Author’s response to reviews

**Title:** Long-Term Survival and Predictors for Mortality among Dialysis Patients in an Endemic Area for Chronic Liver Disease: A National Cohort Study in Taiwan

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**Author’s response to reviews:** see over
Dear Dr. Christopher Morrey,

We are grateful for the opportunity to revise our manuscript entitled “Long-Term Survival and Predictors for Mortality among Dialysis Patients in an Endemic Area for Chronic Liver Disease: A National Cohort Study in Taiwan”. My colleagues and I are excited to have this privilege and appreciate the valuable comments and suggestions from you and the reviewers. Accordingly, a revised manuscript was prepared, and we are attaching a “Reply to the Editor’s and Reviewers’ Comments” to state clearly on a point-by-point basis the changes made in accordance with the comments. The trial registration number has been added to the Abstract and the Materials and Methods section. The tracks of revised statements according to the editor and reviewers have been also included at the end of revised manuscript.

We are eager to publish this work in your journal and believe this paper is of interest to the readers of BioMed Central Nephrology. If you have any further requests or questions, please do not hesitate to contact me.

Sincerely,
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Reply to the Editor’s and Reviewers’ Comments

Editors

Comment 1 . Ethics - Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Reply:
This is an administrative data obtained from the National Health Insurance Research Database with trial registration number (NHRI-NHIRD-99182). We have added the trial registration number (NHRI-NHIRD-99182) to the abstract (Abstract section; page 2, line 8) and revised the Methods sections by adding, “As the dataset was released with de-identified secondary data for public research purposes, the study was exempt from full review by the Institutional Review Board (NHRI-NHIRD-99182).” (Methods section, paragraph 2; page 5, line 21)

Comment 2 . Abstract ? Please re-write the abstract to provide more background and context.

Reply:
As requested by the editor, we have re-written the abstract to enrich the context of abstract, especially the Background section by adding “Background: Patients with end-stage renal disease are at higher risk for chronic hepatitis, liver cirrhosis (LC) and mortality than general population. Optimal modalities of renal replacement therapy for ESRD patients with concomitant end-stage liver disease remain controversial. We investigated the long-term outcome among dialysis patients with different dialysis modalities in an endemic area for chronic liver disease” and revised other section as follows: “Results: PD patients tended to be younger and less likely to have comorbidities compared with those on HD. A high prevalence rate (6.16%) of LC was diagnosed when dialysis began. Other than well-known risk factors, LC (hazard ratio [HR] 1.473, 95% CI: 1.329-1.634) and dementia (HR 1.376, 95% CI: 1.083-1.750) were also independent predictors of mortality. Hypertension and mortality were inversely associated. Dialysis modality and three individual comorbidities (diabetes mellitus, chronic lung disease, and dementia) significantly interacted on mortality risk” and “Conclusions: LC was an important predictor of mortality; however, the effect on mortality was not different between HD and PD patients.” (Abstract section; page 2)
Comment 3. Database Access - Please clarify if the Taiwan NHI database from which the data is taken is publicly accessible and provide a link to it in your manuscript.

Reply:
As requested by the editor, we revised our Methods section by adding “Data were obtained from the National Health Insurance Research Database (NHIRD) [Bureau of National Health Insurance. Available at: www.doh.gov.tw/statistic/index.htm [In Chinese] (accessed November 25, 2011); http://www.doh.gov.tw/EN2006/index_EN.aspx [In English], released for research by the Taiwan National Health Research Institute (NHRI).” (Methods section, paragraph 2; page 5, line 9-12)
Reviewer 1 (Dr. Bernard G. Jaar)

Major Compulsory Revisions

Introduction

Comment 1: Overall, the introduction is a bit confusing and needs more focus. Are the authors assessing the risk of death between HD and PD in a special population or are they assessing the impact of liver cirrhosis on mortality in that population.

Reply:

Thanks for the reviewer’s valuable suggestions. We revised the introduction to be much more focus on assessing the risk of death, and the impact of liver cirrhosis on mortality between HD and PD in a special (dialysis) population. In Background section, we revised “However, several studies have shown conflicting results on the impact of baseline comorbidities like hypertension (HTN). Recent data have questioned the link between HTN and survival in dialysis patients [7-10].” to “The survival ramifications of hemodialysis (HD) and peritoneal dialysis (PD) seem inconclusive [8]. It is well known that age, type of dialysis [7], diabetes mellitus (DM), and other comorbidities need to be considered when estimating mortality among dialysis patients [3-5]. In the elderly, a poor prognosis seems evident in PD groups [4-6]. In diabetes patients, the mortality rate was higher in the PD than in the HD group [3, 4, 6]. However, Jaar BG et al. reported that ESRD patients who had higher propensity for initially receiving PD, survival did not differ by dialysis type [7].

