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LOWER EDUCATION LEVEL IS A MAJOR RISK FACTOR FOR PERITONITIS INCIDENCE IN CHRONIC PERITONEAL DIALYSIS PATIENTS: A RETROSPECTIVE COHORT STUDY WITH 12-YEAR FOLLOW-UP

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♦ ***Background:*** **Peritoneal dialysis (PD)–related peritonitis remains an important complication in PD patients, potentially causing technique failure and influencing patient outcome. To date, no comprehensive study in the Taiwanese PD population has used a time-dependent statistical method to analyze the factors associated with PD-related peritonitis.**

♦ ***Methods:*** **Our single-center retrospective cohort study, conducted in southern Taiwan between February 1999 and July 2010, used time-dependent statistical methods to analyze the factors associated with PD-related peritonitis.**

♦ ***Results:*** **The study recruited 404 PD patients for analysis, 150 of whom experienced at least 1 episode of peritonitis during the follow-up period. The incidence rate of peritonitis was highest during the first 6 months after PD start. A comparison of patients in the two groups (peritonitis vs null-peritonitis) by univariate analysis showed that the peritonitis group included fewer men ($p = 0.048$) and more patients of older age (≥65 years, $p = 0.049$). In addition, patients who had never received compulsory education showed a statistically higher incidence of PD-related peritonitis in the univariate analysis ($p = 0.04$). A proportional hazards model identified education level (less than elementary school vs any higher education level) as having an independent association with PD-related peritonitis [hazard ratio (HR): 1.45; 95% confidence interval (CI): 1.01 to 2.06; $p = 0.045$). Comorbidities measured using the Charlson comorbidity index (score >2 vs ≤2) showed borderline statistical significance (HR: 1.44; 95% CI: 1.00 to 2.13; $p = 0.053$).**

♦ ***Conclusions:*** **A lower education level is a major risk factor for PD-related peritonitis independent of age, sex, hypoalbuminemia, and comorbidities. Our study emphasizes that a comprehensive PD education program is crucial for PD patients with a lower education level.**

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KEY WORDS: Comorbidities; education level; peritonitis.

Peritonitis is one of the major complications of peritoneal dialysis (PD), and it is associated with increased morbidity and mortality in the PD patient population (1–7). Repeated peritonitis episodes may result in irreversible damage to the peritoneal membrane, which is associated with discontinuation of PD and a permanent switch to hemodialysis.

In various studies, conflicting results have been reported with respect to the factors associated with PD-related peritonitis. Previous studies have reported associations between PD-related peritonitis and hypoalbuminemia, diabetes mellitus, catheter connection technique, advanced age, obesity, reduced residual renal function, lower education level, long distance from the dialysis center, comorbidities, not receiving vitamin D supplementation, modality of PD, aboriginal ethnicity, race, staphylococcal nasal carrier positivity, components of PD solutions, not wearing a face mask, colon diverticulosis, the experience of nurses in general medicine, and the type of caregiver (8–25). However, most of those studies did not use time-dependent methods and came to diverse conclusions. In PD patients, the peritonitis potential should be calculated as a time-to-event function and not simply determined as the number of peritonitis cases divided by the total number of patients.

In general, a crude calculation according to the event itself may contribute to bias. That bias is a result of the varying follow-up periods for the PD patients, with longer follow-up periods clearly resulting in higher peritonitis incidences. A person-time peritonitis rate is therefore more accurate in terms of cross-population comparisons. The aim of the present study was therefore to use time-dependent statistical methods to retrospectively analyze

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factors related to the peritonitis incidence in chronic PD patients at a single PD center in southern Taiwan.

METHODS

PATIENT POPULATION AND CLINICAL BASELINE DATA COLLECTION

Adult end-stage renal disease patients who consulted the PD unit of a medical center in southern Taiwan between February 1999 and July 2010 were enrolled in our retrospective study. To satisfy the study protocol, all patients had to have completed at least 3 consecutive months of PD therapy, meaning that 404 clinically stable patients (171 men, 233 women) were finally eligible for the study. Among the recruited patients, 93 used continuous ambulatory PD, and 311 used automated PD. The mean age of patients was 46.9 ± 15.3 years. All patients were dialyzed using commercially available dialysate [Dianeal: Baxter, Singapore (pH 5.2)] containing 40 mmol/L lactate. A standard peritoneal equilibration test was performed within the first 3 months after PD initiation.

