Association of Peritonitis With Cardiovascular Mortality Over Time in the Peritoneal Dialysis Population: An Australia and New Zealand Dialysis and Transplant Registry Study

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Introduction: Though peritonitis is associated with increased mortality in patients receiving peritoneal dialysis (PD), its association with cardiovascular mortality remains uncertain.

Methods: The study participants included adult patients (≥18 years old) commencing PD in Australia (from October 2003 to December 2019) using the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. Association between peritonitis and cardiovascular mortality was evaluated using Cox proportional hazards analysis and competing risks analysis. Associations between peritonitis rates between different eras and cardiovascular mortality were also compared using Jointpoint regression model to determine the time point when a significant change in peritonitis trend occurred to define the era for cardiovascular mortality. Subgroup analysis dividing the groups into 0, 1 and ≥2 episodes of peritonitis and sensitivity analysis censoring at 90 days post-transfer to hemodialysis (HD) were performed.

Results: The study included 9699 incident PD patients. The overall peritonitis rate was 0.37 episodes per patient-year and declined by 4.7% (95% confidence interval [CI] 3.6–5.8%) during the study period. Peritonitis was associated with increased cardiovascular mortality risk (subdistribution hazard ratio [SHR] 1.53, 95% CI 1.39–1.69, P < 0.001) with increasing peritonitis episodes associated with higher risk (1 episode of peritonitis SHR 1.41, 95%CI 1.24–1.61; ≥2 episodes of peritonitis SHR 1.69, 95% CI 1.47–1.93, P < 0.001). Patients who commenced PD between 2012 and 2019 had a lower risk of cardiovascular mortality (SHR 0.60, 95% CI 0.50–0.72, P < 0.001), compared to patients who commenced between 2003 and 2011. Results were consistent in the sensitivity analysis.

Conclusion: Peritonitis is independently associated with an increased risk of cardiovascular mortality, and the association is episode-dependent. Prevention and adequate treatment of PD peritonitis may improve cardiovascular outcomes among patients receiving PD.

Kidney Int Rep (2022) 7, 2388–2396; https://doi.org/10.1016/j.ekir.2022.08.008

KEYWORDS: ANZDATA; cardiovascular mortality; mortality; peritoneal dialysis; peritonitis; time factors

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event, it remains uncertain if PD peritonitis increases the risk of subsequent mortality. Similarly, an analysis of the Brazilian Peritoneal Dialysis Multicenter Study (BRAZPD II) cohort between 2004 and 2011 found that peritonitis was associated with a 22% increased risk of cardiovascular mortality that progressively increased with each additional episode of peritonitis. Nevertheless, the study did not consider competing risks from other causes of mortality and its findings may not have been generalizable outside of South America.

We therefore aimed to evaluate the association between PD-associated peritonitis and cardiovascular mortality and to examine the association of peritonitis rates over time with cardiovascular mortality risk.

METHODS

Participants

The study included all adult patients (≥18 years old) commencing PD in Australia between October 1, 2003, and December 31, 2019 using deidentified data from the ANZDATA registry. Patients on dialysis for less than 90 days were excluded. This study was approved by the University of Wollongong and Illawarra Shoalhaven Local Health District Health Medical Human Research Ethics Committee (2021/ETH00044), Wollongong, Australia. Permission to use the data was granted by the ANZDATA executive and the study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data Collection

Baseline sociodemographic and clinical characteristics were collected at PD initiation. These included gender, age, ethnicity, primary kidney disease (diabetes, renovascular disease, glomerulonephritis, cystic disease, and other), body mass index, smoking status (never, former, or current smoker), state or territory of PD commencement, comorbid conditions (chronic lung disease, coronary artery disease, peripheral vascular disease, diabetes, cerebrovascular disease, and previous cancer), late referral to nephrologist (defined as referral to nephrologist less than 3 months before dialysis initiation) and geographical location (urban, rural, or remote). Socio-economic status was evaluated by socio-economic indexes for areas, measured by Index of Relative Socio-economic Advantage and Disadvantage categorized into tertiles.

Peritonitis and Outcome

Our exposure factor was an episode of peritonitis. We divided our cohort into a peritonitis group and a peritonitis-free group. To assess the effect of the frequency of exposure on outcome, we further divided our peritonitis group into, 1 peritonitis or ≥2 peritonitis categories for subgroup analysis. We did not differentiate between recurrent, relapsing or new peritonitis episodes for patients with ≥2 peritonitis episodes.

