

An Analysis of Elderly End-stage Chronic Kidney Disease Patients Who Did Not Undergo Renal Replacement Therapy in Japan

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ABSTRACT: There is little descriptive information regarding the conservative management of Japanese end-stage chronic kidney disease (CKD) patients. We carried out a retrospective case series analysis of elderly Japanese end-stage CKD patients who were hospitalized and died without the provision of renal replacement therapy (RRT) programs. A total of 25 consecutive patients followed by a nephrologist for a median of 443 days with a mean age of 81.7 ± 7.5 years were included. The most common symptom on admission was appetite loss in 17 patients (68%). Fifty percent of the patients died within 394 days of follow-up after their estimated glomerular filtration rate (eGFR) fell below $15 \text{ mL/min/1.73 m}^2$ and 222 days of follow-up after the eGFR fell below $10 \text{ mL/min/1.73 m}^2$. The validity of our findings for Japanese patients with end-stage CKD must be evaluated in greater detail.

KEYWORDS: chronic kidney disease, elderly, geriatric care, renal replacement therapy

CITATION: Akimoto et al. An Analysis of Elderly End-stage Chronic Kidney Disease Patients Who Did Not Undergo Renal Replacement Therapy in Japan. *Clinical Medicine Insights: Geriatrics* 2015:8 1–6 doi:10.4137/CMGer.S21947.

TYPE: Rapid Communication

RECEIVED: February 5, 2015. **RESUBMITTED:** June 24, 2015. **ACCEPTED FOR PUBLICATION:** June 26, 2015.

ACADEMIC EDITOR: Atsushi Sakuraba, Editor in Chief

PEER REVIEW: Three peer reviewers contributed to the peer review report. Reviewers' reports totaled 482 words, excluding any confidential comments to the academic editor.

FUNDING: This study was supported in part by a Grant-in-Aid for Research on Advanced Chronic Kidney Disease, Practical Research Project for Renal Diseases from Japan Agency for Medical Research and development, AMED. The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

The incidence of advanced chronic kidney disease (CKD) in the elderly continues to rise because of the increase in longevity of the general population and improvements in medical management.^{1,2} Old age is no longer considered to be an absolute contraindication to commence periodic renal replacement therapy (RRT),³ while recent studies have demonstrated the gradual increase in the mean age of new patients started on dialysis, as well as chronic dialysis patients overall.^{4,5} Although several national registry databases have provided practical information regarding the outcomes and factors affecting the survival of patients commencing chronic dialysis treatment, they do not systemically follow patients with end-stage CKD who do not receive RRT.^{6,7} Factors affecting the decision of whether to start dialysis treatment have been evaluated as well.⁸ However, qualitative and quantitative analyses regarding the outcomes of end-stage CKD patients who opt for conservative managements are limited,^{3,6,8–13} although a few studies have compared the survival of conservatively managed patients with the subjects commencing dialysis treatment and demonstrated the scarce benefit of such a procedure among the dependent patients with significant comorbidities.^{3,6,8,10}

The decisions regarding terminal health care of the elderly are complex and confusing in Japan, presumably because of family emotions, religion, social customs, and public opinion.¹⁴ Therefore, it may be difficult to conduct a thorough discussion concerning the inclusion or exclusion criteria for RRT among Japanese elderly end-stage CKD patients regardless of the presence or absence of multiple comorbid conditions. Not surprisingly, there is little descriptions currently available regarding the conservative management of elderly Japanese end-stage CKD patients; however, organizational, social, and cultural specificities are so pertinent to this particular issue that it is hard to introduce the experience procured in other countries,¹⁵ and thus, there may be a growing need to better define the basis for the prognosis assessment of such patient population. In this regard, we herein report a retrospective case series analysis to assess the clinical characteristics, survival, and pathophysiological backgrounds of Japanese CKD patients who died without the provision of RRT programs.

Patients and Methods

A retrospective analysis was conducted using the clinical records from the CKD stage 5 patients who were admitted and died at one of the three teaching hospitals (Koga Red Cross Hospital,



Nasu Minami Hospital, and Haga Red Cross Hospital) between January 1, 2008 and December 31, 2012. Twenty-five patients, who had been followed by a nephrologist at least six months prior to admission and were also treated by a nephrologist after admission, who decided not to initiate RRT and ultimately died at each hospital were identified and included in the present study. Meanwhile, 403 patients newly started on chronic dialysis treatment at the hospitals where the current study was conducted. They had been followed by a nephrologist in the same manner, and their mean age was 67.7 ± 12.4 years with subjects over 65 years of age accounting for ~67% of the cohort. Any patient who died unexpectedly was excluded. The patients presenting late CKD, which was previously undiagnosed and those whose serial data of their renal function were not available for at least six months before admission were also excluded. The local ethical committees of the hospitals approved this study and waived the requirement for informed consent because of the retrospective nature of the study design.

