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Factors Associated with Mortality in Patients with End-Stage Renal Disease During the First and Second Years After a Dialysis Initiation

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Factors Associated with Mortality in Patients with End-Stage Renal Disease During the First and Second Years After a Dialysis Initiation

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Epidemiology

by

Lilia Rebecca Lukowsky

2012

ABSTRACT OF THE DISSERTATION

Factors Associated with Mortality in Patients
with End-Stage Renal Disease During the First and Second Years
After a Dialysis Initiation

by

Lilia Rebecca Lukowsky

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2012

Professor Leeka Kheifets, Chair

Mortality is high among incident hemodialysis patients especially during the first several months after initiation of dialysis and can be influenced by many factors. Age, vascular access, co-morbid conditions, serum levels of albumin, and dialysis modality may affect survival. We attempted to identify factors that influence survival of incident hemodialysis patients and to determine if changes in clinical practices could improve survival. We hypothesized that patients surviving at least 24 months differ in their characteristics from those who died and so indentifying those differences and making changes may improve survival in all hemodilaysis patients.

Standardized mortality ratios (SMR) were calculated for each of the first 24 months on dialysis to determine the temporal pattern of mortality. Cox proportional hazard models were fitted to examine mortality at several *a priory* determined time periods for each predictor using case-mix

adjustments. The associations between all-cause mortality and combined serum levels of albumin and nPCR were studied for each of first 8 quarters on dialysis. Changes in serum albumin and nPCR levels from the prior quarter were examined separately. Finally, marginal structural models (MSM) were fitted to analyze the association between mortality and dialysis modality during 24 months of treatment. Inverse probability weights were created to account for time varying confounding of quarterly measured laboratory values and changes in dialysis modality over the first 8 quarters.

SMRs were the highest during the 3-6 months after starting dialysis. Use of central venous catheters and low levels of serum albumin at the time of dialysis initiation were associated with all-cause and infection-related mortality during the first 24 months of treatment. Volume overload was associated with cardio-vascular mortality especially in non-hypoalbuminemic patients. Decrease in albumin and nPCR was associated with mortality during 24 months on dialysis. Patients on peritoneal dialysis showed better survival compared to hemodialysis patients after adjusting for modality changes by using MSMs. Patients who changed modalities at least once showed a survival advantage over those who remained on initial modality during 24 months of dialysis treatment.

The dissertation of Lilia Rebecca Lukowsky is approved.

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2012

Dedication

In loving memory of Dr. Yeva Gomberg, Lubov' Gomberg,

my parents Elizaveta (Lilia) Churkina and Anatoliy Churkin

I also dedicate this work to my stepmother Nata Churkina who always gives me unconditional love and who supported me throughout this process and to my son Edward who brings so much joy into my life

Finally, I want to thank my dissertation committee for their help and support with this research.

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Chapter 4 is a version of: Lukowsky LR, Kheifets L, Arah AO, Nissenson AR, Kalntar-Zadheh K. Patterns and predictors of early mortality in hemodialysis patients: new insights. AJN (in press)

Chapter 5 is a version of: Lukowsky LR, Kheifets L, Arah AO, Nissenson AR, Kalntar-Zadheh K. Nutritional predictors of early mortality in hemodialysis patietnts.

Dr. Kalantar-Zadeh was the PI of the study and a dissertation committee member; the other co-authors were dissertation committee members.

Chapter 6 is a version of: Lukowsky LR, Mehrotra R, Kheifets L, Arah AO, Nissenson AR, Kalntar-Zadheh K. Comparative effect of peritoneal vs. hemodialysis on mortality in the first two years: a marginal structural model analysis.

Dr Mehrotra was a PI of the study; Dr. Kalantar-Zadeh was co-PI of the study and a dissertation committee member; the other co-authors were dissertation committee members.

VITA/Biographical Sketch

Lilia Lukowsky received Master of Public Health from University of Los Angeles in September of 2006. She received a Bachelor of Science in biology in June of 2002.

She started PhD program in epidemiology in September of 2006 at School of Public Health at University of Los Angeles.

Ms. Lukowsky began her career in public health in January of 2001 when she became an undergraduate research assistant for the PEG study headed by Dr. Ritz at the department of Epidemiology at School of Public Health at University of Los Angeles. During her work on PEG study she became inspired by the impact that public health makes on people's lives and decided to become a public health professional. In September of 2003, Ms Lukowsky started graduate studies at the department of Epidemiology at School of Public Health at UCLA.

From December of 2006 to June 2011 Lilia Lukowsky was a statistical associate for the HERO study, a randomized behavioral intervention trial with the objectives of decreasing the recovery time, increasing survival and quality of life by increasing duration and quality of sleep in elderly veterans admitted to inpatient rehabilitation unit after major health crisis. The study was conducted in Great Los Angeles Area by the Geriatric Research department of Veteran Administration.

Starting from May 2009 Ms. Lukowsky joined a team of researchers at Harold Simmons Laboratory at Los Angles Biomedical Institute in Torrance, CA where she has been working on a number of projects geared toward improving survival and quality of life of dialysis patients. The topics she was working on included examining the factors associated with mortality in patients with Polycystic Kidney Disease, comparing survival among dialysis patients with different dialysis modalities, and examining changes in laboratory parameters over 5 year time period among maintenance hemodialysis patients. Her work at the Harold Simmons Laboratory resulted in co-authorship of eight publications and ten poster presentations.

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Chapter 1 Introduction

1.1 Chronic Kidney Disease

1.1.a Definition and Prevalence

Chronic Kidney Disease (CKD) is a serious condition when the loss of renal function progressively occurs usually within a course of several years. It can be caused by the factors such as cardio-vascular disease, hypertension, diabetes, and obesity among others. If untreated it can progress to the End-Stage Renal Disease (ESRD) and dialysis treatment or kidney transplant would be needed. Patients with CKD can experience poor quality of life, increased health care expenses, and increase the risk of death.[1] Risk factors for CKD include age (65 and older), as well as being African American or Native American.[2]

CKD is defined as either by reduced glomerular filtration rate (GFR) or by signs or kidney damage such as protinurea, hematuria, or abnormal imaging or biopsy. These abnormalities have to be present for at least 3 month to be diagnosed as CKD and not an acute kidney injury. [3]

It is estimated that 19.2 million Americans have CKD.[2] The crude prevalence estimate for adults was reported to be 15.1% of US population. [1] Prevalence by disease stage was determined to be: 5.7% for stage 1, 5.4% for stage 2, 5.4% for stage 3, and 0.4% for stages 4 and 5 [1]. Also 11% of adults age 65+ excluding people with diabetes and hypertension were found to have some level of decreased kidney function.[2]

National Health and Nutrition Examination Survey (NHANES) examined the trends in CKD in 2001-200. The report showed an increase in prevalence of CKD stages 1-4 by 31% from 10 to 13.1 % in the US population. [4] It was noted that such rise cannot be explained adequately

by rising rates of obesity, hypertension, and diabetes. Some researchers suggested that nutritional status may play an important role in CKD prevalence and prognosis.[5]

In 2006, the initiative on CKD prevention was launched by CDC. A panel of experts reviewed epidemiologic data on CKD from US federal agencies and issued recommendations on primary, secondary and tertiary prevention. A 10 point plan to improve surveillance, screening, education and awareness about CKD was issued. It targeted three populations: patients with CKD, health care providers, hospitals, labs, and a general public. One of the key recommendations issued was to insure cooperation between federal, state, local governments as well as with private organizations in effort to improve the outcomes for CKD patients.[6]

