Obesity Is Associated with Worse Peritoneal Dialysis Outcomes in the Australia and New Zealand Patient Populations

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Abstract. Although obesity is associated with increased risks of morbidity and death in the general population, a number of studies of patients undergoing hemodialysis have demonstrated that increasing body mass index (BMI) is correlated with decreased mortality risk. Whether this association holds true among patients treated with peritoneal dialysis (PD) has been less well studied. The aim of this investigation was to examine the association between BMI and outcomes among new PD patients in a large cohort, with long-term follow-up monitoring. Using data from the Australia and New Zealand Dialysis and Transplant Registry, an analysis of all new adult patients ($n = 9679$) who underwent an episode of PD treatment in Australia or New Zealand between April 1, 1991, and March 31, 2002, was performed. Patients were classified as obese (BMI of $\geq$30 kg/m^2), overweight (BMI of 25.0 to 29.9 kg/m^2), normal weight (BMI of 20 to 24.9 kg/m^2), or underweight (BMI of $<$20 kg/m^2). In multivariate analyses, obesity was independently associated with death during PD treatment (hazard ratio, 1.36; 95% confidence interval, 1.14 to 1.54; $P < 0.05$) and technique failure (hazard ratio, 1.17; 95% confidence interval, 1.07 to 1.26; $P < 0.01$), except among patients of New Zealand Maori/Pacific Islander origin, for whom there was no significant relationship between BMI and death during PD treatment. A supplementary fractional polynomial analysis modeled BMI as a continuous predictor and indicated a J-shaped relationship between BMI and patient mortality rates and a steady increase in death-censored technique failure rates up to a BMI of 40 kg/m^2; the mortality risk was lowest for BMI values of approximately 20 kg/m^2. In conclusion, obesity at the commencement of renal replacement therapy is a significant risk factor for death and technique failure. Such patients should be closely monitored during PD and should be considered for early transfer to an alternative renal replacement therapy if difficulties are experienced.

Body mass index (BMI) (weight in kilograms divided by the square of height in meters) is known to be a significant risk factor for morbidity and death in the general population (1–4). However, this relationship varies according to the presence or absence of comorbid illness (3,4). For example, among patients undergoing hemodialysis, higher BMI values have consistently been demonstrated to be associated with reduced mortality risk (5–10). Among patients undergoing peritoneal dialysis (PD), however, the results are conflicting, with one study demonstrating a survival advantage for patients with a higher BMI (11) and two studies by the same group (12,13) demonstrating a lack of effect of body size on outcomes. Those investigations, however, were limited to small numbers of patients treated in one or a few dialysis centers and monitored for relatively short periods. The aim of this study was to determine the effects of BMI at the start of renal replacement therapy (RRT) on subsequent patient and technique survival rates in a large PD patient population, using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry.

Materials and Methods

The ANZDATA Registry collects information every 6 mo from all renal units throughout Australia and New Zealand, concerning all patients receiving chronic RRT. The ANZDATA Registry includes data on all patients who begin RRT with a diagnosis of chronic renal failure and for whom RRT is intended to be a chronic indefinite treatment. Complete details of the structure and methods of the registry have been reported elsewhere (14). The collection is complete from the first RRT procedures performed in Australasia in 1963 and includes all renal units in both countries. The data collected consist of information on the underlying cause of ESRD, demographic details, a limited range of comorbidities (the presence of coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, treated hypertension, and smoking), the type and dose of dialysis treatment, and details of renal transplantation. In the event of patient death, units were asked to provide a cause of death, but death certificates were not directly reviewed for the ANZDATA Registry.

This analysis included all patients in the ANZDATA Registry who were $\geq$15 yr of age at the time of commencement of RRT, began RRT after April 1, 1991, and underwent a period (of any duration) of PD. Patients were monitored until death or March 31, 2002, at which point data were censored. For this study, PD included continuous ambulatory PD, automated PD using cyclers, and tidal PD. For the reported comorbidities, "suspected" was included with "yes" for analyses. BMI

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values were calculated from the quotient of the weight and the square of the height at the commencement of RRT and were analyzed in categories (obese, ≥30 kg/m^2; overweight, 25 to 29.9 kg/m^2; normal weight, 20 to 24.9 kg/m^2; underweight, <20 kg/m^2) (15) and also as a continuous variable, where indicated. Because BMI cannot be assumed to be linearly related to patient outcomes, it was also modeled as a fractional polynomial function. This technique allowed fitting of a smooth curve without the artifacts observed with cubic splines (16,17) and avoided the problems associated with arbitrary selection of categories (18).

