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ORIGINAL ARTICLES

CENTER-SPECIFIC FACTORS ASSOCIATED WITH PERITONITIS RISK—A MULTI-CENTER REGISTRY ANALYSIS

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♦ ***Background:*** **Previous studies have reported significant variation in peritonitis rates across dialysis centers. Limited evidence is available to explain this variability. The aim of this study was to assess center-level predictors of peritonitis and their relationship with peritonitis rate variations.**

♦ ***Methods:*** **All incident peritoneal dialysis (PD) patients treated in Australia between October 2003 and December 2013 were included. Data were accessed through the Australia and New Zealand Dialysis and Transplant Registry. The primary outcome was peritonitis rate, evaluated in a mixed effects negative binomial regression model. Peritonitis-free survival was assessed as a secondary outcome in a Cox proportional hazards model.**

♦ ***Results:*** **Overall, 8,711 incident PD patients from 51 dialysis centers were included in the study. Center-level predictors of lower peritonitis rates included smaller center size, high proportion of PD, low peritoneal equilibration test use at PD start, and low proportion of hospitalization for peritonitis. In contrast, a low proportion of automated PD exposure, high icodextrin exposure and low or high use of antifungal prophylaxis at the time of peritonitis were associated with a higher peritonitis rate. Similar results were obtained for peritonitis-free survival. Overall, accounting for center-level characteristics appreciably decreased peritonitis variability among dialysis centers ($p = 0.02$).**

♦ ***Conclusion:*** **This study identified specific center-level characteristics associated with the variation in peritonitis risk. Whether these factors are directly related to peritonitis risk or surrogate markers for other center characteristics is uncertain and should be validated in further studies.**

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Peritonitis is a frequent complication encountered in peritoneal dialysis (PD) and is associated with technique failure, morbidity, and mortality (1–4). Numerous studies have addressed patient-related factors associated with increased peritonitis risk. The most frequently identified risk factors include age, race, higher body mass index (BMI), and comorbidities (e.g. diabetes and coronary artery disease) (4–9). Other less traditional risk factors have also been reported, such as distance from the PD unit, climate, and hypoalbuminemia (7–13).

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Despite these known risk factors, many registry studies still report a large variability in peritonitis rates with 5- to 10-fold variations across different dialysis centers (4,14–16). To date, very few studies have assessed the center-related factors associated with this peritonitis rate variability and most have focused on center size (4,17) or topical antibiotic prophylaxis (15,16).

Considering the limited evidence regarding center-level peritonitis risk factors, the primary objective of this study was to identify center-level factors associated with higher peritonitis counts. The secondary objective was to identify center-level characteristics associated with peritonitis-free survival.

METHODS

STUDY DESIGN AND POPULATION

This study included all incident PD patients in Australia between 1 October 2003 and 31 December 2013. Data were accessed through the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) (http://www.anzdata.org.au) (18). Patients less than 18 years old were excluded.

PATIENT- AND CENTER-LEVEL COVARIATES

All baseline characteristics were obtained at the time of renal replacement therapy (RRT) initiation and included age, gender, primary kidney disease, race, diabetes, cardiovascular disease (any of coronary heart disease, peripheral vascular disease and cerebrovascular disease), chronic lung disease, BMI, late nephrology referral (< 3 months before dialysis start), and PD as the first RRT modality.

For each patient, dialysis center was defined as the center at time of PD start, irrespective of subsequent center transfer. Center size was calculated based on total PD patient-year follow-up during the study period. Peritoneal dialysis proportion reflected the mean proportion of patients treated with PD compared with the total dialysis population. Centers were considered to be transplantation centers if they performed at least 1 kidney transplant during the study period. The proportion of automated PD (APD), icodextrin, and biocompatible exposure represented the proportion of patients from each center treated at least once with these solutions during the study period. Peritoneal equilibration test (PET) represented the proportion of patients for whom a PET was performed at least once during the first 6 months of PD.

The proportion of 'in target' phosphate was defined as the number of patients with a mean phosphate < 1.8 mmol/L in each center (19). Similarly, 'in target' hemoglobin was defined as hemoglobin between 100 and 120 g/L (2004 – 2010) or 100 – 115 g/L (2011 – 2013) (20). Proportions of hospitalizations, catheter removals, and anti-fungal prophylaxis were defined as the number of patients with these characteristics at the time of peritonitis divided by the total number of peritonitis episodes. In the study main models, center-level covariates were categorized based on quartiles. The second and third quartiles were merged to become the reference category, creating a 3-category variable (1 = first quartile; 2 = second and third quartiles [reference]; 3 = fourth quartile).

OUTCOMES ASSESSMENT

The primary outcome of this study was peritonitis rate, calculated as the total number of peritonitis episodes for each patient during his or her PD exposure in the study period. Patients were followed until death, transplantation, PD technique failure (defined as ≥30 days of hemodialysis), or the end of the study (31 December 2013). The secondary outcome was time to first peritonitis. Data were censored at the time of technique failure, death, or transplantation. In patients with multiple periods of PD therapy, only the first period was included in the analysis.

