





Citation: Lu Y-A, Tu K-H, Lee C-C, Wu PW, Chang C-J, Tian Y-C, et al. (2017) Prognostic impact of peritonitis in hemodialysis patients: A national-wide longitudinal study in Taiwan. PLoS ONE 12(3): e0173710. https://doi.org/10.1371/journal.pone.0173710

Editor: Tatsuo Shimosawa, The University of

Tokyo, JAPAN

Received: August 14, 2016

Accepted: February 24, 2017

Published: March 16, 2017

Copyright: © 2017 Lu et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: Data are available from the NHRID Institutional Data Access / Ethics Committee for researchers who meet the criteria for access to confidential data. https://nhird.nhri.org.tw/en/Data_Protection.html. Only citizens of the Republic of China who fulfill the requirements of conducting research projects are eligible to apply for the National Health Insurance Research Database (NHIRD). The use of NHIRD is limited to research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Law (http://www.winklerpartners.com/?p=987)

RESEARCH ARTICLE

Prognostic impact of peritonitis in hemodialysis patients: A national-wide longitudinal study in Taiwan

Yueh-An Lu 1,2 , Kun-Hua Tu 1,2,3 , Cheng-Chia Lee 1,2,3 , Patricia W. Wu 4 , Chee-Jen Chang 5,6,7,8 , Ya-Chung Tian 1,2 , Chih-Wei Yang 1,2,3 , Pao-Hsien Chu 8,9,10 *

- 1 Kidney Research Center, Department of Nephrology, Linkou Chang Gung Memorial Hospital, Taipei, Taiwan, 2 Department of Medicine, Chang Gung University, Taoyuan, Taiwan, 3 Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan, 4 Department of Radiology, Chang Gung Memorial Hospital, Linkou, Taiwan, 5 Graduate Institute of Clinical Medicine, Chang Gung University, Tao-Yuan, Taiwan, 6 Research Services Center for Health Information, Chang Gung University, Tao-Yuan, Taiwan, 7 Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Tao-Yuan, Taiwan, 8 Department of Cardiology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan, 9 Healthcare Center, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan, 10 Heart Failure Center, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan
- These authors contributed equally to this work.
- * taipei.chu@gmail.com

Abstract

Background

Peritonitis has been independently associated with increased morbidity and mortality in peritoneal dialysis patients. However, there are few reports on peritonitis in hemodialysis patients. We aim at investigating both the risk profiles and prognostic impact of peritonitis in hemodialysis patients.

Methods

This nation-wide longitudinal study uses claims data obtained from the Taiwan National Health Insurance Research Database. A total of 80,733 incident hemodialysis patients of age \geq 20 years without a history of peritonitis were identified between January 1, 1998 and December 31, 2009. Predictors of peritonitis events were estimated using Cox proportional hazard models. Time-dependent Cox proportional hazard models were used to estimate hazard ratio for mortality attributed to peritonitis exposure.

Results

Of 80,733 incident hemodialysis patients over a 13-year study period, peritonitis was diagnosed in 935 (1.16%), yielding an incidence rate of 2.91 per 1000 person-years. Female gender, liver cirrhosis and polycystic kidney disease were three of the most significant factors for peritonitis in both non-diabetic and diabetic hemodialysis patients. The cumulative survival rate of patients with peritonitis was 38.8% at 1 year and 10.1% at 5 years. A time-dependent Cox multivariate analysis showed that peritonitis had significantly increased



and related regulations of National Health Insurance Administration and NHRI (National Health Research Institutes), and an agreement must be signed by the applicant and his/her supervisor upon application submission. All applications are reviewed for approval of data release.

Funding: This work was supported by the Research Grant of Linkou Chang-Gung Memorial Hospital, grant number CMRPG3F2691, CMRPG3B1352 and CORPG3F581. The authors wish to acknowledge the Biostatistical Center for Clinical Research, Chang Gung Memorial Hospital (Grant CLRPG3D0042) and Research Services Center For Health Information, Chang Gung University (Grant CIRPD1D0031) for statistical consultation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

hazard ratio for all cause mortality. Additionally, the risk of mortality remained significantly higher for non-diabetic hemodialysis patients that experienced peritonitis.

Conclusions

The risk of peritonitis in hemodialysis patients is higher in female gender, liver cirrhosis and polycystic kidney disease. Although peritonitis is a rare condition, it is associated with significantly poorer outcome in hemodialysis patients.

Introduction

The rapidly expanding global population of dialysis patients represents an important public health challenge not only in Taiwan, but all around the world [1–4]. At the end of 2013, there were over 70,000 patients living with end-stage renal disease (ESRD) and treated with either hemodialysis (HD) or peritoneal dialysis (PD) in Taiwan [5]. Recent published data from the international comparisons of the United States Renal Data System (USRDS) also revealed that Taiwan continues to report the highest prevalence (3,138 per million population) of treated ESRD [2]. Notably, individuals with ESRD have an increased risk of mortality and hospitalization [6]. Following cardiovascular disease, infections are the second most likely cause of hospitalization and mortality in dialysis patients [2, 6]. It has been established that disturbances in both innate and adaptive immune systems significantly contribute to this susceptibility [7–9]. The leading causes of infection-related hospitalization in HD patient were infection of central venous catheters, blood stream infection and pulmonary infection. In addition, peritonitis and other intra-abdominal infections cause 6.7~12.2% of infection events in HD patients [10, 11].

