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Shorter length dialysis sessions are associated with increased mortality, independent of body weight

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Abstract

Hemodialysis patients have high rates of mortality that may be related to aspects of the dialytic procedure. In prior studies, shorter length dialysis sessions have been associated with decreased survival, but these studies may have been confounded by body size differences. Here we tested whether in-center thrice-weekly hemodialysis patients with adequate urea clearances but shorter dialysis session length is associated with mortality independent of body size. Data were taken from a large national cohort of patients from a large dialysis organization undergoing thrice-weekly, in-center hemodialysis. In the primary analysis, patients with prescribed dialysis sessions greater and less than 240 minutes were pair-matched on post-dialysis weight as well as on age, gender, and vascular access type. Compared to prescribed longer dialysis sessions, session lengths less than 240 minutes were significantly associated with increased all-cause mortality (adjusted hazard ratio 1.26). The association was consistent across strata of age, gender, and dialysis post-weight. Secondary analyses found a dose-response between prescribed session length and survival. Thus, among patients with adequate urea clearance, shorter dialysis session lengths are associated with increased mortality independent of body weight.

Keywords

hemodialysis; session length; body size; mortality

INTRODUCTION

The United States is home to over 380,000 chronic hemodialysis (HD) patients, a population expected to surpass 500,000 by 2020.(1) The vast majority of these patients undergo thrice weekly, in-center dialysis. Mortality rates among US HD patients have remained unacceptably high over the past several decades despite advances in dialysate purity, membrane technology, and patient monitoring.(1) US HD patients fair worse than their counterparts in Europe, Japan, and Australia/New Zealand even when case-mix differences

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DISCLOSURES

In the past, SMB has served on advisory boards for Amgen and C.B. Fleet and has received speaking honoraria from Fresenius Medical Care; his spouse is an employee at AstraZeneca.

are accounted for,(2) suggesting that differences in dialysis processes may have significant bearing on mortality.

Prior observational studies have demonstrated that shorter dialysis session length (DSL) is associated with increased mortality.(3–7) This association may be mediated through consequent need for more rapid ultrafiltration (3, 8, 9) or through limitations in solute clearance not reflected by standard clinical biochemical markers. However, absent supporting evidence from randomized controlled trials, such observational findings are subject to circumspection. Detractors have rightfully noted that body size is an important determinant of DSL and is also (presumably independently) associated with mortality, suggesting that past studies have been residually confounded by body size discrepancies.(10, 11) Specifically, smaller body size is associated with greater mortality, and smaller patients are typically dialyzed for shorter times; ergo, the resultant bias would favor longer DSL.(12–14)

It is critical to further clarify whether the association between DSL and mortality is potentially causal. If so, extension of DSL would provide a readily modifiable means by which to improve patient longevity. If not, extension of DSL may unnecessarily contribute to patient burden and dissatisfaction.

Therefore, we undertook this study to clarify whether—in the setting of thrice-weekly incenter HD and absent compelling indication to extend DSL on the basis of clearance (i.e., URR<65%)—longer DSL is associated with reduced mortality independently of body size differences. We used data from a large, contemporary, prevalent cohort from a large dialysis organization (LDO) that is similar to the broader US HD population in terms of patient characteristics and dialytic practice patterns. To tightly control for confounding on the basis of body size as well as other key covariates, patients were matched according to post-dialysis weight, sex, age, and vascular access type.

RESULTS

Baseline characteristics of cohort

Demographic, clinical, and biochemical characteristics of the source population are shown in Table 1. The source cohort (of eligible participants) consisted of 10,571 subjects with a mean age of 62.2 ± 15.0 years; 48.3% were women and 39.5% were black. At baseline, 37.8% had a history of congestive heart failure and 52.5% were diabetic; mean URR was 74.5%; patients were dialyzed via a fistula (37.3%), graft (31.9%), and catheter (30.0%). The mean RxDSL was 217 ± 26 minutes; 6,791 (64.2%) and 3,780 (35.8%) patients had RxDSL <240 and ≥240 minutes, respectively. The mean dialytic vintage of this prevalent cohort was 2.5 years at study start. Overall, the RxDSL<240 and RxDSL≥240 groups were similar in terms of dialytic vintage, pre-dialysis systolic blood pressure, and the number of missed sessions during the 30 day exposure period. Prior to matching, RxDSL<240 subjects were more likely to be lighter, older, and female; RxDSL≥240 subjects were more likely be black and to have diabetes, congestive heart failure, and coronary artery disease.

Primary analysis

In the primary analysis, 2,382 RxDSL≥240 subjects (63%) of those in the source population) were successfully matched to one RxDSL<240 individual. The matched pairs demonstrated excellent balance on all matching factors including weight (Table 2; Supplemental Figure A). Mean age was 61.6 ± 13.0 and 61.7 ± 13.0 years in the RxDSL≥240 versus RxDSL<240 groups. In both groups, mean post-dialysis weight was 76.7 ± 14.9 kg.

Overall, 1,477 deaths occurred during 9,676 patient-years of at-risk time. Median at-risk time was 24.4 months after study start. Compared with RxDSL≥240, RxDSL<240 was associated with an unadjusted HR (95% CI) of 1.11 (0.97–1.26; p=0.12). When residual imbalances between RxDSL groups were accounted for, a potent and statistically significant association between RxDSL<240 and mortality was observed: adjusted HR (95% CI) 1.26 (1.07–1.48; p=0.005) (Figure 1). Results were slightly attenuated when URR was considered as a variable in the multivariable model (adjusted HR (95% CI) 1.23 (1.04–1.45)), but URR was excluded from the final model on the presumption that it functions as an intermediate on one causal pathway linking RxDSL to mortality. Restriction subgroup analyses demonstrated stable estimates across strata of age (p-interaction=0.61), gender (p-interaction=0.79), race (p-interaction=0.76), and post-dialysis weight (p-interaction=0.76) (Figure 2).