The characteristics of all patients, including demographic and biochemical data, PD adequacy indices (renal and peritoneal Kt/V urea, residual urine volume), and indices of nutrition (serum albumin, normalized protein catabolic rate) were collected for statistical analysis within 3 months of the start of PD therapy.

All patients started to receive their PD training upon deciding to choose PD as their renal replacement therapy. Each patient's socio-economic status, education level, family support, physical capacity, knowledge of his or her underlying renal disease, dietary preferences, and main caregiver were assessed at the start of PD training. Experienced PD nurses trained patients one-to-one. A 24-hour supportive counseling system was provided through mobile phone communication between the patient and his or her designated nurse.

The PD nurses taught their assigned patients and helpers sound knowledge about performance of the PD technique and lifestyle modifications for end-stage renal disease and other underlying illness. The patients were trained using models and illustrations of PD connectology, aseptic management, and dialysate bag exchange techniques, which were also demonstrated by the PD nurses and performed by the patients, with careful examination by the PD nurses, until the patients could perform the techniques at home independently. The PD performance skills were examined regularly whenever the patient attended an outpatient visit. The training program and material underwent no significant changes during the study period, and patients were followed and assessed in a sustained and consistent fashion.

Comorbidity data were collected for all patients at the start of dialysis, and comorbidities were scored using the Charlson comorbidity index (CCI) at the start of PD (26). Recorded peritonitis episodes met at least 2 of the following 3 criteria from the 2005 International Society for Peritoneal Dialysis guideline recommendations (27):

- Symptoms of peritoneal inflammation such as abdominal pain
- An effluent white blood cell count exceeding 100/mL after a dwell time of at least 2 hours, with at least 50% polymorphonuclear neutrophilic cells
- Presence of organisms on Gram stain or subsequent culturing of PD fluid

The protocol for the present study was approved by the Committee on Human Research at Kaohsiung Chang Gung Memorial Hospital (CMRPG880091) and was conducted in accordance with the Declaration of Helsinki.

STATISTICAL ANALYSIS

The chi-square test was used to compare variable distributions in PD patients and in patients with PD-related peritonitis. Time-to-event analysis involves estimating the probability that an event will occur at various points in time. The endpoint for follow-up in patients who developed peritonitis was the first date of peritonitis detection, and patients lost to follow-up were coded by the date of their last visit as censored observations. The most common time-to-event statistical methods are the Kaplan–Meier method and the Cox proportional hazards model. Kaplan–Meier estimates were computed to determine the probability of peritonitis-free survival. Cox proportional hazards models were applied to analyze the effect of single and multiple covariates in predicting development of a first peritonitis. All statistical analyses were performed using the SPSS software application (version 14.0: SPSS, Chicago, IL, USA).

RESULTS

DEMOGRAPHIC AND BASELINE CLINICAL DATA

The study population comprised 404 adult PD patients (mean age: 47.1 ± 14.8 years; range: 18 – 81 years; 42.3% men) who were followed for a mean of 37.9 ± 27.3 months (range: 5 – 127 months) and for a total of 15 317 patient–months. In the present study, chronic glomerulonephritis was the most common cause of end-stage renal disease (64.6%); diabetes accounted for 17.8% of the cases.

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During the follow-up period, 288 episodes of PD-related peritonitis were documented in 150 patients. The average time to development of a first PD-related peritonitis after PD start was 18.1 ± 14.9 months. Among the patients who experienced at least 1 peritonitis episode, 80 experienced 1 episode, 33 experienced 2 episodes, 21 experienced 3 episodes, and 16 experienced at least 4 episodes. The overall peritonitis rate was 0.226 per year at risk. Figure 1 and Table 1 show the cumulative incidence rate. The highest incidence of PD-related peritonitis (13.1%) was observed within the first 6 months after PD start.

ANALYSIS OF FACTORS RELATED TO PERITONITIS

Patients were categorized into a null-peritonitis (patients who never developed peritonitis, n = 254) and a peritonitis group (n = 150). Table 2 presents the differences between the groups. Male sex and younger age (<65 years) were marginally more common in the null-peritonitis group than in the peritonitis group (Table 2). The incidences of a lower education level (below elementary school) and the patient receiving care from a foreign caregiver were significantly higher in the peritonitis group than in the null-peritonitis group. However, the patients who received care from foreign and native caregivers were relatively few in number.

