

RESEARCH ARTICLE

Prevalences of hyperuricemia and electrolyte abnormalities in patients with chronic kidney disease in Japan: A nationwide, cross-sectional cohort study using data from the Japan Chronic Kidney Disease Database (J-CKD-DB)

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Abstract

Background

The Japan Chronic Kidney Disease Database (J-CKD-DB) is a nationwide clinical database of patients with chronic kidney disease (CKD) based on electronic health records. The

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objective of this study was to assess the prevalences of hyperuricemia and electrolyte abnormalities in Japanese patients with CKD.

Methods

In total, 35,508 adult outpatients with estimated glomerular filtration rates of 5–60 ml/min/1.73 m² in seven university hospitals were included this analysis. The proportions of patients with CKD stages G3b, G4, and G5 were 23.5%, 7.6%, and 3.1%, respectively.

Results

Logistic regression analysis showed that prevalence of hyperuricemia was associated with CKD stages G3b (adjusted odds ratio [95% confidence interval]: 2.12 [1.90–2.37]), G4 (4.57 [3.92–5.32]), and G5 (2.25 [1.80–2.80]). The respective prevalences of hyponatremia, hypercalcemia, hyperphosphatemia, and narrower difference between serum sodium and chloride concentrations were elevated in patients with CKD stages G3b, G4, and G5, compared with those prevalences in patients with CKD stage G3a. The prevalences of hyperkalemia were 8.3% and 11.6% in patients with CKD stages G4 and G5, respectively. In patients with CKD stage G5, the proportions of patients with optimal ranges of serum uric acid, potassium, corrected calcium, and phosphate were 49.6%, 73.5%, 81.9%, and 56.1%, respectively.

Conclusions

We determined the prevalences of hyperuricemia and electrolyte abnormalities in Japanese patients with CKD using data from a nationwide cohort study.

Introduction

A reduction in estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² is regarded as a sign of chronic kidney disease (CKD), as are structural or functional renal abnormalities [1]. Approximately 13% of Japanese adults are estimated to have CKD [2]. Cross-sectional estimates of the prevalence of CKD in the United States range from 1.5% to 15.6% [3]. CKD is categorized on the basis of eGFR and the degree of proteinuria [4], and is reportedly a major risk factor for cardiovascular disease [5]. Moreover, the socioeconomic impacts of CKD are important global problems [6].

Important complications of CKD include hyperuricemia and electrolyte abnormalities (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia, and metabolic acidosis), as well as renal anemia [7, 8]. Although it remains controversial, asymptomatic hyperuricemia has been reported as a risk factor for eGFR decline in patients with CKD [9, 10]. Hyperkalemia and hyperphosphatemia are known risk factors for cardiovascular disease and mortality in patients with CKD [11–16].

The prevalences of hyperuricemia and electrolyte abnormalities in patients with CKD have been reported in clinical and epidemiological studies [8–11, 13–18]. Recently, analyses of real-world conditions of patients with CKD were performed based on electronic health records [12, 19–22]; these studies included analyses of electrolyte abnormality prevalences among patients with CKD [12]. However, electronic health record analyses of the prevalences of hyperuricemia and electrolyte abnormalities according to CKD G category have been limited.

The Japan Chronic Kidney Disease Database (J-CKD-DB) is a large-scale, nationwide comprehensive clinical database of patients with CKD based on electronic health records data from participating university hospitals [23, 24]. Using a standardized method for information exchange (Standardized Structured Medical Information eXchange; SS-MIX2) [25], the J-CKD-DB efficiently compiles clinical data of patients with CKD across hospitals, regardless of differences in electronic health records systems. The J-CKD-DB cohort includes automatically extracted data regarding all patients with CKD in Japan. Therefore, the J-CKD-DB enables investigations of real-world CKD practices in Japan through both cross-sectional and prospective studies.

The aim of this study was to assess the real-world prevalences of hyperuricemia and electrolyte abnormalities in Japanese patients with CKD by using automatically extracted data from a nationwide, large-scale cohort study in Japan.

Materials and methods

Study setting and participants

The J-CKD-DB is a multicenter, automatically extracted comprehensive database of patients with CKD from 21 university hospitals in Japan (UMIN trial number, UMIN000026272) [23, 24]. The inclusion criteria for the J-CKD-DB are as follows: 1) age ≥ 18 years; 2) proteinuria $\geq 1+$ (dipstick test) and/or eGFR < 60 ml/min/1.73 m², where eGFR is calculated using the Japanese eGFR equation: $\text{eGFR (ml/min/1.73 m}^2) = 194 \times \text{serum creatinine value}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ [for women]})$ [26]. All data elements are extracted in a semiautomatic manner via the SS-MIX2 format and stored in the Multipurpose Clinical Data Registry System [23, 27]. Patients undergoing renal replacement therapy (i.e., hemodialysis, peritoneal dialysis, and kidney transplantation) are manually omitted.

