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Different Risk of Common Gastrointestinal Disease Between Groups Undergoing Hemodialysis or Peritoneal Dialysis or With Non-End Stage Renal Disease

A Nationwide Population-Based Cohort Study

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Abstract: Peritoneal dialysis (PD) is one type of renal replacement therapy, but potential peritoneal damage and gastrointestinal (GI) tract adverse effects during long-term exposure to bio-incompatible dialysate remain a concern. Although GI disease frequently occurs in dialysis patients, whether the risk of GI diseases differs among PD and hemodialysis (HD) or non-uremic groups is still uncertain.

In this retrospective cohort study, data were obtained from the National Health Insurance Research Database, which includes almost all dialysis patients in Taiwan. Between 2000 and 2009, a total of 1791 PD and 8955 HD incident patients were enrolled and matched for age and sex or for propensity score. In addition, a comparison cohort of 8955 non-uremic patients was also selected. Individuals were monitored for the occurrence of common GI diseases until 2010, and data were analyzed using several different models.

Generally speaking, the results showed that the risk of gastroesophageal reflux, intestinal obstruction or adhesions, and abdominal hernia was significantly higher in the PD group, whereas the risk of peptic ulcer disease and lower GI diverticula and bleeding was significantly greater in the HD group. Meanwhile, the risk of mesenteric ischemia, liver cirrhosis, and acute pancreatitis was higher in dialysis patients, but was not significantly different between the PD and HD groups; moreover, the risk of appendicitis in the PD group appeared to be lower than that in the HD group.

In conclusion, dialysis patients have a higher risk of most common GI diseases, and PD and HD modalities are associated with different GI diseases.

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Abbreviations: Af = atrial fibrillation, CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ESRD = end stage renal disease, GERD = gastroesophageal reflux, GI = gastrointestinal, HR = hazard ratio, HTN = hypertension, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, MSCT = musculoskeletal system and connective tissue, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PD = peritoneal dialysis, PUD = peptic ulcer disease.

INTRODUCTION

Peritoneal dialysis (PD) is used as renal replacement therapy. The main adverse effect of PD is progressive deterioration of the structure and function of the peritoneal membrane.[1,2] These peritoneal membrane changes are mainly due to long-term exposure to conventional bio-incompatible dialysate, which is acidic and contains high concentrations of glucose and its degradation products.[3] Meanwhile, despite gastrointestinal (GI) disease being an important issue in PD patients, whether long-term exposure to bio-incompatible dialysate induces side effects on the GI system is uncertain. Although previous studies have described the relationship between PD and GI disease, these studies had several limitations.[4–23] First, they included a relatively small number of subjects. Second, GI cancer patients were not excluded or adjusted for in the design and analysis in these studies. Third, PD patients usually have different baseline characteristics from hemodialysis (HD) patients, and using only an age- and sex-matched model may introduce bias. Fourth, death may act as a competing risk with

common GI diseases, but these studies did not apply competing risk models. In addition, many studies were cross-sectional or case-control studies and did not report on the actual incidence rate of GI diseases. Furthermore, some studies did not include patients with non-end stage renal disease (ESRD) as a comparison group. The most important limitation was that the results of these studies were controversial. Therefore, we conducted a large-scale, retrospective cohort study using a nationwide database from the Taiwan National Health Insurance Research Database (NHIRD), which enrolls almost all dialysis patients in the country. The aim of this study was to compare the risk of common GI diseases between cohorts undergoing HD or PD or who had non-ESRD.

METHODS

This study was designed as a retrospective cohort study. In this longitudinal observational study, patients who started receiving PD or HD within a defined period (2000–2009) were enrolled as the dialysis study cohort (PD or HD group). Within the same study period, we also enrolled a group of individuals with non-ESRD as a comparison cohort (comparison group). We then monitored the clinical outcomes (in terms of common GI disease) in these groups over time until 2010.

Database

The National Health Insurance (NHI) of Taiwan is a mandatory social health insurance plan that was launched in 1995. Almost 99% of the nation's population of 23 million is enrolled in this program. The NHIRD encrypts the personal identification data from the NHI to extract numerous database sets for research purposes. This database has been used for epidemiological research and information on prescription use, among other purposes. These results have been shown to be of high quality.[24]

