PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Obstructive spirometry pattern and the risk of chronic kidney disease: Analysis from the community-based prospective Ansan-Ansung cohort in Korea
AUTHORS	Kim, Sang Hyuk; Kim, Hyeon Sam; Min, Hyang Ki; Lee, Sung Woo

VERSION 1 – REVIEW

REVIEWER	Chung-Yu Chen National Taiwan University Hospital Yunlin Branch
REVIEW RETURNED	30-Sep-2020

GENERAL COMMENTS	1. GOLD guidelines support using the traditional postbronchodilator FEV1/FVC ratio less than 0.7 as the threshold that indicates airflow limitation. However, the FEV1/FVC ratio decreases with age, so use of the fifth percentile lower limit of normal (LLN) of the FEV1/FVC ratio, rather than the absolute value of <0.7, has been advocated by some as a dividing point for the diagnosis of COPD. 2. The main exposure of this study was the FEV1/FVC ratio, which was obtained by prebronchodilator testing using spirometry, which was not suitable for definition of COPD, 3. The mean ± SD of FEV1/FVC ratio, FEV1, and FVC were 0.80 ± 0.08, 96.8 ± 14.1%-predicted. The first through fourth quartiles of the FEV1/FVC ratio were <0.76 (n=1967), 0.76-0.80 (n = 2044), 0.81-0.84 (n = 2099), and ≥0.85 (n = 1925), respectively. The results indicated that most of the study participants were not COPD.

REVIEWER	Rudolf A. Jörres Occupational Medicine, LMU Hospital, Munich, Germany
REVIEW RETURNED	25-Nov-2020

GENERAL COMMENTS	This a well-written manuscript including a careful analysis. In my view, however, some parts could be improved. Specific comments: 1. Why was age categorized exactly at 65 and eGFR at 90? (line 167) 2. What were the results for FVC %predicted and especially for FEV1/FVC % predicted? Was there a difference against the results obtained for the FEV1/FVC raw values? This is relevant, as the %predicted value, e.g., corrects for the dependence on age and age is a known risk factor for CKD. One should not assume a priori that an adjustment for age as a binary category adequately takes into account age for a continuous variable. The argument that the evaluation of FEV1/FVC needs no computation of predicted values, seems only marginally convincing in a complex

	statistical analysis that aims at the detection of statistical relationships. 3. Were the predictors of model 1 added to those listed to model 2? Please clarify. 4. Is there any value for the incidence of CKD solely expected from the ageing of the population? Can this be computed from the data? It probably needs to use FEV1%FVC %predicted. 5. Do the authors have a thorough explanation for the U-shaped pattern regarding the dependence of CKD risk on lung function? It deserves some discussion. However, I am not fully surprised, since I have seen as yet unpublished data also showing a U-shaped relationship. 6. The difficulties regarding the adequate predicted values of FEV1 might be circumvented by performing the analysis with FEV1 in liters and including sex as binary, and age and height as continuous covariates. Same for FVC. 7. It is interesting that FEV1/FVC had its highest predicted value in the subgroup without metabolic disorders. This fits to the observation that there was no significant relationship at BMI>25 and in subjects with central obesity. This might be related to the fact that obese subjects often show a restrictive lung function pattern with an elevated FEV1/FVC. If this happens, it may destroy the relationship of CKD risk to lung function. It might be worthwhile to have a closer look onto these subjects and relationships.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Chung-Yu Chen, National Taiwan University Hospital
Comments to the Author:
1. GOLD guidelines support using the traditional postbronchodilator FEV1/FVC ratio less than 0.7 as the threshold that indicates airflow limitation. However, the FEV1/FVC ratio decreases with age, so use of the fifth percentile lower limit of normal (LLN) of the FEV1/FVC ratio, rather than the absolute value of <0.7, has been advocated by some as a dividing point for the diagnosis of COPD.

-> Sorry for the confusion. Some expressions may be interpreted differently from our purpose. We have been trying to investigate association between obstructive spirometry pattern and the risk of incident CKD, not effect of COPD on the risk of incident CKD. Therefore, to avoid misunderstanding, we have changed the word ‘obstructive lung function’ to ‘obstructive spirometry pattern’ and revised the manuscript properly.

2. The main exposure of this study was the FEV1/FVC ratio, which was obtained by prebronchodilator testing using spirometry, which was not suitable for definition of COPD.

-> We have focused on continuous analysis between obstructive spirometry pattern and risk of incident CKD in the general population. Our analysis was a study for the potential renal hazard of early airflow impairment, not for the potential renal hazard of COPD. Since postbronchodilator testing may not be clearly superior to prebronchodilator test for detecting early airflow impairment [Daniel Hoesterey et al. Respir Med. 2019 Sep;156:58-68], it might be acceptable to use prebronchodilator testing results to define early airflow impairment in general population. This was why excluded 75 subjects with chronic lung diseases. We described these points in more detail in the limitation section.

3. The mean ± SD of FEV1/FVC ratio, FEV1, and FVC were 0.80 ± 0.08, 96.8 ± 14.1%-predicted. The first through fourth quartiles of the FEV1/FVC ratio were <0.76 (n=1967), 0.76-0.80 (n = 2044), 0.81-0.84 (n = 2099), and ≥0.85 (n = 1925), respectively. The results indicated that most of the study participants were not COPD.