In this study, we performed an observational cross-sectional investigation. To exclude most patients with acute kidney injury, we omitted inpatients from this analysis [24]. We identified 39,121 adult outpatients with at least one measurement of serum creatinine in seven university hospitals from January 1, 2014 to December 31, 2014. We included 35,508 patients with CKD based on outpatient laboratory data that indicated eGFR of 5–60 ml/min/1.73 m² [24, 28, 29].

Data collection

CKD G categories were defined as follows: stage G3a, eGFR of ≥ 45 and < 60 ml/min/1.73 m²; stage G3b, eGFR of ≥ 30 and < 45 ml/min/1.73 m²; stage 4, eGFR of ≥ 15 and < 30 ml/min/1.73 m²; and stage 5, eGFR < 15 ml/min/1.73 m² [1, 24]. eGFR5 categories were divided into 11 subgroups based on eGFR ranges of 5 ml/min/1.73 m² each, as performed in a previous study [24].

Data for this analysis that were obtained from the SSMIX-2 system included age, sex, eGFR, dipstick proteinuria, hemoglobin, serum albumin, total cholesterol, sodium, potassium, chloride, calcium, phosphate, and C-reactive protein. The lowest value of eGFR during the study period was selected as the eGFR value for analysis. Data without related eGFR values were extracted for 1 week before or 1 week after an eGFR value was recorded [23]. The difference between serum sodium and chloride concentrations was determined as serum Na–serum Cl (mEq/L) [30]. Serum corrected calcium level was calculated using Payne's correction formula: measured serum calcium level + (4 – serum albumin level) (mg/dl) [31]. Mean serum uric acid (UA) level was analyzed according to G category, eGFR5 category, age, and sex strata. Mean electrolyte levels were analyzed according to G category and eGFR5 category.

The optimal range for serum UA level was defined as < 6.0 mg/dl, based on Japanese clinical practice guidelines during the study period [32]. The optimal ranges of electrolytes were

defined as serum sodium >135 mEq/L to <145 mEq/L [33], serum potassium >3.5 mEq/L to <5.5 mEq/L [34], serum corrected calcium >8.4 mg/dl to <10.3 mg/dl [35], and serum phosphate >2.5 mg/dl to <4.5 mg/dl [35]. Hyperuricemia was defined as serum UA level ≥ 7.0 mg/dl [32]. Electrolyte disorders were defined as follows: hyponatremia and hypernatremia as serum sodium levels of ≥ 145 mEq/L and ≤ 135 mEq/L, respectively; hyperkalemia and hypokalemia as serum potassium levels of ≥ 5.5 mEq/L and ≤ 3.5 mEq/L, respectively; hypercalcemia and hypocalcemia as serum corrected calcium levels of ≥ 10.3 mg/dl and ≤ 8.4 mg/dl, respectively; and hyperphosphatemia and hypophosphatemia as serum phosphate levels of ≥ 4.5 mg/dl and ≤ 2.5 mg/dl, respectively [33–35]. Narrower serum Na–Cl level was defined as ≤ 30 mEq/L [30]. To identify the effect of season on the prevalence of hyperuricemia, participants were divided into four subgroups according to the date of blood sample collection: winter (December, January, and February), spring (March, April, and May), summer (June, July, and August), and autumn (September, October, and November).

Ethics statement

The J-CKD-DB study was comprehensively approved by the ethics committee of Kawasaki Medical School and Japanese Society of Nephrology (JSN-28) and individually approved by local committees of participating university hospitals (Kagawa University Hospital, Asahikawa Medical University Hospital, University of Tokyo Graduate School of Medicine, Nagoya University Hospital, Kanazawa University Hospital, Kochi University Hospital, University of Tsukuba Hospital, Niigata University Hospital, Kyoto University Hospital, Okayama University Hospital, Wakayama Medical University Hospital, Shimane University Hospital, Yokohama City University Hospital, Osaka University Hospital, Saitama Medical University Hospital, Nara Medical University Hospital, Kanazawa Medical University Hospital and Kyushu University Hospital). The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. Because all data had been fully anonymized prior to retrieval for this study, informed consent was obtained in the form of opt-out on the website of each participating university hospital. Patients who declined to participate in the J-CKD-DB were not registered.

Statistical analysis

Values are presented as medians with interquartile intervals, means with standard deviations, or counts with percentages, as appropriate. Distributions of variables were evaluated by histogram, quantile-quantile plot, and the Kolmogorov–Smirnov test. Clinical variables were compared between groups using the χ^2 test for categorical variables and Student's t-test, one-way analysis of variance, two-way analysis of variance, or the Mann–Whitney U test for continuous variables. Tukey's multiple comparison test was used for post hoc corrections for multiple comparisons. All data were statistically analyzed using IBM SPSS Advanced Statistics, version 27.0 (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered to indicate significant differences.