1.1.b Stages of CKD

Clinically five stages of Chronic Kidney Disease have been defined based on measuring the glomerular filtration rate (GFR). There are two different approaches that are commonly used to determine GFR. The first approach includes measuring levels of Cystatin C, a protein with low molecular weight, and the second one looks at the serum creatinine. It has been suggested that the methods using Cystatin C may be more accurate because they monitor albumin/creatinine ratios (ACR) of 30mg/g and above, which are more stable than creatinine estimates alone to monitor GFR rates of less than 60ml/min.[7]

National Kidney Foundation (NKF) uses the following CKD stage markers:

Stage1: GFR >=90ml/min/173m^3, ACR>=30mg/g

Stage 2: GFR 60-89 ml/min/173m^3 ACR >=30mh/g

Stage 3: GFR 30-59 ml/min/173m^3

Stage 4: GFR 15-29 ml/min/173m^3

Stage 5: GFR< 15 ml/min/173m^3

1.2 End-Stage Renal Disease (ESRD)

1.2.a Definition

ESRD can be defined as a condition which requires a start of Replacement Renal Therapy (RRT) or death with documented levels of GFR less than 15 ml/min/1.73m^3 or other indications of RRT before death.[8] There may be problems with this definition because patients with diabetes can require RRT at higher levels of GFR. However a combination of low GFR and proteinuria are usually good indicators of progression to ESRD. [8] It was reported that the median time between the patient's withdrawal from RRT and death was 7 days.[9]

1.2.b Trends in Incidence and Prevalence

In the past several decades the number of patients with End-Stage Renal Disease increased from about 60,000 in 1980 to 570,000 in 2009. [7] In 2009, the incident rate of ESRD was 355 per million, while the prevalent rate was reported to be 1738 per million.[10] The incidence rate higher than the 2010 Healthy people target rate of 221 per million. The highest incident rate was among African Americans (976 per million) followed by Hispanics (523 per million). It is projected that the number of ESRD patients will increase even more by 2020 and will reach almost 800,000 patients.[10]

In Europe, the stabilization of incident rates of RRT was reported by Kramer and colleagues based on the analysis of nineteen European National or regional renal registries from 1997 to 2006.[11] Even though the incident rates continue to increase, the speed of increase considerably slowed down after 2000. Authors cited several reasons for this trend such as early

detection and prevention of CKD, interventions aimed to slow progression to ESRD in CKD patients, as well as better treatment of patients with diabetes. After 2004, incident rates of dialysis initiation due to hypertension, renal/vascular disease and miscellaneous causes showed some stabilization while rates due to unknown or missing causes were still rising.[11]

1.3 Dialysis in US

Caring for End-Stage Renal Disease patients results in an economic burden on society. It is estimated that even though ESRD patients represent about 1% of all Medicare recipients, their care takes 6.4% of the Medicare and Medicaid budget. In 2001, $22 billion were spent on care for ESRD patients, most of which were paid by Medicare.[2]

The number of patients receiving dialysis treatment increased dramatically over the past two decades. In 2007, 566,000 patients were receiving a dialysis treatment, compared to 123,000 in 1989. [12] The hospitalization rate of dialysis patients was 2.02 admissions per patient year with median hospital stay of 5 days. In 2007, there were 162,389 hospitalizations among patients receiving dialysis at the outpatient clinics run by Fresenius Medical Care North America.[13] In 2003, ESRD patients on average spent 14 days in the hospital.[14]

Recent studies suggest that early intervention aimed at physical and psychological well-being during a transitional time of pre- and right after initiation of dialysis can improve the outcome in ESRD patients.[15]

It was reported by Wingard et al that early interventions in management of anemia, dialysis dose, nutrition, vascular access, and education at the time of dialysis initiation improve the outcomes in dialysis patients during the first year. A program called Right Start was evaluated and

showed promising results in reducing hospitalization and mortality rates in the incident dialysis patients.[14]

Study by Crews et al compared patient characteristics and outcomes for inpatient and outpatient dialysis initiation and reported that patients who had inpatient dialysis initiation had more co-morbidities, low social support, were more likely to be unmarried, and had less pre-dialysis referrals to a nephrologist. However, among patients with late referrals to a nephrologist, patients that had inpatient initiations were less likely to have subsequent hospitalizations (IRR=0.92; 95% CI 0.89-0.94).[16]

Implementing the post-discharge intervention of monitoring patients' hemoglobin levels within the first 7 days after discharge and adjusting the erythropoietin and vitamin D doses was shown to decrease repeated hospitalization rates in dialysis patients.[13]

A recent study by Chen et al showed that an early nephrology referral, 6 month or more before the initiation of RRT, was associated with lower mortality among incident dialysis patients. The study reported a hazard ratio of 2.8 ($p=0.049$) when comparing patients with late referrals to the patients with early referrals.[17] Patients with early referrals were less likely to have hypoalbuminemia and more likely to receive drugs for correcting anemia, have permanent vascular access before the first dialysis treatment, and take phosphate binders in comparison to those with late nephrology referrals.

A meta-analysis by Chan et al evaluated 22 studies looking at late referral (less than 3 months for mortality outcomes and less than 4 months for hospitalization outcomes) to a nephrology specialist before the dialysis initiation also reported significant increase in overall mortality (RR=1.99 95% CI 1.66-2.39) associated with late referrals.[18] The same study observed

an increase in the length of hospital stay at the time of dialysis initiation among patients with late referrals compared to patients with early referrals (25.3 days vs. 13.5 days).

1.4 Mortality among dialysis patients

1.4.a Risk factors / Dialysis paradox

USRDS reported that the highest mortality rates were during the month 2 and 3 after dialysis initiation. The most common causes of death were cardio-vascular and infectious diseases. An age of over 65, lower serum creatinine, higher estimated glomerular filtration rates (eGFR) and higher BMI at the time of dialysis initiation were associated with higher mortality in the first three months of dialysis treatment.[10]

However, there have been numerous reports that found a reverse association between mortality and obesity, blood pressure and serum lipid levels, a phenomenon referred as dialysis-risk paradox.[19, 20] Fifteen studies reviewed by Salahudeen conducted in USA, Europe and Japan from 1982 to 2002 reported better survival for dialysis patients with higher BMI.[20] Moreover, a pooled analysis from Dialysis Outcomes and Practice Patterns Study (DOPPS) of about 10,000 patients showed significantly lower mortality risk for overweight patients compared to the normally weighted patients (RR=0.84 p=0.008), as well as for mildly obese patients (RR=0.73 p=0.0003), and moderately obese patients (RR=0.76 p=0.02). [20]

A recent study by Huang et al examined the association between mortality and muscle fat mass in 1,709 dialysis patients. Using patients with lowest muscle and fat mass quartiles as a reference group, the authors reported decrease in mortality risks in both high muscle and fat mass groups. The adjusted hazard ratios for triceps skin-fold thickness quartiles (the muscle mass

indicator) ranged from 0.55 to 0.70 ($p<0.001$), and in mid-arm muscle circumference (fat mass indicator) adjusted HR ranged from 0.68 to 0.70 ($p=0.003$). [21]

Study by Tsirpanlis and colleagues found that low cholesterol was associated with increased mortality in dialysis patients. They reported that levels of interleukin-10 in 24-month survivors were 11.29 vs. 5.51 in non-survivors ($p<0.018$), and TChol levels were 167.37 in survivors vs. 122.04 in non-survivors ($p<0.00001$) for CV mortality. For all-cause mortality the TChol levels were 169.26 in survivors vs. 133.6 in non-survivors ($p<0.003$).[22]

