

## Entity of Stage 4 CKD over 75 Years Old is Different from that of Less than 75 Years of Age: Characteristics of Elderly Patients with Stage 4 CKD

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### Abstract

**Background:** Although age had a strong effect on the risk of development to end-stage renal disease (ESRD), it is reported that stage 4 CKD patients aged >75 years were less likely to subsequently commence renal replacement therapy (RRT) than those aged <75 years. In the present study, the longitudinal follow-up of elderly patients with stage 4 CKD was carried out in a single center in order to evaluate the prognosis of the patients >75 years in comparison with those between 74 and 65 years and to characterize patients with stage 4 CKD older than 75 years.

**Methods:** This was a prospective, observational, single-center cohort study. Patients were recruited from specialist renal clinics from January 2004 to December 2005. All participating patients were followed for 5 years or until death, commencement of dialysis therapy, receiving renal transplantation, finding of neoplasm, or occurrence of a cardiovascular event. We utilized electronic databases to determine the incidence of RRT and morbidity.

**Results:** The underlying renal disease of CKD included diabetic nephropathy (DM) (91 patients, 51%) chronic glomerulonephritis (GN) (41 patients, 23%), hypertensive nephrosclerosis (HT) (44 patients, 25%), and other diseases (3 patients, 1%) in the younger group (74 and 65 years) and DM (24 patients, 23%), GN (24 patients, 23%), HT (54 patients, 51%), and other diseases (4 patients, 4%) in the elderly population (older than 75 years). A proportion of the underlying renal diseases were significantly different between the two groups. In the elderly group, the prevalence of diabetic nephropathy was significantly lower ( $P<0.01$ ) and that of HT was significantly higher ( $P<0.01$ ). The incidence-free rates at 1 year and 3 years were 90% and 81% in the elderly group and those were 90% and 57% in the younger group, respectively. In the patients without diabetic nephropathy, introduction to RRT was significantly lower compared with those with diabetic nephropathy in the younger group ( $P<0.05$ ). The incidence-free rates at 1 year and 3 years were 88% and 80% in the patients without diabetic nephropathy and those were 87% and 38% in the patients with diabetic nephropathy, respectively. In the late referral patients, the prevalence of diabetic nephropathy were significantly higher and that of GN and HT were significantly lower compared with those of the non-late referral patients ( $P<0.01$ ).

**Conclusions:** From these findings, it is concluded that in the patients >75 years, the values of eGFR may be overestimated and a prognosis of diabetic nephropathy was poor. Besides, the early nephrology referral is encouraged.

**Keywords:** eGFR; Late nephrology referral; Diabetic nephropathy; Renal replacement therapy

### Introduction

The proportion of older people in the general population is steadily increasing and the fastest growing segment of that population during the past decade is older than 75 years. With this increase in prevalence of elderly people, proportion of prevalent chronic kidney disease (CKD) increased in parallel [1,2]. In spite of these situations, the appropriate treatment of older patients with CKD remains unclear. Moreover, there are a lot of unresolved problems in real world [3]. For example, are there any differences in underlying renal diseases in CKD patients <75 and >75 years?; what are the age-related risk factors for progression to end-stage renal disease (ESRD) and incidence of cardiovascular disease (CVD) [4,5]; is a chance of more cohesive multidisciplinary team approach to CKD producing catastrophic results in elderly CKD patients [6]. Previous reported cross sectional cohort studies failed to reveal what factors are more important for progression to ESRD and for occurrence of CVD in these populations [7]. Besides, it still remains uncertain whether the effects of multidisciplinary care are beneficial or not. Two studies correlated multidisciplinary care with modest improvements in survival [8], but another study showed no differences in kidney function or mortality between patients who received multidisciplinary, intensive care and those who did not [6].

Therefore, in the present study, the longitudinal follow-up of elderly patients with stage 4 CKD was carried out in a single center in

order to evaluate the characteristics and the prognosis of stage 4 CKD patients >75 years in comparison with those between 74 and 65 years and outcome of late nephrology referral in these patients.

### Subjects and Methods

This was a prospective, observational, single-center cohort study. This study was conducted in accordance with the Declaration of Helsinki. Approval for the study was obtained from the Saitama Medical University Ethics Committee, and written informed consent was obtained from each participant.