Peritonitis is caused by bacterial invasion of the peritoneal cavity. Patients often present with abdominal pain, ascites formation, systemic inflammation response syndrome (SIRS) and even multi-organ failure. Primary peritonitis is usually caused by bacterial translocation from the gut in patients with massive ascites. Secondary peritonitis is often related to hollow organ perforation, acute cholecystitis, mesenteric ischemia, and pyonephrosis [12]. Peritonitis is a well-known direct cause of mortality in PD patients, reported in around 1-6% in different studies [13, 14]. In addition, many studies have also explored the impact of peritonitis on the clinical outcome of PD patients [13, 15, 16]. It has been reported that peritonitis is a "contributing factor" to death in around 15% of deaths on PD [16], and that peritonitis rate is a significant predictor for mortality in non-diabetic patients and patients over the age of 60 [13]. However, few reports in the literature focus on peritonitis in HD patients. We hypothesized that, like PD patients, incident peritonitis is a significant factor for poor prognosis in HD patients. Because of the low incidence of peritonitis in HD cohorts, we analyzed datasets from the Taiwan National Health Insurance Research Database (NHIRD). The aim of this longitudinal cohort study is to investigate the risk profiles that determine the development of peritonitis in HD patients, and to investigate the prognostic impact of peritonitis in HD patients.

Materials and methods

Data source

This national-wide longitudinal cohort study was conducted by analyzing data from the Taiwan NHIRD. The National Health Insurance program of Taiwan has provided compulsory universal health insurance in Taiwan since 1995 and covered more than 99.6% of citizens and



over 90% of hospitals. Therefore, NHIRD contains detailed healthcare data and offers researchers encrypted datasets including each patient's gender, date of birth, date and dosage of prescriptions, procedure charge codes, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes and outcome. This study was approved by the institutional review board of Chang Gung Memorial Hospital (approval number: 102-4175B), and the need for individual consent was waived because all personal information was de-identified in the encrypted datasets before being released to the public for medical research.

Patient selection

A flow chart of the enrollment process of this study cohort is shown in Fig 1. Using data from NHIRD, we identified 91,508 patients who had newly diagnosed ESRD and undergone regular dialysis (either PD or HD) for at least 90 days in the outpatient department between January 1, 1998 and December 31, 2009. The index date was defined as the date 90 days after dialysis initiation. We excluded patients that were younger than 20 years old (N = 465) or had incomplete sex-age data at the date of dialysis initiation (N = 56). Patients with a history of peritonitis or retroperitoneal infections before dialysis initiation (N = 1,332) were also excluded. Some HD patients may have received PD initially and later switched to HD because of technique failure. Because predictors identified from this population might related to PD instead of HD, 2,197 patients who switched from PD to HD and 579 patients who switched from HD to PD were excluded to avoid confounding a potential impact of one modality to another. The remaining 86,879 patients were then assigned to either HD group or PD group, according to their modality on day 90. We finally analyzed a study population of 80,733 incident HD patients without any history of peritonitis.

Definition of peritonitis, comorbid variables, and outcome

The demographic results of age and sex were recorded from NHIRD at the date of dialysis initiation. Peritonitis was defined by ICD-9-CM diagnostic code 567.x in at least one outpatient

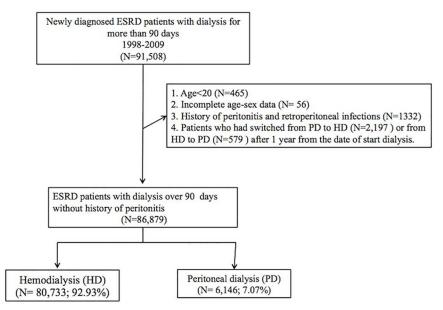


Fig 1. Flow diagram of patient enrollment.

https://doi.org/10.1371/journal.pone.0173710.g001



visit or discharge medical record. Diabetic mellitus (DM), hypertension (HTN), and hyperlipidemia were defined by ICD-9-CM diagnostic codes 401–405, 250, and 272 in patients who used medication for more than 90 days per year. Myocardial infraction (MI) and stroke were defined as disease diagnosed on previous hospitalization using diagnostic codes 410–414 and 431–434, 436. Other comorbidities were defined as diagnostic codes in admission or at least 3 ambulatory outpatient visits for heart failure (ICD-9-CM 428), atrial fibrillation (ICD-9-CM 427.31), liver cirrhosis (ICD-9-CM 571.5), connective tissue disease (ICD-9-CM 710, 714, 728), malignancy (ICD-9-CM 140–208) and polycystic kidney disease (ICD-9-CM 573.12). All patients were followed from the initiation of dialysis to the primary end point, namely, the diagnosis of peritonitis, death, or until December 31, 2010.

