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Body size, dialysis dose and death risk relationships among hemodialysis patients

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Background. The normalized treatment ratio, Kt/V derived from urea kinetic models (UKM), is a commonly used measure of dialysis dose. This measure assumes that smaller patients with low volume of urea distribution (V) require proportionately less total treatment (Kt) than larger patients. The conclusion has been questioned because the UKM use assumptions that could make them invalid for accurately predicting a clinical outcome like survival. It is possible that a relationship exists between Kt and body size whereby a different Kt is required for different sizes. This study therefore explored the relationships among body size, Kt, and death risk focusing on possible interactions between Kt and size.

Methods. The sample included 43,334 patients treated on January 1, 1999. Survival time was modeled using Kt or body size groups to evaluate the shape of the risk profiles. Kt and the size measures were then evaluated together as continuous functions both in main effects (that is, Kt and size) and interaction models to see if the association of Kt with risk might be different for different sizes. The size measures were body weight, weight adjusted statistically for height, body surface area (BSA), weight divided by height (wt/ht) and the body mass index (BMI).

Results. The log of risk decreased in rough linear fashion for Kt, weight, weight for height, and BSA. The log-risk relationships were "reverse J-shaped" for wt/ht and BMI. The main effects models suggested improved survival with increasing Kt and all of the size measures. Adding an interaction term increased the benefit associated with increasing Kt and for weight, weight for height and BSA at low values of Kt and size. A significant, positive interaction term mitigated those effects at higher values. Thus, the death risk penalties associated with reducing Kt among small patients were as great as or greater than they were among large patients. A similar pattern was observed for V. Adding the interaction to the BMI model destroyed the main effects, so that there was no significant association between risk and either Kt or BMI. A cross-categorical model of BMI and Kt, however, revealed improving survival with increasing Kt among both low and high BMI patients throughout the range of Kt.

Conclusions. Evidence supporting the intuition that smaller patients require proportionately lower dialysis dose than larger patients was not found. To the contrary, smaller patients suffer as much risk as or more risk than larger patients from reducing Kt. Deciding dialysis treatment using a Kt/V based intuition may lead to avoidable under-dialysis particularly among small patients.

Key words: dialysis, ESRD, BSA, BMI, survival, end-stage renal disease, kidney disease, overweight.

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The volume of urea distribution (V) is often divided into total dialysis treatment (Kt; the product of average urea clearance during dialysis and the length of the treatment) to give a normalized treatment ratio (Kt/V). Kt/V evolved from mathematical models of urea kinetics (UKM) during dialysis used in a clinical trial to control blood urea nitrogen concentration (BUN) [1, 2]. It and a related quantity, the urea reduction ratio (URR), are commonly used in clinical practice as outcome-based measures of dialysis dose [3–5].

The UKM and its use as an outcome based measure have been challenged recently on the grounds that certain premises on which the UKM rest are not valid when they are used to judge a clinical outcome [6–9]. The Kt/V ratio originated from the solution of a simple one-compartment, first-order mass balance on urea during dialysis. The urea mass balance requires that any urea removed by the dialyzer during treatment originated from the urea distributed throughout V. The numerator Kt (clearance K times time t) represents the volume of blood cleared of urea during the treatment, and the denominator V represents the total volume of fluid that potentially could be cleared during the treatment. While the UKM have become more sophisticated to more closely mimic the human body (two compartments, variable plasma volume, residual renal function, etc.), the basic concept of UKM remains that the amount of dialysis required is proportional to the distribution volume V.

At the same time, the basic assumption that urea is a surrogate marker for one or more critical uremic toxins, and that those toxins are removed proportionally along with urea, may have been invalidated with the changes

in typical treatment parameters (such as, high membrane permeability or short treatment time) and patient population (for example, older, more diabetic, less anemic) since the UKM were conceived [1, 2]. For example, if a critical toxin is not transported as rapidly as urea to the plasma compartment, current shorter treatments may simply not provide as much toxin removal as longer treatments thirty years ago. Given the implicit assumptions in UKM, it makes sense to re-evaluate the relationship between dialysis dose and risk of death with more recent data.