Patients with ESRD are at a higher risk for chronic hepatitis, which are more likely to be contributed to higher rates of complications (LC and hepatocellular carcinoma) and mortality than the general population [9-16]. Taiwan is an endemic area of HCV infection, with a prevalence rate of 10% – 15% for PD patients [17, 18], 15% – 20% for HD patients, and 5% – 10% for the general population [12, 13]. Approximately 10% of incident dialysis patients are positive for anti-HCV antibody [14] and 5.8% of incident HD patients have LC [15] on initiation of renal replacement therapy in Taiwan. Optimal modalities of renal replacement therapy for these patients also remain controversial [19-21]. Potential disadvantages of HD therapy are unstable hemodynamics and the risk of bleeding [19, 22]. PD therapy offers a more stable hemodynamic profile. However, it may increase the possibility of early catheter leak, peritonitis, and ongoing protein loss. It has been reported that HD could not prolong the lifespan in LC patients who have acute kidney injury (AKI), but not been carefully examined in those with maintained HD. PD is also unhelpful in LC with AKI, but it has been found to produce viable results in some LC patients with ESRD [20].”

(Background section, Paragraph 2)
Methods

Comment 2: The data source seems good as it reportedly covers almost 99% of inpatient and outpatient claims. Any data on sensitivity and specificity of the underlying diagnosis codes captured by this national database?

Reply:
In response to the reviewer’s comment, we revised the description in the Methods section by adding “Those comorbidities that had been determined should fit one of the definitions below: (1) Diagnostic codes in outpatient visits if the patient had an initial diagnosis at any time in the 1 year before the start of dialysis and then experienced one or more additional diagnoses within the subsequent 12 months. The first and last outpatient visit within 1 year must be >30 days apart to avoid accidental inclusion of miscoded patients. [27, 28] (2) Diagnostic codes in hospitalization databases at least 1 time in the 1 year before the start of dialysis.” The method to identify the comorbidities had been used extensively in various studies of Taiwan National Health Research Institute and many articles have been published [Bureau of National Health Insurance. Available at: www.doh.gov.tw/statistic/index.htm [In Chinese] (accessed November 25, 2011); http://www.doh.gov.tw/EN2006/index_EN.aspx [In English].” (Methods section, Paragraph 4; page 6, line 22~). Thanks for your suggestion.

Comment 3: Patients were enrolled if they had survived the first 90 days on dialysis. What was the rationale for this choice? Please clarify. Authors might be missing early mortality related to liver cirrhosis.

Reply:
ESRD patients on maintenance dialysis were usually defined as starting dialysis for more than 90 days. If the patient couldn’t withdraw from dialysis after 90 days, then most likely, he would need to receive maintained dialysis for the rest of life. The method had been used extensively in various studies [Reference 3, 15]. Indeed, this way might be missing some early mortality related to liver cirrhosis. Therefore, we revised the patient’s selection and definition in the Methods section by adding “ESRD patients on maintenance dialysis were defined as starting dialysis for more than 90 days [3, 13], which means these patients needed long-term dialysis.” (Methods section, Paragraph 3, page 6, line 2-4) and revised the limitations in the Discussion section by adding “Using the definition of ESRD on maintenance dialysis as starting dialysis for more than 90 days might be missing some early mortality related to liver cirrhosis.” (Discussion section, Paragraph 8; page 13, line 24~)

Comment 4: It is surprising that only 83 patients had multiple switches between
dialysis modalities. In other prospective cohort studies these numbers are higher.

Reply:
We rechecked that the dialysis modality switches followed the “60-days rule” [Reference 25] and came to the same conclusion that only 83 patients had multiple switches between dialysis.

Comment 5: It’s unclear if authors maintain in the dataset patients who had only one switch. Please clarify.

