PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of Retinopathy and Chronic Kidney Disease on Long-term Mortality in Type 2 Diabetic Inpatients with Normal Urinary Albumin or Protein: A Retrospective Cohort Study
AUTHORS	Li, Yu-Hsuan; Sheu, Wayne; Lee, I-Te

VERSION 1 – REVIEW

REVIEWER	Pierre Jean Saulnier Inserm CIC 1402 CHU de Poitiers 86000 Poitiers, France
REVIEW RETURNED	25-Jan-2018

GENERAL COMMENTS	Comments to the Authors The authors assessed the prognostic value of diabetic retinopathy (DR) for all-cause mortality and cardiovascular mortality in patients in type 2 diabetes mellitus (T2D) and chronic kidney disease (CKD) and specifically normoalbuminuria and GFR<60mL:min). Their major results were the following: among 2482 participants from a mono-center retrospective study (included from 1996 to 2007 and followed-up until 2011), 665 were selected including 306 CDK-DR-, 130 CDK-DR+,149 CDK+DR- and 80 CDK+DR+. A total of 315 deaths were recorded including 138 from cardiovascular causes. Authors concluded that DR is an independent risk factor for death (from all cause and cardiovascular cause) in participants with T2D and normoalbuminuria. Comments: The study has major drawbacks in its design and analysis of the data. 1. It is unclear how diabetes status was handled: a. ADA definition criteria were not clearly applied. b. Impaired Fasting glucose state or impaired glucose tolerance are not clearly managed neither. 2. It is unclear how causes of death have been assessed and how cardiovascular death have been defined. Authors may want to code causes of death according to the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). 1. It is questionable why the data after 2007 have not been added to the present manuscript since it was a retrospective design. 2. There is a major concern regarding the Diabetic nephropathy [DN]

	phenotype and subsequently with the design of the study. a. DN is a major complication of diabetes and international definition are largely uses (chronic kidney disease may be staged according to KDIGO recommendations). Albuminuria is internationally defined as Albumin Excretion Rate ≥30 mg/24 hours or Albumin-to-creatinine ratio ≥30 mg/g [≥3 mg/mmol]. Categories for albuminuria and proteinuria are defined as well. KDIGO defined “Normal to mildly increased” stage according to protein-to-creatinine ratio <15 mg/mmol or protein excretion rate < mg/24 hours. b. These established thresholds and definitions led the paragraph of the search for cutoff with the ROC curves unnecessary to the present work. c. The use of Renin-angiotensin-aldosterone system (RAAS) inhibitor can prevent progression of CKD and potentially reverse patient from microalbuminuria to norma-albuminuria. There is no mention of this drug exposure in the selection criteria nor in the characteristics presentation d. From the perspective of the announced aim, the selection of the patient should have been made in order to retain patient with confirmed T2D, normoalbuminuria without RAAS inhibitor use and GFR <60mL/min. Categorization of patient (CKD+DR+, CKD+DR-, CKD-DR+, CKD-DR-)is here not appropriate. Authors are in fact looking for the difference in mortality between normoalbuminuric CKD+DR+ and normoalbuminuric CKD+DR-. 3. The design of the study is rather unusual. In the statistical analysis section, it is expected to better describe or precise a. The way missing data have been handled b. The way non-normally distributed parameters have been described or compared (please precise which non-parametric test was used if any). Skewed data is the main issue in statistical models. This should be considered attempt to normalize variables should be tried. c. The choice of the risk factors set for the Cox model adjustment should be announced in this section. d. It is not clear if authors tested assumptions for the proposed proportional hazard cox models. 4. In the Result section: a. Figure 1 should be removed since there is no justification for this approach b. Absolute number of death and CV death should be précised in addition to what is shown in Figure 2 c. Table 1 should show pharmaco-therapeutic classes of antihypertensive agent since RAAS inhibitor are of special interest here d. For the dummy variable (4 categories CKD+DR+, CKD+DR-, CKD-DR+, CKD-DR-) one single P value (the overall P value)should be shown • Based on the inconsistency between announced aim, the design and the statistical analysis plan, conclusion cannot be properly reviewed. I encourage authors to readjust their design to get a more fitted approach.

