Author’s response to reviews

Title: Is combined peritoneal dialysis and hemodialysis redundant? A nationwide study from Taiwan

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Version: 1 Date: 04 May 2020

Author’s response to reviews:

Ms. No.: BNEP-D-20-00038
Title: Is combined peritoneal dialysis and hemodialysis redundant? A nationwide study from Taiwan

Dear Dr. Cassady-Cain,

Thank you very much for your letter dated April 2, 2020 and the reviewers’ comments on the abovementioned article. We truly appreciate the opportunity to revise the manuscript. We have completed the revisions according to your suggestions and the reviewers’ comments. In addition, we rechecked and confirmed all statistical reporting in your manuscript were suitable in the present study. The revised manuscript and point-by-point responses to the reviewers’ comments are attached. The major revisions in the manuscript are written in red and bold for your convenience.
Thank you for your attention.
Yours sincerely,

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Response to Reviewer’s Comments
To Reviewer #1:
Thank you for reviewing our manuscript. The manuscript has been revised point-by-point according to your suggestions and comments. The major revisions in the manuscript are written in red and bold for your convenience.

Comments:
1. You state in your introduction page 5 line 55 that this is a full exploration. Don't you think that is an overstatement? You explain your limitations so this not "full."
   Reply: We revised this sentence “The present study aimed to explore the current practice of combined therapy and to clarify the long-term prognosis for mortality and admission risks if PD patients select it as bridge therapy.” on page 4, line 55.

2. On page 6 line 38 "PD maintenance" could be simply "stayed on PD"
   Reply: We revised this sentence “Patients aged < 18 years were excluded, as well as those with a history of kidney transplantation, stayed on PD, and death or kidney transplantation on PD.” on page 5, line 48.

3. What is mandatory is analysis of the vascular access used. I could not sort this out and it may be buried some place, but make it clear. What fraction of those on 2/mo HD had CVCs, AVGs or AVFs?
   Reply: Thanks for your suggestion. We revised the Table 1 to present more detailed information. In addition we added the description for this result in Results section in the manuscript: “Patients from combined group were further divided into two groups by hemodialysis frequency (HD ≤ 3 and HD = 4) (Table 1). Compared with HD ≤ 3 group, HD = 4 group had more females (54.8% vs. 45.2%), a higher usage of APD (27.4% vs. 19.1%), usage of icodextrin (47.1% vs. 38.1%), recent peritonitis (38.1% vs. 25.1%), use of tunneled catheter as vascular access for HD (32.3% vs. 8.73%).” on page 8, line 29.

4. I would argue that several observations are internal validity. If you agree I would recommend stating that. For example, patients with recent peritonitis of needing frequent HD had higher risks of admission is that the sicker (or at least in more trouble clinically) are more likely to be admitted. To me that is internal validity.
   Reply: Thanks for your suggestion. In order to validate our primary
analysis; thus, we added the sensitivity analysis using propensity score matching method in supplementary Table 1 and in supplementary Table 2, which also showed similar outcome in mortality and admission risk. In the present analysis, we tried our best to consider possible and significant confounders like PD duration (might reflect the skilled in PD technique), use of APD, icodextrin (might reflect the fluid status) and recent peritonitis (might reflect the most important factor of technique failure). However, we had to admit there were still some important factors not included in our analysis, which were written into the limitation section.

5. The cost paragraph on page 12 lines 15-29 belongs under results. You need to state that the 2/month is 26 sessions/yr, which is what I confirmed going backwards from your dollar amounts. However, how many twice/month pts stayed at twice per month? How many at 4 per month reduced. So an average seems reasonable. 4 HD sessions/m for a year would be $24,107 so now much more costly than transfer to HD. This is worthy of its own result section.

Reply: Thanks for your question. We revised this paragraph: “For combined therapy, two HD sessions per month were covered by the TNHI system, but the other two sessions need to be paid by the patients themselves. Previous work reported PD and HD costs (US$/per year) in Taiwan of 17,723 and 21,367, respectively, including outpatient and inpatient expenses. Each HD session costs $133 in Taiwan. Thus, combined therapy with two HD sessions per month costs $21,192 per year (26 HD sessions per year), which is still lower than the cost of pure HD; in contrast, combined therapy with four HD sessions per month is more expensive than pure HD. From insurance aspect, combined therapy with two HD sessions per month was an acceptable choice.” on page 11, line 51, in Discussion section of the revised manuscript. For HD frequency, around 80% twice HD per month will stay at twice per month and more than 90% four times HD per month will stay at four times HD.

6. In table 2 in the left column under overall instead of 2 (N....) write 2 HD sessions/m (N....) because some readers only brows tables, some may want to copy your tables. So this is an easy fix.

Reply: We revised the Table 2 according to your suggestion in the revised manuscript.

To Reviewer #2:
Thank you for reviewing our manuscript. The manuscript has been revised point-by-point according to your suggestions and comments. The major revisions in the manuscript are written in red and bold for your convenience.

Comments:
1. In this study, after matching with age, gender, and duration of PD, there were various biases, including patient status, frequency of peritonitis, and possibility of continuing PD therapy, in the selection of dialysis modality between combined and transfer groups.

Reply: Thanks for your question. We tried our best to consider possible and significant confounders like PD duration (might reflect the skilled in PD technique), use of APD, icodextrin (might reflect the fluid status) and recent peritonitis (might reflect the most important factor of technique failure). However, we had to admit there were still some important factors such as clinical parameters of dialysis not included in the databases, which were written into the limitation section. “We could not identify the albumin level, residual renal function, nutritional status, ultrafiltration rate, peritoneal function test, plasma β2-microglobulin level, hyperphosphatemia, and dialysis clearance (weekly Kt/V and weekly creatinine clearance), all of which might be
associated with the outcome. Second, despite age, sex, and PD duration being matched between patients with combined therapy and those who transferred to HD, there were still residual biases between the groups, including indications and numerical data of changing the dialysis modality to combined or transfer therapy, fluid status, poor self-management of fluid balance, possibility of continuing PD therapy and the patients' requests.” on page 13, line 1, in Discussion section of the revised manuscript.

