Geographic and Educational Factors and Risk of the First Peritonitis Episode in Brazilian Peritoneal Dialysis Study (BRAZPD) Patients

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Summary

Background and objectives Peritonitis remains as the most frequent cause of peritoneal dialysis (PD) failure, impairing patient's outcome. No large multicenter study has addressed socioeconomic, educational, and geographic issues as peritonitis risk factors in countries with a large geographic area and diverse socioeconomic conditions, such as Brazil.

Design, setting, participants, & measurements Incident PD patients recruited from 114 dialysis centers and reporting to BRAZPD, a multicenter observational study, from December 2004 through October 2007 were included. Clinical, dialysis-related, demographic, and socioeconomic variables were analyzed. Patients were followed up until their first peritonitis. Cox proportional model was used to determine independent factors associated with peritonitis.

Results In a cumulative follow-up of 2032 patients during 22.026 patient-months, 474 (23.3%) presented a first peritonitis episode. In contrast to earlier findings, PD modality, previous hemodialysis, diabetes, gender, age, and family income were not risk predictors. Factors independently associated with increased hazard risk were lower educational level, non-white race, region where patients live, shorter distance from dialysis center, and lower number of patients per center.

Conclusions Educational level and geographic factors as well as race and center size are associated with risk for the first peritonitis, independent of socioeconomic status, PD modality, and comorbidities.

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Introduction

Peritonitis continues to be the most frequent cause of peritoneal dialysis (PD) failure, with significant effect on patient morbidity and mortality, despite the strong reduction of its incidence observed over the past decades (1). A clustered distribution of patients with higher incidence of peritonitis has been consistently described; in addition, differences in peritonitis rate between centers and regions have been observed (2). These observations suggest that patient characteristics, as well as factors related to the therapy and the environment, may influence peritonitis risk.

Among patient-related factors, black race (3,4), diabetes (3,4), and advanced age (3) are the most frequently reported peritonitis predictors, although conflicting results are observed in different studies (5,6). Obesity (7), malnutrition (8), chronic inflammation (9), reduced residual renal function (10), and previous peritonitis have also been described as risk factors (3). In addition, there are conflicting results regarding the comparison between continuous ambulatory PD (CAPD) and automated PD (APD) (3,11,12). The effect of other comorbid conditions has not been emphasized until the present.

Moreover, peritonitis rates can be influenced by other factors, such as educational level, geographic region, distance from the PD center, or by socioeconomic status. In a previous study, patients living far from the nearest dialysis center presented significantly higher chance of being prescribed PD (13), and therefore the distance from the center could potentially influence PD outcome and peritonitis rate (14,15); however, this hypothesis has not been evaluated in detail. Socioeconomic condition has also been described as a factor determining peritonitis risk (16), although isolated analysis of the effect of income has not been studied in depth.

Because there is a lack of large multicenter studies analyzing peritonitis risk factors in countries with large geographic area and social disparities addressing socioeconomic, educational, and geographic issues, the objective of this study was to identify factors that are associated with first peritonitis in a large Brazilian PD cohort.

Materials and Methods

Patient Population

The study included patients from 114 centers reporting monthly to the BRAZPD (17), a Brazilian cohort study. Monthly data were obtained using software specifically designed to collect data, which were transferred to a central database. The database includes prospectively collected information on incident and prevalent patients recruited in the study from December 2004 through October 2007, totaling 6198 patients (3439 incident and 2759 prevalent patients). Out of a total of 3439 incident patients, 2032 patients 18 years or older who remained at least 90 days on PD were eligible for the study, whereas 867 were excluded for not completing 90 days on PD, 239 were pediatric patients, and 301 did not have information about peritonitis. This study was performed in accordance with the Declaration of Helsinki and all participants provided written informed consent before enrollment.

