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Risk-Stratified Incidence of Renal Replacement Therapy Initiation: A Longitudinal Analysis Using Medical Claims and Health Checkup Data

Takehiro Sugiyama,[1,2,3] Koji Oba[4] and Yasuki Kobayashi[3]

[1]Diabetes and Metabolism Information Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan
[2]Department of Health Services Research, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
[3]Department of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[4]Department of Biostatistics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Intervention for higher-risk participants of health checkups especially with diabetes has been started in Japan to prevent renal replacement therapy (RRT) initiation, but evidence about RRT initiation risk among checkup participants has been scarce. To estimate the incidence by risk factors, we conducted a retrospective cohort study using medical claims and checkup data of a community-based insurance scheme in Japan. Beneficiaries who participated in the checkup in 2012-2013 were included and followed up for about five years. We estimated the incidence of RRT initiation by the subject characteristics, followed by investigation for risk factors in bivariate analyses and multivariable regression analyses with Bayesian prior probability distributions. As a result, among 49,252 participants, 37 initiated dialysis (0.21/1,000 person-years); no kidney transplantation was performed during the period. Baseline estimated glomerular filtration rate was strongly associated with dialysis initiation. No dialysis was initiated among those without baseline hypertension; cumulative incidence by hypertension status was significantly different ($p < 0.001$). Diabetes was significantly associated with dialysis initiation in bivariate analysis, but the association was not significant in multivariable regression analysis [reference: no diabetes; incidence rate ratio (IRR) for diabetes without medication, 3.30 (95% credible interval, 0.48-15.56); IRR for diabetes with medication, 1.69 (95% credible interval, 0.68-3.47)]. In conclusion, potential risk factors for RRT initiation include male sex, comorbid hypertension, and current smoking status, in addition to advanced chronic kidney disease, proteinuria, and diabetes. New initiatives should consider these factors to increase the efficacy of the programs at the population level.

Keywords: claims data; dialysis; health checkup; incidence; Japan
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Introduction

Chronic kidney disease (CKD) can deteriorate into end-stage renal disease (ESRD) that eventually requires renal replacement therapy (RRT). In Japan, over 40,000 patients initiated dialysis in 2016; over 330,000 patients are on dialysis (Masakane et al. 2018), whereas kidney transplantation is much less common (1,600 patients/year) (Japanese Society for Clinical Renal Transplantation and The Japan Society for Transplantation 2017). RRT not only undermines the quality of life but also raises national medical expenses; thus, preventing RRT, especially dialysis, is one of the most critical public health issues in Japan. Diabetic nephropathy (DN) accounts for 40% of dialysis incidence and prevalence in Japan (Masakane et al. 2018).

The National Health Insurance (NHI) is one of the health insurance plans that constitute universal healthcare coverage in Japan (Ikegami et al. 2011). Each NHI insurer is run by a local municipality; this community insurance mainly covers self-employed persons, pensioners, and unemployed residents of the region and their dependents, whereas those aged 75 or older as well as those aged 65 or older with a certified disability are covered by the Medical Care System for Elderly in the Latter Stage of Life, a separate entity. Since 2016, the Government of Japan has introduced a system to financially encourage NHI insurers to increase the efficacy of medical expenses (Ministry of Health, Labour and Welfare 2017). Among these measures, the Project to Prevent the Worsening of Diabetic Nephropathy attempts to reduce the number of patients with

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Correspondence: Takehiro Sugiyama, M.D., M.S.H.S., Ph.D., Diabetes and Metabolism Information Center, Research Institute, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
e-mail: tsugiyama-tky@umin.ac.jp

ESRD requiring RRT in the following ways: 1) detection of higher-risk beneficiaries with diabetes based on the results of specific medical checkup and medical claims data that are owned by the insurers, and 2) intervention of these patients by public health nurses through several measures such as health education, dietary counseling, and medical consultation facilitation. A majority of NHI insurers have started or have planned to start these measures. As shown in its name, the targets of the projects are mostly patients with diabetes; they are further classified into strata by known risk factors of kidney deterioration.

Some previous studies reported that declined estimated glomerular filtration rate (eGFR), proteinuria, and higher blood pressure were risk factors of further decreased eGFR from participants of health checkup in Japan (Imai et al. 2008; Hirayama et al. 2015). Meanwhile, assessment of more critical health outcome, the incidence of RRT initiation, stratified by risk factors using health checkup and claims data in Japan has been rarely reported. Furthermore, whether the focus should be on DN rather than CKD has not been clarified. Analysis of these real-world data available for insurers to estimate absolute risk or the corresponding incidence should be useful when insurers plan for appropriate strategies to capture subjects at higher risk.

In this study, to identify factors that can be utilized to determine patients at higher risk for RRT initiation, we determined the risk of RRT initiation across various subject subgroups using the specific health checkup and medical claims data obtained from a local municipality.

Materials and Methods

We conducted a retrospective longitudinal study using the medical claims and specific health checkup data of the NHI insurer operated by a large city within the Tokyo metropolitan area in Japan. Specific health checkup, based on the Act on Assurance of Medical Care for Elderly People, aims to screen and prevent metabolic syndrome and is performed at healthcare centers or hospitals/clinics (Matsuzawa et al. 2011). In Japan, insurers must offer the opportunity for a specific health checkup to their beneficiaries aged 40 to 74 years. Under a research agreement between the city and the University of Tokyo, the specific health checkup and medical claims data were obtained in an anonymous format. The study protocol was approved by the University of Tokyo Institutional Review Board (No: 10834). Consents from the beneficiaries were waived as the data were used in an anonymized format.

This study included specific health checkup and medical claims data from April 2012 to January 2017. The RRT prevention project had not yet been conducted in the city during this period. Among the beneficiaries of the insurance, only participants of the specific health checkup from May 2012 to March 2013 were included. Subjects were excluded if their insurance coverage during the previous and the exact months of the health checkup was not confirmed. Besides, patients who were already on RRT before the checkup date were excluded from the current study, and 49,252 subjects were included in the final analyses (Fig. 1).

