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Distribution of nephrologists and regional variation in the clinical severity of IgA nephropathy at biopsy diagnosis in Japan: A cross-sectional ecological study

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Abstract

Objectives: The clinical severity of IgA nephropathy (IgAN) at the time of biopsy diagnosis differs significantly among cases. One possible determinant of any such difference is the time taken for referral from the primary care physician to a nephrologist, but the definitive cause remains unclear. This study examined the contribution of the number of nephrologists per regional population as a potential social factor influencing the clinical severity at diagnosis among IgAN patients in Japan, which has an ethnically homogeneous population.

Design: A cross-sectional ecological study.

Setting & participants: Patients were registered in the Japan Renal Biopsy Registry (J-RBR), a nationwide multicenter registry, and 6426 patients diagnosed with IgAN were analyzed. The facilities registered to the J-RBR were divided into 10 regions and the clinical features of IgAN at biopsy diagnosis, including renal function, level of proteinuria were examined.

Main outcome measures: Renal prognosis risk at the time of biopsy diagnosis defined by Kidney Disease Improving Global Outcomes guideline 2012.

Results: Among the regions, there were significant differences in the estimated glomerular filtration rate (67.5–91.4 ml/min/1.73 m^2), urinary protein excretion rate (0.93–1.93 g/day), and renal prognosis risk group distribution at diagnosis. The severity of all clinical parameters was inversely

correlated with the number of nephrologists per regional population, which showed an up to 2.7-fold difference among regions. A generalized linear mixed model revealed that a low number of nephrologists per regional population was significantly associated with fulfilment of clinical criteria indicating a very-high-risk renal prognosis (β =-0.484, 95% CI -0.959 to -0.010).

Conclusions: Among Japanese patients with IgAN, significant regional differences were detected in clinical severity at the time of diagnosis. Social factors, such as an uneven distribution of nephrologists across regions, may influence the timing of biopsy and determine such differences.

Article Summary

Strengths and limitations of this study

- This is the first reported study to reveal regional differences in the clinical severity of the patients with IgA nephropathy (IgAN) at biopsy diagnosis in Japan.
- Lower number of nephrologists per regional population in Japan was associated with an increase in the frequency of clinical criteria indicating the very-high-risk renal prognosis of IgAN patients in each region, which was determined by renal function and amount of proteinuria at the time of biopsy diagnosis.
- The uneven regional distribution of nephrologists may influence the time taken for referral to a nephrologist and the likelihood of earlier interventions in IgAN patients.
- Japan is one of only a few countries in the world that screen for kidney diseases by urinalysis, thus the applicability of the findings to countries other than Japan is unclear.

Introduction

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis and a major cause of end-stage renal disease (ESRD) worldwide [1,2]. Impaired renal function and severe proteinuria at presentation are among the strongest predictors of a poor renal prognosis in patients with IgAN [3-5]. Advanced age, hypertension, male gender, obesity, and absence of gross hematuria are considered poor prognostic indicators, although controversy exists in the degree of involvement of these factors, which varies by study depending on the subject characteristics [6-8]. Previous studies have shown racial/ethnic differences in the prevalence of IgAN, and the relative number of patients diagnosed with IgAN is higher in Asian countries than in other countries [9-11]. Recent genome-wide analyses have demonstrated that genetic factors may underlie the diversity in the incidence and severity of IgAN [12-15].

Except for cases showing gross hematuria, the onset of IgAN is often asymptomatic [16]. In addition, IgAN cannot be diagnosed unless a renal biopsy is performed, as deposition of IgA in glomeruli can be demonstrated histopathologically. Social factors, such as the penetration rate of urinalysis screening for kidney disease or the time taken for referral from the primary care physician to a nephrologist, may considerably influence the latency to IgAN diagnosis. In fact, in most patients in Japan, IgAN is first identified at a health checkup, followed by referral to a nephrologist [17,18].

Such differences in survival related to the duration of disease at time of presentation rather than true variability in disease severity is called lead-time bias, and may be associated with disease prognosis in IgAN patients [19].

Few studies have focused on regional variation in the clinical characteristics of IgAN [13,15]. In addition, other than race/ethnicity, no factors that may affect such regional variation in disease severity have been determined. In this study, we analyzed patients with IgAN in Japan, which has an ethnically homogeneous population [20]. Social factors that may affect the biopsy diagnosis of IgAN were examined in the context of potential differences in the clinical severity of IgAN among various regions of Japan.

Materials and Methods

Registry system and patient selection

The Japan Renal Biopsy Registry (J-RBR) is a nationwide, multicenter registry system, which was established in 2007 by the Committee for Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology (JSN) [21]. This cross-sectional ecological study included Japanese patients with primary IgAN registered on the J-RBR from January 1, 2007 through June 30, 2013. During the registration period, 7,970 patients diagnosed with IgAN were included in the J-RBR. Of these 7,970 patients, 1,544 were excluded because of missing data critical for the analysis. A total of 6,426 patients were finally subjected to the analysis. The diagnosis of IgAN was histopathologically determined based on the basic glomerular changes described in the classification of glomerular diseases of the World Health Organization, and by immunohistological identification of IgA in glomeruli [22]. Patients who were diagnosed with other renal or systemic diseases, including those with Henoch–Schönlein purpura, systemic lupus erythematosus, and liver cirrhosis were excluded. Clinical data, including age, sex, body mass index (BMI), systolic and diastolic blood pressure, the presence or absence of hypertension, estimated glomerular filtration rate (eGFR), urinary protein excretion (UPE) rate, urinary sediment, serum albumin, and serum total cholesterol were evaluated.

All clinical data were obtained at the time of the diagnostic renal biopsy. Patients with missing data necessary for the study, such as renal function measurements, the presence or absence of hypertension and/or the UPE rate, were excluded from the analyses. The J-RBR is registered in the UMIN Clinical Trials Registry (registered number: UMIN000000618).

Measurements and definitions

The J-RBR registration facilities were divided into 10 regions of Japan: Hokkaido, Tohoku, Kanto, Koshinetsu, Hokuriku, Tokai, Kinki, Chugoku, Shikoku, and Kyusyu (**Figure 1**). The Japanese populations in these regions are considered ethnically homogeneous [20].

The eGFR was calculated using a three-variable equation modified for Japanese populations, as follows: $eGFR = 194 \times age^{-0.287} \times sCr^{-1.094}$ ($\times 0.739$ if female), where sCr is the serum creatinine concentration [23]. Hematuria was graded based on the number of red blood cells per high power field in urinary sediment: 1, 2, 3, and 4 for 0–4, 5–10, 11–30, and ≥ 30, respectively. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2014 [24], or usage of antihypertensive medications. Patients ≥ 65 years of age were defined as elderly [25].

In the Kidney Disease Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, patients with chronic kidney disease (CKD) are classified into 18 categories and four risk groups (low, moderately increased, high, and very high risk) based on eGFR and albuminuria categories on a CKD heat map [26]. In Japan, this CKD risk classification system has been modified according to the cause of kidney disease. Except for diabetes cases, the UPE rate, instead of the urinary albumin excretion rate, is applied for patients with CKD including IgAN, based on the requirements of the Japanese national insurance system [27]. Based on the KDIGO 2012 guidelines, which were modified for the Japanese population, the UPE rate at the time of biopsy is classified as normal (< 0.15 g/day or g/gCr; A1), mild (0.15–0.49 g/day or g/gCr; A2), or severe (≥ 0.5 g/day or g/gCr; A3) [26,27]. Similarly, eGFR at the time of biopsy is classified into five groups: G1, G2, G3a, G3b, G4, and G5 for ≥ 90, 60–89, 45–59, 30–44, 15–29, and < 15 ml/min/1.73 m^2, respectively. According to the CKD heat map of the 2012 KDIGO guidelines, which is based on the eGFR level and UPE rate, the renal prognosis is categorized as low, moderately increased, high, or very high.

