Impact of Environmental Particulate Matter and Peritoneal Dialysis-related Infection in Patients Undergoing Peritoneal Dialysis

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Abstract: In patients undergoing peritoneal dialysis (PD), PD-related infection is a major cause of PD failure and hospital admission. Good air quality is required when dialysate exchange or exit site wound care is performed. To our knowledge, investigation of air pollution as a factor for PD-related infection in patients undergoing dialysis is limited. This study aimed to assess the effect of environmental particulate matter (PM) and other important risk factors on 1-year PD-related infection in patients undergoing PD.

A total of 175 patients undergoing PD were recruited in this 1-year retrospective observational study. Differences in environmental PMs (PM_{10} and $PM_{2.5}$) were analyzed with respect to the patients' living areas. The patients undergoing PD were categorized into 2 groups according to $PM_{2.5}$ exposure: high (n = 61) and low (n = 114). Demographic, hematological, nutritional, inflammatory, biochemical, and dialysis-related data were analyzed. Multivariate binary logistic and multivariate Cox regression analyses were used to analyze 1-year PD-related infection.

A total of 175 patients undergoing PD (50 men and 125 women) were enrolled. Thirty-five patients had PD-related infection within 1 year. Multivariate Cox regression analysis showed that high environmental $PM_{2.5}$ exposure (hazard ratio (HR): 2.0, 95% confidence interval [CI] [1.03–3.91]; $P = .04$) and female sex (HR: 2.77, 95% CI [1.07–7.19]; $P = .03$) were risk factors for 1-year PD-related infection.

Patients undergoing PD with high environmental $PM_{2.5}$ exposure had a higher 1-year PD-related infection rate than that in those with low exposure. Therefore, air pollution may be associated with PD-related infection in such patients.

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INTRODUCTION

Peritoneal dialysis (PD)-related infection is a major cause of PD failure and hospital admission.[1,2] The risk factors associated with PD-related infection include age, female sex, current smoking status, the instruments of PD connection systems,[3] higher body mass index (BMI), and comorbidities such as coronary artery disease and diabetes mellitus.[4,5] Recently, the World Health Organization stated that 7 million premature deaths annually are linked to air pollution, and the major areas are in South-East Asia and the Western Pacific regions.[6] Especially for particulate matter (PM), a small particle could enter the lung via the nasal cavity and cause lung damage.[7] Several studies showed that the concentration of airborne bacteria is associated with the concentration of air PM,[8,9] and airborne PM is a carrier of microorganisms.[10,11] To our knowledge, good air quality when performing dialysate fluid exchange is important to avoid unnecessary infection and prolong the period of PD. However, to date, no study has focused on the association between air quality and PD-related infection. Therefore, the aim of this retrospective observational survey was to assess the role of air PM and other clinical variables on PD-related infection in patients undergoing PD.

METHODS

This retrospective observational study complied with the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital. In addition, all information was securely protected (by delinking identifying information from the main data set) and available to investigators only. Furthermore, all the data were analyzed anonymously, and all patients' records and information were anonymized and de-identified before analysis. Finally, all primary data were collected according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Study Population

One hundred seventy-five patients who had been undergoing continuous ambulatory PD (CAPD) or automated PD (APD) for at least 4 months and regularly followed up at a PD center in Chang Gung Memorial Hospital were recruited. Patients with a history of dialysis-related infection or other

types of active infections within 3 months before study inclusion were excluded. Recruitment started in October 2009, and follow-up ended in December 2010. Age, sex, smoking status, and clinical data were obtained from the patients' medical records within the study period. PD supplies (CAPD and APD solutions) were obtained from Baxter Healthcare SA, Singapore. The primary end point was PD-related infection such as PD perito-nitis, tunnel infection, or exit site infection.

Sample Collection

Fasting blood, urine, and dialysate samples were collected. The plasma, dialysate, and urine concentrations of creatinine (Cr), serum albumin, and urea nitrogen were measured using routine laboratory methods. Calcium concentration was corrected and calculated using the following equation: C-cal-cium = serum calcium (mg/dL) + (0.8 [4.0 − serum albumin] [g/dL]). Anuria was defined as a 24-h urine volume $<50 \, cm^3$. Residual renal function was calculated as follows: (renal normalized urea nitrogen clearance + renal normalized Cr clearance) / 2. Protein nitrogen appearance was normalized to body weight (nPNA). $PM_{2.5}$ and PM_{10} levels of living areas were estimated using the database from the Taiwan Air Quality Monitoring Network, which is operated by the Environmental Protection Administration.[12] A high PM_{10} level was defined as the value higher than or equal to median value of 49.1 μg/m³. A high $PM_{2.5}$ level was defined as the value higher than or equal to median value of 29.6 μg/m³. Education level was categorized as low (ie, less than senior high school) and high (ie, senior high school or above). The Charlson Comorbidity Index[12] was used to predict 1-year peritoneal dialysis-related infection in these patients.