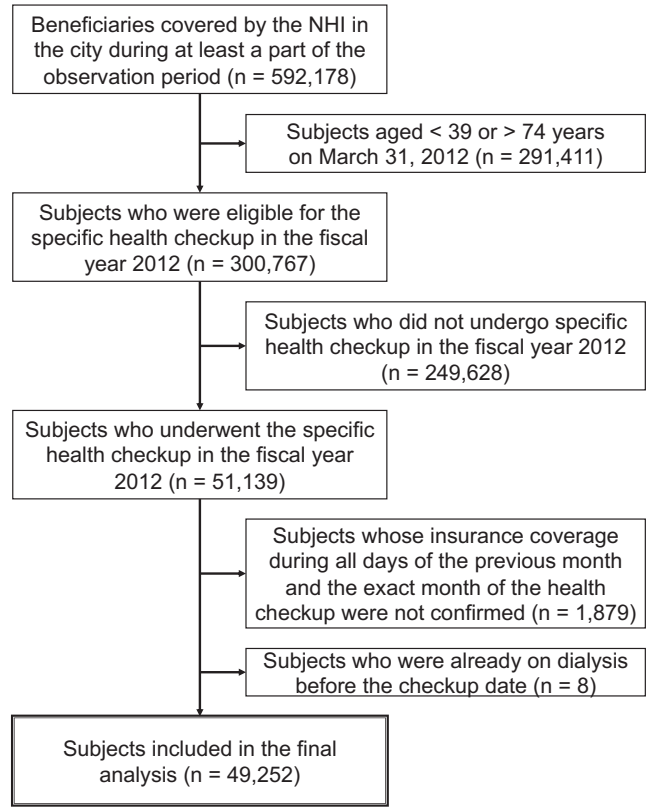

Fig. 1. Flow chart showing the selection of study samples. NHI, National Health Insurance.

Measurements

RRT initiation was defined based on the earliest appearance of the medical claims for RRT, which included hemodialysis, peritoneal dialysis, and kidney transplantation. For diabetes, the subjects were categorized into the following categories: patients with antidiabetic medication, patients with diabetes (HbA1c ≥ 6.5%) not on antidiabetic medication, and those without apparent diabetes. We did not use the data of blood sugar for the definition of diabetes because the fasting status was not guaranteed. For hypertension, the subjects were categorized as follows: those on antihypertensive medication, those with hypertension but not on medication (blood pressure ≥ 140/90 mmHg without antihypertensive medication), and those without apparent hypertension. Detailed information about these variables was described in Table 1. We included the answer to the question on medication use in the questionnaire because prescription information before the specific health checkup may not have been obtainable from claims data especially on patients who participated in the checkup earlier in the fiscal year 2012.

We also extracted information on body mass index (BMI), eGFR, urine protein, and current smoking status from the specific health checkup data. According to BMI, subjects were categorized as overweight or obese (≥ 25 kg/m^2) and normal or underweight (< 25 kg/m^2). The subjects were categorized based on eGFR (mL/min/1.73 m^2), calculated from 194 * Serum creatinine$^{-1.094}$* Age$^{-0.287}$* 0.739 (if female) (Matsuo et al. 2009), using the CKD staging as follows: G1 or G2 (eGFR ≥ 60 mL/min/1.73m^2), G3a (45 ≤ eGFR < 60), G3b (30 ≤ eGFR < 45), G4 (15 ≤ eGFR < 30), and G5 (eGFR < 15), whereas those with an eGFR over 500 were considered as outliers (n = 1).

Table 1. Detailed information on variables.

		Source information
Outcome variable		
	Hemodialysis and peritoneal dialysis	Japanese Medical Treatment Classification codes: J038-00, J042-00, medical management of outpatients receiving chronic maintenance dialysis in B001-00.
	Kidney transplantation	Japanese Medical Treatment Classification codes: K780 and K709-05.
Predictors		
	Diabetes	The following three information sources and definitions for diabetes were used: 1) Medical claim for antidiabetic medications (Japanese Drug Effect Classification codes 396 [antidiabetic drugs] and a part of 249 [other hormonal drugs; we only included insulin and glucagon-like peptide 1 analogues,]) before the specific health checkup, 2) an affirmative answer to the question on antidiabetic medication use in the specific health checkup questionnaire, and 3) hemoglobin A1c (HbA1c) ≥ 6.5% according to the National Glycohemoglobin Standardization Program determined at the time of the specific health checkup.
	Hypertension	The following three information sources and definitions were used to define hypertension: 1) medical claim for medications possibly used for hypertension (Japanese Drug Effect Classification codes 212 [anti-arrhythmic drugs], 213 [diuretics], 214 [blood pressure-lowering drugs], 217 [vasodilators], and a part of 219 [other drugs for circulatory organs; we only included combination drugs containing amlodipine besilate and atorvastatin calcium hydrate]), 2) an affirmative answer to the question on antihypertensive medication use in the specific health checkup questionnaire, and 3) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg during the specific health checkup. In contrast to the antidiabetic medications, drugs with antihypertensive effects can be used for other purposes such as arrhythmia, angina pectoris, and congestive heart failure; thus, the medications were considered to be used specifically for hypertension only when the drugs listed were on the same claims with the ICD-10 (International Statistical Classification of Disease and Related Health Problems, 10th Revision) code of I10-I15 for the diagnosis of hypertension.

Categorization according to urine protein included "negative or negative/positive" and "1+ or greater." The subjects were categorized into smokers and nonsmokers based on the current smoking status at the time of specific health checkup. The information on sex and birth month were obtained from the beneficiary's register; age was defined based on the month of the specific health checkup, categorized into the < 60, 60-69, and ≥ 70 age groups. Considering that the explanation about the Project to Prevent the Worsening of Diabetic Nephropathy clearly states that the project targets not only DN but also kidney dysfunction caused by other factors among patients with diabetes and that the explanation recommends the DN staging for all patients with diabetes (The Japan Medical Association et al. 2016), the subjects with diabetes were further categorized according to the DN staging by the Japan Diabetes Society as follows: stage 1 or 2 (eGFR ≥ 30, no overt proteinuria), stage 3 (eGFR ≥ 30 with overt proteinuria), and stage 4 (eGFR < 30, irrelevant of proteinuria). Although the Japanese Society of Nephrology and the Japanese Diabetes Society recommend urine quantitative albumin/protein measurements for the classification of the DN staging, quantitative measurements were not included in the health checkup; we instead used urine qualitative exam to distinguish between no overt proteinuria (that can include microalbuminuria that may not be detectable with dipstick urine analysis alone) and overt proteinuria (1+ or greater), as other studies adopted the definition (Hirayama et al. 2015; Nishikawa et al. 2017).