To explore for dose response in the RxDSL--mortality association, we calculated the difference in RxDSL between members of each matched pair. Pairs were then categorized as having an RxDSL difference of <30, =30, or >30 minutes, and the association between RxDSL<240 and RxDSL≥240 was estimated within each stratum. As demonstrated in Table 3, the magnitude of the association between RxDSL<240 (compared with RxDSL≥240) and mortality was incrementally more potent when differences in RxDSL were greater, suggestive of a dose-response trend.

Secondary analyses

To further examine the association between RxDSL and mortality, we categorized subjects as having RxDSL<210, RxDSL210-239, and RxDSL≥240. In this analysis, 691 RxDSL≥240 subjects were successfully matched to both one RxDSL210-239 and one RxDSL<210 subject. The matched triplets demonstrated excellent balance on all matching factors (Table 4). Overall, 686 deaths occurred during 4,141 patient-years of at-risk time. Median at-risk time was 22.8 months after study start. Compared with RxDSL≥240, shorter RxDSL was incrementally associated with greater mortality: adjusted HRs (95% CIs) 1.28 (0.98–1.67) for RxDSL210-239 and 1.30 (1.02–1.68) for RxDSL<210 (p-trend=0.038) (Figure 1).

DISCUSSION

Prior analyses of the DSL--mortality association may have failed to adequately account for potential confounding on the basis of body size differences and, as a result, the validity of their conclusions has been questioned. In this analysis, we demonstrate that shorter RxDSL is associated with increased mortality even when body weight differences are strictly controlled through matching. In addition, the data suggest a dose-response relationship between DSL and survival. These findings add credence to the notion that longer DSL—beyond what is necessary to achieve contemporary urea clearance targets—may promote greater survival. Sub-group analyses suggest that the observed associations are similar across strata of age, gender, and post-dialysis weight.

Prior observational studies examining the DSL--mortality relationship have shown an association between shorter DSL and mortality. In an Australian and New Zealand cohort, Marshall et al demonstrated that DSL<3.5 hours was associated with increased mortality (HR 1.57; 95% CI 1.14–2.17) compared with 4–4.4 hours of dialysis.(5) In a subsequent study using data from the Dialysis Outcomes and Practice Patterns Study, Saran et al showed that DSL 211–240 minutes was associated with worse survival (HR 1.19; p=0.01) compared with DSL>240 minutes.(3) In a more recent study of incident HD patients, Brunelli et al demonstrated a HR of 1.42 (95% CI 1.24–1.62) for RxDSL <240 minutes compared to sessions ≥240 minutes; because that study considered an *incident* dialysis

cohort and session length was frequently titrated during follow up, marginal structural analysis was used to account for session length titrations made throughout the period of observation.(6) These observational studies stand in contrast to the HEMO Study, a randomized trial of dialysis dose that demonstrated no benefit to enhanced dialysis intensity.(15) The HEMO Study, however, was not designed to study treatment time independently of other factors. The HEMO investigators note: "In the design of the HEMO Study, treatment time was closely coupled with the patients' randomized dose target, volume of urea distribution, and achievable blood flow. As a consequence, the HEMO Study did not provide a favorable setting for evaluating the effect of treatment time independently of these other factors…"(16) Additionally, subjects were not randomized to differing treatment times, DSL varied within study arms, and delivered DSL spanned a limited range (only 335 (18.2%) of randomized subjects had RxDSL≥240 minutes), hampering the study's ability to adequately evaluate the independent effect of RxDSL<240 versus RxDSL≥240 on mortality. In the absence of any contemporary randomized trial data, we are left to cautiously interpret observational data with respect to treatment time.

Each of the above observational studies was adjusted for some measure of body size through inclusion of covariate terms in multivariable models. However, multivariable adjustment is imperfect and may engender residual confounding. The influence of such residual confounding is proportionate to several factors including: 1) imbalance in body size across RxDSL groups, 2) strength of the association between body size and mortality, 3) misspecification of the body size--mortality association in the statistical model, 4) interactions between body size and other covariates, and 5) over-influence of extreme outliers (e.g., the fate of one or two 250 kg patients).

Some have (rightfully) questioned the validity of past findings on this basis.(10) On average, heavier patients are dialyzed for longer,(3, 17) and body size is a strong predictor of survival.(12–14) By tightly matching, we were able to exactly balance post dialysis weight across RxDSL groups and greatly reduce the opportunity for confounding on this basis. In addition, by matching on additional factors that weigh heavily in DSL determination and are also key mortality determinants (age, gender, and vascular access), we minimized confounding on these bases. Because matching obviates the need for assumptions regarding the pattern of association between matching factors and outcome, errors due to model misspecification are averted. Matching also accounts for interaction between the matching factor and other confounders (e.g., a serum creatinine of 12 has a different implication in 130 kg males than in 50 kg females). Such interactions are often not considered in standard multivariable analyses. Finally, and perhaps most importantly, matching implicitly excludes patients in whom DSL is deterministic (e.g., patients at the extremes of body weight for whom a suitable match cannot be identified) and who are not appropriate targets for inference because the decision between <240 and ≥240 is immaterial. Such "trimming" limited the range of post-dialysis weights to 41.5–153.3 kg in our matched cohort. This improves the validity of inference within the population studied, though comes at the expense of generalizability. Hence, this matched analysis is better able to address confounding by body size than were prior studies. As empiric demonstration, we repeated the primary analysis without matching but instead with covariate adjustment terms for age, weight, sex, and vascular access: we observed an effect estimate that was markedly attenuated (1.08; 95% CI 0.98–1.20) and which was similar to estimates from other cohorts in which weight was markedly imbalanced across DSL groups and not matched on.(7)