The outcomes examined were patient death and technique failure (excluding patient death). If a patient died within 60 d after transfer to hemodialysis, then the death was attributed to PD, because such early deaths were considered to reflect the health status of patients during the period of failing PD therapy. In contrast, deaths that occurred <60 d after cessation of PD because of renal transplantation were not attributed to PD, and such episodes were censored at the end of PD treatment. Technique failure was defined as a transfer from PD to hemodialysis for >1 mo and was examined without counting death during treatment as a failure ("death-censored technique failure"). Times to death or technique failure were examined with standard survival analysis methods, including Kaplan-Meier models and Cox regressions for multivariate analyses. PD treatment episodes were censored at the time of transplantation. For technique failure, multiple failures were analyzed with a Cox model stratified according to initial or subsequent episodes of PD. Standard errors were calculated by using robust variance techniques (19), clustered according to the hospital of initial treatment to address correlations within centers (20,21). The covariates included in the Cox models were age, gender, race, type I and type II diabetes mellitus, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, treated hypertension, current smoking, country, and size of the center at which dialysis was initiated. Multivariate models initially included all of the variables; those with $P > 0.20$ were dropped in a backward stepwise manner. First-level interactions of BMI with relevant factors were examined in all models and were tested with the Wald test. A possible association of outcomes with the number of PD patients treated (center size) was examined by dividing the treating hospitals into approximate quartiles of <150, 150 to 249, 250 to 300, and ≥400 first PD treatment episodes during the study period. To address possible bias resulting from informative censoring, a supplementary mortality analysis was performed with intent-to-treat principles. This analysis ignored technique failure but censored data at the time of the first transplant. PD episodes that began after the first transplant were also ignored in the supplementary analysis.

Results

Patient Characteristics

Of 19,635 people who began RRT in Australia or New Zealand between April 1, 1991, and March 30, 2002, 9679 people (49%) underwent at least one PD treatment. In total, 11,392 episodes of PD in 17,973 person-yr were recorded. During this period, the use of PD techniques (compared with hemodialysis) decreased slightly. The vast majority of PD was performed with continuous ambulatory PD, but an increasing minority of patients used automated cyclers in recent years (Figure 1). Information regarding weight and height at the start of RRT was available for 9440 (98%) of the PD cohort. For 5754 people, PD was the RRT modality used at the commencement of RRT. For the remainder, the median time from the commencement of RRT to the first PD treatment was 38 d (interquartile range, 20 to 89 d). As expected for a group beginning RRT during this period, most people were approximately 60 yr of age or older at RRT commencement, and type II diabetes mellitus, coronary artery disease, and hypertension were very prevalent (Table 1). According to BMI criteria, 17% of people were obese (including 513 patients, 5%, with BMI values of ≥35 kg/m^2), and an additional 31% were overweight.

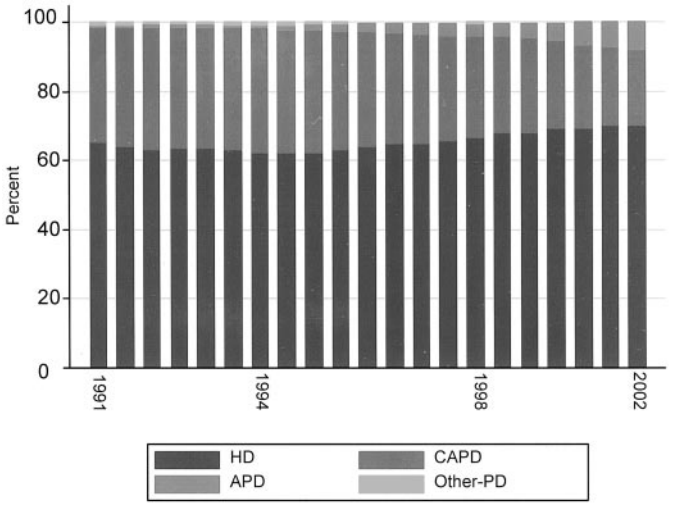

Figure 1. Distributions of patients according to the mode of dialysis in each of the 6-mo Australia and New Zealand Dialysis and Transplant Registry surveys between 1991 and 2002. HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis (PD); APD, automated PD.