To identify independent associations of G category with the prevalences of hyperuricemia and electrolyte abnormalities, multivariable logistic regression models were used. The adjusted odds ratios and corresponding two-sided 95% confidence intervals of the predictors were determined. Model 1 (including age, sex, G grade, A grade, hemoglobin level, albumin level, C-reactive protein, hypernatremia, hypokalemia, and season of sample collection as covariates) was used for hyperuricemia; model 2 (including age, sex, G grade, A grade, hemoglobin level, albumin level, and C-reactive protein as covariates) was used for hypernatremia, hyponatremia, hyperkalemia, hypokalemia, narrower serum Na–Cl level, hyperphosphatemia, and

hypophosphatemia; model 3 (including age, sex, G grade, A grade, hemoglobin level, and C-reactive protein as covariates) was used for hypercalcemia and hypocalcemia; and model 4 (including age, sex, G grade, A grade, albumin level, hemoglobin level, and narrower serum Na–Cl level as covariates) was used for hyperkalemia.

Results

Baseline characteristics of enrolled outpatients

The sampling rate stratification of the 35,508 patients, according to G category strata, is shown in Table 1. Serum UA and potassium were collected in 73.0% and 80.5% of patients with CKD, respectively; serum calcium and phosphate were collected in 41.9% and 30.4% of patients with CKD, respectively. However, the sampling rate of each electrolyte, especially serum calcium and phosphate, increased in accordance with the progression of G category.

Baseline characteristics of enrolled outpatients are shown in Table 2. The median age was 72 [interquartile interval, 64–79] years, 54.5% were men, and median eGFR was 50.0 [interquartile interval, 40.9–55.6] ml/min/1.73 m². The numbers of patients with CKD stages G3a, G3b, G4, and G5 were 23,333 (65.7%), 8,357 (23.5%), 2,710 (7.6%), and 1,108 (3.1%), respectively. The mean hemoglobin level (standard deviation) of all patients was 13.0 (1.9) g/dl. Stratification of patients according to eGFR category, age, and sex strata is shown in S1 Table. Serum UA and electrolyte status stratifications according to G category strata are shown in Table 3.

Association between serum UA level and eGFR

Mean serum UA levels according to eGFR5 category and sex strata are shown in Fig 1. The mean serum UA level increased in accordance with the progression of eGFR5 category in both male and female patients. However, the mean serum UA level was lower in patients with an eGFR category of ≥ 5 and < 10 ml/min/1.73 m² than in patients with an eGFR category of ≥ 10 and < 15 ml/min/1.73 m². The mean serum UA level was higher in male patients than in female patients among patients with an eGFR category of > 30 ml/min/1.73 m², and an eGFR of ≥ 15 and < 20 ml/min/1.73 m². Serum UA distribution according to G category and sex strata is shown in Fig 2. The proportion of patients with high serum UA level increased in accordance with the progression of G category in both male and female patients, except among patients with CKD stage G5.

The mean serum UA levels according to G category, age, and sex strata are shown in S2 Table. The mean serum UA level gradually increased in accordance with the progression of G

Table 1. Sampling rate stratification according to G category strata.

		UA	Na	K	Cl	Ca	P
G3a	%	70.1	61.7	76.7	54.6	38.1	25.7
G3b	%	75.5*	68.8*	85.4*	60.5*	43.2*	31.9*
G4	%	84.6*	74.5*	93.1*	68.6*	58.1*	50.6*
G5	%	85.4*	75.0*	94.7*	71.3*	71.8*	67.2*
Total	%	73.0 [†]	64.8	80.5 [†]	57.6 [†]	41.9 [†]	30.4 [†]

Sampling rate is expressed as % of each population.

Abbreviations: UA, serum uric acid; Na, serum sodium; K, serum potassium; Cl, serum chloride; Ca, serum calcium; P, serum phosphate.

*:p<0.05 vs. G3a

[†]:p<0.05 vs. Na.

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Table 2. General characteristics of study cohort upon enrollment.

N		35,508
Age (years)		72.0 [64.0–79.0]
Age category		
	18–45 years	1,173 (3.3%)
	45–64 years	7,966 (22.4%)
	65–74 years	11,628 (32.7%)
	75–84 years	11,309 (31.8%)
	≥ 85 years	3,432 (9.7%)
Gender: men		19,360 (54.5%)
eGFR (ml/min/1.73m ²)		50.0 [40.9–55.6]
eGFR stage		
	G3a	23,333 (65.7%)
	G3b	8,357 (23.5%)
	G4	2,710 (7.6%)
	G5	1,108 (3.1%)
Dipstick proteinuria		Overall: 15,442
	(-)	9,357 (60.6%)
	(±)	2,295 (14.9%)
	(1+)	1,849 (12.0%)
	(2+)	1,277 (8.3%)
	(3+)	598 (3.9%)
	(4+)	66 (0.4%)
Hemoglobin (g/dL)		13.02 (1.88)
Serum albumin (g/dL)		4.04 (0.47)
Serum uric acid (mg/dL)		6.05 (1.49)
Serum total cholesterol (mg/dL)		187.9 (38.3)
Serum sodium (mEq/L)		141.0 (2.84)
Serum potassium (mEq/L)		4.41 (0.54)
Serum chloride (mEq/L)		104.6 (3.34)
Serum calcium (mg/dL)		9.08 (0.54)
Serum phosphate (mg/dL)		3.52 (0.94)
Serum C-reactive protein (mg/dL)		0.10 [0.04–0.28]

Continuous variables are expressed as median [interquartile interval] or mean (standard deviation). Factors are expressed as n (%).