STATISTICAL ANALYSIS

There were 14 patients from 12 dialysis centers with fewer than 5 patient-years of total follow-up and 188 patients with missing data. These patients (< 2% of the total cohort) were excluded from all statistical analysis.

PRIMARY OUTCOME – PERITONITIS EPISODES

Peritonitis counts were evaluated in a multivariable, 2-level mixed effects negative binomial regression model with a random intercept for dialysis centers. All patient- and center-level covariates were analyzed as fixed-effects. Pre-specified patient-level variables were age, gender, race, and diabetes. As a parsimonious model was aimed for, other patient-level variables were included in the model only if their multivariable p value in a patient-level only model was < 0.05. Pre-specified center-level variables were center size, PD proportion, APD exposure, icodextrin exposure, PET performance, hospitalization, and antifungal prophylaxis for peritonitis treatment. Other center-level variables were to be added to the final model if their multivariable p value was < 0.05 (no additional covariates met this criterion). The final model included the following covariates: age, gender, race, diabetes, BMI, cardiovascular disease, PD as the first RRT modality, center size, PD proportion, APD exposure, icodextrin exposure, PET use, hospitalization, and anti-fungal prophylaxis at time of peritonitis.

SENSITIVITY ANALYSIS

The association between center-level covariates and peritonitis counts was evaluated in a multivariable fractional polynomial negative binomial model to allow evaluation of the original continuous versions of these variables. Patient- and center-level covariates were the same as in the main model. To evaluate a potential era effect, a sensitivity analysis was performed with stratification on PD initiation date (before 2008 versus 2008 and after).

SECONDARY OUTCOME

Time to first peritonitis was evaluated in a multivariable Cox proportional hazards survival model, with shared-frailty to account for patient clustering within centers and using the same covariates as those included in the primary outcome model. Patients were censored at the time of technique failure, death, transplantation, or end of follow-up.

The time to first peritonitis was also evaluated in a multivariable competing risk model, with robust variance estimator to account for clustering of patients within centers. Technique failure, death, and kidney transplantation were defined as competing events.

MODEL DISCRIMINATION

The predictive value of adding center-level covariates to models with patient-level covariates was evaluated using 3 methods. First, the mixed effects negative binomial regression model with patient-level and center-level variables (final model) was compared with a model with patient-level covariates only using a likelihood ratio test. Second, Harrell's C test for the peritonitis-free survival model with patient-level variables only was compared with the C test for the final model. Finally, variation in peritonitis rates across centers was graphically assessed by plotting incidence rate ratios (IRR) for each center from 3 mixed-effect negative binomial regression models: an intercept-only model without covariate adjustment, a model with patient-level adjustment only, and the final model with adjustment for patient- and center-level covariates. The IRR estimates were obtained using an empirical Bayes approach (21). The 3 sets of estimates were compared using a mixed effects linear regression model with "estimation model" as a fixed effect categorical variable represented by 2 binary indicator variables and center as a random effect.

All statistical analyses were performed using Stata IC software (version 13.1 StataCorp, College Station, TX, USA). A 2-tailed p value < 0.05 was considered statistically significant.

RESULTS

POPULATION CHARACTERISTICS

The study included 8,711 incident PD patients from 51 PD centers. Baseline characteristics of the study cohort are presented in Table 1, whilst the characteristics of the PD centers are presented in Table 2. Overall, there were 7,665 peritonitis episodes among 3,893 patients, giving an overall peritonitis rate of 0.51 (95% confidence interval [CI] 0.50 – 0.52) episodes per patient-year. The peritonitis rate in dialysis centers varied from 0.17 (95% CI 0.04 – 0.50) episodes per patient-year to 1.74 (95% CI 1.40 – 2.13) episodes per patient-year.

ALL PERITONITIS EPISODES

In a multivariable mixed-effects negative binomial regression model, peritonitis count was predicted on a patient level by older age, race, diabetes, cardiovascular comorbidities, active cigarette smoking, and other RRT modality before PD initiation. Smaller center size, higher proportion of PD, lower rates of performance of PET at PD start, and lower proportion of hospitalization for peritonitis (compared with the median 50%) were associated with a lower peritonitis count. In contrast, lower proportion of APD exposure, greater icodextrin exposure, and lower or higher use of antifungal prophylaxis at time of peritonitis were associated with a higher peritonitis count (Table 3, Figure 1).

