Risk factors for higher mortality at the highest levels of spKt/V in haemodialysis patients

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Abstract

Background. The survival of patients on haemodialysis improves as the delivered doses of dialysis attain a Kt/V of 1.2 or more. However, a consistent yet paradoxical finding in the Kt/V survival relationship is that the mortality tends to increase at the higher ends of Kt/V.

Method. To determine the relationship of Kt/V with survival at a time when increasing doses of dialysis are being delivered and to examine the effect of body mass and nutritional markers including serum pre-albumin on the paradoxical relationship, we analysed relative mortality risk (RR) as a function of single-pool Kt/V (spKt/V) in the Cox proportional hazard model. We used body mass index (BMI), dry body weight and nutritional parameters including serum pre-albumin obtained in 1151 patients on chronic haemodialysis as covariates.

Results. The mean spKt/V for February and March of 1997 was 1.46 ± 0.28 (± SD). A spKt/V of >1.2 was achieved in 82.5% of patients and 20% of patients received a spKt/V of >1.68. Using spKt/V in deciles and assigning the third decile (spKt/V 1.2–1.3) as the reference group with an RR of 1, the extreme first and the tenth deciles displayed a higher RR imparting a U-shaped configuration to the curve. In this unadjusted analysis, there was no dependency between delivered dose of spKt/V and RR values. spKt/V values were re-analysed in quintiles. The U-shaped relationship persisted between spKt/V and RR, and an unadjusted analysis again exhibited no clear dependency between spKt/V and RR. The patients in the highest fifth spKt/V quintile, who received the highest dose of dialysis and had the paradoxical increase in RR, had the lowest body weight, BMI, serum pre-albumin and creatinine. Adjustments for case-mix characteristics (age, gender, race and diabetes) in the Cox multivariate model did not reduce the paradoxical increase in RR. However, introduction of BMI or dry body weight along with serum creatinine and pre-albumin to the above case-mix covariates for the first time produced a dose-dependent inverse relationship between the first four quintiles of the spKt/V and their respective RR. With the above variables adjusted, the fifth quintile RR of 1.6 (0.9, 3.1) was reduced to 0.9 (0.4, 2.0), but was not corrected to the lowest RR of 0.6 (0.2, 1.2) noted in the fifth spKt/V quintile. This difference between the adjusted RR of fifth and fourth quintile was not statistically significant, but persisted after adjusting for any clustering variation.

Conclusions. Our analysis, which is the first to include serum pre-albumin in the Kt/V survival analysis, demonstrates a steeper rise in the unadjusted RR at the highest end of spKt/V levels than reported previously and suggests that patients with lower weight and nutritional parameters may mostly account for the spKt/V and RR paradox. As we find a worsening in the spKt/V–RR paradox at a time when higher doses of dialysis are being delivered, we speculate that factors other than underweight and malnutrition such as ‘toxicity’ of rapid dialysis, especially in sick and underweight patients, may contribute to the paradox. If future studies were to verify this possibility, sick and underweight patients could benefit from less vigorous but frequent sessions of haemodialysis.

Keywords: BMI; body weight; dialysis-dose-paradox; nutrition; pre-albumin; survival; toxic dialysis

Introduction

The single-pool (sp)Kt/V, used widely in clinical practice, represents a quantitative measure of the dialysis dose and is derived as a product of dialyser clearance (K) and dialysis duration (t) indexed to body weight (V). Several studies have demonstrated a
positive correlation between dialysis delivered and patients’ survival [1–3]. This relationship is, however, imperfect and tends to flatten out or even reverse at the higher ends of dialysis doses [3]. A simple interpretation of the existing spKt/V survival relationship data would suggest that increasing levels of dialysis are beneficial to the patients up to a threshold beyond which ‘excess dialysis’ might contribute to higher mortality. We have shown previously that overweight patients receive less dialysis as measured by spKt/V and, conversely, those with lower body mass index (BMI) receive higher spKt/V [4]. We hypothesized that the increase in mortality at the higher end of Kt/V is likely a function of under-nutrition and underweight rather than increased spKt/V, i.e. over dialysis. Although attempts are being made to increase the delivered doses of dialysis over the past few years, the effect of increased dialysis on the Kt/V survival relationship remains unclear [5]. Furthermore, few studies have examined the effect serum pre-albumin adjustment in the dialysis dose-survival relationship. Pre-albumin, a visceral protein of shorter half-life than albumin has emerged as a sensitive marker in haemodialysis patients [6,7]. It is independent of serum albumin and other established predictors of mortality in this population [6]. We therefore re-examined the relationship between dialysis dose and survival in a group of patients receiving higher doses of dialysis and determined the effect of BMI and nutritional parameters including serum pre-albumin on the relationship.