The primary outcome was cardiovascular death, which was defined as death due to myocardial ischemia or infarction, cardiac failure, cardiac arrest, cerebrovascular accident, or aortic aneurysm rupture. All other deaths were classified as noncardiovascular. Patients were entered into analysis from date of PD initiation until date of cardiovascular death with censoring at the following: (i) death from a non-cardiovascular cause, (ii) kidney transplantation, (iii) loss of follow-up, or (iv) end of study follow-up on December 31, 2019. During the primary analysis we did not censor patients who transferred to HD, because peritonitis is a significant cause of technique failure and the effect of a peritonitis on cardiovascular health would persist even after transferring to HD. A sensitivity analysis was performed, censoring patients at 90 days post-transfer to HD, to be consistent with previous studies.

Statistical Analysis

For baseline characteristics, categorical data are expressed as number (percentage) and compared using the chi-square test. Continuous data are expressed as mean with SD or median with interquartile range and analyzed as per distribution using t test and the Mann-Whitney U test. Annual incidence rates of PD peritonitis were calculated as the total number of peritonitis episodes divided by patient year follow-up for the peritonitis episode per patient year (excluding time on HD). Crude cardiovascular mortality rates were calculated as death per 1000 person-years annually (including time on HD) for patients with peritonitis and without peritonitis. Trends of incidence rates were examined using Jointpoint regression model to estimate the annual percentage change with the corresponding 95% CI and to determine the time point when a significant change in peritonitis trend occurred for the time definition in era analysis for cardiovascular mortality. The association between peritonitis and cardiovascular death was first examined by Cox proportional hazards regressions. The time was defined as time from PD initiation to death or censor date. Peritonitis was entered as a time varying exposure. Patients with no peritonitis episodes served as the referent. In subgroup analysis, time to first and second peritonitis episodes were entered as time varying exposures. Cox model included a shared frailty term for treatment center, to account for the peritonitis rate variation between dialysis centers in Australia (ranging from...
0.17 to 1.74 episodes per patient year. A multivariable-adjusted model was created with backward selection using covariates with P values <0.2, and covariates based on biological confounders. Fine-Gray’s extension of the Cox proportional hazards model was used to fit competing risk regression models considering kidney transplantation and non-cardiovascular death as competing event with robust variance estimator used to account for treatment center. The covariates for Cox proportional hazards models and competing risk analysis were the same. Results were expressed as hazard ratio for Cox proportional hazard analysis and SHR for competing risk analysis with 95% CI. Proportional hazard assumptions of the models were checked graphically and assessed visually by plotting Schoenfeld residuals. Missing data for ethnicity (2.9%) and primary kidney disease (6.3%) were treated by multiple imputation with the chained equation method. Ten iterations were performed, and all variables included in the analytical models were included as predictors. Other variables with missing data were either not included in the analytical models (late referral and geographical location) or had <0.5% missing data (smoking status, chronic lung disease, coronary artery disease, cerebrovascular disease, diabetes, and Index of Relative Socio-economic Advantage and Disadvantage). Finally, a sensitivity analysis was performed censoring at 90 days transfer to HD. Statistical analysis was performed using STATA 15.1 (Stata-Corp, College Station, TX) and Jointpoint (version 4.9.0.0). P values <0.05 were considered statistically significant.

## RESULTS

### Study Population

The study cohort included 9699 patients, and 436 patients with time on PD for less than 90 days were excluded (Figure 1). Median (interquartile range) follow-up time was 2.6 years (1.3–4.6) with a total of 32,455 patient years of follow-up. The mean (SD) age at dialysis initiation was 60 (15) years, 5871 patients (61%) were male and 6564 (70%) were Caucasian. The predominant cause of kidney failure was diabetic nephropathy (37%) followed by glomerulonephritis (26%).

