




ORIGINAL ARTICLE

Anemia and atrial fibrillation as independent risk factors for new-onset chronic kidney disease: the TAMA-MED Project—CKD and AF

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ABSTRACT

Background. Various risk factors have been identified for the new onset or rapid deterioration of chronic kidney disease (CKD). However, it is thought that many risk factors that have not yet been clarified remain.

Methods. Based on the results of specific annual health checkups at Tama City ($n = 18\,383$) in 2017 and 2018, we analyzed the factors that cause new-onset CKD and the risk factors that rapidly worsen renal function. For new-onset CKD, proteinuria and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² were examined separately. Rapid deterioration of renal function was defined as an eGFR $\geq 25\%$ less than the previous year.

Results. Multivariate analysis showed that in addition to age and impaired glucose tolerance, anemia and atrial fibrillation (AF) were risk factors for the new appearance of proteinuria. Risk factors for a decrease in eGFR to <60 mL/min/1.73 m² were age and hyperuricemia. Age, systolic hypertension, urinary protein and urinary occult blood, high triglycerides and anemia were significant risk factors for the rapid deterioration of renal function in patients with CKD Stage ≥ 3 .

Conclusions. From the results of specific annual health checkups at Tama City, AF, anemia and hyperuricemia were identified as risk factors for new-onset CKD over a short period of 1 year. Anemia was also a factor for the rapid deterioration of kidney function in subjects with renal dysfunction.

Keywords: anemia, atrial fibrillation, chronic kidney disease, hyperuricemia, specific annual health checkups

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INTRODUCTION

Chronic kidney disease (CKD) patients are at risk of developing end-stage renal disease (ESRD), and the number of affected people is increasing worldwide, which poses a major health economic problem. CKD has been shown to be a significant risk factor for brain and cardiovascular diseases such as myocardial infarction and stroke and preventing new-onset CKD, as well as the rapid worsening thereof, can help prevent these diseases. In other words, finding risk factors that cause or exacerbate CKD will contribute to maintaining activities of daily living and extending healthy life expectancy in the face of an increasingly aging population.

The causes of CKD range from primary, such as chronic glomerulonephritis, interstitial nephritis, vasculitis and hereditary renal disease, to secondary, such as systemic disease and drug-related causes. It has also been found that there are common mechanisms that contribute to the development and worsening of CKD regardless of the underlying disease. Hypertension, impaired glucose tolerance, obesity, smoking, etc. have been reported as factors that cause or worsen CKD [1–3]. Many risk factors have not yet been clarified and remain unclear. In addition, although it was not indicated until the previous year, there are cases where CKD is newly recognized as a result of annual health checkups even if there are no symptoms.

The Tama Medical Association in Tokyo has added electrocardiography since 2008 and urine occult blood and serum creatinine (SCr) since 2012 as mandatory items for health checkups to detect CKD and atrial fibrillation (AF) in the early stages (TAMA MED Project-CKD and Project-AF). In the present study, based on this health examination data, we examined the factors involved in the development or worsening of CKD over a short period of 1 year.

MATERIALS AND METHODS

Study design of the TAMA MED Project-CKD and Project-AF

The TAMA MED Project-CKD and Project-AF were conducted as retrospective cohort studies to clarify the prevalence and incidence of CKD [4] and AF [5] in the general population and simultaneously research frailty [6]. The study protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of our institution [approval number 529 (2017)].

A consecutive series of subjects who had national health insurance or public late-elderly health insurance and had undergone annual specific health checkups at a clinic or hospital belonging to the Tama City Medical Association were recruited. All participants were measured for body height and weight, waist circumference and systolic and diastolic blood pressure (SBP and DBP). Body mass index (BMI) was calculated and smoking habits were determined. Moreover, plasma hemoglobin (Hb), fasting plasma glucose, HbA1c, serum high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides (TGs) and urine sugar and protein were examined (using the test paper method). In addition, a standard 12-lead electrocardiogram (ECG) was recorded in all participants as a Tama City-specific mandatory optional examination since 2008. SCr and urine blood (using the test paper method) have been measured since 2012 and serum uric acid (UA) has been measured since 2015 in all participants.

Diagnosis of CKD and AF

Proteinuria was measured by the test paper method and classified into five levels: –, ±, +, ++ and +++. Positive proteinuria was defined as + or more. The approximate values of proteinuria indicated by the test paper method were ±, equating to >15 mg/dL; +, equating to >30 mg/dL; ++, equating to >100 mg/dL and +++, equating to >300 mg/dL.