A separate (but often conflated) consideration is whether the association between RxDSL and mortality pertains equally to all patients or whether there is effect modification. Marshall et al observed that DSL was potently associated with mortality among patients with high and intermediate but not low BMI.(5) Miller et al showed a DSL--mortality

association among women but not among men,(7) presumably related to issues of body size and composition. Likewise, Depner's post-hoc analysis of the HEMO Study demonstrated that more intensive dialysis (though defined in terms of eKt/V, not DSL *per se*) reduced mortality among women but not men.(16) However, in this same analysis, Depner did not detect effect modification on the basis of body size, whether considered as weight, body surface area, or body mass index.(16) It is unclear whether the latter observation relates to limited statistical power (further complicated by strong implied relationships between gender and body size(18)) or indicates a true absence of biological effect modification. In this study, we did not observe effect modification on the bases of body weight, gender, or age. However, in as much as these were secondary analyses (though stipulated *a priori*) and contained few patients at the extremes of body size (due to matching), further investigation is needed.

Mechanisms underlying the RxDSL--mortality association may be multi-factorial and likely relate in part to fluid dynamics and enhanced solute clearance not represented by URR or Kt/V. Shorter DSL implies less time for fluid removal, ergo higher ultrafiltration rates. In our study ultrafiltration rates were lower among RxDSL≥240 subjects than their matched RxDSL<240 counterparts despite the fact that RxDSL>240 subjects had higher IDWG. Prior studies indicate that higher ultrafiltration rates are associated with increased all-cause(3, 8, 9) and cardiovascular mortality(9), possibly on the basis of consequent cardiac stunning and subclinical ischemia(19), and hemodynamic destabilization(20). The role of enhanced solute clearance with longer membrane contact should not be discounted. Longer DSL enables greater removal of urea, creatinine, phosphorus, and beta-2-microglobulin, even under experimental conditions where Kt/V is held constant.(21–23) The present study was unable to mechanistically determine whether and to what degree differences in ultrafiltration rates and solute clearance may mediate the DSL--mortality association. However, our results did show mild attenuation of the hazard ratio for RxDSL<240 when URR was included in the model, suggesting that enhanced solute clearance may represent one causal pathway. Further study in this regard is needed.

Strengths of this study include its large, nationally representative cohort, the use of standardized protocols for data collection across HD units, and the use of tight matching parameters to create strict control for the most influential confounders. Several limitations of this study bear mention. First, observational data carries an inherent risk of uncontrolled confounding and bias. To minimize the risk of residual confounding, we matched subjects on factors identified as the strongest confounders of the RxDSL--mortality association, resulting in near-perfect balance in weight, age, sex, and vascular access type. To minimize confounding from other factors, we adjusted estimates for additional variables plausibly associated with both mortality and RxDSL such as dialytic vintage, relevant co-morbidities, and biochemical indices. Due to data limitations, we were unable to consider additional nutritional markers such as CRP and nPCR and were unable to include a detailed analysis of cardiac status (e.g., left ventricular ejection fraction). We cannot exclude the possibility of residual confounding related to these variables or other unconsidered variables. A second weakness may be in the consideration of RxDSL as the exposure of interest. RxDSL is less directly biologically relevant than delivered DSL. The selection of RxDSL, however, allowed us to study treatment *intention,* and to reduce confounding from sessions that may have been truncated due to hemodynamic instability or non-adherence (manifest as willful curtailment of HD sessions) which would bias estimates. Third, we excluded patients with URR<65% so as to consider the effects of DSL extension beyond what is required to meet basic clearance goals. Our results, therefore, should not be extrapolated to patients who have inadequate clearance metrics, although independent data suggest dialysis should be intensified in this setting.(24–26)

Fourth, DSL was dictated by treating physicians, so the degree to which DSL differences reflect other practice pattern differences across providers is unknown, and such differences could confound study results. Due to data limitations, we cannot provide insight into why some patients had longer RxDSL compared to others despite similar clearance goals. We attempted to minimize center effect by excluding patients dialyzed at facilities where there was not at least one subject in each RxDSL category; however, residual confounding related to individual physician practices could remain. Additionally, prior studies have demonstrated that longer RxDSL increases clearance of middle molecules such as phosphate and beta-2-microglobulins even when URR remains constant.(21–23) Our multivariable adjustment for URR does not adequately control for confounding introduced by enhanced middle molecule clearance; thus, residual confounding from clearance not reflected by URR may remain. Similarly, lower ultrafiltration rates driven by longer DSL may lead to more consistent dry weight attainment with fewer hemodynamic complications, and we are unable to account for such differences in our analysis. Prospective trials are needed to adequately address the roles of these important potential clearance and hemodynamic confounders. Finally, we limited consideration to patients dialyzing thrice weekly in-center with treatment times between 2.5 and 4.5 hours (because this represents the treatment paradigm for vast majority of US HD patients). By matching, we further (implicitly) excluded patients for whom DSL was deterministic, most notably those at the extremes of body weight. Thus, our results should not be extrapolated to patients dialyzing according to other paradigms, to those with body weights outside the range studied, or to HD populations dissimilar from our cohort. In this context, the reader should be mindful that this study considered data from a single LDO and generalizability to the broader US dialysis population should be undertaken cautiously.

