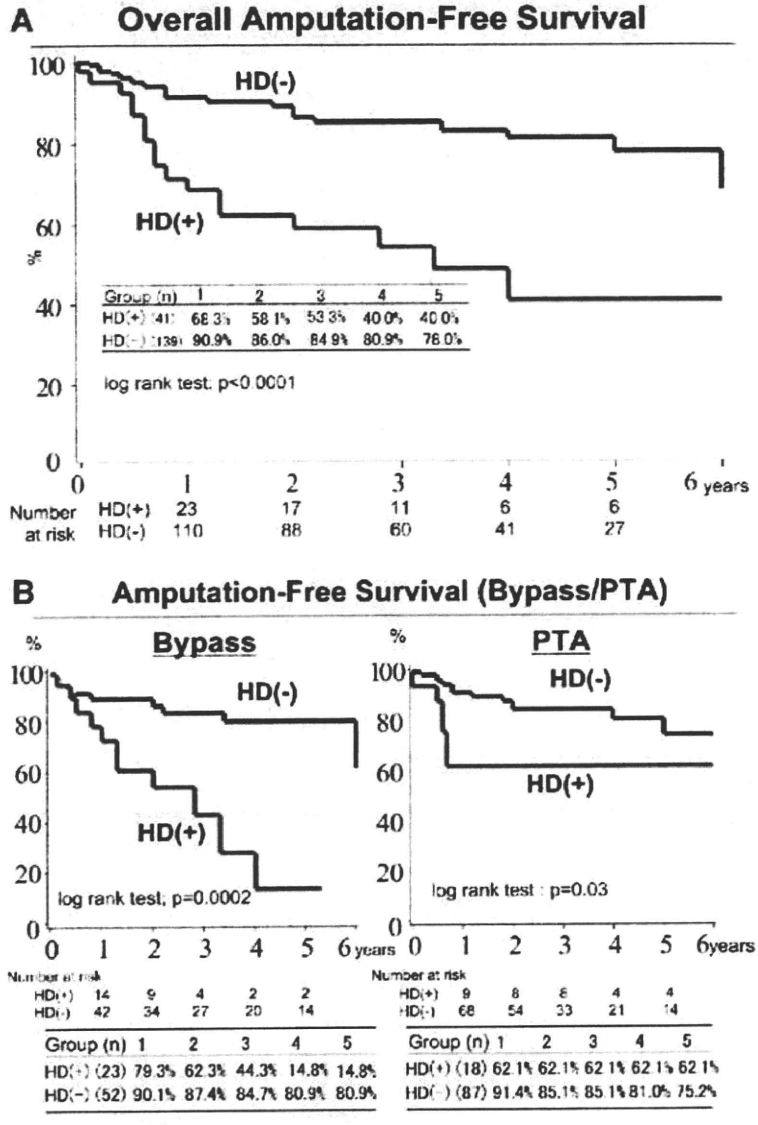

Figure 1. (**A**) Overall amputation-free survival after bypass surgery (bypass) and balloon angioplasty (PTA). The median amputation-free survivals for PTA and bypass groups were 2.2 years and 2.2 years, respectively. Amputation-free survival was defined as the time to amputation of the ischemic leg or death (whichever came first). (**B**) Overall amputation-free survival among patients who were or were not receiving dialysis (HD) in each of the bypass or PTA groups. The median amputation-free survivals for bypass-non HD, bypass-HD, PTA-non HD, PTA-HD groups were 3.0, 1.3, 2.2, 0.85 years, respectively.

whereas it was TASC A, 22%; TASC B, 55%; and TASC C, 23% in patients without HD. The types of surgical bypass were femoropopliteal artery bypass (57%), femoral femoral bypass (13%), Y-graft bypass (8%), axillo-femoral bypass (5%), distal bypass (5%), and others (12%). Saphenous veins were used in 13% of the patients who received femoropopliteal artery bypass. In the PTA group, 64.6% of the patients received a stent placement after the PTA procedure. The percentage of stent placement was higher in patients having infrainguinal target lesions than in patients having supra inguinal target lesions (72.7% vs 53.2%, P=0.05). No major periprocedural complications were observed. Causes of death during follow up in HD and non-HD patients were infection [n=8 (53.3%) and 5 (21.7%)], malignancy [0 (0%), 6 (26.1%)], cardio and cerebrovascular diseases [5 (33.3%), 10 (43.5%)], and gastrointestinal disease [2 (13.3%), 2 (8.7%)], respectively (P<0.05).