REVIEWER	Giuseppe Pugliese Department of Clinical and Molecular Medicine, La Sapienza University, Rome, Italy
REVIEW RETURNED	08-Feb-2018

GENERAL COMMENTS	The Authors examined retrospectively normoalbuminuric patients admitted to hospital for poorly controlled diabetes to investigate the effects of DR and chronic kidney disease (CKD) on mortality in type 2 diabetic patients with normoalbuminuria. They found that DR is an independent predictor for all-cause and cardiovascular mortality and exerts a synergic effect with CKD on all-cause and cardiovascular mortality. The paper is interesting, though it has several limitations, which are acknowledged by the Authors (retrospective design, measurement of proteinuria instead of albuminuria, etc.). Major Higher levels of albuminuria within the normoalbuminuric range have been reported to predict mortality in diabetic and nondiabetic individuals. Therefore, it would be useful to divide patients in those with normal (<10 mg/day) and high-normal (10-29 mg/day) albuminuria to establishe whether the association of DR with mortality is driven by higher, albeit normal levels of albuminuria. Minor In the abstract, the sentence "The risks of all-cause mortality (HR: 2.422; 95% CI: 1.652, 3.552) and cardiovascular mortality (HR: 2.550; 95% CI: 1.469, 4.429) were significantly higher in patients with CKD and DR than those without CKD and DR" should be ""The risks of all-cause mortality (HR: 2.422; 95% CI: 1.652, 3.552) and cardiovascular mortality (HR: 2.550; 95% CI: 1.469, 4.429) were significantly higher in patients with CKD and DR than those without CKD or DR".

REVIEWER	Salinero-Fort MA Consejería de Sanidad, Madrid, Spain
REVIEW RETURNED	13-Feb-2018

GENERAL COMMENTS	The manuscript is a very interesting, well-written practical and scientifically sound study of an important health problem. However, I would seek for some explanations. First, given that it is a retrospective study and the clinical data were obtained by reviewing medical records of diabetic patients hospitalized, I do not understand well how the Helsinki declaration was complied, given that the data collection was prior to the begining of the study. It would also be advisable to clarify if the patients signed the informed consent. Second, it would be convenient to comment the reason why the MDRD equation was chosen instead of CKD-EPI formula to calculate the eGFR. Third, the mortality data, provided by the Collaboration Center of Health Information Application, Department of Health, Executive Yuan, were based on the information of the death certificates? Were the diagnoses based on the international classification diseases? Fourth, when the ROC analysis curve was applied, I do not understand well which was the reference test (gold standard) to classify albuminuria as positive. Fifth; Why was the correlation between proteinuria and albuminuria done?, In which way does it contribute to the study? Sixth, the figure 2 is confuse. I propose a more simplified figure. The second box is unnecessary. Finally, since the publication of the K/DOQI clinical practice guidelines for the classification of CKD in 2002 (National Kidney Foundation, 2002), several studies based on this classification system have shown their prevalence estimates for CKD in the

	general population and in patients with Type 2 Diabetes Mellitus This classification is based on values of albuminuria and eGFR, as indicated Levey et al. (2011) that provides the definitions of the categories. Normo albuminuric CKD (NA-CKD) corresponds to eGFR stages G3-G5 (<60 mL/min/1.73 m2) and A1 albuminuria stage (<30 mg/g). I think that the authors should conveniently justify the reason for not having using this classification. . National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. American Journal of Kidney Diseases, 39(2 Suppl. 1), S1–S266. Levey, A. S., de Jong, P. E., Coresh, J., El Nahas, M., Astor, B. C., Matsushita, K.,... Eckardt, K.U. (2011). The definition, classification, and prognosis of c-hronic kidney disease: A KDIGO Controversies Conference report. Kidney International, 80(1), 17–28.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Pierre Jean Saulnier
Inserm CIC 1402, CHU de Poitiers, 86000 Poitiers, France

(1). It is unclear how diabetes status was handled:
a. ADA definition criteria were not clearly applied.
b. Impaired Fasting glucose state or impaired glucose tolerance are not clearly managed neither.
Response: line 14, page 5
We greatly appreciate the comment. The study was designed as a retrospective cohort study. All candidate subjects had been clinically diagnosed with diabetes mellitus before admission. No data on the oral glucose tolerance test were available in this study. Therefore, we revised the including criteria "… diabetic inpatients" to "… diabetic inpatients based on the clinical diagnosis".