While the concept that larger patients need more dialysis is intuitively appealing, recent attempts to demonstrate how much urea removal is enough, that is, a threshold Kt/V beyond which risk of death no longer improves, have been seriously confounded by the fact that small body size is itself a risk factor for dialysis patients [8–14]. Thus, the mathematical relationship between adequate dialysis (as Kt) and body size may be more complicated than a simple linear increase from a zero intercept as represented by Kt/V.

We therefore evaluated the association between a measure of total dialysis dose per treatment (Kt) and several measures of body size with death risk in a large sample of hemodialysis patients. The strategy evaluated possible interactions between dose and size to see if greater dose might be required for larger patients to preserve life. By alternative, can dose be safely reduced in smaller patients without exposing them to unnecessary risk?

METHODS

The data were taken from the Fresenius Medical Care (NA) clinical data system that has been described previously [9, 14–16]. Patients receiving hemodialysis three times weekly on December 31, 1998 were selected for analysis. Values for age, gender, race, and diabetic status (the case mix measures) were taken as of year-end, 1998. Values for post dialysis body weight, body height, and the dialyzer urea clearance × dialysis time product (Kt) were taken as the average of all such measurements performed on patients during the last three months of 1988. Patients were then followed during calendar year 1999 until death or time of censor.

Cox regression analyses [17] using Kt and/or different body size measures were performed with and without case mix adjustments. Kt and the body size measures were treated as categorical or continuous measures in different models. The main effects for Kt and body size were evaluated both without, (the simple models) and with interaction terms (interaction models). Categorical data were used to evaluate the linearity of association between the measures and log mortal hazard.

The body size measures were body weight (adjusted and not adjusted for body height), body surface area (BSA), the weight to height ratio, and the body mass index (BMI). BSA was estimated according to the method of DuBois and DuBois [18]. The BMI, so called by Keys [19], was calculated according to Quételet [20] as the ratio of body weight to the square of body height.

The clearance × time products, Kt, were estimated by taking the negative logarithms the patients' post-dialysis to predialysis BUN ratios to estimate a single pool Kt/V as described before [6, 7, 9, 14, 21]. The pre- to post-BUN ratio also can be calculated as one minus the urea reduction ratio divided by one hundred (URR/100). The Kt/V was then multiplied by V to give Kt. V was estimated from Chertow et al's equation [22, 23].

Table 1. Distribution of case mix, body size and dialysis dose measures among 43,334 patients

				Percentiles		
Variable	Units	Mean	SD	1st	Median	99th
Age	*years*	60.30	15.11	24.00	62.00	88.00
Gender	*% male*	51.98				
Race						
	% white	50.24				
	% black	42.68				
	% other	7.09				
Diabetes	*% with*	47.89				
Height	*cm*	165.75	12.80	122.00	166.00	191.00
Weight	*kg*	73.46	20.56	40.00	70.30	99.00
Wt/Ht	*kg/cm*	0.44	0.11	0.26	0.42	0.79
BSA	m^2	1.80	0.26	1.27	1.79	2.51
BMI	kg/m^2	26.92	8.03	15.74	25.33	56.46
Kt	*l/Rx*	48.91	11.04	25.56	48.21	78.53
V	*l*	40.16	8.84	24.21	39.13	65.51
URR	%	70.20	7.26	48.50	70.85	85.00

RESULTS

Table 1 describes the essential attributes the patient population. The distributions of both Kt and the body size measures were reasonably wide. The 98% confidence range for Kt spanned 25.6 to 78.3 l/Rx, for example, a threefold difference. The range for body weight spanned 40 kg to nearly 100 kg, about a 2.5-fold difference. The ranges for such measures such BSA and the BMI were also wide. All body size measures were inversely correlated with the URR (r's = −0.26, −0.38, −0.42, −0.41, −0.33, and −0.23 for height, weight, V, BSA weight/height, and BMI; all $P < 0.001$). They were directly correlated with Kt (r's = 0.49, 0.41, 0.56, 0.52, 0.27, and 0.08 respectively; all $P < 0.001$).