Statins were initiated in 60.9% (39/64) of the patients with hyperlipidemia and in 0.9% (1/116) of the patients without hyperlipidemia, showing a significant difference (P<0.01). Anticoagulants and/or aspirin was initiated after treatment in all patients except those with active bleeding and those needing amputation, and there was no difference in the percentage of patients who were treated with anticoagulants and/or aspirin between HD and non-HD patients, bypass and PTA groups.

Amputation-Free Survivals

Figure 1A shows Kaplan-Meier survival curves of the time to amputation or death (whichever came first). Overall, amputation-free survivals at 1, 3, and 5 years were 68.3%, 53.3%, 40.0% in the HD group, and 90.9%, 84.9%, and 78.0% in the non-HD group, respectively (Figure 1A, P<0.0001).

Factors Predicting Survival and Amputation-Free Survival

Next, we determined factors affecting survival and amputation-free survival among patients who were or were not receiving HD. The significant predictors of amputation-free survival among all patients were presence of HD (HR, 2.48 [95%CI, 1.25–4.82]) and Fontaine classifications class IV

Table 2. Factors Predicting Survival and Amputation-Free Survival

	Survival		Amputatio-free survival	
	HR (95%CI)	P value	HR (95%CI)	P value
Non-HD	Referent		Referent	
HD	2.89 (1.44–5.69)	0.003	2.48 (1.25–4.82)	0.010
Fontaine				
II	Referent		Referent	
III	1.87 (0.55–4.99)	0.07	1.83 (0.52–4.69)	0.32
IV	2.87 (1.10–6.54)	0.03	4.32 (1.91–9.37)	0.0009
Hyperlipidemia				
(–)	Referent		Referent	
(+)	0.48 (0.19–1.06)	0.07	0.50 (0.21–1.06)	0.07
Diabetes mellitus				
(–)	Referent		Referent	
(+)	0.83 (0.43–1.61)	0.57	0.96 (0.52–1.81)	0.90
Gender				
Female	Referent		Referent	
Male	0.55 (0.25–1.36)	0.18	0.47 (0.23–1.09)	0.08
Treatment				
PTA	Referent		Referent	
Bypass	1.39 (0.72–2.68)	0.33	1.54 (0.83–2.89)	0.17

Adjusted for age, history of heart disease, hypertension, and smoking history.
P<0.05 was used to determine statistical significance.
HR, hazard ratio; CI, confidence interval. Other abbreviation see in Table 1.

Table 3. Prognositic Factors Among HD/Non-HD Patients

	Survival		Amputation-free survival	
	HR (95%CI)	P value	HR (95%CI)	P value
HD patients				
Fontaine				
II	Referent		Referent	
III	1.89 (0.55–4.99)	0.46	1.73 (0.25–7.05)	0.54
IV	4.58 (1.15–13.77)	0.03	3.23 (0.94–10.31)	0.06
Hyperlipidemia	0.58 (0.13–1.82)	0.38	0.54 (0.12–1.66)	0.31
Diabetes mellitus	4.55 (1.58–14.23)	0.005	8.34 (1.91–46.98)	0.004
Gender				
Female	Referent		Referent	
Male	0.36 (0.13–1.06)	0.06	0.19 (0.06–0.63)	0.007
Treatment				
PTA	Referent		Referent	
Bypass	2.48 (0.89–8.00)	0.08	1.69 (0.63–4.99)	0.30
Non-HD patients				
Fontaine				
II	Referent		Referent	
III	1.99 (0.31–7.03)	0.40	1.98 (0.31–7.03)	0.40
IV	2.02 (0.32–7.14)	0.39	6.12 (1.99–15.75)	0.003
Hyperlipidemia	0.40 (0.11–1.12)	0.08	0.36 (0.12–0.94)	0.04
Diabetes mellitus	0.55 (0.22–1.34)	0.19	0.71 (0.31–1.65)	0.43
Gender				
Female	Referent		Referent	
Male	2.16 (0.45–38.77)	0.40	2.49 (0.52–44.62)	0.30
Treatment				
PTA	Referent		Referent	
Bypass	1.33 (0.54–3.58)	0.54	1.13 (0.48–2.60)	0.77

Adjusted for age, history of heart disease, hypertension, and smoking history.
P<0.05 was used to determine statistical significance.
Abbreviations see in Tables 1,2.