Statistical Analysis

First, subject characteristics at the time of the specific health checkup as well as the incidences of RRT initiation according to the subject characteristics were analyzed. We used Kaplan-Meier method to describe cumulative incidences of RRT initiation according to specific subject characteristics. The month in which the specific health checkup was conducted set as time zero; Time to the first event was defined as the interval between time zero and the month in which the first RRT occurred. Data were censored at the final month of the insurance coverage period for the subject or the final month of observation (January 2017) for subjects who did not experience the events. Cumulative incidences among the groups were compared using the log-rank test.

For adjusted incidence rate ratios, multivariable Poisson regression analyses were conducted to control for covariates. A generalized linear model with a log link and Poisson distribution were used to model the incidence of RRT initiation according to the subject characteristics (age group, sex, diabetes mellitus, hypertension, BMI category, current smoking, CKD stage, and proteinuria). Because the incidence of RRT was low, no events were observed when stratified by some covariates. For example, no RRT initiation was observed among the subjects without hypertension. Therefore, a Bayesian approach (Greenland 2006) was used for the multivariable Poisson model with a vague normal prior distribution for ln (incidence rate ratio) (mean = 0.00, variance = 34.5) adopted for factors except for CKD staging and proteinuria. This variance of prior corresponds to a 95% probability for an incidence rate ratio between 0.05 and 20. The

analyses were repeated among the subjects only in stage G1-G3 CKD at baseline, because we wanted to investigate the risk factors among patients with less severe CKD and the association between the factors other than CKD staging and the incidence of RRT initiation might differ by CKD staging. Besides, hypertension among those in severer CKD stages may be caused by the impaired kidney function itself; the analysis restricted to patients in stage G1-G3 CKD at baseline would indicate the causal relationship from hypertension to renal replacement therapy initiation more strongly.

Additionally, several *post hoc* analyses were performed to assess appropriate targets of future interventions for RRT prevention by identifying higher-risk strata of RRT initiation. First, the incidence of RRT initiation was calculated among the subjects with diabetes in stage 3 DN stratified by sex, comorbid hypertension, and smoking status. Next, the incidence of RRT initiation was calculated among the subjects without diabetes in stage 3A and 3B CKD stratified by sex, comorbid hypertension, smoking status, and proteinuria. These analyses enabled us to compare the risk among the patients in CKD stage G3b without DM (who may not be the targets for the intervention) and that among the patients in stage 3 DN (who are currently targets for the intervention).

All statistical analyses were performed upon complete data using Stata 14.1 (StataCorp, College station, TX, USA) and SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Characteristics, incidences, and cumulative incidences

Table 2 shows the characteristics of the subjects included in the present study. Over half of the subjects were in their 60s (mean age: 64.6 years old); approximately 10% were current smokers; 74 (0.2%) subjects with stage G4 CKD and 22 (0.05%) subjects with stage G5 CKD underwent specific health checkup. Among the subjects with diabetes, 490 (12.5%) and 32 (0.8%) were in stages 3 and 4 DN, respectively. Out of a total of 49,252 subjects (described in Fig. 2), contributing to 177,228 person-years, 37 subjects initiated RRT; none of those underwent kidney transplantation, whereas peritoneal dialysis was administered in one subject. Fig. 2 shows the cumulative incidence for RRT initiation based on subject characteristics. For diabetes (Fig. 2A), the difference of the curves was significant between no diabetes and diabetes without medication ($p = 0.02$) and between no diabetes and diabetes with medication ($p < 0.001$), where the difference was not significant between diabetes with medication and diabetes without medication ($p = 0.23$). For hypertension (Fig. 2B), the three curves were significantly different ($p = 0.005$ between no hypertension and hypertension without medication, $p < 0.001$ between no hypertension and hypertension with medication, $p = 0.002$ between hypertension with medication and hypertension without medication). For smoking (Fig. 2C), the two curves were different ($p = 0.001$). For kidney function (Fig. 2D, E), the stage-stratified cumulative incidence was clearly illustrated; the differences between the adjacent pair of the curves were all significant ($p = 0.007$ between G1 or G2 and G3a, $p < 0.001$ between G3a and G3b, $p < 0.001$ between G3b and G4, and $p < 0.001$ between G4 and G5). P values shown here were not corrected for multiple comparisons.

Multivariable regression analyses with and without prior distribution

In the multivariable regression analyses (Table 3), the coefficient of hypertension variable did not converge in the Poisson regression without prior distribution; it converged within the meaningful range in the Bayesian Poisson regression with a vague prior distribution. In the model with Bayesian Poisson regression, we found considerably higher incidence rate ratios for the stages G4 (195.96; 95% credible interval, 55.14-581.38) or G5 (1,237.19; 95% credible interval, 447.51-4,469.36) CKD, with reference to the stages G1 or G2 CKD and low incidence rate ratios for no hypertension (0.01; 95% credible interval, 0.00-0.16) with reference to hypertension with medication. Compared to the absence of diabetes, diabetes without medication and diabetes with medication at baseline were insignificantly associated with 3.30-fold (95% credible interval, 0.48-15.56) and 1.69-fold (95% credible interval, 0.68-3.47) higher incidence, respectively. Male sex, smoking, and overt proteinuria were associated with higher incidence of RRT initiation; however, the associations were not statistically significant. In the analyses for the subjects with stage G1-G3 CKD at baseline only, we additionally set prior information for the age category; the results were similar to those obtained with regression for all study subjects, although the point estimates of the coefficients for sex, diabetes, and hypertension deviated further from the null.