Statistical analysis

The demographic results were summarized using descriptive statistics. Continuous data were expressed as the mean \pm standard deviation (SD) and categorical data were expressed as numbers or percentages (%) of each item. The Cox proportional hazards model was used to estimate the risk of peritonitis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox proportional hazards models. We stratified patients to diabetic and non-diabetic groups when evaluating risk factors of peritonitis since they had different clinical characteristics and outcomes after entering ESRD. We further used Cox proportional hazards model to identify factors determining patient mortality. Because peritonitis may develop during the follow-up period, we treated peritonitis exposure as a time-dependent covariate for survival analysis. Patient survival curves and survival probabilities in patients with or without peritonitis exposure were generated according to the Kaplan–Meier method. Differences in the survival curves between two groups were evaluated using the log rank test. A P value of < 0.05 was considered statistically significant. This study used statistical analysis software (SAS, version 9.4) for data analysis.

Results

Incidence of peritonitis

Over a 13-year study period, a total of 80,733 incident HD patients without a history of peritonitis were enrolled. Table 1 lists the features of the study population. The mean age of patients was 61.9 ± 13.6 years; 50.5% of patients were female, and 41.2% of patients had prevalent DM.

Table 1. Baseline characteristics of the study cohort (N = 80,733).

	Patient number	Percentage
Sex _Female	40,748	(50.5%)
Hypertension	47,481	(58.8%)
Diabetes mellitus	33,241	(41.2%)
Hyperlipidemia	16,080	(19.9%)
Myocardial infraction	21,093	(26.1%)
Stroke	10,506	(13.0%)
Heart failure	23,675	(29.3%)
Atrial fibrillation	3,328	(4.1%)
Liver cirrhosis	4,347	(5.4%)
Connective tissue disease	7,669	(9.5%)
Malignancy	8,650	(10.7%)
Polycystic kidney disease	1,130	(1.4%)

https://doi.org/10.1371/journal.pone.0173710.t001



Table 2. Predictors of peritonitis in incident HD patient by using cox proportional hazard model (simple regression).

Group	All			Non-DM			DM		
	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value
Age	1.01	1.01-1.02	< .0001	1.02	1.01-1.02	< .0001	1.01	1.00-1.02	0.067
Female gender	1.24	1.09-1.41	0.001	1.18	1.02-1.37	0.031	1.37	1.06–1.77	0.015
Hypertension	0.91	0.80-1.04	0.164	0.97	0.83-1.15	0.741	1.10	0.79-1.53	0.583
Diabetes mellitus	0.78	0.67-0.91	0.001						
Hyperlipidemia	0.94	0.78–1.14	0.536	1.02	0.74-1.41	0.907	1.10	0.85-1.43	0.470
Myocardial infraction	1.11	0.95-1.30	0.197	1.23	1.00-1.51	0.050	1.13	0.87-1.46	0.379
Stroke	1.04	0.84-1.31	0.703	1.14	0.83-1.57	0.409	1.10	0.80-1.52	0.563
Heart failure	1.16	1.00-1.35	0.056	1.28	1.06-1.55	0.012	1.16	0.90-1.50	0.261
Atrial fibrillation	1.56	1.12-2.16	0.009	1.59	1.06-2.39	0.026	1.57	0.90-2.74	0.116
Liver cirrhosis	3.17	2.5-3.90	< .0001	3.36	2.63-4.31	< .0001	3.00	2.07-4.33	< .0001
Connective tissue disease	1.44	1.16–1.78	0.001	1.45	1.12-1.89	0.005	1.49	1.02-2.16	0.038
Malignancy	1.71	1.41-2.08	< .0001	1.76	1.40-2.20	< .0001	1.56	1.06-2.30	0.025
Polycystic kidney disease	1.73	1.15–2.62	0.009	1.50	0.96-2.35	0.073	3.94	1.26-12.31	0.018

https://doi.org/10.1371/journal.pone.0173710.t002

Nine hundred thirty-five (1.16%) patients experienced event of peritonitis during a cumulative follow-up period of 320,926 patient-years, with an incidence rate of approximately 2.91 per 1000 person-years. The median (interquartile range) time from the initiation of dialysis to event of peritonitis was 3.2 (1.5–5.8) years.

Risk factors of peritonitis

Table 2 and Table 3 summarized the univariate and multivariate Cox regression analysis for risk factors of peritonitis, respectively. On univariate analysis, age, female sex, liver cirrhosis, connective tissue disease, malignancy and PKD were associated with an increased risk for peritonitis among all HD patients. DM was associated with a decreased risk for peritonitis among all HD patients. These associations remained significant on multivariate analysis. HTN was

Table 3. Predictors of peritonitis in incident HD patient by using cox proportional hazard model (multiple regression).