Patients were recruited from specialist renal clinics at Kidney

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Disease Center, Saitama Medical University from January 2004 to December 2005. All participating patients were followed for 5 years or until death, commencement of renal replacement therapy (RRT), finding of neoplasm, or occurrence of a cardiovascular event (fatal or non-fatal myocardial infarction, cerebrovascular disease, aortic dissection). Accordingly, the main outcomes were death, introduction to RRT, occurrence of neoplasm, and cardiovascular events including fatal and non-fatal disease. Electronic databases were used to obtain information. Inclusion criteria were stage 4 CKD as defined by K/DOQI [9], not yet on dialysis, followed up for at least 6 months stable renal function within the last 3 months ( $<5 \text{ mL/min/1.73 m}^2$  change in GFR), and no change in medication in the preceding 3 months in our renal specialist clinic. eGFR was calculated using a modified three-variable equation for eGFR in Japanese patients:  $\text{eGFR} = 194 \times \text{Age}^{0.287} \times \text{SCr}^{-1.094} (\times 0.739, \text{ if female})$ , where SCr = serum creatinine [10].

Exclusion criteria included known left ventricular dysfunction (ejection fraction  $<50\%$ ), or signs and symptoms of congestive heart failure, significant valvular or coronary heart disease, and use of sedative or hypnotic drugs or any other drugs potentially affecting blood pressure during ambulatory monitoring, e.g., corticosteroids.

Late referral was defined as the patients who were referred from general physician based clinic during the recruitment of this study.

Diabetes mellitus (DM) was defined as HbA1c 5.8% or higher or taking anti-diabetics including insulin. Glomerulonephritis (GN) was defined by biopsy or clinical diagnosis such as urine casts including unregulated red cells. The cause of CKD was assessed by reviewing the clinical history and investigations. Patients were classified as "hypertensive/glomerulosclerosis" if the patients had no clear evidence of active renal disease but had a history of hypertensive diseases and positive urinary protein excretion without casts.

Patients were followed every month during the study period. At each clinic visit, serum creatinine, electrolyte concentrations, complete blood count, and other serum chemistries (uric acid, glucose, and liver enzymes) were measured. Chest radiographs and electrocardiography were obtained every year.

During the study, target home blood pressure (BP) was 130/85 mm Hg or lower and home BP measurements were encouraged [11]. The selection of an antihypertensive agent depended on the physicians' preference. All patients were treated with antihypertensive drugs including renin-angiotensin inhibitors, and blood pressure was well-controlled in all patients [12,13].

Subjects were treated with recombinant human erythropoietin (rHuEPO) as necessary and their hemoglobin levels were maintained between 11 to 12 g/dL [14]. Subjects were given oral iron supplementation if they were diagnosed with iron deficiency.

Subjects with parathyroid hormone levels greater than 300 pg/ml were treated with  $1,25(\text{OH})_2\text{D}_3$  and  $\text{CaCO}_3$  supplements, while patients with levels lower than 70 pg/ml were treated with  $\text{CaCO}_3$  to reduce the degree of hyperphosphatemia. Doses were adjusted based on serum levels of calcium and phosphate. Lipid lowering drugs, primarily statin derivatives, were administered if serum cholesterol levels exceeded 240 mg/dl [15].

### Statistical Analysis

Statistical analyses were performed using JMP software, version 9 (JMP, A Business Unit of SAS, Cary, NC USA). Values are given as the mean  $\pm$  SD. Statistical analysis was performed using Student's "t-test"

for comparing means of unpaired variables (or Mann-Whitney tests when applicable). Comparison of more than two sets of unmatched data were performed by one-way of analysis of variance (ANOVA) using the Tukey-test or Kruskal-Wallis tests dependent on the distribution.

Patient event free curves were calculated by the Kaplan-Meier life-table analysis method, and differences between the groups were evaluated by the log-rank test. Subgroups were compared using the  $\chi^2$ -test for categorical values and continuous variables. P values  $<0.05$  were regarded as statistically significant.

