

Impact of Timing of Initiation of Dialysis on Mortality

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Abstract. Previous studies showed that sicker patients were initiated on dialysis at higher GFR as estimated by the Modification of Diet in Renal Disease (MDRD) formula. It was previously shown that patients with low creatinine production were malnourished and had low serum creatinine levels and creatinine clearances (CrCl) but high MDRD GFR at initiation of dialysis. Therefore, a propensity score approach was used to examine the associations of MDRD GFR and measured CrCl at the initiation of dialysis with subsequent mortality. Baseline data and outcomes were obtained from the Dialysis Morbidity Mortality Study Wave II. Propensity scores for early initiation derived by logistic regression were used in Cox models to

examine mortality. Each 5-ml/min increase in MDRD GFR at initiation of dialysis in the entire cohort was associated with increased hazard of death in multivariable Cox model (hazard ratio [HR] 1.14; $P = 0.002$). In the subgroup of patients with reported CrCl, higher MDRD GFR was associated with increased risk of death (for each 5-ml/min increase, HR 1.27; $P < 0.001$) but not CrCl (for each 5-ml/min increase, HR 0.98; $P = 0.81$). These divergent results might reflect erroneous GFR estimation by the MDRD formula. Furthermore, these data do not support earlier initiation of dialysis. Therefore, for patients without clinical indications for initiation of dialysis, the appropriate GFR level for initiation of dialysis is unknown.

Early initiation of dialysis might improve nutrition with consequent decrease in hospitalization, mortality, and costs (1–8). However, early initiation of dialysis also exposes the patient to complications of dialysis, unnecessary lifestyle restriction, and potential increased costs. Thus, the optimal timing of initiation of dialysis is unclear.

There are two methodologic issues that need to be considered in observational studies of optimal timing of dialysis. First, randomized controlled trials are considered the gold standard in comparison of different interventions, as effective randomization coupled with sufficient sample size would result in equal distribution of baseline factors across treatment groups. There may be significant imbalances in distribution of key parameters across treatment groups in observational studies because certain clinical conditions might be indications for therapy with one intervention (in this case, early initiation of dialysis) than the other. Indeed, previous studies of the United States Renal Data System (USRDS) data showed that sicker patients were initiated on dialysis at higher GFR as estimated by the Modification of Diet in Renal Disease (MDRD) formula (9). The use of propensity stratification based on propensity

scores has been shown to reduce or eliminate the imbalances in distribution of baseline covariables across treatment groups in nonrandomized studies (10,11).

Second, the MDRD formula has not been validated in patients with advanced renal failure. Our earlier study showed that patients with low creatinine production were malnourished and had low serum creatinine levels and creatinine clearances (CrCl) but high MDRD GFR at initiation of dialysis (12). These resulted in a spurious association of malnutrition with higher MDRD GFR at initiation of dialysis. The misclassification of low creatinine producers as early initiators of dialysis by the MDRD formula and *vice versa* in high creatinine producers might lead to erroneous interpretation of the effect of timing of dialysis on mortality. In this study, we adopted the propensity score approach to examine the associations of levels of estimated MDRD GFR and measured CrCl at the initiation of dialysis with subsequent mortality in the Dialysis Morbidity Mortality Study Wave II (DMMS II).

Materials and Methods

This study was reviewed and approved by the Institutional Review Board at the University of Utah.

Study Population

The USRDS DMMS II is a prospective registry of a national, random sample of incident chronic hemodialysis and peritoneal dialysis patients who initiated dialysis therapy in 1996 and early 1997 in the United States (13–15). Patients with previous renal replacement therapy, duplicate entries, missing USRDS identification numbers, or missing follow-up data and patients younger than 18 yr were ex-

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cluded. Patients with missing data for age, sex, race, height, weight, blood urea nitrogen (BUN), serum creatinine, serum albumin, hematocrit, and serum bicarbonate were also excluded.

Baseline Data

The DMMS II patient questionnaire data on demographics (age, sex, and race), cause of ESRD (diabetes or other), insurance status (Medicare or non-Medicare), comorbid conditions (coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, left ventricular hypertrophy, malignancy, acquired immunodeficiency syndrome, and chronic lung disease), smoking, nutritional status (serum albumin, clinical diagnosis of malnutrition as determined by the dialysis unit personnel and body mass index [BMI]), functional ability, BUN and serum creatinine before the initiation of dialysis, and dialysis modality were used in this analysis (13–15). Baseline hematocrit and bicarbonate levels at the initiation of dialysis were used as markers of the level of predialysis care (16,17). Functional impairment (presence of any of the following: inability to independently eat, ambulate, or transfer) was used as a marker of disease severity.