Study Sample

This retrospective cohort study consisted of PD, HD, and comparison groups. Diagnosis codes were assigned according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). First, patients with diagnoses of ESRD (catastrophic illness registration cards for ESRD with ICD-9-CM code 585) were included as the dialysis cohort (Figure 1).[25] Patients who had received dialysis for <3 months were excluded. In Taiwan, uremic patients who require long-term dialysis therapy qualify to apply to the NHI for a catastrophic illness card. Patients who have catastrophic illness registration cards for ESRD do not need to pay for their dialysis
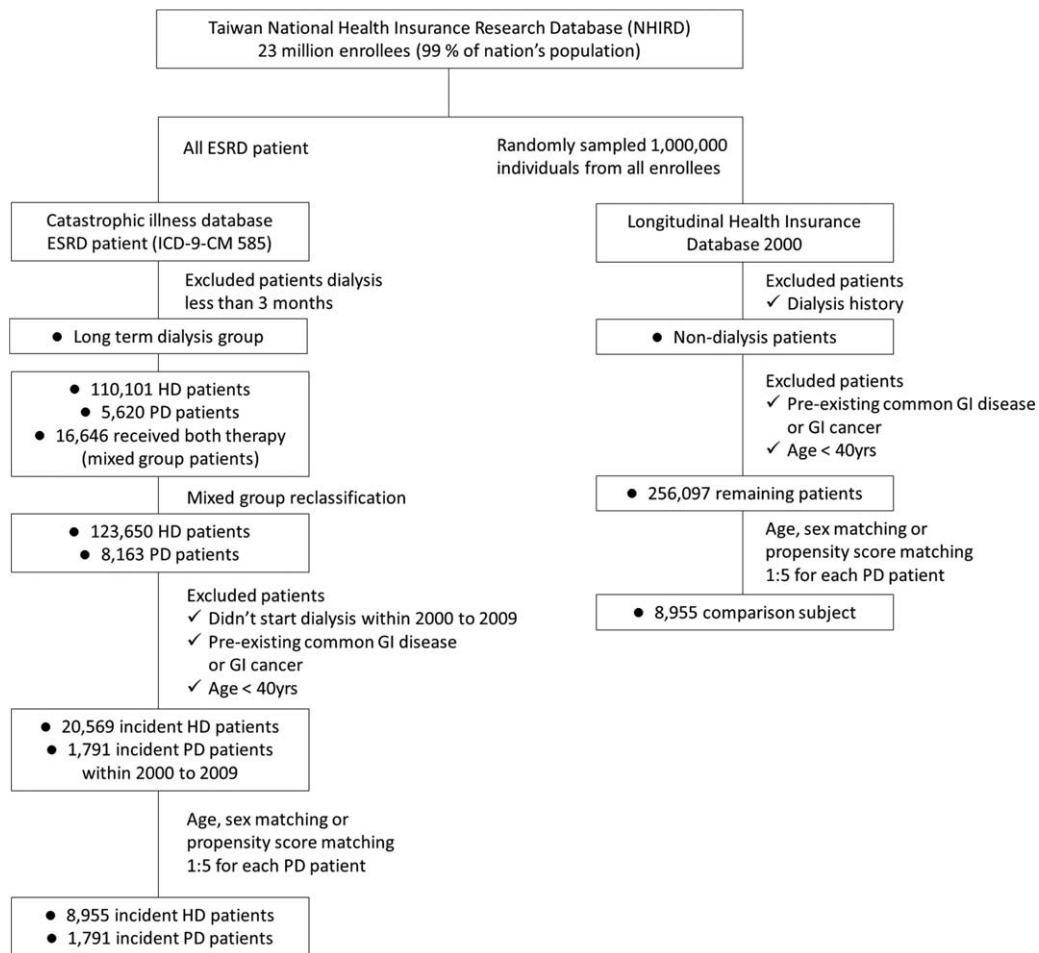

FIGURE 1. Study flow chart. ESRD = end-stage renal disease; GI = gastrointestinal disease; HD = hemodialysis; ICD-9-CM = International Classification of Diseases, 9th Revision Clinical Modification, mixed group = patients ever receive both HD and PD therapy; PD = peritoneal dialysis.

therapy. These patients were then divided into PD and HD groups: patients who had received both dialysis modalities were classified as HD if the HD duration was 3 months longer than the PD duration, and they were classified as PD if the PD duration was 3 months longer than the HD duration. Patients who received HD 1 to 2 months longer than the duration of PD were excluded, and patients who received PD 1 to 2 months longer than the duration of HD were also excluded. In addition, patients who did not start receiving dialysis therapy between January 2000 and December 2009 were excluded. Patients who had a common GI disease or GI cancer history before enrollment were excluded from the study. To focus on high-risk patients, we also excluded those who were younger than 40 years. Finally, PD and HD patients, in the ratio 1:5, were matched according to age and sex or according to propensity score. Individuals were followed up until 2010.

According to a report of the NHI of Taiwan, there were approximately 23 million enrollees (99% of nation's population) in 2000. Of these, 1,000,000 individuals were randomly sampled, and all the original claim data of these 1,000,000 individuals constitute the Longitudinal Health Insurance Database (LHID) 2000. There was no significant difference in age, sex, or healthcare costs between the sample group and all enrollees. LHID 2000 has been used for epidemiological research and information on prescription use, among other purposes. These results have been shown to be of high quality.[26,27] The comparison group was selected from these 1,000,000 individuals in LHID 2000. Of these individuals, those who had ever received dialysis therapy were excluded. Then, to ensure comparability, we also excluded individuals younger than 40 years and those with existing GI disease or a history of GI cancer before enrollment. Finally, the comparison group was randomly selected from the remaining patients at a ratio of 1:5 with PD patients, matched for age and sex or for propensity score. Individuals were followed up until 2010.

Matching

To ensure comparability in terms of sex and age between the groups, we used frequency matching for age (4 categories, 40–49, 50–59, 60–69, and >70 yr) and sex. In addition, because PD and HD patients tend to have different baseline characteristics and clinical comorbidities, we also used propensity score matching (stratification matching with intervals of 0.1) to match the differences in predialysis conditions. Here, the propensity score is defined as the probability of PD as the first dialysis modality, given all covariates. For each patient, an estimated propensity score was calculated using logistic regression to estimate the differences in baseline characteristics and clinical comorbidities between PD patients, HD patients, and the comparison group. The covariates in the propensity score model included age, sex, diabetes mellitus (DM), hyperlipidemia, hypertension (HTN), congestive heart failure (CHF), coronary artery disease (CAD), atrial fibrillation (Af), cerebrovascular disease, asthma, chronic obstructive pulmonary disease (COPD), diseases of the musculoskeletal system and connective tissue (MSCT), chronic hepatitis (including hepatitis B, hepatitis C and alcoholic liver disease), depression, dementia, obesity, alcohol-related illness, and non-GI cancer. The c-statistic for the propensity score models was 0.867.

Potential Confounders

We identified potential confounding risk factors for common GI disease for individuals in all 3 groups. These risk factors included DM, hyperlipidemia, HTN, CHF, CAD, Af, cerebrovascular disease, asthma, COPD, diseases of the MSCT, chronic hepatitis, depression, dementia, obesity, alcohol-related illness, and non-GI cancer.