Air Quality Status and Analysis

Air pollution levels were recorded by a network of 27 monitoring stations near or in the patients' living areas in Taiwan. Data from the Taiwan Air Quality Monitoring Network, including the database on the air quality status in Taiwan, were analyzed.[13] Because no previous studies focused on this issue, the previous 1-year (about 365 days) average exposure concentration of PMs was considered for each subject. The reference items included previous 1-year average concentrations of PM_{10} and $PM_{2.5}$. The level of PMs was checked every hour for 1 year. As a result, we calculated the average of approximately 8760 ($24 \times 365 = 8760$) pieces of data for every monitoring station to determine the previous 1-year average level of PMs in this study. Air quality was classified as high or low according to the exposure to airborne PMs on the basis of the median of the previous 1-year average concentration of each airborne PM. PMs data were generally obtained from monitoring stations in the same district. If a patient lived between 2 monitoring stations, the air pollutant data of the nearest station was selected for analysis. If a patient lived in a district without a monitoring station, PMs data was referenced from the nearest station ($<15 \, km$). Terrain was also considered; the data of the nearest monitoring station on the same side of a mountain that a patient lived on were analyzed.

Statistical Analysis

Data are expressed in terms of median and interquartile range for non-normal distribution variables and as mean ± SD for normal distribution variables. The Kolmogorov–Smirnov test showed all variables to be normally distributed. A P value >0.05 was required to assume a normal distribution. Correlations were tested according to Pearson correlation analysis.

Comparisons between groups were performed using the Mann–Whitney U test and the Student t test. Chi-square or Fisher exact tests were used to analyze the correlation between categorical variables. Linear trends were used to analyze the correlation between ordinal variables. Multivariate Cox regression analyses (Forward Method) were used to analyze 1-year PD-related infection. PD-related infection data were compared using the Kaplan–Meier method, and significance was tested using the log-rank test. Logarithmic conversion was made for high-sensitivity C-reactive protein (hs-CRP) and nPNA levels. The following factors were investigated: high PM_{10}, high $PM_{2.5}$, age, female sex, PD duration, smoking condition, white blood count (WBC), log nPNA, serum albumin level, BMI, high education level, log hs-CRP, hepatitis B virus infection, hepatitis C virus infection, diabetes mellitus, and hypertension. All the nominal variables in linear regression were dummy-coding transformed. Missing data were approached with list-wise deletion. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS Inc, Chicago, IL). A P value <0.05 was considered statistically significant.

RESULTS

Table 1 lists the characteristics of the study subjects. A total of 175 patients from a single PD center were enrolled in this study. The causes of end-stage renal disease were diabetic nephropathy (n = 21), polycystic kidney disease (n = 1), glo-merular disease (n = 79), malignant hypertension (n = 15), obstructive nephropathy (n = 3), lupus nephritis (n = 4), gouty nephropathy (n = 2), tubulointerstitial disease (n = 2), and unknown factors (n = 48). Fourteen patients received APD, and 161 patients received CAPD. One hundred twenty-five patients were women. Seventy-eight patients had anuria. The median hs-CRP level was 2.8 mg/L (range 1.2–7.6 mg/L). Seventeen patients had exit site or tunnel infection, and 18 had PD peritonitis. The pathogens that most often caused PD peritonitis were *Streptococcus* (n = 4) and *Escherichia coli* (n = 4). The pathogen that most often caused exit site or tunnel infection was *Staphylococcus* (n = 6). Fifteen patients (8.5%) were habitual users of tobacco. The median value of PM_{10} was 49.1 μg/m³ (range 44.9–56.2 μg/m³) and of $PM_{2.5}$ was 29.6 μg/m³ (range 26.4–29.8 μg/m³). The concentration of $PM_{2.5}$ was positively correlated with the concentration of PM_{10} ($r = 0.391$, $P < .0001$).