The multivariate Cox proportional hazards model (Table 3) showed that age [≥65 years vs <65 years: hazard ratio (HR): 1.73; 95% confidence interval (CI): 1.06 to 2.72; p = 0.029] and education level (below elementary school vs any higher education level: HR: 1.45; 95% CI: 1.01 to 2.06; p = 0.045) were independently associated with an increased risk of peritonitis when adjusted for age, sex, education level, CCI score, serum albumin, and a prior exit-site or tunnel infection (Table 3). Higher CCI scores showed a marginal and borderline significant association with peritonitis (>2 vs ≤2: HR: 1.44; 95% CI: 1.00 to 2.13; p = 0.053). Figure 2 shows the probability, as determined by the Kaplan–Meier method, of developing PD-related peritonitis according to education level and CCI score. At 6 months after PD start, the cumulative incidences of PD-related peritonitis were approximately 15% and 10% respectively for the below-elementary-school and any-higher-education-level subgroups. Caregiver type was not considered in the multivariate Cox regression model because of the small number of foreign caregivers.

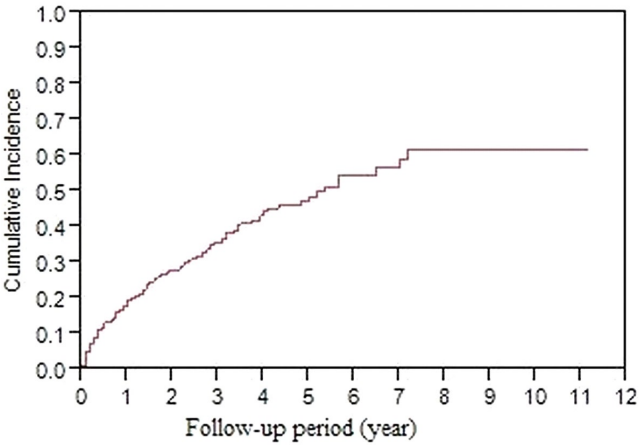

Figure 1 — Cumulative incidence of peritoneal dialysis–related peritonitis during the follow-up period.

TABLE 1
Cumulative Peritonitis Incidence Rate[a] at Various Time Points

Follow-up	Incidence
6 Months	13.10±1.69
12 Months	19.25±1.99
18 Months	24.66±2.21
24 Months	27.65±2.33
30 Months	31.49±2.51
36 Months	35.59±2.71
42 Months	41.05±2.98
48 Months	44.49±3.18
54 Months	46.09±3.28
60 Months	48.39±3.52

[a] Mean ± standard error.

DISCUSSION

This retrospective cohort study identified associations for older age and a lower education level with PD-related peritonitis in PD patients. Results reported by previous studies have been inconsistent concerning the association between age and peritonitis. Nessim *et al.* (10) found that older age was associated with a higher rate of peritonitis in patients who started PD between 1996 and 2000; however, that association disappeared in patients who started PD between 2001 and 2005, which might be related to advances in PD connection technology and exit-site care. In our study, a similar era effect was observed. When patients who started PD between 2005 and 2010 were included, the association between age and peritonitis became insignificant (p = 0.39; 95% CI: 0.52 to 5.33; data not shown). Thus, a more simplified PD connection device and advanced exit-site care might reduce the incidence of PD-related peritonitis. However, in the present study, we could not confirm whether such measures are effective in elderly patients.

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TABLE 2
Characteristics of the Patients in the Study Groups