During the follow-up period, patients were evaluated monthly by nephrologists and nurses at the PD clinic and data was collected, including age (years), gender, race, cause of end-stage renal disease (ESRD), previous hemodialysis (HD), PD modality (CAPD or APD), body mass index (kg/m^2), blood pressure (BP) (mmHg), serum albumin (g/dl), hemoglobin levels (g/dl), PD indication (medical, patient's option, or only option), previous nephrology referral, family income (minimum wages [MW] per month: 0 to 2, 3 to 5, >5), education level (illiteracy, elementary, secondary, and higher), distance from dialysis center (<25, 25 to 50, >50 km), region where patients live and its Human Development Index (HDI) (18), number of patients per dialysis center (in quintiles), microbiological characteristics of peritonitis, and total follow-up period (months). The presence of comorbid conditions (collagenosis, malignancy, cardiopathy, left ventricular hypertrophy, and diabetes) was registered as present or absent.

To define the three levels of family income, we considered the concept of Ethical Poverty Line (EPL) (19), the Brazilian Gross Domestic Product (GDP) *per capita*, and the mean Brazilian MW in the period of study, which was $150.42 US dollars (USD) ($4.94/d) (20). The International Poverty Centre suggests $2.70 USD per person per day as the EPL (19) and considering that 3.2 is the average number of individuals per family living in private dwellings (21), 2 MW of monthly family income ($3.08 USD per person per day) is the closest to the corresponding EPL in Brazil. The monthly income of 5 MW ($7.71 USD per person per day) was considered as a reference for Brazilian GDP *per capita* that was $7.87 USD per person per day (22). More detailed information on the family income characterization were described by Bastos *et al.* (23), which covers family income effect on survival of the BRAZPD population.

Definition of Peritonitis

The definition of peritonitis followed the recommendations of the International Society for Peritoneal Dialysis guidelines (24). Prescription of antibiotics was based on the patient's clinical conditions according to each center's protocol. Patients were hospitalized whenever necessary.

Statistical Analyses

Patients were followed up until the primary end point, namely, the first peritonitis; those with end of follow-up before reaching end point were censored. Clinical, demographic, dialysis-related, geographic, and socioeconomic variables were included in peritonitis risk analysis. Univariate analyses using Cox proportional hazard regression were performed to select variables to the final model and the elimination criterion for them was $P > 0.10$. Multivariate analysis using Cox proportional hazards regression model was used to determine independent factors associated with the primary end point. Collinearity among variables was tested and if statistically significant interactions were presented, one of them was excluded. Peritonitis-free survival curve was constructed according to the Kaplan–Meier method. The chi-squared test was used when appropriate. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS 16.0 (SPSS Inc.) software.

Results

The study population consisted of 2032 incident adult PD patients, who were followed for a median of 12.2 months (range 1 to 32 months). Patient characteristics at baseline are summarized in Table 1. Four hundred seventy-four (23.3%) patients presented at least one episode of peritonitis during a cumulative follow-up period of 22026 patient-months, whereas the remaining 1558 patients had no peritonitis. The overall peritonitis rate was one episode per 34.6 patient-months, the median peritonitis-free time was 26 months, and the cumulative peritonitis-free survival was 44% in 32 months (Figure 1).

Microbiological information was not reported in 33 episodes and negative culture was observed in 181 (38.1%). Of the 260 cases with etiologic definition, 161 (61.9%) were due to gram-positive agents, 90 (34.6%) to gram negatives, and nine (3.5%) to fungi. Among gram positive, the most frequent was *Staphylococcus aureus* (50.9%), followed by coagulase-negative staphylococci (37.3%), *Enterococcus* spp (6.2%), *Streptococcus* spp (5%), and *Corinebacterium* spp (0.6%). *Escherichia coli* was the main gram-negative germ

Table 1. Summary of patient characteristics at baseline (n = 2032)

	Frequency	%
Age >65 years	723	35.6
Men	942	46.4
White race	1267	62.4
Diabetics	1176	57.9
Cause of ESRD		
chronic glomerulonephritis	210	10.3
hypertensive nephrosclerosis	441	21.7
diabetic nephropathy	761	37.5
unknown	297	14.6
others	323	15.9
PD modality		
APD	1002	49.3
CAPD	1030	50.7

APD, automated PD; CAPD, continuous ambulatory PD; PD, peritoneal dialysis.