In conclusion, this study demonstrates that among chronic HD patients with adequate urea clearance, shorter RxDSL is associated with increased all-cause mortality independently of body size. This association follows a dose-response pattern: incrementally shorter sessions are associated with higher hazard. Further prospective studies are needed to confirm and generalize findings, and to explore therapeutic alternatives that might be more acceptable to patients than DSL extension.

METHODS

Study design

This study was deemed exempt by the Partners Health Care Institutional Review Board. All study data were derived from a cohort of 14,643 randomly selected prevalent adult patients receiving thrice weekly in-center HD at one LDO. Cohort entry was between January 1, 2005 and January 16, 2009. Patients dialyzed at one of 1,247 out-patient dialysis facilities located across a diverse geographic distribution within the United States. Because our intent was to estimate whether longer prescribed dialysis session length (RxDSL)—beyond that necessary to achieve current adequacy standards—is associated with improved survival, we excluded subjects with urea reduction ratios (URR) <65%.(26) URR was selected over Kt/V to minimize collinearity between the clearance metric and the exposure of interest. To limit undue influence of patients receiving very short or very long dialysis (who likely differ in fundamental ways from the general HD population and in whom decisions between standard-shorter and standard-longer DSL are likely moot), we excluded patients with RxDSL<150 or >270 minutes. To minimize center effect derived from units in which RxDSL was deterministic, we excluded patients dialyzing at facilities without at least one subject in each RxDSL category.

Data collection

Study data were obtained from the LDO's comprehensive electronic medical record and was collected in keeping with the LDO's standard clinical protocols. Demographic data were recorded by unit personnel at the time of entry into a LDO unit. Comorbidity assessment was made by the attending nephrologist upon subject enrollment into a LDO unit based on interview, examination, and medical record review and was then updated as dictated by clinical course. Laboratory parameters were measured at the time of entry into a LDO unit and thereafter on a biweekly or monthly basis. Per standard clinical procedure, dialytic session data including the exposure, RxDSL, was recorded on a session-by-session basis. Pre-dialysis systolic blood pressure was measured at the start of each dialysis session and post-dialysis weight was measured following the conclusion of each dialytic procedure. Post-dialysis weight was selected over estimated dry weight as the operational metric of body size because documentation of the latter often lags behind actual body weight changes. A high degree of missingness for height precluded the use of body mass index, body surface area, or other anthropometrics. Date of death and attributed cause of death were recorded in the medical record by dialysis unit staff.

Time sequence and designation of exposures and outcome

The exposure of interest, RxDSL, was considered as the mean of (typically 12) values over the 30-day period following cohort entry. [Thirty-day mean RxDSL demonstrated excellent correlation with 60-day (r=0.98) and 90-day (r=0.96) means; a 30–day exposure window was thus adopted to minimize potential survivor bias.] RxDSL was selected over delivered session length as the exposure of interest because use of RxDSL: 1) better reflects treatment intention, 2) minimizes bias otherwise incurred due to differential adherence to RxDSL (i.e., willful curtailment of treatments), and 3) minimizes confounding on the basis of health events that trigger premature cessation of dialysis and independently predispose to death.

Covariate data on demographic characteristics (age, sex, race, vascular access type, and dialytic vintage) and co-morbidities (diabetes, coronary artery disease, congestive heart failure) were considered as of cohort entry. Biochemical covariates (urea reduction ratio, albumin, creatinine, and phosphate) were considered as the latest value measured during the 30-day exposure window. Dialysis session data (post-dialysis weight, interdialytic weight gain, and pre-dialysis systolic blood pressure) were considered as per RxDSL.

The outcome of interest was death from any cause. Cause-specific mortality was not considered given that attributed cause of death data has not been validated and was in some instances missing. Subjects were considered at-risk for outcome starting on day 31 following cohort entry and remained at risk until they died or were censored for transfer of care, change in dialysis modality, renal transplant, or end of study (February 21, 2009). Subjects failing to maintain LDO enrollment during the 30-day exposure period were excluded from analysis. Based on varying cohort entry times, subjects were eligible to contribute up to 48.7 months of potential at-risk time.

Statistical analyses

In the primary analysis, RxDSL was considered as a dichotomous variable (<240 and ≥240 minutes) based on a clinically relevant cut-point. In the secondary analysis, RxDSL was considered as a three-level categorical variable (<210, 210–239, and ≥240 minutes). Baseline subject characteristics were described as counts and proportions for categorical variables and as means and standard deviations for continuous variables. Bivariable comparisons across RxDSL categories were made using contingency table methods and χ^2 testing, Student's t-tests, or analysis of variance.

To maximally control for the most compelling confounders, subjects were matched on the basis of age (±2.5 years), gender (identical), vascular access type (identical), and post-dialysis weight (nearest neighbor with caliper width not exceeding ±1kg). In the primary analysis, RxDSL<240 and RxDSL≥240 subjects were matched 1:1; in the secondary analysis RxDSL<210, RxDSL210-239, and RxDSL≥240 subjects were matched 1:1:1. All survival analyses were then stratified on matched pair/triplet assignment. Adjusted associations were estimated using multivariable Cox proportional hazards models with inclusion of covariate terms for other variables thought to be plausibly associated with both RxDSL and survival and that exhibited significant unadjusted associations with RxDSL and survival. Multivariable models were adjusted for age, race (black, non-black), post-dialysis weight (kg), vintage (<1, 2, 3, ≥4 years), diabetes, coronary artery disease, congestive heart failure, missed dialysis sessions over 30 days (0, 1, 2, 3, ≥4), creatinine (quartiles mg/dL), albumin (≤3, 3–3.5, 3.5–4, >4 g/dL), phosphorus (≤4, 4–5, 5–6, ≥6 mg/dL), and pre-dialysis systolic blood pressure (≤130, 130–150, 150–170, >170 mmHg). Pre-dialysis systolic blood pressure, missed dialysis sessions, and vintage were not significantly associated with RxDSL on univariate analyses but were included due to their strong associations with mortality and for congruity with the published literature. Ultrafiltration rate and URR were not included because they were thought to represent plausible causal pathway intermediate (i.e., means by which RxDSL may impact survival). In addition, covariate terms for age and post-dialysis weight were included in the multivariable model to adjust for imbalance that may have persisted despite matching. Specification of continuous covariates (linear versus categorical) was guided by each covariate's observed association with outcome as assessed by regression coefficient graphical evaluation, Akaike's Information Criterion, and Martingale residual plots. The proportionality assumption for each model was tested graphically and by Schoenfeld residual testing (no variables were in violation). The adjusted R^2 for the final model was 0.81.