Calculations for Renal Function

The MDRD equation ($GFR = 270 \times [\text{serum creatinine}^{-1.007}] \times [\text{age}^{-0.18}] \times 0.775$ if female $\times 1.18$ if black $\times [\text{bun}^{-0.169}]$) (18,19), Cockcroft-Gault formula (20), and reciprocal of serum creatinine were used to determine GFR values at the initiation of dialysis therapy in the entire cohort. Measured CrCl in addition to GFR estimation equations were used in the subgroup of patients with reported measured CrCl in the Medical Evidence Form.

Follow-up and Outcomes

The USRDS_ID variable enabled the linkage of Wave 2 data to other USRDS files. The treatment history, claims, and patients files provided data on follow-up periods, mortality, and transplantation. Patients were tracked until loss to follow-up, transplantation, death, or the administrative censor date of December 31, 1998. Death was the outcome of interest.

Statistical Analyses

Even though it is customary to statistically compare baseline differences across treatment groups, because of the large sample size and concerns about multiple comparisons, baseline characteristics of patients in the higher and lower MDRD GFR groups were not compared. The propensity score method was used to account for the confounding that arises because patients in whom dialysis was started at a high MDRD GFR were not otherwise equivalent to patients in whom dialysis was started at low MDRD GFR. First, factors that seemed to influence the likelihood of having a high MDRD GFR at initiation of dialysis were studied using logistic regression. A stepwise variable selection method was used to select patient characteristics that were independently associated with high MDRD GFR at initiation of dialysis. On the basis of the value of each independent factor multiplied by its β coefficient, subjects were ranked with respect to their predicted probability (propensity score) of high MDRD GFR at initiation of dialysis (10,11). Three propensity score strata were created using the 33rd and 66th percentiles as cut points. Second, these strata were applied to a stratified Cox proportional hazards regression model of mortality, as described in further detail below. The aim of the propensity score method is to form strata within which the distributions of relevant measured factors across treatment groups (high and low MDRD GFR) are equalized. This desired consequence is tested by

comparing characteristics of patients initiated on dialysis at high *versus* low MDRD GFR within each stratum. Categorical variables were compared using a χ^2 test. Independent groups *t* tests were used for continuous variables that met the homogeneity of variance assumption, and unequal variance (Satterthwaite's degrees of freedom approximation) *t* tests were used when the homogeneity of variance assumption was not met.

All baseline variables with the exception of GFR estimations were selected for a forward stepwise Cox regression model to identify factors independently associated with mortality. The association of MDRD GFR with mortality was examined by adding MDRD GFR as a continuous variable to the identified independent predictors of mortality in a Cox model stratified by propensity scores. The proportional hazards assumption of Cox regression was evaluated by analysis of the scaled Schoenfeld residuals (21). Proportionality assumptions were not violated by MDRD GFR. Variables that were significantly associated with mortality in the stepwise Cox regression model but violated the proportionality assumptions were stratified. Both the simultaneous and individual variable significance tests based on the scaled Schoenfeld residuals were negative for proportionality assumption violations in the stratified model. These analyses were repeated with GFR estimated by 100/serum creatinine and Cockcroft-Gault formula.

Sensitivity Analyses

In an intent-to-treat model, additional Cox proportional hazards regression analyses were performed without censoring subjects at the time of transplantation. In the subgroup of patients with reported CrCl in the Medical Evidence Form and with other nonmissing data, propensity scores for early initiation of dialysis (above median CrCl) were derived. Independent predictors of death in this subgroup were derived from Cox regression as described above. Associations of measured CrCl, MDRD GFR, Cockcroft-Gault CrCl, and reciprocal of serum creatinine at initiation of dialysis with mortality were examined in different Cox models stratified by propensity scores with and without independent predictors of death. These analyses were repeated within each of the propensity strata.

Results

Of the 4024 patients entered in the DMMS II Study, 2920 patients met the inclusion criteria and were studied. The baseline characteristics of the study population are summarized in Table 1. There were 342 (11.7%) transplants and 1070 (36.7%) deaths in 5585 patient-years of follow-up.