Subjects and methods

Of the 1335 patients attending the limited-care haemodialysis units (run by the Renal Care Group of Jackson, MS, USA) 1151 patients met the study criteria of having spKt/V available for 2 consecutive months (February and March of 1997), of being on haemodialysis for at least 90 days and of having no amputations. The computer data on routine clinical and laboratory measurements for February and March 1997 was obtained and the average values were used for analysis. The BMI was calculated by the formula of post-dialysis bodyweight in kilograms per height in m². The data were obtained for all the patients over the entire observation period and the data in their entirety were used for analysis. spKt/V was measured using the second generation in formula: $\text{spKt/V} = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W$, where $R = (\text{pre-dialysis BUN} - \text{post-dialysis BUN}) / \text{pre-dialysis BUN}$; UF stands for the actual ultrafiltration and W for the post-dialysis bodyweight. Pre-dialysis BUN was drawn before the start of the blood pump and post-dialysis BUN was obtained at the end of dialysis using the slow flow technique described in the DOQI guidelines. This protocol for spKt/V measurement is used uniformly in all the centres. The average of 2 months spKt/V was used for analysis. The data on patient survival for the ensuing 9 months (April 1997 to December 1997) were used for analysis. Some of the data from this cohort of patients were analysed previously to examine the effect of excessive body weight on survival [8] and dialysis adequacy [4].

Statistical analysis

The data are reported as mean ± SD or median (range) or mean (95% CI), a $P<0.05$ was considered as statistically significant. For analysis, patients were grouped according to spKt/V deciles or quintiles. Relative risk (RR) was assessed by Cox proportional hazard model in univariate and multivariate modes. RR was reassessed factoring for case-mix characteristics (age, gender, race and diabetes), BMI, serum creatinine and pre-albumin. As the data originated from multiple centres and centre effect might have existed in blood sample collection for Kt/V, the Cox analyses were carried out with clustering (bootstrap) adjustments. The latter was performed using a SAS macro incorporating the Cox regression procedure using 1000 samples. StatView (Abacus Concepts, Inc., Berkeley, CA) and Statistical Analysis Software (SAS Institute, Cary, NC) programs were used.

Results

Patient and dialysis characteristics

Of the 1151 patients, 90% were African-Americans and the rest were Caucasians. The mean age was 55.8 ± 0.47 (range 13–96) years, and 45% were male. The reported causes of renal failure were hypertension in 37%, diabetes in 28% and the rest were glomerulonephritis, lupus erythematosus, polycystic and undiagnosed. The patients had been on haemodialysis for an average duration of 4.3 (range 0.25–25) years. The average duration of the dialysis session was 240 min (range 180–300 min) per session, three times a week. The majority of the patients were dialysed through arterio-venous (AV) grafts (89.5%). AV fistulae and vascular catheters were used in 4.9 and 5.7%, respectively. The blood flow was maintained at 400–450 ml/min. The dialysate flow was 500–800 ml/min. The majority (72%) of the patients were dialysed with polysulfon-based membranes that were reused by reprocessing them with heated citric acid.

Analysis of spKt/V

The mean spKt/V of the whole population was 1.46 ± 0.28, with a range of 0.65–2.58. The spKt/V frequency distribution, displayed on Figure 1, shows that the majority of patients (82.5%) had achieved the

![Fig. 1. The frequency distribution of spKt/V: 82% of patients achieved a spKt/V of ≥1.2 and 20% received a spKt/V > 1.68.](https://academic.oup.com/ndt/article-abstract/18/7/1339/1809834)
Higher mortality at the highest levels of spKt/V

NKF-K/DOQI guideline suggested 1.2 or above target of spKt/V and a 20% of the patients received a Kt/V >1.68. As we have reported earlier [4], the spKt/V had a negative correlation with BMI (r = −0.29, P < 0.0001), and very high spKt/V were seen in patients with very low BMI.