(2). It is unclear how causes of death have been assessed and how cardiovascular death have been defined. Authors may want to code causes of death according to the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).
Response: lines 10–12, page 7
According the database of the Collaboration Center of Health Information Application, the cause of death was categorized according to the ICD-9 CM before 2008 and ICD-10 after 01 Jan, 2008. Cardiovascular disease was defined as CAD (401–405, 410–414,420–429, 440), cerebrovascular disease (430-438), and peripheral artery disease (440, 443.8, 443.9, 444.2) according to ICD-9 CM or CAD (I05-I09, I10-I15, I20-I25, I27, I30-I52), cerebrovascular disease (I60-I69), and peripheral artery disease (I70) according to ICD-10 in the present study. Therefore, we added the description "The causes of death were categorized according to the International Classification of Disease (ICD), 9th Revision, Clinical Modification diagnostic criteria before 2008 and according to the ICD-10 after 01 January, 2008." on page 7, lines 10–12.

(3). It is questionable why the data after 2007 have not been added to the present manuscript since it was a retrospective design.
Response: lines 7–8, page 7
We were permitted to review the medical information in diabetic patients, who were admitted to our Endocrinology and Metabolism section between August 1996 and August 2007. After the medical information was collected, the list of these patients was linked to the mortality information according to the research protocol approved by the Institutional Review Board of Taichung Veterans General

Hospital. Therefore, we did not review the medical information of the diabetic inpatients after August 2007. To avoid confusion, we revised the description of study design “Mortality data up to December 2011 were provided …” to “After medical information was collected from our hospital, we also obtained the mortality data up to December 2011 were provided …” on page 7, lines 7–8

(4). There is a major concern regarding the Diabetic nephropathy [DN] phenotype and subsequently with the design of the study.
a. DN is a major complication of diabetes and international definition are largely uses (chronic kidney disease may be staged according to KDIGO recommendations). Albuminuria is internationally defined as Albumin Excretion Rate ≥30 mg/24 hours or Albumin-to-creatinine ratio ≥30 mg/g [≥3 mg/mmol]. Categories for albuminuria and proteinuria are defined as well. KDIGO defined “Normal to mildly increased” stage according to protein-to-creatinine ratio <15 mg/mmol or protein excretion rate < mg/24 hours.
b. These established thresholds and definitions led the paragraph of the search for cutoff with the ROC curves unnecessary to the present work.
c. The use of Renin-angiotensin-aldosterone system (RAAS) inhibitor can prevent progression of CKD and potentially reverse patient from microalbuminuria to norma-albuminuria. There is no mention of this drug exposure in the selection criteria nor in the characteristics presentation
d. From the perspective of the announced aim, the selection of the patient should have been made in order to retain patient with confirmed T2D, normoalbuminuria without RAAS inhibitor use and GFR <60mL/min. Categorization of patient (CKD+DR+, CKD+DR-, CKD-DR+, CKD-DR-)is here not appropriate. Authors are in fact looking for the difference in mortality between normoalbuminuric CKD+DR+ and normoalbuminuric CKD+DR-.
Response: lines 14–19, page 14; Table 1; lines 6–7, page 5; supplementary figure
a. There are various definitions for normal daily urinary protein excretion. Using ROC curve analysis in our data, we determined that a cutoff value of 150 mg protein/day might be suitable for daily urinary albumin of 30 mg/day (original Figure 1). This finding is also consistent with a recent review article on CKD (Webster et al. Lancet. 2017;389:1238–1252).
b. We agree with your suggestion, and have moved the paragraph on the search for the cutoff with the ROC curves from the Results section to the Methods section. We also provided the original Figure 1 as a supplementary figure.
c. Thank you for this important comment. In addition to information on anti-diabetic drugs, we also added information on the types of anti-hypertensive agents in Table 1. We also added the following statement: “In the present study, patients using ACE inhibitors or ARBs showed a higher risk of cardiovascular mortality in the univariate model, and this finding may result from the higher proportion of CKD patients using these drugs at baseline. In the multivariate model, the use of ACE inhibitors or ARBs at baseline was not significantly associated with cardiovascular mortality. Consistent with these findings, early ARB treatment was not found to significantly improve eGFR in type 2 diabetic patients with urine albumin-to-creatinine ratio <300 mg/g.44” to discuss the findings between ACE inhibitor/ABR use and cardiovascular mortality on page 14, lines 14–19, along with reference 44.
d. We greatly appreciate this important comment. Accordingly we have revised the description of the study aim from “… long-term mortality in type 2 diabetic patients with NA-CKD” to “…long-term mortality in type 2 diabetic patients with NA-CKD or without NA-CKD.” on page 5, lines 6–7.