The symptoms, the mode of presentation, and the known duration of follow-up for CKD by the nephrologist before admission were recorded. The underlying causes for CKD were established according to the clinical history and laboratory findings. The following clinical and demographic characteristics were evaluated: sex, age, functional status according to the Karnofsky Performance Scale (KPS) score,¹⁶ comorbid conditions, and the estimated glomerular filtration rate (eGFR) based on the revised Japanese equation calculated as $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{serum creatinine (sCr)}^{-1.094}$ (if female $\times 0.739$).¹⁷ The dates on which the eGFR was first $<15 \text{ mL/min/1.73 m}^2$ and $<10 \text{ mL/min/1.73 m}^2$ during the regular outpatient visits were identified for each patient, and the survival from these dates until death was computed, if appropriate.

The data were expressed as either the number of participants or the percentage of the study population. Descriptive statistics were presented when necessary. The remaining data were expressed as the means \pm standard deviation. Variables with a skewed distribution were expressed as medians with interquartile range (IR). The differences between several categorized groups were analyzed using the nonpaired Student's *t*-test. The eGFR were plotted against time for each patient, and the data were then analyzed by a least-squares linear regression. The Kaplan–Meier and log-rank test methods were used to estimate and compare survival. Clinical presentations were entered into a stepwise forward multivariate logistic regression analysis in which the odds ratio (OR) and 95% confidence interval (CI) were determined to evaluate their contributions in predicting the causes of death. Statistical significance was considered to exist at $P < 0.05$. Statistical analyses were performed using the SigmaPlot software package (version 12 for Windows; Systat Software, Inc.).

Results

A total of 25 patients with a mean age of 81.7 ± 7.5 years were included in the present study. The mean age of these

subjects was significantly higher ($P < 0.0001$) than that of the 403 patients who underwent RRT, and their clinical and demographic profiles are summarized in Table 1. Twelve patients were female. Nephrosclerosis was the presumed underlying cause of CKD in 14 patients (56%); additionally, four had diabetic nephropathy (DN; 16%), four had chronic glomerulonephritis (CGN; 16%), two had had drug-induced nephropathy (8%), and one had myeloma kidney (4%). Comorbid factors were also evaluated and 19 patients (72%) had a severe neurogenic disorder impairing the functional capacity, including 11 with nonuremic dementia (44%), seven with major stroke (28%), and one had mental retardation (4%). Four of the remaining six patients had chronic cardiac failure (16%), one had pulmonary carcinoma (4%), and one had multiple myeloma (4%). The mean KPS score at admission was 22 ± 10 , and the median duration of survival after admission was 23 days (IR: 7–33 days). The clinical presentations at the time of admission are listed in Table 2. The most common symptoms were appetite loss in 17 patients (68%) and drowsiness in 13 patients (52%). Other common presentations included dyspnea and swelling of the extremities. Two patients (8%) suffered from chronic pain because of pulmonary carcinoma or myeloma. Seventeen patients (68%) received antihypertensive treatment with oral administration at the time of admission. Angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers were prescribed in 11 (44%) patients, 13 (52%) received a calcium channel antagonists, and six (24%) were administered diuretics. There was no significant difference in the age, blood pressure, sCr, or the eGFR between the patients receiving antihypertensive agents and those not receiving antihypertensives (data not shown).

The patients were followed by a nephrologist for a median of 443 days prior to admission (IR: 309–779). When the follow-up was started, the eGFR values were already below $15 \text{ mL/min/1.73 m}^2$ in ten patients, while there were four patients with eGFR values below $10 \text{ mL/min/1.73 m}^2$. Figure 1 shows the regression lines of the eGFR over time for each patient. The correlation coefficients ranged from -0.983 to -0.430 (median: -0.925 ; IR: -0.925 to -0.795), and the median decline in the eGFR was $7.41 \text{ mL/min/1.73 m}^2/\text{year}$ (IR: 3.84–17.41). The survival data for the patients presented as a Kaplan–Meier plot are shown in Figure 2. Fifty percent of the patients died within 394 days (IR: 129–617) of follow-up after the eGFR fell below $15 \text{ mL/min/1.73 m}^2$ ($n = 15$) and 222 days (IR: 79–402) of follow-up after the eGFR fell below $10 \text{ mL/min/1.73 m}^2$ ($n = 21$). The median survival of the patients whose eGFR values were already below $10 \text{ mL/min/1.73 m}^2$ at the initial point of follow-up was 336 days (IR: 282–352). Uremia was the most frequent presumable cause of death in 13 patients (52%), and other presumable causes included infections, cardiac failure, pulmonary edema, and malignancy (Table 3). A stepwise forward multivariate logistic regression analysis revealed that only drowsiness was selected