Effects of BMI on Survival Rates

There were 3133 deaths during periods of PD treatment, with an additional 296 deaths occurring within 60 d after transfer to hemodialysis. Of the deaths, 56% were attributable to cardiovascular causes, with a greater proportion of cardiovascular deaths in the more obese group. The overall death rates did not differ between initial and subsequent episodes of PD treatment (log rank test, $P = 0.3$). Obesity (BMI of ≥30 kg/m^2) was associated with an increase in the risk of death in univariate analyses (Figure 2); there was no difference in the obesity risks for death <2 yr after the commencement of PD (hazard ratio, 1.19; 95% confidence interval, 1.04 to 1.35; $P = 0.01$) and later death (hazard ratio, 1.24; 95% confidence interval, 1.07 to 1.44; $P = 0.004$). There was no interaction between center size and mortality rates. There was, however, a significant interaction between Maori/Pacific Islander racial origin and BMI in the multivariate analysis ($P = 0.03$), and this group was analyzed separately. After adjustment for other factors also associated with death (female gender, age category, race, diabetes mellitus, coronary artery disease, chronic lung disease, and high BP), obesity remained associated with an increased risk of death (Table 2) except for the Maori/Pacific Islander group, for which no significant association with BMI was observed. When BMI was modeled as a continuous predictor, the mortality risk was lowest for BMI values

Table 1. Characteristics of initial cohort, at commencement of RRT[a]

Characteristic	Underweight (BMI of <20 kg/m^2) (n = 1127)	Normal Weight (BMI of 20 to 24 kg/m^2) (n = 3771)	Overweight (BMI of 25 to 29 kg/m^2) (n = 2937)	Obese (BMI of ≥30 kg/m^2) (n = 1605)
No. (% of all new RRT patients)[b]	1127/2501 (45%)	3771/7499 (50%)	2937/5775 (51%)	1605/2261 (71%)
Age (yr) (median, IQR)	59 (40 to 70)	61 (47 to 70)	62 (51 to 69)	58 (49 to 66)
Male[b]	392 (35%)	2053 (54%)	1755 (60%)	711 (44%)
New Zealand[b]	160 (14%)	780 (21%)	780 (27%)	562 (35%)
Australian Aboriginal	55 (5%)	186 (5%)	185 (6%)	138 (9%)
Maori/Pacific Islander[b]	44 (4%)	255 (7%)	459 (16%)	448 (28%)
Diabetes mellitus[b]				
type I	55 (5%)	275 (7%)	175 (6%)	59 (4%)
type II	160 (14%)	784 (21%)	1068 (36%)	829 (52%)
Coronary artery disease[b]	397 (35%)	1507 (40%)	1311 (45%)	723 (45%)
Cerebrovascular disease	173 (15%)	642 (17%)	475 (16%)	236 (15%)
Peripheral vascular disease[b]	297 (26%)	1083 (29%)	973 (33%)	522 (33%)
Chronic lung disease[c]	211 (19%)	591 (16%)	428 (15%)	248 (15%)
Hypertension at RRT start[b]	842/1034 (81%)	2999/3500 (86%)	2409/2747 (88%)	1336/1520 (88%)
Current smoking[b]	184 (16%)	509 (14%)	337 (11%)	169 (11%)
Height (cm) (median, IQR)	163 (157 to 170)	166 (160 to 174)	166 (160 to 173)	163 (157 to 170)
Weight (kg) (median, IQR)[b]	49 (45 to 54)	63 (57 to 69)	75 (69 to 82)	89 (81 to 98)
Deaths (n = 3296 with BMI recorded at RRT start)	395	1316	991	594
Death rate per 100 person-years (95% CI)[b]	17.2 (15.6 to 19.0)	18.4 (17.4 to 19.4)	18.6 (17.4 to 19.8)	21.3 (19.6 to 23.0)
Cardiovascular deaths	194 (49%)	705 (54%)	576 (58%)	363 (61%)

The proportions in each body mass index (BMI) category were compared with a chi-squared test, or ANOVA (for continuous variables).
[a] RRT, renal replacement therapy; IQR, interquartile range; CI, confidence interval.
[b] $P < 0.001$.
[c] $P < 0.01$.