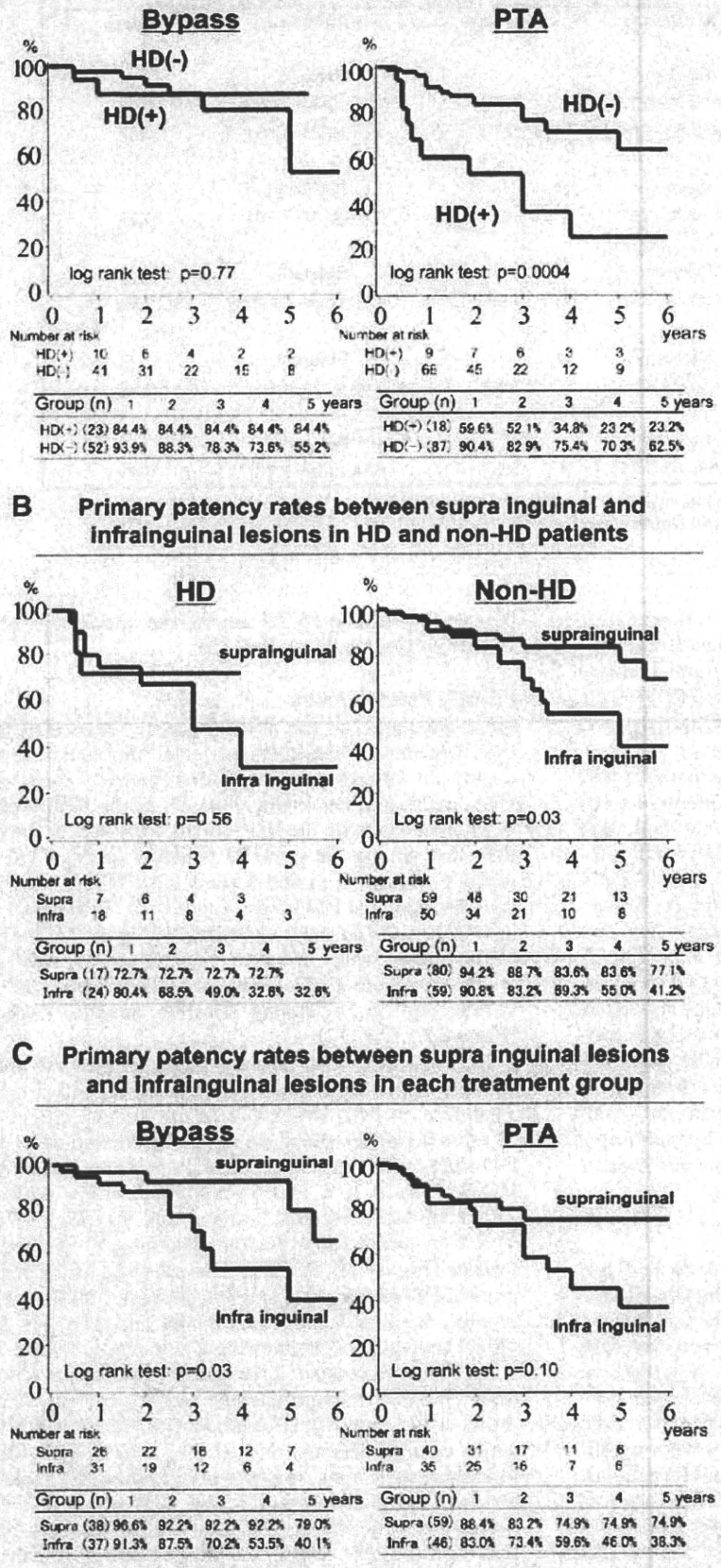

Figure 2. (**A**) Primary patency rates among patients who were or were not receiving dialysis (HD) after bypass surgery (bypass) and balloon angioplasty (PTA). The primary patency period was defined as the time after treatment to occlusion. Occlusion was defined as angiographic occlusion, loss of distal pulsation, or worsened symptoms requiring another treatment. (**B**) Primary patency rates between supra inguinal and infrainguinal lesions in patients who were or were not receiving HD. Supra, suprainguinal lesion; Infra, infrainguinal lesion. (**C**) Primary patency rates among patients having supra inguinal and infrainguinal lesions in each of the bypass or PTA group. Supra, suprainguinal lesion; Infra, infrainguinal lesion.