Abbreviation: eGFR, estimated glomerular filtration rate.

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category, except among patients with CKD stage G5. Differences in UA level according to sex and age disappeared with the progression of G category.

Prevalences of hyperuricemia and rates of patients in the optimal range for serum UA level

The prevalences of hyperuricemia according to G category, age, and sex strata are shown in [S3 Table](#). The prevalence of hyperuricemia increased in accordance with the progression of G category. However, the prevalence of hyperuricemia was lower in patients with CKD stage G5 than in patients with CKD stage G4. Differences in prevalence of hyperuricemia according to sex and age disappeared with the progression of G category.

Table 3. Serum uric acid and electrolyte status stratification according to G category strata.

	unit	UA	Na	K	Cl	Na-Cl	cCa	P
		(mg/dl)	(mEq/L)	(mEq/L)	(mEq/L)	(mEq/L)	(mg/dl)	(mg/dl)
G3a	mean	5.80	141.3	4.33	104.6	36.8	9.23	3.40
	SD	1.33	2.51	0.44	2.82	2.1	0.42	0.69
G3b	mean	6.36*	140.8*	4.46*	104.6	36.3*	9.29	3.44
	SD	1.47	2.99	0.59	3.49	2.6	0.50	0.95
G4	mean	6.94*	140.4*	4.68*	105.3*	35.2*	9.30	3.70*
	SD	1.78	3.62	0.73	4.65	3.4	0.63	1.22
G5	mean	6.20*	139.8*	4.71*	103.9*	36.0*	9.19	4.44*
	SD	2.23	4.17	0.76	5.57	4.3	0.77	1.39

Values are expressed as mean and SD.

*:p<0.05 vs. G3a.

Abbreviations: UA, serum uric acid; Na, serum sodium; K, serum potassium; Cl, serum chloride; Na-Cl, difference between serum sodium and chloride concentrations; cCa, serum corrected calcium; P, serum phosphate; SD, standard deviation.

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Logistic regression analysis using model 1 showed that the adjusted odds ratios and 95% confidence intervals for the prevalences of hyperuricemia in patients with CKD stages G3b, G4, and G5 were 2.12 [1.90–2.37], 4.57 [3.92–5.32], and 2.25 [1.80–2.80], respectively (Table 4). Hypernatremia and hypokalemia were also independent risk factors for greater prevalence of hyperuricemia. There was no significant seasonal effect on the prevalence of hyperuricemia.

The rates of serum UA level within the optimal range according to G category, age, and sex strata are shown in Table 5; these were 29.6% in patients with CKD stage G4 and 49.6% in patients with CKD stage G5. The rates of serum UA level within the optimal range in patients with CKD stage G4 were 27.0% in male patients and 32.6% in female patients.

Associations between electrolyte disorders and eGFR

The mean serum levels of each electrolyte according to eGFR5 category are shown in Fig 3. The mean serum potassium and phosphate levels increased in accordance with the progression of eGFR5 category, whereas the mean serum chloride and corrected calcium levels decreased in accordance with the progression of eGFR5 category. However, mean serum chloride and

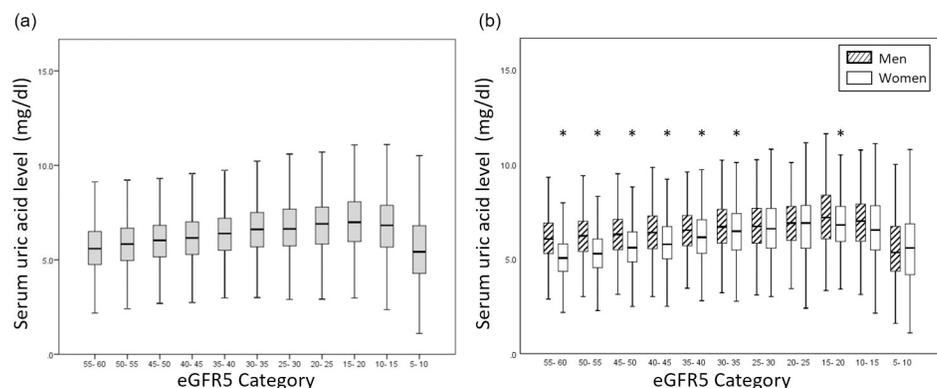


Fig 1. Mean serum uric acid level according to eGFR5 category. (a) All participants; (b) Men and women shown separately. Abbreviation: eGFR, estimated glomerular filtration rate. *, p<0.05.