Effect modification of the DSL--survival association on the basis of age, gender, and post-dialysis weight was explored through restriction subgroup analysis; for these analyses, age and post-dialysis weight were dichotomized at their medians. Significance of interaction was assessed by likelihood ratio testing of nested models that did and did not include two-way cross product terms (factor-by-exposure). All analyses were performed using STATA 10.0MP (College Station, TX).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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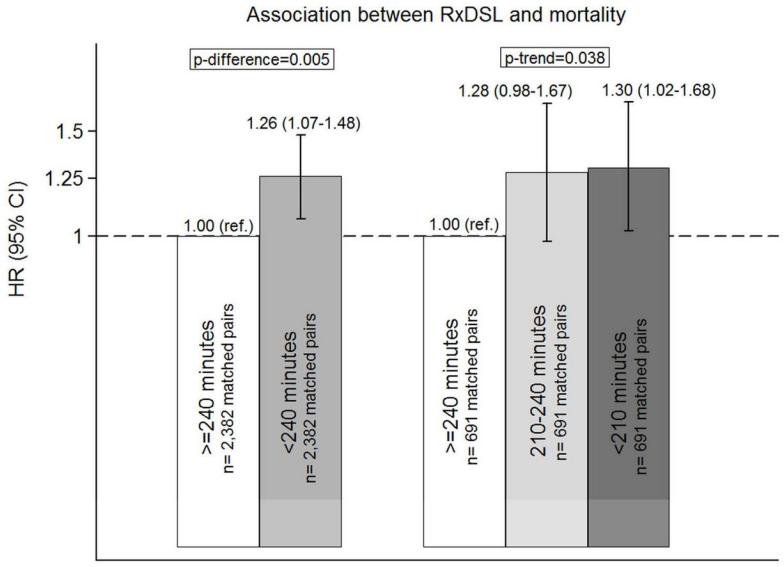

Figure 1. Adjusted associations between prescribed dialysis session length and mortality based on Cox regression models

Subjects were matched on sex, access type (fistula, graft, catheter), age (±2.5 years), and post-dialysis weight (± 1 kg). Multivariable models contained covariate terms for age, race (black, non-black), post-dialysis weight, interdialytic weight gain (≤0, 1–1.49, 1.5–2.99, 3.0–3.99, and ≥4.0 kg), vintage (<1, 2, 3, ≥4 years), diabetes, coronary artery disease, congestive heart failure, missed dialysis sessions over 30 days (0, 1, 2, 3, ≥4), creatinine (quartiles), albumin (≤3, 3–3.5, 3.5–4, >4 g/dL), phosphorus (≤4, 4–5, 5–6, ≥6 mg/dL), and pre-dialysis systolic blood pressure (≤130, 130–150, 150–170, >170 mmHg). Models were stratified on matched pair assignment. Abbreviations: RxDSL, prescribed dialysis session length

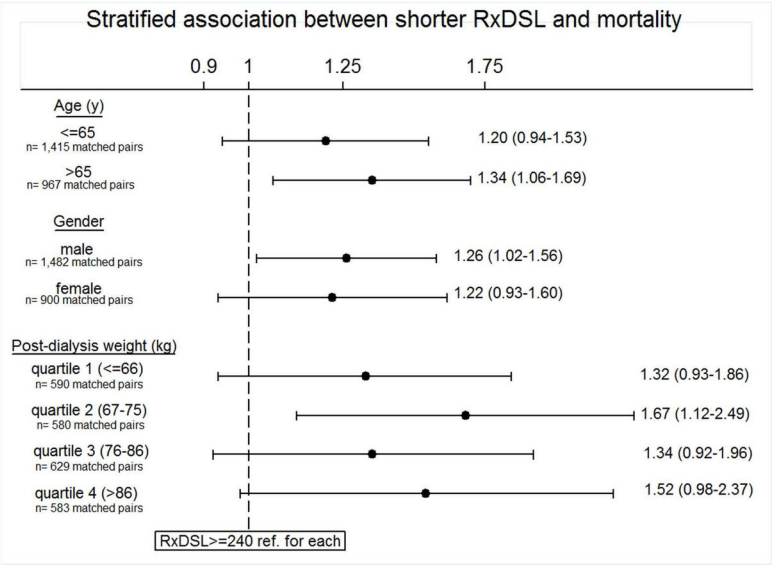

Figure 2. Adjusted associations between RxDSL<240 (ref *RXDSL*≥240) and mortality in restriction subgroup analysis considering age, gender, and post-dialysis weight

RxDSL<240 and RxDSL≥240 subjects were pair matched on sex, access type (fistula, graft, catheter), age (±2.5 years), and post-dialysis weight (± 1 kilogram). Multivariable models contained covariate terms for age, race (black, non-black), post-dialysis weight, interdialytic weight gain (≤0, 1–1.49, 1.5–2.99, 3.0–3.99, and ≥4.0 kg), vintage (<1, 2, 3, ≥4 years), diabetes, coronary artery disease, congestive heart failure, missed dialysis sessions over 30 days (0, 1, 2, 3, ≥4), creatinine (quartiles), albumin (≤3, 2–3.5, 3.5–4, >4 g/dL), phosphorus (≤4, 4–5, 5–6, ≥6 mg/dL), and pre-dialysis systolic blood pressure (≤130, 130–150, 150–170, >170 mmHg). Models were stratified on matched pair assignment. The reference group for all analyses was RxDSL ≥ 240 minutes.