Post hoc analyses focusing on stage 3 DN and stage G3a and G3b CKD without diabetes

We then analyzed focusing on stage 3 DN and stage G3a and G3b CKD without diabetes (Table 4). Briefly, the estimated incidences of RRT initiation among the subjects with stage 3 DN (1.18/1,000 person-years) increased when restricted to males (1.64/1,000 person-years), those with hypertension (1.43/1,000 person-years), and those currently smoking (2.29/1,000 person-years). The incidence among the subjects with stage G3b CKD without diabetes was comparable to that among the subjects with stage 3 DN (1.23 vs. 1.18/1,000 person-years), whereas that among the subjects with stage G3a CKD without diabetes was quite low (0.10/1,000 person-years). Restriction by risk factors (male sex, comorbid hypertension, current smoking, and overt proteinuria) increased the incidence of RRT initiation for both groups.

Discussion

Using specific health checkup data and five-year medical claims data of an NHI scheme in Japan, we successfully showed that incidence of RRT initiation by risk factors for the whole and G3 stages of CKD was calculable from claims and health checkup data. To our knowledge, this is the first study to calculate the incidence of RRT initiation

Table 2. Characteristics of the study subjects and incidence of renal replacement therapy initiation according to the characteristics.

	No. of Subjects at Baseline (%, categorical) or Mean ± SD (continuous)	Person-years	No. of RRT Cases	Incidence/1,000 Person-years (95% CI)	p value[a]
Total	49,252	177,228	37	0.21 (0.15-0.29)	
Age at baseline (years)[b]					
39-59	8,343 (16.9%)	29,899	1	0.033 (0.0047-0.24)	
60-69	27,213 (55.3%)	110,428	25	0.23 (0.15-0.34)	0.04
70-74	13,696 (27.8%)	36,901	11	0.30 (0.17-0.54)	
(Continuous)	64.6 ± 7.8				
Sex					
Male	17,353 (35.2%)	64,859	23	0.35 (0.24-0.53)	0.001
Female	31,899 (64.8%)	112,369	14	0.12 (0.074-0.21)	
Diabetes mellitus					
No diabetes	45,280 (91.9%)	163,115	20	0.12 (0.079-0.19)	
Diabetes without medication	927 (1.9%)	3,413	2	0.59 (0.15-2.34)	< 0.001
Diabetes with medication	3,045 (6.2%)	10,701	15	1.40 (0.85-2.33)	
Hypertension					
No hypertension	25,964 (52.7%)	94,776	0	0	
Hypertension without medication	6,734 (13.7%)	24,271	2	0.082 (0.021-0.33)	< 0.001
Hypertension with medication	16,554 (33.6%)	58,182	35	0.60 (0.43-0.84)	
Body mass index[c]					
normal or underweight (< 25 kg/m^2)	37,940 (77.1%)	136,650	25	0.18 (0.12-0.27)	0.17
overweight or obese (≥ 25 kg/m^2)	11,296 (22.9%)	40,530	12	0.30 (0.17-0.52)	
(Continuous)	22.8 ± 3.4				
Current smoking					
No	43,482 (88.3%)	155,941	26	0.17 (0.11-0.24)	0.001
Yes	5,770 (11.7%)	21,287	11	0.52 (0.29-0.93)	
Estimated glomerular filtration rate (CKD stage)[c] (mL/min/1.73m^2)					
G1 or G2 (≥ 60)	41,752 (85.9%)	151,375	6	0.040 (0.018-0.088)	
G3a (≥ 45, < 60)	6,152 (12.7%)	21,154	4	0.19 (0.071-0.50)	
G3b (≥ 30, < 45)	579 (1.2%)	1,943	5	2.57 (1.07-6.18)	< 0.001
G4 (≥ 15, < 30)	74 (0.2%)	222	10	45.10 (24.26-83.81)	
G5 (< 15)	22 (0.05%)	47.4	12	253.08 (143.72-445.63)	
(Continuous)	74.2 ± 14.7				
Proteinuria[c]					
(–) or (±)	46,939 (95.4%)	169,202	11	0.065 (0.036-0.12)	< 0.001
(+) or greater	2,270 (4.6%)	7,892	25	3.17 (2.14-4.69)	
Diabetic nephropathy stage[d]					
1 or 2 (G1-G3, no overt proteinuria)	3,397 (86.7%)	12,118	4	0.33 (0.12-0.88)	
3 (G1-G3, overt proteinuria)	490 (12.5%)	1,700	2	1.18 (0.29-4.70)	< 0.001
4 (G4-G5, not on RRT)	32 (0.8%)	87.1	11	126.31 (69.95-228.09)	

[a]p values are calculated by the log-rank test.

[b]Includes subjects who were 39 years old at the time of the health checkup but were 40 years old at the end of the fiscal year 2012.

[c]Including subjects with missing values – Body mass index: 16 subjects; CKD stage: 643 subjects; Proteinuria: 43 subjects; Diabetic nephropathy stage: 53 subjects (among patients with diabetes).

[d]Limited to only those with diabetes (with and without medication). Percentages were calculated based on subjects with diabetes.

SD, standard deviation; RRT, renal replacement therapy; CI, confidence interval; CKD, chronic kidney disease.