Characteristic	Patient groups [*n* (%)] Overall	Peritonitis Yes	Peritonitis No	*p* Value (univariate)
Patients (*n*)	404	150	254	
Sex				
Men	171 (42.32)	54 (36)	117 (46.06)	0.048
Women	233 (57.68)	96 (64)	137 (53.94)	
Age group				
<65 Years	356 (88.12)	126 (84)	230 (90.55)	0.049
≥65 Years	48 (11.88)	24 (16)	24 (9.45)	
Education level				
<Elementary school	126 (31.19)	56 (37.33)	70 (27.56)	0.041
≥Elementary school	278 (68.81)	94 (62.67)	184 (72.44)	
CCI score				
≤2	116 (28.71)	36 (24)	80 (31.5)	0.108
>2	288 (71.29)	114 (76)	174 (68.5)	
Exit-site or tunnel infection				
No	313 (77.48)	114 (76)	199 (78.35)	0.585
Yes	91 (22.53)	36 (24)	55 (21.65)	
Initial serum albumin				
<3.5 g/dL	128 (31.76)	42 (28)	86 (33.86)	0.212
≥3.5 g/dL	275 (68.24)	108 (72)	167 (66.14)	
Ca×P				
<55	337 (83.62)	127 (84.67)	210 (83.00)	0.663
≥55	66 (16.38)	23 (15.33)	43 (17.00)	
nPCR[a]				
≥0.8 g/kg/d	366 (91.27)	138 (92.62)	228 (90.48)	0.463
<0.8 g/kg/d	36 (8.73)	11 (7.38)	24 (9.52)	
Residual urine[a]				
≥100 mL/d	371 (92.75)	137 (91.95)	234 (93.23)	0.63
<100 mL/d	29 (7.25)	12 (8.05)	17 (6.77)	
Weekly Kt/V[a]				
≥1.7	342 (85.29)	132 (88.59)	210 (83.33)	0.151
<1.7	59 (14.71)	17 (11.41)	42 (16.67)	
Caregiver				
Self	348 (86.78)	126 (84)	222 (87.4)	0.0121
Spouse	18 (4.49)	4 (2.7)	14 (5.5)	
Other caregiver[b]	25 (6.23)	12 (8)	13 (5.1)	
Foreign caregiver	10 (2.49)	8 (5.3)	2 (2)	

CCI = Charlson comorbidity index; nPCR = normalized protein catabolic rate.
[a] Within 3 months of dialysis start.
[b] Family member other than spouse, or Taiwanese caregiver.

Martin *et al.* (11) conducted a multicenter observational study from December 2004 to October 2007 and analyzed 2032 patients for a cumulative 22 026 patient–months. They showed that a lower education level was associated with a higher risk of a first episode of PD-related peritonitis. Chow *et al.* (28) reported illiteracy as one of the factors associated with time to a first peritonitis episode in a cohort of 102 incident PD patients with 85 patient–years of observation. Our study enrolled 404 incident PD patients during a 12-year period. After adjustment for age, sex, and important comorbidities as measured by CCI score, we found an association between lower education levels and peritonitis. The impact of education level on the cumulative incidence of PD-related

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TABLE 3
Cox Proportional Hazards Model for the Development of Peritoneal Dialysis–Related Peritonitis

Variable	Comparison	HR	95% CI	*p* Value
Sex	Female vs male	1.16	0.83 to 1.65	0.3787
Age (years)	>65 vs ≤65	1.73	1.06 to 2.72	0.0288
Educational level	<Elementary vs ≥elementary	1.45	1.01 to 2.06	0.0454
CCI score	>2 vs ≤2	1.44	1.00 to 2.13	0.053
Prior ESI or TI	No vs yes	1.22	0.84 to 1.81	0.3055
Serum albumin (g/dL)	≥3.5 vs <3.5	1.14	0.80 to 1.66	0.4623

HR = hazard ratio; CI = confidence interval; CCI = Charlson comorbidity index; ESI = exit-site infection; TI = tunnel infection.