Unadjusted associations of baseline factors with higher MDRD GFR at initiation of dialysis are also summarized in Table 1. A multivariable logistic regression model of factors associated with higher MDRD GFR at initiation of dialysis was used to develop propensity strata for early initiation of dialysis. In this model, male sex (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.21 to 1.65) black race (OR, 1.33; 95% CI, 1.12 to 1.58), Medicare insurance (OR, 1.36; 95% CI, 1.16 to 1.60), diabetes (OR, 1.73; 95% CI, 1.48 to 2.03), coronary artery disease (OR, 1.33; 95% CI, 1.11 to 1.59), congestive heart failure (OR, 1.67; 95% CI, 1.40 to 2.00), cerebrovascular disease (OR, 1.37; 95% CI, 1.07 to 1.74), each 5% increase in hematocrit (OR, 1.14; 95% CI, 1.05 to 1.22), each mEq/L increase in serum bicarbonate (OR, 1.04; 95% CI, 1.03 to 1.06), each 5-kg/m² increase in BMI (OR, 0.92; 95% CI, 0.86

Table 1. Baseline characteristics of the study population

	All Patients (N = 2920)	GFR ≤ 7.5 ml/min (N = 1476)	GFR > 7.5 ml/min (N = 1444)
Demographics			
age (mean ± SD; years)	59 ± 15	57 ± 16	61 ± 15
male gender (n [%])	1,548 (53)	730 (49)	818 (57)
race (n [%])			
white	1,859 (64)	924 (63)	935 (65)
black	825 (28)	416 (28)	409 (28)
other	236 (8)	136 (9)	100 (7)
hemodialysis:peritoneal dialysis (n [%])	1535:1385 (53:47)	771:705 (52:48)	764:680 (53:47)
Medicare (n [%])	1,494 (51)	655 (44)	839 (58)
Comorbid conditions			
diabetes as cause of renal failure (n [%])	1,237 (42)	509 (34)	728 (50)
coronary artery disease (n [%])	1,110 (38)	444 (30)	666 (46)
congestive heart failure (n [%])	1,001 (34)	374 (25)	627 (43)
left ventricular hypertrophy (n [%])	612 (21)	278 (19)	334 (23)
cerebrovascular disease (n [%])	348 (12)	135 (9)	213 (15)
peripheral vascular disease (n [%])	551 (19)	212 (14)	339 (23)
malignancy (n [%])	252 (9)	129 (9)	123 (9)
AIDS (n [%])	45 (2)	29 (2)	16 (1)
smoker (n [%])	1,136 (39)	563 (38)	573 (40)
chronic lung disease (n [%])	247 (8)	104 (7)	143 (10)
functional impairment (n [%])	370 (13)	144 (10)	226 (16)
Renal function parameters			
MDRD GFR (mean ± SD; ml/min)	8.2 ± 3.9	5.6 ± 1.3	10.9 ± 3.9
serum creatinine (mean ± SD; mg/dl)	8.3 ± 3.7	10.6 ± 3.7	5.8 ± 1.6
blood urea nitrogen (mean ± SD; mg/dl)	87 ± 31	99 ± 31	75 ± 26
Markers of pre-ESRD care			
hemotocrit (mean ± SD; %)	30.8 ± 5.4	30.4 ± 5.4	31.3 ± 5.4
serum bicarbonate (mean ± SD; mEq/l)	22.0 ± 4.6	21.5 ± 4.7	22.6 ± 4.5
Nutritional parameters			
clinical diagnosis of malnutrition (n [%])	388 (13)	163 (11)	225 (16)
body mass index (mean ± SD; kg/m ²)	26.3 ± 5.8	26.6 ± 5.7	26.0 ± 5.8
serum albumin (mean ± SD; g/dl)	3.46 ± 0.57	3.52 ± 0.55	3.40 ± 0.55

to 0.98), and each g/dl increase in serum albumin (OR, 0.79; 95% CI, 0.68 to 0.92) were associated with higher MDRD GFR at initiation of dialysis. OR >1 indicate an increased likelihood of starting dialysis at a high MDRD GFR and <1 a decreased likelihood of starting dialysis at a high MDRD GFR.

Propensity scores for early initiation of dialysis were derived from β coefficients in the above logistic regression model of factors associated with early initiation of dialysis. Higher the β coefficient of a given variable, the more likely that patients with that specific variable were initiated early on dialysis. In other words, patients with variables that were associated with early initiation of dialysis had a high propensity for early initiation of dialysis. Thus, patients with high propensity scores had a higher distribution of those factors associated with early initiation of dialysis than those with low propensity scores. Nonetheless, not all patients with high propensity scores were actually initiated on dialysis at a higher GFR. Therefore, within the high-propensity stratum, most patients were initiated on

dialysis at higher GFR, but there were still some patients initiated on dialysis at lower GFR. Similarly, in the low-propensity stratum, most patients were initiated on dialysis at a lower GFR, but some were initiated on dialysis at higher GFR. If baseline factors that were associated with both mortality and early initiation of dialysis were similarly distributed across early *versus* late groups within each of the strata, then the bias in estimation of the effect of GFR on mortality within each stratum could be minimized. The differences in the distribution of key parameters across early and late dialysis groups (Table 1) were markedly reduced or eliminated within each of the propensity strata (Table 2), indicating that the propensity score approach succeeded at balancing the baseline characteristics of early and late dialysis groups within propensity strata.