Table 4. Factors Predicting the Patency Period

	Non-HD patients		HD patients	
	HR (95%CI)	P value	HR (95%CI)	P value
Fontaine				
II	Referent		Referent	
III	1.97 (0.31–6.72)	0.40	2.39 (0.35–11.38)	0.41
IV	2.63 (0.61–7.54)	0.17	1.67 (0.25–8.48)	0.52
Hyperlipidemia				
(–)	Referent		Referent	
(+)	0.77 (0.33–1.67)	0.51	0.45 (0.07–1.74)	0.27
Diabetes mellitus				
(–)	Referent		Referent	
(+)	1.42 (0.64–3.46)	0.39	4.22 (1.04–21.26)	0.04
Gender				
Female	Referent		Referent	
Male	3.21 (0.68–51.34)	0.17	0.66 (0.16–4.51)	0.63
Treatment				
PTA	Referent		Referent	
Bypass	1.07 (0.49–2.28)	0.87	0.18 (0.03–0.70)	0.01

Adjusted for age, history of heart disease, hypertension, and smoking history.
P<0.05 was used to determine statistical significance.
Abbreviations see in Tables 1,2.

(referent, class II) (HR, 4.32 [95%CI, 1.91–9.37]), similar to the significant predictors of survival among all patients {presence of HD (HR, 2.89 [95%CI, 1.44–5.69]) and Fontaine classifications class IV (referent, class II) (HR, 2.87 [95%CI, 1.10–6.54])} (Table 2). Both results clearly showed a poorer prognosis in HD patients than in non-HD patients.

Next, we analyzed these predictors among patients who were or were not receiving HD (Table 3). Among non-HD patients, the predictors for amputation-free survival were Fontaine classification {class IV (referent, class II) (HR, 6.12 [95%CI, 1.99–5.75])} and hyperlipidemia (HR, 0.36 [95%CI, 0.12–0.94]), and there were no significant predictors for survival. Among the HD patients, however, significant predictors for survival were presence of DM (HR, 4.55 [95%CI, 1.58–14.27]) and Fontaine classification {class IV (referent, class II) (HR, 4.58 [95%CI, 1.15–3.77])}, and the significant predictors for amputation-free survival were diabetic mellitus (HR, 8.34 [95%CI, 1.91–46.98]) and gender (HR, 0.19 [95%CI, 0.06–0.63]). These findings were quite different from those among non-HD patients. Although it was not significant (P=0.08), therapeutic selection (PTA or bypass) might have some influence on the survival of limb ischemia patients on HD.

Therapeutic Methods (PTA and Bypass)

In the bypass group, amputation-free survivals at 1, 3, and 5 years were 79.3%, 44.3%, and 14.8% among the HD patients, and 90.1%, 84.7%, and 80.9% among the non-HD patients, respectively (Figure 1B, P=0.0002). Overall survivals at 1, 3, and 5 years were 73.1%, 44.0% and 14.7% among the HD patients, and 95.7%, 90.2%, and 86.1% among the non-HD patients, respectively (log rank test, P<0.0001). Both amputation-free survivals and overall survivals were significantly lower in the HD patients than in the non-HD patients. In the PTA group, however, amputation-free survivals at 1, 3, 5 years were all 62.1% among the HD patients, and 91.4%, 85.1%, and 75.2% among the non-HD patients, respectively (Figure 1B, P=0.03). Overall survivals at 1, 3, and 5 years were 74.7%, 66.5% and 66.5% among the HD patients, and 91.4%, 85.1%, and 75.2% among the non-HD patients, respectively (log rank test, P=0.18).

Primary Patency Rates

Next, we compared the primary patency rates difference in the HD patients and non-HD patients. Although there was no significant difference in the primary patency rates between PTA and bypass treatment (P=0.32) in the PTA group, the patency rates among the HD patients were significantly lower than that among the non-HD patients. In the PTA group, patency rates at 1, 3, and 5 years were 59.6%, 34.8%, and 23.2% among the HD group, and 90.4%, 75.4%, and 62.5% among the non-HD group, respectively (Figure 2A, P=0.0004). In the bypass group, however, primary patency rates at 1, 3, and 5 years were all 84.4% among HD patients, and 93.9%, 78.3%, and 55.2% among non-HD patients, respectively (Figure 2A, P=0.77).