Figure 1, top panel, shows the log hazard profiles for Kt. The profiles were close to linear throughout the range of Kt observed here. Adjustment for the case mix measures made little difference in the shape of the profile or the relative magnitudes of risk.

The bottom panels of Figure 2 show the profiles for BSA (left panel), an absolute measure of body size, and

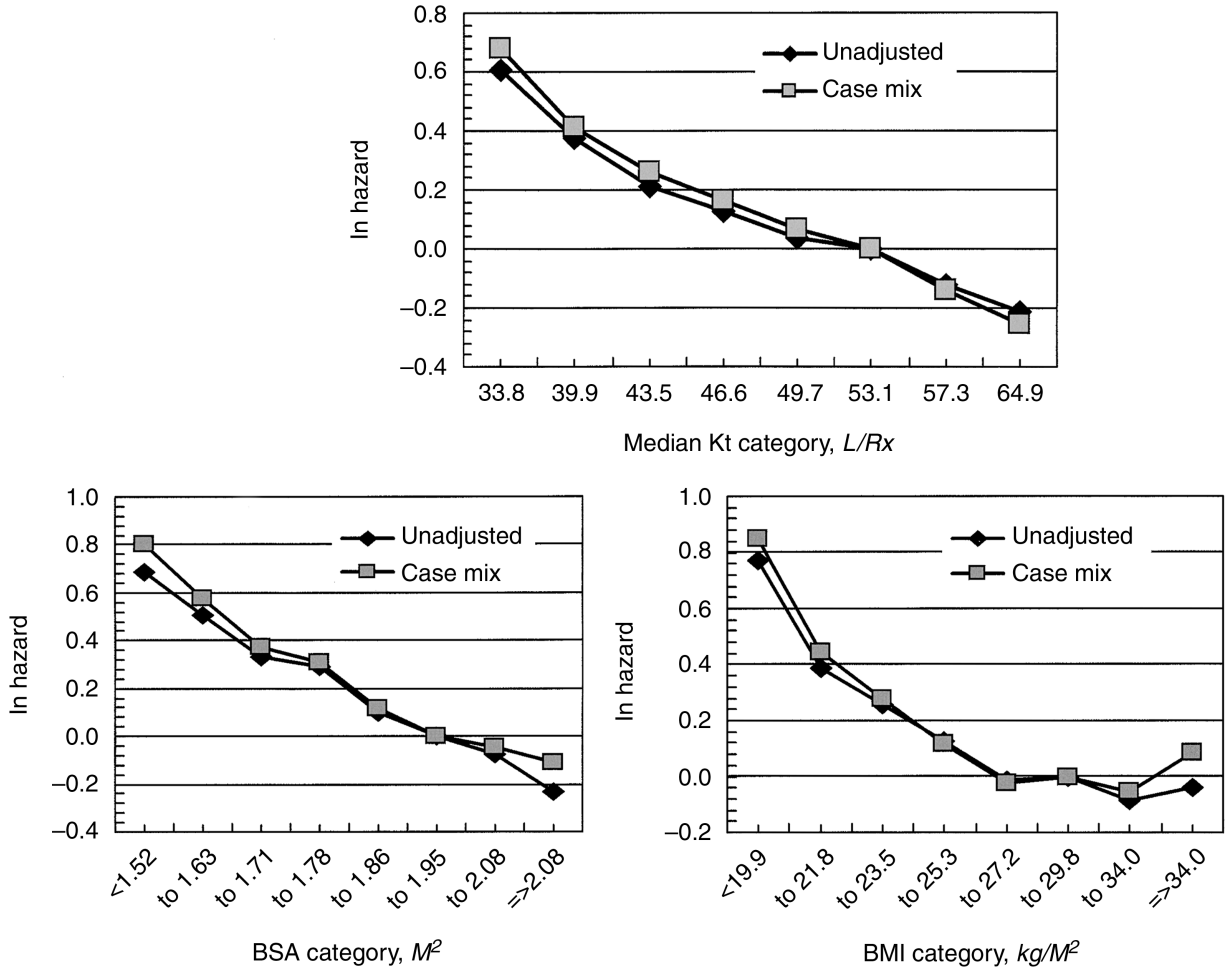

Fig. 1. Log hazard response profile for Kt, body surface area (BSA; an absolute measure of body size), and body mass index (BMI; a relative measure of body size). Analyses were unadjusted and adjusted for age, gender, race, and diabetic status. Symbols are: (◆) unadjusted; (□) case mix adjusted.

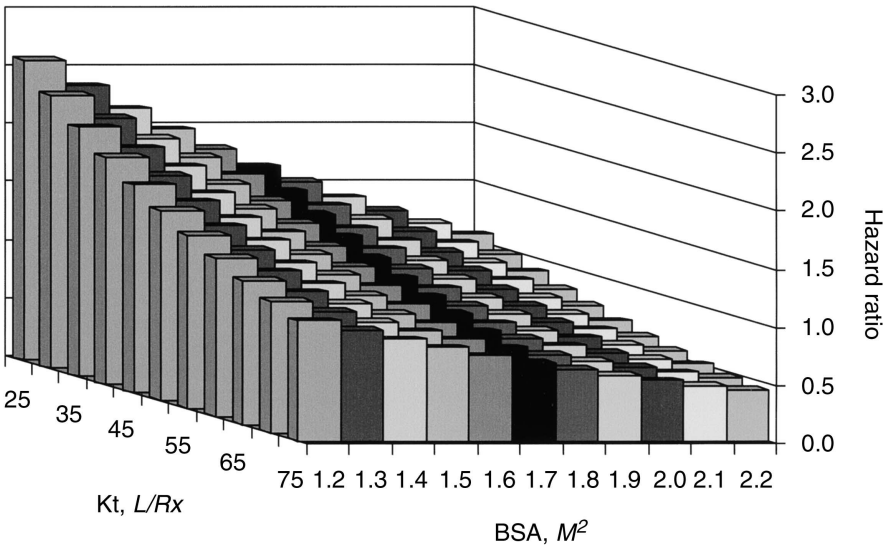

Fig. 2. Continuous risk (hazard) plane for Kt and BSA. The analysis did not include an interaction term between Kt and BSA and was case mix adjusted. The estimated hazard ratio at Kt = 75 and BSA = 2.2 was 0.44 compared to the ratio (1.0) at the mean Kt and BSA. It deteriorated from 0.44 to 1.10 when Kt declined from 75 to 25 at the highest BSA (2.2), a 2.5-fold deterioration. It deteriorated from 0.44 to 1.04 as BSA fell from 2.2 to 1.2 at the highest Kt (75), a 2.4-fold deterioration. Finally, it deteriorated from 1.04 to 2.59 when Kt declined from 75 to 25 among small patients (BSA = 1.2), a 2.5-fold deterioration.

Table 2. Models evaluating dialysis dose, body size, and their possible interactions