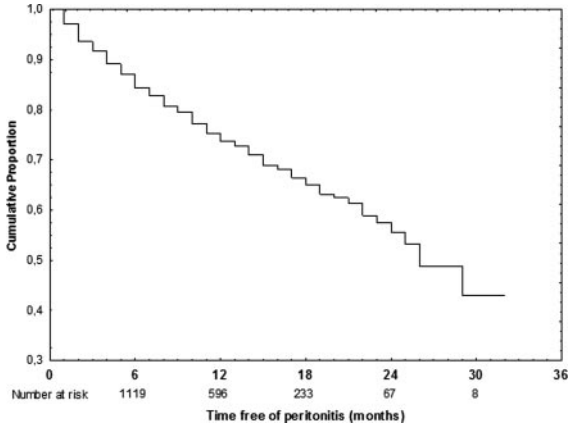

Figure 1. | Peritonitis-free survival of 2032 incident peritoneal dialysis patients of BRAZPD Registry from December 2004 to October 2007.

causing 26.7% of the cases, followed by *Pseudomonas aeruginosa* (24.4%), *Klebsiella* spp (13.3%), *Acinetobacter* spp (11.1%), and *Enterobacter* (8.9%). Other Enterobacteriaccea were identified in 11.1% and other nonfermentative gram-negative bacilli in 3.4% of the cases. *Neisseria* spp caused one episode (1.1%). There were significant differences in proportion of episodes by etiology throughout regions ($P = 0.65$).

The frequency of peritonitis episodes and the median time to the first peritonitis according to demographic, dialysis-related, clinical, geographic, and socioeconomic variables are expressed in Tables 2 and 3. Age, race, educational level, distance from dialysis center, region where patients live, systolic BP (SBP), dialysis indication, number of patients per center, and presence of diabetes were associated with risk for the first episode of peritonitis in the univariate analysis (Tables 2 and 3) and therefore were included in the multivariate Cox proportional hazard model. The regional HDI were as follows: Northeast = 0.749, North = 0.786, West Center = 0.838, Southeast = 0.847, and South = 0.85. The cause of ESRD was excluded because of collinearity between diabetic nephropathy and presence of diabetes, whereas the association between HDI and outcome was not analyzed because of its strict association with regions. No significant interaction was found between other variables.

The multivariate analysis demonstrated that factors independently associated with increased hazard risk (HR) for the first peritonitis were as follows: educational level (illiteracy *versus* higher: HR = 1.75, 95% confidence interval [CI] = 1.04 to 2.92, $P = 0.03$; elementary *versus* higher: HR = 1.64, 95% CI = 1.06 to 2.54, $P = 0.02$; and secondary *versus* higher: HR = 1.57, 95% CI = 0.99 to 2.49, $P = 0.05$), race (non-white *versus* white race: HR = 1.26, 95% CI = 1.003 to 1.58, $P = 0.04$), region where patients live (Northeast *versus* South: HR = 1.77, 95% CI = 1.23 to 2.55, $P = 0.002$), distance from dialysis center ($\leq$25 km *versus* >50 km: HR = 1.40, 95% CI = 1.07 to 1.83, $P = 0.01$), and number of patients per dialysis center (<40 *versus* 157 to 226: HR = 1.49, 95% CI = 1.02 to 2.18, $P = 0.03$, $P = 0.03$) (Figure 2). The other variables had no statistically significant association with the primary end point (Figure 2).

Discussion

Peritonitis remains a major problem for the wide utilization of PD because it is associated with high morbidity and technique failure (1,25). Identification of risk factors in large prospective cohorts, particularly analyzing incident patients, may help to identify populations at high risk.