It is reported that primary patency rates are different between supra inguinal lesions and infrainguinal lesions.[15] Therefore, at first, we examined the primary patency rates of supra inguinal lesions and those of infrainguinal lesions in HD and non-HD patients. The primary patency rates of non-HD patients at 1, 3, and 5 years were 94.2%, 83.6%, and 77.1% in supra inguinal lesions, and 90.8%, 69.3%, and 41.2% in infrainguinal lesions, showing a significant difference (Figure 2B, P=0.03). However, the primary patency rates of HD patients at 1 and 3 years were 72.7% and 72.7% in supra inguinal lesions, and 80.4% and 49.0% in infrainguinal lesions, without showing significance (Figure 2B, P=0.56). Then we compared the primary patency rates between the PTA and bypass groups, the patency rates in the bypass group at 1, 3, and 5 years were 96.6%, 92.2% and 79.0% in supra inguinal lesions, and 91.3%, 70.2%, and 40.1% in infrainguinal lesions, respectively (Figure 2C, P=0.03). In contrast, the patency rates in the PTA group at 1, 3, and 5 years were 88.4%, 74.9%, and 74.9% in supra inguinal lesions, and 83.0%, 59.6%, and 38.3% in infrainguinal lesions, respectively (Figure 2C, P=0.10). The primary patency rates of supra inguinal lesions are higher than those of infrain-

Table 5. Cause of Death

	Infection	Carcinoma	Gastrointestinal	Cardiovascular
HD (–)	5 (22%)	6 (26%)	2 (9%)	10 (43%)
HD (+)	8 (53%)	0 (0%)	2 (13%)	5 (33%)

Abbreviation see in Table 1.

guinal lesions in both treatments.

Next, we determined factors affecting the patency rate. The significant predictor of patency period among all patients was the presence of HD (HR, 2.32 [95%CI, 1.13–4.50], P=0.02), which clearly showed a poorer patency rate in HD patients than in non-HD patients.

Therefore, we analyzed these predictors among patients who were or were not receiving HD (Table 4). Among HD patients, the predictors for patency rate were treatment method {bypass (referent, PTA) (HR, 0.18 [95%CI, 0.03–0.70], P=0.01)} and DM (HR, 4.22 [95%CI, 1.04–21.26], P=0.04), whereas there was no significant predictor for patency rate among the non-HD patients. Thus, therapeutic selection (PTA or bypass) and presence of DM were considered to have a significant influence on the patency rate of HD patients.

In summary, in the bypass group, the patency rates were similar among patients who were or were not receiving HD (P=0.77), whereas both amputation-free survivals and overall survivals were significantly lower in the HD patients than in the non-HD patients. In contrast, in the PTA group, the primary patency rates among the HD patients were significantly lower than that among the non-HD patients.

Causes of death is shown in Table 5. Infectious death was higher in HD patients (53%) than in non-HD patients (22%) (P<0.05).

Fontaine II Group Analysis

Next, we analyzed the outcomes of Fontaine II patients from this cohort to eliminate the ischemic condition (Fontaine classification) bias between PTA and bypass groups. The characteristics of Fontaine II patients were similar between HD and non-HD. We compared the overall survivals and amputation-free survivals in patients with Fontaine II. These survival curves were almost the same as those among all patients. In the bypass group, amputation-free survivals at 1, 3, and 5 years were 82.5%, 51.3%, and 17.1% among the HD patients, and 100%, 93.4%, and 93.4% among the non-HD patients, respectively (log rank test, P<0.0001). In the PTA group, however, the amputation-free survivals at 1, 3, and 5 years were all 76.6% among the HD patients, and 92.0%, 85.0, and 73.8% among the non-HD patients, respectively (log rank test, P=0.45). These results suggest that treatment selection peculiarly affects HD patients' amputation-free survival, independent of ischemic conditions.

Discussion

Chronic dialysis is associated with a higher prevalence of PAD. Also, a lower extremity amputation level is closely related to the patient's activity of daily living.[16] As the life expectancy is further decreased in patients on HD who are receiving PAD treatment,[17] and PAD is accompanied by diffuse vascular calcification and is involved in distal infrapopliteal and foot arteries, the treatment of PAD in HD patients has been controversial.[18]

This is the first report directly showing characteristics of PAD treatments of bypass and PTA between HD and non-HD patients, giving us many suggestions even though this was a retrospective study. There were some different backgrounds of Fontaine classification in the bypass and PTA groups. However, considering the TASC criteria and that bypass surgery tends to be performed on more severe ischemic limbs, this difference should be acceptable for clinicians. Furthermore, our study clearly revealed different outcomes between HD and non-HD patients with the same ischemic conditions. We should notice that the survival and amputation-free survival after bypass surgery were significantly decreased in HD patients than in non-HD patients, in contrast to similar survival after PTA between HD and non-HD patients. This significant difference was regardless of whether the treated lesions were patented or not.