Relationship between spKt/V and survival

Of the 1151 patients, 149 (12.9%) patients died over the 9-month period. Of the remaining patients, 0.6% were transferred to CAPD, 1.0% were transplanted and 4% transferred out of our facilities or were lost to follow up. As reported previously [8], BMI influenced patients’ survival: the underweight (UW, BMI < 20) patient had the highest rate of mortality (20.1%), which was significantly higher (10.5%) than in the normal weight (NW, BMI 20–27.5). The overweight (OW, BMI > 27.5) patient had the best survival rate (8.2%). Unlike BMI, types of dialyser use did not have any significant effect on mortality [11.8% in poly-sulfone (high flux) versus 12.8% in cuprophane (low flux) dialysers].

As displayed in Figure 2, the RR of the first decile (patients with the lowest spKt/V, <0.7) was significantly higher compared with reference third decile (spKt/V 1.2–1.3) (RR 2.8, P < 0.05). After the first decile, the RR was mostly flat until the tenth decile (>2.4), after which the RR increased again to 2.5 (Figure 2, P < 0.05). A simple interpretation of this spKt/V–RR relationship would suggest that very high doses of dialysis might be associated with higher mortality. However, patients who had received higher doses of dialysis were patients with very low BMI. A low BMI independent of dialysis dose is associated with higher mortality. Therefore, the higher mortality observed here at high end of spKt/V could be related to underweight and malnutrition. To test this possibility, we used a multivariate analysis in the Cox proportional hazard model. First, in the univariate mode, age, race, serum albumin, BMI, spKt/V <1.2 and presence of diabetes were individually associated with significant increase in RR as reported earlier (data not shown) [4]. In the multivariate analysis, that is in the presence of all the above variables, the spKt/V <1.2 (under dialysis) persisted as a significant risk factor (2.27, 95% CI 1.42–3.60, P < 0.001).

To determine the effect of adjusting for BMI and nutritional parameters on the Kt/V–RR paradox, we first adjusted for age, gender, race and diabetes. As displayed in Figure 3, adjustment for age, gender, race and diabetes had little influence on the shape of the curve, and notably, there was no improvement in the lack of dose dependency between dialysis dose in quintiles and RR. Inclusion of BMI, creatinine and serum pre-albumin to the case-mix covariates, however, caused an appreciable dose-dependent inverse relationship between the first four spKt/V quintiles and their respective RR (Figure 3). The unadjusted relationship between RR and spKt/V (the first bar in each group) is the same as in Figure 2, including the sharp up swing of RR at the very high end of Kt/V. The first (the lowest spKt/V <1.23) and the fifth quintile (the highest spKt/V >1.68) had significantly higher RR (P < 0.05) than the reference second quintile. Adjusting for the case-mix (second bar in each group) had little effect on the curve. However, adding BMI (third bar) and creatinine and pre-albumin (fourth bar) progressively but insignificantly reduced the RR, producing a dose dependency between Kt/V and RR except for the fifth quintile. The combined adjustment reduced the paradoxically higher RR of the fifth quintile, from 1.6 (0.9, 3.1) to 0.9 (0.4, 2.0), but this did not reach the nadir of 0.6 (0.2, 1.2) RR observed in the fourth quintile; however, the difference between fourth and fifth quintiles did not reach statistical significance (Figure 3).

The effect of dry body weight in the place of BMI was also examined. The dry weight closely correlated with BMI (simple regression with BMI as the dependent variable: r = 0.92, P < 0.0001). As with BMI, body weight (Table 1) was inversely related to the RR (RR 0.97; 95% CI 0.94–0.98; P < 0.0002), and its introduction to the Kt/V survival analysis in the place of BMI produced similar RR changes. RR (without adjustment with all the variables plus weight adjustment) for each quintile of Kt/V compared with the reference quintile two in the final multivariate model (with all the variables present as in Figure 3) were Q1 = 1.6/1.9, Q2 = 1.0/1.0, Q3 = 1.0/0.84, Q4 = 0.82/0.70 and Q5 = 1.7/0.9.

Nutritional parameters by spKt/V quintiles

Using analysis of variance (ANOVA) with post-hoc correction for multiple comparison, BMI, serum creatinine and serum pre-albumin demonstrated a progressive and statistically significant decline in these measures with increasing spKt/V quintiles. This is presented in Table 1. Serum albumin did not differ significantly among the groups. The fifth quintile, which had patients with the highest spKt/V, had the lowest mean BMI, body weight, serum creatinine and

![Fig. 2. RR vs spKt/V in deciles in unadjusted Cox Proportional Hazard analysis. The first decile (the lowest spKt/V <0.7) and the tenth decile (the highest spKt/V >2.4) had significantly higher RR (P < 0.05) than the reference third decile (spKt/V of 1.2–1.3). The reference third decile, which has an assigned RR of 1, is displayed in the figure as a solid bar. There is, however, a clear up swing in the RR at the highest end of Kt/V.](http://academic.oup.com/ndt/article-abstract/18/7/1339/1809834/15February2019)
pre-albumin and these were significantly lower than those in fourth quintile (Table 1). The age, gender, race or Hct was not different across the quintiles.