-> We agree that only a small number of COPD participants were included in this study. However, what we tried to investigate is not COPD, but serial lung function change including normal lung function. We believe that this study will provide a perspective on the relationship between early lung function change and CKD development. We really appreciate you sharing your opinion with us. Thanks to your constructive comments, purpose of our study was revised more clearly.

Reviewer: 2

Dr. Rudolf Joerres, Ludwig-Maximilians-University Munich
Comments to the Author: This a well-written manuscript including a careful analysis. In my view, however, some parts could be improved.
Specific comments:

1. Why was age categorized exactly at 65 and eGFR at 90? (line 167)

-> Age and eGFR have an extreme impact on CKD development. CKD is defined by eGFR and eGFR is calculated using age. Thus, increased hazard of CKD over time with age and eGFR is inevitable. It was almost impossible to adjust for age and eGFR without violating the proportional hazards assumption. So, we had categorized age and eGFR using clinically significant cut-off value by the working age definition of OECD and CKD stage 1 definition of KDIGO.

2. What were the results for FVC %predicted and especially for FEV1/FVC % predicted? Was there a difference against the results obtained for the FEV1/FVC raw values? This is relevant, as the %predicted value, e.g., corrects for the dependence on age and age is a known risk factor for CKD. One should not assume a priori that an adjustment for age as a binary category adequately takes into account age for a continuous variable. The argument that the evaluation of FEV1/FVC needs no computation of predicted values, seems only marginally convincing in a complex statistical analysis that aims at the detection of statistical relationships.

-> After consultation from two different statisticians, we concluded that the cox regression analysis in our study can be performed without adjustments for age. Age is already used to adjust eGFR and CKD was defined using eGFR. Age extremely violated the proportional hazard assumption due to high correlation with incident CKD. In addition, the superiority of further adjustment for already adjusted variable is not clear. Repeated adjustment of the same variable can cause bias. The analysis without adjustment for age was described as a limitation of our study.
In the analysis with FEV1/FVC % predicted, the risk of incident CKD was decreased as FEV1/FVC % predicted decreased, suggesting early airflow limitation may have beneficial effects on incident CKD. We postulated that overlapped adjustment of age during making FEV1/FVC % predicted may cause these un-understandable results.
Diagnosis of obstructive lung diseases have been suggested using FEV1/FVC rather than FEV1/FVC % predicted in GOLD and GINA guidelines. So we maintain FEV1/FVC ratio as our primary exposure, Although FVC % predicted showed statistically significant risk of incident CKD, the potential renal hazard of restrictive spirometry pattern was beyond our study hypothesis. Therefore, we added the result of FVC % predicted as a supplementary table.

3. Were the predictors of model 1 added to those listed to model 2? Please clarify.

-> The predictors of model 1 was included in the model 2. We clarify adjustment variables accordingly.

4. Is there any value for the incidence of CKD solely expected from the ageing of the population? Can this be computed from the data? It probably needs to use FEV1%FVC %predicted.

-> The Kaplan-Meier curve with the ageing of the population is presented as a supplementary figure.

5. Do the authors have a thorough explanation for the U-shaped pattern regarding the dependence of CKD risk on lung function? It deserves some discussion. However, I am not fully surprised, since I have seen as yet unpublished data also showing a U-shaped relationship.

-> Subjects with FEV1/FVC had a decreased FEV % predicted. The upper limit of FEV1/FVC is not established, but most of those with FEV1/FVC above 0.9 had a decreased FVC % predicted. This may be due to neuromuscular causes such as chest wall abnormalities and respiratory muscle weakness. These disorders may increase risk of CKD. We added this to the discussion section.

6. The difficulties regarding the adequate predicted values of FEV1 might be circumvented by performing the analysis with FEV1 in liters and including sex as binary, and age and height as continuous covariates. Same for FVC.

-> We absolutely agree with your opinion. However, as mentioned before, adjustment for age is difficult in the cox regression analysis due to the correlation between incident CKD and age. Since the incident CKD was adjusted with age, we believe that FEV1 % predicted, FVC % predicted, and FEV1/FVC can be analyzed without further adjustment for age.

7. It is interesting that FEV1/FVC had its highest predicted value in the subgroup without metabolic disorders. This fits to the observation that there was no significant relationship at BMI>25 and in subjects with central obesity. This might be related to the fact that obese subjects often show a restrictive lung function pattern with an elevated FEV1/FVC. If this happens, it may destroy the relationship of CKD risk to lung function. It might be worthwhile to have a closer look onto these subjects and relationships.
-> Thank you for important comment. We thought that this result came from different lung function pattern between subgroup with metabolic disorder and the general population. In the restrictive lung function pattern, we agree that FEV1/FVC needs to be interpretated differently, and this is mentioned in the discussion section. Thank you again for the considerate comments.

VERSION 2 – REVIEW

REVIEWER	Chung-Yu Chen National Taiwan University Hospital Yunlin Branch
REVIEW RETURNED	09-Feb-2021

GENERAL COMMENTS	Accept the authors' response and revision.

REVIEWER	PD Dr Rudolf A Jörres Ludwig-Maximilians-University, Munich, Germany
REVIEW RETURNED	11-Feb-2021

GENERAL COMMENTS	Thank you for the detailed responses to my comments. The manuscript has been satisfactorily revised and extended.