This prospective cohort study of incident patients showed that predictors of peritonitis include non-white race, lower educational level, region where the patient lives, shorter distance from the dialysis center, and a lower number of patients per center.

Only few large cohort studies tried to identify risk factors for peritonitis. Oo *et al.* (3) studied variables associated with peritonitis using the US Renal Data System (USRDS) including 11,975 patients who were on PD from 1994 to 1997 and identified that the peritonitis risk was lower for CAPD than for APD. Other significant risk factors included age, black race, diabetes, peritonitis in the early period of PD, and congestive heart failure. The ANZDATA analysis, which included data on 3162 patients who started PD from 1999 to 2003, identified Aboriginal race, obesity, and older age as predictors of peritonitis (26). Moreover, in a Canadian study (27) of 4247 incident patients from 25 centers between January 1996 and September 2005, independent predictors of peritonitis included age, black race, diabetes among women, and transfer from HD to PD, whereas CAPD and APD had similar risk. Unfortunately, these studies did not address socioeconomic, educational, and geographic issues and their results were not adjusted for important comorbidities such as collagenosis, malignancies, and cardiac disturbances.

In contrast to the aforementioned studies, age, diabetes, and PD modality did not influence the peritonitis risk in this study. Data on age and diabetes have been conflicting; although the majority of authors have reported that older age and presence of diabetes are associated with higher peritonitis risk, the USRDS results (3) showed that older age was not a predictor of risk whereas in the ANZDATA analysis (26) presence of diabetes was not associated with peritonitis rate. Regarding socioeconomic status, Chow *et al.* (16) showed in a single-center retrospective cohort of 102 incident patients that the need for social security assistance and illiteracy were the only statistically significant factors associated with time to the first peritonitis, after adjustment for age and medical factors, such as diabetes and serum albumin.

Regarding PD modality, some studies found that APD is associated with a lower peritonitis risk (11,12); however, our results showing no differences between APD and CAPD are in agreement with more recent and larger studies (3,27).

Non-white race was associated with a higher peritonitis rate, confirming data from previous reports. Black race was identified several times as a peritonitis risk factor (3,4) and Aboriginal race was an independent predictor for peritonitis in the ANZDATA cohort (26). It is important to notice that non-white race in Brazil comprises not only black but also brown, yellow, and indigenous races. White race was associated with a lower peritonitis risk adjusted to confounding factors such as educational level or family income; however, the influence of other social factors such as sanitary conditions cannot be excluded. It is difficult to

Table 2. Frequency and median time to the first peritonitis episode according to demographic factors

Variable	*n*	First Peritonitis Frequency (%)	Median Time to the First Peritonitis (months)	*P* (univariate)
Age (years)				
≤65	1309	295 (22.5)	6	
>65	723	179 (24.8)	6	0.02
Gender				
women	1090	252 (23.1)	6	
men	942	222 (23.6)	5	0.54
Race				
white	1267	308 (24.3)	6	
non-white	765	166 (21.7)	6	0.10
Educational level				
illiteracy	239	55 (23.0)	5	0.04
elementary	1129	272 (24.1)	5	0.03
secondary	507	124 (24.5)	7	0.06
higher	157	23 (14.6)	4	
Distance from dialysis center (km)				
≤25	1186	297 (25.1)	6	0.08
26 to 50	397	88 (22.2)	5	0.50
>50	449	89 (19.8)	6	
Region where patients live[a]				
Southeast	1083	269 (24.9)	6	0.05
Northeast	352	89 (25.3)	4	0.01
South	368	71 (19.3)	5	
West Center	51	11 (21.6)	4	0.17
North	94	18 (19.1)	5	0.99
No. patients per dialysis center (quintiles)				
first (<40)	402	112 (23.6)	5	0.03
second (40 to 60)	403	76 (16.0)	6	0.75
third (61 to 89)	386	82 (17.3)	6	0.71
fourth (90 to 156)	439	114 (24.1)	5	0.04
fifth (157 to 256)	402	90 (19.0)	7	
Family income (minimal wages per month)				
≤2	737	154 (20.9)	6	0.94
3 to 5	883	222 (25.1)	6	0.32
>5	412	98 (23.8)	6	
PD modality				
APD	1002	231 (23.1)	6	
CAPD	1030	243 (23.6)	5	0.30
Dialysis indication[a]				
patient option	1083	233 (21.5)	6	
medical	569	144 (25.3)	6	0.63
only option	374	97 (25.9)	4	0.07
Previous hemodialysis[a]				
yes	1382	317 (23.0)	5	
no	649	157 (24.2)	8	0.18
Previous nephrology referral[a]				
yes	1106	277 (58.4)	8	
no	920	197 (41.6)	7	0.99