Main Outcome Measure

The endpoint of the study was the occurrence of any of the following: gastroesophageal reflux (GERD; ICD-9-CM code 530.11 and 530.81),[17] peptic ulcer disease (PUD; 531, 532, and 533),[16] mesenteric ischemia (557),[13] intestinal obstruction or adhesions (560, 568.0, 614.6), appendicitis (540–541),[12] lower GI diverticula or bleeding (562.02, 562.03, 562.1, 569.3, 569.83, 569.85, 569.86, 578.1),[28] liver cirrhosis (571.2, 571.5, 571.6),[29] acute pancreatitis (577.0),[30] or abdominal hernia (550–553).[18]

Statistical Analysis

Baseline descriptive data are presented as the mean ± standard deviation for continuous variables and percentage for categorical variables. The Pearson χ^2 test and one-way ANOVA were used to compare the clinical characteristics and comorbidities among the 3 patient groups. To compare the relative risk of common GI disease in groups with different dialysis modalities, propensity score matching was used to minimize potential selection bias introduced by the different dialysis therapies. Multivariable Cox proportional hazard models were then used to investigate the impact of these 2 dialysis modalities on common GI disease. Competing risk models were also used to adjust for risk of death (R package "cmprsk").[31] All statistical analyses in this study were conducted using SAS 9.3 statistical software (SAS Institute Inc., Cary, NC) and R statistical software, version 3.0.3 (R Foundation for Statistical Computing).

Sensitivity Analyses

To explore the effect of other potential residual confounding factors on our results, we used sensitivity analyses according to the R-package "obsSens".[32] We added another hypothetical unmeasured risk factor. We then investigated how this factor confounded our observations with regard to the different prevalence between the dialysis and comparison groups.

Ethics Statement

The study was approved by the ethics committee/institutional review board of National Cheng Kung University Hospital (IRB number: A-EX-103-026).

RESULTS

In our database, there were a total of 132,367 long-term dialysis patients, including 110,101 HD patients, 5,620 PD patients, and 16,646 patients who had received both PD and HD therapy (mixed group) between January 1, 1997 and December 31, 2010. Finally, we enrolled 8,955 incident HD patients and 1,791 incident PD patients in our study as mentioned previously. Within the same study period, we randomly selected 8,955 nondialysis patients as our comparison group at a ratio of 1:5 for each PD patient matched for age and sex or for propensity score (Figure 1).

Table 1 presents the demographic characteristics and clinical comorbidities for the 3 patient groups in the age- and sex-matched model and the propensity score-matched model. In both models, the dialysis patients all had a higher rate of most comorbidities than the comparison cohort.

TABLE 1. Demographic Characteristics and Comorbidities of Peritoneal Dialysis, Hemodialysis and Nondialysis Comparison Cohorts

Characteristic	Age and Sex Matched				Propensity Score Matched			
	PD (N = 1791)	HD (N = 8955)	Comparison (N = 8955)	*P* Value	PD (N = 1791)	HD (N = 8955)	Comparison (N = 8955)	p-value
Age, yr (%)								
40−49	653 (36.5)	3265 (36.5)	3265 (36.5)	1.000	653 (36.4)	2376 (26.5)	3835 (42.8)	<0.001*
50−59	639 (35.7)	3195 (35.7)	3195 (35.7)		639 (35.7)	2822 (31.5)	2682 (30.0)	
60−69	315 (17.6)	1575 (17.6)	1575 (17.6)		315 (17.6)	2128 (23.8)	1672 (18.6)	
≥70	184 (10.2)	920 (10.2)	920 (10.2)		184 (10.3)	1629 (18.2)	766 (8.6)	
mean ± SD	55.1 ± 10.3	55.5 ± 10.3	55.0 ± 10.6	0.003*	55.1 ± 10.3	58.6 ± 11.3	54.1 ± 10.1	<0.001*
Male, n (%)	862 (48.1)	4310 (48.1)	4310 (48.1)	1.000	862 (48.1)	4673 (52.2)	4156 (46.4)	<0.001*
Comorbidities (%)								
Diabetes mellitus	618 (34.5)	4540 (50.7)	930 (10.4)	<0.001*	618 (34.5)	5038 (56.3)	2436 (27.2)	<0.001*
Hyperlipidemia	555 (31.0)	2523 (28.2)	600 (6.7)	<0.001*	555 (31.0)	3104 (34.7)	2707 (30.2)	<0.001*
Hypertension	1505 (84.0)	7479 (83.5)	2112 (23.6)	<0.001*	1505 (84.0)	7770 (86.8)	7307 (81.6)	<0.001*
Congestive heart failure	104 (5.8)	1019 (11.4)	138 (1.5)	<0.001*	104 (5.8)	1165 (13.0)	323 (3.6)	<0.001*
Coronary artery disease	351 (19.6)	2717 (30.3)	862 (9.6)	<0.001*	351 (19.6)	2820 (31.5)	1452 (16.2)	<0.001*
Atrial fibrillation	45 (2.5)	248 (2.8)	20 (0.2)	<0.001*	45 (2.5)	417 (4.7)	103 (1.2)	<0.001*
Cerebrovascular disease	187 (10.4)	1415 (15.8)	523 (5.8)	<0.001*	187 (10.4)	1501 (16.8)	744 (8.3)	<0.001*
Asthma or COPD	160 (8.9)	1156 (12.9)	753 (8.4)	<0.001*	160 (8.9)	1193 (13.3)	677 (7.6)	<0.001*
Diseases of MSCT	126 (7.0)	720 (8.0)	546 (6.1)	<0.001*	126 (7.0)	754 (8.4)	587 (6.6)	0.001*
Chronic hepatitis	205 (11.5)	1342 (15.0)	865 (9.7)	0.004*	205 (11.5)	1141 (12.7)	1041 (11.6)	0.048*
Depression	36 (2.0)	198 (2.2)	73 (0.8)	<0.001*	36 (2.0)	214 (2.4)	162 (1.8)	0.024*
Dementia	22 (1.2)	102 (1.1)	38 (0.4)	<0.001*	22 (1.2)	193 (2.2)	84 (0.9)	<0.001*
Obesity	2 (0.1)	20 (0.2)	33 (0.4)	0.068	2 (0.1)	11 (0.1)	14 (0.2)	0.795
Alcohol related illness	2 (0.1)	29 (0.3)	13 (0.2)	0.023*	2 (0.1)	20 (0.2)	4 (0.1)	0.004*
Non-GI Cancer	96 (5.4)	637 (7.1)	218 (2.4)	<0.001*	96 (5.4)	693 (7.7)	411 (4.6)	<0.001*

COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; MSCT = musculoskeletal system and connective tissue; SD = standard deviation. *$P < 0.05$.

Table 2 shows that in the age- and sex-matched model, after adjusting for age, sex, and comorbid clinical illnesses, the adjusted hazard ratio (HR) of most GI diseases in dialysis patients was higher than that in the comparison cohort, including GERD, mesenteric ischemia, intestinal obstruction or adhesions, lower GI diverticula and bleeding, liver cirrhosis, acute pancreatitis, and abdominal hernia. However, the risk of PUD was higher in HD patients, but not in PD patients. The same results were observed in the propensity score-matched model.

Further validation analysis using competing risk in the age- and sex-matched model showed that the risk of some GI diseases in both HD and PD patients was higher than that in the comparison cohort, including GERD, intestinal obstruction or adhesions, lower GI diverticula and bleeding, liver cirrhosis, and acute pancreatitis (Table 3). However, the risk of PUD and mesenteric ischemia was only higher in HD patients, and the risk of abdominal hernia was higher only in PD patients. A similar pattern of results was observed in the propensity score-matched model. However, the risk of intestinal obstruction or adhesions was only higher in the PD group, and the risk of liver cirrhosis was only higher in the HD group. Besides, the risk of PUD was not higher in HD group.

Supplemental Table 1, http://links.lww.com/MD/A403 shows the total incidence rates of common GI diseases in the HD group, PD group, and comparison group. Supplemental Table 2, http://links.lww.com/MD/A403 shows the incidence

rates of common GI diseases stratified by age for each group. Supplemental Table 3, http://links.lww.com/MD/A403 shows the number of changes in modality, deaths, and renal transplants in the HD and PD groups.

Figure 2 shows Kaplan–Meier curves illustrating the disease-free survival rate for these common GI diseases in the HD and PD groups in propensity score-matched models.

We also choose 2 diseases, acute pancreatitis and liver cirrhosis, and used sensitivity analysis to investigate the effect of other potential residual confounding factors on the observed results. We choose acute pancreatitis because the results of previous studies remain controversial. We selected liver cirrhosis because PD patients suffer from a higher risk of liver cirrhosis, a novel finding. We investigated the trend estimates for the HR in the dialysis group of these 2 diseases using a multivariable-adjusted Cox regression model with the add-on of a residual confounding factor (Supplemental Figures 1 to 4, http://links.lww.com/MD/A403). In most situations, PD and HD patients had a higher risk of the occurrence of acute pancreatitis and liver cirrhosis relative to the comparison group, even when an unmeasured confounder existed.

Because one of the main purposes of this study was to compare the risk of development of GI diseases between PD and HD patients, we further compared the risk of the above diseases between the HD and PD groups using the HD group as the reference group. Table 4 shows that in the age- and sex-matched

TABLE 2. Age and Sex Matched and Propensity Score Matched Multivariable-Adjusted Cox Regression Model Hazard Ratios of Common Gastrointestinal Disease Among the Hemodialysis, Peritoneal Dialysis and Nondialysis Comparison Cohorts During Follow-Up