**Table 1.** The clinical and demographic profile of each patient who died without the provision of RRT programs.

CASE NO.	SEX	AGE	ETIOLOGY OF CKD	COMORBID FACTORS	KPS SCALE AT ADMISSION	DURATION OF SURVIVAL AFTER ADMISSION (DAYS)
1	M	79	Nephrosclerosis	Pulmonary carcinoma	20	39
2	F	87	Nephrosclerosis	Nonuremic dementia	20	10
3	M	77	DN	Major stroke	40	31
4	M	80	Nephrosclerosis	Nonuremic dementia	20	10
5	M	87	Analgesic nephropathy	Nonuremic dementia	40	40
6	M	72	CGN	Mental retardation	10	5
7	F	92	DN	Chronic cardiac failure	30	67
8	M	69	CGN	Major stroke	20	23
9	F	87	Nephrosclerosis	Nonuremic dementia	40	56
10	M	77	DN	Chronic cardiac failure	10	3
11	F	82	CGN	Nonuremic dementia	30	10
12	F	83	CGN	Nonuremic dementia	30	44
13	F	70	Myeloma kidney	Multiple myeloma	30	35
14	F	86	Nephrosclerosis	Nonuremic dementia	30	23
15	M	82	Drug induced nephropathy	Nonuremic dementia	30	27
16	F	79	DN	Major stroke	30	29
17	M	69	DN	Nonuremic dementia	20	25
18	F	90	Nephrosclerosis	Major stroke	20	14
19	M	87	Nephrosclerosis	Major stroke	30	26
20	M	80	DN	Chronic cardiac failure	10	1
21	M	70	Nephrosclerosis	Major stroke	10	6
22	F	94	Nephrosclerosis	Major stroke	20	29
23	F	92	Nephrosclerosis	Nonuremic dementia	10	3
24	F	85	Nephrosclerosis	Nonuremic dementia	10	8
25	M	86	Nephrosclerosis	Chronic cardiac failure	10	3

to be an explanatory factor for decrease by uremia (OR 132.0, 95% CI 7.334–2375.8, $P=0.0009$), whereas none of the clinical presentations at admission were identified to be significant predictors for death by infection, cardiac failure/pulmonary edema, or malignancy.

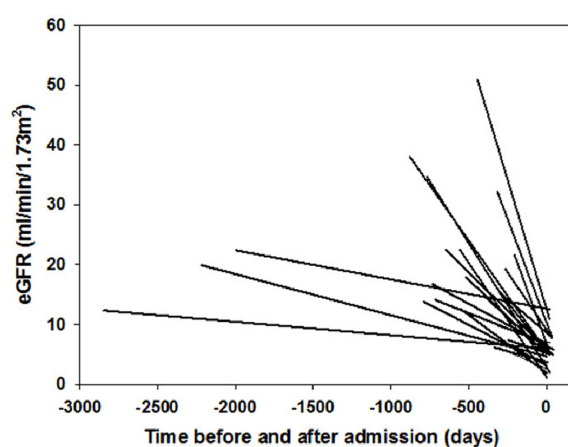
Discussion

There are some limitations associated with this study. The sample size of the present study was quite small, implying that the study may be underpowered for the evaluation of the impact of several clinical parameters thereby making definitive conclusions difficult. A varied degree of decline in

the renal function with time was noticed, thus suggesting that these subjects may be heterogeneous. Considering the data regarding the mean age and the percentage of the subjects over 65 years of age demonstrated in the nationwide

Table 2. The clinical presentations of the patients at the time of admission.

CLINICAL PRESENTATION	NO. (%)
Appetite loss	17 (68)
Drowsiness	13 (52)
Swelling of arm and/or legs	10 (40)
Dyspnea	10 (40)
Pain	2 (8)

**Figure 1.** The regression lines of the eGFR versus time. A significant linear regression was confirmed in each patient. The regression lines of eGFR versus time of each patient clearly demonstrated a gradual and varied degree of decrease in the renal function over time. The number “0” is designated as the point of admission.