### Results

Two hundred and eighty five elderly patients with stage 4 CKD were enrolled in this study. Their baseline characteristics are summarized in the (Table 1). There were no differences in eGFR between the two groups, however, a proportion of the underlying renal diseases were significantly different between the two groups. In the elderly group, the prevalence of diabetic nephropathy was significantly lower ( $P < 0.01$ ) and that of HT was significantly higher ( $P < 0.01$ ). In the (Table 2), the hemodynamic variables and laboratory findings are shown. Among these variables, the levels of diastolic blood pressure were significantly lower in patients of the elderly group compared with that of the younger population ( $P < 0.05$ ). In the (Table 3), there were no significant differences except HbA1c, which was significantly lower in the patients with non-diabetic nephropathy, between the two groups ( $P < 0.01$ ). In the (Table 4), a comparison of underlying renal disease between the total patients and the patients who were referred during the recruitment period (late referral) is shown. In the late referral patients, the prevalence of diabetic nephropathy were significantly

Variables	Younger Group	Elderly Group
Number	179	106
Age (years)	70.8 $\pm$ 2.0	79.2 $\pm$ 2.6*
Male (%)	106/73	58/48
eGFR (ml/min/1.73m <sup>2</sup> )	21.6 $\pm$ 3.3	22.1 $\pm$ 4.1
Underlying disease(male/female)(%)		
DM	91 (60/31)(51)	24**(15/7)(23)
GN	41 (25/16)(23)	24 (17/9)(23)
HT	44 (18/26)(24)	54**(25/29)(51)
others	3 (3/0)(2)	4 (1/3)(3)
Late Referral (male/female) (%)	44 (28/16)(25)	23 (11/12)(22)

Values are expressed as mean $\pm$ SD. eGFR, estimated glomerular filtration; DM, diabetic nephropathy; GN, glomerular nephritis; HT, hypertensive nephrosclerosis. \*\* indicates  $P < 0.01$  compared with younger group.

Table 1: Patients Characteristics.

Variables	Younger group	Elderly group
Number	179	106
SBP (mmHg)	137.5 $\pm$ 13.7	140.9 $\pm$ 18.3
DBP (mmHg)	81.9 $\pm$ 6.1	77.9 $\pm$ 6.5*
HR (beats/min)	72.3 $\pm$ 8.6	68.3 $\pm$ 5.4
Serum albumin (g/dL)	4.0 $\pm$ 0.3	3.8 $\pm$ 0.6
Hemoglobin (g/dL)	11.6 $\pm$ 0.7	11.2 $\pm$ 0.8
Total cholesterol (mg/dL)	189.2 $\pm$ 42.3	177.2 $\pm$ 46.3
Phosphate (mg/dL)	4.1 $\pm$ 1.7	4.3 $\pm$ 1.5
Calcium (mg/dL)	9.1 $\pm$ 1.1	9.4 $\pm$ 1.0
Urinary protein excretion (g/gCr)	1.34 $\pm$ 0.88	1.23 $\pm$ 0.90

Values are expressed as mean $\pm$ SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

\* indicates  $P < 0.05$  compared with younger group.

Table 2: Baseline characteristics of the study population.

Variables	DM nephropathy		Non DM nephropathy	
	75<	75≥	75<	75≥
Number	91	24	88	82
eGFR (ml/min/1.73m <sup>2</sup> )	21.4± 2.3	22.1 ± 4.0	22.1 ± 4.1	22.1 ± 4.5
SBP (mmHg)	121.6± 32.2	133.8 ± 20.2	136.5 ± 12.9	135.2 ± 19.5
DBP (mmHg)	82.4 ± 7.0	74.4 ± 16.6*	82.6± 7.2	77.1 ± 12.5*
HR (beats/min)	71.4± 7.9	69.2 ± 4.5	73.0 ± 7.6	67.8 ± 6.3
Serum albumin (g/dL)	4.0 ± 0.3	3.8± 0.6	4.0 ± 0.3	3.8 ± 0.6
Hemoglobin (g/dL)	12.4 ± 1.8	11.2 ± 0.8	12.8 ± 0.7	12.6 ± 0.8
Total cholesterol (mg/dL)	189.2 ± 42.3	177.2 ± 46.3	186.2 ± 32.7	175.1 ± 38.7
Phosphate (mg/dL)	3.7 ± 1.9	3.5± 1.0	4.1 ± 2.0	3.5 ± 0.9
Calcium (mg/dL)	9.2 ± 0.6	9.0± 0.5	9.1 ± 0.7	9.6 ± 0.4
Urinary protein excretion (g/gCr)	1.34 ± 0.88	1.23 ± 0.90	0.98 ± 1.22	0.88 ± 1.15
HbA1C (%)	6.3± 0.4	6.1± 0.6	5.2 ± 0.3**	5.1 ± 0.6**

Values are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

\*indicates P<0.05 compared with the values of each corresponding of younger group and \*\* indicates P<0.01 compared with the patients with DM nephropathy of each corresponding age.