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**Table 1. Baseline characteristics of all study group and by peritonitis group**

| Variable                        | All study group | Peritonitis |
|---------------------------------|-----------------|-------------|
|                                | N = 9699        | Yes n = 4353 (45%) | No n = 5346 (55%) |
| Male                            | 5871 (61)       | 2601 (60) | 3270 (61) |
| Age (yr)                        | 60 (15)         | 61 (15)    | 59 (15)   |
| Ethnicity                       |                 |            |           |
| Caucasian                       | 6564 (70)       | 2933 (69) | 3631 (70) |
| Asian                           | 1160 (12)       | 486 (11)  | 674 (13)  |
| Indigenous                      | 1098 (12)       | 585 (14)  | 513 (10)  |
| Other                           | 593 (6)         | 248 (6)   | 345 (7)   |
| Cause of kidney failure         |                 |            |           |
| Diabetic nephropathy            | 3323 (37)       | 1621 (37) | 1702 (32) |
| Renal-vascular                  | 1422 (16)       | 648 (16)  | 774 (16)  |
| Glomerulonephritis              | 2387 (28)       | 978 (24)  | 1409 (28) |
| Cystic                          | 729 (8)         | 287 (7)   | 442 (9)   |
| Other                           | 1228 (14)       | 554 (14)  | 674 (14)  |
| Late referral to nephrologist   | 1102 (12)       | 521 (12)  | 581 (11)  |
| Smoking Status                  |                 |            |           |
| Nonsmoker                       | 4784 (50)       | 2016 (47) | 2768 (52) |
| Ex-smoker                       | 3743 (39)       | 1734 (40) | 2009 (38) |
| Current smoker                  | 1078 (11)       | 573 (13)  | 505 (10)  |
| BMI (Kg/m²)                     | 27.3 (6)        | 27.7 (6)  | 27.0 (6)  |
| BMI Categories                  |                 |            |           |
| Underweight                     | 265 (3)         | 109 (3)   | 156 (3)   |
| Normal                          | 3215 (34)       | 1378 (32) | 1837 (35) |
| Overweight                      | 3447 (38)       | 1618 (35) | 1929 (37) |
| Obese                           | 2675 (28)       | 1318 (31) | 1357 (26) |
| Comorbidities                   |                 |            |           |
| Chronic lung disease            | 1200 (12)       | 587 (14)  | 613 (12)  |
| Coronary artery disease         | 3081 (32)       | 1533 (35) | 1548 (29) |
| Peripheral vascular disease     | 1934 (20)       | 975 (22)  | 959 (18)  |
| Cerebrovascular disease         | 1167 (12)       | 568 (13)  | 599 (11)  |
| Diabetes mellitus               | 4333 (45)       | 2101 (48) | 2232 (42) |
| Cancer                          | 838 (9)         | 401 (9)   | 437 (8)   |
| Geographical location           |                 |            |           |
| Major city                      | 6703 (69)       | 2925 (67) | 3778 (71) |
| Regional                        | 2547 (26)       | 1163 (27) | 1384 (26) |
| Remote                          | 405 (4)         | 251 (6)   | 154 (3)   |
| Socio-economic status           |                 |            |           |
| High                            | 3064 (32)       | 1288 (30) | 1729 (33) |
| Mid                             | 3323 (34)       | 1513 (35) | 1810 (34) |
| Low                             | 3266 (34)       | 1537 (35) | 1776 (33) |
| State/Territory                 |                 |            |           |
| New South Wales                 | 3625 (37)       | 1691 (39) | 1934 (36) |
| Queensland                      | 1897 (20)       | 888 (20)  | 1008 (19) |
| Victoria                        | 2279 (23)       | 906 (20)  | 1373 (25) |
| Australian Capital Territory    | 135 (1)         | 78 (2)    | 56 (1)    |
| South Australia                 | 629 (7)         | 227 (5)   | 402 (8)   |
| Western Australia               | 900 (9)         | 466 (10)  | 454 (9)   |
| Northern Territory              | 115 (1)         | 70 (2)    | 45 (1)    |
| Tasmania                        | 179 (2)         | 77 (1)    | 102 (2)   |

BMI, body mass index.

Data expressed as number (percentage) or mean (SD).
(26%). Death occurred in 3948 patients (41%), kidney transplant in 2896 (30%), and loss of follow-up in 30 (0.3%). Baseline characteristics are summarized in Table 1.

### Peritonitis Episodes

There were no peritonitis episodes in 5346 patients (55%) and at least 1 peritonitis episode among 4353 patients (45%), with a median (interquartile range) time to first peritonitis of 10.8 (4.8–22.8) months. Among patients who had a peritonitis episode, 2190 patients (23%) had only 1 episode of peritonitis whereas 2163 patients (22%) had ≥2 episodes of peritonitis. The total peritonitis count was 8936 infections over 24,270 exposure-years yielding an infection rate of 0.37 peritonitis episodes per patient year.