Table 3 summarizes independent factors associated with death in the multivariable Cox model in the entire cohort. Each 5-ml/min increase in MDRD GFR was associated with 36% increased hazard of death in univariable Cox model (HR, 1.36;

Table 2. Distribution of independent predictors of mortality in early and late initiation of dialysis groups within propensity strata

	Low Likelihood of Early Initiation			Moderate Likelihood of Early Initiation			High Likelihood of Early Initiation		
	GFR ≤ 7.5 ml/min (N = 655)	GFR > 7.5 ml/min (N = 318)	P Value	GFR ≤ 7.5 ml/min (N = 508)	GFR > 7.5 ml/min (N = 466)	P Value	GFR ≤ 7.5 ml/min (N = 313)	GFR > 7.5 ml/min (N = 660)	P Value
Age (mean ± SD; years)	51 ± 15	53 ± 16	0.050	59 ± 15	61 ± 16	0.077	66 ± 12	65 ± 13	0.217
Race (n [%])			0.716			0.321			0.096
white	413 (63)	192 (60)		314 (62)	298 (64)		197 (63)	444 (67)	
black	183 (28)	96 (30)		147 (29)	136 (29)		86 (27)	177 (27)	
other	59 (9)	30 (9)		47 (9)	31 (7)		30 (10)	59 (6)	
Medicare insurance (n [%])	154 (24)	91 (29)	0.085	267 (53)	254 (55)	0.543	234 (75)	494 (75)	0.976
Hemodialysis (n [%])	332 (51)	161 (51)	0.986	268 (53)	260 (56)	0.342	171 (55)	343 (52)	0.437
Diabetes as cause of renal failure (n [%])	76 (12)	54 (17)	0.021	210 (41)	197 (42)	0.767	223 (71)	477 (72)	0.739
Congestive heart failure (n [%])	26 (4)	14 (4)	0.750	130 (26)	128 (27)	0.507	218 (70)	485 (73)	0.212
Peripheral vascular disease (n [%])	34 (5)	29 (9)	0.019	82 (16)	79 (17)	0.734	96 (31)	231 (35)	0.182
Chronic lung disease (n [%])	23 (4)	21 (7)	0.029	43 (8)	42 (9)	0.762	38 (12)	80 (12)	0.993
Clinical diagnosis of malnutrition (n [%])	40 (6)	25 (8)	0.304	61 (12)	66 (14)	0.318	62 (20)	134 (20)	0.857
Body mass index (mean ± SD; kg/m ²)	27.6 ± 6.2	27.1 ± 6.9	0.309	26.0 ± 5.5	25.8 ± 5.8	0.505	25.3 ± 4.3	25.7 ± 5.1	0.244
Serum albumin (mean ± SD; g/dl)	3.7 ± 0.5	3.7 ± 0.5	0.173	3.4 ± 0.5	3.4 ± 0.5	0.709	3.3 ± 0.5	3.3 ± 0.5	0.698
Functional impairment (n [%])	33 (5)	17 (5)	0.838	49 (10)	62 (13)	0.073	62 (20)	147 (22)	0.382

Table 3. Multivariable Cox regression model of predictors of death in the entire cohort (n = 2920)^a

	Hazard Ratio	95% Confidence Interval
Age (each 10-year increase)	1.25	1.18–1.33
Black ^b	0.79	0.68–0.92
Other races ^b	0.55	0.42–0.73
Medicare insurance	1.19	1.02–1.40
Peripheral vascular disease	1.27	1.10–1.46
Chronic lung disease	1.31	1.09–1.58
Clinical diagnosis of malnutrition	1.32	1.11–1.55
Body mass index (each 5-kg/m ² increase)	0.89	0.84–0.95

^a Variables considered for inclusion in model that fell out as nonsignificant were gender, coronary artery disease, cerebrovascular disease, left ventricular hypertrophy, malignancy, AIDS, smoker, hematocrit, and serum bicarbonate. Diabetes, functional impairment, congestive heart failure, serum albumin quartiles, and treatment modality were significant but stratified because of proportionality violations.