To further investigate the influence of clinical features on 1-year PD-related infection, we used multivariate Cox regression analysis to evaluate the association between 1-year PD-related infection and clinical variables in the patients. We included all the variables into a multivariate Cox regression analysis (Forward Method). The result indicated that high $PM_{2.5}$ (HR: 2.0; 95% CI [1.03–3.91]; $P = .04$) and female sex (HR: 2.77; 95% CI [1.07–7.19]; $P = .03$) were significant risk factors for 1-year PD-related infection (Table 2).

We categorized our patients undergoing PD into 2 sub-groups according to the median value of $PM_{2.5}$ concentration as follows: patients with low environmental $PM_{2.5}$ exposure (n = 114) and patients with high environmental $PM_{2.5}$ exposure (n = 61). Age (49.58 ± 10.47 vs 50.26 ± 11.59 years), male sex (25.4% vs 34.4%), PD duration (60.68 ± 40.21 vs 65.21 ± 40.26 months), WBC count (7.87 ± 2.55 vs 7.21 ± 1.91 × 10⁹ cells/L), serum albumin levels (4.06 ± 0.35 vs 4.09 ± 0.32 g/dL), nPNA (1.02 ± 0.22 vs 1.01 ± 0.21 g/kg/day), hs-CRP levels (2.72 [1.15, 7.16] vs 2.87 [1.27, 9.38]), and

TABLE 1. Characteristics of the 175 Patients Undergoing PD and Comparison of Patients With low and Those With High Environmental PM$_{2.5}$ Exposure

N = 175	Mean ± SD/Median (IR)	Low PM$_{2.5}$ (n = 114)	High PM$_{2.5}$ (n = 61)	P
Age	49.8 ± 10.8	49.58 ± 10.47	50.26 ± 11.59	0.70
BMI, kg/m^2	22.72 ± 3.71	22.91 ± 4.11	22.36 ± 2.8	0.29
Drain volume, L/day	9.85 ± 2.09	9.88 ± 2.19	9.78 ± 1.89	0.75
Urine volume, L/day	0.1 (0–0.4)	0.1 (0–0.41)	0.08 (0–0.4)	0.08
PD duration, mo	62.3 ± 40.2	60.68 ± 40.21	65.21 ± 40.26	0.48
Sex (M/F)	50/125	29/85	21/40	0.22
Serum Cr, mg/dL	11.44 ± 2.64	11.21 ± 2.59	11.88 ± 2.67	0.11
WBC, (×109 cells/L)	7.64 ± 2.36	7.87 ± 2.55	7.21 ± 1.91	0.05
Al, μg/L	0.8(0.3–1.3)	0.8 (0.2, 1.3)	0.8 (0.4, 1.3)	0.60
iPTH,(pg/dL	150 (63.2−482)	167 (69.65, 484.5)	116 (48.65, 492)	0.20
Albumin, g/L	4.1 ± 0.3	4.06 ± 0.35	4.09 ± 0.32	0.56
nPNA, g/kg/day	1.01 (0.87–1.15)	1.02 ± 0.22	1.01 ± 0.21	0.82
hs-CRP, mg/L	2.8 (1.2–7.6)	2.72 (1.15, 7.16)	2.87 (1.27, 9.38)	0.70
KT/V$_{urea}$ P	2.03 ± 0.4	2.04 ± 0.43	2 ± 0.35	0.53
KT/V$_{urea}$ K	0.05 (0–0.26)	0.05 (0, 0.28)	0.05 (0, 0.24)	0.91
CCrn K, (L/wk/1.73 m^2)	2.18 (0−10.81)	2.55 (0, 11.05)	1.91 (0, 10.19)	0.92
CCrn P (L/wk/1.73 m^2	46.82 ± 11.39	51.69 ± 12.69	50.75 ± 9.5	0.61
High education level (n)	94	59 (51%)	35 (57%)	0.21
DM (n)	21	15 (13%)	6 (10%)	0.62
HTN (n)	78	59 (51%)	19 (31%)	0.01
CAD (n)	3	3 (3%)	0 (0%)	0.55
Malignancy (n)	1	1 (0.9%)	0 (0%)	0.99
HBV (n)	17	10 (8%)	7 (11%)	0.59
HCV (n)	7	5 (4.3%)	2 (3%)	0.99
PD-related infection (n)	35	18 (15.8%)	17 (27.9%)	0.04
Environmental PM$_{10}$ (μg/m^3)	49.1 (44.9–56.2)			
Environmental PM$_{2.5}$ (μg/m^3)	29.6 (26.4–29.8)			