Compared to patients who did not have a peritonitis episode during the study period, patients with a peritonitis episode were more likely to be diabetic (37% vs. 32%, \( P < 0.001 \)), be a smoker (13% vs. 9%, \( P < 0.001 \)) and had coronary artery disease (35% vs. 29%, \( P < 0.001 \)) and peripheral vascular disease (22% vs. 18%, \( P < 0.001 \)) and cerebrovascular disease (13% vs. 11%, \( P = 0.001 \)) (Table 1).

### Association Between Peritonitis and Cardiovascular Mortality

Of the 3948 patients who died during the study period, 1405 (36%) experienced cardiovascular death, including 616 (44%) with a cardiac arrest, 540 (41%) with myocardial ischemia or infarction, 153 (11%) with cerebrovascular accident, 55 (4%) with cardiac failure and 11 (1%) with aortic aneurysm rupture.

Cardiovascular mortality was more common among patients who experienced peritonitis (751, 17%) than among patients who did not experience peritonitis (654, 12%). The overall cardiovascular mortality rate was 43.3 per 1000 patient years (95% CI 41.1–45.6) (Table 2) with an increase between patients who had a peritonitis episode compared to patients who did not have a peritonitis episode (58.2 vs. 33.5 per 1000 patient years, \( P < 0.001 \)). Using multivariable Cox regression analysis, an episode of peritonitis was associated with a greater risk of a cardiovascular mortality (adjusted hazard ratio 1.31, 95% CI 1.17–1.47, \( P < 0.001 \)). Similar estimates were observed in the competing risk analysis (SHR 1.53, 95% CI 1.39–1.69, \( P < 0.001 \)) (Table 3 and Figure 2). The risk of cardiovascular mortality increased with increasing number of peritonitis episodes in the competing risk analysis (SHR for 1 episode of peritonitis 1.41, 95% CI 1.24–1.61; ≥2 episodes of peritonitis 1.69, 95% CI 1.47–1.93) (Figure 2) but had similar estimates in Cox regression analysis (adjusted hazard ratio for 1 episode of peritonitis 1.31, 95% CI 1.14–1.19; ≥2 episodes of peritonitis 1.31, 95% CI 1.14–1.51).

### Association Between Peritonitis Rate Over Time and Cardiovascular Mortality

During the study period, there was a significant decrease in annual peritonitis rates by 4.7% per year (95% CI 3.6–5.8%, \( P < 0.05 \)). JointPoint analysis showed the change was more substantial during the period from 2003 to 2011 (8.0% per year, 95% CI 4.8–11.1%, \( P < 0.05 \)) than during the period from 2012 to 2019 (2.4% per year, 95% CI 0.0–4.8%, \( P = 0.1 \)) (Figure 3). We therefore defined our eras as 2003 to 2011 and 2012 to 2019. In the competing risk analysis, patients commencing PD in the era 2012 to 2019 had a significantly lower risk of cardiovascular mortality than those who commenced PD in the 2003 to 2011 era (SHR 0.60, 95% CI 0.50–0.72, \( P < 0.001 \)).

### Sensitivity Analysis

In the sensitivity analysis, censoring at 90 days transfer to HD, a mortality occurred with 2489 (26%) of patients, kidney transplantation among 2056 (21%), transfer to HD among 3483 (36%) and loss of follow up in 23 (0.2%). Results of the sensitivity analysis were consistent with our primary analysis (Supplementary Tables S1-S3, Supplementary Figures S1 and S2).

### DISCUSSION

The present longitudinal observational cohort study demonstrated that PD peritonitis was independently associated with an increased risk of cardiovascular mortality and that this increased with increasing number of peritonitis episodes. The risk of cardiovascular mortality was also higher in the earlier era (2003–2011) when peritonitis rates were higher.