A study by Kalantar-Zadeh et al of 40,933 MHD patients followed for 15 months in the US showed that pre-dialysis systolic hypertension was associated with lower mortality (systolic blood pressure between 160 and 189mmHg) while normal blood pressure was associated with significantly higher mortality. Hazard ratios for 15-month survival for patients with systolic blood pressure of 160-169 was 0.74 (0.67-0.82), while for the patients with systolic blood pressure of 120-129 hazard ratios were 1.22 (1.10-1.35), and 2.11 (1.87-2.78) for patients with blood pressure less than 110mmHg (using a reference group of 130-139).[23]

These findings lead to questions such as: what is an optimal BMI for dialysis patients, should dialysis patients be encouraged to gain weight, can nutritional interventions aimed to increase appetite lead to better survival, and should the same guidelines for BMI, lipids and blood pressure used for the general population be applied to dialysis patients.[24] Many of these questions are widely debated and the answers to them will require further research to understand and explain them.

One of the explanations for the dialysis paradox may be that high mortality in dialysis patients could be associated with malnutrition-inflammation syndrome (MIS). Loss of nutrients

through dialysis process, loss of appetite causing low nutrient intake and anorexia, uremic toxins, oxidative and carbonyl stress, decreased clearance of inflammatory cytokines, co-morbid conditions, and low quality of life can be associated with MIS. All of the above can lead to a decrease in BIM, hypocholesterolemia, hypocreatininemia, hypohomocysteinemia which then can lead to high mortality.

Therefore, high BMI, high cholesterol levels, and increase in systolic blood pressure can be protective factors associated with better survival in dialysis patients.[25] While these factors may be long-term "killers" they may give a protective advantage against under-nutrition and wasting in dialysis patients in the short term.[26, 27] A study by Beberashvili and colleagues supported this view showing that dialysis patients with high BMI had better nutritional status compared to patients with normal BMI.[28]

A longitudinal study of uric acid levels in incident hemodialysis patients found that low levels were associated with higher mortality (HR=2.23; 95%CI 1.21-4.11) while increase in uric acid levels was not (HR=0.89; 95%CI 0.47-1.71). Low uric acid was associated with markers of malnutrition, and high co-morbidity, which was consistent with evidence oxidative stress.[29]

1.4.b Overall mortality

Over the past two decades overall mortality among dialysis patients decreased substantially. Five-year mortality decreased 7.5% between years 1992-96 and 1997-2001. However, it still remained high compared to the general population. In 2009, USRDS reported that all-cause mortality among dialysis patients aged 65 or older was 7 times higher than in the general population.[10] In 2007, the mortality rate was 245.1 per 1,000 patients in patients with older vintage (time on dialysis) compared to 203.3 in patients with younger vintage, which represented 20.6% difference. The female dialysis patients aged 30-50 were the group with the highest

difference in life expectancy between the ERSD patients and the general population. Their life expectancy was estimated to be only one fifth of what is expected for females of the same age without ESRD.[10]

Kramer et al reported 11% decrease in risk of death among dialysis patients in Europe in 2002-2006 compared to 1997-2001 time periods, adjusted for age, gender, primary renal disease, and country.[11] Dialysis Outcomes and Practice Patterns Study reported that mortality among dialysis patients in the US was higher than in Europe or Japan.[30] After adjusting for age, gender, race, and 25 co-morbid conditions, risk ratio for mortality among dialysis patients was 3.78 ($p<0.0001$) when comparing the USA to Japan and 1.33 ($p<0.0001$) when comparing the USA to Europe. In the USA, the age of the patients was significantly higher than in other countries, a therefore, the prevalence of age-related co-morbidities was also higher. The risk ratios for mortality among dialysis patients with co-morbidities ranged from 1.06 to 2.96 for different conditions with the exception of hypertension (RR= 0.74 in multivariate analysis). Diabetes, obesity and serum lipid levels were not examined in this analysis.

Differences in mortality patterns were observed while comparing different subgroups among the dialysis patients. An American study by Lopez et al, also part of DOPPS, reported better survival in African American, Asian, Hispanic and Native American patients in comparison to Whites.[31] Reported Risk Ratios were 0.78 (95%CI 0.69-0.89) for African Americans, 0.68 (95% CI 0.50 – 092) for Asians, 0.51 (95% CI 0.33-0.77) for Native Americans, and 0.92 (95%CI 0.79-1.08) for Hispanics compared to Whites. Survival was associated with health-related quality of life scores (HRQOL) scores that were higher in all reported racial groups than in Whites.

1.4.c Mortality during the first year after initiation of dialysis

In 2009, United States Renal Data System reported that during the first six months after dialysis initiation cardio-vascular mortality decreased while mortality for other or unknown causes increased, which could be due to changes in the Death Notification form and may show increase in misclassification and underreporting of cause-specific outcomes.[10]

In the US, from 1993 to 2005, mortality was lower in the first month after dialysis initiation but rose to the highest levels during months 2 and 3. After that it declined slowly, and to mortality for the months 4-12 was similar to the mortality during the first month.[12]

Comparing to other countries, the USA had higher crude mortality rates during the first year after dialysis initiation: 21.7% compared to 15.6% in Europe and 6.6% in Japan.[30]A study conducted in the UK showed that while Blacks and South Asians had higher rates of RRT, they had better survival compared to Whites.[32] Lower prevalence of cardio-vascular diseases, higher PTH levels at baseline, better social support and lower withdrawal rates were cited as possible reasons for better survival in those groups. Results were consistent with the US study by Lopez et al that looked at overall mortality patterns among different ethnic groups.[31]

Bradbury and colleagues examined early mortality among incident hemodialysis patients in the DOPPS study in the US and reported elevated mortality risk during the first 120 days after dialysis initiation comparing to the subsequent 121 to 365 days.[9] They also noted that cardio-vascular causes were the most common for the first year mortality with the rate of cardio-vascular related deaths being the highest in the first 120 days. In the first 120 days, predictors associated with high mortality were: old age, white race, low albumin levels at baseline, catheter use for the first dialysis, HIV/AIDS, Congestive Heart Failure, cancer, lung disease, neurologic or psychiatric disorder, and not visiting a nephrologist at least one month before the dialysis initiation. In the

subsequent 121 to 365 days HIV/AIDS, old age, white race, history of lung disease or a psychiatric disorder remained strong predictors of the mortality in dialysis patients.[9]

1.5 Albumin and nPCR as mortality predictors

1.5.a Guidelines for nutritional status in dialysis patients

Outcomes in dialysis patients depend on their nutritional status. Several guidelines for nutritional care of dialysis patients have been issued over the past several decades. The Guidelines for Nutritional Care for Renal Patients have been developed by American Dietetic Association's Medical Nutritional Therapy (MNT) and issued for dietitians working with this population. These guidelines indicated the goal values for the patient's nutrition markers after the medical nutrition therapy and maintained values for important clinical markers and behavioral outcomes such as: albumin >=4.0g/dl, phosphorous 4-6mg/gl, calcium 8.5-10.5mg/dl, hemoglobin 11-12g/dl, hematocrit 33-36%, ferritin 100-800ng/ml, nPNA (nPCR) >=0.8 g/kg/d, Kt/V>=1.2, creatinine clearance >=60L/wk/1.73m^2, food intake >80% of recommended level, and fluid intake of 1,000 ml/d in anuric patients among others.[33] They were consistent with the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Nutrition in Chronic Renal Failure (K-DOQI), which included additional recommendations for nutrition for hemodialysis patients. Hence, it is recommended that the dietary energy intake should be 35kcal/kg/day for those under 60 years of age and 30kcal/kg/day for patients who are 60years of age or older. Protein intake should be 1.2g/kg/day and at least 50% of protein should be of high biologic value.[34]