^b Reference group: white.

95% CI, 1.28 to 1.44). In a multivariable Cox model stratified by propensity scores, congestive heart failure, dialysis modality, functional impairment, and serum albumin and adjusted for other factors listed in Table 3, each 5-ml/min increase in MDRD GFR was associated with 14% higher hazard of death (HR, 1.14; 95% CI, 1.06 to 1.22). Diabetes was not stratified in this model, as it did not violate proportionality assumptions. Substitution of MDRD GFR with CrCl estimated by the Cockcroft-Gault formula (for each 5-ml/min increase: HR, 1.08; 95% CI, 1.02 to 1.14) or reciprocal of serum creatinine (for each 5-ml/min increase: HR, 1.09; 95% CI, 1.04 to 1.14) in the above Cox model yielded similar results.

The association of MDRD GFR with increased mortality was consistently significant within each of the sensitivity analyses in multivariable Cox models. In the intent-to-treat model of transplant, each 5-ml/min increase in MDRD GFR was associated with 13% higher hazard of death (HR, 1.13; 95% CI, 1.05 to 1.21).

In patients with reported CrCl (n = 1072), male sex (OR, 1.56; 95% CI, 1.21 to 2.01), black race (OR, 0.70; 95% CI, 0.52 to 0.94), hemodialysis modality (OR, 0.75; 95% CI, 0.57 to 0.98), diabetes (OR, 1.98; 95% CI, 1.53 to 2.58), each g/dl increase in serum albumin (OR, 1.29; 95% CI, 1.06 to 1.59), each 5-kg/m² increase in BMI (OR, 1.12; 95% CI, 1.00 to 1.26), functional impairment (OR, 0.63; 95% CI, 0.44 to 0.91), and each mEq/L increase in serum bicarbonate (OR, 1.03; 95% CI, 1.01 to 1.06) were associated with initiation of dialysis above the median CrCl of 8.8 ml/min.

On the basis of the 33rd and 66th percentiles of propensity scores derived from the above logistic regression model, three propensity groups were developed. In a Cox model stratified

by propensity groups without other covariates, each 5-ml/min increase in MDRD GFR was associated with 47% higher hazard of death (HR, 1.47; 95% CI, 1.32 to 1.64). When independent predictors of death were added as covariates, each 5-ml/min increase in MDRD GFR was associated with 28% higher hazard of death (HR, 1.28; 95% CI, 1.12 to 1.46). Substitution of MDRD GFR with CrCl estimated by the Cockcroft-Gault formula (for each 5-ml/min increase: HR, 1.16; 95% CI, 1.05 to 1.29) or reciprocal of serum creatinine (for each 5-ml/min increase: HR, 1.19; 95% CI, 1.11 to 1.29) in the above Cox model yielded similar results. However, when measured CrCl were used, each 5-ml/min increase in CrCl was not associated with increased hazard of death in a Cox model stratified by propensity groups but without covariates (HR, 1.00; 95% CI, 0.87 to 1.14) and in another Cox model stratified by propensity groups with covariate adjustment (HR, 0.98; 95% CI, 0.86 to 1.14). Subgroup analyses of mortality within each of the propensity strata with adjustment for covariates in different Cox models of MDRD GFR, Cockcroft-Gault CrCl, reciprocal of serum creatinine, and measured CrCl are summarized in Figure 1.

Discussion

The strategy of early initiation of dialysis has been advocated on the presumption that it improves nutrition, decreases hospitalization rates, and reduces mortality. The evidence for these was derived from the following observational data. Lower GFR was associated with lower protein intake and lower serum albumin level (22). Serum albumin level at the initiation of dialysis was a powerful predictor of death (23). Thus, it has been argued that early initiation of dialysis will prevent malnutrition and thereby decrease mortality (6,24). The mean urea clearance by the native kidneys at the initiation of dialysis was lower among those who died compared with those who survived in an unadjusted analysis of 63 patients (8). An Italian study from the 1980s showed a 12-yr survival of 77% in 82 patients who were started dialysis early (at mean CrCl of 12.9 ml/min) compared with 51% in 308 patients who were started late (at CrCl of 2.1 to 4.8 ml/min) (4). However, these studies did not adjust for age or other comorbidities at the time of initiation of dialysis. A more recent analysis of incident peritoneal dialysis patients suggested that each 5-ml/min increase in GFR at the initiation dialysis was associated with a 5% decrease in mortality in a multivariable Cox model (5). Although previous observational studies suggested a survival benefit with early initiation of dialysis, a recent, rigorous observational study showed that lead-time bias could account for this benefit (25). Conversely, another European study used the original Cockcroft-Gault formula and found an increased mortality in patients who were initiated early on dialysis (26).