Form of weight and height	Parameter	Unadjusted β	Unadjusted χ^2	Case mix β	Case mix χ^2
Weight only	Weight	−0.01379	283	−0.01317	212
	Kt	−0.01474	113	−0.01938	179
	Weight	−0.02603	80	−0.02911	91
	Kt	−0.03301	57	−0.04311	90
	Kt × wt	0.00025	20	0.00033	30
Height and Weight	Height	0.00604	26	0.00666	26
	Weight	−0.01467	302	−0.01380	227
	Kt	−0.01785	140	−0.02198	207
	Height	0.00643	29	0.00701	29
	Weight	−0.02824	91	−0.03066	100
	Kt	−0.03822	72	−0.04719	104
	Kt × wt	0.00028	23	0.00035	34
BSA	BSA	−0.89324	207	−0.86566	153
	Kt	−0.01330	79	−0.01823	144
	BSA	−1.50257	60	−1.59047	63
	Kt	−0.03688	25	−0.04665	38
	Kt × BSA	0.01322	11	0.01589	15
Weight/height	Weight/Ht	−0.02254	274	−0.02129	212
	Kt	−0.01859	199	−0.02223	252
	Weight/Ht	−0.02664	24	−0.03137	31
	Kt	−0.02244	10	−0.03176	36
	Kt × (wt/ht)	0.00009	NS	0.00022	3
BMI	BMI	−0.02789	195	−0.02574	150
	Kt	−0.02295	325	−0.02556	350
	BMI	0.00657	NS	0.00169	NS
	Kt	−0.00180	NS	−0.00838	3
	Kt × BMI	−0.00079	24	−0.00064	15
Body water	TBW	−0.02032	118	−0.02660	120
	Kt	−0.01511	100	−0.01895	154
	TBW	−0.04452	56	−0.05279	70
	Kt	−0.03508	51	−0.04053	65
	Kt × TBW	0.00051	18	0.00055	20

β means regression coefficient, χ^2 means the chi square statistic. All $P < 0.001$ except "NS" = not significant and $3 = 0.10 > P > 0.05$.

BMI (right panel), a relative measure. The profiles for the other absolute measures, weight and V, were similar to BSA and were reasonably linear throughout their ranges. The profiles for the BMI suggested a curvilinear relationship. The relationship for weight/height, the other relative measure, was similar to BMI but less pronounced.

Table 2 summarizes the statistical models evaluating Kt and the body size descriptors. The coefficients for weight and Kt in the unadjusted and the case mix adjusted models were similar in both the simple (main effects only) and interaction models. Death risk improved (the coefficients were negative) with increasing values of both Kt and weight in all four models. Exponentiating the coefficients in the simple model and subtracting the resulting values from one suggests that death risk improved by about 1.4% per kg of increased body weight and by about 1.5% per L/Rx of increasing Kt in the simple, unadjusted model. Similar values were 1.3% and 1.9% in the simple, adjusted model. Adding the interaction terms (approximately) doubled the coefficients associated with Kt and weight in both models. The interaction terms in the models were positive and of similar magnitude. The net effect of doubling the coefficients associated with the main effects (Kt and weight) with a positive interaction term is to accentuate relative death risk at combined low Kt and weight and to "flatten" it when the values of both measures are high.

Adjusting for body height, so that weight (and Kt) is evaluated at constant height, did not affect materially the relationships described above. The coefficients associated with height were positive while those associated with weight remained negative. Death risk deteriorated by about 0.61% for each cm increase of height at the mean weight and increasing weight improved risk by about 1.46% for each kg at the mean height. The pattern suggests that death risk deteriorated with increasing height at constant weight but improved with increasing weight at constant height. In other words, a taller, thinner person tended to suffer greater death risk than a shorter person of the same weight. Similarly, a heavier person tended to enjoy better survival than a lighter person of the same height.

The BSA and body water model sets were similar to the body weight sets. We illustrate the effect of the interaction in these models using BSA because it combines weight and height in a single body size measure that well accepted and well understood. Figure 2 illustrates the relationships described by the simple (main effects only) model. The hazard plane describes worsening death risk both with decreasing Kt and decreasing BSA so that maximum risk is observed at low values of both measures and minimum risk is observed at high values. Death risk improved, however, throughout the range of Kt even at low BSA.