Social factors

Certain social factors may be associated with regional variation in the clinical features of IgAN. The first such factor is the number of board-certified JSN nephrologists per regional population. A qualified JSN board-certified nephrologist must have ≥ 3 years training at a JSN-accredited facility; have passed a specific exam; and renew their license every 5 years. The second social factor is the proportion of participants who received a health checkup per regional population. To ascertain this, we used data from the Specific Health Checkup, a metabolic syndrome health checkup devised by the Ministry of Health, Labor, and Welfare of Japan that targets people aged 40–74 years who were enrolled in the national health insurance program in 2012 [28]. The Specific Health Checkup comprises a physical examination, blood pressure measurement, blood test, and urinalysis. The third social factor is the proportion of elderly persons relative to the general population. Information on the proportion of elderly persons (age ≥ 65 years) in each regional population was obtained from a national survey performed in 2012 [29]. Based on the ranking of the social factors included in this study, 10 regions of Japan were divided into three groups, as follows: low (three regions), intermediate (four regions), and high (three regions) groups. Analysis was performed within each group according to the clinical characteristics of the IgAN patients at the time of biopsy diagnosis.

Statistical analysis

Continuous variables are expressed as means ± standard deviation. Differences among regions were analyzed by the Kruskal–Wallis test. Differences in the characteristics of the IgAN patients within each social factor group were analyzed by the Mantel–Haenszel test for trend and the Jonckheere–Terpstra trend test, as appropriate. A generalized linear mixed model was constructed to identify the social factors that may influence regional variation in the severity of IgAN at the time of biopsy. In each analysis, social factors, age, sex, and the presence or absence of hypertension were treated as fixed covariates, and the regions and the J-RBR registration facilities as random effects. A p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS statistical software (ver. 24.0; IBM, Armonk, NY, USA).

Patient and public involvement

No patient was involved in the design or conduct of the study, since this was a database research study.

Results

Patient clinical characteristics at the time of biopsy diagnosis

The clinical characteristics of the patients at the time of biopsy diagnosis are summarized in **Table 1**. Their mean age was 39.5 years, and 3,297 (51.3%) were males. The mean eGFR was 74.4 ml/min/1.73 m^2 and the mean UPE rate was 1.16 g/day. A total of 1,813 (28.2%) patients were categorized into the very-high-risk renal prognosis group. The male and female ratio was similar among the 10 regions (p = 0.182). On the other hand, significant regional variation was observed in age (32.2–42.5 years, $p < 0.001$), BMI (21.7–23.5 kg/m^2, $p < 0.001$), prevalence of hypertension (26.8–55.4%, $p < 0.001$), eGFR (67.5–91.4 ml/min/1.73 m^2, $p < 0.001$), UPE rate (0.93–1.93 g/day, $p < 0.001$), degree of hematuria (frequency of grade 3 or 4 = 51.4–71.5%, $p < 0.001$), and renal prognosis risk group distribution ($p < 0.001$). Notably, there were large differences between the lowest and highest regions with respect to the rates of both very high and low renal prognosis risk, as defined by the KDIGO guidelines (3.66- and 4.92-fold, respectively).

Regional variation in social factors

Variation among the 10 regions in terms of the social factors that may influence the severity of IgAN at biopsy diagnosis were assessed (**Table 2**). The social factors included in this study were

the number of board-certified nephrologists, proportion of patients who received a health checkup, and proportion of elderly persons per regional population. The distributions of these three social factors differed significantly among the 10 regions. In particular, an up to 2.7-fold among regions difference was observed in the number of board-certified nephrologists.

Relationships between social factors and regional variation in the clinical characteristics of the IgAN patients at biopsy diagnosis

Trends in the social factors were analyzed according to regional variation in the clinical features of the IgAN patients at biopsy diagnosis. The number of nephrologists per regional population showed a clear trend: the fewer the nephrologists, the more severe were the clinical features at the biopsy diagnosis, including renal function, the UPE rate, and the renal prognosis risk distribution (**Table 3**). The regions with higher proportions of IgAN patients with a very-high-risk renal prognosis and those with fewer nephrologists per regional population showed a similar distribution trend (**Figure 1**). No such similarities were found between the distribution of IgAN patients with a very-high-risk renal prognosis and those of health checkup participants or elderly persons per regional population (**Supplemental Figure 1**).

A generalized linear mixed model was constructed to examine the relationship between the three social factors investigated in this study and regional differences in the proportion of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, as defined by the 2012 KDIGO guidelines. In the model, the number of board-certified nephrologists per regional population was significantly associated with the rate of fulfilment of the clinical criteria for a very-high-risk renal prognosis at the biopsy diagnosis, even after considering the differences in clinical factors among regions (**Table 4, Figure 2**). We did not find a significant relationship between the rate of very-high-risk renal prognosis at biopsy diagnosis and either the proportion of patients who received a health checkup or the proportion of elderly persons per regional population (**Table 4**).

Discussion

In this cross-sectional ecological study, we demonstrated substantial regional variations in Japanese IgAN patient clinical characteristics at the diagnostic renal biopsy, including eGFR and the UPE rate. In addition, a lower number of board-certified nephrologists per regional population was closely associated with the clinical severity of IgAN, including the rate of fulfilment of clinical criteria for a very high risk renal prognosis.

Previous studies have shown apparent regional and national differences in CKD and ESRD incidence in the United States and Europe [30-32]. However, race and ethnicity within a study population must be homogenous to isolate the effects of social factors on regional differences in clinical factors. The Japanese population is useful for the evaluation of such factors, which may influence disease prevalence and severity, because of its ethnic homogeneity. Usami et al. demonstrated significant regional differences in the incidence of ESRD within Japan [33]. Studies of the ethnically homogenous Japanese population suggest that social factors, i.e., factors other than those with a genetic basis, contribute to such regional differences in the presentation of renal diseases. Similarly, our results pertaining to apparent regional differences in the clinical features of Japanese IgAN patients at biopsy diagnosis also suggest that such regional variation is due to social rather than genetic factors.

This is the first reported study to reveal regional differences in the clinical severity of IgAN patients at biopsy diagnosis in Japan. Interestingly, the proportion of IgAN patients fulfilling the clinical criteria for a very-high-risk renal prognosis at biopsy diagnosis showed an up to 3.7-fold difference among the 10 regions. Studies on the natural history of IgAN have consistently identified renal impairment and severe proteinuria as clinically detectable poor prognostic indicators at the time of biopsy diagnosis [3-5]. In addition, such predictors of the progression to ESRD in patients with IgAN are closely associated with pre-existing histopathological findings of advanced chronic renal disease [34]. Thus, our current results showing a significant association between the number of nephrologists per regional population and the clinical severity of IgAN patients at biopsy diagnosis suggest a possible contribution of nephrologist availability to the likelihood of early diagnosis. The uneven regional distribution of nephrologists may influence the time taken for referral from a primary care physician to a nephrologist, who then decides regarding performance of a renal biopsy and the therapeutic intervention.

Other than the number of nephrologists, several other socioeconomic factors may influence the clinical severity of IgAN. Due to the universal health insurance coverage was established in 1961 in Japan, the gap between individuals with a poor medical economic status and the rest of the population is reportedly lower than that in other countries [35]. The rate of health checkups may be

another important social factor influencing IgAN severity. Although urinalysis screening is popular for school-age children, adult participation in such schemes can show significant variation among regions in Japan. However, we did not find any significant effect of health checkup rate on the severity of IgAN at biopsy diagnosis. One possible interpretation of this result is that referral to a nephrologist may play a more important role than health checkups in IgAN severity. The proportion of elderly persons in urban and rural populations differs significantly among regions in Japan, a country in which there has been remarkable aging of rural populations, particularly in recent years. Previous studies have suggested that elderly patients with IgAN have relatively more severe clinical features at the time of diagnosis than do non-elderly patients [36,37]. Thus, we examined the effect of regional variation in the proportion of elderly persons on the clinical severity of IgAN. However, contrary to our expectations, we did not find any significant effect of the proportion of elderly persons on the severity of IgAN at biopsy diagnosis. Referral to a nephrologist and renal biopsy may be performed less often in elderly patients.