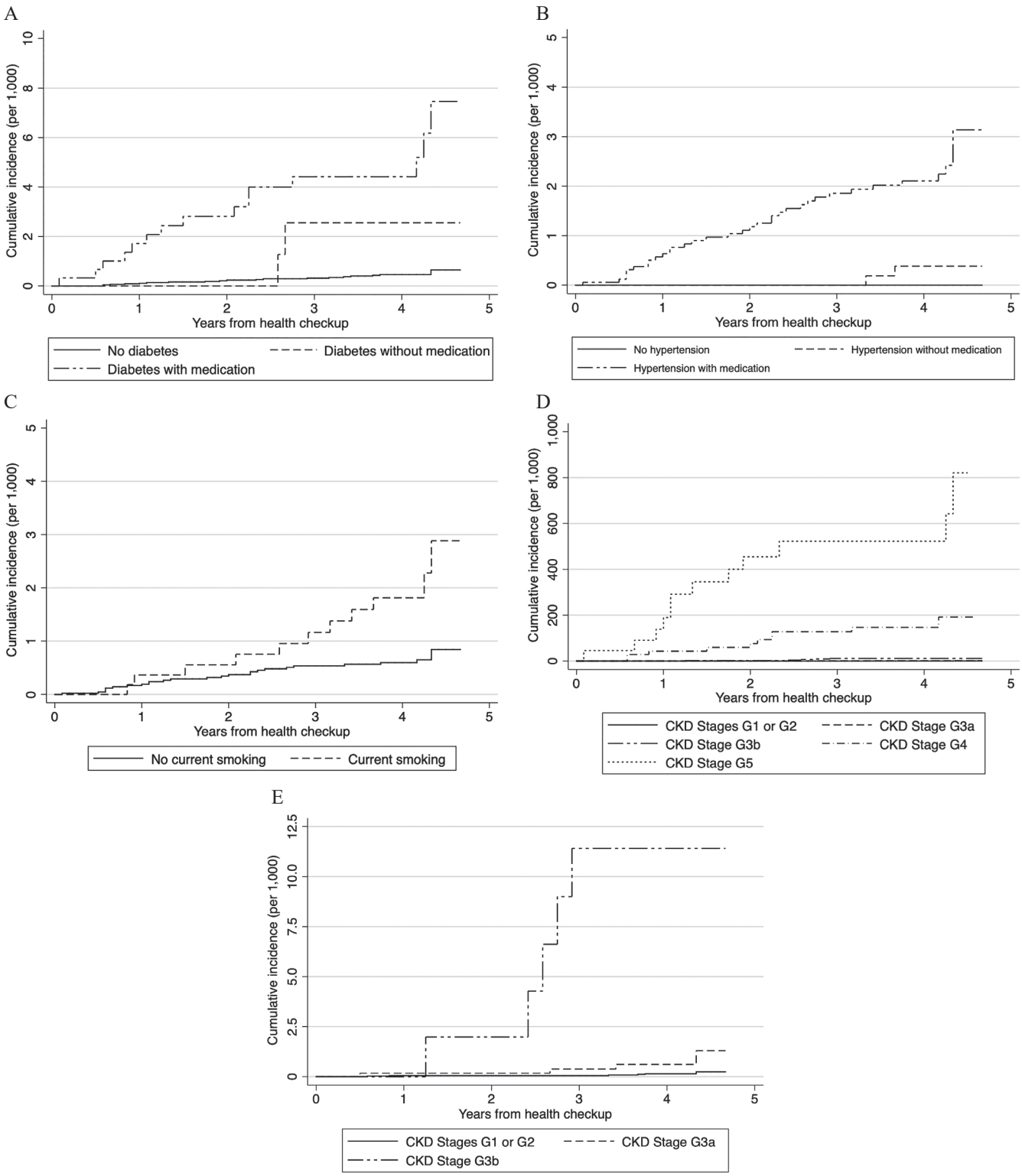

Fig. 2. Cumulative incidence of renal replacement therapy initiation according to the subject characteristics.
(A) Stratification by diabetes mellitus status ($p < 0.001$); (B) stratification by hypertension status ($p < 0.001$); (C) stratification by smoking status ($p = 0.001$); (D) stratification by chronic kidney disease stage ($p < 0.001$); (E) stratification by chronic kidney disease stage, restricted to stage G1-G3 CKD ($p < 0.001$). p-values were calculated by the log-rank test.

Table 3. Association between the baseline subject characteristics and renal replacement therapy initiation[a].

	All Subjects (n = 48,523)[b]		Subjects with Stage G1–G3 CKD at Baseline Only (n = 48,428)[b]	
	Poisson regression	Bayesian Poisson regression with vague prior distribution	Poisson regression	Bayesian Poisson regression with vague prior distribution
	Adjusted IRR (95% CI)	Adjusted IRR (95% credible interval)	Adjusted IRR (95% CI)	Adjusted IRR (95% credible interval)
Age at baseline (years)[c]				
39-59	0.94 (0.12-7.49)	0.62 (0.05-4.24)	0.00 (0.00-0.00)	0.03 (0.00-0.86)
60-69	1 (ref)	1 (ref)	1 (ref)	1 (ref)
70-74	1.14 (0.55-2.39)	1.15 (0.63-2.35)	1.96 (0.68-5.68)	1.65 (0.63-6.33)
Sex				
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	0.75 (0.35-1.61)	0.73 (0.38-1.52)	0.43 (0.12-1.47)	0.39 (0.12-1.30)
Diabetes mellitus				
No diabetes	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Diabetes without medication	3.83 (0.85-17.2)	3.30 (0.48-15.56)	5.45 (1.10-27.00)	5.51 (0.71-19.11)
Diabetes with medication	1.61 (0.74-3.51)	1.69 (0.68-3.47)	2.19 (0.63-7.65)	2.39 (0.79-6.73)
Hypertension				
No hypertension	0.00 (0.00-∞)	0.01 (0.00-0.16)	0.00 (0.00-∞)	0.02 (0.00-0.23)
Hypertension without medication	0.49 (0.11-2.21)	0.45 (0.11-1.41)	0.63 (0.14-2.91)	0.51 (0.13-1.91)
Hypertension with medication	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Body mass index				
normal or underweight (< 25 kg/m^2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
overweight or obese (≥ 25 kg/m^2)	0.79 (0.38-1.62)	0.78 (0.37-1.41)	0.84 (0.28-2.51)	0.69 (0.27-2.04)
Current smoking				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	1.95 (0.80-4.74)	1.82 (0.68-4.20)	2.81 (0.88-8.99)	2.64 (0.76-9.78)
Estimated glomerular filtration rate (CKD stage) (ml/min/1.73m^2)				
G1 or G2 (≥ 60)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
G3a (≥ 45, < 60)	3.42 (0.95-12.3)	3.37 (0.96-15.26)	3.22 (0.90-11.59)	3.31 (1.11-8.23)
G3b (≥ 30, < 45)	20.62 (5.80-73.38)	21.60 (6.17-82.01)	19.79 (5.44-72.06)	15.69 (4.74-52.64)
G4 (≥ 15, <3 0)	187.26 (53.40-656.62)	195.96 (55.14-581.38)	–	–
G5 (< 15)	1081.93 (312.91-3741.34)	1237.19 (447.51-4469.36)	–	–
Proteinuria				
(–) or (±)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
(+) or greater	3.67 (1.46-9.19)	3.70 (1.69-8.07)	2.24 (0.67-7.49)	2.28 (0.68-7.15)

[a]Multivariable regression analysis using generalized linear models with Poisson distribution and Bayesian analyses.

