PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Distribution of nephrologists and regional variation in the clinical severity of IgA nephropathy at biopsy diagnosis in Japan: A cross-sectional study
AUTHORS	Okabayashi, Yusuke; Tsuboi, Nobuo; Amano, Hoichi; Miyazaki, Yoichi; Kawamura, Tetsuya; Ogura, Makoto; Narita, Ichiei; Toshiharu, N; Yokoyama, Hitoshi; Yokoo, Takashi

VERSION 1 – REVIEW

REVIEWER	William J. Placzek The University of Alabama at Birmingham, United States
REVIEW RETURNED	29-Jun-2018

GENERAL COMMENTS	The manuscript is very well written and asks and successfully interrogates an interesting question regarding the relationship between the number of nephrologists and incidence of high-risk renal prognosis in the sample cohort. While all of the conclusions are justified, the authors present the Japanese cohort as an ethnically homogenous population that can be used to ask questions on the impact of clinical care on patient outcomes. To facilitate such use going forward, it would be important to include the regional populations that they used as the denominator for all of their calculations. I would request that a table with these regional populations be added as supplementary data.

REVIEWER	Trimarchi, Hernán Hospital Britanico de Buenos Aires, Nephrology
REVIEW RETURNED	28-Jul-2018

GENERAL COMMENTS	The present manuscript by Okabayashi et al is titled: Distribution of nephrologists and regional in the clinical severity of IgA nephropathy at biopsy diagnosis in Japan: A cross-sectional ecological study. However, this is not an ecological study. It is a study based on the epidemiology of nephrologist distribution in Japan. Thus, it must be changed, not only the title, but also in the limitations, where the word ecology also appears. Key words: Regional differences is not an appropriate key word; replace it by hematuria, and add chronic kidney disease.and glomerulonephritis. Page 4, third line: fulfillment and not fulfilment. Page 6, line 4: I would delete "absence of gross hematuria" and replace it by hematuria, as both macro- and microhematuria and under discussion and under deep debate, particularly the latter. This issue about microhematuria should be briefly addressed.

	Page6, line 54 (last sentence) please redo as follows: "....in Japan, potential cases of IgAN are first....to a nephrologist to assess the patient". Page 7,second line: "....and may also be associated..." Page 8: 1544 patients were excluded because of mssing data. Please, explain what the missing data was about. Page 9, Measurements and definitions: Define microhematuria, as it is graded but not defined. What is the policy in Japan with respect to patients with sole microhematuria, i.e., without proteinuria and/or with normal GFR?. Are they referred to nephrologists and eventually biopsied? Page 13, Results: This section could be summarized due to the high number of figures and tables. Page 16, Discussion. Line 29: Please replace "isolate" by "identify". At the end fo the second paragraph authors should underscore the fact that results may be applicable just to Japanese individuals living in Japan, due not only to the genetic background of the disease, but also to the epigenetics and environment influence these topics exert on the pathogenesis of the disease. Page 17. After the first paragraph, authors could discuss about the reasons why there is an uneven distribution of nephrologists in Japan, and also offer the reader the national nephrologist/individuals ratio and compare it to the European and US data (References 30-32) and discuss the differences and consequences of such differences. Page 18: Is urinalysis screening compulsory for school-age children?. Ifso, please replace in the first line "popular" by "compulsory". Line 29: replace "...do non-elderly..." by just "younger". Page 19. Just at this point of the paper authors comment on the important fact that renal biopsy findings are not included. This issue must be commented on in the Introduction as well. With respect to the fifth limitation, insert a colon after "unclear" and turn the "S" of Since not to a capital letter. Line 26: "Finally, it is a cross-sectional study.". It fits better. References: Some references have doi and others do not. (3, 30 etc)

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1:

We wish to express our appreciation to the Reviewer for his insightful comments. We feel the comments have helped us significantly improve the paper.

Comment: While all of the conclusions are justified, the authors present the Japanese cohort as an ethnically homogenous population that can be used to ask questions on the impact of clinical care on patient outcomes. To facilitate such use going forward, it would be important to include the regional populations that they used as the denominator for all of their calculations. I would request that a table with these regional populations be added as supplementary data.

Response: In accordance with Reviewer’s comment, we have added the following supplementary table:

Supplementary table. 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

We wish to thank the Reviewer again for his valuable comments.