Reply:
According to the reviewer’s suggestion, we revised the Results section by adding “During the follow-up period, 99.3% of HD patients (n = 11216) were on pure HD, 0.7% of HD patients (n = 77) switched to PD, 67.4% of PD patients (n = 513) were on pure PD, and 32.6% of PD patients (n = 248) switched to HD.” (Results section, Paragraph 1; page 8, line 6-8)

Comment 6: Again, provide rationale why selected comorbidities had to be coded 3 times in the year prior to dialysis when analyzing ambulatory visits. Doesn’t this process decreases your sensitivity for capturing comorbidities?

Reply:
We are sorry for your doubt on sensitivity and specificity of the underlying diagnostic codes that may result from not clearly describing the procedure previously. We revised the Methods section by adding “Those comorbidities that had been determined should fit one of the definitions below: (1) Diagnostic codes in outpatient visits if the patient had an initial diagnosis at any time in the 1 year before the start of dialysis and then experienced one or more additional diagnoses within the subsequent 12 months. The first and last outpatient visit within 1 year must be >30 days apart to avoid accidental inclusion of miscoded patients. [27, 28] (2) Diagnostic codes in hospitalization databases at least 1 time in the 1 year before the start of dialysis.” The method to identify the comorbidities had been used extensively in various studies of Taiwan National Health Research Institute and many articles have been published [Bureau of National Health Insurance. Available at: www.doh.gov.tw/statistic/index.htm [In Chinese] (accessed November 25, 2011); http://www.doh.gov.tw/EN2006/index_EN.aspx [In English].” (Methods section, Paragraph 4; page 6, line 22–). The method to identify the candidate group had been used extensively in various studies of Taiwan National Health Research Institute with commonly accepted. Therefore, we greatly appreciate it if the reviewer would agree to this way to capture diagnostic codes from this national database.
Comment 7: Already, using this billing data, there are limited comorbidities, no data on body mass index, on severity of comorbidities, on actual blood pressure values. No data on laboratory values which can affect survival particularly in patients with liver cirrhosis, such as serum albumin. No information on type of vascular access in use for the hemodialysis patients. No information on medication use, such as blood pressure medications, use of erythropoietin stimulating agents, vitamin D analogs, …

Reply:
Thanks for your valuable suggestion. It is an important limitation in our study. We revised the limitation section by adding “Using this billing data, we were unable to take consideration of the body mass index, severity of comorbidities, and actual blood pressure values of the study population. Our study also lacked specific data on dialysis adequacy, type of vascular access use for HD patients, laboratory data, and medical prescriptions, which may affect survival particularly in patients with LC.”

(Discussion section, Paragraph 8; page 13, line 20-24)

Comment 8: One of the main risk factors analyzed was liver cirrhosis. How was this defined? Is it only by ICD-9 codes? If this is the case, this can lead to some significant misclassification as patients might have the disease, maybe subclinical prior to dialysis, maybe not coded for during outpatient ambulatory visit or hospitalization. Do you have information about Hepatitis B or C positivity? Maybe interesting to look at data by viral hepatitis positivity and mortality rather than liver cirrhosis.

Reply:
Thanks for your valuable suggestion. Indeed, it may lead some misclassification as patients might have the disease, maybe subclinical prior to dialysis, maybe not coded for during outpatient ambulatory visit or hospitalization if these comorbidities were only defined by ICD-9 codes. We thus revised the Limitation section by adding “If these comorbidities were only defined by ICD-9 codes, it may lead some misclassification as patients might have LC in several special situations, such as subclinical prior to dialysis, not coded for during outpatient ambulatory visit or hospitalization. In addition, liver cirrhosis may or may not be related to viral hepatitis. However, we can’t have access to information about Hepatitis B or C positivity from this database.”

(Discussion section, Paragraph 8; page 13, line 16-20)

Comment 9: From the statistical standpoint, was this an “intention-to-treat” type analyses were switching of dialysis modalities were not considered?

Reply:
This was an “intention-to-treat” type analyses and switching of dialysis modalities were not considered. We revised the Methods section by adding “Intent-to-treat analysis used the Cox proportional hazards model…….” (Methods section, Paragraph 6; page 7, line 14)

Comment 10: Proportionality assumption was likely not met as the mortality risk between PD and HD changed overtime.

Reply:
Despite a slight cross-over around the 6th months of follow-up, the two log-minus-log survival functions consistently deviate from each other in a certain distance. We calculated the ratios of two hazard rates every 6 months through the study period, and almost all values between 1 and 2. Therefore, we did not consider a significant violation to the proportional hazard assumption.