A survey of renal registered dietitians by Vergili et al found that most of them reported practices consistent with K-DOQI with regard to metabolic parameters and indicated a need for new guidelines in interdialytic weight gain (64%) and vitamin supplementation (80%).[35] A

different web-based survey of renal registered dietitians by McKnight et al found that out of 59 dietitians, 33% indicated that they used some guidelines in identifying and treating protein-energy malnutrition (PEM), and 76% of those said that K-DOQI guidelines were used in their practices.[36]

A cross-sectional study by Cupisti and colleagues compared the use of guidelines in determining nutritional status of 94 stable dialysis patients and 52 healthy subjects.[37] Dialysis patients had lower protein and energy intake compared to controls, but after the results were normalized by body weight, the differences were no longer evident. Age was inversely associated with energy ($r=-0.35$; $p<0.001$) and protein intake ($r=-0.34$; $p<0.001$) in dialysis patients. The study also reported albumin levels less than 35 g/l in 16%, nPNA <1.0g/kg/d in 23%, and BMI <20 in 16.3% of dialysis patients.

1.5.b Albumin and nPCR as indicators of nutritional status of MHD patients

Both serum levels of albumin and nPCR are important indicators of nutritional status in dialysis patients. Several factors may contribute to low levels of albumin in dialysis patients such as urinary or dialytic albumin loss, inadequate dietary intake and inflammation.[38] A retrospective study of DOPPS cohort in the US by Bradbury et al reported that 40% of patients in the cohort had albumin bellow 3.5 g/dl.[9] This study also reported that patients with low albumin levels had higher mortality during the first several months of dialysis therapy.

A prospective cohort study by Kalantar-Zadeh et al showed that a decline in serum albumin over 6 months was associated with increased all-cause and CV mortality. At the same time, increase in serum albumin was associated with better survival (HR=0.78; 95% CI 0.71-0.86 for albumin of >=0.3g/dl increase in 6 months). The Population Attributable Fraction (PAF) of death for MHD patients with albumin levels lower than 3.8g/dl was reported to be 19% (95% CI 16-22%),

indicating that about 10,000 deaths each year hypothetically could be prevented in the US by interventions aimed to rise serum albumin levels to over 3.8g/dl.[39]

A meta analysis that examined serum protein and mortality in long-term MHD patients was performed by Herselman et al. This analysis of 38 studies with total number of 265,330 patients showed the inverse relationship between the albumin levels and all-cause mortality as well as with CV mortality.[40] A study by Shinaberger et al of a 2-year cohort of hemodialysis patients showed the association between normalized protein nitrogen appearance (nPNA also called nPCR) and survival in MHD patients. The results of the study indicated that patients with daily protein intake of 1-1.4 g/kg/d had better survival. The authors also reported that a decrease in protein daily intake by 0.2 g/kg/d during the first 6 months was associated with the increased risk of death in the following 18 months.[41]

A randomized case-crossover study in which dialysis patients were randomly assigned to receive in-center protein supplements showed a significant increase in both albumin and nPCR in a group that received supplements, and a significant decrease in both parameters in the control group after 3-6 months of treatment, which continued to drop significantly in the control group.[42] The same study noted a trend in reduction in the number of hospital admissions and in the length of hospital stay for treatment groups. Dukkipati and colleagues reviewed the studies evaluating the intradialytic parenteral nutrition (IDPN) and intravenous infusion of essential nutrients during hemodialysis treatments and concluded that despite the shortcomings of many reviewed studies, these practices had good safety profile and could potentially improve protein and energy status and decrease the risk of protein energy wasting (PEW).[43]

1.6 Dialysis modality as mortality predictor

A choice of dialysis modality affects programs' funding of renal replacement therapy and influences patients' quality of life and survival.[44] In the US, over 90% of dialysis patients receive hemodialysis (HD) despite of the annual cost per patient of $82,285 in 2009 while the annual expenses for peritoneal dialysis (PD) per patient was $61,588.[44, 45] In 2008, only about 6% of all maintenance dialysis patients in the US received the less expensive PD modality.[46, 47]

While randomized controlled studies are the best way to compare the outcomes of different dialysis modalities, many patients, when properly educated about their choices, would not agree to a randomization.[48]

Many observational studies comparing survival of PD and HD patients were conducted in the past several decades. The most recent studies found that with the improvement of PD techniques, survival of PD patients equates or even surpasses that of HD patients.[47, 49]

Weinhandl et al examined the differences in survival probabilities between the hemodialysis and peritoneal dialysis patients by performing intention –to –treat analysis in a matched-pair cohort of adults starting dialysis in 2003 in the US. The probability of survival was higher among peritoneal dialysis patients compared to hemodialysis patients: 85.8% vs. 80.7% ($p<0.01$) after 12 months, 71.1%vs. 68% ($p<0.01$) after 24 months, 58.1% vs. 56.7% ($p=0.25$) after 36 and 48.4% vs. 47.3% ($p=0.5$) after 48 months.[50] No difference in the first 90-day survival was reported between the two groups (HR=1.05; 95%CI 0.96-1.16). Authors also noted that hemodialysis was associated with better survival among patients with CVD and diabetes. Sens et al, however, reported that patients with congestive heart failure (CHF) had better survival on hemodilysis with HR 1.48(95%CI 1.33-1.65).[51]

Quinn et al suggested that early advantages of PD observed in many recent studies could be due to a selection bias because the sickest patients who initiate dialysis in inpatient settings as an emergency procedure almost always start with hemodialysis.[52] Observational studies have methodological limitations in addition to a non-random assignment of dialysis modality, often resulting in inadequate adjustment for differential modality switches over time (since PD patients are more likely to switch to HD than vice versa) and inappropriate adjustment for the differential longitudinal censorship of transplantation across modalities.[53]

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Chapter 2 Study Implications and Hypothesis

2.1 Clinical and public health implications of the current study

Dialysis patients have very high mortality especially during the first year after initiation of dialysis therapy. Mortality during the first year is over 20%. [1] However, the reasons for such high numbers remain unclear, which makes determining the reasons for high mortality an important question not only in an effort to improve individual outcomes but also for future planning and managing of federal programs such as Medicare and Medicaid.

If there are differences between the patients who survived the first year of dialysis treatment and those who did not, the knowledge about such differences could be valuable to predict the patient's progress and outcome before he or she starts RRT. In that case, based on the characteristics of an individual patient, a physician could recognize potential problems and complications before they happen and could treat each patient according their needs in attempt to improve his/her outcomes. This may even lead to a transition to individualized treatments for dialysis patients, which could then improve quality of life and prolong the survival of ESRD patients.

The nutritional status of dialysis patients can play a crucial role in their survival especially in the transitional time period right after initiation of dialysis treatment. Poor nutrition can contribute to the malnutrition-inflammation syndrome (MIS). Loss of nutrients trough dialysis, poor appetite, and weight loss are common problems for patients receiving dialysis therapy.[2] Therefore it is important to have a balanced diet with substantial amounts of protein, vitamins, and minerals.