Table 1

Baseline characteristics of overall source population across binary prescribed dialysis session length.[a]

	Total N=10,571	RxDSL<240 n=6,791	RxDSL≥240 n=3,780	p
RxDSL (minutes)				
mean ± SD	216.5 ± 26.1	200.8 ± 17.8	244.6 ± 9.6	
median [IQR]	210 [195, 240]	210 [180, 210]	240 [240, 240]	
Delivered DSL (minutes)	215.8 ± 25.6	201.2 ± 18.1	242.0 ± 13.2	<0.001
Age (y)	62.2 ± 15.0	64.2 ± 15.2	58.6 ± 13.8	<0.001
Female	5,107 (48.3%)	3,864 (56.9%)	1,243 (32.9%)	<0.001
Access				<0.001
Fistula	3,946 (37.3%)	2,402 (35.4%)	1,544 (40.9%)	
Graft	3,369 (31.9%)	2,298 (33.8%)	1,071 (28.3%)	
Catheter	3,166 (30.0%)	2,027 (29.9%)	1,139 (30.1%)	
Missing	90 (0.9%)	64 (0.9%)	26 (0.7%)	
Post-dialysis weight (kg)	75.0 ± 19.5	69.5 ± 16.3	84.9 ± 20.8	<0.001
Interdialytic weight gain (kg)	2.6 ± 1.1	2.4 ± 1.0	3.1 ± 1.2	<0.001
Ultrafiltration rate (ml/h/kg)	10.1 ± 4.2	10.6 ± 4.5	9.2 ± 3.5	<0.001
Race				<0.001
Non-black	6,328 (59.9%)	4,302 (63.4%)	2,026 (53.6%)	
Black	4,176 (39.5%)	2,446 (36.0%)	1,730 (45.8%)	
Missing	24 (0.6%)	43 (0.6%)	24 (0.6%)	
Diabetes	5,546 (52.5%)	3,395 (50.0%)	2,151 (56.9%)	<0.001
Coronary artery disease	1,308 (12.4%)	801 (11.8%)	507 (13.4%)	0.02
Congestive heart failure	3,992 (37.8%)	2,384 (35.1%)	1,608 (42.5%)	<0.001
Vintage (y)				0.41
<1	2,598 (24.6%)	1,705 (25.1%)	893 (23.6%)	
1–2	1,550 (14.7%)	1,002 (14.8%)	548 (14.5%)	
2–4	2,651 (25.1%)	1,697 (25.0%)	954 (25.2%)	
≥4	3,734 (35.3%)	2,364 (34.8%)	1,370 (36.2%)	
Missing	38 (0.4%)	23 (0.3%)	15 (0.4%)	
Pre-dialysis SBP (mmHg)				0.14
≤130	1,525 (14.4%)	992 (14.6%)	533 (14.1%)	
130–150	3,441 (32.6%)	2,200 (32.4%)	1,241 (32.8%)	
150–170	3,657 (34.6%)	2,386 (35.1%)	1,271 (33.6%)	
>170	1,948 (18.4%)	1,213 (17.9%)	735 (19.4%)	
Urea reduction ratio (%)	74.5 ± 5.2	74.7 ± 5.2	74.3 ± 5.2	<0.001
Missed sessions[b]				0.54
0	7,480 (70.8%)	4,782 (70.4%)	2,698 (71.4%)	
1	1,049 (9.9%)	670 (9.9%)	379 (10.0%)	
2	916 (8.7%)	589 (8.7%)	327 (8.7%)	
3	314 (3.0%)	210 (3.1%)	104 (2.8%)	
≥4	812 (7.7%)	540 (8.0%)	272 (7.2%)	

	Total N=10,571	RxDSL<240 n=6,791	RxDSL≥240 n=3,780	p
Albumin (g/dL)				0.05
≤3	705 (6.7%)	475 (7.0%)	230 (6.1%)	
3–3.5	1,890 (17.9%)	1,229 (18.1%)	662 (17.5%)	
3.5–4	4,770 (45.1%)	3,073 (45.3%)	1,697 (45.0%)	
>4	3,152 (29.8%)	1,986 (29.2%)	1,166 (30.9%)	
Missing	54 (0.5%)	28 (0.4%)	26 (0.7%)	
Creatinine				<0.001
Quartile 1	2,562 (24.2%)	1,793 (26.4%)	770 (20.4%)	
Quartile 2	2,654 (25.1%)	1,799 (26.5%)	854 (22.6%)	
Quartile 3	2,470 (23.4%)	1,575 (23.2%)	895 (23.7%)	
Quartile 4	2,561 (24.2%)	1,441 (21.2%)	1,120 (29.6%)	
Missing	324 (3.1%)	183 (2.7%)	141 (3.7%)	
Phosphorus (mg/dL)				<0.001
≤4	2,173 (20.6%)	1,490 (21.9%)	684 (18.1%)	
4–5	2,764 (26.2%)	1,827 (26.9%)	937 (24.8%)	
5–6	2,524 (23.9%)	1,594 (23.5%)	929 (24.6%)	
>6	3,076 (29.1%)	1,863 (27.4%)	1,213 (32.1%)	
Missing	34 (0.3%)	17 (0.3%)	17 (0.5%)	
Hemoglobin (g/dL)	12.1 ± 1.4	12.0 ± 1.4	12.2 ± 1.4	<0.001

[a]Values presented as mean (s.d.) or n (%) except where indicated. Across prescribed session length groups significance was assessed by T-test for continuous variables and χ^2 testing for categorical variables.