Furthermore, treatment selection and presence of DM affected survival in HD patients. We should select therapeutic methods carefully especially in DM patients who are on HD. These data suggest the importance of systemic clinical management after surgery. Because the rates of infectious complications and wound trouble in HD patients are higher than those in non-HD patients, team management involving cardiovascular surgeons, nephrologists, and infectious control teams is needed to achieve better patient survival, especially for HD patients.

Hyperlipidemia is considered as one of the risk factors for PAD patients,[19] and statins could reduce this risk.[20,21] In our study, the presence of hyperlipidemia brought better outcomes especially in non-HD patients. This different outcome might be because of a significantly higher rate of administration of statins in patients with hyperlipidemia.

In our study, the patency rates between patients with and without HD in the bypass group did not show a significant difference. However, the patient backgrounds of bypass types between these 2 groups are not equal. The percentage of HD patients who received Y-graft, femoral femoral bypass, and femoropopliteal artery bypass was smaller than that of non-HD patients (P<0.01), even though the number of patients was relatively small. It is reported that 5-year patency estimates are higher in patients who received Y-graft, femoral femoral bypass, and femoropopliteal bypass than patients who received other bypass methods.[14] Therefore, the graft patency rate of HD patients might be different if we could compare patients with the same backgrounds.

It is important to consider operator bias and therapeutic selection bias (the criteria by which bypass or PTA is chosen) when analyzing the outcomes of PAD patients. In most reports, PAD patients on HD who underwent bypass or PTA were treated by different surgeons, cardiovascular physicians, wound care physicians, and nephrologists, which might result in dissimilar quality of care and is a study limitation. Furthermore, in multicenter studies, there might be therapeutic selection bias in each hospital if there are no strict criteria for treatment selection. In contrast, this study was performed at a single general hospital with the same surgeons, cardiovascular physicians, and nephrologists, which could exclude these limitations.

Our results showed better outcomes in both patients who

received bypass or PTA than previous reports.[7-10] This might have been because of the difference in ischemic conditions, technical advantages and improvements in postoperative management. Our study results suggest some considerations and methods that might lead to the future improvement of symptomatic limb ischemic patients on HD. A prospective randomized controlled trial is needed to reveal further information.

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FROM-J

筑波大学大学院人間総合科学研究科疾患制御医学専攻腎臓病態医学分野
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KEY WORDS
●慢性腎臓病
●戦略研究
●FROM-J

はじめに

近年，慢性腎臓病（Chronic Kidney Disease；CKD）が注目されるようになった背景には，わが国で1,300万人ものCKD患者が存在すること[1]や，CKDが心血管病のリスクファクターであると証明されたことがある。またわが国で年々増え続ける透析患者数の増加を抑制するためにも，その原因であるCKDの対策が急務である。

CKDは肥満や喫煙，高血圧，糖尿病や脂質異常症と密接な関連があり，生活習慣の是正を行うことでCKDの発症および進展防止につながる可能性は十分にある。そのためにはCKD啓発活動を広く社会や市民，医療従事者に行い，一般住民から医療従事者，行政から医療機関に至るまで相互に連携して行う医療連携が必要となる。こうした連携が普及するためには，全国に汎用できるような診療システムの構築が必要である。

厚生労働省は，2007年度の戦略研究のテーマとして腎臓病を採択し，腎臓病の重症化防止のための方策として，かかりつけ医/非腎臓専門医と腎臓専門医の連携を促進するための診療システムの有用性を検討する研究「腎疾患重症化予防のための戦略研究（Frontier of Renal Outcome Modification in Japan；FROM-J）」が開始された。本稿ではFROM-Jの概略と今後の展望について述べる。

Ⅰ．戦略研究の概要について

戦略研究とは，わが国を支える多くの国民の健康を維持・増進させるために，優先順位の高い慢性疾患・健康障害を標的として，その予防・治療介入および診療の質改善介入など，国民の健康を守る政策に関連するエビデンスを生み出すために実施される大型の臨床介入研究である[2]。これまでに2005年度の「糖尿病予防に関する戦略研究」，