Our study had several important limitations. First, there were differences in both the number of J-RBR registration facilities and the sample size among regions. Second, there may have been differences in the criteria for performing renal biopsies among facilities. Because no formal criteria for performing a renal biopsy are defined in the registry, all renal biopsies were performed at the

discretion of the attending physician. This may have influenced the regional differences in severity of clinical features at the time of biopsy. Third, we could not exclude the potential influence of other social factors, such as dietary habits or climatic factors, on the regional variation in clinical features of IgAN patients. Fourth, the J-RBR does not include histopathological findings of renal biopsies. Thus, we could not demonstrate that the clinical severity of the IgAN patients correlated with the histopathological findings. Fifth, the applicability of the findings to countries other than Japan is unclear. Since Japan is one of only a few countries in the world that screen for kidney diseases by urinalysis. Finally, this study used a cross-sectional ecological design. Therefore, further studies are required to elucidate the relationship between the number of nephrologists per regional population and the renal prognosis of patients with IgAN.

Conclusions

This study identified considerable regional differences in the clinical severity of IgAN at the biopsy diagnosis in Japanese patients. Our results suggest that an uneven distribution of nephrologists across regions may influence the timing of nephrologist referral and biopsy diagnosis, as well as the likelihood of earlier intervention to prevent progression to ESRD in patients with IgAN.

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Author Contributions: Research idea and study design: YO, NT, YM, TK, MO, TY; data acquisition: YO, NT, IN, TN, HY; data analysis/interpretation: YO, NT; statistical analysis: YO, NT, HA, TN; supervision or mentorship: NT, TY. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Conflict of Interest Statement: None declared.

Patient consent: Not required.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number: the Japanese Society of Nephrology, No. 27, January 19, 2016) and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards.

Data sharing statement: No additional data available.

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Table 1. Clinical characteristics of the patients at biopsy diagnosis.

Variables	Total (n=6426)	Hokkaido (n=148)	Tohoku (n=911)	Kanto (n=1229)	Koshinetsu (n=201)	Hokuriku (n=258)	Tokai (n=1432)	Kinki (n=706)	Chugoku (n=485)	Shikoku (n=183)	Kyushu (n=873)	*p*-value	Maximal fold among regions
Age, mean (SD), years	39.5 (17.7)	41.5 (16.6)	42.5 (18.1)	34.7 (17.5)	39.2 (14.9)	42.2 (16.8)	41.4 (16.6)	38.9 (17.1)	39.4 (17.8)	32.2 (20.2)	40.8 (18.3)	< 0.001	1.32
Male, no. (%)	3297 (51.3)	78 (52.7)	488 (53.6)	652 (53.1)	96 (47.8)	143 (55.4)	707 (49.4)	367 (52.0)	255 (52.6)	86 (47.0)	425 (48.7)	0.182	1.18
BMI mean (SD), kg/m^2	22.6 (4.0)	23.4 (4.2)	23.5 (4.2)	22.0 (4.2)	22.2 (3.7)	22.8 (3.6)	22.6 (3.7)	22.4 (4.1)	22.7 (4.2)	21.7 (4.0)	22.7 (4.0)	< 0.001	1.08
SBP, mean (SD), mm Hg	124 (18)	126 (19)	126 (17)	120 (18)	120 (16)	122 (17)	127 (18)	122 (18)	124 (18)	117 (16)	126 (19)	< 0.001	1.09
DBP, mean (SD), mm Hg	74 (13)	76 (13)	76 (13)	72 (13)	75 (13)	74 (13)	76 (13)	73 (12)	74 (13)	69 (12)	75 (13)	< 0.001	1.10
Hypertension, no. (%)	2790 (43.4)	82 (55.4)	403 (44.2)	457 (37.2)	93 (46.3)	127 (49.2)	709 (49.5)	279 (39.5)	203 (41.9)	49 (26.8)	388 (44.4)	< 0.001	2.07
eGFR, mean (SD), ml/min/1.73 m^2	74.4 (30.3)	67.5 (31.3)	73.3 (29.6)	79.6 (31.5)	71.3 (27.7)	73.2 (27.0)	69.0 (27.8)	74.8 (29.3)	78.0 (30.9)	91.4 (35.2)	73.5 (31.2)	< 0.001	1.35
Serum albumin, mean (SD), g/dl	3.9 (0.6)	3.7 (0.7)	4.0 (0.7)	4.0 (0.6)	4.0 (0.7)	3.8 (1.0)	3.9 (0.6)	3.9 (0.6)	4.0 (0.6)	4.0 (0.6)	3.9 (0.6)	< 0.001	1.08
Total cholesterol, mean (SD), mg/dl	194 (59)	198 (45)	182 (68)	186 (71)	188 (71)	198 (60)	204 (47)	199 (49)	197 (47)	189 (55)	198 (59)	< 0.001	1.12
UPE, mean (SD), g/day	1.16 (1.62)	1.93 (2.63)	1.00 (1.55)	0.97 (1.25)	0.93 (1.22)	1.00 (1.23)	1.42 (1.72)	1.04 (1.46)	0.97 (1.43)	1.08 (2.31)	1.35 (1.83)	< 0.001	2.08
Urinary RBC grade 3,4, No. (%)	4313 (67.1)	101 (68.2)	598 (65.6)	801 (65.2)	142 (70.6)	170 (65.9)	1024 (71.5)	454 (64.3)	327 (67.4)	94 (51.4)	602 (69.0)	< 0.001	1.39
KDIGO prognosis risk of CKD, no. (%)													
Very-high-risk	1813 (28.2)	59 (39.9)	265 (29.1)	289 (23.5)	61 (30.3)	64 (24.8)	495 (34.6)	175 (24.8)	117 (24.1)	20 (10.9)	268 (30.7)	< 0.001	3.66
High risk	2353 (36.6)	48 (32.4)	272 (29.9)	446 (36.3)	66 (32.8)	100 (38.8)	623 (43.5)	248 (35.1)	157 (32.4)	66 (36.1)	327 (37.5)	< 0.001	1.45
Moderately increased risk	1412 (22.0)	24 (16.2)	199 (21.8)	322 (26.2)	53 (26.4)	54 (20.9)	228 (15.9)	183 (25.9)	122 (25.2)	43 (23.5)	184 (21.1)	< 0.001	1.66
Low risk	849 (13.2)	17 (11.5)	175 (19.2)	172 (14.0)	21 (10.4)	40 (15.5)	86 (6.0)	100 (14.2)	89 (18.4)	54 (29.5)	94 (10.8)	< 0.001	4.92

BMI, body mass index; UPE, urinary protein excretion; RBC, red blood cells; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Regional variation in social factors.

Regions	Nephrologists, no. /100,000 populations	Proportion of participants who received a health checkup, %	Proportion of elderly persons relative to the general population, %
Hokkaido	1.58	36.7	27.1
Tohoku	2.75	46.5	27.3
Kanto	4.03	46.4	23.0
Koshinetsu	3.28	50.5	27.9
Hokuriku	4.26	48.7	27.2
Tokai	2.87	47.2	24.2
Kinki	3.47	40.7	25.2
Chugoku	3.08	41.1	27.8
Shikoku	3.07	43.1	29.1
Kyushu	3.21	43.2	26.3
Total mean	3.25	45.0	25.6
Maximal fold among regions	2.70	1.38	1.27
p-value	< 0.001	< 0.001	< 0.001

Table 3. Comparison of patient clinical characteristics among regions categorized according to the number of nephrologists.

Variables	Category of the number of nephrologists			*p*-value for trend
	Lowest three regions (n=2491)	Intermediate four regions (n=1742)	Highest three regions (n=2193)	
Nephrologists /100,000 population	2.75	3.17	3.87	
Age, mean (SD), year	41.8 (17.2)	39.3 (18.2)	36.9 (17.5)	< 0.001
Hypertension, no. (%)	1194 (47.9)	733 (42.1)	863(39.4)	< 0.001
eGFR, mean (SD), ml/min/1.73 m^2	70.5 (28.7)	77.3 (30.4)	77.3 (30.4)	< 0.001
UPE, mean (SD), g/day	1.30 (1.75)	1.17 (1.74)	0.99 (1.32)	< 0.001
KDIGO renal prognosis risk, no. (%)				
Very-high-risk	819 (32.9)	465 (26.7)	528 (24.1)	< 0.001
High risk	943 (37.9)	616 (35.4)	794 (36.2)	0.226
Moderately increased risk	451 (18.1)	402 (23.1)	559 (25.5)	< 0.001
Low risk	278 (11.2)	259 (14.9)	312 (14.2)	0.001

Table 4. Social factors and regional variation in IgAN patients with very-high-risk renal prognosis.