Group	All			Non-DM			DM		
	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value
Age	1.01	1.01-1.02	< .0001	1.01	1.01-1.02	< .0001	1.01	0.99-1.02	0.325
Female gender	1.25	1.09-1.42	0.001	1.21	1.04-1.41	0.016	1.38	1.06–1.79	0.016
Hypertension	0.86	0.74-1.00	0.048	0.82	0.69-0.98	0.031	1.01	0.72-1.43	0.941
Diabetes mellitus	0.75	0.63-0.89	0.001						
Hyperlipidemia	1.09	0.88-1.33	0.435	1.04	0.74-1.44	0.839	1.10	0.85-1.44	0.465
Myocardial infraction	1.04	0.88-1.24	0.634	1.05	0.84-1.31	0.687	1.04	0.79-1.38	0.771
Stroke	1.06	0.84-1.33	0.649	1.05	0.76-1.45	0.772	1.06	0.77-1.48	0.713
Heart failure	1.11	0.94-1.30	0.235	1.13	0.92-1.38	0.243	1.06	0.81-1.40	0.666
Atrial fibrillation	1.32	0.94-1.86	0.105	1.29	0.85-1.97	0.233	1.40	0.79-2.48	0.248
Liver cirrhosis	3.16	2.56-3.89	< .0001	3.21	2.50-4.12	< .0001	3.08	2.12-4.49	< .0001
Connective tissue disease	1.40	1.13–1.73	0.002	1.42	1.09-1.84	0.010	1.39	0.95-2.02	0.087
Malignancy	1.46	1.19–1.77	<0.001	1.50	1.19–1.89	0.001	1.34	0.90-1.99	0.149
Polycystic kidney disease	1.73	1.14-2.63	0.010	1.60	1.02-2.50	0.040	4.06	1.30–12.72	0.016

Multiple Regression: adjusted the variables listed in <u>Table 1</u>.

https://doi.org/10.1371/journal.pone.0173710.t003



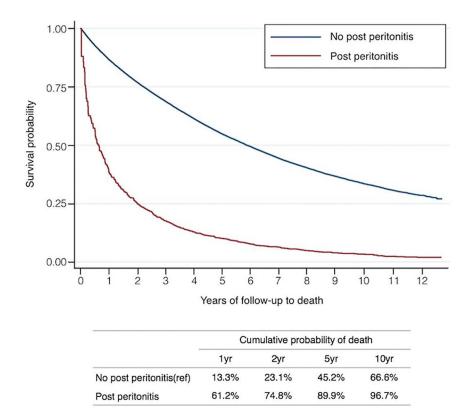


Fig 2. Kaplan-Meier survival curves for HD patients according to having peritonitis or not.

https://doi.org/10.1371/journal.pone.0173710.g002

associated with a decreased risk with borderline significance for peritonitis only on multivariate analysis of all HD patients.

Since the proportion of diabetic patients has increased over time (around 10% in 1998 to 30% in 2009) and they had different clinical characteristics, we stratified patients by the presence or absence of DM and analyzed separately for risk profiles that determine the development of peritonitis. In non-diabetic HD patients, the multivariate analysis demonstrated that factors independently associated with increased HR for event of peritonitis were as follows: age (adjusted HR per year = 1.01, 95% CI = 1.74–2.68, P<0.001), female sex (adjusted HR = 1.21 95% CI = 1.04–1.41, P = 0.016), liver cirrhosis (adjusted HR = 3.21, 95% CI = 2.50–4.12, P<0.001), connective tissue disease (adjusted HR = 1.42, 95% CI = 1.09–1.84, P = 0.01), malignancy (adjusted HR = 1.50, 95% CI = 1.19–1.89, P = 0.001) and PKD (adjusted HR = 1.60, 95% CI = 1.02–2.50, P = 0.04). However, HTN (adjusted HR = 0.82, 95% CI = 0.69–0.98, P<0.031) was associated with a decreased risk of peritonitis in non-diabetic HD patients. In diabetic HD patients, multivariable analysis revealed that female sex (adjusted HR = 1.38, 95% CI = 1.06–1.79, P<0.016), liver cirrhosis (adjusted HR = 3.08, 95% = CI 2.12–4.49, P<0.001), and PKD (adjusted HR = 4.06, 95% CI = 1.30–12.72, P = 0.016) were associated with higher risk of peritonitis.

Prognostic impact of peritonitis

Fig 2 shows the Kaplan-Meier survival curves for HD patients according to peritonitis status. The cumulative survival rate of HD patients who experienced peritonitis was 38.8% at 1 year, 25.2% at 2 years, and 10.1% at 5 years. In comparison, the cumulative survival rate of HD



Table 4. Factors that influence mortality in incident HD patient by using time-dependent covariate for peritonitis exposure (Multiple regression).

Group	AII			Non-DM			DM		
	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value
No post peritonitis(ref)	1			1			1		
Post peritonitis	2.86	2.63-3.12	<0.001	3.09	2.80-3.42	<0.001	2.37	2.00-2.81	<0.001
Age	1.04	1.04-1.04	<0.001	1.04	1.04-1.04	<0.001	1.03	1.03-1.03	<0.001
Sex_Male	1.16	1.14–1.19	<0.001	1.23	1.20–1.27	<0.001	1.02	0.99-1.06	0.134
Hypertension	0.80	0.78-0.82	<0.001	0.78	0.76-0.80	<0.001	0.81	0.78-0.85	<0.001
Diabetes mellitus	1.48	1.44-1.51	<0.001	-	-		-	-	
Hyperlipidemia	0.86	0.84-0.89	<0.001	0.82	0.77-0.87	<0.001	0.86	0.83-0.89	<0.001
Myocardial infraction	1.25	1.22-1.28	<0.001	1.29	1.25-1.34	<0.001	1.20	1.16–1.24	<0.001
Stroke	1.50	1.46–1.55	<0.001	1.71	1.64–1.78	<0.001	1.38	1.33-1.43	<0.001
Heart failure	1.32	1.29-1.35	<0.001	1.37	1.33–1.42	<0.001	1.24	1.20-1.28	<0.001
Atrial fibrillation	1.22	1.17–1.28	<0.001	1.36	1.28–1.44	<0.001	1.19	1.11–1.27	<0.001
Liver cirrhosis	1.74	1.68–1.81	<0.001	1.92	1.82–2.02	<0.001	1.56	1.47–1.65	<0.001
Connective tissue disease	1.06	1.02-1.10	0.001	1.09	1.04–1.15	0.001	1.04	0.99-1.10	0.116
Malignancy	1.38	1.34–1.42	<0.001	1.47	1.41–1.53	<0.001	1.27	1.21-1.34	<0.001
Polycystic kidney disease	0.92	0.83-1.01	0.076	0.91	0.82-1.00	0.061	0.99	0.75-1.29	0.928