The results of the current study, which encompassed a large, national random sample of the U.S. dialysis population, raise several issues. First, higher estimated GFR (by MDRD formula, Cockcroft-Gault formula, and the reciprocal of serum creatinine) at initiation of dialysis was associated with increased risk of death. It is intuitive to infer from Table 1 that the increased mortality associated with higher MDRD GFR at

initiation of dialysis was because sicker patients were initiated early on dialysis. However, the propensity score approach indicates that this might not be the correct interpretation of the data. Table 2 shows that stratification of patients by the propensity score method was a particularly effective method to establish balance in key mortality risk factors across early and late initiation of dialysis patients. Subgroup analyses within each of the propensity strata indicate that the sicker patients in the high-propensity stratum did not drive the observed increased mortality with higher MDRD GFR at initiation of dialysis in the entire cohort.

The biologic plausibility for higher mortality in patients who were initiated on dialysis at higher MDRD GFR but not at lower MDRD GFR is not readily apparent. One possible explanation is that high serum creatinine levels in patients with advanced renal failure might represent not only a diseased state but also a healthier state of high creatinine production, which in turn reflects better nutrition and muscle mass. Adjusting for age, sex, race, and BUN as used in the MDRD formula, total body weight as in the Cockcroft-Gault formula, or the BMI could be poor surrogates for the rate of creatinine production. Indeed, in a study of 1346 patients on hemodialysis for an average of 4.2 yr, higher serum creatinine was associated with lower mortality independent of BMI and other factors in a multivariable Cox model (27). These are consistent with the earlier reported lower mortality with higher serum creatinine levels at initiation of dialysis by Fink *et al.* (28)

In the subgroup of patients with reported CrCl, MDRD GFR still retained the association with mortality, but there was no association of death with CrCl at initiation of dialysis (Figure 1). As shown in our earlier study, there seems to be a misclassification bias with MDRD GFR (12). Thus, some of the “early initiators” by the MDRD formula were actually low creatinine producers with low CrCl and some of the “late initiators” by the MDRD formula were high creatinine producers with high CrCl. In contrast, CrCl accounts for 24-h urinary creatinine, a measure of creatinine production. However, because of tubular secretion of creatinine, CrCl is likely to overestimate GFR consistently. Thus, misclassification bias for early *versus* late initiation of dialysis is greater with the MDRD estimate than with CrCl. The divergent findings between outcomes when the measured CrCl is used rather than the other three calculations of GFR could reflect erroneous estimation of the GFR by these calculations in this relatively low GFR range.

In an opinion-based statement, initiation of dialysis has been recommended when the native GFR falls below 10.5 ml/min (29), except for patients with stable or increasing edema-free body weight, ≥ 0.8 g/kg per day of normalized protein nitrogen appearance rate, or the absence of uremic signs or symptoms. We believe that the proper interpretation of our findings in the context of older studies, which were also observational, is that the relative merits of early or late initiation of dialysis remain uncertain. All observational studies, including this one, are limited by the potential existence of unmeasured confounders (*e.g.*, there are no data on inflammatory markers such as C-reactive protein or other markers such as troponin T in the

