Author's response to reviews

Title: Baseline characteristics and prevalence of cardiovascular disease in newly visiting or referred chronic kidney disease patients to nephrology centers in Japan: a prospective cohort study

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Author's response to reviews: see over
Dear Dr. Maria Merrie Jul Ladag

Regarding our manuscript: “Baseline characteristics and prevalence of cardiovascular disease in newly visiting or referred chronic kidney disease patients to nephrology centers in Japan: a prospective cohort study” (MS: 1827319304866614).

We thank you for all your valuable suggestions and comments. Following your suggestions we have made a number of corrections accordingly. We now here in resubmit a revised manuscript with corrected parts in red characters and underlines. We have made point-by-point descriptions to all comments. We hope our revised manuscript will be acceptable in your journal.

Sincerely,

Soichiro Iimori and Sei Sasaki, on behalf of all authors.

**Editorial Request:**

1. Please add the specific names of all the institutional ethics committees that approved the study to the manuscript.

   Answer: This study was approved by the ethics review boards of each participating institution. We have described this in the Methods and Acknowledgments sections of the revised manuscript, and have provided the approval number from each institution in the Acknowledgments section. (Page 19)

2. Please assign roles to all of the authors in the Authors’ Contributions section.

   Answer: We added the following sentence in the Authors’ contributions section. (Page 18-19)
“YN and SN contributed to the design of this study. SI managed the database, performed statistical analysis and drafted the manuscript. SS contributed to organizing the study and writing the manuscript. EK advised on statistical analysis. SI, YN, TO, SN, TT, YC, MK, RA, YN, YM, HT, TT, SK, EK, SI, MY, RO, MT, TK, KK, TR, SU and SS treated the patients and provided the patients' data. All authors have read and approved the final manuscript.”

Reviewer's report

Reviewer: Stephen Sozio

We thank Dr. Stephen Sozio for all his thoughtful suggestions and comments.

Major:
Comment 1: The authors should be cautious in analyses about the use of CHF in their definition of CVD. CHF may often not be an atherosclerotic equivalent (unlike the other variables in the definition.) As such, sensitivity analyses should be conducted excluding CHF from the definition of CVD to see whether the associations are similar in direction and magnitude, with just less power.

Answer: Thank you for this good suggestion. We reanalyzed the risk factors of CVD after excluding CHF from the definition of CVD, and found that all but three of the risk factors, namely, anemia, use of ESA and use of oral iron supplementation, are still significant. This analysis is shown in supplemental Table 1 in the revised version of the manuscript. We added the following sentence in the Result section. (Page 14 and page 33-34)

“In addition, since we sometimes encounter patients with CHF that is unrelated to atherosclerotic diseases, we analyzed the factors associated with the prevalence of CVD that excludes CHF from the definition. All the risk factors were still significant, except for three factors, namely, anemia, use of ESA and use of oral iron supplementation (Suppl. Table 1).”
Comment 2: For table 1 (or 2), I would like to see more demographics. What are the continuous distributions of lipid profiles (chol, HDL, LDL, triglycerides), calcium, phosphorus, albumin, intact PTH, and hemoglobin, and what is the smoking status of participants?

Answer: We added continuous distributions of total cholesterol, HDL, LDL, triglycerides, calcium, phosphorus, albumin, intact PTH and albumin in Table 2 and albumin in Table 1. Smoking status was not recorded in this study design.

Minor:
Comment 3: The authors omitted the word “was” after diabetes on page 11.

Answer: We added “was” after “diabetes” on page 12.

Comment 4: In tables 1 and 2, footnotes should be made to tell what the numbers are: mean +/- sd, median [IQR], and n, %.

Answer: We added footnotes to Tables 1 and 2 to explain that “continuous variables are presented as mean ± standard deviation and median with interquartile ranges. Categorical data are presented as numbers (n) of patients and percentages in each CKD stage.”

Comment 5: The authors should omit the terms “predictive” in pages 15 and 16, as these are cross-sectional associations rather than longitudinal models.

Answer: We altered “a predictive factor” to “an associated factor” in the Discussion. (Page 16-17)

Discretionary:
Comment 6: I would suggest changing the background in the abstract and your manuscript to “In this report, we describe the baseline characteristics and risk factors for cardiovascular disease prevalence among this cohort.” Comparing this to Western cohorts was not a main part of your results, but was just in the
Answer: We agree with this view and changed the sentences in the Abstract as you suggested.

Comment 7: How was the etiology of kidney disease determined? Other than for GN, this is not entirely clear.

Answer: The etiology of kidney disease in each patient was determined by the respective attending physician. We added the following sentence in the Method section in the revised manuscript. (Page 11)

“Etiology of kidney disease in each patient was determined by the physician who was treating the patient at the time of enrollment, based on patients’ past histories, clinical characteristics and findings, and histological findings in biopsied kidney specimens.”

Comment 8: The reasoning behind the dichotomy of some of the variables in table 2 is unclear, as these are non-standard cutoffs. How were LDL of 120, PTH of 65, and hemoglobin of 11 chosen?