Multiple Regression: adjusted the variables listed in Table 1.

https://doi.org/10.1371/journal.pone.0173710.t004

patients who did not experience peritonitis was 86.7% at 1 year, 76.9% at 2 years, and 54.8% at 5 years. There was a significant difference in survival between the patient groups (log rank, P<0.001). In the multivariate Cox proportional hazard model using time-dependent covariate for peritonitis exposure, the adjusted HRs (95% CI) for mortality was 2.86 (2.63–3.12) (Table 4). We also compared the HRs for mortality between patients in the presence or absence of preexisting DM. Peritonitis exposure was still associated with higher risk of mortality in non-diabetic HD patients (adjusted HR = 3.09, 95% CI = 2.80–3.42, P<0.001) and the magnitude of increased HR was even higher than that in diabetic HD patients (adjusted HR = 2.37, 95% CI = 2.00–2.81, P<0.001). Additionally, age, myocardial infarction, stroke, heart failure, atrial fibrillation, liver cirrhosis and malignancy were all significantly related to an increased mortality risk. Hypertension and hyperlipidemia, by contrast, were associated with survival advantage.

Discussion

Our results showed that the incidence of peritonitis was low in HD patients, occurring in only 1.16% of HD patients over 13-year study period. Female gender, liver cirrhosis and PKD are significant risk factors for developing peritonitis in both non-diabetic and diabetic HD patients. Importantly, our data supported our hypotheses that, like PD patients, peritonitis was associated with a significantly increased risk of subsequent mortality in HD patients.

Liver cirrhosis was one of the most significant risk factors for peritonitis in this study (adjusted HR = 3.21, 95% CI = 2.50–4.12 in non-DM group; adjusted HR = 3.08, 95% CI = 2.12–4.49 in DM group). In both groups, cirrhotic HD patients had more than 3 times increased risk for peritonitis compared with non-cirrhotic HD patients. In our study, there were 4,347 (5.4%) patients with liver cirrhosis at the initiation of dialysis. The prevalence is much higher than that reported in western countries, where the estimate is only $1\sim2\%$ in different studies [17, 18]. This finding is not surprising, because Taiwan is a hyperendemic area of hepatitis B and C virus infections [19]. Patients with advanced stage liver cirrhosis tend to



develop spontaneous bacterial peritonitis because of increased bacterial translocation from the gut and impaired immune systems [20]. Therefore, it is conceivable that dialysis patients with advanced liver cirrhosis should also be potentially susceptible to this complication. However, there is a striking paucity of reports about this association in HD patients. An alternative explanation is that liver cirrhosis is also characterized by disturbances in both innate and adaptive immune systems [21–23], which make them more vulnerable to certain infections. To our knowledge, this is the first study to report that cirrhotic HD patients have a greater risk of peritonitis than non-cirrhotic HD patients. Intriguingly, two small studies demonstrated that the incidence of peritonitis was similar or slightly higher in cirrhotic PD patients [24, 25]. Hypotheses in this area need to be tested in further study.

Female gender was another significant risk factor of developing peritonitis. This finding was consistent with some previous studies in the PD population [16, 26]. Perez et al analyzed 693 episodes of peritonitis in PD patients and demonstrated that the risk of experiencing at least one episode of severe peritonitis was 2 times higher among women (RR = 2.03, 95% CI = 1.29-3.16, P = 0.002) [16]. We are not sure of the mechanism for this phenomenon, but it is possible that the female genitourinary tract may be a potential source of yeast and other microorganisms, leading to higher risk of peritonitis.

Another significant risk factor for peritonitis was PKD (adjusted HR = 1.60, 95% CI = 1.02–2.50 in non-DM group; adjusted HR = 4.06, 95% CI = 1.30–12.72 in DM group). Indeed, patients with PKD face an increased risk of renal cyst infection [27]. It was estimated that 30–50% of patients with ADPKD experience renal cyst infections at least once during their lifetime, and age, female gender and recent instrumentation of the urinary tract pose a higher risk [28, 29]. Although the clinical outcome of renal cyst infection is generally good, there are some reports of intraperitoneal rupture of infected renal or liver cysts causing severe peritonitis [30, 31].

In our study, we observe a conflicting result that DM is associated with a decreased risk of peritonitis in HD patients. Part of this unexpected observation may be explained by the fact that diabetic patients may have died over the first few years of dialysis because of cardiovascular event, possibly too early to manifest peritonitis. Indeed, the median timefrom initiation of dialysis to death was shorter in diabetic HD patients than non-diabetic HD patients (2.5 vs 4.0 years). Another possibility is that some diabetic HD patients might have deteriorated to severe sepsis or death before a definite diagnosis of peritonitis, thereby potentially misclassification to severe sepsis without definite focus and leading to underestimate this rare event. Further studies are warranted to better investigate this unexpected association.