Al = aluminium, BMI = body mass index, CAD = coronary artery disease, CCrn K = normalized renal creatinine clearance, CCrn P = normalized peritoneal creatinine clearance, Cr = creatinine, DM = diabetes mellitus, F = female, HBV = hepatitis B virus, HCV = hepatitis C virus, hs-CRP = high-sensitivity C-reactive protein, HTN = hypertension, iPTH = intact parathyroid hormone, IR = interquartile range, KT/V K = renal KT/V$_{urea}$, KT/V P = peritoneal KT/V$_{urea}$, M = male, nPNA = normalized protein nitrogen appearance, PD = peritoneal dialysis, PM$_{10}$ = particulate matter with aerodynamic diameter less than 10 μm, PM$_{2.5}$ = particulate matter with aerodynamic diameter <2.5 μm, SD = standard deviation, WBC = white blood cell.

TABLE 2. Multivariate Cox Regression Analysis of 1-year Peritoneal Dialysis-related Infection (N = 175)

	1-year PD-related Infection	
	Multivariate Cox Regression (Forward); HR (95% CI)[a]	P Value
High PM$_{2.5}$	2.0 (1.03−3.91)	0.04
High PM$_{10}$		
Age, y		
BMI, kg/m^2		
Female sex	2.77 (1.07−7.19)	0.03
WBC, ×109 cells/L		
Smoking		
Log nPNA		
Albumin, g/L		
Log hs-CRP		
Duration, mo		
High education level		
Charlson Comorbidity Index		

In multivariate Cox regression, high environmental PM$_{2.5}$ exposure and female sex were risk factors for 1-year PD-related infection in 175 patients.
Al = aluminium, BMI = body mass index, HR = hazard ratio, hs-CRP = high-sensitivity C-reactive protein, nPNA = normalized protein nitrogen appearance, OR = odds ratio, PM$_{10}$ = particulate matter with aerodynamic diameter less than 10 μm, PM$_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm, WBC = white blood cell.

high education levels (51% vs 57%) were not significantly different ($P > 0.05$) between patients with low and those with high environmental $PM_{2.5}$ exposure (Table 1). Kaplan–Meier analysis of survival data from patients with high and those with low environmental $PM_{2.5}$ exposure showed that patients with high $PM_{2.5}$ exposure had a higher cumulative 1-year PD-related infection rate compared with that in patients with low $PM_{2.5}$ exposure (log-rank test, χ^2 test = 4.6; $P = .03$) (Figure 1). On comparing men and women, we found that a high education level (76% vs 44.8%) and smoking (24% vs 2.4%) were more common in men than in women (Table 3). We also found that regarding the 1-year PD-related infection, educational levels had interaction with sex (Figure 2).

DISCUSSION

In this retrospective observational study, we showed that patients with high environmental PM exposure, especially $PM_{2.5}$, had a high rate of PD-related infection.

PD-related infection has been the major factor of PD failure. Education for these patients is mainly focused on lifestyle adjustment, improved PD technique, compliance with doctor's orders, and how to reduce exit site infections and episodes of peritonitis.[14] No study has assessed the relationship between air quality of the living environment and PD-related infection. Several studies showed a significant positive relationship between indoor and outdoor PM concentrations.[15,16] Srivastava and Jain[16] pointed out in a study on the relationship between indoor and outdoor airborne particles that outdoor suspended PM concentrations do indeed affect indoor suspended PM concentrations. Lee et al[15] found that indoor concentrations of chemical air pollutants and $PM_{2.5}$ were significantly related to the corresponding outdoor concentrations. It is interesting that no matter how tightly we close the doors and windows of houses, dust still enters easily. Dust is solid suspended matter in the atmosphere that is easily blown along by wind and spreads to every corner of the house. Its particle size is different, and we may not necessarily see it with the naked eye. The diameter of dust particles is typically $<500\,\mu m$. Suspended particulates less than $10\,\mu m$ (ie, PM_{10}) were determined to be harmful to the human body; <2.5-μm fine PM (ie, $PM_{2.5}$) more directly penetrated the alveoli.[17] The