Fixed effects	f-value	Regression coefficient	95% CI	*p*-value
Number of nephrologists (/100,000 populations)	4.008	-0.484	-0.959 − -0.010	0.045
Proportion of patients who received a health checkup (%)	0.489	0.032	-0.057 − 0.120	0.485
Proportion of elderly persons relative to the general population (%)	3.510	-0.137	-0.281 − 0.006	0.061

95% CI, 95% confidence interval; Covariates: age, sex, hypertension: Random effects: region, J-RBR registration facility:

Structure for the random effects, First-order autoregressive.

Figure legends

Figure 1. Distributions of IgAN patients with a very-high-risk renal prognosis and of nephrologists.

Regional differences of the rate of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, which was adjusted for age, sex, and hypertension (**A**), and the number of board-certified nephrologists per regional population (**B**). Based on the ranking of each factor, 10 regions of Japan were divided into three groups, as follows: the three lowest, four intermediate, and three highest groups. The numbers indicate the following regions: 1, Hokkaido; 2, Tohoku; 3, Kanto; 4, Koshinetsu; 5, Hokuriku; 6, Tokai; 7, Kinki; 8, Chugoku; 9, Shikoku; and 10, Kyushu.

Figure 2. Relationship between the rate of IgAN patients with a very-high-risk renal prognosis and the number of nephrologists per regional population.

Circles indicate each region and the areas of the circles are proportional to the regional populations. The rate of IgAN patients with a very-high-risk renal prognosis in each region was adjusted by age, sex, and hypertension. The regression line was obtained from the generalized linear mixed model in **Table 4**.

Supplementary Figure 1. Distributions of IgAN patients with a very-high-risk renal prognosis and those of social factors other than nephrologist number.

Regional differences in the rate of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, which was adjusted for age, sex, and hypertension (**A**), the rate of health checkup participants per regional population (**B**), and the proportion of elderly persons per regional population (**C**). Based on the ranking of each factor, 10 regions of Japan were divided into three groups, as follows: the three lowest, four intermediate, and three highest groups. The numbers indicate the following regions: 1, Hokkaido; 2, Tohoku; 3, Kanto; 4, Koshinetsu; 5, Hokuriku; 6, Tokai; 7, Kinki; 8, Chugoku; 9, Shikoku; and 10, Kyushu.

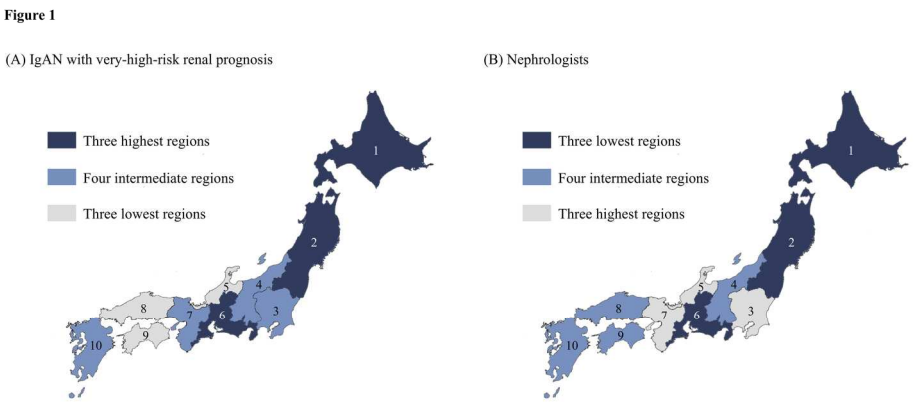

Figure 1. Distributions of IgAN patients with a very-high-risk renal prognosis and of nephrologists.

Regional differences of the rate of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, which was adjusted for age, sex, and hypertension (A), and the number of board-certified nephrologists per regional population (B). Based on the ranking of each factor, 10 regions of Japan were divided into three groups, as follows: the three lowest, four intermediate, and three highest groups. The numbers indicate the following regions: 1, Hokkaido; 2, Tohoku; 3, Kanto; 4, Koshinetsu; 5, Hokuriku; 6, Tokai; 7, Kinki; 8, Chugoku; 9, Shikoku; and 10, Kyushu.

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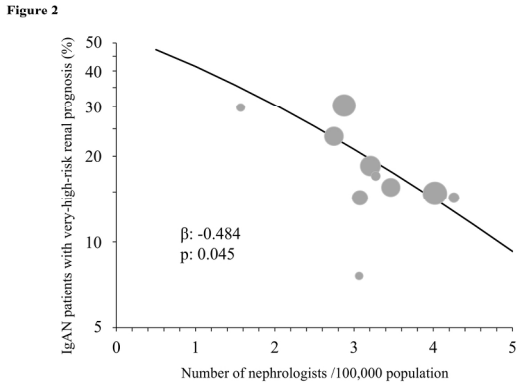

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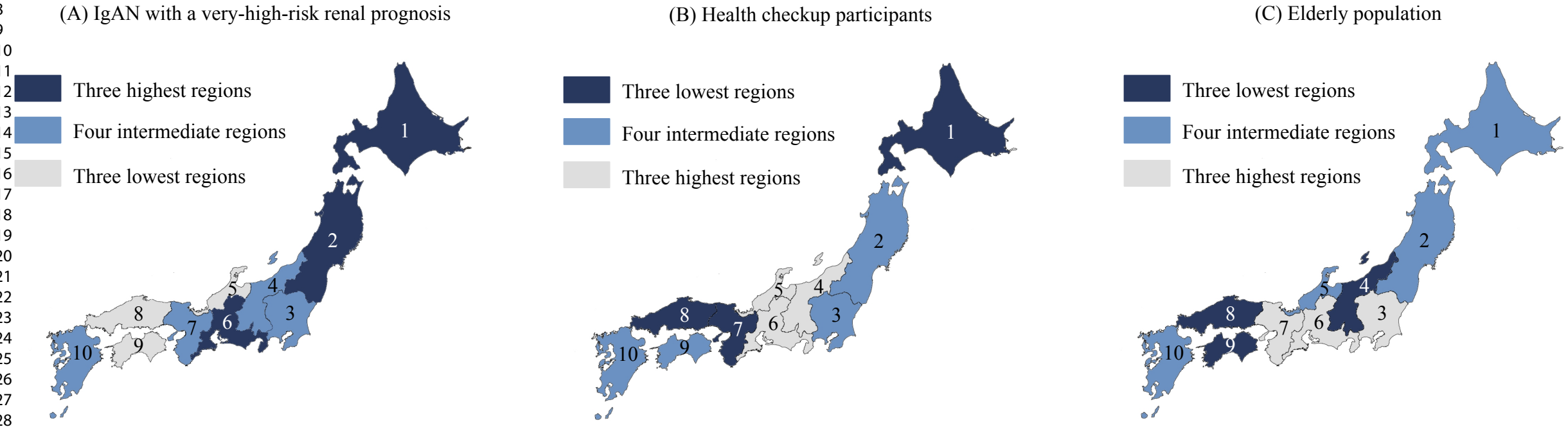
Supplementary Figure 1



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	NA
Bias	9	Describe any efforts to address potential sources of bias	*NA*
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Distribution of nephrologists and regional variation in the clinical severity of IgA nephropathy at biopsy diagnosis in Japan: A cross-sectional study

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Epidemiology
Keywords:	IgA nephropathy, renal biopsy, proteinuria, hematuria, chronic kidney disease, Glomerulonephritis < NEPHROLOGY

Distribution of nephrologists and regional variation in the clinical severity of IgA nephropathy at biopsy diagnosis in Japan: A cross-sectional study

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Running title: Regional variation of IgA nephropathy in Japan

Word count: 3349, abstract: 294

Key words: IgA nephropathy, renal biopsy, proteinuria, hematuria, chronic kidney disease, glomerulonephritis

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Abstract

Objectives: The clinical severity of IgA nephropathy (IgAN) at the time of biopsy diagnosis differs significantly among cases. One possible determinant of any such difference is the time taken for referral from the primary care physician to a nephrologist, but the definitive cause remains unclear. This study examined the contribution of the number of nephrologists per regional population as a potential social factor influencing the clinical severity at diagnosis among IgAN patients in Japan, which has an ethnically homogeneous population.