In our study, age, myocardial infarction, stroke, heart failure, atrial fibrillation, liver cirrhosis and malignancy were all significantly related to the increase of mortality risk in HD patients. Although these factors are well-established risk factors for mortality as proven in previous literature [32–34], we reported the novel finding that peritonitis had strong prognostic impact of mortality on patients receiving HD (adjusted HR = 2.86, 95% CI = 2.63–3.12, p<0.001). The 1-year-survival after peritonitis was only 38.8%. In contrast, although peritonitis was more common in PD patient, the 1-year-survival after peritonitis could be 70–90% [15, 35]. Notably, among general population, cirrhosis patients who suffered from spontaneous bacterial peritonitis also have increased risk of short- and long-term mortality [36–38]. The survival rates at 1 year following an episode of peritonitis are reported to be 30–40% [38, 39], which is approximate to our current report on HD patients. This increased mortality in cirrhotic patients has been largely attributed to multiple interrelated complications, such as gastrointestinal bleeding, bacteremia, or hepatorenal syndrome. Because only 11% of our peritonitis patients had liver cirrhosis, we assume that multiple insults cause high mortality in HD patient after incident peritonitis. First, peritonitis patients have more comorbidities such as



cirrhosis, connective tissue disease, or malignancy. Higher mortality might be related principally to these underlying diseases. Second, peritonitis in HD patients may present with more aggressive forms of peritonitis, which might be more accompanied by septic shock or multiorgan failure. Third, since peritonitis is rare in HD group, incident peritonitis probably suggests impaired immunity or performance status. Further work is needed to explore these possibilities and investigate effective interventions to avoid such events.

There were several limitations of our study. First, the study method was a longitudinal observational study. We could only state the association but not the causality of peritonitis and mortality, and the results might be confounded by diseases that were not calculated in the statistical analysis. Second, we used diagnostic codes to define peritonitis, but there was no detailed description of the cause of peritonitis. We were unable to evaluate etiologic microorganism, the severity, treatment and direct sequela of peritonitis events. Although primary and secondary peritonitis had different pathophysiology, they might both indicate poor outcome. Furthermore, the primary objective of this study was to offer a preliminary assessment of risk for HD patients and to heighten awareness among clinicians about the significance of peritonitis as a cause of poor outcome. Third, the comorbid variables were based on ICD-9-CM diagnostic codes and prescription. We might neglect patients on diet control or those who refused medications. Some information including patient performance status, dialysis prescription and clearance, fasting plasma glucose, glycated hemoglobin, ambulatory blood pressure, or medication compliance were not available. Therefore, our data may reflect inadequate adjustments for these known risk factors.

Conclusion

Although peritonitis is a rare condition in HD patients, it is associated with poor outcome. Female gender, liver cirrhosis and PKD were three of the most significant factors associated with peritonitis in our study. Additional studies are needed to explore the pathogenesis of each risk factor in HD patients and to investigate effective intervention to prevent this unwanted complication.

Acknowledgments

This work was supported by the Research Grant of Linkou Chang-Gung Memorial Hospital, grant number CMRPG3F2691, CMRPG3B1352 and CORPG3F581. The authors wish to acknowledge the Biostatistical Center for Clinical Research, Chang Gung Memorial Hospital (Grant CLRPG3D0042) and Research Services Center For Health Information, Chang Gung University (Grant CIRPD1D0031) for statistical consultation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Conceptualization: P-HC C-CL.

Data curation: Y-AL K-HT C-CL.

Formal analysis: C-CL P-HC C-JC.

Funding acquisition: P-HC C-JC.

Investigation: P-HC C-CL.

Methodology: Y-AL K-HT PWW Y-CT.

Project administration: P-HC.



Resources: Y-AL Y-CT C-WY.

Software: Y-AL PWW.

Supervision: P-HC.

Validation: Y-CT C-WY P-HC.

Visualization: P-HC.

Writing - original draft: Y-AL K-HT C-CL.

Writing – review & editing: P-HC C-WY Y-CT.