FIGURE 1. Kaplan–Meier survival analysis of patients with high and those with low $PM_{2.5}$ exposure. Patients with high $PM_{2.5}$ exposure had significantly greater cumulative 1-year peritoneal dialysis-related infection compared with that in those with low $PM_{2.5}$ exposure (log-rank test, χ^2 test = 4.603; $P = 0.032$). $PM_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm,

positive correlation between the number of airborne bacteria and the amount of suspended dust is also mentioned.[18] In a recent study in an urban area, Alghamdi et al[19] showed that airborne microorganisms are associated with the concentration of PM. Cao et al[20] also found a positive correlation between respiratory allergens and pathogens and PM pollution. Of note, the important role airborne bacteria play in surgical wound infection has well been discussed.[21–24] We know that a PD catheter is a bridge between the peritoneal cavity and the atmosphere. During the procedure of connecting or disconnecting the PD tube and dialysate bags or cleaning the exit site, there is an increased risk of airborne microorganism infection. Therefore, if the air quality around the patient undergoing PD is not good, there is a high possibility of airborne bacterial infection. In addition, several studies have described the correlation between airborne PM and respiratory disease.[25–27] The increased symptoms of coughing and sneezing owing to airway stimulation by air pollution in patients or family members will worsen the indoor air quality and increase airborne microorganisms. In the present study, we found that living in areas with high environmental $PM_{2.5}$ levels is a risk factor for PD-related infection. However, this phenomenon was not found for patients living in areas with high environmental PM_{10} levels. Of note, the study showed a positive correlation between concentrations of $PM_{2.5}$ and PM_{10}. However, because the size of $PM_{2.5}$ is smaller than that of PM_{10}, $PM_{2.5}$ has a better chance of entering the houses of the patients. From the previously mentioned studies and our findings, we can conclude that the environmental air quality of the area in which patients undergoing PD lived is important for PD-related infection.

In addition, our study showed that female sex was a risk factor for 1-year PD-related infection. The role of sex in PD-related infection or technique failure is not clear.[28] Several studies did not find a significant difference between male and female patients with PD peritonitis.[29–32] Kotsanas et al[3] showed that female sex is a risk factor for PD peritonitis. However, a study by Kumar et al[33] reported a contrary finding. They found that female sex is a protective factor for PD peritonitis. Their explanation for this finding was the relationship between BMI and PD peritonitis. In 2004, McDonald et al[5] showed that with each $5\,kg/m^2$ increase in BMI, the rate of PD peritonitis increases by about 7%. However, we did not observe the BMI values between male and female patients reported in the study by Kumar et al Additionally, they did not describe the relationship between sex and education levels. It has been well discussed that a high education level has benefits for reducing mortality in numerous diseases.[34–36] In addition, several studies[37–39] showed that a high education level is a protective factor in male but not female patients. In our previous study with hemodialysis patients, a high education level was a protective factor for mortality in male but not female patients.[40] In our present study, BMI was not significantly different between female and male patients, and the number of male patients with a high education level was greater than that of female patients (Table 3). From the results of previously cited reports and our present study, it can be explained why female sex is a risk factor for 1-year PD-related infection after adjustment for a high education level (Table 2).

This study has some limitations. First, this study was designed as a single-center, and small size of the enrolled patients. However, these study-patients were randomly selected. Second, we did not check the concentration of indoor airborne PMs because of the retrospective observational study design. However, because several studies reported on the positive relationship
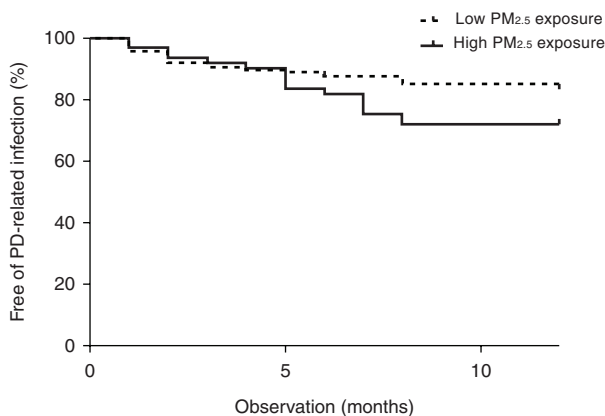
TABLE 3. Comparison of Male and Female Patients