[b]Number of dialysis sessions missed during the 30-day exposure period.

Table 2

Comparison of age, sex, vascular access type and post-dialysis weights between matched RxDSL<240 and RxDSL≥240 subjects in the primary analysis.[a]

	RxDSL<240 N=2,382	RxDSL≥240 N=2,382	p
	Matching factors		
Age (y)			---
mean ± SD	61.7 ± 13.0	61.6 ± 13.0	
median [IQR] (min, max)	62.0 [53.0, 72.0] (22, 96)	62.0 [53.0, 72.0] (20, 94)	
Female	900 (37.8%)	900 (37.8%)	---
Access			---
Fistula	986 (41.4%)	986 (41.4%)	
Graft	665 (27.9%)	665 (27.9%)	
Catheter	730 (30.7%)	730 (30.7%)	
Missing	1 (0.04%)	1 (0.04%)	
Post-dialysis weight (kg)			---
mean ± SD	76.7 ± 14.9	76.7 ± 14.9	
median [IQR] (min, max)	75.3 [66.1, 85.6] (41.5, 153.3)	75.3 [66.0, 85.7] (41.6, 153.2)	
	Other covariates		
Interdialytic weight gain (kg)	2.6 ± 1.0	2.9 ± 1.1	<0.001
Ultrafiltration rate (ml/h/kg)	10.2 ± 4.2	9.5 ± 3.6	<0.001
Race			<0.001
Non-black	1,473 (61.8%)	1,328 (55.8%)	
Black	895 (37.6%)	1,032 (43.3%)	
Missing	14 (0.6%)	22 (0.9%)	
Diabetes	1,271 (53.4%)	1,399 (58.7%)	<0.001
Coronary artery disease	291 (12.2%)	344 (14.4%)	0.02
Congestive heart failure	856 (35.9%)	991 (41.6%)	<0.001
Vintage (y)			0.08
<1	617 (25.9%)	580 (24.4%)	
1–2	380 (16.0%)	341 (14.3%)	
2–4	580 (24.4%)	567 (23.8%)	
≥4	799 (33.5%)	885 (37.2%)	
Missing	6 (0.3%)	9 (0.4%)	
Pre-dialysis SBP (mmHg)			0.53
≤130	326 (13.7%)	351(14.7%)	
130–150	798 (33.5%)	798 (33.5%)	
150–170	822 (34.5%)	822 (34.5%)	
>170	436 (18.3%)	436 (18.3%)	
Urea reduction ratio (%)	73.4 ± 4.9	75.2 ± 5.2	<0.001
Missed sessions[b]			0.88
0	1,677 (70.4%)	1,700 (71.4%)	
1	231 (9.7%)	229 (9.6%)	

	RxDSL<240 N=2,382	RxDSL≥240 N=2,382	p
2	217 (9.1%)	216 (9.1%)	
3	74 (3.1%)	64 (2.7%)	
≥4	183 (7.7%)	173 (7.3%)	
Albumin (g/dL)			0.07
≤3	144 (6.1%)	162 (6.8%)	
3–3.5	406 (17.0%)	454 (19.1%)	
3.5–4	1,061 (44.5%)	1,071 (45.0%)	
>4	760 (31.9%)	680 (28.6%)	
Missing	11 (0.5%)	15 (0.6%)	
Creatinine			0.02
Quartile 1	550 (23.1%)	619 (26.0%)	
Quartile 2	576 (24.2%)	564 (23.7%)	
Quartile 3	591 (24.8%)	593 (24.9%)	
Quartile 4	588 (24.7%)	511 (21.5%)	
Missing	77 (3.2%)	95 (4.0%)	
Phosphorus (mg/dL)			0.38
≤4	465 (19.5%)	493 (20.7%)	
4–5	635 (26.7%)	583 (24.5%)	
5–6	578 (24.3%)	584 (24.5%)	
>6	698 (29.3%)	712 (29.9%)	
Missing	6 (0.3%)	10 (0.4%)	
Hemoglobin (g/dL)	12.0 ± 1.4	12.2 ± 1.5	<0.001

[a] Values presented (%) except where indicated.

[b] Number of dialysis sessions missed during the 30-day exposure period.

Table 3

Adjusted associations between RxDSL<240 (vs RxDSL≥240) and mortality among matched pairs in which differences in prescribed dialysis session length were <30, =30, and >30 minutes.[a]

	RxDSL≥240	RxDSL<240
Time Difference	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)[a]**
<30 minutes (n= 435 matched pairs)	1.00 (ref.)	1.12 (0.75–1.66)
=30 minutes (n=938 matched pairs)	1.00 (ref.)	1.38 (1.03–1.84)
>30 minutes (n=1,009 matched pairs)	1.00 (ref.)	1.41 (1.08–1.84)

[a]RxDSL<240 and RxDSL≥240 subjects were matched on sex, access type (fistula, graft, catheter), age (±2.5 years), and post-dialysis weight (± 1 kg). Multivariable models contained covariate terms for age, race (black, non-black), post-dialysis weight, interdialytic weight gain (≤0, 1–1.49, 1.5–2.99, 3.0–3.99, and ≥4.0 kg), vintage (<1, 2, 3, ≥4 years), diabetes, coronary artery disease, congestive heart failure, missed dialysis sessions over 30 days (0, 1, 2, 3, ≥4), creatinine (quartiles), albumin (≤3, 3–3.5, 3.5–4, >4 g/dL), phosphorus (≤4, 4–5, 5–6, ≥6 mg/dL), and pre-dialysis systolic blood pressure (≤130, 130–150, 150–170, >170 mmHg). Models were stratified on matched pair assignment.