**Table 3:** Comparison of variables between DM and non DM nephropathy.

Variables	Non late referral		Late Referral	
	75<	75≥	75<	75≥
group				
Number (%)	135 (62)	83 (38)	44 (66)	23 (34)
DM	56 (41)	7 (8)	35 (80)**	17 (74)**
GN	37 (32)	21 (63)	4 (9)**	3 (12)
HT	42 (27)	52 (27)	2 (5)**	2 (9)**
Others	0	1 (2)	3 (6)	

Values are expressed as count (percentage). DM, diabetic nephropathy; GN, glomerular nephritis; HT, hypertensive nephrosclerosis. \*\*indicates P<0.01 compared with the values of each corresponding age.

**Table 4:** Comparison of underlying disease of patients between non late referral population and late referral.

higher and that of GN and HT were significantly lower compared with those of the non-late referral patients (P<0.01).

The (Table 5) shows a comparison of the hemodynamic variables and laboratory findings between the late nephrology referral patients and those of the non-late referral patients. The levels of serum calcium were significantly lower and those of serum phosphorus were significantly higher (P<0.05). In the (Table 6), the causes of withdrawal of patients are shown. In both groups, introduction to RRT was the leading cause of withdrawal of the study and in the younger group, the prevalence of introduction to RRT as the cause of withdrawal from the study was significantly higher compared with that in the elderly group (P<0.01). A Kaplan-Meier curve for event free of the patients is shown in (Figure 1). The incidence-free rates at 1 year and 3 years were 90% and 81% in the elderly group and those were 90% and 57% in the younger group, respectively. There is a significant difference between the two groups (log rank test; P=0.008). In the (Table 7), comparison of events between the patients with and without diabetic nephropathy is shown. As the total, event free rate were significantly higher in the patients with diabetic nephropathy compared with those without diabetic nephropathy in both younger and elderly groups (P<0.05 and P<0.01, respectively). In addition, in the patients without diabetic nephropathy, introduction to RRT was significantly lower compared with those with diabetic nephropathy in the younger group (P<0.05). A Kaplan-Meier curve for event free obtained from the patients with or without diabetic nephropathy is shown in (Figure 2). The incidence-free rates

at 1 year and 3 years were 88% and 80% in the patients without diabetic nephropathy and those were 87% and 38% in the patients with diabetic nephropathy, respectively. There is a significant difference between the two groups (log rank test; P=0.003). In the (Table 8), a comparison of events between the late referral patients and the non-late referral patients is shown. The rate of introduction to RRT was significantly

Variables	Non late referral		Late referral	
	75<	75≥	75<	75≥
Age (years)	75<	75≥	75<	75≥
Number	135	83	44	23
Gender (male/female)	(78/57)	(47/36)	(28/16)	(11/12)
eGFR (mL/min/1.73 m <sup>2</sup> )	21.7± 4.3	22.7 ± 3.9	23.1 ± 5.1	23.1 ± 4.9
SBP (mmHg)	128.6 ± 18.2	130.5 ± 16.3	145.2 ± 13.1	141.2 ± 11.9
DBP (mmHg)	81.5 ± 6.7	75.3 ± 15.9	83.6 ± 4.9	73.2 ± 11.4
HR (beats/min)	72.3 ± 6.6	68.1 ± 4.3	71.6 ± 7.5	66.6 ± 7.2
Serum albumin (g/dL)	4.1 ± 0.4	3.9 ± 0.7	3.6 ± 0.9	3.8 ± 1.2
Hemoglobin (g/dL)	12.6 ± 0.7	12.1 ± 0.9	11.3 ± 0.7	11.2 ± 0.9
Total cholesterol (mg/dL)	200.6± 35.3	180.8 ± 28.7	201.3 ± 36.7	172.1 ± 35.3
Phosphate (mg/dL)	3.6± 1.1	3.3 ± 1.0	5.0 ± 1.8*	4.8 ± 0.7*
Calcium (mg/dL)	9.6 ± 0.5	9.8 ± 0.3	8.1 ± 1.1*	8.4 ± 1.5*
Urinary protein excretion (g/gCr)	1.12 ± 0.66	1.00 ± 0.88	1.42 ± 1.34	1.31 ± 1.21