Moreover, since serum level of albumin is associated with both inflammation and malnutrition, monitoring nPCR and albumin levels in dialysis patients could be helpful in determining the nutritional status of the patient. If higher albumin and nPCR levels were predictive of better survival, then increasing dietary protein intake may be recommended to the patients with low albumin and nPCR levels in order to improve their survival after initiating dialysis treatment.

Dialysis modality can also influence early survival in patients receiving RRT. However, given impracticality of randomized clinical trials and methodological difficulties that accompanied previous research about modality implications on survival, it is vital to use methods that can account for the time differential modality switches (much more common in PD compared to HD patients), time-dependent confounding, and informative censoring due to transplantation.[3]

The aim for this study was to examine if patients surviving early stages of RRT have different characteristics that influence their prognosis and a better outcome. If this were the case, then the next step would be to determine if any of those patterns could be changed in an effort to improve survival of dialysis patients. It may also mean that End-Stage Renal Disease patients may require individualized treatments and procedures aimed at the needs of particular patient, which may indicate changes in a "treatment for all" approach that is a common practice for administering dialysis today.

If there is a link between the patients' characteristics and their mortality during the 24 months, then patients can be placed in several risk groups based on those characteristics, which would require different dialysis initiation plans as well as different dialysis maintenance and monitoring practices.

2.2. Study hypothesis

2.2.a Predictors of early mortality in incident hemodialysis patients

We hypothesized that high mortality in dialysis patients in the first year after dialysis initiation (comparing to a subsequent year) may be due to different patients' characteristics such as demographic characteristics (age, gender, marital and socio-economic status among others), as well as pre-existing conditions such as diabetes, cardio-vascular diseases, CVD and vascular access.

The aim of this portion of the study was to examine a relationship between mortality in the first two years after dialysis initiation and those factors. We also examined baseline laboratory parameters such as serum levels of albumin, creatinine, hemoglobin, calcium, phosphorous, nPCR, ferritin, TIBC, white blood count, and % of lymphocytes that may be indicators of MICS condition in dialysis patients.

We examined mortality patterns at four *a priori* specified time periods: first three months, four to six months, seventh to twelfth months, and thirteenth and twenty fourth months since starting dialysis therapy.

2.2. b Association between early mortality and serum levels of albumin and nPCR during the first 8 quarters of hemodialysis treatment

We hypothesized that a combination of albumin and nPCR serum levels may be predictive of mortality in dialysis patients in the first two years after dialysis initiation. The higher levels of albumin and nPCR represent better nutrition status of dialysis patients. Patients with albumin serum levels above 3.5 g/dl and nPCR levels above 1.00 g/kg/day may have better survival during the first two years of dialysis. In order to separate inflammation and malnutrition effects associated

with low albumin, combined categories of albumin and nPCR were created and the associations with mortality were examined using quarterly laboratory measurements for up to 8 quarters.

2.2.c Association between a dialysis modality and mortality during 24 months of dialysis treatment accounting for the changes in modality over time

We hypothesized that a choice of initial dialysis modality and a decision to switch from one modality to another affects survival of incident dialysis patients. The aim of this portion of the study was to use methods that can adequately account for time-dependent confounding, differential modality changes and censorship due to transplantation.

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Chapter 3 Overview of the Methods

3.1 Study population

DaVita is one of the leading dialysis providers in the US. It has over 1,500 outpatient dialysis facilities and 700 hospital-based acute dialysis units in 43 states. It serves about 115,000 dialysis patients nationwide.[1] A contemporary cohort of incident dialysis patients receiving dialysis from 07/01/2001 to 06/30/2006 at DaVita dialysis centers was used for this study.

Incident patients were defined as the patients who joined DaVita cohort from 07/01/01 to 06/30/2006 and either had dialysis initiated at one of the DaVita clinics or joined DaVita within 90 days from the fist dialysis treatment. For the examination of the first two portions of the study, the study population was further restricted to patients who joined the cohort within 7 days from the first dialysis treatment.

3.2 Data sources

3.2.a DaVita Dataset

DaVita dataset has information about 164,801 patients receiving dialysis treatments in one of the DaVita facilities in the US between July of 2001 and June of 2006. Each patient was assigned a unique identification number at the time of enrolment. Information about time when dialysis started, time of enrolled at the DaVita facility, date of death or transplantation if such event occurred during the study period were obtained from DaVita records. A person-time in DaVita cohort was calculated for each patient. This dataset also contained information about demographic characteristics such as age, gender, race, marital status, insurance type as well as information about vascular access for hemodialysis patients, medication patients were taking while in cohort, and the blood samples taken while in cohort. Information about medications and blood

tests were collected on repeatedly, while the demographic information was collected at the baseline.

The blood samples were taken using the same technique by all clinics and transported to the Central DaVita Laboratory located in Deland, FL within twenty four hours.

Serum levels of albumin, creatinin, phosphorus, calcium, bicarbonate, total iron-binding capacity (TIBC), iron (transferrin) saturation ratio (ISAT or TSAT, i.e. iron divided by TIBC), white blood cells count (WBC), and lymphocyte counts were usually measured monthly. Estimate of prescribed dialysis treatment dose, known as Kt/V (single pool) [2] and protein intake known as normalized protein catabolic rate (nPCR)[3] were obtained using urea dynamic equations. All measurement were averaged over each calendar quarter (up to 13 weeks) to calculate one single value for each laboratory parameter per patient per quarter. Since most of these laboratory measurements (albumin, creatinine, phosphorus, calcium, bicarbonate, TIBC, WBC, lymphocyte, ferritin, and nPCR) and body mass index (BMI) may reflect the nutritional and/or inflammatory status of dialysis patients, they are referred to as the "malnutrition-inflammation cachexia syndrome" (MICS) throughout this study.[4]

3.2.b USRDS Dataset

USRDS database was created in 1988 by Urban Institute in Washington, DC. In 1999, USRDS was divided into Coordinating Center and four Special Study Centers, which operate under the National Institute of Diabetes, and Digestive and Kidney Disease at the NIH.[5]

USRDS database contains information about 1.9million patients since 1988. It has over 448 variables that include information on pre-existing conditions, pre-dialysis labs, demographic characteristics of the patients, information about the facility(s) where patients received dialysis

treatments, as well as kidney transplants and death dates and a history of changes in the dialysis modalities for each patient. Every patent in the database carries unique USRDS identifying number.

3.2.c Creating a dataset for a study

A dataset for this study was created by combing variables form DaVita and USRDS databases. Incident patients from DaVita cohort were linked to USRDS database using the crosslink file that had unique identifiers from both datasets. From the DaVita database demographic characteristics, type of vascular access for MHD patients, dates of dialysis initiation, dates of entry in the DaVita cohort, quarterly medications and labs were used. From the USRDS database information about transplants, co-morbidities, and pre-dialysis labs were used. Variables such as date of death where collected from both datasets, and if either one had a date of death for a patient, that patient was considered dead.

Person-time was calculated as a difference between the date when a patient started dialysis therapy and the date when that patient died or had a first kidney transplant, or when the follow-up ended (either patient exited the cohort or the end of a follow-up period).

3.3 Data Analysis

3.3.a Life tables

Based on person-time, the participation time in cohort for each patient was calculated. Maximum participation time in the cohort was set at 1,830 days (5 years). Patients with person-time over 1,830 were censored after 1,830 person-days. Any death that occurred after 06/30/06 was censored. Mortality rates were calculated for each of 60 cohort-months.