Univariate analysis (n = 474 episodes in 2032 patients). APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

[a]There were no data available about the region where patients live (84 cases), dialysis indication (six cases), previous hemodialysis (one case), and previous nephrology referral (six cases).

explain the association between shorter distance from the dialysis center and higher peritonitis risk observed in cohort. We can speculate that a greater availability of diagnosis resources associated with dialysis center proximity could in part explain this observation. However, it is possible that patients residing closer to the dialysis center could in fact represent an urban population with poorer conditions of hygiene compared with those living in more distant sites. In line with our findings, Tonelli *et al.* (14) reported that Canadian patients living >300 km from a dialysis center had a significantly lower risk of technique failure compared with those living closer (50 km). In contrast, Lim *et al.* (15) recently reported in a large Australian PD population that patients residing in a nonmetropolitan

Table 3. Frequency and median time to the first peritonitis episode according to clinical factors

Variable	*n*	First Peritonitis Frequency (%)	Median Time to the First Peritonitis (months)	*P* (univariate)
Cause of ESRD				
chronic glomerulonephritis	210	38 (18.1)	9.5	
hypertensive nephrosclerosis	441	98 (22.2)	6	0.19
diabetic nephropathy	761	182 (23.9)	5	0.04
unknown	296	75 (25.3)	5	0.02
others	322	81 (25.2)	6	0.27
Body mass index (kg/m^2)				
≤20	373	88 (23.6)	5	0.61
20.1 to 25	751	183 (24.4)	6	
>25	604	164 (27.2)	6	0.91
Systolic BP (mmHg)				
≤140	1044	243 (23.3)	6	
>140	586	164 (28.0)	6	0.10
Diastolic BP (mmHg)				
≤90	1292	307 (23.8)	6	
>90	328	95 (29.0)	6	0.23
Serum albumin (g/dl)				
<4	807	202 (25.0)	7	
≥4	359	92 (25.6)	7	0.60
Hemoglobin (g/dl)				
≥11	902	225 (24.9)	7	
<11	691	172 (24.9)	6	0.55
Collagenosis				
absence	1986	464 (23.4)	6	
presence	45	10 (22.2)	7.5	0.79
Malignancy				
absence	1960	457 (23.3)	6	
presence	71	17 (23.9)	8	0.50
Cardiopathy				
absence	1536	349 (22.7)	6	
presence	495	125 (25.3)	5	0.12
Left ventricular hypertrophy				
absence	1236	265 (21.4)	6	
presence	795	209 (26.3)	5	0.46
Diabetes mellitus				
absence	1175	266 (22.6)	6	
presence	856	208 (24.3)	5	0.10

Univariate analysis (n = 474 episodes in 2032 patients).

location, especially remote indigenous, have a greater peritonitis risk. Further studies will need to be designed to particularly address this issue.

Interestingly, educational level was negatively and independently associated with the risk of the first episode of peritonitis. This result is in agreement with those published by Chow *et al.* (16), one of the first to report a strong relationship between social factors and the risk of dialysis-related peritonitis. A similar result has not been previously reported in large cohort studies of incident PD patients. The influence of educational level on peritonitis risk was observed after adjustment for socioeconomic and demographic characteristics as well as relevant coexisting medical factors and comorbidities, showing the strong influence of this variable on peritonitis risk.