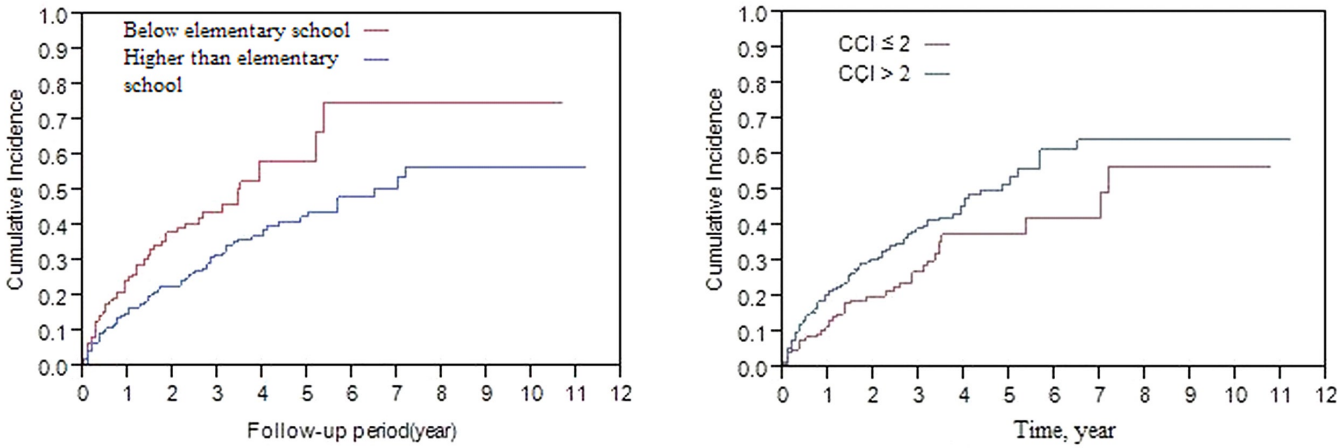

Figure 2 — Kaplan–Meier plots for the probability of chronic peritoneal dialysis (PD) patients developing PD-related peritonitis according to education level (left panel) and Charlson comorbidity index [CCI (right panel)].

peritonitis appeared in the first 6 months and persisted throughout the study period. From the foregoing investigations, we realized that a lower education level was an important issue in PD education programs, especially in the Asian population. A lower education level was common for people living in areas near urban regions in some Asian countries. Many of our study patients lived in rural areas and disclosed a learning deficit. We reasonably speculated that learning difficulties led to PD-related peritonitis in PD patients with lower education levels. A comprehensive PD education program is therefore crucial for PD patients with lower education levels. The long-term benefit of such a program is worthy of further investigation.

The CCI score at PD start has been reported to be a strong predictor of patient survival in end-stage renal disease patients receiving PD (29). In our study, a higher CCI score had a borderline significant impact on the development of PD-related peritonitis. Moreover, the trend of the cumulative incidence of PD-related peritonitis was consistent during the study period. In previous studies, conflicting results were obtained for the association between comorbidities and PD-related peritonitis (8,12,14,16,20), possibly because of the Hawthorne effect and small sample sizes. Nevertheless, it is reasonable to believe that physical disability may disturb the performance of PD.

Caregivers are important in the performance of PD-related procedures such as connecting or disconnecting the patient from dialysate bags or the PD cycler. In Taiwan, patients with multiple comorbidities who require long-term home care can hire a foreign caregiver if the patient has a physician's certificate. Peng *et al.* (21) retrospectively analyzed 154 assisted PD patients in a city in northern Taiwan and found that patients undergoing assisted PD performed by foreign caregivers had a very low peritonitis rate. In contrast, our study showed that, among patients undergoing PD-related procedures performed by foreign caregivers, the peritonitis rate was higher than it was for patients undergoing PD performed by the patient or the patient's spouse. That finding may be a result of differences in the illustrated manuals for PD-related procedures in northern and southern Taiwan. The manuals for PD are translated into the foreign caregiver's mother language in northern, but not

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in southern, Taiwan. Moreover, the number of foreign caregivers was small in our study. An analysis featuring more patients is needed to validate the earlier study.

In our study, the highest rate of PD-related peritonitis was observed during the first 6 months after the start of PD. Kolesnyk *et al.* (30) reported the highest rate of switches to hemodialysis during the first 3 months for patients on PD, with most patients being switched because of PD-related peritonitis. Those findings provide information to nurses and nephrologists about the importance of early identification of high-risk patients among those on PD. A structured protocol can then be developed for the prevention of PD-related peritonitis, focusing on issues such as solving the problem of caregiver illiteracy, providing a more comprehensive PD education program, and making efforts to reduce or eliminate the factors associated with PD-related peritonitis.

The present study used time-dependent statistical methods to investigate the factors associated with PD-related peritonitis. To the best of our knowledge, reports with similar designs are rare. However, our study has several limitations. This single-center study is based on retrospective data and has a relatively small sample size. Moreover, other potential risk factors identified in previous studies (such as obesity, residual glomerular filtration rate, distance to the dialysis center, and a complete socio-economic profile) were not included in the present study. Hence, further studies with larger sample sizes, more complete data collection, and multicenter involvement will be needed to identify the factors associated with PD-related peritonitis in Taiwan.

CONCLUSIONS

A lower education level is an independent and strong predictor of the development of PD-related peritonitis. Comorbidities (evaluated using the CCI score) had a borderline significant association with peritonitis. From the present study, it can be concluded that an individualized, structure-guided PD program is mandatory to reduce the rate of PD-related peritonitis.

DISCLOSURES

We certify that there are no financial conflicts of interest relating to the material discussed in the present manuscript.

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