(5). The design of the study is rather unusual. In the statistical analysis section, it is expected to better describe or precise
a. The way missing data have been handled
b. The way non-normally distributed parameters have been described or compared (please precise which non-parametric test was used if any). Skewed data is the main issue in statistical models. This should be considered attempt to normalize variables should be tried.
c. The choice of the risk factors set for the Cox model adjustment should be announced in this section.

d. It is not clear if authors tested assumptions for the proposed proportional hazard cox models.
Response: lines 16–17, page 9; lines 7–10, page 9; Table 1; lines 13–16, page 9; Table 2;
a. Candidates with missing data for the inclusion/exclusion criteria were excluded. Other missing data were imputed by using the mean of that variable in all other cases. Therefore, we added “Except the inclusion and exclusion criteria, the mean imputation method was used for missing data.” on page 9, lines 16–17.
b. The normal distribution was examined by Kolmogorov-Smirnov test. On page 9, lines 7–10, we added “however, Kruskal-Wallis tests were conducted to determine the significance of the differences in the duration of diabetes, triglycerides levels and eGFR values among groups due to the presence of a skewed distribution in these variables.” in order to indicate the use of the non-parametric test for non-normally distributed parameters. We also added “# Kruskal-Wallis tests to determine the significance of the differences due to skewed distribution in diabetic duration, triglycerides and eGFR” in Table 1.
c. On page 9, lines 13–16, we added “The risk factors in the univariate model were selected based on the findings in Table 1, whereas the risk factors in model 2 were selected based on the statistical significance indicated in the univariate model” to indicate how the risk factors were chosen for the Cox model adjustment. We also added these descriptions in Table 2.
d. The results of Cox proportional hazards regression analyses are detailed in Table 2, which has been revised because the data on anti-hypertensive agents were added.

(6). In the Results section:
a. Figure 1 should be removed since there is no justification for this approach
b. Absolute number of death and CV death should be précised in addition to what is shown in Figure 2
c. Table 1 should show pharmaco-therapeutic classes of antihypertensive agent since RAAS inhibitor are of special interest here
d. For the dummy variable (4 categories CKD+DR+, CKD+DR-, CKD-DR+, CKD-DR-) one single P value (the overall P value) should be shown.
Response: supplementary figure; lines 16–17, page 10; lines 14–19, page 14; Table 1; and Table 2
a. Thank you for the comment. We moved Figure 1 from the Results section to supplementary data.
b. On page 10, lines 16–17, we added “315 (47.4%) patients died from any cause; in particular, 138 patients died of cardiovascular disease (Fig. 1).” to indicate the absolute number of all-cause death and CV death.
c. In addition to anti-diabetic drugs, we added the information about the types of anti-hypertensive agents in Table 1. We also added “In the present study, patients using ACE inhibitors or ARBs showed a higher risk of cardiovascular mortality in the univariate model, and this finding may result from the higher proportion of CKD patients using these drugs at baseline. In the multivariate model, the use of ACE inhibitors or ARBs at baseline was not significantly associated with cardiovascular mortality. Consistent with these findings, early ARB treatment was not found to significantly improve eGFR in type 2 diabetic patients with urine albumin-to-creatinine ratio <300 mg/g.44” to discuss the findings between ACE inhibitor/ABR use and cardiovascular mortality on page 14, lines 14–19. Table 2 has been revised because the data of anti-hypertensive agents were added.
d. The overall P values are less than <0.001 among the CKD(-)DR(-), CKD(-)DR(+), CKD(+)DR(-), CKD(+)DR(+) groups in all models. Therefore, we added “*P value <0.001” in Table 2 for a single P value (the overall P value) among the 4 groups.