SENSITIVITY MODEL

When center-level factors were assessed as continuous variables in a multivariable fractional polynomial model, similar associations were found. Figures representing the relationships between peritonitis rate and center-level factors with non-linear associations are presented in Figure 2 a–d. Graphs for center-level covariates with linear association are displayed in Supplementary Figure S1. Finally, apart from a few exceptions, most of the results remained consistent in analyses stratified for PD initiation era (<2008, 2008, and after). Of note, the association between smaller center size and lower peritonitis count was only significant in the more recent era, while the protective association with higher PD proportion was significant in the older era only. Furthermore, the positive

TABLE 1
Baseline Characteristics of the Study Cohort

Characteristics	Study cohort (n=8,711)
Age (years)	61 (49–71)
Male	5,105 (59%)
Race	
Caucasian	6,508 (75%)
Asian	985 (11%)
ATSI	669 (8%)
Maori – Pacific Islanders	321 (4%)
Other – unknown	228 (3%)
Primary kidney disease	
Glomerulonephritis	2,282 (26%)
Diabetes	2,873 (33%)
Hypertension	1,237 (14%)
Other / unknown	2,319 (27%)
Diabetes	3,723 (43%)
Cardiovascular disease	3,256 (37%)
Respiratory disease	1,329 (15%)
Active smoking	1,103 (13%)
Body mass index (kg/m^2)	26.3 (22.9–30.1)
Late nephrology referral	1,813 (21%)
PD as first RRT modality	5,618 (64%)

ATSI = Aboriginal and Torres Strait Islander; PD = peritoneal dialysis; RRT = renal replacement therapy.
Values are presented as median and interquartile range or count with percentage.

TABLE 2
Center-Level Characteristics

Center-level characteristics	Descriptive statistics (*n*=51)
Center size (total patient-years of follow-up)	220 (113–425)
Percentage of PD (versus overall dialysis population)	20 (16–26)
Transplantation center, *n* (%)	19 (37)
Exposure to APD treatments (% patients in center)	73 (49–85)
Exposure to icodextrin solution (% patients in center)	46 (30–56)
Exposure to biocompatible solutions (% patients in center)	2 (0–10)
PET performed at PD initiation (% patients in center)	54 (36–62)
Hemoglobin in target (% patients in center)	52 (47–56)
Phosphate in target (% patients in center)	66 (61–71)
Anti-fungal prophylaxis with peritonitis (% peritonitis in center)	64 (24–82)
Hospitalization for peritonitis (% peritonitis in center)	49 (28–62)
Catheter removal with peritonitis (% peritonitis in center)	20 (15–24)

PD = peritoneal dialysis; APD = automated PD; PET = peritoneal equilibration test.
Values are presented as median and interquartile range or count with percentage.

association with low proportion of PET performance was also only significant in the older era (Supplementary Table S1).

TIME TO FIRST PERITONITIS

This survival analysis included 3,893 first peritonitis episodes over 10,643 patient-years of follow-up. The unadjusted median peritonitis-free survival time was 1.93 years (95% CI 1.86 – 2.01). In the multivariable model, center-level predictors of a longer peritonitis-free survival included smaller center size and lower or higher proportion of hospitalization for peritonitis. In this analysis, lower APD exposure was the only center-level variable statistically significantly associated with a shorter peritonitis-free survival (Table 4, Figure 1).

A competing risk analysis was performed to assess peritonitis-free survival, taking into account death, technique failure, and transplantation as competing events. Overall, the effect sizes of associations between center-level variables and time to first peritonitis were similar to those in the main survival model (Table 4).

MODEL DISCRIMINATION

The contribution of center-level characteristics to peritonitis prediction was assessed on a patient and center basis.

TABLE 3
Mixed Effects Negative Binomial Regression Analysis of Peritonitis Rates, Expressed as Incident Rate Ratios, for the Period 2004–2013[a]

Covariates	IRR	95% CI	*P*
Patient-level			
Age, per year	1.003	1.000–1.005	0.04
Male	1.04	0.97–1.11	0.30
Race			
Caucasian	1		
Asian	0.83	0.74–0.93	0.001
ATSI	1.67	1.46–1.91	<0.001
Maori – Pacific Islanders	1.12	0.93–1.34	0.23
Other	0.76	0.61–0.95	0.02
Diabetes	1.09	1.01–1.17	0.03
Cardiovascular disease	1.12	1.04–1.21	0.004
Body mass index, per unit increase	1.01	1.01–1.02	<0.001
PD as first RRT modality	0.83	0.77–0.89	<0.001
Center-level[b]			
Size			
<235 patient-years	0.78	0.69–0.90	<0.001
235–1,000 patient-years	1		
>1,000 patient-years	0.96	0.84–1.10	0.54
Proportion of PD			
<20%	1.00	0.88–1.14	0.97
20–30%	1		
>30%	0.87	0.77–0.99	0.04
APD exposure			
<45%	1.24	1.10–1.39	<0.001
45–78%	1		
>78%	1.04	0.91–1.19	0.59
Icodextrin exposure			
<33%	1.09	0.95–1.25	0.23
33–65%	1		
>65%	1.26	1.10–1.44	0.001
PET use at baseline			
<44%	0.78	0.66–0.93	0.004
44–60%	1		
>60%	0.96	0.83–1.11	0.56
Hospitalization for peritonitis			
<36%	0.85	0.75–0.96	0.008
36–60%	1		
>60%	0.88	0.73–1.06	0.17
Antifungal prophylaxis with peritonitis			
<30%	1.25	1.11–1.41	<0.001
30–85%	1		
<85%	1.14	1.01–1.30	0.04