References

- Thomas B, Wulf S, Bikbov B, Perico N, Cortinovis M, Courville de Vaccaro K, et al. Maintenance Dialysis throughout the World in Years 1990 and 2010. J Am Soc Nephrol. 2015; 26(11):2621–33. PubMed Central PMCID: PMCPMC4625679. https://doi.org/10.1681/ASN.2014101017 PMID: 26209712
- Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US Renal Data System 2015
 Annual Data Report: Epidemiology of Kidney Disease in the United States. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2016; 67(3 Suppl 1):Svii, S1-305.
- Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. Lancet. 2008; 371(9631):2173–82. https://doi.org/10.1016/S0140-6736(08)60952-6 PMID: 18586172
- Chiu YL, Chien KL, Lin SL, Chen YM, Tsai TJ, Wu KD. Outcomes of stage 3–5 chronic kidney disease before end-stage renal disease at a single center in Taiwan. Nephron Clin Pract. 2008; 109(3):c109–18. https://doi.org/10.1159/000145453 PMID: 18663322
- 5. 2015 Annual Report on Kidney Disease in Taiwan2016.
- de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA. 2009; 302(16):1782–9. https://doi. org/10.1001/jama.2009.1488 PMID: 19861670
- Eleftheriadis T, Antoniadi G, Liakopoulos V, Kartsios C, Stefanidis I. Disturbances of acquired immunity in hemodialysis patients. Seminars in dialysis. 2007; 20(5):440–51. https://doi.org/10.1111/j.1525-139X.2007.00283.x PMID: 17897251
- Litjens NH, Huisman M, van den Dorpel M, Betjes MG. Impaired immune responses and antigen-specific memory CD4+ T cells in hemodialysis patients. J Am Soc Nephrol. 2008; 19(8):1483–90. PubMed Central PMCID: PMCPMC2488264. https://doi.org/10.1681/ASN.2007090971 PMID: 18480314
- Kim HW, Woo YS, Yang HN, Choi HM, Jo SK, Cho WY, et al. Primed monocytes: putative culprits of chronic low-grade inflammation and impaired innate immune responses in patients on hemodialysis. Clin Exp Nephrol. 2011; 15(2):258–63. https://doi.org/10.1007/s10157-010-0379-8 PMID: 21152946
- Dalrymple LS, Mu Y, Romano PS, Nguyen DV, Chertow GM, Delgado C, et al. Outcomes of infectionrelated hospitalization in Medicare beneficiaries receiving in-center hemodialysis. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2015; 65(5):754–62. PubMed Central PMCID: PMCPMC4414702.
- Abou Dagher G, Harmouche E, Jabbour E, Bachir R, Zebian D, Bou Chebl R. Sepsis in hemodialysis patients. BMC Emerg Med. 2015; 15:30. PubMed Central PMCID: PMCPMC4606908. https://doi.org/ 10.1186/s12873-015-0057-y PMID: 26467100
- Doklestic SK, Bajec DD, Djukic RV, Bumbasirevic V, Detanac AD, Detanac SD, et al. Secondary peritonitis—evaluation of 204 cases and literature review. J Med Life. 2014; 7(2):132–8. PubMed Central PMCID: PMCPMC4197493. PMID: 25408716
- 13. Fried LF, Bernardini J, Johnston JR, Piraino B. Peritonitis influences mortality in peritoneal dialysis patients. Journal of the American Society of Nephrology: JASN. 1996; 7(10):2176–82. PMID: 8915978
- van Esch S, Krediet RT, Struijk DG. 32 years' experience of peritoneal dialysis-related peritonitis in a university hospital. Perit Dial Int. 2014; 34(2):162–70. PubMed Central PMCID: PMCPMC3968101. https://doi.org/10.3747/pdi.2013.00275 PMID: 24584620
- Munoz de Bustillo E, Borras F, Gomez-Roldan C, Perez-Contreras FJ, Olivares J, Garcia R, et al. Impact of peritonitis on long-term survival of peritoneal dialysis patients. Nefrologia. 2011; 31(6):723–32. https://doi.org/10.3265/Nefrologia.pre2011.Oct.10987 PMID: 22130289