In the chronic kidney disease population, the increased risk of cardiovascular event following an infectious episode is well established. Nevertheless, this association is not as well examined in patients with kidney failure. A United States Renal Dara System cohort study of elderly dialysis patients showed a 25% increased risk of cardiovascular event following an infection-related hospitalization, and another US prospective cohort study of incident dialysis patients showed a bacteremia or sepsis resulted in a 78%
increased risk of myocardial infarction. In the PD population, there are a few studies examining the association between infection and cardiovascular risk, with the infection exposure mostly limited to PD peritonitis. These confirm that an episode of PD peritonitis increased the risk of cardiovascular event by
20% to 95%, however they did have limitations. They did not reach statistical significance due to small numbers, were single centre and did not account for a time varying analysis or competing events such as a kidney transplant or noncardiac cause of death. The largest study, the BRAZPD II cohort, was a Brazilian national study which did not include one-third of PD patients in Brazil, thereby potentially introducing ascertainment bias. Nonetheless, our analysis confirmed this association and showed an almost 40% increased risk of cardiovascular mortality following an episode of PD peritonitis. We also accounted for peritonitis rates and cardiovascular mortality over time, which was not previously examined or addressed.

Inflammation has been associated with cardiovascular risk, and chronic inflammation is a feature of patients receiving PD in whom increased levels of inflammatory markers can be associated with an increased risk of mortality. Acute active inflammation during an episode of peritonitis can further add to this load, thereby contributing to the risk of the long-term negative systemic effects. A PD peritonitis episode may further contribute to cardiovascular risk and mortality by inducing local and systemic inflammation. Peritonitis also causes peritoneal membrane structure functional changes through vascular damage, tissue fibrosis, and retention of activated leukocytes in the peritoneal cavity, which can in turn affect the peritoneal solute transport rate. Peritoneal solute transport rate alterations have been linked to worse survival in PD due to less efficient ultrafiltration and excess reabsorption of fluid, which could further increase cardiovascular risk.

Peritonitis remains one of the commonest complications in PD that affects 25% to 50% of patients. In our cohort, the proportion of patients who had at least 1 peritonitis episode was 45%, with 22% having 2 or more episodes. Due to the frequency of PD peritonitis, it is important to examine short-term and long-term adverse events. Examples of short-term adverse events include technique failure (following 30%–45% or PD peritonitis episodes), hospitalization (50%), catheter removal (20%), permanent transfer to HD (20%–30%), and mortality (3%–6%). Due to its important ramifications for patients treated with PD,
the Standardized Outcomes in Nephrology (SONG-PD) initiative identifies PD related peritonitis as a core outcome of critical importance for patients, caregivers, and health care professionals.20

Cardiovascular mortality represents the largest cause of death in the PD population, responsible for 35% to 55% of all-cause mortality.4,10,18 The risk of cardiovascular mortality appears to be higher in the PD population than in the HD population.27 This has been attributed to the higher prevalence of hyperlipidemia in the PD population,28 exposure to dialysate glucose, and overhydration accompanying decline in residual kidney function.29 Nevertheless, the role of peritonitis should also be recognized. Infection rates and infection-related deaths are significantly more frequent in PD patients than in their HD counterparts, with the vast majority driven by peritonitis.30

Though earlier peritonitis rates in Australia did not change,7 they did decline from 2003 to 2011, bringing it in line with the International Society of Peritoneal Dialysis recommendation of <0.5 episodes per patient year.31 This improvement has been attributed to the implementation of a national peritonitis reduction campaign with regular audits, peritonitis prevention trials, updating peritonitis clinical practice guidelines and feedback from kidney care units.12-15 Similar trends in the reduction of peritonitis rates have been observed worldwide.4,36-39

In our study we used one of the largest national registries to specifically examine the association between peritonitis and cardiovascular outcome in incident PD patients, including 9699 patients and 8936 episodes of peritonitis across Australia. To our knowledge, this is the first study that examined peritonitis trends with cardiovascular outcome, showing how reduction in peritonitis rates could be associated with reduced adverse events over time. We used robust statistical analysis methods, including competing risk analysis, to assess the associations. We did not censor at technique failure, as previous studies have done,4,10,15,19 because one-third to two-thirds of PD patients will transfer to HD for ≥30 days,7,8,25 with peritonitis being the leading cause.3,6,7,25 In Australia, 19% of peritonitis episodes results in catheter removal with 18% resulting in transfer to HD for ≥30 days.8 We included this cohort in an intention to treat analysis, because the risk of cardiovascular event following a peritonitis episode will persist even after transferring to HD. Nevertheless, a sensitivity analysis was performed and confirmed the robustness of our findings.