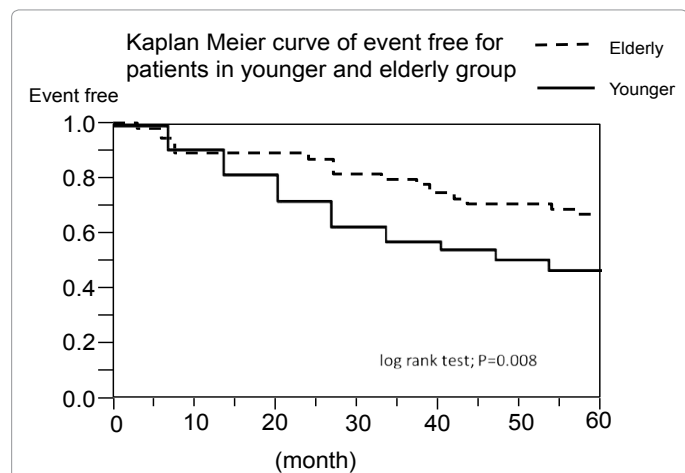
Values are expressed as mean±SD. \* indicates P<0.05 compared with the values of total.

**Table 5:** Comparison of baseline characteristics between non late referral population and patients with late referral.

Variables	Younger Group	Elderly Group
Number	100	35
RRT	75(75)	15(42)**
Myocardial Infarction	5(5)	4(12)
Cerebrovascular Diseases	5(5)	4(12)
Heart Failure	10(10)	6(17)
Neoplasma	5(5)	5(14)
Others		1(3)

Values are expressed as count (percentage). RRT, renal replacement therapy. \*\*indicates P<0.01 compared with younger group.

**Table 6:** Comparison of events between patients in younger and elderly group.

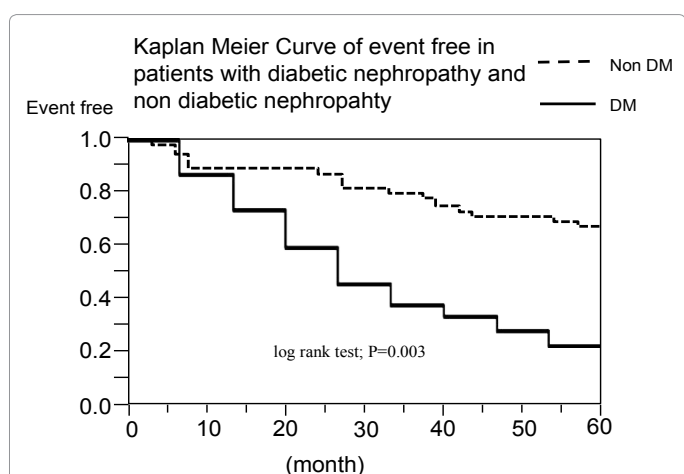


**Figure 1:** A Kaplan-Meier curve for event free of the patients in the younger and the elderly group. The incidence-free rates at 1 year and 3 years were 90% and 81% in the elderly group and those were 90% and 57% in the younger group, respectively. There is a significant difference between the two groups (log rank test; P=0.008).

Variables	DM		Non DM	
Age (years)	75<	75≥	75<	75≥
Number	91	24	88	82
RRT	48 (53)	10 (58)	27* (64)	5 (30)
Myocardial infarction	3 (5)	2 (12)	2 (5)	2 (12)
Cerebrovascular disease	1 (2)	2 (12)	4 (10)	2 (12)
Heart failure	3 (5)	2 (12)	7 (16)	4 (23)
Neoplasms	3 (5)	1 (6)	2 (5)	4 (23)
Total (%)	58 (64)	17 (70)	42* (48)	17** (21)

Values are expressed as count (percentage). DM, diabetic nephropathy; RRT, renal replacement therapy. \* indicates P<0.05 and \*\* indicates P<0.01 in comparison with DM group.