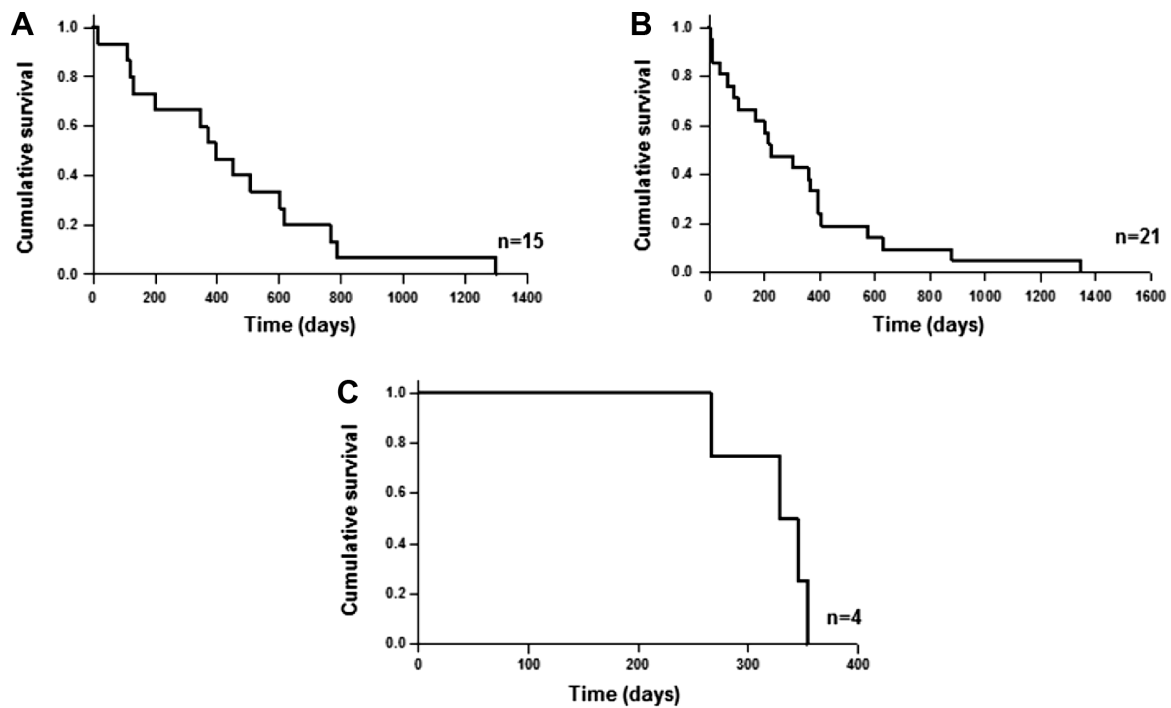


Figure 2. Kaplan–Meier survival curves after the eGFR fell below 15 mL/min/1.73 m² ($n = 15$) (A) and 10 mL/min/1.73 m² ($n = 21$) (B). Note that the longest survival in each observation was 1,299 days and 1,344 days, respectively. The longest and minimum survival in the patients whose eGFR values were already below 10 mL/min/1.73 m² at the initial point of follow-up ($n = 4$) was 356 days and 266 days, respectively (C).

statistical survey of new patients started on dialysis treatment in Japan,⁵ we feel it is reasonable to believe that the geographical impact of potential selection bias is minimized in terms of the patient age distribution. However, the subjects in the present study were not prospectively included on the basis of a research protocol, but were rather selected retrospectively, thereby potentially introducing an intrinsic selection bias in practice. Indeed, numerous elderly patients with advanced CKD were lost because of changing to other medical services, including regional geriatric hospitals and nursing homes, during the ordinary and periodic follow-up by nephrologists. Nevertheless, the current study clearly demonstrated for the first time the survival of elderly Japanese end-stage CKD patients not accepted to periodic dialysis programs despite the care by a nephrologist. In the United States, approximately <5% of CKD patients select to forgo dialysis, while approximately 15%–25% of the patients who present to nephrology clinics choose not to commence dialysis treatment in Great Britain and Canada.^{9,10,18} In our

study population, the prevalence of patients with end-stage CKD who selected to forgo chronic dialysis treatment could be approximately 5.8%, which has thus far only rarely been addressed in the previous literature.