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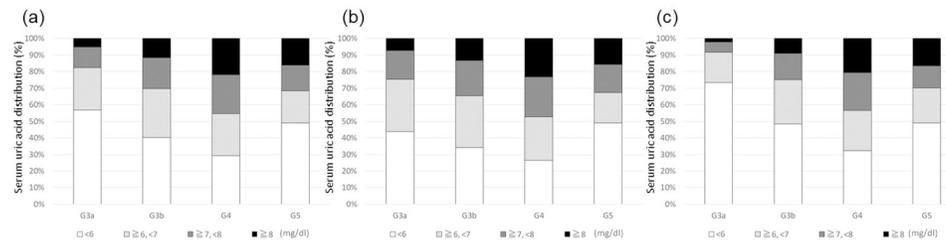


Fig 2. Serum uric acid distribution according to G category. (a) All participants; (b) Men; and (c) Women.

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corrected calcium levels were higher in patients with an eGFR category of ≥ 5 and < 10 ml/min/1.73 m² than in patients with an eGFR category of ≥ 10 and < 15 ml/min/1.73 m².

The distributions of electrolytes according to G category are shown in Fig 4. The rates of patients with high serum potassium and phosphate levels increased in accordance with the progression of G category; the rate of patients with low serum sodium level also increased in accordance with the progression of G category. Furthermore, the rates of patients with low and high serum corrected calcium levels both increased in accordance with the progression of G category.

Prevalence of electrolyte disorders and ratio of optimal range of electrolytes

The prevalences of electrolyte disorders according to G category are shown in S4 Table. The prevalences of hyponatremia, hyperkalemia, hypercalcemia, hyperphosphatemia, and narrower serum Na–Cl level gradually increased in accordance with the progression of G category. Notably, the prevalence of hypokalemia was elevated in patients with CKD stage G5, while the prevalence of hypocalcemia was elevated in patients with CKD stages G4 and G5. In contrast, the prevalence of hypophosphatemia was reduced in patients with CKD stages G4 and G5.

Table 4. Adjusted odds ratios and 95% confidence intervals for hyperuricemia.

covariate		hyperuricemia (UA ≥ 7.0 mg/dl)
G grade	G3a	1
	G3b	2.12 [1.90–2.37]
	G4	4.57 [3.92–5.32]
	G5	2.25 [1.80–2.80]
hypernatremia (Na ≥ 145 mEq/L)		1.42 [1.15–1.76]
hypokalemia (K ≤ 3.5 mEq/L)		1.43 [1.10–1.86]
season of sample collection.	Winter	1
	Spring	0.93 [0.82–1.07]
	Summer	1.12 [0.99–1.27]
	Autumn	1.04 [0.91–1.19]

Covariates: age, sex, G grade, A grade, hemoglobin level, albumin level, C-reactive protein, hypernatremia (Na ≥ 145 mEq/L), hypokalemia (K ≤ 3.5 mEq/L), and season of sample collection.

Adjusted odds ratios and 95% confidence intervals were analyzed by logistic regression analysis using each of the above factors as covariates.

Abbreviations: UA, serum uric acid; Na, serum sodium; K, serum potassium.

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Table 5. Rates of UA level within optimal range (UA ≤ 6.0 mg/dl) according to G category, age, and sex strata.

		18–44 Y	45–64 Y	65–74 Y	75–84 Y	85+ Y	men	women	Subtotal
G3a	%	46.2 [†]	52.4	55.7 [†]	62.0 [†]	68.2 [†]	44.4	73.8 [‡]	57.2
G3b	%	34.2*	34.2*	39.3 ^{†*}	43.0 ^{†*}	48.4 ^{†*}	34.7*	48.9 ^{‡*}	40.8*
G4	%	25.8*	27.1*	28.0*	33.2 ^{†*}	29.4*	27.0*	32.6 ^{‡*}	29.6*
G5	%	49.4	52.9	51.5	45.5*	40.4*	49.7*	49.4*	49.6*

Numbers of patients within optimal ranges are expressed as % of each population.

*:p<0.05 vs. G3a

†:p<0.05 vs. 45–64 Y

‡:p<0.05 vs. men.

Abbreviation: UA, serum uric acid.

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The adjusted odds ratios and 95% confidence intervals for electrolyte disorders according to G category strata are shown in Table 6. Logistic regression analysis demonstrated that the respective prevalences of hyponatremia, hyperkalemia, hypercalcemia, hyperphosphatemia, and narrower serum Na–Cl level were elevated in patients with CKD stages G3b, G4, and G5, compared with those prevalences in patients with CKD stage G3a. The prevalence of hypocalcemia was elevated only in patients with CKD stage G5. Further logistic regression analysis (model 4) showed that a narrower serum Na–Cl level was associated with the prevalence of hyperkalemia (adjusted odds ratio, 3.18 [95% confidence interval, 2.13–4.74]), independent of G category (S5 Table).