**Table 7:** Comparison of events between patients with diabetic nephropathy and non diabetic nephropathy.



**Figure 2:** A Kaplan-Meier curve for event free obtained from the patients with or without diabetic nephropathy. The incidence-free rates at 1 year and 3 years were 88% and 80% in the patients without diabetic nephropathy and those were 87% and 38% in the patients with diabetic nephropathy, respectively. There is a significant difference between the two groups (log rank test; P=0.003).

Variables	Non late referral		Late Referral	
Age	75<	75≥	75<	75≥
Number (percentage)	67 (70)	28 (30)	33 (82)	7 (18)
RRT	45 (67)	9 (32)	30 (91)**	6 (86)**
Myocardial infarction	5 (7)	4 (14)	0	0
Cerebrovascular disease	3 (4)	3 (11)	2 (6)	1 (14)
Heart failure	10 (15)	6 (21)	0	0
Neoplasms	4 (7)	5 (18)	1 (3)	0
Others	0	1 (4)	0	0

Values are expressed as count (percentage). RRT, renal replacement therapy. \*\* indicates P<0.01 in comparison with non late referral patients corresponding the same age group.

**Table 8:** Comparison of events between non late referral population and late referral patients.

higher in the late referral patients compared with those of the non-late referral patients in both the younger and the elderly groups (P<0.01). A Kaplan-Meier curve for event free obtained from the late referral patients and the non-late referral patients is shown in (Figure 3). The incidence-free rates at 1 year and 3 years were 94% and 80% in the total population and those at 1 year and 3 years were 94% and 64% in the late nephrology referral patients. There was a significant difference between the two groups (P<0.05). In the (Table 9), a comparison of causes of introduction to RRT between the patients in the younger and the

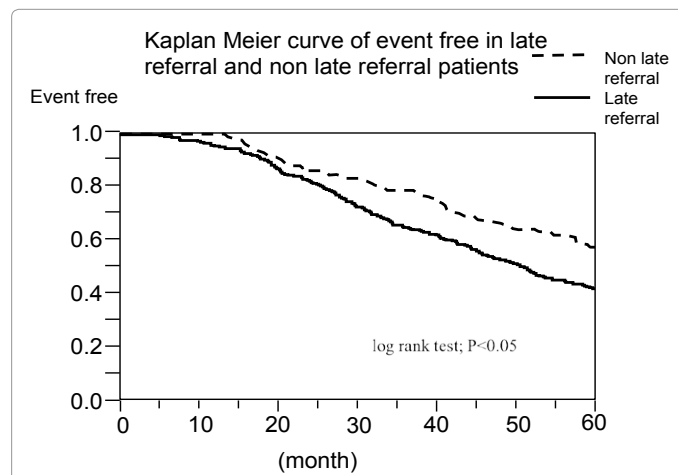
elderly group is shown. In the patients in the elderly group, the reasons of introduction to RRT due to decreases in eGFR were significantly lower and those in over hydration were significantly higher (P<0.01) compared with those in the patients in the elderly group.

Selection of modalities for dialysis therapy showed a significant difference between the patients in the younger and the elderly group and between the total population and the late referral patients (Figures 4 and 5). In the patients in the elderly group selected continuous ambulatory peritoneal dialysis (CAPD) therapy more frequently compared with those in the younger group (P<0.05). However, there were no significant differences in frequency of selection between the late referral patients and the total population.

## Discussion

This long-term prospective observation study provided the following findings. First, event free ratio was significantly higher in the elderly patients compared with the younger patients in stage 4 CKD. Second, diabetic nephropathy had a higher incidence of events compared with the patients without DM nephropathy. Third, late referral produced higher incidence of events compared with the patients regularly cared by nephrologist. Lastly, the elderly patients preferred CAPD as dialysis modality compared with the younger patients.