	Female (n = 125)	Male (n = 50)	*P* Value
High PM$_{2.5}$ exposure	32%	42%	0.22
Age, mo	50.25 ± 10.32	48.74 ± 12.10	0.43
BMI, kg/m^2	22.52 ± 3.63	23.21 ± 3.89	0.28
PD duration, ,mo	65.28 ± 40.62	54.72 ± 38.41	0.11
Residual renal function	2.59 (0, 9.91)	0.6 (0, 10.39)	0.41
Smoking (%)	2.4%	24%	<0.001
CT ratio	0.51 ± 0.06	0.48 ± 0.06	0.005
Serum Cr, mg/dL	10.78 ± 2.28	13.11 ± 2.72	<0.001
WBC (×10^9 cells/L)	7.83 ± 2.43	7.16 ± 2.12	0.072
Al, μg/L	0.8 (0.3, 1.4)	0.6 (0.17, 1.2)	0.11
iPTH, pg/dL	164 (71.75, 501.5)	130 (35.77, 400.25)	0.22
Albumin, g/L	4.06 ± 0.33	4.1 ± 0.36	0.558
nPNA, g/kg/day	1.05 (0.89, 1.2)	0.93 (0.84, 1.03)	0.001
hs-CRP, mg/L	2.7 (1.19, 7.55)	3.25 (1.17, 8.04)	0.55
KT/V P	2.11 ± 0.39	1.82 ± 0.34	<0.001
KT/V K	0.06 (0, 0.27)	0.005 (0, 0.22)	0.164
CCrn K, L/wk/1.73 m^2	2.84 (0, 11.18)	0.88 (0, 10.7)	0.447
CCrn P, L/wk/1.73 m^2	51.32 ± 11.34	51.45 ± 12.55	0.949
High education level (%)	44.8%	76%	<0.001
DM (%)	9.6%	18.0%	0.13
HTN (%)	44.8%	44.0%	0.99
CAD (%)	1.6%	2%	0.99
Malignancy (%)	0.8%	0%	0.99
HBV (%)	10.4%	8%	0.78
HCV (%)	4%	4%	0.99

Al = aluminium, BMI = body mass index, CAD = coronary artery disease, CCrn K = normalized renal creatinine clearance, CCrn P = normalized peritoneal creatinine clearance, Cr = creatinine, CT = cardiothoracic, DM = diabetes mellitus, HBV = hepatitis B virus, HCV = hepatitis C virus, hs-CRP = high-sensitivity C-reactive protein, HTN = hypertension, iPTH = intact parathyroid hormone, KT/V K = renal KT/V$_{urea}$, KT/V P = peritoneal KT/V$_{urea}$, nPNA = normalized protein nitrogen appearance, PM$_{2.5}$ = particulate matter with aerodynamic diameter less than 2.5 μm, WBC = white blood cell.

between indoor and outdoor airborne PM concentrations, it is acceptable that we used outdoor airborne PM concentrations to replace indoor airborne PM concentrations. Third, we had little information on the range of activities of the studied patients; however, dialysate exchange was mainly performed at home in PD patients. Fourth, this was designed as a single-center study. Most of the patients were living in northern Taiwan and few in central Taiwan; therefore, the status of patients from southern Taiwan is not well known. Regardless, additional clinical trials are required to confirm the associations found in the present study.

CONCLUSION

Patients undergoing PD and having high environmental PM$_{2.5}$ exposure have a higher 1-year PD-related infection rate than that in those with low environmental PM$_{2.5}$ exposure. Therefore, the findings of this study suggest the existence of a possible correlation between environmental air quality and PD-related infection in patients undergoing PD.

FIGURE 2. Effect of sex on PD-related infection by different education levels. This graph represents that with respect to the 1-year PD-related infection, educational levels had interaction with sex. PD = peritoneal dialysis.

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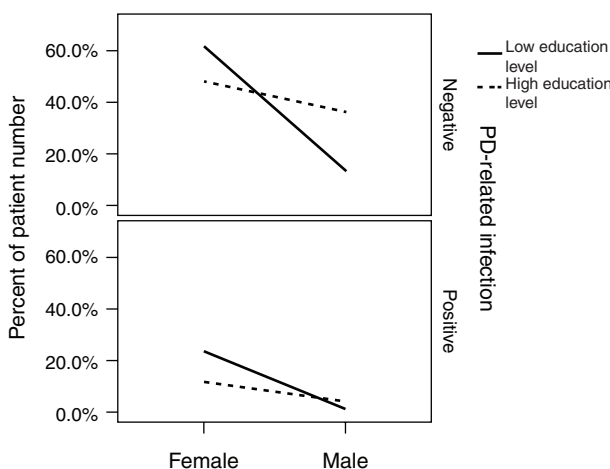
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