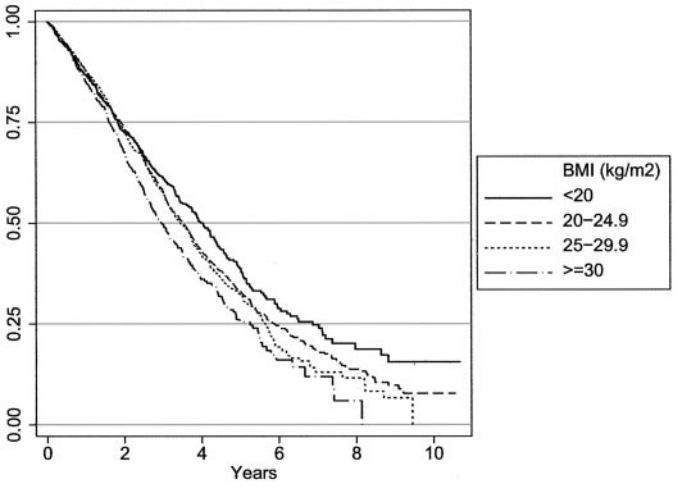

Figure 2. Kaplan-Meier patient survival curves for each of the body mass index (BMI) categories (log rank test, $P < 0.001$).

of approximately 20 kg/m^2 and increased steadily with higher BMI values, although confidence intervals for the multivariate model were broad (Figure 3).

In the supplementary intent-to-treat analysis, 4531 deaths were reported. In that analysis, with the exclusion of patients of Maori/Pacific Islander racial origin, obesity (BMI of ≥30 kg/m^2) was significantly associated with increased mortality rates in univariate analyses (hazard ratio, 1.14; 95% confidence interval, 1.03 to 1.26; $P = 0.009$) and remained significantly associated after adjustment for age, gender, and comorbidities (hazard ratio, 1.27; 95% confidence interval, 1.14 to 1.42; $P < 0.001$).

Effects of BMI on Technique Survival Rates

During the study period, 4237 PD episodes ended in technique failure. The technique failure rate was higher for subsequent episodes, compared with initial episodes, of PD (log rank test, $P < 0.001$) (Table 3). In univariate analyses, obesity tended to be associated with worse technique survival rates (Figure 4). Subsequent analyses with a Cox model stratified according to initial/subsequent episode of PD demonstrated that technique survival rates were significantly worse for the groups with increased BMI (Table 4). The other significant predictors of technique failure were indigenous race and country but not age or comorbidities. No interaction of BMI with center size or Maori/Pacific Islander racial origin was demonstrated. When BMI was modeled as a continuous predictor in a fractional polynomial analysis, the risk of technique failure increased steadily with higher BMI values until approximately 40 kg/m^2; beyond that point, the number of events was too small for reasonable inferences (Figure 5).

Overall, catheter-associated infections (peritonitis, exit site infections, and tunnel infections) represented the most common cause of technique failure (37%), followed by patient preference (20%) and inadequate small-solute clearance (11%). The proportions of technique failures attributed to peritonitis or exit site infections were constant for the BMI

Table 2. Risk of death during PD treatment according to BMI categories[a]