2. In this study, the authors defined combined therapy group as regular PD with at least twice HD per month. However, twice HD per month is too few as combined therapy. This therapy is PD therapy with rescue HD, not combined therapy. 
Reply: Thanks for your question. We revised and added the paragraph “There is no doubt that four HD sessions per month were better for dialysis adequacy than two HD sessions per month, and the latter sometimes was regarded as rescue HD not combined therapy. Combined therapy with four HD sessions was unexpectedly associated with higher admission risk in our study, which might be not only related to complications with frequent hemodialysis, but also reflect the underlined difference between these two groups of patients. Compared to two HD sessions, combined group with four HD sessions had more usage of APD, icodextrin, recent peritonitis and more tunneled catheter as vascular access to HD. Combined therapy with two HD sessions per month was a feasible alternative from clinical and insurance perspective in Taiwan.” on page 12, line 10, in Discussion section. And “For combined therapy, two HD sessions per month were covered by the TNHI system, but the other two sessions need to be paid by the patients themselves.” on page 11, line 51, in Discussion section of the revised manuscript.

3. In this study, the authors did not describe the indications and numerical data of changing the dialysis modality to combined or transfer therapy (ex. fluid overload due to ultrafiltration failure, poor self-management of fluid balance, severe heart failure, insufficient dialysis dose evidenced by an increased plasma β2-microglobulin level, hyperphosphatemia, patients' requests, and others (abdominal hernia, bridging to HD therapy, liver dysfunction, or leakage of PD solution). These factors might affect the overall admission and mortality.
Reply: Thanks for your question. In our analysis, we tried our best to consider possible and significant confounders like PD duration (might reflect the skilled in PD technique), use of APD, icodextrin (might reflect the fluid status) and recent peritonitis (might reflect the most important factor of technique failure). In addition, we included chronic heart failure as an important variable in the multiple regression models. Furthermore we tried to validate our primary analysis; thus, we added the sensitivity analysis using propensity score matching method in supplementary Table 1 and in supplementary Table 2, which also showed similar outcome in mortality and admission risk. However, we had to admit there were still some important factors not included in our analysis, which were written into the limitation section.

To Reviewer #3:
Thank you for reviewing our manuscript. The manuscript has been revised point-by-point according to your suggestions and comments. The major revisions in the manuscript are written in red and bold for your convenience.

Comments:
1. Combination therapy removes solutes and removes water that PD alone cannot handle when renal function declines (or lost). The authors should include residual renal function (renal Kt/V, Ccr), dialysis efficiency (peritoneal Kt/V, Ccr), peritoneal function (D/P), laboratory data such as β2MG, Alb, BNP as patient background.
   Reply: Thanks for your question. We tried our best to consider possible and significant confounders like PD duration (might reflect the skilled in PD technique), use of APD, icodextrin (might reflect the fluid status) and recent peritonitis (might reflect the most important factor of technique failure). However, we had to admit there were still some important factors such as clinical parameters of dialysis not included in the databases, which were written into the limitation section. “We could not identify the albumin level, residual renal function, nutritional status, ultrafiltration rate, peritoneal function test, plasma β2-microglobulin level, hyperphosphatemia, and dialysis clearance (weekly Kt/V and weekly creatinine clearance), all of which might be associated with the outcome. Second, despite age, sex, and PD duration being matched between patients with combined therapy and those who transferred to HD, there were still residual biases between the groups, including indications and numerical data of changing the dialysis modality to combined or transfer therapy, fluid status, poor self-management of fluid balance, possibility of continuing PD therapy and the patients' requests.” on page 13, line 1, in Discussion section of the revised manuscript.

2. Although it has been concluded that only twice-monthly combination therapy is beneficial, the authors should consider the reasons in more detail because it is too few for patients who have lost renal function. Since this is a retrospective study, it should be considered whether selection biases such as residual kidney function, body fluid management, and dietary intake were involved.
   Reply: Thanks for your question and reminder. We advised the content of Table 1 to present more detailed information. In addition, we revised the paragraph “Combined therapy with four HD sessions was unexpectedly associated with higher admission risk in our study, which might be not only related to complications with frequent hemodialysis, but also reflect the underlined difference between these two groups of patients. Compared to two HD sessions, combined group with four HD sessions had more usage of APD, icodextrin, recent peritonitis and more tunneled catheter as vascular access to HD.” on page 11, line 15, in Discussion section of the revised manuscript.

3. The authors perform matching by age, sex, and PD duration. However, considering the hospitalization rate and mortality, it is necessary to take into account the presence of comorbidity and peritonitis.
   Reply: Thanks for your question. In order to validate our primary analysis; thus, we added the sensitivity analysis using propensity score matching method in supplementary Table 1 and in supplementary Table 2. There were no significant differences in combined and transfer group about age, sex, PD duration, comorbidities, APD/ icodextrin use and recent peritonitis and it still showed similar outcome in mortality and admission risk.
4. In line 4 of p11, it is considered that the less icodextrin or APD used, the poorer fluid management is, but the opposite is true. This is because the poorer the body fluid management (reduced renal function or excessive intake), the more they are needed, and the better the management of body fluid, the less the need for use. In any case, the data should be shown.

Reply: Thanks for your question. Because of limitation of our database, possibilities of poor self-management of fluid balance or excessive intake could not be included in our analysis, which were described in the limitation section of the revised manuscript.