Reviewer: 2
Giuseppe Pugliese
Department of Clinical and Molecular Medicine, La Sapienza University, Rome, Italy

Major
(1). Higher levels of albuminuria within the normoalbuminuric range have been reported to predict

mortality in diabetic and nondiabetic individuals. Therefore, it would be useful to divide patients in those with normal (<10 mg/day) and high-normal (10–29 mg/day) albuminuria to establishe whether the association of DR with mortality is driven by higher, albeit normal levels of albuminuria.
Response: lines 5–15, page 16
We appreciate this important suggestion. We attempted to analyze the CKD (–) subgroup of patients with available urine albumin data. However, the proportion of cases with diabetic retinopathy was not significantly different between patients with normal (<10 mg/day) and high-normal (10–29 mg/day) albuminuria (22.2% vs. 24.8%, P = 0.736). Moreover, there was no significant difference in all-cause and cardiovascular mortality (log-rank test P = 0.674 and 0.579, respectively). We described these findings in the discussion “Among type 2 diabetic patients with normoalbumiuria, high urine albumin excretion (10–29 mg/day) was reportedly associated with multiple cardiovascular risk factors, as compared to low urine albumin excretion (< 10 mg/day).52 Recently, the highest tertile of the urine albumin excretion rate was found to be associated with diabetic retinopathy and arterial stiffness, in comparison to the lowest tertile among type 2 diabetic patients with normoalbuminuria.53 54 In the present study, 257 patients without CKD had available urine albumin data, including 108 patients with low normoalbuminuria (< 10 mg/day) and 149 patients with high normoalbuminuria (10–29 mg/day). However, there was no significant difference in DR prevalence (P > 0.05) or all-cause and cardiovascular mortality (both log-rank test P > 0.05). Further investigations with a large number of cases will be needed to evaluate the association between high normoalbuminuria and mortality.” on page 16, line 5–15. If the reviewer suggests it appropriate to include this detailed information, we will be glad to move these data with tables to the Results section.

Minor
(1). In the abstract, the sentence "The risks of all-cause mortality (HR: 2.422; 95% CI: 1.652, 3.552) and cardiovascular mortality (HR: 2.550; 95% CI: 1.469, 4.429) were significantly higher in patients with CKD and DR than those without CKD andDR" should be ""The risks of all-cause mortality (HR: 2.422; 95% CI: 1.652, 3.552) and cardiovascular mortality (HR: 2.550; 95% CI: 1.469, 4.429) were significantly higher in patients with CKD and DR than those without CKD or DR".
Response: in line 19, page 2
Thank you for this comment. We have corrected this error.

Reviewer: 3
Salinero-Fort MA
Consejería de Sanidad, Madrid, Spain

Major points:
(1). First, given that it is a retrospective study and the clinical data were obtained by reviewing medical records of diabetic patients hospitalized, I do not understand well how the Helsinki declaration was complied, given that the data collection was prior to the begining of the study. It would also be advisable to clarify if the patients signed the informed consent.
Response: line 4, page 6
We thank the reviewer for this important comment. The Institutional Review Board had approved this retrospective study, and waived the need for informed consent before reviewing the medical records. However, the requirement of safety in data collection was adhered. Data safety and harmful prevention is part of principles in the Helsinki declaration, and has been seriously considered in our researches. To avoid this confusion, we removed the term of “the Helsinki declaration” since the study complies with the principles of human studies required by the Institutional Review Board of Taichung Veterans General Hospital.

(2). Second, it would be convenient to comment the reason why the MDRD equation was chosen instead of CKD-EPI formula to calculate the eGFR.
Response: lines 2–4, page 17

Thank you for this important suggestion. Further evidence is required regarding the consensus on Taiwan CKD-EPI equation. Hence, we added “Fourth, we calculated eGFR using the MDRD equation instead of the CKD Epidemiology Collaboration (EPI) equation as consensus had not been reached regarding the use of the CKD-EPI equation in the Taiwanese population.56” on page 17, lines 2–4, as a limitation for explaining why the MDRD equation was chosen instead of the CKD-EPI formula, to calculate the eGFR.

(3). Third, the mortality data, provided by the Collaboration Center of Health Information Application, Department of Health, Executive Yuan, were based on the information of the death certificates? Were the diagnoses based on the international classification diseases?
Response: lines 10–12, page 7
Thank you for this important comment. According the database of the Collaboration Center of Health Information Application, the cause of death was categorized according to the ICD-9 CM before 2008 and ICD-10 after 01, January, 2008. Cardiovascular disease was defined as CAD (401–405, 410–414,420–429, 440), cerebrovascular disease (430-438), and peripheral artery disease (440, 443.8, 443.9, 444.2) according to ICD-9 CM or CAD (I05-I09, I10-I15, I20-I25, I27, I30-I52), cerebrovascular disease (I60-I69), and peripheral artery disease (I70) according to ICD-10 in the present study. Hence, we added the description “The causes of death were categorized according to the International Classification of Disease (ICD), 9th Revision, Clinical Modification diagnostic criteria before 2008 and according to the ICD-10 after 01 January, 2008.” on page 7, lines 10–12.