The rates of patients within optimal ranges for serum potassium, corrected calcium, and phosphate levels according to G category are shown in Table 7. The rates of patients within optimal ranges for serum corrected calcium and phosphate levels decreased in accordance with the progression of G category. In patients with CKD stage G5, the rates of patients within

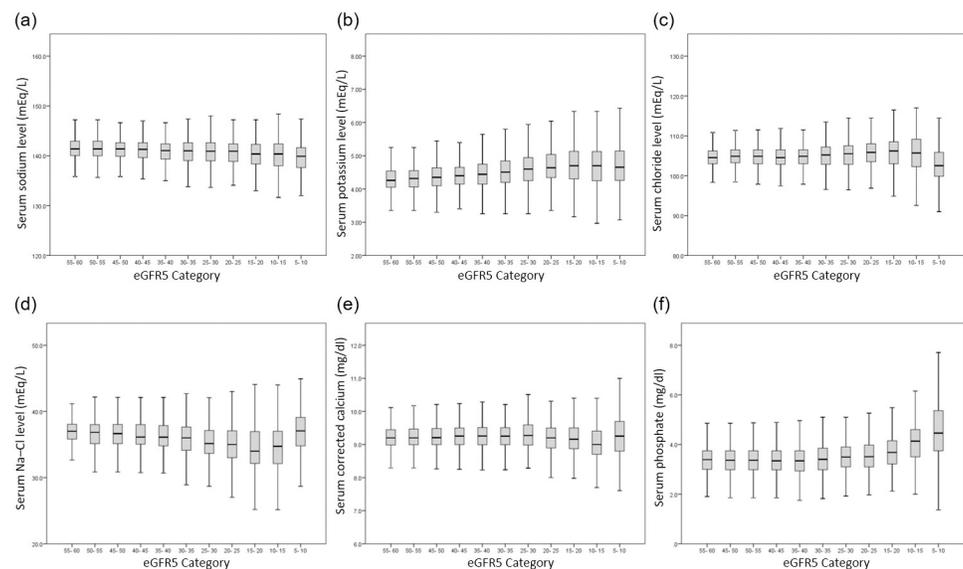


Fig 3. Mean serum electrolyte levels according to eGFR5 category. (a) Serum sodium level; (b) Serum potassium level; (c) Serum chloride level; (d) Serum Na–Cl level; (e) Serum corrected calcium level; and (f) Serum phosphate level. Abbreviations: Serum Na–Cl level, difference between serum sodium and chloride concentrations; eGFR, estimated glomerular filtration rate.

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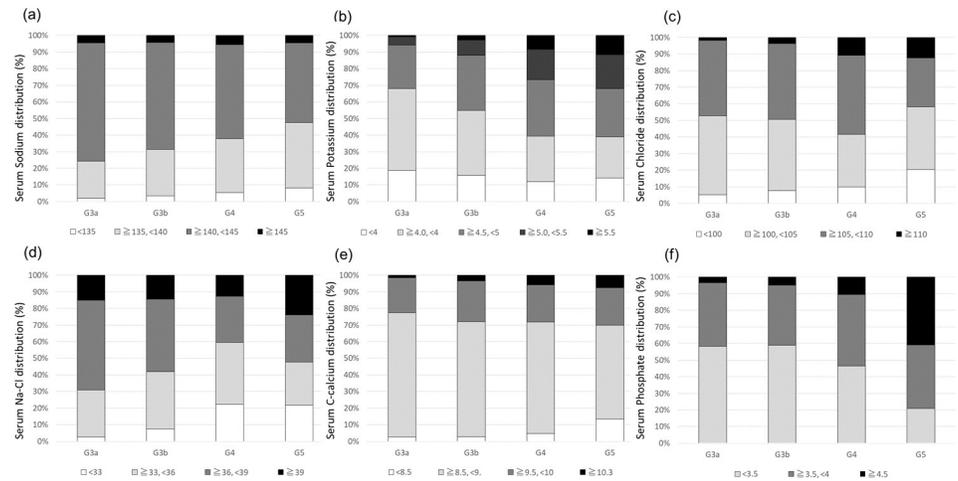


Fig 4. Serum electrolyte distribution according to G category. (a) Serum sodium distribution (%); (b) Serum potassium distribution (%); (c) Serum chloride distribution (%); (d) Serum Na–Cl distribution (%); (e) Serum corrected calcium distribution (%); and (f) Serum phosphate distribution (%). Abbreviations: Serum Na–Cl level, difference between serum sodium and chloride concentrations; C-calcium, corrected calcium.

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optimal ranges for serum potassium, corrected calcium, and phosphate levels were 73.5%, 81.9%, and 56.1%, respectively.

Discussion

In this study, we demonstrated the prevalences of hyperuricemia and electrolyte abnormalities in 35,508 Japanese patients with CKD by using automatically extracted data from a

Table 6. Adjusted odds ratios and 95% confidence intervals for electrolyte disorders according to G category strata.