Design: A cross-sectional study.

Setting & participants: Patients were registered in the Japan Renal Biopsy Registry (J-RBR), a nationwide multicenter registry, and 6426 patients diagnosed with IgAN were analyzed. The facilities registered to the J-RBR were divided into 10 regions and the clinical features of IgAN at biopsy diagnosis, including renal function and level of proteinuria, were examined.

Main outcome measures: Renal prognosis risk at the time of biopsy diagnosis defined by Kidney Disease Improving Global Outcomes guideline 2012.

Results: Among the regions, there were significant differences in the estimated glomerular filtration rate (67.5–91.4 ml/min/1.73 m^2), urinary protein excretion rate (0.93–1.93 g/day), and renal prognosis risk group distribution at diagnosis. The severity of all clinical parameters was inversely

correlated with the number of nephrologists per regional population, which showed an up to 2.7-fold difference among regions. A generalized linear mixed model revealed that a low number of nephrologists per regional population was significantly associated with fulfillment of clinical criteria indicating a very-high-risk renal prognosis (β =-0.484, 95% CI -0.959 to -0.010).

Conclusions: Among Japanese patients with IgAN, significant regional differences were detected in clinical severity at the time of diagnosis. Social factors, such as an uneven distribution of nephrologists across regions, may influence the timing of biopsy and determine such differences.

Article Summary

Strengths and limitations of this study

- This study is based on the largest nationwide multicenter registry system of renal biopsies in Japan.
- The ethnically homogenous Japanese study population provides an opportunity to study the influence of social factors on disease progression.
- Because the registry system does not include detailed findings of renal biopsies, this study cannot elucidate the association between the clinical severity and the histopathological grade.
- Japan is one of only a few countries in the world that screens for kidney diseases by urinalysis, thus the applicability of the findings to other countries is unclear.

Introduction

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis and a major cause of end-stage renal disease (ESRD) worldwide [1,2]. Impaired renal function and severe proteinuria at presentation are among the strongest predictors of a poor renal prognosis in patients with IgAN [3-5]. Advanced age, hypertension, male gender, obesity, and hematuria are considered poor prognostic indicators, although controversy exists in the degree of involvement of these factors, which varies by study depending on the subject characteristics [6-9]. Previous studies have shown racial/ethnic differences in the prevalence of IgAN, and the relative number of patients diagnosed with IgAN is higher in Asian countries than in other countries [10-12]. Recent genome-wide analyses have demonstrated that genetic factors may underlie the diversity in the incidence and severity of IgAN [13-16].

Except for cases showing gross hematuria, the onset of IgAN is often asymptomatic [17]. In addition, IgAN cannot be diagnosed unless a renal biopsy is performed, as deposition of IgA in glomeruli can be demonstrated histopathologically. Social factors, such as the penetration rate of urinalysis screening for kidney disease or the time taken for referral from the primary care physician to a nephrologist, may considerably influence the latency to IgAN diagnosis. In fact, in most patients in Japan, potential cases of IgAN are first identified at a health checkup, followed by referral to a

nephrologist to assess the patient [18,19]. Such differences in survival related to the duration of disease at time of presentation rather than true variability in disease severity is called lead-time bias, and may also be associated with disease prognosis in IgAN patients [20].

Few studies have focused on regional variation in the clinical characteristics of IgAN [14,16]. In addition, other than race/ethnicity, no factors that may affect such regional variation in disease severity have been determined. In this study, we analyzed clinical data of patients with IgAN in Japan, which has an ethnically homogeneous population [21]. Social factors that may affect the biopsy diagnosis of IgAN were examined in the context of potential differences in the clinical severity of IgAN among various regions of Japan.

Materials and Methods

Registry system and patient selection

The Japan Renal Biopsy Registry (J-RBR) is a nationwide, multicenter registry system, which was established in 2007 by the Committee for Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology (JSN) [22]. The J-RBR includes the clinical records for all patients that underwent a renal biopsy including the final renal histopathological diagnosis. However, the registry does not include detailed histopathological findings. This cross-sectional study included Japanese patients with primary IgAN registered on the J-RBR from January 1, 2007 through June 30, 2013. During the registration period, 7,970 patients diagnosed with IgAN were included in the J-RBR. Of these 7,970 patients, 1,544 were excluded because of missing data critical for the analysis, such as renal function measurements, the presence or absence of hypertension, and/or the urinary protein excretion (UPE) rate. A total of 6,426 patients were finally subjected to the analysis. The diagnosis of IgAN was histopathologically determined based on the basic glomerular changes described in the classification of glomerular diseases of the World Health Organization, and by immunohistological identification of IgA in glomeruli [23]. Patients who were diagnosed with other renal or systemic diseases, including those with Henoch–Schönlein purpura, systemic lupus erythematosus, and liver cirrhosis

were excluded. Clinical data, including age, sex, body mass index (BMI), systolic and diastolic blood pressure, the presence or absence of hypertension, estimated glomerular filtration rate (eGFR), UPE rate, urinary sediment, serum albumin, and serum total cholesterol were evaluated. All clinical data were obtained at the time of the diagnostic renal biopsy. The J-RBR is registered in the UMIN Clinical Trials Registry (registered number: UMIN000000618).

Measurements and definitions

The J-RBR registration facilities were divided into 10 regions of Japan: Hokkaido, Tohoku, Kanto, Koshinetsu, Hokuriku, Tokai, Kinki, Chugoku, Shikoku, and Kyusyu (**Figure 1**). The Japanese populations in these regions are considered ethnically homogeneous [21].

The eGFR was calculated using a three-variable equation modified for Japanese populations, as follows: $eGFR = 194 \times age^{-0.287} \times sCr^{-1.094}$ ($\times 0.739$ if female), where sCr is the serum creatinine concentration [24]. Hematuria was defined as the number of red blood cells (RBCs) ≥ 5 per high power field (HPF) in urinary sediment and graded based on the number of RBCs per HPF: 0, 1, 2, and 3 for 0–4, 5–10, 11–30, and ≥ 30, respectively. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, according to the Japanese Society

of Hypertension Guidelines for the Management of Hypertension 2014 [25], or usage of antihypertensive medications. Patients ≥ 65 years of age were defined as elderly [26].

In the Kidney Disease Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, patients with chronic kidney disease (CKD) are classified into 18 categories and four risk groups (low, moderately increased, high, and very high risk) based on eGFR and albuminuria categories on a CKD heat map [27]. In Japan, this CKD risk classification system has been modified according to the cause of kidney disease. Except for diabetes cases, the UPE rate, instead of the urinary albumin excretion rate, is applied for patients with CKD including IgAN, based on the requirements of the Japanese national insurance system [28]. Based on the KDIGO 2012 guidelines, which were modified for the Japanese population, the UPE rate at the time of biopsy is classified as normal (< 0.15 g/day or g/gCr; A1), mild (0.15–0.49 g/day or g/gCr; A2), or severe (≥ 0.5 g/day or g/gCr; A3) [27,28]. Similarly, eGFR at the time of biopsy is classified into five groups: G1, G2, G3a, G3b, G4, and G5 for ≥ 90, 60–89, 45–59, 30–44, 15–29, and < 15 ml/min/1.73 m^2, respectively. According to the CKD heat map of the 2012 KDIGO guidelines, which is based on the eGFR level and UPE rate, the renal prognosis is categorized as low, moderately increased, high, or very high.