The estimated glomerular filtration rate (eGFR) was calculated using the following equation [7]: for males, $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{age} - 0.287 \times \text{SCr (mg/dL)} - 1.094$; and for females, $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{age} - 0.287 \times \text{SCr (mg/dL)} - 1.094 \times 0.739$.

Rapid deterioration of renal function was defined as an eGFR $\geq 25\%$ less than the previous year. In this study we analyzed the data for 2017 and 2018.

Physicians directly diagnosed AF from reports based on automatic analysis of 12-lead ECGs in each clinic or hospital, regardless of the ECG model and vendor.

Statistical analysis

Data are presented as the mean \pm standard deviation. P-values < 0.05 were considered statistically significant in all analyses. A Cox proportional hazards model was used to investigate the influence of clinical factors. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the presence of categorical variables were calculated. We first extracted variables with significant HRs in the univariate analysis. In addition, to determine significant risk factors, multivariate analysis was conducted after simultaneously controlling for potential confounders. Numerical values were analyzed using continuous variables. All statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY, USA).

RESULTS

Prevalence of CKD in 2017

There were 18 383 subjects for whom health screening data were available for both 2017 and 2018. Table 1 shows the various data for the subjects in 2017. Age ranged from 40 to 101 years and SBP was widely distributed with a minimum of 72 mmHg and a maximum of 219 mmHg. The prevalence of AF was 2.1%.

Table 2 shows the number of patients by stage of eGFR, along with the degree of proteinuria. Although there were 75 patients for whom no urine results were available, receipt data revealed that 14 patients with CKD Stage G5 were on dialysis. There were 5962 (32.4%) CKD equivalents with proteinuria or $eGFR < 60 \text{ mL/min/1.73 m}^2$. CKD without proteinuria accounted for 51.7% of all CKD cases.

Risk factors for new-onset CKD (proteinuria)

We analyzed subjects who had newly recognized proteinuria in 2018 even though they did not meet the CKD criteria in 2017. The number of eligible persons was 297. In a univariate analysis, age, female sex, $BMI \geq 25 \text{ kg/m}^2$, $SBP \geq 140 \text{ mmHg}$, $DBP \geq 90 \text{ mmHg}$, $HbA1c \geq 6.0\%$, $Hb < 12 \text{ g/dL}$ (men), $Hb < 11 \text{ g/dL}$ (women) and AF in 2017 were the associated factors. Among these, age, $HbA1c \geq 6.0\%$, $Hb < 12 \text{ g/dL}$ (men), $Hb < 11 \text{ g/dL}$ (women) and AF were listed as significant risk factors in the multivariate analysis (Table 3).

Risk factors for new-onset CKD (eGFR <60 mL/min/1.73 m²)

We analyzed subjects whose eGFR was <60 mL/min/1.73 m² in 2018 even though they did not meet the CKD criteria in 2017. The number of eligible persons was 970. In univariate analysis, age, BMI ≥25 kg/m², SBP ≥140 mmHg, UA ≥7.0 mg/dL and AF were the associated factors. Of these, age and UA ≥7.0 mg/dL were listed as significant risk factors in the multivariate analysis (Table 4). Together with the above proteinuria results, age, impaired glucose tolerance, anemia, AF and hyperuricemia were identified as factors for new-onset CKD.

Risk factors for rapidly worsening CKD

Risk factors that rapidly worsened CKD were analyzed in subjects with an eGFR ≥60 mL/min/1.73 m² and those with an eGFR <60 mL/min/1.73 m² in 2017. There were a total of 159 subjects who met the criteria. In subjects with an eGFR ≥60 mL/min/1.73 m², age, proteinuria, proteinuria + hematuria, SBP ≥140 mmHg, DBP ≥90 mmHg, TGs ≥300 mg/dL and UA ≥9.0 mg/dL in 2017 were the factors associated with rapidly worsening CKD (n = 101). Of these, age, proteinuria, proteinuria +

hematuria and UA ≥9.0 mg/dL were listed as significant risk factors in multivariate analysis (Table 5).

In subjects with eGFR <60 mL/min/1.73 m², age, proteinuria, proteinuria + hematuria, SBP ≥140 mmHg, TGs ≥300 mg/dL, Hb <12 g/dL (men), Hb <11 g/dL (women) and AF in 2017 were the factors associated with rapidly worsening CKD (n = 58). Among these, age, proteinuria + hematuria, SBP ≥140 mmHg, TGs ≥300 mg/dL, Hb <12 g/dL (men) and Hb <11 g/dL (women) were listed as significant risk factors in the multivariate analysis (Table 6).