IRR = incident rate ratio; PD = peritoneal dialysis; CI = confidence interval; ATSI = Aboriginal and Torres Strait Islander; APD = automated PD; PET = peritoneal equilibration test.
[a] Adjusted for patient-level characteristics (8,711 patients) and center-level characteristics (51 Australian PD centers).
[b] Categories presented in all center-level variables: 1st quartile, 2nd and 3rd quartile (merged, reference), and 4th quartile.

First, the likelihood ratio test was statistically significant ($p < 0.001$) when comparing the primary outcome in the final model (with patient- and center-level covariates) and the model with patient-level covariates only. Second, Harrell's C test was modestly improved in the proportional hazard Cox model with patient- and center-level covariates compared with the model with patient-level covariates only (0.59, 95% CI 0.58 – 0.60 versus 0.57, 95% CI 0.56 – 0.58, $p < 0.001$).

Lastly, the variation of peritonitis IRRs in each center from the 3 models (intercept-only, patient-level adjustment only, and patient- and center-level adjustment) was assessed. Center-level adjustment resulted in a significant reduction in peritonitis variation between centers ($p = 0.02$). The mean absolute difference between IRR point estimates across centers decreased from 1.34 ± 0.34 in the unadjusted analysis to 1.29 ± 0.23 following adjustment for patient-level factors and then to 1.19 ± 0.24 following additional adjustment for center-level factors (Figure 3, Supplementary Figure S2).

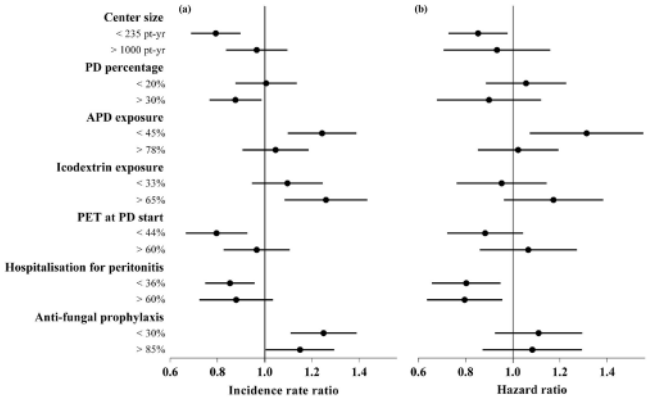

Figure 1 — Forest plots demonstrating the associations between each of 7 center-level variables and (a) peritonitis rates (mixed effects negative binomial regression); and, (b) time to first peritonitis (Cox proportional hazards model with shared-frailty). For each variable, centers in the 1st and 4th quartiles were compared to medium centers (2nd and 3rd quartiles combined – reference group). PD = peritoneal dialysis; APD = automated PD; PET = peritoneal equilibration test.

DISCUSSION

In this multi-center registry study, center-level characteristics were added to the traditionally assessed patient-level factors in the evaluation of peritonitis risk. The addition of