Social factors

Certain social factors may be associated with regional variation in the clinical features of IgAN. The first such factor is the number of board-certified JSN nephrologists per regional population. A qualified JSN board-certified nephrologist must have ≥ 3 years training at a JSN-accredited facility; have passed a specific exam; and renew their license every 5 years. The second social factor is the proportion of participants who received a health checkup per regional population. To ascertain this, we used data from the Specific Health Checkup, a metabolic syndrome health checkup devised by the Ministry of Health, Labor, and Welfare of Japan that targets people aged 40–74 years who were enrolled in the national health insurance program in 2012 [29]. The Specific Health Checkup comprises a physical examination, blood pressure measurement, blood test, and urinalysis. The third social factor is the proportion of elderly persons relative to the general population. Information on the proportion of elderly persons (age ≥ 65 years) in each regional population was obtained from a national survey performed in 2012 (**Supplementary table 1**) [30]. Based on the ranking of the social factors included in this study, 10 regions of Japan were divided into three groups, as follows: low (three regions), intermediate (four regions), and high (three regions) groups. Analysis was performed within each group according to the clinical characteristics of the IgAN patients at the time of biopsy diagnosis.

Statistical analysis

Continuous variables are expressed as means ± standard deviation. Differences among regions were analyzed by the Kruskal–Wallis test. Differences in the characteristics of the IgAN patients within each social factor group were analyzed by the Mantel–Haenszel test for trend and the Jonckheere–Terpstra trend test, as appropriate. A generalized linear mixed model was constructed to identify the social factors that may influence regional variation in the severity of IgAN at the time of biopsy. In each analysis, social factors, age, sex, and the presence or absence of hypertension were treated as fixed covariates, and the regions and the J-RBR registration facilities as random effects. A p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS statistical software (ver. 24.0; IBM, Armonk, NY, USA).

Patient and public involvement

No patient was involved in the design or conduct of the study, since this was a database research study.

Results

Patient clinical characteristics at the time of biopsy diagnosis

The clinical characteristics of the patients at the time of biopsy diagnosis are summarized in **Table 1**. A total of 1,813 (28.2%) patients were categorized into the very-high-risk renal prognosis group. The male and female ratio was similar among the 10 regions. On the other hand, significant regional variation was observed in age, BMI, prevalence of hypertension, eGFR, UPE rate, degree of hematuria, and renal prognosis risk group distribution. Notably, there were large differences between the lowest and highest regions with respect to the rates of both very high and low renal prognosis risk, as defined by the KDIGO guidelines.

Regional variation in social factors

Variation among the 10 regions in terms of the social factors that may influence the severity of IgAN at biopsy diagnosis were assessed (**Table 2**). The social factors included in this study were the number of board-certified nephrologists, proportion of patients who received a health checkup, and proportion of elderly persons per regional population. The distributions of these three social factors differed significantly among the 10 regions. In particular, an up to 2.7-fold among regions difference was observed in the number of board-certified nephrologists.

Relationships between social factors and regional variation in the clinical characteristics of the IgAN patients at biopsy diagnosis

Trends in the social factors were analyzed according to regional variation in the clinical features of the IgAN patients at biopsy diagnosis. The number of nephrologists per regional population showed a clear trend: the fewer the nephrologists, the more severe were the clinical features at the biopsy diagnosis, including renal function, the UPE rate, hematuria and the renal prognosis risk distribution (**Table 3**). The regions with higher proportions of IgAN patients with a very-high-risk renal prognosis and those with fewer nephrologists per regional population showed a similar distribution trend (**Figure 1**). No such similarities were found between the distribution of IgAN patients with a very-high-risk renal prognosis and those of health checkup participants or elderly persons per regional population (**Supplemental Figure 1**).

A generalized linear mixed model was constructed to examine the relationship between the three social factors investigated in this study and regional differences in the proportion of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, as defined by the 2012 KDIGO guidelines. In the model, the number of board-certified nephrologists per regional population was significantly associated with the rate of fulfilment of the clinical criteria for a very-high-risk renal

prognosis at the biopsy diagnosis, even after considering the differences in clinical factors among regions (**Table 4, Figure 2**). We did not find a significant relationship between the rate of very-high-risk renal prognosis at biopsy diagnosis and either the proportion of patients who received a health checkup or the proportion of elderly persons per regional population (**Table 4**).

Discussion

In this cross-sectional study, we demonstrated substantial regional variations in Japanese IgAN patient clinical characteristics at the diagnostic renal biopsy, including eGFR and the UPE rate. In addition, a lower number of board-certified nephrologists per regional population was closely associated with the clinical severity of IgAN, including the rate of fulfilment of clinical criteria for a very high risk renal prognosis.

Previous studies have shown apparent regional and national differences in CKD and ESRD incidence in the United States and Europe [31-33]. However, race and ethnicity within a study population must be homogenous to identify the effects of social factors on regional differences in clinical factors. The Japanese population is useful for the evaluation of such factors, which may influence disease prevalence and severity, because of its ethnic homogeneity. Usami et al. demonstrated significant regional differences in the incidence of ESRD within Japan [34]. Studies of the ethnically homogenous Japanese population suggest that social factors, i.e., factors other than those with a genetic basis, contribute to such regional differences in the presentation of renal diseases. Similarly, our results pertaining to apparent regional differences in the clinical features of Japanese IgAN patients at biopsy diagnosis also suggest that such regional variation is due to social rather than genetic factors. However, the results reported here may not be applicable to individuals

living outside of Japan, since epigenetic and environmental factors also contribute to disease progression.

This is the first reported study to reveal regional differences in the clinical severity of IgAN patients at biopsy diagnosis in Japan. Interestingly, the proportion of IgAN patients fulfilling the clinical criteria for a very-high-risk renal prognosis at biopsy diagnosis showed an up to 3.7-fold difference among the 10 regions. Studies on the natural history of IgAN have consistently identified renal impairment and severe proteinuria as clinically detectable poor prognostic indicators at the time of biopsy diagnosis [3-5]. In addition, such predictors of the progression to ESRD in patients with IgAN are closely associated with pre-existing histopathological findings of advanced chronic renal disease [35]. Thus, our current results showing a significant association between the number of nephrologists per regional population and the clinical severity of IgAN patients at biopsy diagnosis suggest a possible contribution of nephrologist availability to the likelihood of early diagnosis. The uneven regional distribution of nephrologists may influence the time taken for referral from a primary care physician to a nephrologist, who then decides regarding performance of a renal biopsy and the therapeutic intervention. The number of nephrologists practicing in Japan is comparable to that of other developed countries. For example, in Japan there are 34 nephrologists per 1 million population, comparable to the United States and Europe (28 and 31 per 1 million population,

respectively) [36]. However, the number of nephrologists per population in African and southeastern Asian countries is much lower at 1–4 per 1 million population [36]. Further studies aimed at understanding the demand and supply for nephrology workforce may help to explain the uneven distribution of nephrologists.

Other than the number of nephrologists, several other socioeconomic factors may influence the clinical severity of IgAN. Due to the universal health insurance coverage was established in 1961 in Japan, the gap between individuals with a poor medical economic status and the rest of the population is reportedly lower than that in other countries [37]. The rate of health checkups may be another important social factor influencing IgAN severity. Although urinalysis screening is compulsory for school-age children, adult participation in such schemes can show significant variation among regions in Japan. However, we did not find any significant effect of health checkup rate on the severity of IgAN at biopsy diagnosis. One possible interpretation of this result is that referral to a nephrologist may play a more important role than health checkups in IgAN severity. The proportion of elderly persons in urban and rural populations differs significantly among regions in Japan, a country in which there has been remarkable aging of rural populations, particularly in recent years. Previous studies have suggested that elderly patients with IgAN have relatively more severe clinical features at the time of diagnosis than younger patients [38,39]. Thus, we examined the effect

of regional variation in the proportion of elderly persons on the clinical severity of IgAN. However, contrary to our expectations, we did not find any significant effect of the proportion of elderly persons on the severity of IgAN at biopsy diagnosis. Referral to a nephrologist and renal biopsy may be performed less often in elderly patients.