Figure 3 illustrates how adding an interaction term to the statistical model changed the hazard plane. Combining the higher negative values for the main effects (Kt and BSA) with a positive interaction (Kt × BSA) term shifted the plane by increasing relative risk at low values of both measures while flattening it at high values. Evaluate, for example, the relative effect of reducing Kt among large and small persons by examining the shape of changing hazard along the right (large persons) and left (small persons) columns of the plane. Start at high values of both Kt and BSA (75 L/Rx, 2.2 M^2) and trace the increasing hazard ratio at high BSA (HR = 0.18) along the right column of the plane to low Kt (25, 2.2) where HR was 1.38, a near eightfold increase. Now trace the hazard profile at high Kt and low BSA (75, 1.2) where HR was 0.59 to low Kt (25,1.2) where HR was 9.83, a near 17-fold increase. In other words, the consequences of reducing Kt among small patients was at least as great and probably greater than reducing it in large patients.

The coefficients associated with the main effects in the weight/height model set (Table 2) suggested improved survival associated with both Kt and weight/height. The interactions between Kt and weight/height were not sig-

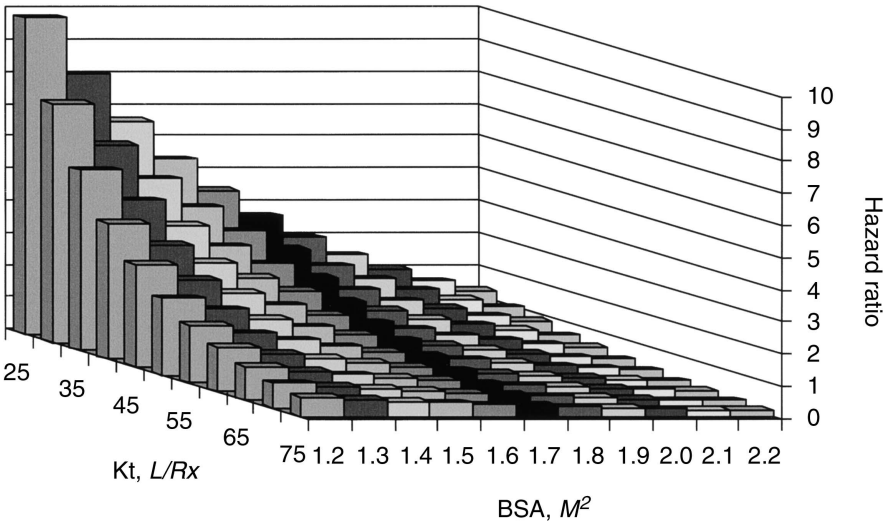

Fig. 3. Continuous risk (hazard) plane for Kt and BSA. The analysis included an interaction term between Kt and BMI and was case mix adjusted. The estimated hazard ratio at Kt = 75 and BSA = 2.2 was 0.18 compared to the ratio (1.0) at the mean Kt and BSA. It deteriorated from 0.18 to 1.38 when Kt declined from 75 to 25 at the highest BSA (2.2), a 7.7-fold deterioration. It deteriorated from 0.18 to 0.59 as BSA fell from 2.2 to 1.2 at the highest Kt (75), a 3.3-fold deterioration. Finally, it deteriorated from 0.59 to 9.83 when Kt declined from 75 to 25 among small patients (BSA = 1.2), a 16.7-fold deterioration.