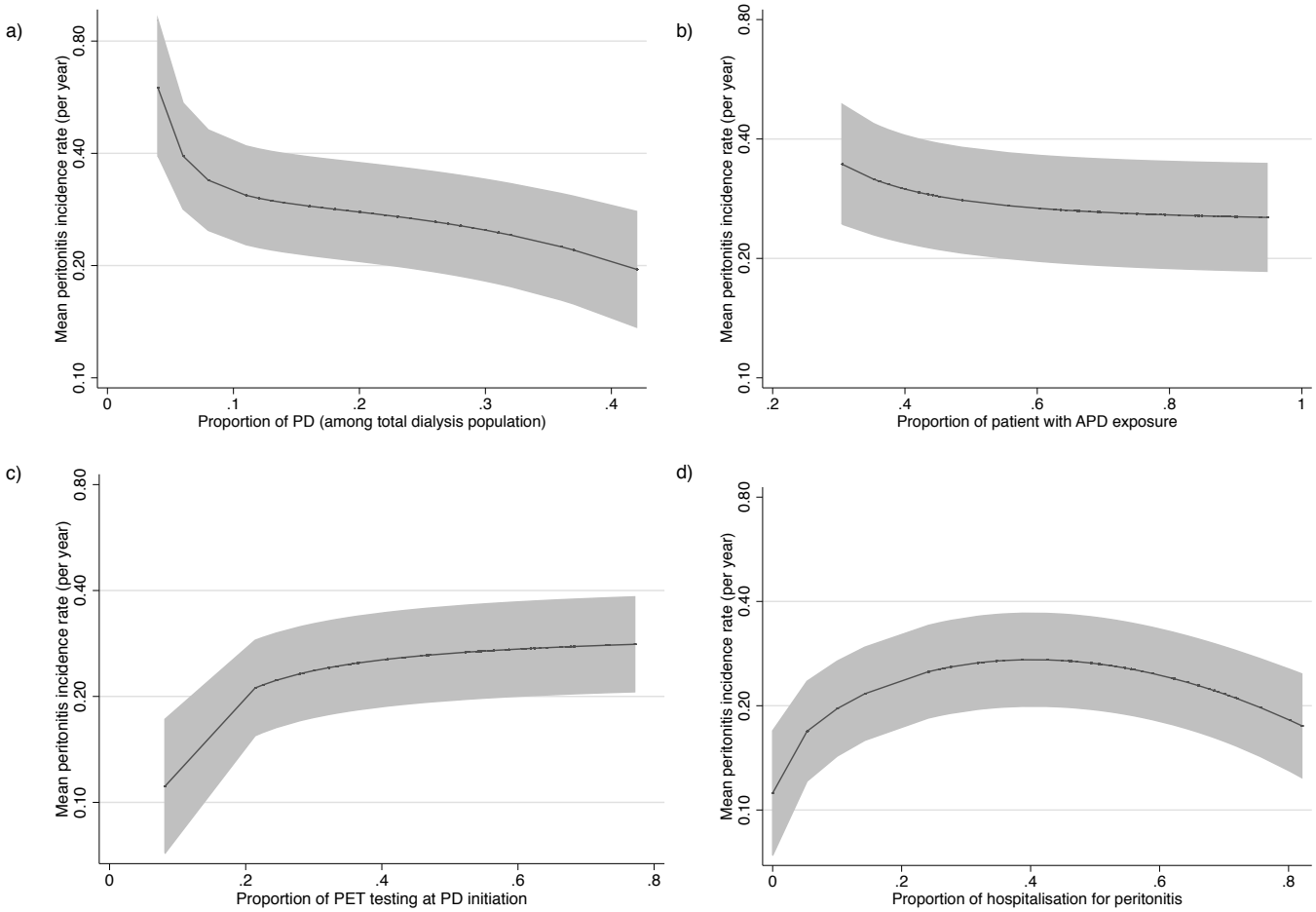

Figure 2 — Fractional polynomial analyses demonstrating the non-linear relationships between 4 characteristics of Australian centers (N=51) and peritonitis rates in those centers during the period 2004–2013. a) PD percentage in center, b) APD exposure, c) PET performance at baseline, d) Hospitalization rate for peritonitis. PD = peritoneal dialysis; APD = automated PD; PET = peritoneal equilibration test.

TABLE 4
Cox Shared-Frailty Model and Competing Risk Model Analyses of Time-to-First Peritonitis, for the Period 2004–2013[a]

Covariates	Cox shared-frailty model HR	95% CI	*P*	Competing risk model HR	95% CI	*P*
Patient-level						
Age, per year	1.001	0.998–1.003	0.34	1.004	1.003–1.007	<0.001
Male	1.03	0.96–1.10	0.38	1.02	0.96–1.09	0.56
Race						
Caucasian	1			1		
Asian	0.85	0.76–0.95	0.005	0.94	0.85–1.03	0.16
ATSI	1.67	1.48–1.90	<0.001	1.74	1.48–2.04	<0.001
Maori – Pacific Islander	1.16	0.98–1.37	0.09	1.22	1.01–1.48	0.04
Other	0.78	0.63–0.97	0.03	0.90	0.73–1.11	0.34
Diabetes	1.08	1.00–1.15	0.045	1.04	0.98–1.12	0.20
Cardiovascular disease	1.15	1.07–1.23	<0.001	1.04	0.96–1.12	0.34
BMI, per unit increase	1.01	1.01–1.02	<0.001	1.01	1.00–1.02	0.001
PD as first RRT modality	0.84	0.78–0.90	<0.001	0.95	0.87–1.03	0.22
Center-level[b]						
Size						
<235 patient-years	0.85	0.73–0.98	0.03	0.83	0.73–0.94	0.004
235–1,000 patient-years	1			1		
>1,000 patient-years	0.91	0.72–1.17	0.48	1.00	0.86–1.16	0.99
Proportion of PD						
<20%	1.05	0.89–1.23	0.56	0.99	0.85–1.14	0.84
20–30%	1			1		
>30%	0.88	0.69–1.13	0.31	0.97	0.82–1.14	0.71
APD exposure						
<45%	1.30	1.08–1.56	0.007	1.10	0.95–1.28	0.20
45–78%	1			1		
>78%	1.01	0.86–1.20	0.87	0.95	0.81–1.13	0.58
Icodextrin exposure						
<33%	0.94	0.77–1.15	0.54	1.04	0.89–1.21	0.64
33–65%	1			1		
>65%	1.16	0.97–1.39	0.10	1.18	1.03–1.35	0.02
PET use at baseline						
<44%	0.87	0.73–1.05	0.14	0.84	0.70–1.00	0.05
44–60%	1			1		
>60%	1.05	0.87–1.28	0.60	1.00	0.85–1.18	0.99
Hospitalization for peritonitis						
<36%	0.80	0.66–0.95	0.01	0.81	0.69–0.95	0.01
36–60%	1			1		
>60%	0.79	0.64–0.96	0.02	0.91	0.73–1.12	0.37
Antifungal prophylaxis with peritonitis						
<30%	1.10	0.93–1.30	0.25	1.15	1.02–1.31	0.03
30–85%	1			1		
>85%	1.07	0.88–1.30	0.48	0.97	0.81–1.16	0.76