Our study had several important limitations. First, there were differences in both the number of J-RBR registration facilities and the sample size among regions. Second, there may have been differences in the criteria for performing renal biopsies among facilities. Because no formal criteria for performing a renal biopsy are defined in the registry, all renal biopsies were performed at the discretion of the attending physician. This may have influenced the regional differences in severity of clinical features at the time of biopsy. Third, we could not exclude the potential influence of other social factors, such as dietary habits or climatic factors, on the regional variation in clinical features of IgAN patients. Fourth, the J-RBR does not include histopathological findings of renal biopsies. Thus, we could not demonstrate that the clinical severity of the IgAN patients correlated with the histopathological findings. Fifth, the applicability of the findings to countries other than Japan is unclear: since Japan is one of only a few countries in the world that screen for kidney diseases by urinalysis. Sixth, we did not fully evaluate hematuria in relation to clinical severity of IgAN. Persistent hematuria in the presence of proteinuria is reportedly associated with the risk for

progression to ESRD in IgAN [9]. The CKD risk classification system of KDIGO 2012 does not include hematuria [27,28] and the association between the degree of hematuria and clinical severity of IgAN is unclear. Finally, it is a cross-sectional study. Therefore, further studies are required to elucidate the relationship between the number of nephrologists per regional population and the renal prognosis of patients with IgAN.

Conclusions

This study identified considerable regional differences in the clinical severity of IgAN at the biopsy diagnosis in Japanese patients. Our results suggest that an uneven distribution of nephrologists across regions may influence the timing of nephrologist referral and biopsy diagnosis, as well as the likelihood of earlier intervention to prevent progression to ESRD in patients with IgAN.

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Patient consent: Not required.

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Data sharing statement: No additional data available.

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Table 1. Clinical characteristics of the patients at biopsy diagnosis.

Variables	Total (n=6426)	Hokkaido (n=148)	Tohoku (n=911)	Kanto (n=1229)	Koshinetsu (n=201)	Hokuriku (n=258)	Tokai (n=1432)	Kinki (n=706)	Chugoku (n=485)	Shikoku (n=183)	Kyushu (n=873)	*p*-value	Maximal fold among regions
Age, mean (SD), years	39.5 (17.7)	41.5 (16.6)	42.5 (18.1)	34.7 (17.5)	39.2 (14.9)	42.2 (16.8)	41.4 (16.6)	38.9 (17.1)	39.4 (17.8)	32.2 (20.2)	40.8 (18.3)	< 0.001	1.32
Male, no. (%)	3297 (51.3)	78 (52.7)	488 (53.6)	652 (53.1)	96 (47.8)	143 (55.4)	707 (49.4)	367 (52.0)	255 (52.6)	86 (47.0)	425 (48.7)	0.182	1.18
BMI mean (SD), kg/m^2	22.6 (4.0)	23.4 (4.2)	23.5 (4.2)	22.0 (4.2)	22.2 (3.7)	22.8 (3.6)	22.6 (3.7)	22.4 (4.1)	22.7 (4.2)	21.7 (4.0)	22.7 (4.0)	< 0.001	1.08
SBP, mean (SD), mm Hg	124 (18)	126 (19)	126 (17)	120 (18)	120 (16)	122 (17)	127 (18)	122 (18)	124 (18)	117 (16)	126 (19)	< 0.001	1.09
DBP, mean (SD), mm Hg	74 (13)	76 (13)	76 (13)	72 (13)	75 (13)	74 (13)	76 (13)	73 (12)	74 (13)	69 (12)	75 (13)	< 0.001	1.10
Hypertension, no. (%)	2790 (43.4)	82 (55.4)	403 (44.2)	457 (37.2)	93 (46.3)	127 (49.2)	709 (49.5)	279 (39.5)	203 (41.9)	49 (26.8)	388 (44.4)	< 0.001	2.07
eGFR, mean (SD), ml/min/1.73 m^2	74.4 (30.3)	67.5 (31.3)	73.3 (29.6)	79.6 (31.5)	71.3 (27.7)	73.2 (27.0)	69.0 (27.8)	74.8 (29.3)	78.0 (30.9)	91.4 (35.2)	73.5 (31.2)	< 0.001	1.35
Serum albumin, mean (SD), g/dl	3.9 (0.6)	3.7 (0.7)	4.0 (0.7)	4.0 (0.6)	4.0 (0.7)	3.8 (1.0)	3.9 (0.6)	3.9 (0.6)	4.0 (0.6)	4.0 (0.6)	3.9 (0.6)	< 0.001	1.08
Total cholesterol, mean (SD), mg/dl	194 (59)	198 (45)	182 (68)	186 (71)	188 (71)	198 (60)	204 (47)	199 (49)	197 (47)	189 (55)	198 (59)	< 0.001	1.12
UPE, mean (SD), g/day	1.16 (1.62)	1.93 (2.63)	1.00 (1.55)	0.97 (1.25)	0.93 (1.22)	1.00 (1.23)	1.42 (1.72)	1.04 (1.46)	0.97 (1.43)	1.08 (2.31)	1.35 (1.83)	< 0.001	2.08
Hematuria grade 2,3, No. (%)	4313 (67.1)	101 (68.2)	598 (65.6)	801 (65.2)	142 (70.6)	170 (65.9)	1024 (71.5)	454 (64.3)	327 (67.4)	94 (51.4)	602 (69.0)	< 0.001	1.39
KDIGO prognosis risk of CKD, no. (%)													
Very-high-risk	1813 (28.2)	59 (39.9)	265 (29.1)	289 (23.5)	61 (30.3)	64 (24.8)	495 (34.6)	175 (24.8)	117 (24.1)	20 (10.9)	268 (30.7)	< 0.001	3.66
High risk	2353 (36.6)	48 (32.4)	272 (29.9)	446 (36.3)	66 (32.8)	100 (38.8)	623 (43.5)	248 (35.1)	157 (32.4)	66 (36.1)	327 (37.5)	< 0.001	1.45
Moderately increased risk	1412 (22.0)	24 (16.2)	199 (21.8)	322 (26.2)	53 (26.4)	54 (20.9)	228 (15.9)	183 (25.9)	122 (25.2)	43 (23.5)	184 (21.1)	< 0.001	1.66
Low risk	849 (13.2)	17 (11.5)	175 (19.2)	172 (14.0)	21 (10.4)	40 (15.5)	86 (6.0)	100 (14.2)	89 (18.4)	54 (29.5)	94 (10.8)	< 0.001	4.92

BMI, body mass index; UPE, urinary protein excretion; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Regional variation in social factors.

Regions	Nephrologists, no. /100,000 populations	Proportion of participants who received a health checkup, %	Proportion of elderly persons relative to the general population, %
Hokkaido	1.58	36.7	26.0
Tohoku	2.73	46.5	26.5
Kanto	4.03	46.4	22.1
Koshinetsu	3.26	50.5	27.0
Hokuriku	4.24	48.7	26.2
Tokai	2.87	47.2	23.3
Kinki	3.46	40.7	24.2
Chugoku	3.07	41.1	26.8
Shikoku	3.05	43.1	28.1
Kyushu	3.20	43.2	25.4
Total mean	3.40	45.0	24.2
Maximal fold among regions	2.68	1.38	1.27
p-value	< 0.001	< 0.001	< 0.001

Table 3. Comparison of patient clinical characteristics among regions categorized according to the number of nephrologists.

Variables	Category of the number of nephrologists			*p*-value for trend
	Lowest three regions (n=2491)	Intermediate four regions (n=1742)	Highest three regions (n=2193)	
Nephrologists /100,000 population	2.59	3.16	3.86	
Age, mean (SD), year	41.8 (17.2)	39.3 (18.2)	36.9 (17.5)	< 0.001
Hypertension, no. (%)	1194 (47.9)	733 (42.1)	863(39.4)	< 0.001
eGFR, mean (SD), ml/min/1.73 m^2	70.5 (28.7)	77.3 (30.4)	77.3 (30.4)	< 0.001
UPE, mean (SD), g/day	1.30 (1.75)	1.17 (1.74)	0.99 (1.32)	< 0.001
Hematuria grade 2 and 3, no (%)	1723 (69.2)	1165 (66.9)	1425 (65.0)	0.002
KDIGO renal prognosis risk, no. (%)				
Very-high-risk	819 (32.9)	465 (26.7)	528 (24.1)	< 0.001
High risk	943 (37.9)	616 (35.4)	794 (36.2)	0.226
Moderately increased risk	451 (18.1)	402 (23.1)	559 (25.5)	< 0.001
Low risk	278 (11.2)	259 (14.9)	312 (14.2)	0.001

Table 4. Social factors and regional variation in IgAN patients with very-high-risk renal prognosis.