		Na ≤ 135 mEq/L*	Na ≥ 145 mEq/L*	K ≤ 3.5 mEq/L*
G3a	Reference	1	1	1
G3b	AOR [95% CI]	1.37 [1.08–1.73]	0.98 [0.79–1.12]	0.94 [0.74–1.19]
G4	AOR [95% CI]	1.67 [1.25–2.25]	1.05 [0.78–1.42]	0.57 [0.39–0.84]
G5	AOR [95% CI]	1.77 [1.23–2.55]	0.98 [0.62–1.54]	0.98 [0.65–1.48]
		K ≥ 5.5 mEq/L*	cCa ≤ 8.4 mg/dl†	cCa ≥ 10.3 mg/dl†
G3a	Reference	1	1	1
G3b	AOR [95% CI]	3.09 [2.32–4.12]	1.04 [0.72–1.51]	2.56 [1.87–3.51]
G4	AOR [95% CI]	9.38 [6.94–12.7]	0.95 [0.59–1.51]	3.89 [2.69–5.64]
G5	AOR [95% CI]	9.33 [6.55–13.3]	3.12 [2.09–4.66]	4.82 [3.14–7.40]
		P ≤ 2.5 mg/dl*	P ≥ 4.5 mg/dl*	Na-Cl ≤ 30 mEq/L*
G3a	Reference	1	1	1
G3b	AOR [95% CI]	1.12 [0.89–1.41]	1.36 [1.02–1.81]	4.79 [2.46–9.33]
G4	AOR [95% CI]	0.44 [0.30–0.65]	2.69 [2.01–3.61]	13.5 [6.96–26.1]
G5	AOR [95% CI]	0.30 [0.18–0.52]	15.6 [11.8–20.7]	15.2 [7.52–30.6]

Covariates:

*age, sex, G grade, A grade, hemoglobin level, albumin level, and C-reactive protein

†age, sex, G grade, A grade, hemoglobin level, and C-reactive protein.

Adjusted odds ratios and 95% confidence intervals were analyzed by logistic regression analysis with each of the above factors as covariates.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; UA, serum uric acid; Na, serum sodium; K, serum potassium; Cl, serum chloride; Na-Cl, difference between serum sodium and chloride concentrations; cCa, serum corrected calcium; P, serum phosphate.

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Table 7. Rates of patients within optimal ranges for serum potassium, corrected calcium, and phosphate levels according to G category.

		K \geq 4.0, \leq 5.5 mEq/L	cCa \geq 8.4, \leq 10.3 mg/dl	P \geq 2.5, \leq 4.5 mg/dl
G3a	%	79.7	97.2	90.9
G3b	%	81.0*	94.6*	87.9*
G4	%	79.1	91.0*	86.2*
G5	%	73.5*	81.9*	56.1*

Numbers of patients within optimal ranges are expressed as % of each population.

Abbreviations: K, serum potassium; cCa, serum corrected calcium; P, serum phosphate.

*:p<0.05 vs. G3a.

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nationwide, large-scale cohort study in Japan. The J-CKD-DB study enables large-scale analysis directly linked to the electronic medical record by using the SS-MIX2 standard, and is an important precursor to large-scale analyses of complications in Japanese patients with CKD.

Previous studies reported the prevalences of electrolyte abnormalities in patients with CKD who were treated by nephrologists [14, 17, 30]. Here, we examined the sampling rate of electrolytes in an electronic health record study cohort, which was not limited to patients receiving treatment from nephrologists. The sampling rate of each electrolyte was low among patients with CKD stage G3 and increased with the progression of G category. A previous electronic health record study showed that 85% of patients with CKD underwent measurement of serum potassium level [36], which was similar to our findings. Notably, the results of this study were analyzed among patients for whom electrolyte data were collected.

In our cohort study of Japanese patients with CKD, we found that the prevalences of hyperuricemia were higher among men and younger patients with CKD stage G3a; however, sex and age differences disappeared with the progression of G category. The prevalences of hyperuricemia were higher in patients with CKD stages G3b, G4, and G5, compared with patients with CKD stage G3a; however, the prevalence of hyperuricemia was lower in patients with CKD stage G5 than in patients with CKD stage G4, regardless of age and sex. Similar results were obtained regarding the rate of patients within the optimal range for serum uric acid level. It was difficult to determine whether these results were due to enhanced use of uric acid-lowering drugs or to the inaccurate inclusion of patients receiving dialysis, because the current analysis did not allow for the evaluation of drugs. Future analyses of prescriptions (HOT reference code [37]) are needed to assess the extent to which drug-based interventions are performed among Japanese patients with CKD. However, the present study showed that hypernatremia and hypokalemia were associated with the prevalence of hyperuricemia, independent of G category; this finding may indicate an effect of diuretics. Participants from whom blood samples were collected in the summer tended to have a higher prevalence of hyperuricemia, but this was not statistically significant. Additional studies are needed to determine how fluid volume and salt reduction affect uric acid levels, in addition to the influences of oral urate-lowering medication and diuretics.