PD = peritoneal dialysis; HR = hazard ratio; CI = confidence interval; ATSI = Aboriginal and Torres Strait Islander; BMI = body mass index; RRT = renal replacement therapy; APD = automated PD; PET = peritoneal equilibration test.

[a] Adjusted for patient-level characteristics (8,711 patients) and center-level characteristics (51 Australian PD centers).

[b] Categories presented in all center-level variables: 1st quartile, 2nd and 3rd quartile (merged, reference) and 4th quartile.

these center-level factors led to a modest improvement in prediction of peritonitis risk on an individual patient basis and significantly reduced unexplained peritonitis rate variability across centers. In the primary outcome of peritonitis count, center-level predictors of lower peritonitis occurrence included smaller center size, larger proportion of PD patients, lower rates of performance of PET at PD start, and lower proportion of hospitalization for peritonitis. In contrast, a lower proportion of APD exposure, higher icodextrin exposure, and lower or higher use of antifungal prophylaxis at the time of peritonitis were associated with a higher peritonitis rate. Overall, these associations were preserved, at least as a trend, in the study's

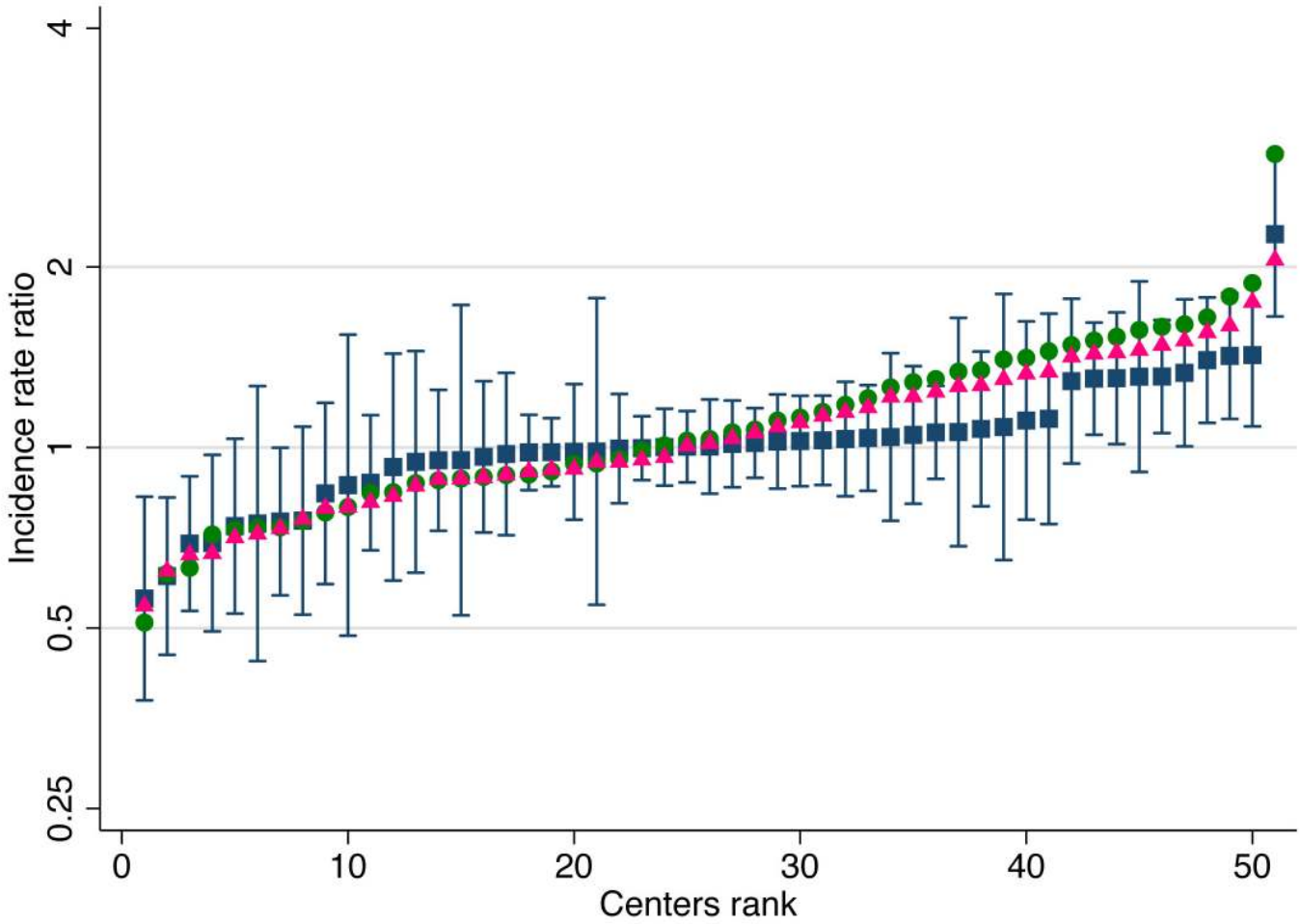

Figure 3 — Variation of peritonitis incidence rate ratios across 51 Australian PD dialysis centers during the period 2004–2013 in unadjusted (green circle), patient-level adjusted (pink triangle) and multilevel (patient and center) adjusted (blue square) models using posterior modal estimates (± 2 standard errors) calculated from empirical Bayes estimates derived from mixed effects models with center-level random intercepts. Dialysis centers are ranked by peritonitis rates in each model. Overall *p* value = 0.02. PD = peritoneal dialysis; APD = automated PD; PET = peritoneal equilibration test.

secondary outcome of peritonitis-free survival and in various sensitivity models.

Variation of peritonitis rates across different centers within the same country has been frequently reported and often attributed to differences in the PD population (4,14–16). Unadjusted analyses of the Scottish and Austrian dialysis registries have shown that centers with *Staphylococcus aureus* prophylaxis strategies had lower peritonitis rates compared with centers not using any prophylaxis (15,16). This information was unfortunately not available in the ANZDATA registry. However, these analyses did not consider other potential differences in the dialysis population of the dialysis centers, limiting the studies' conclusions. Similarly, an ANZDATA study previously reported that unadjusted center size did not explain the variability of peritonitis rate seen across centers (4). To our knowledge, the present study is the first to assess multiple center-related characteristics associated with peritonitis risk in a large PD population while also taking patient-related confounding into account.