Results:
Comment 11: Overall, well presented. First paragraph under “demographics”; would be best to report percentage of patients transferred from PD to HD as a percentage of the total PD population, rather than the whole population. Same comment for patients who switched from HD to PD.

Reply:
In response to the reviewer’s comment, we revised the Results section by adding “During the follow-up period, 99.3% of HD patients (n = 11216) were on pure HD, 0.7% of HD patients (n = 77) switched to PD, 67.4% of PD patients (n = 513) were on pure PD, and 32.6% of PD patients (n = 248) switched to HD.” (Results section, Paragraph 1; page 8, line 6-8)

Discussion:
Comment 12: Again, need more focus in term of the goals of the study; are we comparing HD vs PD or looking at the impact of liver cirrhosis in that population?

Reply:
Thanks for your valuable suggestion. We compared the impact of several comorbidities on HD vs. PD and revised the Discussion Section by adding a new paragraph “Patients on PD had a better crude survival rate compared with those on HD during the following period. Our patients who selected PD were generally less likely to have comorbidities (Table 1). In addition, the HD group seemed to have a disproportionately higher number of the elderly. After adjustment, there was no statistical difference of survive between HD and PD. Old age was the most important factor that influenced survival between HD and PD patients. Patients aged ≥65 were
associated with more than a 4-fold increase in mortality as compared to those aged 18-44 (Table 2). We hypothesize that age confounded the finding of poor survival in HD Population and further checked it. Univariate analysis done to estimate the risk factors for mortality showed that the survival rates of HD versus PD patients were significantly different (HR 1.419, 95% CI: 1.251-1.609) (Table 2). If we further adjust the dialysis modality and age group, the HR goes from 1.419 (95% CI: 1.251-1.609) to 1.024 (95% CI: 0.902-1.162), which proves that age confound the finding of poor prognosis survival in the HD population. The survival in figure 2 also shows varying rates of survival in PD patients and an almost linear pattern in HD patients. Several studies have demonstrated the better survival of PD patients compared with HD patients during the first 2 years of initiation of dialysis [8, 29, 30]. The initial benefit in PD patients may be related to fewer comorbidities, the removal of unidentified solutes by PD, or better preservation of residual renal function during this time period [29, 30]. The concept of PD first and HD second implies that these 2 dialysis modalities are complementary, not as a competition [8].”

We also discussed the impact of liver cirrhosis in that population and revised Discussion Section by adding “Chronic liver disease and ESRD are common and serious medical problems worldwide. Compared with the general population, ESRD patients are at increased risk of hepatitis B and C infection [10, 11]. A period-prevalent data recorded in the national or regional dialysis registries of the 10 Asia-Pacific countries/areas showed the prevalence of HCV infection observed in dialysis patients were considerably higher than those in the corresponding general populations of many Asian countries (range 1.0–2.9%) [23], and and likely contributed to LC and death [16]. We found 6.2% of HD patients and 5.3% of PD patients had LC at the initiation of dialysis in Taiwan between 1999 and 2000. The prevalence is much higher than in western countries [30]. The treatment of ESRD patients with LC is complex and difficult, mainly due to deceased effective arterial volume and hemodynamic instability. The optimal dialysis modality of these patients is still controversial. Unstable hemodynamics and the bleeding risk make HD problematic. Although PD has some disadvantages (early catheter leak, hypokalemia, peritonitis and ongoing protein loss), some reports still suggest ESRD patients with LC can be successfully managed on PD [19, 22]. However, there was no significant difference between HD and PD on all-cause mortality in our study. De Vecchi et al. [33] reported the survival rate was similar between dialysis patients with LC and those without liver disease. In contrast, we found a 47% higher risk of death in dialysis patients with LC than without LC (HR 1.473, 95% CI: 1.329-1.634)”
Minor Essential Revisions

Discussion:

Comment 13: Would add in limitations, that there is residual confounding as with all observational studies. That there is no causality between these risk factors and mortality. Observational studies report only association and not causation.

Reply:
Thanks for your valuable suggestion. We thus revised the limitation section by adding “There is residual confounding as with all observational studies, and thus there is association, not causality, between these risk factors and mortality.” (Discussion section, Paragraph 8; page 14, line 1-3)

Comment 14: Overall, the current study as presented, does not add much to the current scientific literature. Using this dataset, there is a unique opportunity to assess the impact of chronic liver disease (defined as hepatitis B, C and liver cirrhosis) on dialysis patients’ survival, hospitalization rate, access to kidney transplantation. This could be the focus of a revised manuscript. Hope these few comments will help the authors improve on their interesting manuscript.