RESPONSE TO REVIEWER 2:

We wish to express our appreciation to the Reviewer for his insightful comments. We feel the comments have helped us significantly improve the paper.

Comment 1: The present manuscript by Okabayashi et al is titled: Distribution of nephrologists and regional in the clinical severity of IgA nephropathy at biopsy diagnosis in Japan: A cross-sectional ecological study. However, this is not an ecological study. It is a study based on the epidemiology of nephrologist distribution in Japan. Thus, it must be changed, not only the title, but also in the limitations, where the word ecology also appears.

Response: In accordance with Reviewer's comment, we have changed the title and the following text forms (p 1; line 1-2, p 3; line 8, p 8; line 8, p 16; line 2 and p 20; line 4):

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

to

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

"Design: A cross-sectional ecological study."

to

"Design: A cross-sectional study.",

"This cross-sectional ecological study included Japanese patients with primary IgAN registered on the J-RBR from January 1, 2007 through June 30, 2013."

to

“This cross-sectional study included Japanese patients with primary IgAN registered on the J-RBR from January 1, 2007 through June 30, 2013.”,

“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.”

to

“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.”

and

“Finally, this study used a cross-sectional ecological design.”

to

“Finally, this study used a cross-sectional design.”

Comment 2: Key words: Regional differences is not an appropriate key word; replace it by hematuria, and add chronic kidney disease.and glomerulonephritis.

Response: In accordance with Reviewer’s comment, we have changed the key words (p 2; line 1):

“IgA nephropathy, regional differences, nephrologist, renal biopsy, proteinuria”

to

“IgA nephropathy, nephrologist, renal biopsy, proteinuria, hematuria, chronic kidney disease, glomerulonephritis”

Comment 3: Page 4, third line: fulfillment and not fulfilment.

Response: We have changed the text form according to Reviewer’s comment.

Comment 4: Page 6, line 4: I would delete "absence of gross hematuria" and replace it by hematuria, as both macro- and microhematuria and under discussion and under deep debate, particularly the latter. This issue about microhematuria should be briefly addressed.

Response: In accordance with Reviewer’s comment, we have changed the following text form (p 6; line 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].”

to

“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].

and added the following reference (p 24; line 4-5):

“9. Sevillano A, Gutiérrez E, Yuste C, et al. Remission of Hematuria Improves Renal Survival in IgA Nephropathy. J Am Soc Nephrol 2017;28:3089–3099. doi:10.1681/ASN.2017010108”

Moreover, we have added the following sentences in discussion (p 19-20; line 17-4):

“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]. Since, the CKD risk classification system of KDIGO 2012 modified in Japan does not include hematuria [27,28], the association between the degree of hematuria and clinical severity of IgAN is unclear but warrants evaluation.”

Comment 5: Page6, line 54 (last sentence) please redo as follows: "....in Japan, potential cases of IgAN are first....to a nephrologist to assess the patient".

Response: We have changed the text form according to Reviewer’s comment.

Comment 6: Page 7,second line: "....and may also be associated..."

Response: We have changed the text form according to Reviewer’s comment.

Comment 7: Page 8: 1544 patients were excluded because of missing data. Please, explain what the missing data was about.

Response: In accordance with Reviewer’s comment, we have changed the following text form (p 8; line 10-12):

“Of these 7,970 patients, 1,544 were excluded because of missing data critical for the analysis.”

to

“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.”

Moreover, we have delated the following sentence (p 9; line 3-5):

“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.”

Comment 8: Page 9, Measurements and definitions:
Define microhematuria, as it is graded but not defined.

What is the policy in Japan with respect to patients with sole microhematuria, i.e., without proteinuria and/or with normal GFR?. Are they referred to nephrologists and eventually biopsied?

Response: In Japanese clinical practice guideline for the diagnosis of hematuria, patients with sole microhematuria without proteinuria or renal insufficiency are firstly examined for urothelial and kidney cancers. Patients who have no evidence for cancers receive a follow-up examination from the primary care physicians every one year. If patients develop proteinuria and/or renal insufficiency during a follow-up, primary care physicians refer the patients to the nephrologists, and then they consider for renal biopsy. Therefore, almost all of the patients included in this study had the events that they developed proteinuria and/or renal insufficiency with or without hematuria.