(4). Fourth, when the ROC analysis curve was applied, I do not understand well which was the reference test (gold standard) to classify albuminuria as positive.
Response: supplementary figure
Thank you for this important suggestion. In 2482 diabetic inpatients who had undergone 24-hour urine collection, 245 patients had available data for both urine albumin and protein levels in the same urine sample. We used the daily urine albumin < 30 mg/day as a reference for normoalbuminuria, and assessed the cutoff value of daily urine protein (continuous data) for diagnosis of normoalbuminuria. Based on the suggestion of Reviewer 1, we moved this figure to the supplementary data in the revised version of this article.

(5). Fifth; Why was the correlation between proteinuria and albuminuria done?, In which way does it contribute to the study?
Response: line 4–16, page 8
Thank you for this important comment. Prior to the definition of normoalbuminuria using daily urine protein excretion, we demonstrated the high correlation between urine albumin and protein excretion, and estimated the diagnostic rate of urine protein for normoalbuminuria. These analyses were performed to confirm that the cutoff value of 150 mg protein/day is suitable for normoabluminuria. Based on the suggestion of Reviewer 1, we moved the paragraph on the search for cutoff with the ROC curves from the Results section to the Methods section

(6). Sixth, the figure 2 is confused. I propose a more simplified figure. The second box is unnecessary.
Response: Figure 1
Thank you for this important suggestion. We revised “Type 2 diabetic patients” to “Diabetic patients” in the first box, because type 1 diabetes was excluded in the second box. We apologize for the typographical error and the resulting confusion. Therefore, we have retained the second box to explain why the subjects were excluded from the analyses. If the reviewer suggests it necessary to further simplify Figure 1 (original Figure 2), we will be glad to remove the second box.

(7). Finally, since the publication of the K/DOQI clinical practice guidelines for the classification of CKD in 2002 (National Kidney Foundation, 2002), several studies based on this classification system

have shown their prevalence estimates for CKD in the general population and in patients with Type 2 Diabetes Mellitus This classification is based on values of albuminuria and eGFR, as indicated Levey et al. (2011) that provides the definitions of the categories. Normo albuminuric CKD (NA-CKD) corresponds to eGFR stages G3–G5 (<60 mL/min/1.73 m2) and A1 albuminuria stage (<30 mg/g). I think that the authors should conveniently justify the reason for not having using this classification. [National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. American Journal of Kidney Diseases, 39 (2 Suppl. 1), S1–S266; Levey, A. S., de Jong, P. E., Coresh, J., El Nahas, M., Astor, B. C., Matsushita, K.,... Eckardt, K.U. (2011). The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. Kidney International, 80(1), 17–28.].
Response: lines 16–19, page 16
Thank you for this important comment. The strength of the present study is that 24-hour urine data collected during the hospitalization period, and we used daily urine albumin/protein excretion instead of spot-urine ACR data. Therefore, we used these definitions of CKD (G3–G5: eGFR <60 mL/min/1.73 m2) and normoalbuminuria (< 30 mg/day). However, due to the limited number of cases overall, we included patients with urine protein excretion < 150 mg/day, and this limitation has been specified in the discussion. On page 16, lines 16–19, we explained the reasons for this “First, we enrolled patients with not only normoabluminuria, but also normoproteinuria, due to the limited numbers of cases overall. Second, we used the 24-hour urine data instead of spot-urine data, since the latter has been well reported in type 2 outpatients previously.55” as limitations.

Editor:
(1). Please ensure that your MANUSCRIPT’S TITLE in your main document and Scholar One submission system are the same.
Response: title
Thank you for correction. We have confirmed that MANUSCRIPT’S TITLE in the main document and Scholar One submission system are the same.
(2). Please embed your DATA SHARING STATEMENT in your main document file as shown in scholar one.
Response: line 6, page 18
Thank you for your reminding. We have confirmed that DATA SHARING STATEMENT in the main document file is the same as that in scholar one.

(3). We have implemented an additional requirement to all articles to include 'Patient and Public Involvement’ statement within the main text of your main document. Please refer below for more information regarding this new instruction: Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions:
How was the development of the research question and outcome measures informed by patients’ priorities, experience, and preferences?
How did you involve patients in the design of this study?
Were patients involved in the recruitment to and conduct of the study?
How will the results be disseminated to study participants?
For randomised controlled trials, was the burden of the intervention assessed by patients themselves?
Patient advisers should also be thanked in the contributorship statement/acknowledgements.