BMI (kg/m^2)	Hazard Ratio			
	All Other Groups		Maori/Pacific Islander Racial Origin	
	Crude	Adjusted	Crude	Adjusted
<20	0.90 (0.80 to 1.02) ($P = 0.09$)	1.02 (0.90 to 1.17) ($P = 0.7$)	0.88 (0.52 to 1.51)	1.27 (0.76 to 2.14) ($P = 0.4$)
20 to 24	1 (reference)	1 (reference)	1 (reference)	1 (reference)
25 to 29	1.03 (0.95 to 1.12) ($P = 0.5$)	1.01 (0.92 to 1.11) ($P = 0.8$)	1.05 (0.83 to 1.33) ($P = 0.7$)	0.85 (0.65 to 1.12) ($P = 0.3$)
≥30	1.20 (1.09 to 1.32) ($P < 0.001$)	1.36 (1.20 to 1.54) ($P < 0.001$)	1.12 (0.88 to 1.42) ($P = 0.4$)	0.88 (0.68 to 1.13) ($P = 0.4$)

[a] Hazard ratios are crude and adjusted for age, gender, and comorbidities. Values in parentheses are 95% confidence intervals. PD, peritoneal dialysis.

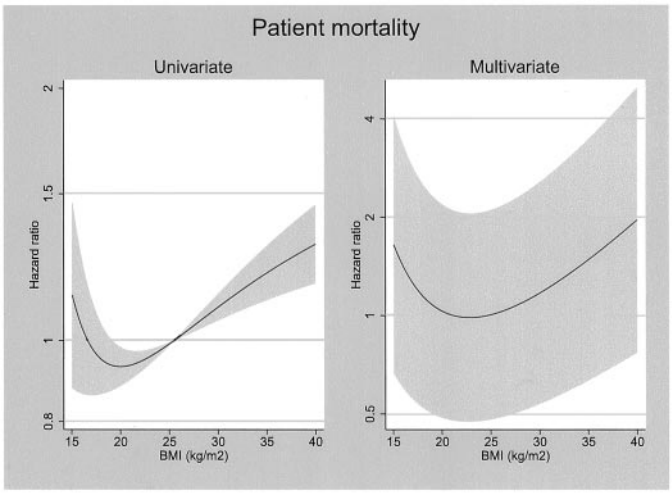

Figure 3. Univariate and multivariate fractional polynomial graphs depicting the relationship between BMI and mortality risk. Shaded areas indicate the 95% confidence limits.

categories. However, clearance problems were more frequently indicated as the cause of PD discontinuation among patients with higher BMI (underweight, 13%; normal weight, 18%; overweight, 20%; obese, 23%; $P < 0.01$), whereas patient preference was more common among patients with lower BMI (underweight, 27%; normal weight, 21%; overweight, 17%; obese, 15%; $P < 0.05$).

Discussion

The results of this study indicated that obesity was associated with significantly worse PD patient outcomes in Australia and New Zealand, with respect to overall survival and technique survival rates. These findings contrast with the results of previous studies, which demonstrated either beneficial (11) or neutral (11–13) effects of obesity (or increased body surface area) on PD outcomes. Part of the disparity in these observations may be related to the fact that the previous studies were all small (50 to 204 patients), of short duration, and limited to only one or a few centers. Our cohort also contained a greater proportion of morbidly obese patients (BMI of $\geq$35 kg/m^2) than did previously studied groups.

In a recently reported, randomized, controlled trial of two different PD doses among 965 patients undergoing continuous ambulatory PD (the Adequacy of Peritoneal Dialysis in Mexico study), Paniagua *et al.* (22) stratified patient outcomes according to tertiles of three different indices of body size (body surface area, calculated total body water, and BMI). Those authors observed no significant differences in survival rates among the strata, but subjects were monitored for only slightly more than 2 yr. Although no variation in the effects of BMI with time was demonstrated in our study, the modest relative risk meant that the separation of survival curves for the different BMI categories was particularly apparent only after 2.5 to 3 yr. Furthermore, patients in the Adequacy of Peritoneal Dialysis in Mexico study had lower average BMI values (control, 25.3 kg/m^2; intervention, 25.8 kg/m^2) than did patients in this study, included a larger number (58%) of patients undergoing chronic treatment (thus increasing the potential for survivor bias), and represented only a fraction of the total dialysis population. By comparison, our investigation had greater external validity because it included all PD patients from all dialysis centers in Australia and New Zealand.