Fixed effects	f-value	Regression coefficient	95% CI	*p*-value
Number of nephrologists (/100,000 populations)	4.022	-0.489	-0.967 − -0.011	0.045
Proportion of patients who received a health checkup (%)	0.521	0.033	-0.056 − 0.122	0.471
Proportion of elderly persons relative to the general population (%)	3.512	-0.140	-0.287 − 0.006	0.061

95% CI, 95% confidence interval; Covariates: age, sex, hypertension: Random effects: region, J-RBR registration facility:

Structure for the random effects, First-order autoregressive.

Figure legends

Figure 1. Distributions of IgAN patients with a very-high-risk renal prognosis and nephrologists.

Regional differences of the rate of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, which was adjusted for age, sex, and hypertension (**A**), and the number of board-certified nephrologists per regional population (**B**). Based on the ranking of each factor, 10 regions of Japan were divided into three groups, as follows: the three lowest, four intermediate, and three highest groups. The numbers indicate the following regions: 1, Hokkaido; 2, Tohoku; 3, Kanto; 4, Koshinetsu; 5, Hokuriku; 6, Tokai; 7, Kinki; 8, Chugoku; 9, Shikoku; and 10, Kyushu.

Figure 2. Relationship between the rate of IgAN patients with a very-high-risk renal prognosis and the number of nephrologists per regional population.

Circles indicate each region and the areas of the circles are proportional to the regional populations. The rate of IgAN patients with a very-high-risk renal prognosis in each region was adjusted by age, sex, and hypertension. The regression line was obtained from the generalized linear mixed model in **Table 4**.

Supplementary Figure 1. Distributions of IgAN patients with a very-high-risk renal prognosis and social factors other than nephrologist number.

Regional differences in the rate of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, which was adjusted for age, sex, and hypertension (**A**), the rate of health checkup participants per regional population (**B**), and the proportion of elderly persons per regional population (**C**). Based on the ranking of each factor, 10 regions of Japan were divided into three groups, as follows: the three lowest, four intermediate, and three highest groups. The numbers indicate the following regions: 1, Hokkaido; 2, Tohoku; 3, Kanto; 4, Koshinetsu; 5, Hokuriku; 6, Tokai; 7, Kinki; 8, Chugoku; 9, Shikoku; and 10, Kyushu.

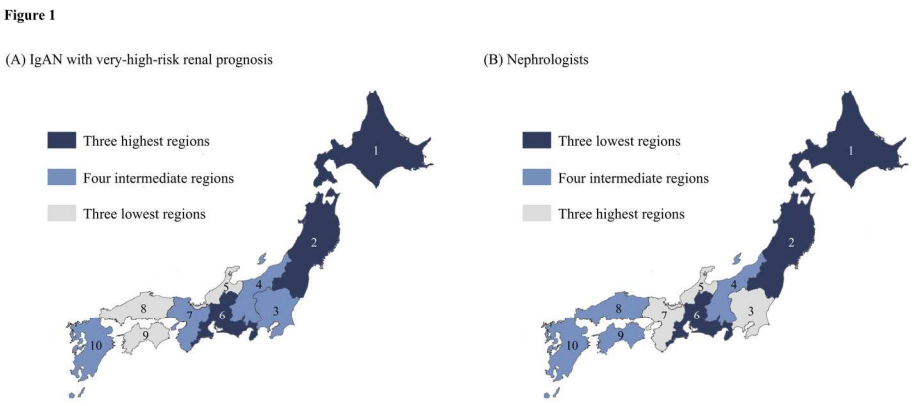

Figure 1. Distributions of IgAN patients with a very-high-risk renal prognosis and of nephrologists.

Regional differences of the rate of IgAN patients with a very-high-risk renal prognosis at biopsy diagnosis, which was adjusted for age, sex, and hypertension (A), and the number of board-certified nephrologists per regional population (B). Based on the ranking of each factor, 10 regions of Japan were divided into three groups, as follows: the three lowest, four intermediate, and three highest groups. The numbers indicate the following regions: 1, Hokkaido; 2, Tohoku; 3, Kanto; 4, Koshinetsu; 5, Hokuriku; 6, Tokai; 7, Kinki; 8, Chugoku; 9, Shikoku; and 10, Kyushu.

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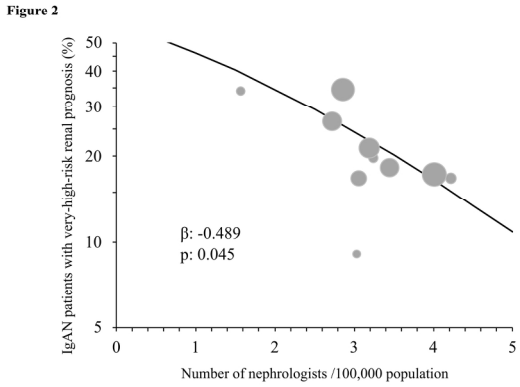

Figure 2. Relationship between the rate of IgAN patients with a very-high-risk renal prognosis and the number of nephrologists per regional population. ⊦ ⊤ Circles indicate each region and the areas of the circles are proportional to the regional populations. The rate of IgAN patients with a very-high-risk renal prognosis in each region was adjusted by age, sex, and hypertension. The regression line was obtained from the generalized linear mixed model in Table 4.

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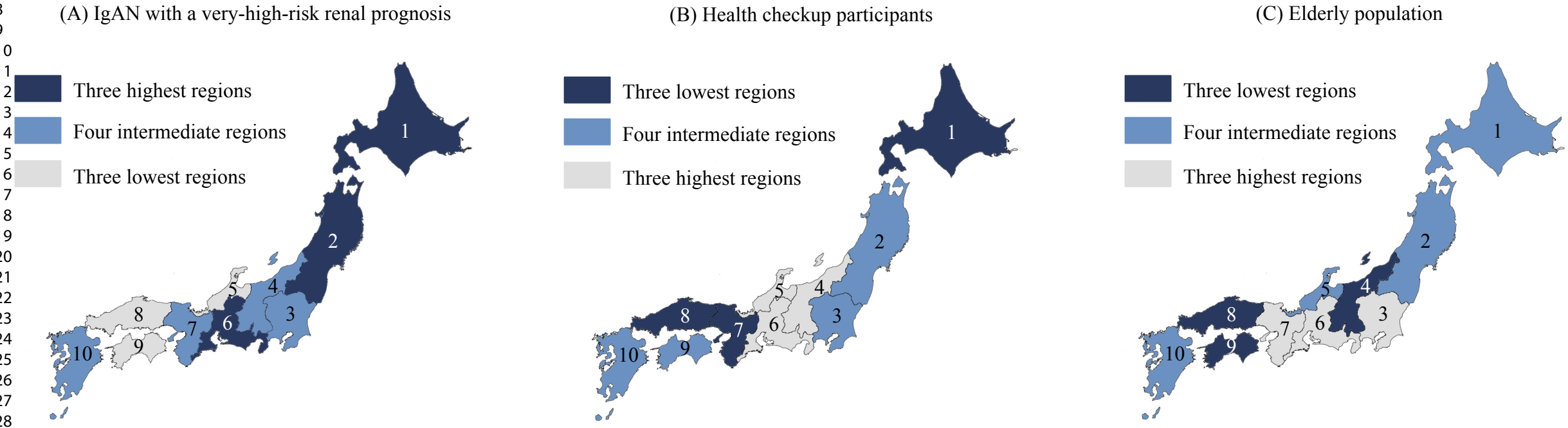
Supplementary table 1. Regional populations and the number of nephrologists in Japan.

Regions	Populations (×1,000)	Number of nephrologists
Hokkaido	5460	86
Tohoku	9155	250
Kanto	42631	1719
Koshinetsu	5331	174
Hokuriku	3044	129
Tokai	15063	432
Kinki	20845	721
Chugoku	7504	230
Shikoku	3932	120
Kyushu	13144	421
Total	126109	4282

Supplementary Figure 1



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	NA
Bias	9	Describe any efforts to address potential sources of bias	*NA*
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.