Answer: In this study, we treat the patients according to the Japanese CKD guidelines in which these cutoff values are used. We added the following sentences in the Method section of the revision. (Page 10)

“Since the therapeutic targets of treatment of renal anemia and dyslipidemia in the Japanese CKD guidelines are a Hb over 11 g/dl and LDL-cholesterol below 120 mg/dl, respectively, anemia and dyslipidemia were defined as hemoglobin (Hb) < 11 g/dl and LDL-cholesterol ≥ 120 mg/dl (ref).”

“As the normal range of intact parathyroid hormone (PTH) as measured by ECLIA is 10 - 65 pg/ml, high intact PTH was defined as levels over 65 pg/ml.”

Comment 9: The categories of proteinuria are not what we typically analyze or describe clinically (ie usually described as normal, microalbuminuria, macroalbuminuria). Was this selected a priori? Overall, I found the topic clinically relevant, as identifying risk factors for kidney disease progression in multiple
populations is an important topic. The CKD-ROUTE study may ultimately add significantly to that literature.

Answer: We added the following sentence in the Method section to explain the different clinical practice for albuminuria in Japan. (Page 10)
“Urinary protein to creatinine ratios (UPCR) were measured because urinary albumin is not routinely measured due to a regulation of the Japanese Medicare system, and were categorized as: optimal, UPCR < 0.15 g/gCr (gram per gram creatinine); high, UPCR 0.15-0.49 g/gCr; and very high, UPCR ≥ 0.5 g/gCr. This categorization is recommended by Japanese CKD guidelines (ref).”

Reviewer's report
Reviewer: Rulan Parekh

We thank Dr. Rulan Parekh for all his suggestions and comments.

Reviewer's report:

Major Comments
1) The study is interesting as it will be important for future international comparisons of CKD progression to other cohorts. The paper is presented as an independent analyses for prevalent cardiovascular, however, it does not provide unique information in terms of outcomes and analyses. Nonetheless, it is important to understand the methods of the specific cohort study in terms of clinical data collection, hence it may be more valuable to restructure as a methods paper.

Answer: Thank you for your valuable suggestions. The methods section was expanded to describe the details of clinical data collection.

2) There is limited discussion of the participant selection, target population, power, sample size etc. It would be important to provide that data to understand
the generalizability of the study. Furthermore, it is not clear if the goal of the study was to recruit participants representative of Japan ie across regions age, gender etc. Were the 16 centers different in terms of academic vs clinical centers? How are patients recruited from medical clinics or nephrology clinics? What data are collected?

Answer: Explanation of the sample size of this study was added as a new sentence in the Method section of the paper. (Page 9)

“One of the major endpoints of the CKD-ROUTE study is initiation of dialysis. If the event rate of initiation of dialysis is presumed to be about 30% according to the rates shown in previous studies (ref), in the case of 1000 subjects, the cumulative event number for the initiation of dialysis is expected to be around 300. This will have 80% power to detect a hazard ratio of 1.38 with a significant difference of 5% or less. Therefore, we considered the necessary sample size of this study as 1000 subjects.”

Also, an explanation was added in the Methods section to explain that the target population was those who live in the urban area of the Tokyo metropolitan area, where one third of the Japanese population lives, and our affiliated hospitals are larger than mid-sized clinical centers. (Page 8)

“Over 1000 participants were enrolled at the Tokyo Medical and Dental University Hospital and its 15 affiliated, larger than mid-sized clinical centers located in the Tokyo metropolitan district of Japan, where one third of the Japanese population lives. Most patients were referred from primary care clinics.”

Explanation of concrete collected data was added in the Methods section of the revision. (Page 10)

“Blood and urine samples were collected to measure white blood cell, hemoglobin, platelet, total protein, albumin, urea nitrogen, creatinine, sodium,
potassium, chloride, calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (PTH), glucose, hemoglobin A1c (HbA1c), iron, unsaturated iron binding capacity, ferritin, C-reactive protein, urinary occult blood, urinary protein and urinary creatinine.”

3) It is not clear why stage 5 was included in the study population and the rationale for the inclusion needs to be presented. Also, the use of the eGFR equation among the Japanese should be further described especially across the spectrum of GFR.

Answer: We added the following sentence in the Method section of the paper. (Page 9)

“Stage 5 CKD patients were included in this study, because a recent study showed that 35% of CKD stage 5 patients did not enter renal replacement therapy over a 3-year observation period (ref).”

About the eGFR equation for Japanese people, we modified the following sentence in the Method section. (Page 10)

“Estimated glomerular filtration rate (eGFR) was calculated using the modified three-variable Modification of Diet in Renal Disease (MDRD) equation developed by the Japanese Society of Nephrology, to adjust for Japanese physical characteristics: eGFR = 194 × serum creatinine \(^{-1.094}\) × age \(^{-0.287}\) (if female, × 0.739) (ref)”

Minor Comments
1) There is a discrepancy of the number of centers ie 16 in the abstract and 15 in the text.

Answer: The number 16 indicates the university hospital plus 15 affiliated clinical
centers; this was explained in the Methods section of the revised paper.