Gastrointestinal Disease	Age and Sex Matched			Propensity Score Matched		
	PD (N = 1791)	HD (N = 8955)	Comparison (N = 8955)	PD (N = 1791)	HD (N = 8955)	Comparison (N = 8955)
Total GI event	587 (32.8); 1.53 (1.39, 1.69), <0.001*	3802 (42.5); 1.47 (1.38, 1.56), <0.001*	3402 (38.0); 1	587 (32.8); 1.47 (1.34, 1.60), <0.001*	3748 (41.9); 1.37 (1.30, 1.44), <0.001*	3826 (42.7) 1
Gastroesophageal reflux	61 (3.4); 5.51 (3.92, 7.73), <0.001*	218 (2.4); 1.80 (1.39, 2.32), <0.001*	177 (2.0); 1	61 (3.4); 6.42 (4.69, 8.78), <0.001*	210 (2.4) 2.10 (1.68, 2.62), <0.001*	185 (2.1) 1
Peptic ulcer disease	355 (19.8); 1.06 (0.94, 1.19), 0.352	2882 (32.2); 1.26 (1.18, 1.35), <0.001*	2774 (31.0); 1	355 (19.8); 1.00 (0.89, 1.11), 0.950	2801 (31.3) 1.16 (1.10, 1.23), <0.001*	3211 (35.9) 1
Mesenteric ischemia	10 (0.6); 6.78 (2.93, 15.7), <0.001*	97 (1.1); 7.39 (4.09, 13.4), <0.001*	17 (0.2); 1	10 (0.6); 4.69 (2.18, 10.1), <0.001*	96 (1.1); 4.51 (2.77, 7.34), <0.001*	23 (0.3) 1
Intestinal obstruction or adhesions	57 (3.2); 2.47 (1.80, 3.38), <0.001*	295 (3.3); 1.57 (1.28, 1.93), <0.001*	263 (3.0); 1	57 (3.2); 2.37 (1.76, 3.19), <0.001*	291 (3.3) 1.33 (1.11, 1.59), <0.001*	275 (3.1) 1
Appendicitis	5 (0.3); 0.49 (0.19, 1.24), 0.129	100 (1.1); 1.33 (0.92, 1.92), 0.132	96 (1.1); 1	5 (0.3); 0.44 (0.18, 1.08), 0.074	86 (1.0); 1.12 (0.82, 1.52), 0.495	111 (1.2) 1
Lower GI diverticula and bleeding	143 (8.0); 3.26 (2.66, 4.00), <0.001*	1237 (13.8); 3.64 (3.19, 4.14), <0.001*	479 (5.4); 1	143 (8.0); 3.20 (2.65, 3.87), <0.001*	1274 (14.2) 3.42 (3.07, 3.82), <0.001*	545 (6.1) 1
Liver cirrhosis	42 (2.4); 1.96 (1.38, 2.79), <0.001*	390 (4.4); 2.29 (1.87, 2.80), <0.001*	231 (2.6); 1	42 (2.4); 1.61 (1.16, 2.26), 0.005*	395 (4.4) 1.94 (1.63, 2.31), <0.001*	250 (2.8) 1
Acute pancreatitis	28 (1.6); 4.35 (2.67, 7.140), <0.001*	204 (2.3); 4.11 (2.92, 5.80), <0.001*	62 (0.7); 1	28 (1.6); 3.03 (1.97, 4.65), <0.001*	210 (2.4) 2.92 (2.27, 3.76), <0.001*	110 (1.2) 1
Abdominal hernia	105 (5.9); 5.25 (4.00, 6.89), <0.001*	181 (2.0); 1.32 (1.04, 1.67), 0.023*	257 (2.9); 1	105 (5.9); 6.73 (5.20, 8.70), <0.001*	168 (1.9) 1.40 (1.12, 1.75), 0.004*	200 (2.2) 1

CI = confidence interval; GI = gastrointestinal; HD = hemodialysis; HR = hazard ratio; PD = peritoneal dialysis. Data are presented as number of events (percentage of group with event), adjusted HR (95% CI) and P value; *P < 0.05. Adjustments were made for age, sex, and comorbidities.

model, the risk of GERD (2.53; 95% CI, 1.88–3.41), intestinal obstruction or adhesions (1.56; 95% CI, 1.17–2.1), and abdominal hernia (3.45; 95% CI, 2.69–4.44) was significantly higher in the PD group. In contrast, the risk of PUD (0.8; 95% CI, 0.71–0.89) and appendicitis (0.34; 95% CI, 0.14–0.85) was significantly higher in the HD group. The same results were observed in the propensity score-matched model.

Further validation analysis using competing risk in the age- and sex-matched model showed the risk of GERD (2.29; 95% CI, 1.69–3.1), intestinal obstruction or adhesions (1.47; 95% CI, 1.06–2.02), and abdominal hernia (3.72; 95% CI, 2.89–4.79) was significantly higher in the PD group (Table 5). In contrast, the risk of PUD (0.78; 95% CI, 0.69–0.88), appendicitis (0.28; 95% CI, 0.10–0.75), and lower GI diverticula and bleeding (0.77; 95% CI, 0.63–0.94) was significantly higher in the HD group. The same results were observed in the propensity score-matched model.

Because patients who had received both PD and HD therapy (mixed group) may induce bias, we also use another pure PD and HD model for further analysis (Supplemental Figure 5, http://links.lww.com/MD/A403). In this model, patients who ever change their dialysis modalities were excluded. Supplemental Table 4, http://links.lww.com/MD/A403 presents the demographic characteristics and clinical comorbidities for the 3 patient groups. Supplemental Table 5, http://links.lww.com/MD/A403 showed the adjusted HR of GI disease in both pure HD and PD patients. Supplemental Table 6, http://links.lww.com/MD/A403 showed the adjusted HR of competing-risk model.

Another unmatched cohort model was also performed. We randomly selected 1,791 incident PD patients, 8,955 incident HD patients, and 8,955 nondialysis patients without matching as our study group at a ratio of 1:5:5 (Supplemental Figure 6, http://links.lww.com/MD/A403). Supplemental Table 7, http://links.lww.com/MD/A403 presents the demographic characteristics and clinical comorbidities for the 3 patient groups. Supplemental Table 8, http://links.lww.com/MD/A403 shows the adjusted HR of GI disease in both HD and PD patients after adjusting for age, sex, and comorbid clinical illnesses. Supplemental Table 9, http://links.lww.com/MD/A403 shows the adjusted HR using the competing risk model.

Additionally, we also performed an intent-to-treat analysis model to assess the risk of GI disease between the 3 groups (Supplemental Figure 7, http://links.lww.com/MD/A403). In this model, dialysis patients were classified according to their initial treatment modalities. The results are shown in Supplemental Tables 10–12, http://links.lww.com/MD/A403.