The relationships observed here were similar with differing end points and analytical methods, with the exception of the association between BMI and death, which was not observed among patients of Maori or Pacific Islander racial origin. This is consistent with the findings of other studies, which were similarly not able to identify a relationship between BMI and death in Pacific Islander groups (23) or certain other racial groups, such as African Americans (3,24).

An interesting finding of this study was that, when BMI was considered as a categorical variable, only obesity (BMI of $\geq$30 kg/m^2) was associated with an increased risk of death in the multivariate analysis. Neither the overweight (25 to 29.9 kg/m^2) nor underweight ($<$20 kg/m^2) category demonstrated a mortality risk that was significantly different from that for individuals with normal BMI (20 to 24.9 kg/m^2). The apparent difference between these results and the findings of studies that demonstrated reduced survival rates for underweight and overweight patients (22,25,26) may be related to differences in the statistical handling of BMI as a variable. There is substantial evidence, in both general and hemodialysis populations, suggesting that the relationship between BMI and mortality rates may not be linear. The univariate and multivariate fractional polynomial analyses used in our investigation supported this, with a J-shaped relationship between BMI and patient mortality rates being observed. Nevertheless, in all analyses for the BMI range of 20 to 40 kg/m^2, containing a large majority (87%) of patients, both patient and death-censored technique survival rates worsened with higher BMI. A decrease in survival rates was observed for underweight patients (BMI of $<$20 kg/m^2). Such an association was well recognized in previous studies of PD patients (25–27).

The strengths of this study included its very large sample size for a PD patient population, its unusually long follow-up period, and the robustness of its findings with different statistical methodologies. Because we included all centers in both countries, we could avoid the bias associated with reports from single centers. Moreover, our cohort consisted solely of new patients, thus avoiding the potentially confounding factor of survivor bias that is associated with chronically treated population studies (3).

The strength of registry analyses with respect to their extent of coverage must be balanced against their main weakness, which is a limited depth of coverage. Consequently, only a limited number of potential confounders were included in the multivariate analyses. Certain parameters, such as patient compliance, were not recorded in the ANZDATA Registry. Moreover, although we were able to adjust for reported comorbidities on a categorical basis, the ANZDATA Registry does not collect information on the severity of comorbidities. Therefore, residual confounding could have explained some of the observed trends in mortality rates.

Table 3. Outcome events stratified according to PD treatment number[a]

PD Episode	*n*	Person-yr	No. of Technique Failures	Technique Failure Rate (no./100 person-yr)	No. of Deaths	Death Rate (no./100 person-yr)
Initial	9679	15,945	3452	21.6 (20.9 to 22.3)	2924	18.3 (17.7 to 19.0)
Subsequent	1713	2028	785	38.7 (36.1 to 41.5)	505	24.8 (22.8 to 27.1)

[a] Technique failure excludes deaths, but includes all discontinuations of PD for ≥30 d other than for transplantation. Values in parentheses are 95% confidence intervals.

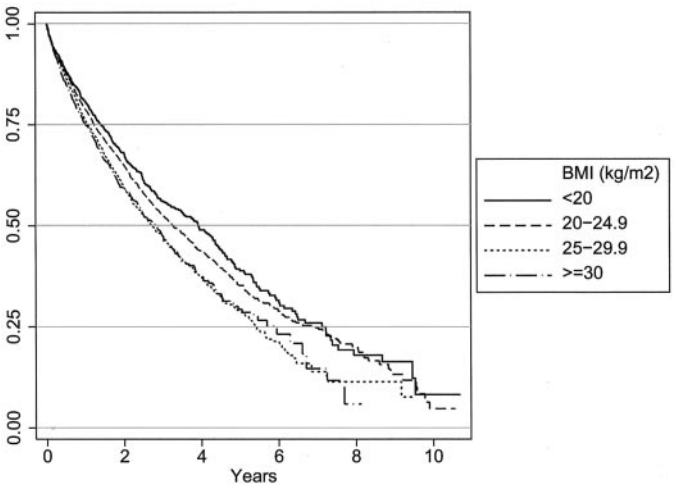

Figure 4. Kaplan-Meier death-censored technique survival curves for each of the BMI categories (log rank test, $P < 0.001$).