To the best of our knowledge, this is the first large-scale evaluation of electrolyte abnormalities in patients with CKD, using automatically extracted data in Japan. With the progression of G category, the prevalences of hyperkalemia, hypocalcemia, and hyperphosphatemia increased, as did the prevalences of hyponatremia, hypokalemia, narrower serum Na-Cl level, and hypercalcemia. The prevalence of hyponatremia increased with the progression of G category, compared with CKD stage G3b, implying that the use of diuretics may contribute to hyponatremia. An increase in the prevalence of hypercalcemia was observed with the

progression of G category. The prevalence of hypocalcemia is generally presumed to increase with the progression of CKD. However, a recent report showed an increased prevalence of hypercalcemia in patients with CKD [38]. Importantly, the use of vitamin D preparations may contribute to hypercalcemia. Furthermore, differences in the prevalences of hypernatremia and hypokalemia, due to the progression of G category, disappeared after adjustment for confounding factors. The prevalences of electrolyte abnormalities in relation to G category progression are likely to change over time with the advent of new drugs. Therefore, a longitudinal study of patients with CKD is necessary.

The rates of patients within optimal ranges for potassium, calcium, and phosphate decreased with the progression of G category. This result is presumably because the sampling rate of each electrolyte increased with the progression of G category. The percentage of patients within the optimal range for each electrolyte was assessed in accordance with the clinical practice guidelines for the study period. The achievement rates and quality indicators of clinical practice guidelines should be assessed in further longitudinal studies.

Although hyperkalemia is a well-recognized complication of CKD, a previous study reported that the prevalences of hyperkalemia (14%–20%) and hypokalemia (12%–18%) were similar [39]. In patients with CKD, hypokalemia and hyperkalemia have both been reported to enhance the risk of mortality [16]. CKD severity, use of medications such as renin-angiotensin-aldosterone system inhibitors and diuretics, and dietary potassium intake are major determinants of serum potassium concentration in patients with CKD. The results of our electronic health record study showed that the prevalence of hypokalemia was not elevated among Japanese patients with CKD.

Metabolic acidosis is known to be associated with worsening kidney function in patients with CKD [40]. Bicarbonate supplementation has been reported to slow the progression of CKD among patients with CKD stage G4 who exhibit a low serum bicarbonate concentration [41]. The serum Na–Cl level is not equivalent to the serum bicarbonate level, but has been described as a simple parameter for assessment of acid–base status [30, 42]. A previous study reported that a narrower serum Na–Cl level was associated with worsening kidney function in patients with CKD stage G4 [30]. In this study, a narrower serum Na–Cl level was a risk factor for hyperkalemia, independent of G category. Although the rate of sodium bicarbonate administration was not determined, metabolic acidosis is a possible cause of hyperkalemia, in addition to renal dysfunction.

Several limitations of our study should be noted, in relation to its cross-sectional design. First, we were unable to obtain information concerning the prevalence of gout, administration or types and dosages of drugs, and differences in practice patterns between nephrologists and other clinicians because we could not readily convert some of the local codes regarding medical care and tests to standardized codes, despite the availability of reference mapping tables. More accurate analysis might be achieved by information regarding the use and frequency of medications such as renin-angiotensin-aldosterone system inhibitors, beta blockers, urate-lowering drugs, diuretics, potassium adsorbents, vitamin D drugs, and anti-hyperphosphatemia drugs. Parathyroid hormone and magnesium levels were also collected, but could not be analyzed because local code settings were not yet available. Second, we were unable to obtain information regarding the cause of CKD, body mass index, presence or absence of diabetes and cardiovascular diseases, or blood pressure levels because these elements are not included in the SS-MIX2 system; thus, it was difficult to investigate research questions related to these variables.

In conclusion, we demonstrated the prevalences of hyperuricemia and electrolyte abnormalities in Japanese patients with CKD by using automatically extracted data from a nationwide, large-scale cohort study in Japan. We also assessed the influences of G category and

other factors on the prevalences of hyperuricemia and electrolyte abnormalities. Further prospective investigations including drugs and health insurance claim data, as well as analyses regarding quality indicators for clinical practice guidelines, may contribute to improvements in the quality of care for patients with CKD.

Supporting information

S1 Table. Participant stratification according to eGFR category, age, and sex strata.

(PDF)

S2 Table. Serum uric acid status according to G category, age, and sex strata.

(PDF)

S3 Table. Prevalence of hyperuricemia according to G category, age, and sex strata.

(PDF)

S4 Table. Prevalences of electrolyte abnormalities according to G category strata.

(PDF)

S5 Table. Adjusted odds ratios and 95% confidence intervals for hyperkalemia ($K \geq 5.5$ mEq/L).

(PDF)

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