Reply:
We learned much from your comments, and have revised our manuscript in several paragraphs of Discussion section as possible. However, this database we obtained still lacked some information as your mention, and need re-application with decoding, which is much time-consuming. We will perform further analyses in the future according to your valuable suggestions.
Reviewer 2 (Dr. Kunal Chaudhary)

Major Compulsory Revisions

Comment 1: The study is a retrospective data analysis conducted from a large national insurance dataset, but the authors reference other publications on the endemicity of hepatitis B and C, and utilize the diagnosis of liver cirrhosis as a variable. Liver cirrhosis may or may not be related to viral hepatitis in these cases and this question has not been addressed.

Reply:

Thanks for your suggestion. Indeed, liver cirrhosis may or may not be related to viral hepatitis. However, our dataset was enrolled the ESRD patients who began maintained dialysis between January 1st, 1999, and December 31st, 2000. At that time, hepatitis B and C profiles had not routinely checked and coded in Taiwan. Therefore, the prevalence of hepatitis B and C positivity might be underestimated in this study population. We revised the topic as “Long-Term Survival and Predictors for Mortality among Dialysis Patients in an Endemic Area for Chronic Liver Disease: A National Cohort Study in Taiwan” and revised Limitation section by adding “Liver cirrhosis may or may not be related to viral hepatitis. However, our dataset enrolled the ESRD patients who began maintained dialysis between January 1st, 1999, and December 31st, 2000. At that time, hepatitis B and C profiles had not routinely checked and recorded prior to dialysis in Taiwan. Therefore, the prevalence of hepatitis B and C positivity might be underestimated from this database. Because these patients couldn’t be accurately classified according to Hepatitis B or C positivity, we focused on their common clinical presentation of chronic liver disease.” (Discussion section, Paragraph 8; page 13, line 18-25)

Comment 2: No information is provided about the prevalence of viral hepatitis, or even liver cirrhosis, in the general population, as compared to ESRD patients, which would provide evidence to statement that ESRD patients are higher risk for chronic hepatitis and about endemic nature of hepatitis in Taiwan.

Reply:

As requested by the reviewer, we revised our background section by adding, “Patients with ESRD are at a higher risk for chronic hepatitis, which are more likely to be contributed to higher rates of complications (LC and hepatocellular carcinoma) and mortality than the general population [9-16]. Taiwan is an endemic area of HCV infection, with a prevalence rate of 10% – 15% for PD patients [17, 18], 15% – 20% for HD patients, and 5% – 10% for the general population [12, 13]. Approximately 10% of incident dialysis patients are positive for anti-HCV antibody [14] and 5.8% of
incident HD patients have LC [15] on initiation of renal replacement therapy in Taylor. Optimal modalities of renal replacement therapy for these patients also remain controversial [19-21]. Potential disadvantages of HD therapy are unstable hemodynamics and the risk of bleeding [19, 22]. PD therapy offers a more stable hemodynamic profile. However, it may increase the possibility of early catheter leak, peritonitis, and ongoing protein loss. It has been reported that HD could not prolong the lifespan in LC patients who have acute kidney injury (AKI), but not been carefully examined in those with maintained HD. PD is also unhelpful in LC with AKI, but it has been found to produce viable results in some LC patients with ESRD [20].”

(Background section, Paragraph 2; page 3, line 12~)

**Comment 3:** Age has been categorized as an interval variable, but overall average age in HD and PD patients has not been stated. Based on proportion of patients, the HD group seems to have a disproportionately higher number of elderly populations. How does this confound the finding of poor survival in HD population?

**Reply:**

In response to the reviewer’s comment, we revised the Results section by adding “Patients on PD were predominantly younger than those on HD (53.95 ± 15.09 years vs. 59.87 ± 13.45 years).” (Results section, Paragraph 1; page 8, line 4-5)