Response: lines 8–12, page 6
Thank you for this comment. Because this study is designed as a retrospective cohort, we added the description “All-cause mortality served as the primary outcome in this retrospective cohort study, and the mortality data were obtained from the national registry in Taiwan. We collected clinical information from the medical records at Taichung Veterans General Hospital. The Institutional Review Board

waived the need for informed consent before reviewing the medical records." on page 6, lines 8–12, under the sub-heading "Patient and Public Involvement" in the methods section.

VERSION 2 – REVIEW

REVIEWER	Pierre Jean Saulnier Clinical Investigation Centre, CHU Poitiers, CIC1402, INSERM, Poitiers, France
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	Comments to the Authors The authors assessed the prognostic value of diabetic retinopathy (DR) for all-cause mortality and cardiovascular mortality in patients in type 2 diabetes mellitus (T2D) and chronic kidney disease (CKD) and specifically normoalbuminuria and GFR<60mL:min). Their major results were the following: among 2482 participants from a mono-center retrospective study (included from 1996 to 2007 and followed-up until 2011), 665 were selected including 306 CDK-DR-, 130 CDK-DR+,149 CDK+DR- and 80 CDK+DR+. A total of 315 deaths were recorded including 138 from cardiovascular causes. Authors concluded that DR is an independent risk factor for death (from all cause and cardiovascular cause) in participants with T2D and normoalbuminuria. Comments: The statistical plan chosen by the authors does not allow to assess a synergistic effect of CKD and DR for the risk of death. Since synergistic effect means that the combined effect of two predictors taken together is greater than the sum of their separate effect, there is no demonstration of "synergestic effect" between CKD and DR. Categorization of patient (CKD+DR+, CKD+DR-, CKD-DR+, CKD-DR-)is not consistent with this approach. Even CKD+DR+ patient had graphically the highest mortality rate, no interaction between CKD and DR –selected a proper covariates- was assessed. In that context, the final statement of the author seems over conclusive.

REVIEWER	Giuseppe Pugliese Department of Clinical and Molecular Medicine, La Sapienza University, Rome, Italy
REVIEW RETURNED	20-Mar-2018

GENERAL COMMENTS	No further comments

REVIEWER	Salinero-Fort MA Consejería de Sanidad, Madrid, Spain.
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	The authors have responded satisfactorily to all my comments and suggestions

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Giuseppe Pugliese

(1). No further comments

Response:

Thank you very much.

Reviewer: 3

Salinero-Fort MA

(1). The authors have responded satisfactorily to all my comments and suggestions.

Response:

We deeply appreciate the comments and suggestions which the reviewer provided.

Reviewer: 1

Pierre Jean Saulnier

(1). The statistical plan chosen by the authors does not allow to assess a synergistic effect of CKD and DR for the risk of death. Since synergistic effect means that the combined effect of two predictors taken together is greater than the sum of their separate effect, there is no demonstration of "synergestic effect" between CKD and DR. Categorization of patient (CKD+DR+, CKD+DR-, CKD-DR+, CKD-DR-) is not consistent with this approach. Even CKD+DR+ patient had graphically the highest mortality rate, no interaction between CKD and DR –selected a proper covariates- was assessed. In that context, the final statement of the author seems over conclusive.

Response: Title, Page 3, lines 3－4; Page 11, line 7; Page 15, lines 4－6.

We greatly appreciate the comment. To avoid the over conclusive term, we delete "synergistic" in this article. We have changed the title of this article to "Effects of Retinopathy and Chronic Kidney Disease on Long-term Mortality in Type 2 Diabetic Inpatients with Normal Urinary Albumin or Protein: A Retrospective Cohort Study". We change to the statement "DR with CKD exerts a synergistic effect on all-cause and cardiovascular mortality." to "DR with CKD shows the highest risks of all-cause and cardiovascular mortality among these patients" in the conclusion of Abstract. We changed "*A synergistic effect*" to "*A combined effect*" in page 11 line 7. We change "However, our results showed a synergistic effect of CKD and DR on all-cause mortality and cardiovascular mortality" to "However, the highest risks of all-cause mortality and cardiovascular mortality were shown in the patients with CKD and DR" in Page 15 line 4－6.