DISCUSSION

We conducted a large-scale, retrospective cohort study using a nationwide database to investigate the risk of common GI diseases between cohorts undergoing HD or PD or who had non-ESRD. Our database enrolled almost all dialysis patients in the country, which indicates that our dialysis sample is almost equal to the country's entire dialysis population. We used several different models to answer this question. Generally speaking, the results showed that the risk of GERD, intestinal obstruction or adhesions, and abdominal hernia was significantly higher in the PD group, whereas the risk of PUD and lower GI diverticula and bleeding was significantly greater in the HD group. Meanwhile, the risk of mesenteric ischemia, liver cirrhosis, and acute pancreatitis was higher in dialysis patients, but was not significantly different between the PD and HD

TABLE 3. Age and Sex Matched and Propensity Score Matched Multivariable-Adjusted Competing-Risk Regression (CRR) Models Hazard Ratios of Common Gastrointestinal Disease Among the Hemodialysis, Peritoneal Dialysis and Nondialysis Comparison Cohorts During Follow-Up

Gastrointestinal Disease	Age and Sex Matched		Propensity Score Matched	
	PD (N = 1791)	HD (N = 8955)	PD (N = 1791)	HD (N = 8955)
Total GI event	1.30 (1.18, 1.44), <0.001[*]	1.26 (1.18, 1.34), <0.001[*]	1.23 (1.12, 1.35), <0.001[*]	1.14 (1.08, 1.20), <0.001[*]
Gastroesophageal reflux	4.20 (3.02, 5.83), <0.001[*]	1.60 (1.24, 2.05), <0.001[*]	4.92 (3.69, 6.57), <0.001[*]	1.84 (1.48, 2.28), <0.001[*]
Peptic ulcer disease	0.91 (0.80, 1.03), 0.140	1.11 (1.03, 1.19), 0.001[*]	0.85 (0.76, 1.01), 0.060	1.00 (0.94, 1.06), 0.900
Mesenteric ischemia	2.95 (0.90, 9.60), 0.073	6.21 (3.11, 12.4), <0.001[*]	2.13 (0.72, 6.29), 0.170	4.37 (2.60, 7.33), <0.001[*]
Intestinal obstruction or adhesions	2.10 (1.48, 2.98), <0.001[*]	1.43 (1.14, 1.79), 0.002[*]	2.02 (1.46, 2.79), <0.001[*]	1.20 (0.98, 1.46), 0.079
Appendicitis	0.37 (0.13, 1.04), 0.059	1.23 (0.83, 1.83), 0.300	0.33 (0.12, 1.01), 0.051	0.94 (0.66, 1.33), 0.720
Lower GI diverticula and bleeding	2.42 (1.92, 3.04), <0.001[*]	3.10 (2.69, 3.57), <0.001[*]	2.36 (1.91, 2.91), <0.001[*]	2.85 (2.54, 3.20), <0.001[*]
Liver cirrhosis	1.58 (1.05, 2.37), 0.029[*]	2.02 (1.60, 2.55), <0.001[*]	1.37 (0.93, 2.02), 0.120	1.79 (1.47, 2.17), <0.001[*]
Acute pancreatitis	4.35 (2.66, 7.12), <0.001[*]	4.11 (2.94, 5.74), <0.001[*]	2.53 (1.62, 3.40), <0.001[*]	2.71 (2.07, 3.54), <0.001[*]
Abdominal hernia	5.20 (4.00, 6.78), <0.001[*]	1.23 (0.97, 1.56), 0.092	6.14 (4.82, 7.83), <0.001[*]	1.18 (0.93, 1.50), 0.170

CI = confidence interval; CRR = fine and gray competing-risk regression; HR = hazard ratio. Data are presented as adjusted competing-risk HR (95% CI) and P value; [*]$P < 0.05$. Adjustments were made for age, sex, and comorbidities.
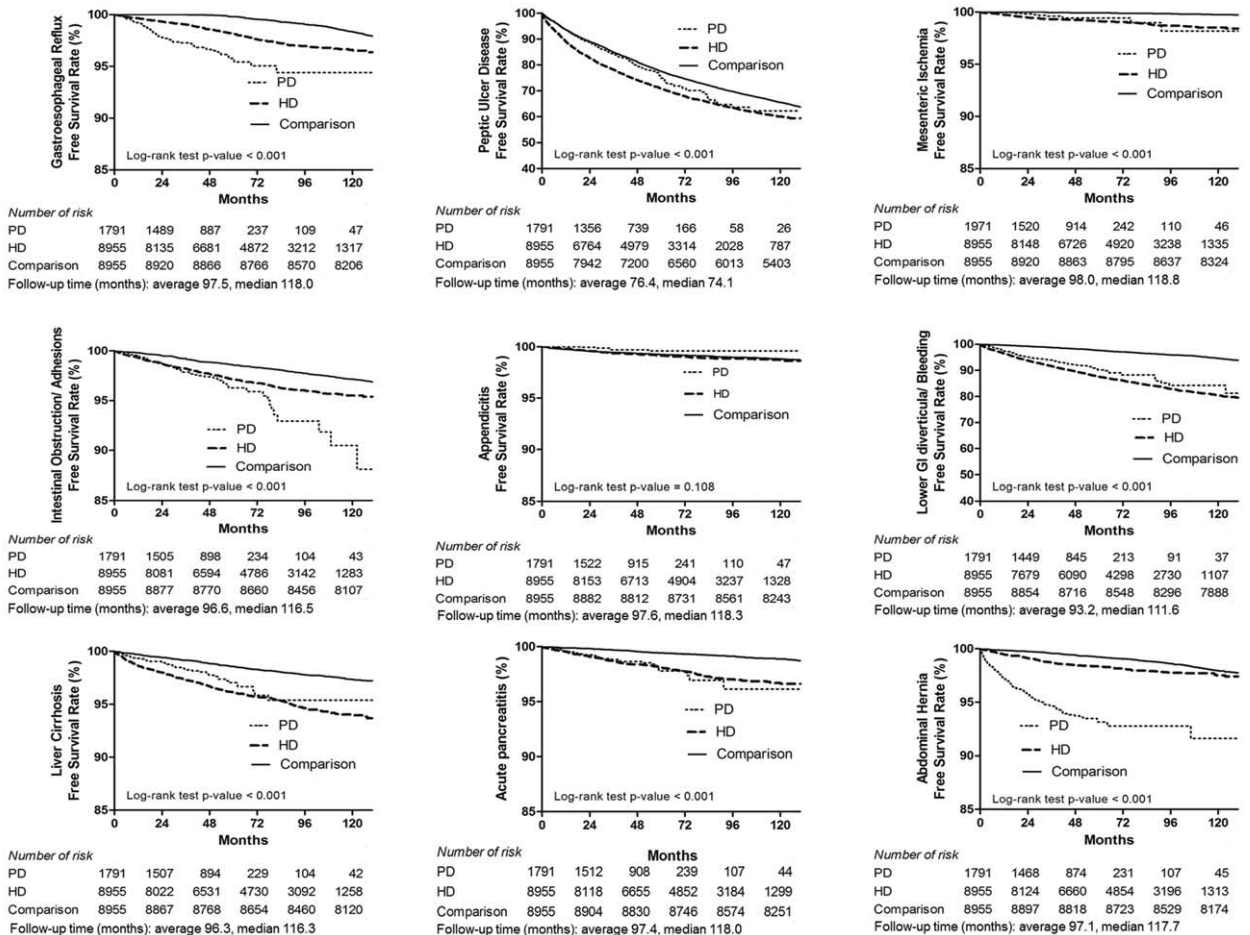