Regarding AF, morbidity in 2017 was not an associated factor. However, morbidity of AF in 2018 was a factor associated with rapid deterioration of renal function in the eGFR ≥60 mL/min/1.73 m² [HR 3.410 (95% CI 1.482–7.845); P = 0.004] and eGFR <60 mL/min/1.73 m² [HR 2.456 (95% CI 1.048–5.760); P = 0.039] groups.

DISCUSSION

In this study we used the results of specific annual health checkups in Tama City, Tokyo, to analyze the factors that cause new-onset CKD and rapid deterioration of kidney function over a short period of 1 year. The major findings were as follows. First, anemia and AF were newly identified as risk factors for new-onset CKD. Second, proteinuria, proteinuria + hematuria and hyperuricemia were significant risk factors for rapid deterioration of renal function in subjects with normal kidney function. Third, proteinuria + hematuria, systolic hypertension, high TGs and anemia were identified as significant risk factors for rapid deterioration of kidney function in subjects with impaired kidney function.

The prevalence of CKD in this study was 32.4%. The study enrolled subjects 40–74 years of age with national health insurance and subjects ≥75 years of age with public late-elderly health insurance. The average age was 73.1 ± 9.0 years. In our previous report, the prevalence of CKD in specific health checkups for people 40–74 years of age (67.0 ± 7.3 years) in 2015 was 19.8% [4]. This also reveals that the prevalence of CKD increases with age. The prevalence of AF was 2.1%, which is considerably greater than the 1.4% in 2015, which also targeted people 40–74 years of age [5].

This study has shown that anemia is involved in both new-onset and worsening CKD. Interstitial fibroblasts have the ability to produce erythropoietin (EPO), but when interstitial fibrosis progresses due to CKD, they become myofibroblasts and lose the ability to produce EPO. Therefore, as CKD progresses, renal anemia develops, but there have been few reports that anemia itself, before the appearance of renal anemia, is a risk factor for proteinuria. Previous reports have demonstrated that anemia is associated with increased mortality and morbidity rates in

Table 1. Subject characteristics

Subjects, N	18 383
Age (years), mean ± SD	73.1 ± 9.0
Male, n (%)	7754 (42.2)
BMI (kg/m ²), mean ± SD	22.7 ± 3.3
SBP (mmHg), mean ± SD	128.9 ± 16.4
DBP (mmHg), mean ± SD	73.1 ± 10.5
Current smoker, n (%)	2132 (11.6)
Blood examinations, mean ± SD	
Hb (g/dL)	13.7 ± 1.4
LDL-C (mg/dL)	120.1 ± 29.1
TGs (mg/dL)	113.1 ± 70.8
Glucose (mg/dL)	99.1 ± 20.2
HbA1c (National Glycohemoglobin Standardization Program) (%)	5.8 ± 0.6
Cr (mg/dL)	0.8 ± 0.4
eGFR (mL/min/1.73 m ²)	67.9 ± 19.8
UA (mg/dL)	5.3 ± 1.3
Urinalysis, n (%)	
Urine protein ^a	1262 (6.9)
Urine blood ^a	1282 (7.0)
EKG, n (%)	
AF	382 (2.1)

LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

^aPositive urine protein and blood were defined as + or more using the test paper method.

Table 2. Numbers and prevalence of eGFR and proteinuria categories in 2017

GFR stage	eGFR (mL/min/1.73 m ²)	Proteinuria ^a – or ±, n	Proteinuria ^a +, n	Proteinuria ++ or +++, n	No urine data
G1	≥90	1144	46	15	7
G2	60–89	11 246	462	142	24
G3a	45–59	3930	249	119	15
G3b	30–44	639	108	80	15
G4	15–29	62	21	33	0
G5	<15	5	4	3	14

^aThe approximate values of proteinuria are indicated as ± (>15 mg/dL), + (>30 mg/dL), ++ (>100 mg/dL) and +++ (> 300 mg/dL).

Table 3. Significant indicators of new-onset CKD (proteinuria) in 2018 (Cox proportional hazards model)

Variables (2017 data)	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (1-year increase)	1.022 (1.008–1.036)	0.002	1.017 (1.003–1.031)	0.021
Sex (women)	1.345 (1.067–1.695)	0.012	0.795 (0.628–1.005)	0.055
BMI ≥ 25 kg/m ²	1.346 (1.024–1.771)	0.033	1.237 (0.935–1.636)	0.137
SBP ≥ 140 mmHg	1.310 (1.012–1.696)	0.041	1.123 (0.841–1.500)	0.431
DBP ≥ 90 mmHg	1.529 (1.046–2.235)	0.029	1.505 (0.984–2.303)	0.060
HbA1c ≥ 6.0	1.682 (1.311–2.159)	<0.001	1.545 (1.196–1.996)	0.001
Hb <12 g/dL (men)	2.456 (1.459–4.135)	0.001	2.215 (1.285–3.817)	0.004
Hb <11 g/dL (women)				
AF	2.928 (1.467–5.845)	0.002	2.298 (1.139–4.635)	0.020

Nonsignificant variables in univariate analysis are not shown.