3.3. b. Kaplan-Meier (KM) Survival curves

Survival curves can be useful for descriptive preliminary analysis as well as for calculating median survival time or the probably of survival for a specified time period.[6] Kaplan-Meier (KM) estimation is the most common method used to create survival curves. The KM estimator than is defined as:

$S(t) = \prod_{j:t_j <= t} [1-d_j/n_j]$.[6]

The survival curves were generated for the 2 and 5-year survival of the whole cohort. A median survival time as well as a probability of survival for 3, 6, 12, and 24 months were calculated. Survival curves for covariates such as gender, diabetes, race, and CHF among others were examined. All survival curves were adjusted for gender, age, diabetes status, and race (African Americans vs. non African American).

3.3.c Standardized Mortality Ratios (SMRs)

Standardization refers to taking weighted averages of the stratum-specific measures of outcomes such as risks or rates.[7] Standardized Mortality Ratios (SMRs) were calculated for the patients entering DaVita cohort within 7 days from dialysis initiation. The rest of the incident cohort consisting of the patients who joined DaVita cohort within three months after dialysis initiation was used as the unexposed population to which those rates were standardized. The adjustments for age (3 categories), gender, diabetes status, and race (white vs. non-white) were performed.

A logistic regression procedure was used to calculate predicted mortality rates for each month among the incident patients. The procedure described in the article by Roalfe et al was

followed in this analysis [8]. 95% Confidence Intervals for the Standardized Mortality Ratios were calculated as well.[9]

3.4 Cox proportional hazard models

The models measured the time to the event (death) for the patients from the time they started dialysis treatment. The model could generally be written as:

$I(t;x_1) \approx exp(\alpha_1 + \beta_1 x_1)$.

It implies that some time span Δt is so small that the risk of the event in any interval of t to Δt is among those surviving to t without having an event is very small. Therefore, the rates in this very short interval would follow the exponential model were α can vary over time t, but β would not vary with time. The assumption for this model is that at each time t the rate $I(t;x_1)$ is approaching the limit ($h(t; x_1)$) as Δt goes to zero. This limit is typically referred a hazard.[7]

The assumption is that hazard is proportional, which means that hazard for an individual is a fixed proportion of the hazards and it is the same for any other individual in the group. Hazard is constant over time.[6]

3.4.a Three types of proportional hazard models

1). *Minimally adjusted models* that included the variable of interest, age and gender as well as the quarter of entry for each patient and mortality data (death indicator and a person time) as an outcome.

2). *Case-Mix and dialysis dose adjusted models* that included mortality data as an outcome and the variable of interest as an exposure as well as a number of potential confounders such as age, gender, diabetes status, race (white, black, Hispanic, and other), primary insurance (Medicare,

Medicaid, and others), marital status (married, single, divorced, widowed), and the Kt/V (single pool) during the first quarter, as well as 9 co-morbid conditions and a smoking status. There have been reports indicating that including co-morbidities in Case-Mix model adds independent predictive information that cannot be substituted by the clinical or laboratory parameters.[10]

3). *Case-Mix and MICS models* that included mortality data as an outcome, a variable of interests as a main exposure, same set of covariates used in Case-Mix models as well as the 8 MICS indicators and BMI index measured during the first quarter.

3.5 Marginal Structural Models

Marginal Structural Model **(**MSM) can yield estimates comparable to those achieved in randomized trials by simulating randomization in observational data assuming no unmeasured confounding and no measurement error. [11]

MSMs could be used to estimate causal effects of exposure when time-dependent confounding is present by estimating relationships between treatment variables and corresponding potential outcomes.[12] Inverse Probability-of-Treatment Weights (IPTW) can be used to estimate the effects of time-varying measurements on probability of receiving treatment. Additionally, estimation of Inverse Probability-of-Censoring allows accounting for informative censoring events such as transplantation or a loss to a follow-up. These two weighs are then combined in order to estimate stabilized inverse probability weighs (by fitting four pulled logistic regression models). A distribution of standardized weights should always have mean around 1 and variance could increase over time.[12]

MSMs were used to account for transplant censorship, modality changes over time, and time-varying laboratory measures during each calendar quarter while estimating probability of

dialysis modality and examining the association between modality and mortality among dialysis patients.

All the analyses were conducted by using SAS 9.2 or 9.3software (SAS Inc., NC).

3.6 Strengths and Limitations of the study

The strengths of this study include a contemporary cohort of incident dialysis patients from the entire US. Information on detailed laboratory measures that were processed in a single laboratory center gave us the opportunity to account for time-dependent variations in those laboratory parameters. Statistical approaches such as MSMs were used to account for time-varying modality changes and transplant censorship. The detailed comparisons between the conventional models such as Cox proportional hazard and marginal structural models were made.

This study was based entirely on the patients' records from DaVita and USRDS databases. Therefore all the data were limited to information collected at the time of dialysis treatments, and were limited to the variables present in these databases. They were collected mostly for diagnostic and billing purposes and may not include all the variables important to answer research questions. Information about co-morbid conditions was obtained from the Medical Evidence Form 2728 from USRDS database. It may not contain the information on all the co-morbidities that dialysis patients have due to underreporting of those conditions by the physicians. Furthermore, the severity of the reported conditions cannot be determined, and often patients with severe and mild symptoms are categorized are assigned to a same category, which then could bias the results.

Very little information about pre-dialysis history was available. No data on environmental or occupational exposures, family history or patient history were available either. We had no data on nutritional and physical status of patients beyond the laboratory indicators. Any of these factors

could be potential confounders and therefore could potentially bias the results if not included in the analysis.

On a positive side, the fact that no questionnaires were used to collect data meant that the selection and recall biases in this cohort were minimal, which should increase the validity of this analysis. It is reasonable to assume that the data missing in the cohort were missing at random. There was a considerable amount of missing data especially on laboratory parameters. Missing data raged from 5% to 32%. In order to deal with missing data problem multiple imputations were performed using Proc MI and Proc MIANALYZE, procedures available in SAS to address the missing data problem.

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Chapter 4 Patterns and Predictors of Early Mortality in Incident Hemodialysis Patients: New Insights

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4.1 Abstract

Background: Incident hemodialysis patients have the highest mortality in the first several months after starting dialysis treatments. We hypothesized that the patterns and the risk factors associated with this early mortality differ from those in later dialysis therapy periods.

Methods: We examined mortality patterns and predictors during the first several months of hemodialysis treatment in 18,707 incident patients since the first week of hemodialysis therapy and estimated the population attributable fractions for selected time periods in the first 24 months.

Results: The 18,707 incident hemodialysis patients were 45% women and 54% diabetics. The standardized mortality ratio (95% confidence interval) in the 1st to 3rd month of hemodialysis therapy were 1.81 (1.74-1.88), 1.79 (1.72-1.86), and 1.34 (1.27-1.40), respectively. SMR reached prevalent mortality only by 7th month. No survival advantage for African Americans existed in the first 6 months. Patients with low albumin <3.5 g/dL had the highest proportion of infection-related deaths while patients with higher albumin levels had higher CV deaths including76% of death during the first 3 months. Use of catheter as vascular access and hypoalbuminemia <3.5 g/dL explained 34% (17%-54%) and 33% (19%-45%) of all deaths in the first 90 days, respectively.

Conclusions: Incident hemodialysis patients have the highest mortality during the first 6 months including 80% higher death risk in the first 2 months. The presence of a central venous catheter and hypoalbuminemia<3.5 g/dl each explain 1/3 of all deaths in the first 90 days.