FIGURE 2. Kaplan–Meier curves of common gastrointestinal disease-free survival rate in hemodialysis (HD), peritoneal dialysis (PD), and nondialysis comparison cohorts in propensity score-matched models.

TABLE 4. Age and Sex Matched and Propensity Score Matched Multivariable-Adjusted Cox Regression Model Hazard Ratios of Common Gastrointestinal Disease Among the Hemodialysis and Peritoneal Dialysis Cohorts During Follow-Up

	Age and Sex Matched		Propensity Score Matched	
Gastrointestinal Disease	PD (N = 1791)	HD (N = 8955)	PD (N = 1791)	HD (N = 8955)
Total GI event	1.00 (0.91, 1.09), 0.978	1	1.01 (0.92, 1.10), 0.868	1
Gastroesophageal reflux	2.53 (1.88, 3.41), <0.001[*]	1	2.47 (1.83, 3.33), <0.001[*]	1
Peptic ulcer disease	0.80 (0.71, 0.89), <0.001[*]	1	0.80 (0.72, 0.90), <0.001[*]	1
Mesenteric ischemia	0.88 (0.45, 1.71), 0.701	1	0.98 (0.50, 1.90), 0.981	1
Intestinal obstruction or adhesions	1.56 (1.17, 2.10), 0.003[*]	1	1.62 (1.21, 2.17), 0.001[*]	1
Appendicitis	0.34 (0.14, 0.85), 0.020[*]	1	0.36 (0.14, 0.89), 0.027[*]	1
Lower GI diverticula and bleeding	0.87 (0.73, 1.04), 0.127	1	0.88 (0.73, 1.05), 0.143	1
Liver cirrhosis	0.85 (0.61, 1.17), 0.318	1	0.80 (0.58, 1.10), 0.120	1
Acute pancreatitis	0.96 (0.64, 1.44), 0.853	1	0.91 (0.60, 1.36), 0.633	1
Abdominal hernia	3.45 (2.69, 4.44), <0.001[*]	1	3.79 (2.93, 4.90), <0.001[*]	1

CI = confidence interval; GI = gastrointestinal; HD = hemodialysis; HR = hazard ratio; PD = peritoneal dialysis. Data are presented as adjusted HR (95% CI) and *P* value; [*]*P* < 0.05. Adjustments were made for age, sex, and comorbidities.

groups; moreover, the risk of appendicitis in the PD group appeared to be lower than that in the HD group. In summary, our results showed that dialysis patients had a higher risk of most GI diseases and that different dialysis modalities are associated with different GI diseases.

Previous studies have investigated the association between GI disease and PD therapy.[4–18] However, there were several limitations in these studies. First, the prevalence of some GI diseases was low, but most studies included only a small number of subjects. Besides, the follow-up time in most was relatively short and only enrolled a local population. Second, most of these studies did not exclude GI cancer patients in their initial study design or adjust for it in their analysis. As is known, GI cancer may induce many GI symptoms as well as GI disease, which may affect the findings of the study. Third, PD patients usually had different baseline characteristics and comorbidities than HD patients, which might have induced selection bias if only age and sex matching were used in the analysis.

Notwithstanding, among these previous studies, none used a propensity score match to correct for this bias. Fourth, death may act as a competing risk for common GI diseases, but these studies did not use a competing risk model to adjust for the risk of death. In addition, many of these studies were not cohort studies, and a cause-and-effect type of relationship between the dialysis modality and GI diseases could not be determined. Furthermore, some cohort studies did not exclude non-incident dialysis patients, and the actual incidence rate of GI diseases in these studies is unknown. Moreover, some studies also lacked non-ESRD patients as a comparison group.

Some of the findings of previous studies differ from our results. For example, in contrast to some of the previous studies, our results showed that the incidence of acute pancreatitis was not significantly different in the PD and HD groups. In addition to some of the aforementioned limitations of these studies, there are some other possible explanations for this. First, different ethnic groups may have a different GI response to PD dialysate.