Table 4. Significant indicators of new-onset CKD (eGFR <60 mL/min/1.73 m²) in 2018 (Cox proportional hazards model)

Variables (2017 data)	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (1-year increase)	1.054 (1.045–1.063)	<0.001	1.055 (1.046–1.064)	<0.001
BMI ≥ 25 kg/m ²	1.179 (1.002–1.386)	0.047	1.175 (0.996–1.386)	0.056
SBP ≥ 140 mmHg	1.219 (1.049–1.417)	0.010	1.060 (0.909–1.235)	0.457
UA ≥ 7.0 mg/dL	1.619 (1.262–2.078)	<0.001	1.722 (1.325–2.238)	<0.001
AF	1.671 (1.011–2.761)	0.045	1.256 (0.754–2.093)	0.381

Nonsignificant variables in univariate analysis are not shown.

Table 5. Significant indicators of rapid deterioration of renal function in the group of eGFR ≥ 60 mL/min/1.73 m² in 2017 (Cox proportional hazards model)

Variables (2017 data)	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (1-year increase)	1.046 (1.022–1.071)	<0.001	1.042 (1.017–1.069)	0.001
Proteinuria	4.175 (2.543–6.855)	<0.001	3.976 (2.249–7.030)	<0.001
Proteinuria + hematuria	3.210 (1.294–7.964)	0.012	2.815 (1.102–7.190)	0.031
SBP ≥ 140 mmHg	1.621 (1.096–2.395)	0.015	1.271 (0.798–2.023)	0.313
DBP ≥ 90 mmHg	2.054 (1.206–3.497)	0.008	1.763 (0.926–3.356)	0.084
TGs ≥ 300 mg/dL	2.649 (1.154–6.079)	0.022	2.563 (1.000–6.568)	0.050
UA ≥ 9.0 mg/dL	10.911 (2.528–47.085)	0.001	13.523 (2.827–64.682)	0.001

Nonsignificant variables in univariate analysis are not shown.

Table 6. Significant indicators of rapid deterioration of renal function in the group of eGFR <60 mL/min/1.73 m² in 2017 (Cox proportional hazards model)

Variables (2017 data)	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (1-year increase)	1.066 (1.030–1.103)	<0.001	1.045 (1.008–1.084)	0.017
Proteinuria	3.495 (2.020–6.046)	<0.001	2.003 (0.987–4.063)	0.054
Proteinuria + hematuria	5.168 (2.506–10.659)	<0.001	3.979 (1.834–8.634)	<0.001
SBP ≥ 140 mmHg	2.320 (1.403–3.837)	0.001	2.209 (1.296–3.765)	0.004
TGs ≥ 300 mg/dL	2.888 (1.032–8.079)	0.043	4.117 (1.412–12.000)	0.010
Hb <12 g/dL (men)	3.869 (2.147–6.972)	<0.001	2.618 (1.324–5.175)	0.006
Hb <11 g/dL (women)				

Nonsignificant variables in univariate analysis are not shown.

patients with various diseases such as heart failure [8], angina pectoris [9], acute coronary syndrome [10] and cancer [11]. One possible reason is the increased risk of developing CKD due to chronic tubular interstitial hypoxia caused by anemia. It has also been reported that proteinuria is more likely to appear in heart failure [12]. Vascular endothelial dysfunction and the activation of neurohumoral factors associated with heart failure are thought to be mechanisms underlying the appearance of proteinuria. It is therefore possible that chronic anemia may have been a risk factor for the appearance of proteinuria via heart failure. In addition, if the presence of chronic inflammation was the cause of the anemia, it is conceivable that it could subsequently cause CKD [13]. Therefore, it should be noted that when anemia is identified, CKD may soon develop.

We previously reported that CKD classification is significantly associated with new-onset AF in the general population [14]. AF may cause kidney dysfunction and vice versa [15]. Evidence suggesting a role for the renin-angiotensin-aldosterone system in the pathogenesis of AF has been reported [16]. Treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers reduced the incidence of AF [17]. Activation of the renin-angiotensin-aldosterone system causes the appearance of proteinuria through mechanisms such as increased glomerular pressure, podocyte injury and decreased barrier function of the slit membrane [18, 19]. Therefore, it is possible that AF became an independent risk factor for the appearance of proteinuria.