Age difference in the prognosis observed here probably reflects a variety of different phenomena. The lower incidence of introduction to RRT among the elderly group compared with the younger group

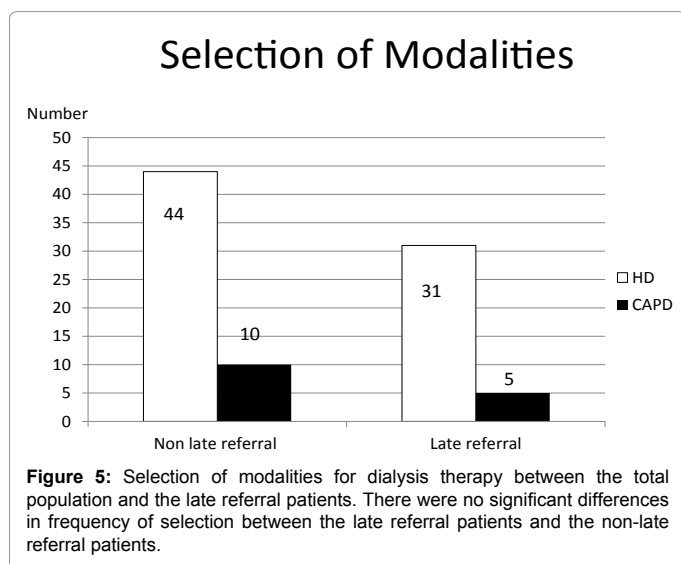
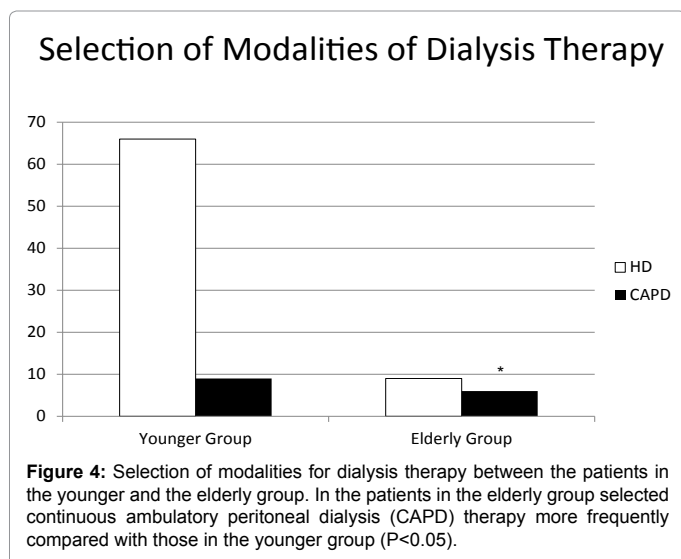


**Figure 3:** A Kaplan-Meier curve for event free obtained from the late referral patients and the total population. The incidence-free rates at 1 year and 3 years were 94% and 80% in the total population and those at 1 year and 3 years were 94% and 64% in the late nephrology referral patients. There was a significant difference between the two groups (P<0.05).

Variables	Younger Group	Elderly Group
Number	75	15
Decreases in eGFR	55 (73)	4 (26)**
Overhydration	10 (13)	6 (40)**
Anemia	1 (1)	1 (7)
Increases in Serum Potassium	1 (1)	3 (20)
Anorexia	8 (11)	1 (7)

Values are expressed as count (percentage). GFR, glomerular filtration rate. Number and (%) \*\* indicates P<0.01 compared with younger group.

**Table 9:** Comparison of reasons for introduction of dialysis therapy between younger and elderly patients.



with similar levels of eGFR is likely due, at least in part to their greater proportion of diabetic nephropathy as the underlying cause of renal disease. In addition, in the elderly group, the prevalence of HT and GN were significantly greater. These renal diseases are known to be slowly progressive disease [16,17].

Previously, Lindeman [18] reported that the rate of decline of inulin or creatinine clearance increase as patients aged. However, recently O'Hare et al. have demonstrated the contrast findings in that older age was associated with slower decline in eGFR [3]. First, there is 20 years difference between the two studies was carried out. During the two decades, an innovative formula for evaluation of renal function, eGFR, was introduced [19]. This formula is dependent on both age and serum creatinine. If aging produces decreases in muscle mass, eGFR is underestimated. Or conversely, the effects of age on eGFR are overestimated. Combining with these two factors, evaluation of renal function using eGFR formula will need some cautions. Second, several interventions [20] such as antihypertensive agents, especially the renin-angiotensin inhibitors [13], rHuEPO [14], phosphate binders [21] and so on, will decrease morbidity and mortality. These two major factors might relate to slower development to ESRD in the patients in