FROM-J
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「自殺関連うつ予防に関する戦略研究」に始まり，2006年度の「がん戦略研究」，「エイズ戦略研究」に続き，2007年度に「腎臓病戦略研究」，「感覚器戦略研究」がテーマとして取り上げられてきた。

戦略研究の目標は，「アウトカム研究」あるいは「診療直結研究」である。

「アウトカム研究」とは，実際の医療現場で提供される検査法や治療法などの医療サービスのばらつきと患者アウトカムとの関連，影響を分析する研究であり，発症率・重症化率・死亡率などとともに，QOLや患者満足度，入院・病欠・医療資源活用，費用対効果分析などの指標を取り入れることが特徴である。「アウトカム研究」の意義には，「研究成果が，診療上の意思決定をよりよく行うためのエビデンスとして，診療現場に還元される」こと，「研究成果が，診療現場での臨床家の行動を変える」こと，「研究成果が，医療政策や制度にインパクトを与える」こと，「研究成果により患者や国民の健康アウトカムが改善する」こと，が含まれる。

「診療直結研究」は，臨床医の診療上の疑問を一定の仮説に構造化して検証する研究であり，前述のアウトカム研究とも重複しうる。そのテーマには，「診断法の選択と有効性に関する研究」と，「診療の質測定と改善に関する研究」がある。特に後者は，質の高いエビデンスをできるだけ速やかに臨床の場に普及させる方策を講じ，「エビデンス-診療ギャップ」を解消する方策の1つである。

Ⅱ．研究課題と成果目標

腎臓病が戦略研究のテーマの1つとして採択された背景には，前述のようにCKD対策が急務であることが大きい。今回の腎臓病戦略研究においては，かかりつけ医/非腎臓専門医と腎臓専門医の連携を促進することが重要課題であると厚生労働省より提唱された。かかりつけ医/非腎臓専門医におけるCKDの早期発見および血圧・血糖管理や食事療法の厳格な管理や，腎臓専門医との連携を密接に行うことで，CKDの診療に早期から取り組み進展防止を図ることを目的の1つとしている。そこで本研究の課題名は「かかりつけ医/非腎臓専門医と腎臓専門医の協力を促進する慢性腎臓病患者の重症化予防のための診療システムの有用性を検討する研究」と定められ，主要評価項目と副次評価項目が設定された。

主要評価項目は①受診継続率，②かかりつけ医/非腎臓専門医と腎臓専門医の連携達成，③CKDのステージ進行率の3つであり，副次評価項目としては①CKD診療目標の実施率，②血圧の管理目標達成率，③尿蛋白50％減少達成率，④血清クレアチニン値の2倍化到達数，eGFR50％低下到達，⑤新規透析導入患者数の年次推移，⑥心血管系イベントの発生率があげられている。

成果目標はCKD診療ガイドの遵守率，達成目標の達成度を上げることとされ，その結果として5年後の透析導入患者を5年後に予測される導入数の15％減少になることが期待されている。

Ⅲ．研究デザインと体制

FROM-Jの研究実施団体は財団法人日本腎臓財団(酒井　紀理事長)が選定され，研究リーダーは公募により，筑波大学大学院人間総合科学研究科疾患制御医学専攻腎臓病態医学分野 山縣邦弘が選定された。

本研究においては，かかりつけ医と腎臓専門医との連携が評価項目の1つとなっているため，個々の患者の評価を行うだけではなく，地域すなわち地区医師会単位での連携も評価する必要がある。このため研究デザインは地区医師会をクラスターとして，介入方法をクラスターごとに割り付けるクラスターランダム化比較研究が提案された。地区医師会の選定にあたっては，新規透析導入者数の増加率により全国を4つのブロックに分割し，公募により全国から15の幹事施設が選定され，幹事施設により全国で49の参加地区医師会が選定された。

本研究の実施にあたっては日本医師会の協力を得て，都道府県医師会を介して，参加地区医師会へかかりつけ医の参加登録の呼びかけと継続的な研究への協力要請が行われた。またかかりつけ医が円滑に病診連携を達成できるように，腎臓専門医に紹介を広く受け入れる態勢を整えるため，日本腎臓学会より腎臓専門医へ研究への参加協力が要請された。日本栄養士会においては，全国都道府県の病院栄養士協議会とともに，各地区の栄養ケアステーションへ研究への協力を要請し，FROM-Jの生活・食事指導を担う管理栄養士の人選および手配が行われた。このように各方面の強力なサポートの存在が本研究を支えている。