- 16. Perez Fontan M, Rodriguez-Carmona A, Garcia-Naveiro R, Rosales M, Villaverde P, Valdes F. Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis. 2005; 25(3):274–84.
- van Manen JG, Korevaar JC, Dekker FW, Boeschoten EW, Bossuyt PM, Krediet RT, et al. How to adjust for comorbidity in survival studies in ESRD patients: a comparison of different indices. Am J Kidney Dis. 2002; 40(1):82–9. https://doi.org/10.1053/ajkd.2002.33916 PMID: 12087565
- Heaf JG, Lokkegaard H, Madsen M. Initial survival advantage of peritoneal dialysis relative to haemodialysis. Nephrol Dial Transplant. 2002; 17(1):112–7. PMID: 11773473
- Chen CH, Yang PM, Huang GT, Lee HS, Sung JL, Sheu JC. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. J Formos Med Assoc. 2007; 106(2):148–55. https://doi.org/10.1016/S0929-6646(09)60231-X PMID: 17339159
- Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol. 2014; 60(1):197–209. https://doi.org/10.1016/j.jhep.2013.07.044 PMID: 23993913
- Schirren CA, Jung MC, Zachoval R, Diepolder H, Hoffmann R, Riethmuller G, et al. Analysis of T cell activation pathways in patients with liver cirrhosis, impaired delayed hypersensitivity and other T cell-dependent functions. Clin Exp Immunol. 1997; 108(1):144–50. PubMed Central PMCID: PMCPMC1904621. https://doi.org/10.1046/j.1365-2249.1997.d01-985.x PMID: 9097923
- Ono Y, Watanabe T, Matsumoto K, Ito T, Kunii O, Goldstein E. Opsonophagocytic dysfunction in patients with liver cirrhosis and low responses to tumor necrosis factor-alpha and lipopolysaccharide in patients' blood. J Infect Chemother. 2004; 10(4):200–7. https://doi.org/10.1007/s10156-004-0321-7 PMID: 15365859
- Taylor NJ, Manakkat Vijay GK, Abeles RD, Auzinger G, Bernal W, Ma Y, et al. The severity of circulating neutrophil dysfunction in patients with cirrhosis is associated with 90-day and 1-year mortality. Aliment Pharmacol Ther. 2014; 40(6):705–15. https://doi.org/10.1111/apt.12886 PMID: 25060167
- 24. Selgas R, Bajo MA, Del Peso G, Sanchez-Villanueva R, Gonzalez E, Romero S, et al. Peritoneal dialysis in the comprehensive management of end-stage renal disease patients with liver cirrhosis and ascites: practical aspects and review of the literature. Perit Dial Int. 2008; 28(2):118–22. PMID: 18332443
- De Vecchi AF, Colucci P, Salerno F, Scalamogna A, Ponticelli C. Outcome of peritoneal dialysis in cirrhotic patients with chronic renal failure. Am J Kidney Dis. 2002; 40(1):161–8. https://doi.org/10.1053/ajkd.2002.33925 PMID: 12087574
- Nessim SJ, Bargman JM, Austin PC, Nisenbaum R, Jassal SV. Predictors of peritonitis in patients on peritoneal dialysis: results of a large, prospective Canadian database. Clin J Am Soc Nephrol. 2009; 4 (7):1195–200. PubMed Central PMCID: PMCPMC2709510. https://doi.org/10.2215/CJN.00910209 PMID: 19406969
- 27. Lantinga MA, Casteleijn NF, Geudens A, de Sevaux RG, van Assen S, Leliveld AM, et al. Management of renal cyst infection in patients with autosomal dominant polycystic kidney disease: a systematic review. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2016.
- 28. Sklar AH, Caruana RJ, Lammers JE, Strauser GD. Renal infections in autosomal dominant polycystic kidney disease. American journal of kidney diseases: the official journal of the National Kidney Foundation. 1987; 10(2):81–8.
- Suwabe T, Araoka H, Ubara Y, Kikuchi K, Hazue R, Mise K, et al. Cyst infection in autosomal dominant polycystic kidney disease: causative microorganisms and susceptibility to lipid-soluble antibiotics. Eur J Clin Microbiol Infect Dis. 2015; 34(7):1369–79. https://doi.org/10.1007/s10096-015-2361-6 PMID: 25851811
- Hammami M, Guirat A, Ksibi H, Azzaza M, Rekik N, Beyrouti MI. Intraperitoneal rupture of renal cyst in autosomal dominant polycystic kidney disease. N Am J Med Sci. 2010; 2(5):238–40. PubMed Central PMCID: PMCPMC3347651. PMID: 22574296
- Zahir M, Al Muttairi H, Upadhyay SP, Mallick PN. Rupture in polycystic kidney disease presented as generalized peritonitis with severe sepsis: a rare case report. Case Rep Urol. 2013; 2013:927676. PubMed Central PMCID: PMCPMC3600282. https://doi.org/10.1155/2013/927676 PMID: 23533936
- Bradbury BD, Fissell RB, Albert JM, Anthony MS, Critchlow CW, Pisoni RL, et al. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Clin J Am Soc Nephrol. 2007; 2(1):89–99. https://doi.org/10.2215/CJN.01170905 PMID: 17699392
- Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and metaanalysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. Nephrol Dial Transplant. 2012; 27(10):3816–22. https://doi.org/10.1093/ndt/qfs416 PMID: 23114904



- **34.** Kotwal S, Webster AC, Cass A, Gallagher M. Comorbidity recording and predictive power of comorbidities in the Australia and New Zealand dialysis and transplant registry compared to administrative data: 2000–2010. Nephrology (Carlton). 2015.
- Klaric D, Knotek M. Long-term effects of peritonitis on peritoneal dialysis outcomes. International urology and nephrology. 2013; 45(2):519–25. https://doi.org/10.1007/s11255-012-0257-2 PMID: 22893493
- Gunjaca I, Francetic I. Prevalence and clinical outcome of spontaneous bacterial peritonitis in hospitalized patients with liver cirrhosis: a prospective observational study in central part of Croatia. Acta Clin Croat. 2010; 49(1):11–8. PMID: 20635579
- Kraja B, Sina M, Mone I, Pupuleku F, Babameto A, Prifti S, et al. Predictive Value of the Model of End-Stage Liver Disease in Cirrhotic Patients with and without Spontaneous Bacterial Peritonitis. Gastroenterol Res Pract. 2012; 2012:539059. PubMed Central PMCID: PMCPMC3296141. https://doi.org/10.1155/2012/539059 PMID: 22474442
- Ra G, Tsien C, Renner EL, Wong FS. The Negative Prognostic Impact of a First Ever Episode of Spontaneous Bacterial Peritonitis in Cirrhosis and Ascites. J Clin Gastroenterol. 2015; 49(10):858–65. https://doi.org/10.1097/MCG.000000000000011 PMID: 25811112
- 39. Tsung PC, Ryu SH, Cha IH, Cho HW, Kim JN, Kim YS, et al. Predictive factors that influence the survival rates in liver cirrhosis patients with spontaneous bacterial peritonitis. Clin Mol Hepatol. 2013; 19 (2):131–9. PubMed Central PMCID: PMCPMC3701845. https://doi.org/10.3350/cmh.2013.19.2.131 PMID: 23837137