In accordance with Reviewer's comment, we have changed the following text form (p 9; line 15-17):

"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."

to

"Hematuria was defined as the number of red blood cells (RBC) ≥ 5 per high power field (HPF) in urinary sediment and graded based on the number of RBC per HPF: 0, 1, 2, and 3 for 0–4, 5–10, 11–30, and ≥ 30, respectively."

Comment 9: Page 13, Results: This section could be summarized due to the high number of figures and tables.

Response: In accordance with Reviewer's comment, we have removed the following sentence (p 13; line 4-5):

"Their mean age was 39.5 years, and 3,297 (51.3%) were males. The mean eGFR was 74.4 ml/min/1.73 m2 and the mean UPE rate was 1.16 g/day."

and deleted the following numeric data (p 13; line 6-13):

"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/m2, $p < 0.001$), prevalence of hypertension (26.8–55.4%, $p < 0.001$), eGFR (67.5–91.4 ml/min/1.73 m2, $p < 0.001$), 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)."

Comment 10: Page 16, Discussion. Line 29: Please replace "isolate" by "identify".

Response: We have changed the text form according to Reviewer's comment.

Comment 11: At the end to the second paragraph authors should underscore the fact that results may be applicable just to Japanese individuals living in Japan, due not only to the genetic background of

the disease, but also to the epigenetics and environment influence these topics exert on the pathogenesis of the disease.

Response: In accordance with Reviewer's comment, we have added the following text form (p 16-17; line 17-2):

"However, it should be noted that these results may be applicable just to Japanese individuals living in Japan. Because, not only to the genetic background, but also the epigenetics and environment factors may influence on the disease progression."

Comment 12: Page 17. After the first paragraph, authors could discuss about the reasons why there is an uneven distribution of nephrologists in Japan, and also offer the reader the national nephrologist/individuals ratio and compare it to the European and US data (References 30-32) and discuss the differences and consequences of such differences.

Response: In accordance with Reviewer's comment, we have added the following text form in discussion (p 17-18; line 15-5):

"Importantly, differences in nephrologist number are not so serious among the regions in Japan than those found among the countries over the world. For example, the number of nephrologists per population in Japan is 34 per million populations, which is almost comparable to those of the United States and Europe (28 and 31 per million population, respectively) [36]. However, the number of nephrologists per population in African and East-South Asian countries is much lower and is 1-4 per million populations [36]. Further study of detailed analyses on demand and supply for nephrology workforce is required to prove the reasons for the uneven distribution of nephrologists among the regions or countries."

and added the following reference:

"36. Sharif M, Elsayed M, Stack A. The global nephrology workforce: emerging threats and potential solutions! Clin Kidney J 2016;9:11–22. doi:10.1093/ckj/sfv111"

Comment 13: Page 18: Is urinalysis screening compulsory for school-age children?. If so, please replace in the first line "popular" by "compulsory".

Response: We have changed the following text form (p 18; line 10-12)

"Although urinalysis screening is popular for school-age children, adult participation in such schemes can show significant variation among regions in Japan."

to

"Although urinalysis screening is compulsory for school-age children, adult participation in such schemes can show significant variation among regions in Japan."

Comment 14: Line 29: replace "...do non-elderly..." by just "younger".

Response: We have changed the text form according to Reviewer's comment.

Comment 15: Page 19. Just at this point of the paper authors comment on the important fact that renal biopsy findings are not included. This issue must be commented on in the Introduction as well.

Response: In accordance with Reviewer's comment, we have changed the following text form (p 7; line 6-7):

"In this study, we analyzed patients with IgAN in Japan, which has an ethnically homogeneous population [20]"

to

"In this study, we analyzed clinical data of patients with IgAN in Japan, which has an ethnically homogeneous population [21]"

and added the following sentences in the Materials and Methods (p 8; line 6-8):

"The clinical data of the patients who performed renal biopsy are registered to the J-RBR. The J-RBR include final renal histopathological diagnosis, but not the details of histopathological findings."

Comment 16: With respect to the fifth limitation, insert a colon after "unclear" and turn the "S" of Since not to a capital letter.

Response: We have changed the text form according to Reviewer's comment.

Comment 17: Line 26: "Finally, it is a cross-sectional study.". It fits better.

Response: We have changed the text form according to Reviewer's comment.

Comment 18: References: Some references have doi and others do not. (3, 30 etc)

Response: We have added the DOI to 31th reference. However, third and eleventh references are not given the DOI, so we could not add the DOI to these references.

We wish to thank the Reviewer again for his valuable comments.