Ⅳ．対象患者と研究期間

FROM-Jで対象となるCKD患者の条件は，①年齢が40歳以上75歳未満，②CKDステージ1，2および4，5の

表．CKDの診療目標

CKDステージ	生活習慣改善	食事指導	血圧管理	血糖管理	脂質管理	貧血管理
ステージ1	禁煙 BMI＜25kg/m^2	高血圧があれば 減塩6.0g/日未満	130/80mmHg未満	HbA_{1c} 6.5％未満	LDL-cho 120mg/dL未満	腎性貧血以外の 原因検索
ステージ2	禁煙 BMI＜25kg/m^2	高血圧があれば 減塩6.0g/日未満	130/80mmHg未満	HbA_{1c} 6.5％未満	LDL-cho 120mg/dL未満	腎性貧血以外の 原因検索
ステージ3	禁煙 BMI＜25kg/m^2	減塩6.0g/日未満 蛋白質制限 0.6～0.8g/kg体重/日	130/80mmHg未満	HbA_{1c} 6.5％未満	LDL-cho 120mg/dL未満	Hb 10g/dL以上 12g/dL未満
ステージ4	禁煙 BMI＜25kg/m^2	減塩6.0g/日未満 蛋白質制限 0.6～0.8g/kg体重/日 高K血症あればK制限	130/80mmHg未満	HbA_{1c} 6.5％未満	LDL-cho 120mg/dL未満	Hb 10g/dL以上 12g/dL未満
ステージ5	禁煙 BMI＜25kg/m^2	減塩6.0g/日未満 蛋白質制限 0.6～0.8g/kg体重/日 高K血症あればK制限	130/80mmHg未満	HbA_{1c} 6.5％未満	LDL-cho 120mg/dL未満	Hb 10g/dL以上 12g/dL未満
備考			蛋白尿1.0g/gCr以上は 125/75mmHg未満			

患者，③CKDステージ3の場合は，尿蛋白を有し，糖尿病あるいは高血圧を有していること，と設定した。CKDステージ3の登録条件の理由は，最も人数の多いCKDステージ3の患者のなかで，腎機能悪化の危険性の高い患者を対象とするためである[3)-5)]。

目標症例数の設定にあたり，成果目標である5年後の新規透析導入数の予測数より15％減少をもとに，介入によりGFRの悪化速度を15％改善させるために必要な症例数の設定を，日本腎臓学会CKD対策委員会疫学ワーキンググループのデータ[6)]および，糖尿病性腎症のGFR低下速度のデータ[7)]より算出したところ，10％の脱落を加味し，全体で2,264例の登録数が必要であることがわかった。そこで今回の目標症例数を2,500例と設定した。研究を開始するにあたり，491名のかかりつけ医，2,494名の参加者の登録連絡があり，2,413名が最終的に登録された。

V．介入方法

FROM-Jでは，CKD診療ガイドに準拠して診療にあたる介入A群と，介入A群の内容に加え，参加者への受診促進支援，かかりつけ医への目標達成度の外部評価を定期的に行い，管理栄養士による生活・食事指導を行う介入B群の2つを設定し，その効果を比較検討する。

2007年に発刊された「CKD診療ガイド」[2)]には，CKDステージごとに生活習慣，食事内容，血圧，血糖，脂質などの診療目標(表)や，腎臓専門医への紹介のタイミングが記載されており，本研究では両群において診療目標や紹介基準の達成率と遵守率を評価する。腎臓専門医への紹介の基準はCKD診療ガイドに則り，①尿蛋白2＋以上または尿蛋白が0.5g/gCr以上，②尿蛋白1＋以上かつ尿潜血1＋以上，③推算GFR＜50mL/min/1.73m^2，④その他，医師が必要と認めた場合，の4項目とした。

生活・食事指導では，各地域の栄養ケアステーションに所属する管理栄養士が3ヵ月に1回，かかりつけ医の医療機関内で1回当たり約30分の個別指導を行う。指導内容については，全国の介入B群で均質な指導を行うためのマニュアルや指導講習会の開催を行い，すべての参加管理栄養士に受講を義務付けている。

参加者登録終了後に地区医師会ごとに介入A群，介入B群の割付が行われ，介入A群の参加者数は1,211名，介入B群は参加者数1,202名となった。各介入群の参加者の属性を図1，図2，図3に示す。2008年10月20日よりそれぞれの介入を開始，2012年3月まで継続する予定である(図4)。