The influence of PD program size on technique survival and peritonitis risk has been previously reported; although centers with a higher number of patients have presented lower risk to technique failure (28), the effect of this variable on peritonitis risk has not been properly addressed until the present time. Davenport (1) reported that there was no significant correlation between size center and peritonitis rate in dialysis units of the London region. Similar results were reported by Kavanagh *et al.* (29) in Scottish units. In contrast, center size correlated with infectious complications rate in a large American cohort (30). Our results showed a significant effect of center size on the peritonitis risk, reinforcing the hypothesis that center experience may have a positive effect on the outcome of PD patients.

Finally, we observed a significant difference on peritonitis risk among country regions. The Northeast was significantly associated with a higher risk after adjustment for different confounding variables. Brazilian territory is large and reaches across several latitudes. Consequently, different types of climate are observed. A Korean study (31), analyzing a wide range of temperature and humidity showed correlation between peritonitis rate and climatic

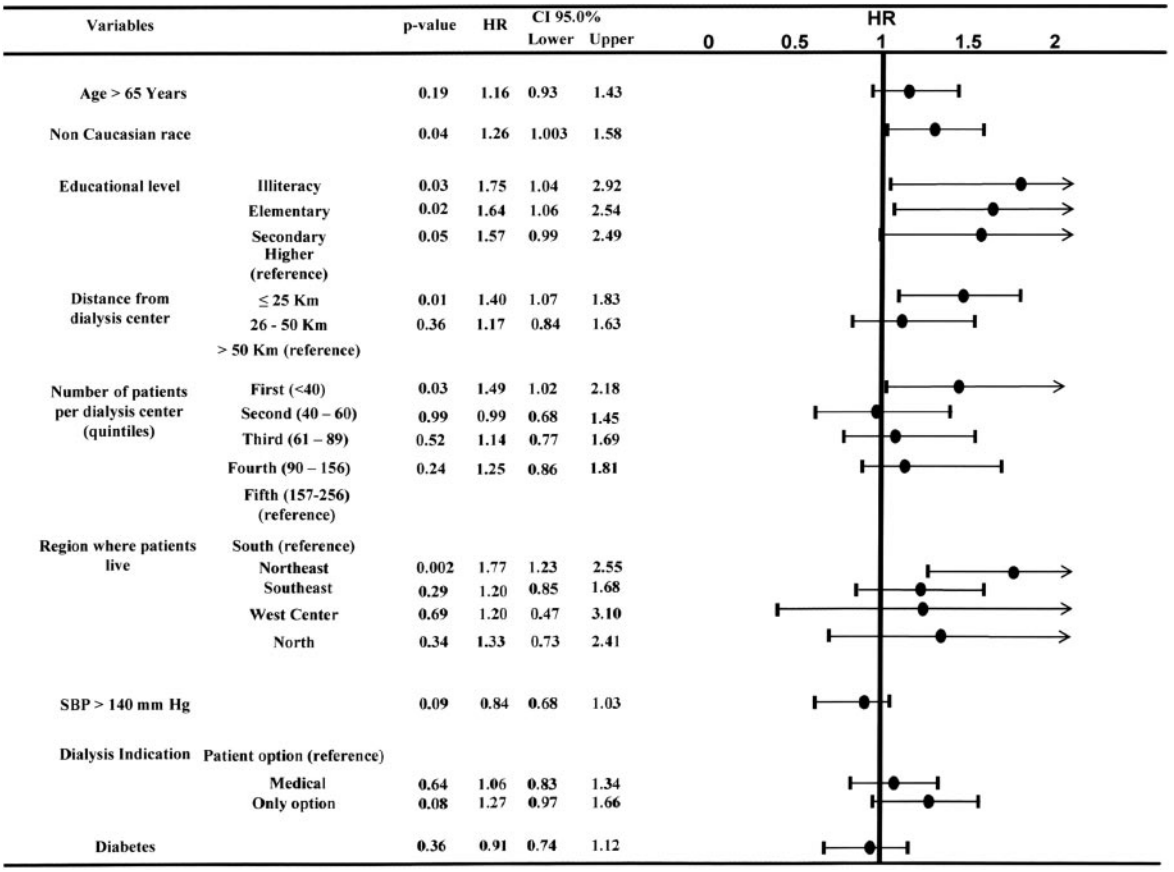

Figure 2. | **Cox proportional hazards regression model (n = 474 episodes in 2032 patients).** CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure.

factors, with peak incidence during the warm humid months. A similar result has been reported in a study performed in Hong Kong (32). Northeast is the warmest Brazilian region; thus, it is possible to attribute our result to climatic conditions. In addition, social disparities could also influence peritonitis risk; in fact, Northeast has a lowest HDI among Brazilian regions, whereas South has the highest, which can be correlated with better infrastructural and living conditions, explaining, at least in part, the regional differences in peritonitis risk. Another possibility would be the fact that Northeast presents the highest incidence of diarrhea (33); however, the effect of this condition may be blunted in the present analysis of adult patients because children present four times higher incidence of this problem than adults (33), who were excluded from the analysis. Interestingly, the frequency of peritonitis etiologies was similar among regions, without higher proportion of episodes by intestinal germs in Northeast.

This study has several limitations. First, our data set did not include data on individual patient's training (according to different educational level and domiciliary conditions such as water supply), dedicated space to dialysis procedure, exit site catheter care, appropriate dialysis procedure, private nurse support, and residual renal function, all factors that could represent peritonitis risk factors. However, Borras *et al.