[b]Data with missing variables (n = 729 for all subjects and n = 55 for subjects with State G1-G3 CKD at baseline only) were excluded from the regression analyses.

[c]Includes subjects who were 39 years old at the time of the health checkup but were 40 years old at the end of the fiscal year 2012.

CKD, chronic kidney disease; IRR, incidence rate ratio; CI, confidence interval.

during a five-year period stratified by risk factors based on the analysis of specific health checkup data and medical claims data of beneficiaries of an NHI insurer in Japan.

The obtained evidence would facilitate the risk stratification of beneficiaries for the Project to Prevent the Worsening of Diabetic Nephropathy in the following ways. First, hypertension was a predictor of RRT initiation with high sensitivity. Information related to comorbid hypertension can be used to screen for individuals with RRT initiation risk at baseline. The additional analysis restricted to

Table 4. Incidences of renal replacement therapy among patients with stage 3 diabetic nephropathy or stage G3 chronic kidney disease without diabetes mellitus.

	No. of Subjects at Baseline (%)	Person-years	No. of RRT Cases	Incidence/1,000 Person-years (95% CI)
Stage 3 DN				
Total of patients with Stage 3 DN	490	1,700	2	1.18 (0.29-4.70)
Sex				
Stage 3 DN, male	347	1,220	2	1.64 (0.41-6.55)
Stage 3 DN, female	143	480	0	0
Hypertension				
Stage 3 DN, without hypertension	86	305	0	0
Stage 3 DN, with hypertension	404	1,396	2	1.43 (0.36-5.73)
Current smoking				
Stage 3 DN, without current smoking	371	1,265	1	0.79 (0.11-5.61)
Stage 3 DN, with current smoking	119	436	1	2.29 (0.32-16.29)
CKD stage G3a or G3b without DM				
Total of patients with stage G3a CKD, no DM	5,598	19,264	2	0.10 (0.026-0.42)
Total of patients with stage G3b CKD, no DM	479	1,623	2	1.23 (0.31-4.93)
Sex				
G3a, no DM, male	1,997	7,326	2	0.27 (0.068-1.09)
G3a, no DM, female	3,601	11,939	0	0
G3b, no DM, male	214	782	2	2.56 (0.64-10.23)
G3b, no DM, female	265	841	0	0
Hypertension				
G3a, no DM, without hypertension	2,580	9,098	0	0
G3a, no DM, with hypertension	3,018	10,167	2	0.20 (0.049-0.79)
G3b, no DM, without hypertension	130	462	0	0
G3b, no DM, with hypertension	349	1,161	2	1.72 (0.43-6.89)
Current smoking				
G3a, no DM, without current smoking	5,171	17,724	1	0.056 (0.0079-0.40)
G3a, no DM, with current smoking	427	1,541	1	0.65 (0.091-4.61)
G3b, no DM, without current smoking	433	1,458	1	0.69 (0.097-4.87)
G3b, no DM, with current smoking	46	165	1	6.08 (0.86-43.13)
Proteinuria				
G3a, no DM, (–) or (±)	5,263	18,125	2	0.11 (0.028-0.44)
G3a, no DM, (+) or greater	330	1,128	0	0
G3b, no DM, (–) or (±)	380	1,297	1	0.77 (0.11-5.48)
G3b, no DM, (+) or greater	98	322	1	3.11 (0.44-22.06)

RRT, renal replacement therapy; DN, diabetic nephropathy; CKD, chronic kidney disease; DM, diabetes mellitus.

those with stage G1-G3 CKD also corroborated that hypertension at baseline could be an indicator to screen for those who are at higher risk of RRT initiation among those in less severe CKD stages. Second, while diabetes was a risk factor for RRT initiation, subjects without diabetes, such as those with stage G3b CKD and those with proteinuria, may also be good candidates for preventive interventions with appropriate risk stratification. Third, smokers may be good candidates for intervention. Five years may be relatively short to comprehensively overview the effects of these risk factors on the incidence of RRT initiation; future studies in other areas, with a longer duration of follow-up, are necessary to verify the general applicability of the current study findings.

Several previous studies have investigated the absolute risk of RRT or ESRD. The Kidney Disease: Improving Global Outcomes (KDIGO) conducted meta-analyses on the relationships of eGFR and albuminuria with mortality, cardiovascular risk, and kidney outcomes (Astor et al. 2011; Gansevoort et al. 2011; van der Velde et al. 2011; Fox et al. 2012), which were used to create the heat map shown in the KDIGO 2012 Clinical Practice Guideline (Levey et al. 2011; Levin et al. 2013). Overall, the incidence rate ratios in the present study were comparable to the relative risks shown in the KDIGO heat map. The community-based cohort study in Okinawa showed that BMI was associated with the development of ESRD, which was not observed in the present study (Iseki et al. 2004). This discrepancy may be due to the differences in region, the observation period, or the distribution of covariates (e.g., eGFR at baseline, which was not observable in the study by Iseki et al. (2004).

Several other studies examined the incidence of ESRD stratified by eGFR or albuminuria as well (Tonelli et al. 2011; Coresh et al. 2014; Wada et al. 2014; Tanaka et al. 2015). Nishikawa et al. (2017) used data from one employer-based insurer, including health checkup and claims data, to investigate the risk of dialysis initiation among male workers in Japan. The incidence according to eGFR level in their study was not different from that found in the current study, except for the rate of the subjects with

stage G3b CKD (12.5/1,000 by Nishikawa et al. (2017) vs. 2.57/1,000 in the present study); the discrepancy might stem from differences in patient characteristics, such as sex, age, and employment status, as well as the observation periods (2006-2013 vs. 2012-2017). Smaller sample size may also have caused larger chance errors and resulting discrepancies, especially in the stratified analyses.