In this study, smaller center size was associated with a lower peritonitis rate after adjustment for other patient- and center-level factors. Although somewhat unexpected, this association could be related to the higher nurse-to-patient ratios of smaller centers or to residual confounding related to more highly selected PD patients. Interestingly, a contrasting association was recently reported in a study by the BRAZPD investigators whereby larger centers (defined by number of prevalent PD patients) had longer peritonitis-free survival (17). There were, however, no other center-level variables, such as proportion of PD patients, as reported in the BRAZPD multivariable model, which could explain this difference in center-size effect. On the other hand, the discordant results between the Brazilian and Australian findings may be related to Australia's home dialysis 'culture' and expertise such that even smaller centers have access to experienced and qualified home dialysis teams (22).

In contrast to the center-size association described above, centers with a higher proportion of PD patients had lower peritonitis rates. A similar positive association of higher PD proportion and technique survival was reported in a Dutch study (23). Benefits of a higher proportion of patients treated

with PD may be related to the resources directed toward PD and, perhaps, the dialysis team embracing PD, irrespective of center size. This study suggests that the association found between center size and proportion of PD could mean that centers' structural organization and commitment to PD (reflected by PD proportion) are more important factors than the size *per se*.

Centers with lower proportions of hospitalization for peritonitis treatment had lower peritonitis rates. Differences in 'outpatient-clinic' resources for peritonitis prevention and treatment may explain this association, with, for instance, disparities in access to home visits (24,25) or outpatient support over the weekends (26). Alternatively, this association could be due to less aggressive peritonitis episodes in centers with lower hospitalization rates (4) or related to under-reporting of peritonitis in centers more likely to treat peritonitis in an outpatient setting.

Unexpectedly, this study showed an association between lower rates of performance of PET at the time of PD initiation and lower peritonitis rates. An inverse association was anticipated since PET is recommended at PD initiation in the Kidney Health Australia – Caring for Australians with Renal Impairment (KHA-CARI) guidelines, and it was hypothesized that it might therefore act as a marker of a center's overall adherence to guidelines, which in turn might be associated with better patient outcomes (27). It is unclear why the opposite finding was observed. This may reflect how units with finite resources prioritize their efforts, such that centers with lower peritonitis rates may have prioritized adherence to infection control guidelines at the expense of other clinical practice guideline recommendations. It is also possible that the association between PET use and peritonitis rates is related to other unmeasured characteristics or reporting bias of these centers, such as under-reporting of peritonitis episodes in centers with low adherence to recognized clinical practices (e.g. low PET performance).