Index Words: Incident hemodialysis patients, mortality predictor, population attributable fraction

4.2 Introduction

The number of patients with end-stage renal disease (ESRD) in the United States has increased from about 60,000 in 1980 to over half a million in 2008.(1) It is projected that this number would surpass 800,000 by 2020.(2) These patients would not have survived without kidney transplantation or dialysis therapy, which currently comprises mostly of hemodialysis treatment in this country. However, dialysis patient mortality is unacceptably high, currently approximately 20% per year in the United States. Mortality appears to be even higher during the first year of dialysis therapy, especially in the first few months,(2) while factors contributing to early death are widely unknown.

The most common cause of death in dialysis patients is cardiovascular followed by infectious disease. In a recent study that examined the early mortality among incident hemodialysis patients during the first 120 days vs. subsequent 121 to 365,(3) cardiovascular causes were still the most common for the entire first year. Even though previous studies identified several important factors associated with elevated mortality among incident hemodialysis patients, few have addressed the risk factor patterns and their changes over time during the first few months of dialysis therapy. It is crucial to assess whether those risks remain constant or whether the risk patterns are altered over time, so that focused interventions can be used at different periods of time. Comorbidities including severity of kidney disease at the time of dialysis initiation could play an important role in survival of dialysis patients.(3) Several recent observational studies(4-6) and at least one randomized trial(7) have indicated that the higher glomerular filtration rate (GFR) at the time of dialysis initiation was associated with elevated mortality risk in dialysis patients, although this may be due to the fact that sicker and older patients start dialysis therapy earlier.(8) Use of central venous catheters (CVC), which exits in up to 82% patients at the start of

hemodialysis therapy,(9-12) has been implicated as an important mortality predictor in several studies.(9, 12)

We hypothesized that mortality rate is substantially higher during the first few months of dialysis initiation and that the risk factors associated with this high mortality are different from those in later periods of dialysis therapy. We examined the associations between the mortality and the putative risk factors during different time periods within the first 24 months after the start of hemodialysis therapy among a large group of incident hemodialysis patients who had started treatment at one of the DaVita dialysis facilities in the United States between 7/2001 and 6/2006 and whose clinical outcomes were followed during the 5-year period.

4.3 Methods

4.3.a Sources of Data, Study Population and Follow-up

DaVita is one of the largest dialysis providers in United States. For this study we examined the cohort of all incident hemodialysis patients who started the first week of hemodialysis treatment from July 01, 2001, to June 30, 2006, at one of DaVita dialysis centers. Patients who used peritoneal dialysis modality at any given time were excluded. Information about the date when patient entered the DaVita cohort, dialysis treatment modality, date when the first hemodialysis treatment started, demographic characteristics, co-morbidities, and laboratory and other clinical measures were collected at the time of the start of enrollment in DaVita. Using unique identifiers, data form DaVita and the United States Renal Data System (USRDS) databases were cross-linked to corroborate the information about dates of the events including death and transplantation, and co-morbidities at the start of dialysis therapy, dialysis modality and laboratory data prior to the dialysis treatment were verified as well.(13) To examine the patterns of survival in the first 2 years of hemodialysis treatment, the cohort time was divided into *a priori* selected

smaller groups, i.e. <3 months, 3 to <6 months, 6 to <12 months, and 12 to 24 months. Patients were followed for up to 5 years (1,830 days) or until death, kidney transplantation, or the end of the follow-up. Person-time was obtained by calculating the difference between the dates when the first hemodialysis treatment started at one of the DaVita clinics and the end of follow-up or other censoring events.

4.3.b Laboratory Parameters

All blood samples were drawn using standardized procedure and transported to the Central DaVita Laboratory located in Deland, FL usually within 24 hours. Blood or serum levels of albumin, creatinine, phosphorus, calcium, bicarbonate, total iron-binding capacity (TIBC), iron (transferrin) saturation ratio (ISAT or TSAT, i.e. iron divided by TIBC), white blood cells count (WBC), and lymphocyte counts were usually measured monthly. Serum ferritin was measured at least quarterly. Hemoglobin was measured weekly to biweekly. Estimate of prescribed dialysis treatment dose, known as Kt/V (single pool) (14) and protein intake known as normalized protein catabolic rate (nPCR)(15) were obtained using urea dynamic equations. All measurement were averaged over the first calendar quarter (up to 13 weeks) to calculate one single value for each laboratory parameter per each patient. Since most of these laboratory measurements (albumin, creatinine, phosphorus, calcium, bicarbonate, TIBC, WBC, lymphocyte, ferritin, and nPCR) and body mass index (BMI) may reflect the nutritional and/or inflammatory status of dialysis patients, they are referred to as the "malnutrition-inflammation cachexia syndrome" (MICS) throughout this study.(16)

In order to calculate summary estimates of the exposure variability as putative risk of death in a clinically relevant and commensurate format, we rescaled some laboratory measures by defining biologically and clinically meaningful increments including 0.2 g/dl of albumin, 0.2

g/kg/day of nPCR, 2 mEq/L of bicarbonate, 2 kg/m^2 of BMI, 10% of lymphocyte percentage, 100 pg/ml of PTH, 10% of ISAT, 50 mg/dl of TIBC, 500 ng/ml of ferretin, and $5x10^3$/HPF of WBC. For other laboratory values, one conventional unit was used such as 1 mg/dL increase in serum calcium or phosphorus concentrations. Age was also examined as decades of increments. Additionally we also examined the associations between the mortality and clinically relevant dichotomies for selected laboratory variables including serum albumin (comparing mortality for patients with <3.5 g/dL vs. >=3.5 g/dL), hemoglobin (>=10 g/dL vs. <10 g/dL), and nPCR (>=1 g/kg/day vs. <1 g/kg/day).

4.3.c Statistical Analyses

Descriptive analyses were conducted to examine the population characteristics across the *a priori* selected survival periods of <3 mo, 3-<6 mo, 6-<12 mo and 12-<24 mo. Estimated hazard functions were examined by the life table methods. Five-year unadjusted and adjusted survival curves using Kaplan-Meier (KM) estimation were produced for the entire population as well as for the important demographic characteristics and co-morbidities. Survival curves were adjusted for four main demographic features including age, gender, presence or absence of diabetes mellitus upon dialysis therapy and race, i.e. African Americans vs. others. We also calculated monthly *Standardized Mortality Ratios* (SMRs) for each of the first 24 months of dialysis treatment for the incident hemodialysis patients under the study. The rates were standardized to age, gender, diabetes status, and race using the cohort of all other patients who started hemodialysis treatment in a DaVita clinic within 90 days from dialysis initiation. Multivariate logistic regression models were fit in order to estimate the SMR for each month(17) Cox proportional hazard models were used to calculate hazard ratios of death at different time periods during the 24 months and for the 5-year survival for the patient characteristics including demographics, co-morbidities and

laboratory values. For each selected period deaths before and after the period were censored and the person time was limited to the given period.

Two levels of multivariate adjustments were used in most survival analyses: (A) *Case-mix and dialysis treatment adjusted models* which included adjustment for age, gender, four mutually exclusive race/ethnicity categories (African Americans, Hispanics, non-Hispanic whites, and others), primary insurance (Medicare, Medicaid, and other), marital status (married, single, divorced, widowed), dialysis vascular access, i.e., central venous catheter (CVC), arteriovenous fistula (AVF), or arteriovenous graft (AVG); dialysis dose (single pool Kt/V), diabetes mellitus as well as 11 additional co-morbid conditions including atherosclerosis, congestive heart failure (CHF), other cardiac conditions, cerebrovascular disease (CVA), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), cancer, hypertension, inability to ambulate, and smoking status; and entry calendar quarter for secular trend. (B) *Fully adjusted models*, which included adjusted all of the above, as well as 10 above-mentioned laboratory surrogates of the MICS and BMI. Some of the adjustors were also examined as independent predictors of death risk.