We also revised the Discussion section by adding “In addition, the HD group seemed to have a disproportionately higher number of the elderly. After adjustment, there was no statistical difference of survive between HD and PD. Old age was the most important factor that influenced survival between HD and PD patients. Patients aged ≥65 were associated with more than a 4-fold increase in mortality as compared to those aged 18-44 (Table 2). We hypothesizes that age confounded the finding of poor survival in HD Population and further checked it. Univariate analysis done to estimate the risk factors for mortality showed that the survival rates of HD versus PD patients were significantly different (HR 1.419, 95% CI: 1.251-1.609) (Table 2). If we further adjust the dialysis modality and age group, the HR goes from 1.419 (95% CI: 1.251-1.609) to 1.024 (95% CI: 0.902-1.162), which proves that age confound the finding of poor prognosis survival in the HD population.” (Discussion section, Paragraph 2; page 10, line 11-21)

**Comment 4:** The statistical model is not explicitly stated and appears inadequate. Parametric pearson’s chi square test is utilized to compare each variable in HD and PD patients. Non-parametric tests are used for other analysis.
Reply:
Thanks for your reminder, and we had also analyzed our data as your mention. We revised our statistical statement by adding “Parametric Pearson’s chi-square test is utilized to compare each variable in HD and PD patients. Non-parametric tests are used for other analyses.” (Statistical analyses section, Paragraph 2; page 7, line 10-12)

Comment 5: Interaction is checked for statistical significance, but the complete model used for cox regression analysis is not stated. The clinical significance of this interaction is unclear to me.

Reply:
As requested by the reviewer, we revised our statistical statement by adding “Further interactions were tested. The complete model included all the covariates listed in table 2 was used for cox regression analysis. Then, each interaction term was included separately once at a time.” (Statistical analyses section, Paragraph 2; page 7, line 19-21)

In addition, we are sorry for the ambiguous statement about interaction. We clarify the clinical significance of this interaction by revising Paragraph 3, Discussion section “After the interaction test, 3 baseline comorbidities (DM, chronic lung disease, and dementia) interacted significantly with dialysis modality, which proved that these 3 factors had different impact on mortality between HD and PD patients. Similar to previous findings [3, 4, 11], diabetes patients had a higher mortality rate in the PD group (HR = 2.210) than in the HD group (HR = 1.821). Dementia diagnosed before initiation on dialysis has been reported as a predictor of subsequent death [32]. Our results further showed a greater disadvantage for survival in PD patients with dementia (HR = 3.473); the possible causes may be their peritonitis and their inability to do self-dialysis. Cavanaugh et al. [32] reported a greater risk of death in dialysis patients who had chronic obstructive pulmonary disease. Our multivariate analysis revealed that chronic lung disease was an important predictor of mortality, even in patients on PD. We found a 21% increase in the risk of death in patients on HD and an 82% increase in those on PD. It should be individualized to select an optimal dialysis modality. Three important factors (DM, chronic lung disease, and dementia) that have different impact on survival between HD and PD should be taken into account. From our study, ESRD patients with these 3 baseline comorbidities had higher mortality on PD than those on HD.” (Discussion section, Paragraph 3)

Comment 6: Log rank statistic used to measure statistical significance in survival of patient on PD vs HD provides a cumulative measurement over 10 year period and
does not provide any other information. The survival in figure 2 shows varying rates of survival in PD patients and an almost linear pattern in HD patients. What could be the possible reason for the initial benefit in PD patients has not been analyzed.

Reply:
Thanks for your valuable suggestion. Indeed, Log rank statistic used to measure statistical significance in survival only provides a cumulative measurement and does not provide any other information. We added a statement in Discussion section to explain the initial benefit in PD patients, “The survival in figure 2 also shows varying rates of survival in PD patients and an almost linear pattern in HD patients. Several studies have demonstrated the better survival of PD patients compared with HD patients during the first 2 years of initiation of dialysis [8, 29, 30]. The initial benefit in PD patients may be related to fewer comorbidities, the removal of unidentified solutes by PD, or better preservation of residual renal function during this time period [29, 30]. The concept of PD first and HD second implies that these 2 dialysis modalities are complementary, not as a competition [8].” (Discussion section, Paragraph 2; page 10, line 22~)

Minor Essential Revisions

Comment 7: There are some grammatical errors thru the manuscript which need attention.

Reply:
In response to the reviewer’s comment, we have corrected the grammatical errors in our manuscript while rechecked with attention.

Discretionary Revisions

Comment 8: The cause of death in each modality has not been reported. If this data is available it may be of benefit to report in HD and PD cases.

Reply:
We agree that it would be better to describe the causes of death; however, the Taiwan Bureau of National Health Insurance does not afford the cross-link information between this and the database of “causes of death”. Thanks for your valuable suggestions.