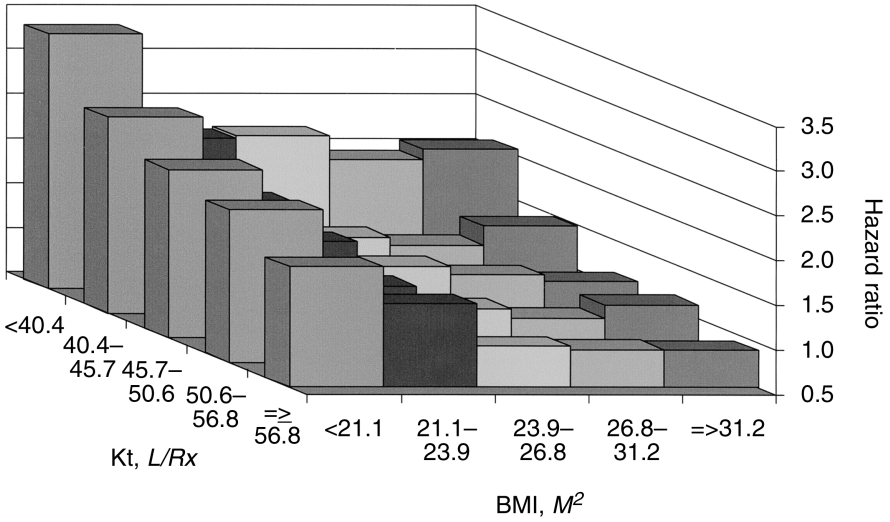

Fig. 4. Categorical risk (hazard) plane using 25 groups of patients cross classified by Kt and BMI.

nificant. The simple models of the BMI set also suggested improved survival with increasing Kt and increasing BMI. Adding interaction terms to the BMI models, however, extinguished the significance of the main effects, even changing the sign associated with the BMI. The only remaining significant terms were the interaction terms that were negative. In other words, the effect of the interaction in these models using relative body size (wt/ht and BMI) was different from those using absolute body size (the other size measures). Emphasizing height by taking its square, destroyed the integrity of the model set likely due to the highly non-linear nature of relationship between log risk and BMI (Fig. 1).

We therefore constructed a categorical response plane for the BMI that is shown as Figure 4. Patients were cross classified by Kt quintile and BMI quintile into 25 groups. The fourth Kt–BMI quintile was selected as the reference group. Monotonic improvement of death risk with increasing Kt was observed in each BMI quintile except the fifth. The hazard ratio for the fourth Kt quintile of it (1.146) was slightly higher than the third (1.135). Risk in the fifth Kt quintile of these high BMI patients, however, was lower (0.907) than in both the third and fourth quintile. The unadjusted and case mix adjusted models gave similar results. Both models showed progressive improvement of death risk with increasing Kt among the lowest BMI patients.

DISCUSSION

The validity of the urea kinetic equation systems (UKM) for judging clinical outcome has been challenged because they are based on invalid premises [6–9, 14]. The most important of those for these purposes is that

V, presumed to reflect total body water, is only a diluent for urea without other properties [1, 2]. In reality, however, V also reflects body cell mass increasing with body size. Evidence here and elsewhere [9–14, 16] demonstrates that greater body size is associated with better survival among dialysis patients, thus showing the incorrect nature of the implied premise about V when it is used to predict survival. Therefore, the UKM systems and the parameters following from them like the Kt/V and the URR lack a valid theoretical foundation as outcome based measures of dialysis dose.

Furthermore, practical inconsistencies attend the use of those measures when they are used to judge clinical care. Black dialysis patients are treated at lower URR than whites but enjoy better survival [24]. Black patients also tend to have higher serum creatinine concentration than whites, suggesting that the contributing cause is greater body mass rather than better renal function [25]. Thus, blacks enjoy better survival on dialysis than whites not because blacks need less dialysis, but rather because they tend to have greater body mass than whites. Blacks tend to be treated at similar Kt to whites. Dividing the same Kt by a larger V gives a smaller Kt/V ratio and thus a lower URR.

Kopple and colleagues have shown that smaller patients are treated at higher URR but suffer greater death risk than larger patients [10]. The fact did not evolve from efficient removal of nutrients (at higher URR) among small patients causing malnutrition and death. Rather, smaller patients suffered greater death risk due to small body size but had higher Kt/V, and thus greater URR, due also to small body size.

Higher death risk at higher URR has been described [14, 21]. The risk profiles (charts of death risk by URR) were "U-shaped" or "reverse J-shaped" with higher risk at both ends of the URR distribution than at its middle. Such a profile must be interpreted as providing evidence for "toxic dialysis" or dialyses "over dose" if measures like the URR and single pool Kt/V are deemed pure and perfect measures of dialysis dose. In fact, however, smaller patients were at greater death risk due to small body mass and also tend to be treated at higher Kt/V and URR than larger patients with more mass and therefore lower risk.