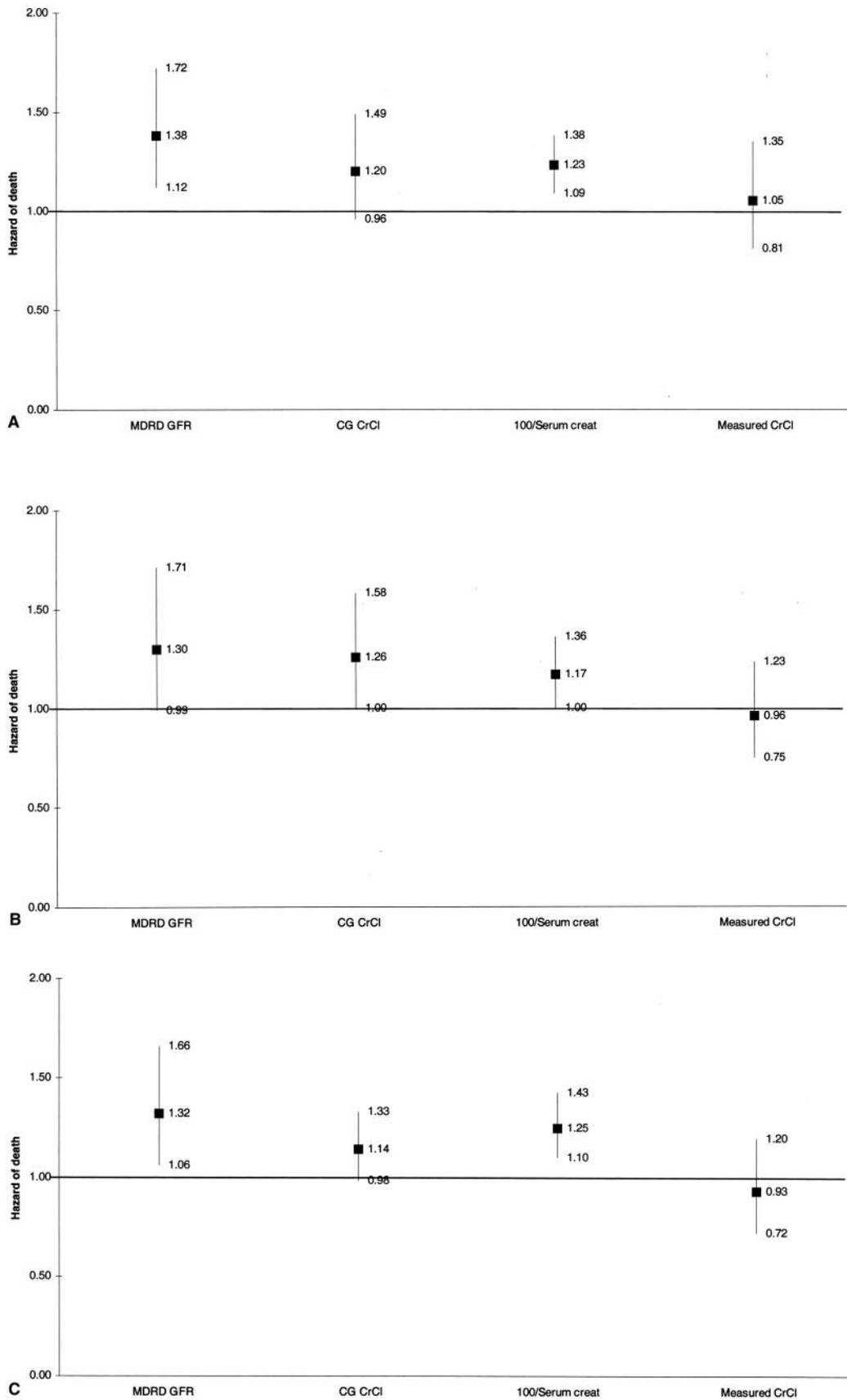


Figure 1. (A) Association of each 5-ml/min increase in GFR estimations with mortality in low-propensity strata ($n = 357$). (B) Association of each 5-ml/min increase in GFR estimations with mortality in moderate-propensity strata ($n = 357$). (C) Association of each 5-ml/min increase in GFR estimations with mortality in high-propensity strata ($n = 358$).

USRDS database). The use of propensity scores does not mitigate unmeasured confounders as calculation of propensity scores relies on explicitly measured factors only. However, randomization coupled with adequate sample size would result in equal distribution of both measured and unmeasured confounders across treatment groups. Therefore, a sufficiently powered randomized trial with non-creatinine-based GFR measurements is the only study design that overcomes this deficiency.

A limitation of this study was that the study population was composed only of patients who were initiated on dialysis, so it was also subject to lead-time and survival bias. Clinical diagnosis of malnutrition as determined by the dialysis unit personnel has not been validated as a measure of nutrition. However, this variable was associated with both higher MDRD GFR at initiation of dialysis and subsequent death in this study. Data are not available to determine whether the adjusted mortality rate before initiation of dialysis in individuals whose dialysis was delayed was higher or lower than the equivalent period in early dialysis patients, so the net direction of these biases is unknown. Further limitations of the study include unavailability of information on clinical indications for initiation of dialysis and also that of any observational study based on existent databases.

We conclude that there is insufficient evidence to advocate early initiation of dialysis. Therefore, we think that in patients with clinical indications for dialysis such as volume overload, dialysis should be initiated irrespective of the level of GFR, and for patients without obvious clinical indications, the appropriate GFR level for initiation of dialysis is unknown.