Anemia was detected as a factor that rapidly worsened kidney function in subjects with already impaired kidney function. It has been reported that a decrease in hematocrit is apparent even among patients with mild to moderate renal insufficiency [20], and that subjects with low hematocrits, <40% for men and <35% for women, have a significantly increased risk of ESRD [21]. Our study revealed that the presence of anemia is a risk factor for the rapid deterioration of renal function. It should be noted that a vicious cycle of ischemia and hypoxia in the kidneys occurs during the progression of CKD, and it has been reported experimentally that decreased blood flow or loss of peritubular capillaries can be observed from very early on [22]. This vicious cycle of ischemia and hypoxia also progresses due to the reduced oxygen-carrying capacity caused by anemia. There are also many reports that the maintenance of renal function was obtained by treating anemia, and it is expected that the renal protective effect for conservative CKD patients, including hypoxia-inducible factor prolyl hydroxylase inhibitors, will be reported in the future.

AF was not a risk factor for rapid deterioration of renal function in the previous year's data, but the incidence of AF increased with deteriorating renal function. Previous studies showed that new-onset AF in hypertensive patients was associated with a decrease in eGFR [23] and that the elimination of AF by catheter ablation was associated with an improvement in kidney function over a 1-year follow-up in patients with mild to moderate kidney dysfunction [24]. There have also been reports of worsening renal function in CKD patients treated with oral anticoagulants and antiplatelet agents used for AF [25, 26]. It is possible that the onset of AF during the year may have contributed to the rapid deterioration of renal function, which requires further investigation.

Proteinuria was a risk factor for the rapid deterioration of renal function in patients with normal renal function. When proteinuria is observed, the cause should be investigated and efforts should be made to reduce it. On the other hand, proteinuria alone was not a risk factor for rapid renal function

deterioration in persons with impaired renal function, but both proteinuria and hematuria were risk factors for rapid deterioration of renal function. The complication of hematuria is thought to suggest the presence of active nephritis and vasculitis and early intervention by a nephrologist is desirable to prevent the rapid deterioration of renal function.

Hyperuricemia was a risk factor for newly impaired renal function (UA \geq 7.0 mg/dL) as well as for rapid deterioration of renal function in patients with normal renal function (UA \geq 9.0 mg/dL). Sonoda *et al.* [27] reported that baseline serum UA levels and annual increases in serum UA levels increased the risk of developing CKD in individuals with normal renal function in a review of 7078 health screenings. The progress of CKD was investigated using the propensity score matching method in a retrospective cohort study of 803 patients. There was a significant increase in the HR for the development of renal failure in the high UA group [28]. Control of serum UA levels is considered important in terms of reducing the development of CKD and preventing it from worsening.

A TG level \geq 300 mg/dL was a significant risk factor for the rapid deterioration of renal function in subjects with impaired renal function. In a study of Finnish patients with type I diabetes mellitus, high blood TG levels at baseline were reported to significantly increase the risk of progression/exacerbation of nephropathy [29]. Our study was conducted on all CKD-causing diseases, and the effects of drugs such as fibrates cannot be ruled out.

The present study had several limitations. First, the participants of specific annual health checkups were limited to those \geq 40 years of age. People <40 years of age did not participate in this study. Second, the diagnosis of CKD was based solely on the results of a single health checkup. CKD was defined as having aberrant test results over a period of >3 months, and this may have resulted in overestimating the number of CKD-diagnosed participants. Third, the diagnostic accuracy of the automatic analysis of ECGs was not validated. As there are many models and vendors of ECGs and diagnostic algorithms are not unified. Fourth, since the medication status of the subjects was not known, the influence of drugs on new-onset or rapid deterioration of CKD cannot be overlooked.

In conclusion, anemia and AF were determined as risk factors of new-onset CKD based on the results of specific annual health checkups of people \geq 40 years of age in Tama City, Tokyo. Anemia is also a factor for the rapid deterioration of renal function in subjects with renal dysfunction, therefore treatment for anemia and AF may be useful in reducing the development and progression of CKD.

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AUTHORS' CONTRIBUTIONS

T.K., E.K., H.F. and Y.T. were involved in the research idea and study design. T.K., E.K., R.A., M.S. and R.N. were involved in data analysis/interpretation. T.K., E.K., H.N., H.S.

and Y.T. were involved in the statistical analysis. All authors gave final approval of the submitted manuscript.

CONFLICT OF INTEREST STATEMENT

E.K. received remuneration from Daiichi-Sankyo, Bristol-Myers Squibb and Ono Pharmaceutical. All other authors have declared no conflicts of interest.

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