All of those inconsistencies can be traced to the incorrect premise about V that is part of the UKM. These data provide evidence for a more serious consequence arising from the use of those UKM based measures to judge clinical care that also can be traced to the incorrect premise about V.

Adding an interaction term to the absolute size models informs the shapes of risk planes such as that illustrated by Figure 3. The positive interaction term modulated the benefit of increasing Kt and BSA at higher values. The risk plane would have been steeper at high body size than low, and the profile at low size less steep than it appears here, had the interaction term been negative instead of positive. Thus, information such as that given in Table 2 and Figures 3 and 4 indicate that small patients as well as large, and perhaps more than large, experienced greater death risk as a consequence of low Kt. Small patients as well as large, and perhaps more than large, benefited from greater Kt. The information contradicts conclusions derived from the premise that indexing Kt to V, as Kt/V, is the optimum measure of dialysis dose and further suggests that intuition derived from it exposes smaller patients to avoidable death risk.

The Kt/V based intuition, for example, would lead clinicians to believe that a 50 kg patient with V of 25 L (say) is treated in optimum fashion at Kt = 30 L/Rx if the target Kt/V = 1.2. A larger 100 kg patient with V of 50 L (say) would require Kt = 60 L/Rx. These data suggest that the larger patient has lower underlying risk than the smaller patient but that both can benefit from the greater Kt. They suggest that patients with lower body mass (kg) are at risk compared to larger patients. Reducing Kt for smaller persons in proportion to their size not only adds to but also compounds the risk. Exposing smaller patients to lower Kt, using Kt/V based intuition, would expose them to at least some measure of additional and avoidable risk.

The "Height & Weight" model set may be the best way to account for height in these analyses because weight is evaluated at constant height rather than as an arbitrary ratio of it. BSA also accounts for height combining it with weight and the patterns of association for it were similar to height and weight. The BSA is also a single number that is frequently used in physiological studies. Hence, we chose it to illustrate the nature of the interaction between Kt and body size. The failure of the relative weight interaction models (wt/ht and BMI) likely resulted from the nonlinear relationship of relative weight to death risk that was more pronounced for the BMI. Nonetheless, the shape of categorical risk plane associated with the BMI was similar in shape to the others illustrating progressive reduction of risk with increasing Kt even in the lowest BMI group.

Others have demonstrated the independent associations of dialysis dose and body size with death risk [6, 9, 11, 12, 13]. Port and coworkers recently evaluated survival as a function of the URR in three groups of patients ordered by BMI [12]. Higher BMI was associated with better survival at each level of URR. While risk appeared to flatten at high URR among the largest patients, there otherwise appeared progressive improvement of survival with increasing URR in each body weight group. Unfortunately, the URR was measured in categories (that is, 5 classes from $<60\%$ to $>75\%$) rather than as precise values for each patient. Thus, an exact value for URR could not be matched with body

size for each patient to estimate a Kt. The information nonetheless suggests, as do these data, that increasing Kt among small patients may result in improved survival despite achieving URR values much larger than commonly deemed necessary.

These data do not permit a firm recommendation about target values for "adequate" Kt. They only suggest that clinicians should be cautious about reducing Kt, particularly for small patients, based on Kt/V informed intuition. Earlier studies suggested a target Kt in the range of 45 to 50 L/Rx [9]. Those studies used measurements made during the last three months of 1993. However, URR based thresholds for adequate treatment appear to have increased progressively over the years [26]. The URR threshold appeared to be about 61% during 1994 increasing to 70% during 1997 [26]. The change likely resulted from a systematic change in the post-dialysis BUN sampling technique that occurred over the years [26]. We used pre- and post-dialysis BUN measurements to estimate the Kt, just as they are to calculate a URR. Thus, the apparent Kt thresholds today are likely higher than they were in 1993 through 1997 because the clinical measurement technique has changed. Whatever the urea-based Kt target one selects for larger patients, however, these data suggest that it should not be reduced proportionately simply because patients are small.

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