In this study, centers with a lower proportion of patients with APD exposure had higher peritonitis rates compared with centers with average APD exposure. The presence of a patient-level effect of PD modality on peritonitis risk has been inconsistent in the literature, with studies variously reporting similar (5,15,28,29), decreased (30–32), or increased (33,34) risks with APD compared with continuous ambulatory PD (CAPD). Similarly, in the present study, centers with higher icodextrin exposure had higher peritonitis rates, although a recent systematic review found no effect of icodextrin on patient-level peritonitis (35). While dialysis modality and prescription pattern might not necessarily influence peritonitis rate on a patient level, it could be postulated that centers with lower APD usage rates or with systematic, indiscriminate prescription of icodextrin might not as closely adjust PD prescription to specific patient needs, thereby influencing peritonitis rate. On the other hand, the negative association with higher icodextrin exposure could be related to unmeasured differences in the PD populations of these centers. For instance, higher icodextrin usage may reflect a higher proportion of patients with suboptimal treatment adherence or malnutrition/inflammation syndromes, who are therefore more prone to infection, or a center's propensity to extend such patients' time on PD beyond the point where other centers would have already converted them to hemodialysis.

Finally, centers with lower and higher use of antifungal prophylaxis had lower peritonitis rates compared with centers with 'average' use of anti-fungal prophylaxis at the time of peritonitis treatment. Although antifungal prophylaxis is used routinely by a number of PD centers, the International Society for Peritoneal Dialysis (ISPD) does not firmly recommend antifungal prophylaxis but rather suggests its use, especially for centers with higher rates of fungal infections (36). Similarly, recent KHA-CARI guidelines state that antifungal prophylaxis should be considered with peritonitis treatment (37). Hence, the higher peritonitis rate among centers with lower antifungal use could be a surrogate marker of poorer attention toward infection-related prevention strategies in general, while the negative association with higher antifungal prophylaxis use could be related to a selection bias such that centers with higher fungal (and overall) peritonitis rates are more prone to use prophylaxis on the basis of current guidelines.

In the present study, the variation in peritonitis rate across Australian dialysis centers decreased by 16% with the inclusion of patient-level characteristics and by a further 34% with the addition of center-level characteristics. The ISPD guidelines state that peritonitis rate should be lower than 0.67 episodes per patient-year (1 episode every 18 months) (38) and that a rate of 0.36 episodes per patient-year can probably be reached by most programs (36). While Australia's mean peritonitis rate is within the ISPD's acceptable limits, a significant proportion of Australian centers still have higher-than-expected peritonitis rates. Hence, identification of center-specific characteristics associated with differences in peritonitis rate is a critical step to the implementation of changes targeting modifiable differences across centers.

This study has several strengths. Firstly, incident PD patients from all training PD centers across Australia were included, which provided a unique opportunity to evaluate center-level characteristics in a cohort with similar resources and guidelines. Secondly, center-level characteristics were evaluated with various statistical models, including a mixed-effects count model specifically tailored to the study question, with results globally similar across the different analyses. Thirdly, this study allowed for multivariable adjustment of both patient- and center-level covariates, thereby limiting residual confounding on a center-level basis.

Nevertheless, the study's strengths need to be balanced against its limitations. The registry design of this study prevented inclusion of important data not recorded in ANZDATA on patient level (e.g. compliance, education, and socioeconomic factors), as well as on center level (e.g. specific dialysis practices such as topical antibiotic prophylaxis and training specifics). Similarly, it was not possible to include climatic regions and mean distance between patients' residence and units in the

present study. Further studies, such as those supported by the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) (39), will help to identify modifiable practices that should be monitored by dialysis centers and registries. It should also be acknowledged that although specific center-level factors have been identified as positively or negatively associated with peritonitis rate, residual confounding could have persisted despite multivariable adjustment and accounted for part of the study's findings. Furthermore, due to the complexity of statistical modeling, PD centers were evaluated as a fixed variable defined at PD start, and any changes in dialysis center were not considered. Since this study only included Australian centers, results, especially on a center-level basis, might not be generalizable to other countries with different dialysis practices. Finally, while the inclusion of center-level characteristics decreased peritonitis rate variability between centers, it did not meaningfully increase peritonitis prediction on a patient basis.

In conclusion, this study identified center-level characteristics associated with variation in peritonitis risk. Factors associated with a lower risk of peritonitis included smaller center size, higher proportion of PD, lower performance of PET at baseline, and lower rate of hospitalization for peritonitis. In contrast, centers with lower exposure to APD, higher icodextrin exposure, and higher or lower use of antifungal prophylaxis had a higher risk of peritonitis. The addition of these center-level factors led to a modest improvement in prediction of peritonitis risk on an individual patient basis but significantly reduced peritonitis rate variability across Australian PD centers. Whether or not these factors are directly related to peritonitis risk or are surrogate markers of other center characteristics is uncertain and should be validated in further studies to identify greater monitoring of modifiable center-level practices.

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