elderly group. Similar findings were previously reported by Eriksen and Ingebretsen [22] demonstrated that 27% had no decline in eGFR for 10 years in a population of patients average age 75 with a baseline eGFR of 25-55 ml/min/1.73m<sup>2</sup>. In contrast to the reported data, in which the incidence of stage 4 CKD patients were higher than that of development to RRT, the present data showed that CVD was less even in patients with diabetic nephropathy. These data might reflect the incidence of CVD in Japanese general population, in which CVD is less prevalent in proportion of causes of death than that of Western countries [23,24]. The proportion of DM was more prevalent in 64-75 patients than patients >75. In Japan DM was diagnosed at the age of around 40 years and DM nephropathy is the most prevalent in aged 60 years. Since prognosis of DM nephropathy is expected to be less than 10 years, the patients with DM nephropathy are unable to survive more than 75 years [25]. Besides, in the patients aged >75 years, HT is the leading cause of the underlying renal disease in the present study. The cause of nephrosclerosis still remain unclear [26] and some investigators reported that nephrosclerosis is not a product of long term of hypertension [27] and/or atherosclerosis. In elderly CKD 3 to 5 stage patients, there is no decisive renal biopsy proven data for the causes of renal diseases. Generally, the cause of age-related increases in renal fibrosis, which is supposed lead to glomerular sclerosis, interstitial fibrosis, tubular atrophy, vascular sclerosis, and loss of renal function, is poorly understood [3]. Moreover, at the time of when CKD is found in elderly people, the kidneys are already shrunken and nephrologists hesitate to attempt to do renal biopsy.

Recently Smart [28] reported the results of meta-analysis discussing the outcomes of early versus late nephrology referral in CKD patients. In their large meta-analysis, early nephrology referral reduced mortality and hospitalization, better uptake of PD, and earlier placement of arteriovenous fistula for HD in comparison with late nephrology referral. In the present study, a large proportion of the late referral patients were diabetic nephropathy. Moreover, during 5-year observation period, the incidence of introduction to RRT was greater than the total population of the present study. Compared with the other renal specialist clinic, the rate of hospitalization was not counted. However, the rate of selection of dialysis modalities was similar, in which PD was not selected by the late referral patients.

In the present study, we did not count the death rate, because no sudden death was noted and some patients died during hospitalization and some did after introduction to RRT. In these situations, it was very difficult to determine when a patient was dead. With this regard, death rate was not counted.

Several investigators demonstrated that proteinuria was strongly associated with introduction to RRT [2,29], however, our analysis failed to determine a role of proteinuria. This might be due to heterogeneity of underlying renal diseases, because other data were based on population study, in that the prevalence of diabetic nephropathy was less.

### Study Limitations

First, this study was conducted in a single center and the results may be less generalizable to other settings. However, the early nephrology referral would be recommended and moderately advanced CKD elderly patients, evaluation of eGFR must be cautious. Second, the number of participated patients was small and more number of these patients is absolutely needed to finalize our current findings. Third, in the present study, patients with hypertension and renal failure without evidence of primary renal disease or DM nephropathy are intentionally diagnosed as having hypertensive renal disease.

Recently since incidence of ischemic nephropathy is suggested to be higher than previously reported [30,31], possibilities of renovascular disease due to atherosclerosis should be considered. In the present study, this diagnosis was not applicable to the participated patients. In spite of these several limitations, this study was carried out in a single center cancelling out the heterogeneity produced by center-to-center interactions.

In summary, this 5-year prospective observation study demonstrated that, if elderly people > 65 years is divided into 2; 65-74 and >75 years in CKD patients, a proportion of the underlying renal disease was completely different. In the elderly patients >75 years, HT nephrosclerosis and GN were predominant. In contrast, in the patients 65 to 74 years, diabetic nephropathy was predominant. In addition, the ratio of development to RRT was higher in the patients 65 to 74 years, probably being due to a large proportion of diabetic nephropathy as the leading cause of renal disease. Second, a prognosis of diabetic nephropathy, regardless of age groups, was poor. Third, a prognosis of the late referral patients was also not well.

From these findings, it is concluded that in the patients >75 years, the values of eGFR may be overestimated and a prognosis of diabetic nephropathy was poor. And lastly, the early nephrology referral is encouraged.

## Conflict of Interest

The authors declare that they have no conflicts of interest in this study.

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