### Discussion

Our analysis demonstrates the presence of a sharper upturn in the unadjusted RR at the highest doses of spKt/V imparting a U-shape to the dialysis dose and the mortality risk relationship. Furthermore, our data suggest that adjustment for body mass and biochemical markers for nutrition, while correcting most of the paradox, may not fully account for the upswing of the unadjusted mortality observed at the highest end of spKt/V doses.

The previous reports of a trend for reversed j-curve relationship between delivered dose of dialysis and patients' survival were based on the analysis of earlier URR data [1,3]. Our analysis was based on spKt/V

### Table 1. Nutrition- and other patient-related parameters by spKt/V quintiles

<table>
<thead>
<tr>
<th>spKt/V quintiles (Q)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>spKt/Vs</td>
<td>&lt;1.23</td>
<td>1.23–1.39</td>
<td>1.39–1.52</td>
<td>1.53–1.68</td>
<td>&gt;1.68</td>
</tr>
<tr>
<td>Number of patients</td>
<td>229</td>
<td>239</td>
<td>232</td>
<td>229</td>
<td>231</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>60%</td>
<td>50%</td>
<td>50%</td>
<td>42%</td>
<td>26%</td>
</tr>
<tr>
<td>Race (Af.Am.)</td>
<td>94%</td>
<td>93%</td>
<td>91%</td>
<td>88%</td>
<td>87%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26%</td>
<td>29%</td>
<td>30%</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 15%</td>
<td>57 ± 16%</td>
<td>55 ± 15%</td>
<td>57 ± 16%</td>
<td>59 ± 16%</td>
</tr>
<tr>
<td>BMI</td>
<td>29.3 ± 0.51</td>
<td>28.6 ± 0.45</td>
<td>26.3 ± 0.39</td>
<td>25.8 ± 0.39</td>
<td>23.7 ± 0.33</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>87 ± 24</td>
<td>82 ± 20</td>
<td>75 ± 17</td>
<td>72 ± 17</td>
<td>64 ± 14</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>13.8 ± 0.26</td>
<td>13.0 ± 0.23</td>
<td>12.7 ± 0.24</td>
<td>12.2 ± 0.19</td>
<td>11.3 ± 0.16</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>4.02 ± 0.38</td>
<td>4.00 ± 0.41</td>
<td>3.99 ± 0.40</td>
<td>4.02 ± 0.40</td>
<td>4.04 ± 0.37</td>
</tr>
<tr>
<td>Serum pre-albumin (mg/dl)</td>
<td>48.4 ± 0.81</td>
<td>48.5 ± 0.77</td>
<td>47.3 ± 0.84</td>
<td>47.0 ± 0.84</td>
<td>46.8 ± 0.84</td>
</tr>
</tbody>
</table>

Body weight, BMI, serum creatinine and pre-albumin (mean ± SD) were progressively lower from Q1 to Q5, and these measurements were significantly \( P < 0.05 \) lower in Q3, Q4 and Q5 from Q1 and in Q5 from Q4 (ANOVA with Dunn post-hoc test).
that were collected after aiming for the DOQI recommended target of a minimum of 1.2 spKt/V in our dialysis units. Accordingly, the average spKt/V in our study was 1.46 ± 0.28, the vast majority of our patients (82%) received a spKt/V of ≥ 1.2 and 20% of patients received much higher doses of dialysis (> 1.68 spKt/V). The provision of higher dialysis dose in our patients may provide a partial explanation for the sharper upturn in the ‘dialysis-dose-paradox’ than reported previously. This suggestion is further supported by the finding of Li et al. [9] who using data of 1998 examined the effect of URR on mortality in 37 108 haemodialysis patients and reported a U-shaped than the previously reported reversed J-shaped relationship. The dialysis-survival relationship noted in our study can not simply be due to the predominance of African-Americans in our subjects as an upturn in the RR is also reported in a cohort that was predominately Caucasians [9], and, furthermore, the case-mix adjustment in our study that included race had very little effect on the shape of the curve. Although our study subjects had certain characteristic variations than the US national samples such as lower age, hypertension rather than diabetes as the leading cause of ESRD and a high prevalence of AV-graft and dialysar reuse, it is difficult to explain how these variations can account for the paradoxical increase in the RR we found at the highest levels of spKt/V.