The number of patients treated with RRT has continued to increase in Japan.⁵ The 50% survival time of Japanese dialysis patients is approximately 7–8 years after initiating dialysis treatment; in addition, the recent 1- to 10-year survival rates are increasing.^{4,5} Although RRT undoubtedly improves the survival and quality of life greatly for numerous end-stage CKD patients,^{8,10,12,13} there is no way to accurately estimate the survival time of the patients in the current study had they received RRT given the impossibility of performing a controlled trial despite the fact that uremia was the most prevalent cause of death among the current subjects. On the other hand, there is a growing recognition that RRT may not necessarily be the optimal choice in all the patients with end-stage CKD since the survival advantage of RRT is substantially diminished in patients with multiple comorbid conditions and a poor functional status,^{2,3,8,10} while the bedridden status may have little impact on the survival of dialysis patients despite the poorer prognosis in dialysis patients compared with the Japanese general population.⁴

The present study attempted to evaluate the clinical characteristics and survival of Japanese elderly patients with end-stage CKD that were not accepted to RRT. Elderly end-stage CKD patients and/or their guardians frequently ask what their estimated survival might be without RRT.

Table 3. Presumable causes of death.

PRESUMABLE CAUSES OF DEATH	NO. (%)
Uremia	13 (52)
Infections	5 (20)
Cardiac failure/Pulmonary edema	5 (20)
Malignancy	2 (8)

Table 4. Recently reported studies that assessed the survival of patients who did not undergo dialysis treatment.

AUTHOR (REF NO.)	YEAR OF STUDY	NUMBER OF PATIENTS	MEDIAN SURVIVAL	STARTING POINT OF OBSERVATION
Murtagh FE et al ³	2003 to 2004	77	540 days	Date eGFR first <15
Ellam T et al ⁶	2004 to 2006	69	21 months	Date eGFR first <15
Joly D et al ⁸	1989 to 2000	37	8.9 months	Date of decision not to start dialysis
Hirsch DJ et al ⁹	1992	23	10 weeks	Date of decision not to start dialysis
Smith C et al ¹⁰	1996 to 2000	26	8.3 months	Date eGFR first <10 to 12
Wong CF et al ¹¹	2003 to 2006	70	1.95 years	NA
Carson RC et al ¹²	1997 to 2003	29	13.9 months	Date eGFR first <10.8
Chandna SM et al ¹³	1990 to 2008	155	21.1 months	Date eGFR first <15

Note: Note that there is a disparity in the unit of the median survival.
Abbreviation: NA, not available.

Until recently, several studies have focused on the survival of patients with end-stage CKD after the initiation of RRT with discordant conclusions,^{3,4,8,19} while the patients' characteristics, rates of dialysis commencement, and survival estimates vary extensively among the studies describing the survival of elderly end-stage CKD patients being managed conservatively (Table 4).^{3,6–13} We believe that our data, which show the median survival after the decline in the eGFR to less than 15 mL/min/1.73 m² of more than one year, may be reasonable, while it must be noted that that our cohort included an elderly CKD patient who survived for more than three years and two patients who survived for more than one year after the initial referral with eGFRs already below 15 mL/min/1.73 m². This may not be surprising since more than one-third of the subjects over 80 years of age referred to a nephrology center has a severe but nonprogressive renal dysfunction, and this subgroup has a lower mortality rate than those with a progressive deterioration of the renal function.²⁰ Indeed, all three patients mentioned above were octogenarians. Obviously, the validity of our findings should be evaluated in detail with a greater accumulation of Japanese subjects with end-stage CKD.

This study did not address the complex process of how and why conservative management was selected in the present patients. There is currently no public policy regarding the acceptance of patients for RRT. Moreover, there are no validated criteria to make it possible to adequately predict the duration of the survival of patients with advanced CKD without RRT. These strategic and prognostic uncertainties make clinical decisions difficult for caregivers, patients, and their families. Any decision of nonacceptance into a dialysis program must take into consideration the specific condition of the patients, information about the family support system, and a detailed understanding of the consequences of either initiating or forgoing RRT.^{21,22} We believe that nephrologists should be required to initiate end-of-life discussions, in the larger context of the development of a care plan, for patients with advanced CKD managed without RRT since such patients will have considerable symptom control needs, similar to patients with advanced malignancy.^{21–23}

Author Contributions

Drafted the manuscript: TA. Contributed to the acquisition of the clinical data: CI, HT, YM, TK, and SH. Provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document: YA, EK and DN. All the authors have read and approved the final manuscript.

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