Table 4

Comparison of age, sex, vascular access type and post-dialysis weights between matched RxDSL<210, RxDSL210-239, and RxDSL≥240 subjects. [a]

	RxDSL<210 N=691	RxDSL210-239 N=691	RxDSL≥240 N=691	p
		Matching factors		
Age (y)				---
mean +/− SD	64.9 ± 11.9	64.8 ± 11.8	64.8 ± 11.8	
median [IQR] (min, max)	65.0 [57.0, 75.0] (25.0, 87.0)	66.0 [57.0, 74.0] (22.0, 90.0)	65.0 [56.0, 74.0] (24.0, 88.0)	
Female	290 (42.0%)	290 (42.0%)	290 (42.0%)	
Access				---
Fistula	271 (39.2%)	271 (39.2%)	271 (39.2%)	
Graft	212 (30.7%)	212 (30.7%)	212 (30.7%)	
Catheter	208 (30.1%)	208 (30.1%)	208 (30.1%)	
Post-dialysis weight (kg)				---
mean +/− SD	71.6 ± 11.0	71.6 ±11.0	71.6 ± 11.0	
median [IQR] (min, max)	70.7 [63.7, 78.7] (45.8, 118.5)	70.6 [63.6, 78.7] (45.8, 117.7)	70.6 [63.6, 78.6] (45.5, 117.8)	
		Other covariates		
Interdialytic weight gain (kg)	2.3 ± 0.9	2.6 ± 1.1	2.7 ± 1.1	<0.001
Ultrafiltration rate (ml/h/kg)	10.7 ± 4.3	10.2 ± 4.0	9.5 ± 3.7	<0.001
Race				<0.001
Non-black	486 (70.4%)	421 (60.9%)	381 (55.1%)	
Black	204 (29.5%)	265 (38.4%)	305 (44.2%)	
Missing	1 (0.1%)	5 (0.7%	5 (0.7%)	
Diabetes	342 (49.5%)	381 (55.1%)	413 (59.8%)	0.001
Coronary artery disease	88 (12.7%)	94 (13.6%)	105 (15.2%)	0.41
Congestive heart failure	231 (33.4%)	253 (36.6%)	273 (39.5%)	0.06
Vintage (y)				0.05
<1	171 (24.7%)	185 (26.8%)	160 (23.1%)	
1–2	107 (15.5%)	113 (16.4%)	87 (12.6%)	
2–4	186 (26.9%)	148 (21.4%)	174 (25.2%)	
≥4	225 (32.6%)	245 (35.5%)	268 (38.8%)	
Missing	2 (0.3%)	0 (0.0%)	2 (0.3%)	
Pre-dialysis SBP (mmHg)				0.97
≤130	99 (14.3%)	97 (14.0%)	105 (15.2%)	
130–150	222 (32.1%)	219 (31.7%)	226 (32.7%)	
150–170	246 (35.6%)	242 (35.0%)	230 (33.3%)	
>170	124 (18.0%)	133 (19.3%)	130 (18.8%)	
Urea reduction ratio (%)	73.2 ± 4.6	74.4 ± 4.9	76.1 ± 5.0	0.18
Missed sessions[b]				0.37
0	486 (70.4%)	511 (74.0%)	514 (74.4%)	
1	63 (9.1%)	66 (9.5%)	57 (8.3%)	
2	52 (7.5%)	47 (6.8%)	56 (8.1%)	

	RxDSL<210 N=691	RxDSL210-239 N=691	RxDSL≥240 N=691	p
3	25 (3.6%)	17 (2.5%)	21 (3.0%)	
≥4	65 (9.4%)	50 (7.2%)	43 (6.2%)	
Albumin (g/dL)				0.02
≤3	36 (5.2%)	45 (6.5%)	57 (8.3%)	
3–3.5	116 (16.8%)	131 (19.0%)	134 (19.4%)	
3.5–4	302 (43.7%)	316 (45.7%)	327 (47.3%)	
>4	235 (34.0%)	196 (28.4%)	171 (24.7%)	
Missing	2 (0.3%)	3 (0.4%)	2 (0.3%)	
Creatinine				0.89
Quartile 1	164 (23.7%)	167 (24.2%)	180 (26.1%)	
Quartile 2	174 (25.2%)	162 (23.4%)	172 (24.9%)	
Quartile 3	163 (23.6%)	176 (25.5%)	168 (24.3%)	
Quartile 4	172 (24.9%)	166 (24.0%)	150 (21.7%)	
Missing	18 (2.6%)	20 (2.9%)	21 (3.0%)	
Phosphorus (mg/dL)				0.29
≤4	150 (21.7%)	150 (21.7%)	163 (23.6%)	
4–5	205 (29.7%)	185 (26.8%)	165 (23.9%)	
5–6	168 (24.3%)	170 (24.6%)	171 (24.8%)	
>6	167 (24.2%)	184 (26.6%)	187 (27.1%)	
Missing	1 (0.1%)	2 (0.3%)	5 (0.7%)	
Hemoglobin (g/dL)	12.0 ± 1.3	12.1 ± 1.5	12.2 ± 1.4	0.006

[a] Values presented as n (%), except where indicated.

[b] Number of dialysis sessions missed during the 30-day exposure period.