The strength of the present study is that we successfully estimated the incidence of RRT initiation by risk factors using a real-world database of health checkup data and medical claims data as a retrospective cohort database. The incidence rates themselves, rather than incidence rate ratios, would be useful when policymakers assess the effectiveness of the Project to Prevent the Worsening of Diabetic Nephropathy. Also, now the insurers or municipals are encouraged to use health checkup data and medical claims data for health promotion, our method would be especially useful to insurers or municipals for estimating the incidence of RRT initiation by risk factors based on their own data, which would serve as compelling evidence of policymaking.

The present study has several limitations. First, we targeted only on those who underwent specific health checkup in 2012. The candidates of the Project to Prevent the Worsening of Diabetic Nephropathy were often selected from those who participated in specific health checkup in most municipalities; risk stratification among the participants is therefore essential. However, the obtained results were neither generalizable to non-participants of specific health checkup nor comparable to those from the previous community-based studies. For example, the municipality-based NHI held more females than the general population. The present study results should be generalized with caution using strata-specific incidences. Second, because of the observational study design stratified by the minimum number of factors, a causal relationship between the factors and RRT initiation cannot be concluded. Third, potential misclassification of variables is possible. For example, some subjects might have underreported their actual use of antidiabetic medication. Fourth, the study lacked information on the socioeconomic status (SES) of subjects. The increased risk among smokers may have been caused by confounding by SES because subjects with lower SES are more likely to be smokers, and lower SES might be an independent risk factor for RRT initiation (Fored et al. 2003; Volkova et al. 2008). The results, however, are still useful for risk stratification, as identification of subjects currently smoking and tailoring interventions to that specific group can be a practical intervention approach. Fifth, transfer to other schemes or death were not captured in the current study. For example, subjects aged 65-74 years might have transferred from the National Health Insurance to the Medical Care System for Elderly in the Latter Stage of Life when beneficiaries were qualified based on the disease or disability. If some subjects were qualified and left the National Health Insurance just before RRT initiation, this might have led to an underestimation of the RRT initiation risk. Meanwhile, the degree of underestimation is predicted to be none or small, given that the current disease/disability qualification process usually takes several months and often happens after the initiation of dialysis; therefore, we suppose that we could capture the initiation of dialysis among these patients even though they eventually transferred to another insurance system. Sixth, the number of outcome events was small within the current study cohort, partly because the shorter observation period compared with the previous community-based cohort studies (Iseki et al. 2004) and the selection from health checkups; the timing of RRT initiation can differ among physicians and regions. To increase the precision and to obtain more generalized evidence, the study analyses should be conducted on data from other insurers, or pooled analysis is needed. However, the present results may be very informative especially for the insurer and its beneficiaries who were the source population of the study. Seventh, some may think that the comparison between patients with stage 3 diabetic nephropathy and patients with stage G3 chronic kidney disease without diabetes was not appropriate. Although we understand that the comparison appears to be unusual from the viewpoint of clinicians, this comparison was conducted mainly to reevaluate the appropriateness of the Project from the viewpoint of policymakers or insurers who would think that the result is useful. Eighth, the effect of future programs targeting the risk factors on RRT prevention at the individual level was beyond the scope of this study. Even though we found higher-risk strata for RRT initiation in the present study, a higher absolute risk is only a prerequisite for a lower number needed to treat (or a higher absolute risk reduction) (Bender 2005). Future studies should investigate effective programs for RRT prevention in higher-risk subjects.

In conclusion, the current study has revealed that certain factors such as male sex, comorbid hypertension, and current smoking status, in addition to CKD staging, proteinuria, and diabetes, may confer a higher risk for RRT initiation. Even in the absence of diabetes, the risk of RRT initiation was quite high among subjects with more advanced CKD stage. Projects for RRT reduction that target subjects with these risk factors with or without diabetes might be the most efficient approach for the entire population. Given that an RRT prevention program enrolling candidates based on their diabetes and DN stage has been initiated in Japan, consideration of other factors including hypertension might increase the efficacy of the program at the population level.

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Author Contributions

All authors made substantial contributions to conception and design or analysis, interpretation of data, and drafting of the article or critical revision for important intellectual content. T.S. and Y.K. designed the study. T.S. wrote the first draft of the manuscript. T.S. and K.O. analyzed the data. T.S., K.O., and Y.K. reviewed and edited the manuscript. T.S. is the guarantor of this article. The research presented in this paper is that of the authors and does not reflect the official policy of the organizations. Please contact the corresponding author (T.S.) when any supplemental information is needed.

Conflict of Interest

The authors declare no conflict of interest.

References

Astor, B.C., Matsushita, K., Gansevoort, R.T., van der Velde, M., Woodward, M., Levey, A.S., Jong, P.E. & Coresh, J.; Chronic Kidney Disease Prognosis Consortium (2011) Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int.*, **79**, 1331-1340.

Bender, R. (2005) Number needed to treat (NNT). In *Encyclopedia of biostatistics*, edited by Armitage, P. & Colton, T. doi: 10.1002/0470011815.b2a04032.

Coresh, J., Turin, T.C., Matsushita, K., Sang, Y., Ballew, S.H., Appel, L.J., Arima, H., Chadban, S.J., Cirillo, M., Djurdjev, O., Green, J.A., Heine, G.H., Inker, L.A., Irie, F., Ishani, A., et al. (2014) Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*, **311**, 2518-2531.

Fored, C.M., Ejerblad, E., Fryzek, J.P., Lambe, M., Lindblad, P., Nyren, O. & Elinder, C.G. (2003) Socio-economic status and chronic renal failure: a population-based case-control study in Sweden. *Nephrol. Dial. Transplant.*, **18**, 82-88.

Fox, C.S., Matsushita, K., Woodward, M., Bilo, H.J., Chalmers, J., Heerspink, H.J., Lee, B.J., Perkins, R.M., Rossing, P., Sairenchi, T., Tonelli, M., Vassalotti, J.A., Yamagishi, K., Coresh, J., de Jong, P.E., et al. (2012) Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*, **380**, 1662-1673.