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References

- Bonomini V, Albertazzi A, Vangelista A, Bortolotti GC, Stefoni S, Scolari MP: Residual renal function and effective rehabilitation in chronic dialysis. *Nephron* 16: 89–102, 1976
- Bonomini V, Baldrati L, Stefoni S: Comparative cost/benefit analysis in early and late dialysis. *Nephron* 33: 1–4, 1983
- Bonomini V, Feletti C, Scolari MP, Stefoni S: Benefits of early initiation of dialysis. *Kidney Int Suppl* 17: S57–S59, 1985
- Bonomini V, Vangelista A, Stefoni S: Early dialysis in renal substitutive programs. *Kidney Int Suppl* S112: 116, 1978
- Churchill DN: An evidence-based approach to earlier initiation of dialysis. *Am J Kidney Dis* 30: 899–906, 1997
- Churchill DN, Blake PG, Jindal KK, Toffelmire EB, Goldstein MB: Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. *J Am Soc Nephrol* 10[Suppl 13]: S289–S291, 1999
- Obrador GT, Pereira BJ: Initiation of dialysis: Current trends and the case for timely initiation. *Perit Dial Int* 20: S142–S149, 2000
- Tattersall J, Greenwood R, Farrington K: Urea kinetics and when to commence dialysis. *Am J Nephrol* 15: 283–289, 1995
- Kausz AT, Obrador GT, Arora P, Ruthazer R, Levey AS, Pereira BJ: Late initiation of dialysis among women and ethnic minorities in the United States. *J Am Soc Nephrol* 11: 2351–2357, 2000
- Joffe MM, Rosenbaum PR: Invited commentary: Propensity scores. *Am J Epidemiol* 150: 327–333, 1999
- D'Agostino RB Jr: Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 17: 2265–2281, 1998
- Beddhu S, Samore MH, Roberts M, Stoddard G, Pappas L, Cheung AK: Creatinine production, nutrition, and glomerular filtration rate estimation. *J Am Soc Nephrol* 14: 1000–1005, 2003
- U.S. Renal Data System: The USRDS Dialysis Morbidity and Mortality Study (Wave2). USRDS 1997 Annual Data Report. Bethesda, MD, NIH, NIDDK, 1997, pp 49–67
- U.S. Renal Data System: The DMMS and Other USRDS Special Studies. Researcher's Guide to the USRDS Database. Bethesda MD, NIH, NIDDK, 1999, pp 83–89
- U.S. Renal Data System: Medication Use Among Dialysis Patients in the Dialysis Morbidity and Mortality Study. USRDS 1998 Annual Data Report. Bethesda, MD, NIH, NIDDK, 1998, pp 51–62
- Obrador GT, Ruthazer R, Arora P, Kausz AT, Pereira BJ: Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. *J Am Soc Nephrol* 10: 1793–1800, 1999
- Kausz AT, Khan SS, Abichandani R, Kazmi WH, Obrador GT, Ruthazer R, Pereira BJ: Management of patients with chronic renal insufficiency in the Northeastern United States. *J Am Soc Nephrol* 12: 1501–1507, 2001
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470, 1999
- Levey AS, Kusek JW, Beck GJ: A simplified equation to predict GFR from serum creatinine. MDRD Study Group. [Abstract]. *J Am Soc Nephrol* 11: A0828, 2000
- Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
- Grambsch PM, Therneau TM: Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 81: 515–526, 1994
- Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS: Relationship between nutritional status and the glomerular filtration rate: Results from the MDRD study. *Kidney Int* 57: 1688–1703, 2000
- Comorbid conditions and correlations with mortality risk among 3,399 incident hemodialysis patients. *Am J Kidney Dis* 20: 32–38, 1992
- Hakim RM, Lazarus JM: Initiation of dialysis. *J Am Soc Nephrol* 6: 1319–1328, 1995
- Korevaar JC, Jansen MA, Dekker FW, Jager KJ, Boeschoten EW, Krediet RT, Bossuyt PM: When to initiate dialysis: Effect of proposed US guidelines on survival. Netherlands Cooperative Study on the Adequacy of Dialysis Study Group. *Lancet* 358: 1046–1050, 2001

26. Traynor JP, Simpson K, Geddes CC, Deighan CJ, Fox JG: Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. *J Am Soc Nephrol* 13: 2125–2132, 2002
27. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 55: 1560–1567, 1999
28. Fink JC, Burdick RA, Kurth SJ, Blahut SA, Armistead NC, Turner MS, Shickle LM, Light PD: Significance of serum creatinine values in new end-stage renal disease patients. *Am J Kidney Dis* 34: 694–701, 1999
29. NKF-DOQI clinical practice guidelines for peritoneal dialysis adequacy. National Kidney Foundation. *Am J Kidney Dis* 30: S67–S136, 1997

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