* (34) found no relation between educational level and training period time. Also, in this study there was a high proportion of culture-negative episodes, which makes difficult the analysis of peritonitis risk according to different etiologies. These results should stimulate the review of laboratory methods currently utilized and generate new protocols to improve the results in the country. It is also noticeable that there was in this study a high percentage of patients originating from HD. Possibly this is a consequence of late referral because approximately 45% of patients were not monitored by nephrologists during the predialysis period. Data from a large retrospective Brazilian single-center cohort (35) showed that the number of incident PD patients originating from HD increased threefold over the last 25 years.

The main strength of this study is the fact that it is a large multicenter cohort analysis of incident PD patients, incorporating several potentially important demographic, geographic, socioeconomic, and educational factors beyond relevant clinical pre-existent conditions. Moreover, this is the first Latin American study designed to address whether these factors are predictors of peritonitis risk. Our results reinforce that illiteracy is a strong predictor of risk, in agreement with findings of Chow *et al.* (16). Indeed, this is the first report showing that poverty is not an independent predictor of peritonitis risk, corroborating the results of Bastos *et al.* (23), which demonstrated that economic status, based on family income, is not independently asso-

ciated with outcomes in patients of the same cohort (BRAZPD). Taken together, these studies suggest strongly that low economic status should not be considered a limiting factor to PD indication.

Conclusions

The present study has identified educational level as a strong risk predictor for the first peritonitis episode, independent of socioeconomic status, PD modality, and comorbidities. In addition, we identified non-white race, PD center size, and geographic aspects such as the region where patients live and the distance from dialysis center as independent predictors of the peritonitis risk. In contrast to previous studies, socioeconomic status, gender, age, diabetes, and PD modality did not have an effect on peritonitis risk. Our results may be helpful in identifying the patients starting dialysis treatment who are at the highest risk for peritonitis, particularly in countries with heterogeneous geographic and socioeconomic characteristics where PD may be an interesting alternative to increase access to renal replacement therapy. These results reinforce the need for further studies looking at factors that influence peritonitis incidence, including those which are considered nonmodifiable today, to identify intervention alternatives and thereby improve PD outcomes.

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Disclosures

Jose Carolino Divino Filho is a full-time employee of Baxter Healthcare.

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