TABLE 5. Age and Sex Matched and Propensity Score Matched Multivariable-Adjusted Competing-Risk Regression (CRR) Models Hazard Ratios of Common Gastrointestinal Disease Among the Hemodialysis and Peritoneal Dialysis Cohorts During Follow-Up

	Age and Sex Matched		Propensity Score Matched	
Gastrointestinal Disease	PD (N = 1791)	HD (N = 8955)	PD (N = 1791)	HD (N = 8955)
Total GI event	0.99 (0.90, 1.09), 0.810	1	1.00 (0.91, 1.10), 0.960	1
Gastroesophageal reflux	2.29 (1.69, 3.10), <0.001[*]	1	2.25 (1.65, 3.06), <0.001[*]	1
Peptic ulcer disease	0.78 (0.69, 0.88), <0.001[*]	1	0.78 (0.70, 0.88), <0.001[*]	1
Mesenteric ischemia	0.48 (0.17, 1.33), 0.160	1	0.47 (0.17, 1.32), 0.150	1
Intestinal obstruction or adhesions	1.47 (1.06, 2.02), 0.019[*]	1	1.52 (1.10, 2.09), 0.011[*]	1
Appendicitis	0.28 (0.10, 0.75), 0.012[*]	1	0.31 (0.11, 0.85), 0.022[*]	1
Lower GI diverticula and bleeding	0.77 (0.63, 0.94), 0.011[*]	1	0.78 (0.64, 0.96), 0.019[*]	1
Liver cirrhosis	0.78 (0.54, 1.14), 0.200	1	0.74 (0.50, 1.09), 0.120	1
Acute pancreatitis	0.91 (0.59, 1.41), 0.680	1	0.81 (0.52, 1.27), 0.360	1
Abdominal hernia	3.72 (2.89, 4.79), <0.001[*]	1	4.13 (3.20, 5.34), <0.001[*]	1

CI = confidence interval; CRR = fine and gray competing-risk regression; HR = hazard ratio. Data are presented as adjusted competing-risk HR (95% CI) and *P* value; [*]*P* < 0.05. Adjustments were made for age, sex, and comorbidities.

Our study was conducted in an Asian population, whereas the patients in the previous studies primarily included European or North American populations. Second, the studies were conducted over different time periods, and dialysis techniques have changed significantly in recent years. For example, the decreased PD peritonitis rate, the improved penetration rates of newer, more biocompatible dialysates, and more popular use of automatic PD all reflect recent remarkable advances. Third, to focus on high risk patients, we enrolled only patients ≥40 years old, whereas the other studies also enrolled younger patients.

The proposed mechanism by which PD increases risk of GERD and abdominal hernia may be due to an increase in intraabdominal pressure, and the higher risk of intestinal obstruction or adhesions in PD may be because of peritoneal membrane fibrosis and damage due to long-term bio-incompatible dialysate exposure. The higher risk of PUD and lower GI bleeding with HD may be due to frequent anticoagulation use, and the higher risk of lower GI diverticula may be due to hemodynamic instability-induced bowel ischemia during HD therapy.

Because several factors may influence the outcome of the study, there are some potential limitations. First, the diagnoses of common GI diseases and other comorbid medical conditions relied on administrative claims data, which could have been misclassified. However, previous epidemiological database studies have demonstrated that the quality of the NHIRD data is acceptable. Second, certain personal information such as medication history, body mass index (BMI), alcoholism, and smoking status was not available in our database, and these factors may be important determinants in the occurrence of some GI diseases. For example, some studies have shown that anticoagulant use is a risk factor for PUD and lower GI bleeding and is a protective factor for mesenteric ischemia, which, if unmeasured, may bias the results if it differs among the 3 groups. To resolve the problem, we adjusted for DM, CAD, cerebrovascular disease, and Af in the multivariable analysis, not only because these diseases are risk factors for some GI diseases, but also because they are highly associated with anticoagulant use. In addition, we also adjusted for diseases of the MSCT, not only because these diseases are risk factors for some GI diseases, but also because they are highly associated with nonsteroidal anti-inflammatory drug or steroid use, which is highly associated with PUD. Moreover, we also used the obesity code (278.0) in the analysis instead of BMI, and the alcohol-related illness code (571.2, 571.3) instead of alcoholism. In addition, to investigate the effect of other potential residual confounders on the observed result, we also used sensitivity analyses. In these analyses, we added another hypothetical unmeasured confounding risk factor. We then investigated how adding this risk factor confounded our observations of a different prevalence between different groups (Supplemental Figures 1 to 4, http://links.lww.com/MD/A403). Third, in our study design, patients who had received both dialysis modalities were reclassified according to their main modalities. But mixed group reclassification may induce bias. To resolve the problem, we also performed another pure PD, pure HD model. In this model, we exclude dialysis patients who have ever changed their dialysis modalities. One of different results in this model is that the risk of liver cirrhosis in the PD group was not significantly higher than the comparison group. Finally, in our study, we excluded patients younger than 40 years, so the variation in the risk for common GI disease risks based on dialysis modalities in children and young adult groups could not be determined.

In conclusion, our study found that dialysis patients had a higher risk of GERD, PUD, mesenteric ischemia, intestinal obstruction or adhesions, lower GI diverticula and bleeding, liver cirrhosis, acute pancreatitis, and abdominal hernia. Moreover, different dialysis modalities affected the clinical outcomes. We suggest that patients undergoing dialysis should receive regular assessments regarding GI events and that an increased awareness and a higher suspicion for GERD, intestinal obstruction or adhesions, and abdominal hernia should be maintained for PD patients, and that this increased vigilance concerning PUD and lower GI diverticula and bleeding should be maintained for HD patients.

Practical Points

Since the risk of most common GI diseases is higher in dialysis patients and different dialysis modalities are associated with different GI diseases, patients undergoing dialysis should receive a regular GI assessment. In addition, more attention should be paid to specific types of GI disease, depending on the dialysis modality.

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