These strengths should be balanced against the limitations, which include the study’s retrospective design and the inability to exclude selection bias with residual confounding. There was also an element of immortal time bias because patients experiencing peritonitis had to survive on PD to the time that they developed peritonitis. Nevertheless, this would have biased results in favor of the null hypothesis. We were only able to consider peritonitis infections and were not able to account for any other type of infection. Similarly for clinical outcomes, we were only able to examine cardiovascular mortality instead of specific cardiovascular event. The reduction in cardiovascular mortality between our 2 eras may not have only been attributable to reduction in peritonitis rates. Other factors, which we were unable to account for, could have influenced this result. We were unable to account for risk factor identification and modification during clinical practice over the different eras, such as increased statin use, blood pressure control, fluid management, and modifiable cardiovascular risk modifications. Due to the limited data collection through ANZDATA we were unable to account for possible differences in laboratory parameters between the 2 eras (such as C-reactive protein or cholesterol levels). In addition, we were unable to include baseline residual urine volume or other laboratory parameters (such as albumin or C-reactive protein). We are unable to audit the data so are unable to exclude the possibility of coding bias. In particular ANZDATA defines peritonitis as per reporting personnel, so we were unable to verify if the definition of peritonitis across the Australian dialysis units is consistent with the International Society of Peritoneal Dialysis guidelines. These results reflect an Australian population that may not be generalizable to other countries. Finally, our analysis included a time-varying analysis in the competing risk model to confirm the consistency of the association using kidney transplantation as a competing risk. Nevertheless, estimated SHR should be interpreted with caution when time-varying analysis is included in the Fine-Gray SHR model since the assumed covariate definition may be misleading.40

In conclusion, our study showed that peritonitis was a significant, independent, and long-term risk factor for cardiovascular mortality in the Australian PD population, with the risk increasing with the number of peritonitis episodes. There was a decline in peritonitis rates over the study period, which could have been a factor in the reduction in the risk of cardiovascular mortality over the 2 eras we examined. These findings reinforce the importance of targeting further reduction in peritonitis rates through continuous quality improvements. Future studies should focus on examining closely the trend between peritonitis rate.
and adverse events, considering other factors which could be influencing such trends.

DISCLOSURE

DJ has received consultancy fees, research grants, speaker’s honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care, consultancy fees from Astra Zeneca, Bayer, and AWAK, speaker’s honoraria from ONO and BI & Lilly, and travel sponsorships from Ono and Amgen. He is a current recipient of an Australian National Health and Medical Research Council Leadership Investigator Grant. All the other authors declare no conflicting interests.

AUTHOR CONTRIBUTIONS

All authors have contributed to this manuscript and approve of this submission. HCH and JC participated in the design and analysis of this study. All authors participated in the interpretation of data and drafting/revising the paper. The results presented in this paper have not been published previously in whole or part, except in abstract form.

ACKNOWLEDGMENTS

The authors thank the entire Australian and New Zealand nephrology community that provides information to and maintain the ANZDATA registry databases. The data reported here have been supplied by the Australian and New Zealand Dialysis and Transplant Registry. The interpretation and reporting of these data are the responsibility of the authors and should not be seen as an official policy or interpretation of the Australian and New Zealand Dialysis and Transplant Registry. The authors received no financial support for the research, authorship, and/or publication of this article.

The results presented in this paper have not been published previously in whole or part, except in abstract form.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Annual peritonitis episode rate, 2003 to 2019 in sensitivity analysis cohort.
Figure S2. Cumulation incidence graph, in sensitivity analysis censoring at 90 days post transfer to hemodialysis, showing time to cardiovascular mortality by (A) no peritonitis and any peritonitis episode and (B) 0, 1 and ≥2 peritonitis episodes, using transplantation and noncardiovascular mortality as a competing risk to calculate cumulative incidence function estimate.
Table S1. Baseline characteristics of all study group and by peritonitis group in the sensitivity analysis.
Table S2. Crude rates and number of cardiovascular mortality in the total cohort and stratified by peritonitis episode in the sensitivity analysis.

Table S3. Cox proportional hazard models and competing risk analysis, with transplant and, noncardiovascular death considered as a competing risk, for cardiovascular mortality risk in sensitivity analysis.

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