In this study, and as reported earlier, patients with the lowest body mass had the highest delivered doses of dialysis (Table 1) [4,10,11]. These patients in our study also had significantly lower serum creatinine and pre-albumin than in the reference group. Thus, these patients represent a relatively undernourished patient population and, therefore, they are susceptible to higher mortality [8,12,13]. Our finding that most of the increase in the unadjusted RR at the highest end of spKt/V could be explained on the basis of underweight and reduced nutrition supports the similar findings of Chertow et al. [3]. However, unlike Chertow et al. [3], who reported an unadjusted RR of 1.2 for the highest dialysis-dose-quintile, ours was 1.6, suggesting a sharper increase in the dialysis-dose-paradox. However, the finding that the adjustment for BMI, serum creatinine and pre-albumin in our study reduced the unadjusted RR of 1.6 to 0.9, should not be interpreted to suggest that there is no recent increase in RR at the highest end of spKt/V. An alternate interpretation might be that with the use of increasingly larger doses of dialysis, the deleterious effect of very high doses of dialysis on sick and malnourished patients is more noticeable than before.

Our finding that adjusting for body mass along with nutritional parameters did not fully correct the higher RR has to be discussed. It is clear that the adjustment did bring the unadjusted high RR in the highest spKt/V quintile to that in the reference second quintile (spKt/V 1.23–1.39). Thus, after this correction highest spKt/V was no longer associated with higher mortality as compared with the reference value, but it was still associated with worse mortality compared with the fourth quintile, albeit insignificant. The strength of the finding can be questioned because of the lack of statistical significance. On the other hand, with a larger sample size, future study might find this RR difference stronger and significant and is necessary to separate these important issues.

In our study, a large proportion of patients had higher than the least recommended spKt/V and, indeed, many had very high spKt/V (Figure 1). As we used the spKt/V as the dialysis dose measure, it is plausible that higher Kt/V values achieved in some of our patients might have been erroneous. Assessing rebound or using double-pool Kt/V, not carried out in this study, might have unmasked this effect if present. However, blood for Kt/V analysis was drawn using the slow flow technique described in the DOQI guidelines and had been used uniformly in all the centres. Then again, patients with very high Kt/Vs were the patients with the lowest body mass and biochemical markers of nutrition (Table 1). Thus, some of these patients might include sicker patients with systemic inflammation and higher cardiovascular disease burden. These patients, often with reduced cardiac output, tend to have lower blood pressure and tissue perfusion towards the end of dialysis and, thus, might be susceptible to spKt/V overestimate. If this is proven to be the case, then that will further underscore the limitation of the use of spKt/V particularly in underweight and malnourished patients.

One hypothesis to account for our finding of higher mortality in the highest spKt/V quintile despite body mass and nutritional measure adjustment relates to the potential toxic effects of rapid and vigorous dialysis. Such dialysis (for example, achieving a Kt/V > 2 in 4 h) might be particularly detrimental to the underweight and undernourished patients through hypotension, cardiac ischaemia, electrolytes imbalance, osmotic disequilibrium or a combination of these. A recent report of the prospective randomized controlled HEMO study [5] suggests that use of higher doses of dialysis may not reduce the morbidity and mortality in haemodialysis patients as hoped for; one possibility is that at least part of the lack of benefit with higher doses of dialysis might be due to the offsetting deleterious effect of vigorous dialysis in sicker and underweight patients. That is that, even if there were roughly same number of sicker and underweight patients in the ‘normal dialysis dose’ and ‘higher dialysis dose’ groups, any deleterious effect from intensive dialysis arguably would be more pronounced in the sicker and underweight patients in the higher dose group.

In summary, we find a steep rise in RR at the highest end of Kt/V in the unadjusted Kt/V–RR relationship. The paradoxical rise in RR was explained to a large extent by the BMI and other nutritional measures. As we find a worsening in the spKt/V–RR paradox at a time when increasingly more dialysis is being delivered, we posit that other factors in addition to underweight and malnutrition such as toxicity of vigorous, short dialysis in sick and malnourished patients may account for the increase in the dialysis–mortality paradox.
Furthermore, such worsening paradox, if proven to be correct, may be masking the benefit of delivering higher doses of dialysis. If future studies were to verify this possibility, sick and underweight patients could benefit from less vigorous but frequent sessions of haemodialysis.

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