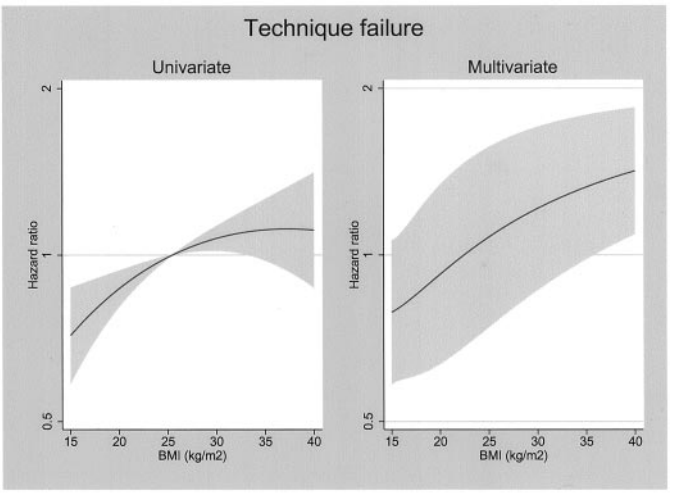

Figure 5. Univariate and multivariate fractional polynomial graphs depicting the relationship between BMI and risk of death-censored technique failure. Shaded areas indicate the 95% confidence limits.

Another concern was selection bias, which was suggested by the fact that patients who were obese at the commencement of RRT were more likely to have undergone an episode of PD and were more likely to exhibit diabetes mellitus. Although the ANZDATA Registry does not collect data on how the units selected patients for PD, it is possible that patients with higher risks of either death or technique complications were preferentially treated with PD. This point is important, because studies in the general population have revealed that the increase in mortality risk with increasing BMI is greater in groups of healthier individuals, compared with those with greater burdens of comorbid illnesses (including diabetes mellitus and cardiovascular disease) (3,28). Such an explanation does not seem likely to be applicable in this study, because comorbidities such as diabetes mellitus and cardiovascular disease were highly prevalent in our study population and rates were similar to those reported for other studies that examined the effects of BMI on PD outcomes (11,13,26).

The observation of increased mortality risks with increasing BMI among PD patients is also at odds with findings in large hemodialysis populations, in which obesity has consistently been observed to confer a significant survival advantage (5–10). This may be partly attributable to the fact that PD affords less efficient small-solute clearance than does hemodialysis, which may be particularly limiting for large patients (29–33). Another possibility is that residual renal function, which is strongly correlated with PD outcomes (34,35), may be ad-

Table 4. Risk of PD technique failure (censored for patient death) according to BMI categories[a]

BMI (kg/m^2)	Hazard Ratio	
	Crude	Adjusted
<20	0.90 (0.80 to 1.01) ($P = 0.09$)	0.89 (0.80 to 1.99) ($P = 0.3$)
20 to 24	1 (reference)	1 (reference)
25 to 29	1.15 (1.00 to 1.25) ($P = 0.001$)	1.15 (1.06 to 1.24) ($P < 0.001$)
≥30	1.15 (1.02 to 1.31) ($P = 0.03$)	1.16 (1.07 to 1.26) ($P < 0.001$)

[a] Hazard ratios are crude and adjusted for age, gender, and comorbidities. Values in parentheses are 95% confidence intervals.

versely affected by obesity. Although the ANZDATA Registry now records residual renal function at the initiation of PD, the recent commencement and changes in the measurement of residual renal function precluded the use of this variable as a covariate in this study. A recent study, however, reported that obese PD patients lose residual renal function more rapidly after PD commencement than do normal or underweight patients (36), which would be consistent with a negative effect of increasing BMI on technique and patient survival rates.

In conclusion, this registry-based study of new PD patients in Australia and New Zealand demonstrated that obesity at the commencement of PD is a significant risk factor for death (except among patients of Maori/Pacific Islander racial origin) and technique failure. Whether patients with higher BMI would benefit from receiving hemodialysis from the beginning was not specifically addressed by this investigation. Obese patients undergoing PD should be closely monitored for problems and considered for intervention strategies targeted at weight reduction.

Acknowledgments

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