Gansevoort, R.T., Matsushita, K., van der Velde, M., Astor, B.C., Woodward, M., Levey, A.S., de Jong, P.E.& Coresh, J.; Chronic Kidney Disease Prognosis Consortium (2011) Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int.*, **80**, 93-104.

Greenland, S. (2006) Bayesian perspectives for epidemiological research: I. foundations and basic methods. *Int. J. Epidemiol.*, **35**, 765-775.

Hirayama, A., Konta, T., Kamei, K., Suzuki, K., Ichikawa, K., Fujimoto, S., Iseki, K., Moriyama, T., Yamagata, K., Tsuruya, K., Kimura, K., Narita, I., Kondo, M., Asahi, K., Kurahashi, I., et al. (2015) Blood pressure, proteinuria, and renal function decline: associations in a large community-based population. *Am. J. Hypertens.*, **28**, 1150-1156.

Ikegami, N., Yoo, B.K., Hashimoto, H., Matsumoto, M., Ogata, H., Babazono, A., Watanabe, R., Shibuya, K., Yang, B.M., Reich, M.R. & Kobayashi, Y. (2011) Japanese universal health coverage: evolution, achievements, and challenges. *Lancet*, **378**, 1106-1115.

Imai, E., Horio, M., Yamagata, K., Iseki, K., Hara, S., Ura, N., Kiyohara, Y., Makino, H., Hishida, A. & Matsuo, S. (2008) Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. *Hypertens. Res.*, **31**, 433-441.

Iseki, K., Ikemiya, Y., Kinjo, K., Inoue, T., Iseki, C. & Takishita, S. (2004) Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int.*, **65**, 1870-1876.

Japanese Society for Clinical Renal Transplantation; The Japan Society for Transplantation (2017) Annual progress report from the Japanese Renal Transplant Registry: number of renal transplantations in 2016 and follow-up survey. *Jpn. J. Transplant.*, **52**, 113-133.

Levey, A.S., de Jong, P.E., Coresh, J., El Nahas, M., Astor, B.C., Matsushita, K., Gansevoort, R.T., Kasiske, B.L. & Eckardt, K.U. (2011) The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. *Kidney Int.*, **80**, 17-28.

Levin, A., Stevens, P.E., Bilous, R.W., Coresh, J., De Francisco, A.L., De Jong, P.E., Griffith, K.E., Hemmelgarn, B.R., Iseki, K., Lamb, E.J., Levey, A.S., Riella, M.C., Shlipac, M.G., Wang, H., White, C.T. & Winearls, C.G. (2013) Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.*, **3**, 1-150.

Masakane, I., Taniguchi, M., Nakai, S., Tsuchida, T., Wada, A., Ogata, S., Hasegawa, T., Hamano, T., Hanafusa, N., Hoshino, J., Goto, S., Mizuguchi, J., Yamamoto, K. & Nakamoto, H. (2018) 2016 Annual dialysis data report, JSDT renal data registry. *Jpn. J. Transplant.*, **51**, 1-51.

Matsuo, S., Imai, E., Horio, M., Yasuda, Y., Tomita, K., Nitta, K., Yamagata, K., Tomino, Y., Yokoyama, H. & Hishida, A.; Collaborators developing the Japanese equation for estimated GFR (2009) Revised equations for estimated GFR from serum creatinine in Japan. *Am. J. Kidney Dis.*, **53**, 982-992.

Matsuzawa, Y., Funahashi, T. & Nakamura, T. (2011) The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism. *J. Atheroscler. Thromb.*, **18**, 629-639.

Ministry of Health, Labour and Welfare (2017) System supporting insurer's effort. https://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/02_1.pdf [*Accessed:* June 1, 2019] (in Japanese).

Nishikawa, K., Takahashi, K., Yamada, R., Kinaga, T., Masato, M. & Yamamoto, M. (2017) Influence of chronic kidney disease on hospitalization, chronic dialysis, and mortality in Japanese men: a longitudinal analysis. *Clin. Exp. Nephrol.*, **21**, 316-323.

Tanaka, N., Babazono, T., Takagi, M., Yoshida, N., Toya, K., Nyumura, I., Hanai, K. & Uchigata, Y. (2015) Albuminuria and reduced glomerular filtration rate for predicting the renal outcomes in type 2 diabetic patients. *Nephrology* (*Carlton*), **20**, 531-538.

The Japan Medical Association, Japan Council for Promotion of Countermeasures against Diabetes & The Ministry of Health, Labour and Welfare (2016) The project to prevent the wors-

ening of diabetic nephropathy. https://www.mhlw.go.jp/file/04-Houdouhappyou-12401000-Hokenkyoku-Soumuka/0000121902.pdf [*Accessed*: June 1, 2019].

Tonelli, M., Klarenbach, S.W., Lloyd, A.M., James, M.T., Bello, A.K., Manns, B.J. & Hemmelgarn, B.R. (2011) Higher estimated glomerular filtration rates may be associated with increased risk of adverse outcomes, especially with concomitant proteinuria. *Kidney Int.*, **80**, 1306-1314.

van der Velde, M., Matsushita, K., Coresh, J., Astor, B.C., Woodward, M., Levey, A., de Jong, P. & Gansevoort, R.T.; Chronic Kidney Disease Prognosis Consortium (2011) Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int.*, **79**, 1341-1352.

Volkova, N., McClellan, W., Klein, M., Flanders, D., Kleinbaum, D., Soucie, J.M. & Presley, R. (2008) Neighborhood poverty and racial differences in ESRD incidence. *J. Am. Soc. Nephrol.*, **19**, 356-364.

Wada, T., Haneda, M., Furuichi, K., Babazono, T., Yokoyama, H., Iseki, K., Araki, S., Ninomiya, T., Hara, S., Suzuki, Y., Iwano, M., Kusano, E., Moriya, T., Satoh, H., Nakamura, H., et al. (2014) Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. *Clin. Exp. Nephrol.*, **18**, 613-620.