The *Population Attributable Fractions* (PAF)(18) were calculated for the relevant co-morbidities and the CVC vascular access to assess the percent of deaths that could be attributable to those factors, and therefore, hypothetically preventable proportion by eliminating or reducing them. The 95% confidence interval for each PAF was calculated by the substitution method.(19) All the analyses were conducted by using SAS 9.2 software (SAS Inc., NC).

4.4 Results

From 1 July 2001 to 30 June 2006 a total of 82,566 incident (new) dialysis patients started chronic dialysis treatment in a DaVita dialysis clinic within the first 90 days of therapy initiation. After excluding patients younger than 18 years (n=637), incident peritoneal dialysis patients or those who switched modality at any given time (n=4,763), hemodialysis patients with missing person-time (n=6) and hemodialysis patients who initiated the first week of dialysis therapy outside of a DaVita clinic (n=58,453, which served as the "reference" population to calculate SMRs, see above and below), a total of 18,707 incident hemodialysis patients who had never switched modality remained in the cohort. These patients had received at least one treatment of the first therapy week in a DaVita clinic and had remained in DaVita throughout the entire first 90 days or until death or transplantation.

During the first 24 months, 6,666 patients died (36% or 30 deaths per 100 person years) and 1,399 received a kidney transplant. **Table 4.1S** compares the baseline demographic, clinical and laboratory features of the entire 18,707 patents with the reference cohort of 58,453 patients. The overall probability of survival of these incident HD patients for 3 mo, 6 mo, 1 yr, 2 yrs, and 5 yrs were 0.90 (0.89-0.91), 0.80 (0.79-0.82), 0.72 (0.71-0.73), 0.58 (0.57-0.59), and 0.26 (0.25-0.27), respectively. **Figure 4.1** shows the monthly SMRs over the first 24 months after dialysis therapy initiation in 18,707 incident hemodialysis patients under the study using the cohort of other 58,453 incident hemodialysis patients (see above) as the reference population. The highest mortality occurred during Months 1 and 2, and mortality rates decreased over a period of 7 months. The calculated SMR (and 95% CL) for the 1^{st} to 4^{th} month of dialysis therapy were 1.81 (1.74-1.88), 1.79 (1.72-1.86), 1.34 (1.27-1.40) and 1.35 (1.28-1.41) respectively (see Figure 4.1).

Examining the distribution of 6,666 deaths in the first 24 mo, crude mortality rates during the 4 *a priori* selected periods of <3 mo, 3-<6 mo, 6-<12 mo, and 12-<24 mo were 1,994 (30% of all deaths or 47 deaths per 100 person-years), 1,271 (19% or 35 per 100 person-years), 1,550 (23% or 25 per 100 person-years), and 1,851 (28% or 22 per 100 person-years), respectively. **Table 4.1** shows the characteristics for the deceased patients across the 4 *a priori* selected mortality periods of <3 mo, 3-<6 mo, 6-<12 mo, and 12-<24 mo compared to >=24 mo survivors. Early death was associated with more advanced age, higher proportion of CVC, and higher prevalence of cardiovascular diseases. Those who died during the first 3 months had 1.9 co-morbidities per person compared to 1.1 among those who survived >=2 years. **Figure 4.2** shows the common kidney disease etiologies, i.e., ESRD diagnoses, among patients who died during each of the a priori selected periods of the first 24 months. Diabetes and hypertension were the 2 most common ESRD diagnoses; however, hypertension was more frequent among those with earlier deaths, whereas diabetes was more frequent among those who survived the earlier months. **Figure 4.3** shows the causes of death during the first 24 months. Nearly similar death cause distribution was noticed in the first 90 days indicating that half of all deaths were marked as cardiovascular. Mortality due to withdrawal from dialysis was the lowest during the first 90 days and rose over time from 2% to 8% in second year. **Table 4.2** shows case-mix adjusted death hazard ratios during the 4 survival periods. The known survival advantage of African American race was noticeable only after 6 months of therapy but not prior to that. Diabetes mellitus and lower nPCR were paradoxically associated with greater survival at early time periods but they were predictors of higher mortality during later periods.

In addition to all-cause mortality, we also examined the associations of cause-specific mortality, i.e., CV and infection-related deaths, with race (non-Hispanic whites, African

Americans and Hispanics), history of CHF, CVC vascular access and hypoalbuminemia as presented in **Table 4.3**. Compared to Whites, both African Americans and Hispanics showed slightly better survival in terms of CV and infection-related mortality, although the associations were uncertain initially. Of note, patients with CHF showed elevated risk of death independently of the cause of death. Moreover the associations were higher for both CV (1.68 [1.41-1.99] during the first quarter) and infection related deaths (1.56 [1.14-2.14] during the first quarter) comparing to all-cause mortality (1.31 [1.11-1.54]). Use of CVC access was associated with the deaths from infections much stronger (3.32 [2.14-5.16] during the 1st quarter) comparing to CV deaths. Similarly, low serum albumin levels were associated with the infection related mortality much stronger (4.92 [3.45-7.00] in the first 3 months) than with CV mortality during the same time period.

Table 4.2S (online) shows selected Population Attributable Fractions including for vascular access and co-morbidities. CVC as the dialysis access could explain 34% of all deaths in the first 3 months of dialysis therapy. A low serum albumin<3.5 g/dL had a similar death contribution, i.e., 33% of deaths in the first 90 days could have been prevented if albumin levels were above 3.5 g/dL. CHF and serum level of hemoglobin under 10g/ml each contributed to 10 and 9% of all deaths during the first 90 days.

4.5 Discussion

Examining the mortality patterns during the first 24 months of a contemporary (2001-2006) and nationally representative cohort of 18,707 incident hemodialysis patients who received treatment from the first week of hemodialysis therapy in a DaVita dialysis clinic, we found that mortality was exceptionally high in the first 6 months, especially during Months 1 and 2. SMRs were 1.81 and 1.79, respectively, compared to all incident hemodialysis patients of the same cohort

period. We also assessed the risk of death during different time periods to identify modifiable risk factors and their contributions to death over time and found that use of CVC as the vascular access and hypoalbuminemia <3.5 mg/dL could explain 34% and 33% of all deaths in the first 90 days, respectively. These novel findings may have important clinical and public health implications, since they may offer impetus for designing interventions and trials to reduce early death among incident dialysis patients.

We found that both all-cause and cardiovascular mortality rates were the highest during the first 2 months of dialysis therapy, which is consistent with several previous reports.(3, 12) Among demographic predictors of death, older age, white race, Medicaid coverage, and being single or widowed were also associated with higher death risk in the first 24 months.

Worse survival of non-Hispanic white dialysis patients is consistent with previous reports.(3, 20) Even though it is remains unclear as to why African Americans have lower dialysis mortality risk, in our study the survival advantage of African Americans or other minorities was almost non-existent in the first 6 months. Of note, the racial distribution of patients who died within the first 3 months consisted of 62% non-Hispanic whites, 20% blacks and 12% Hispanics in contrast to 47% whites, 27% blacks, and 15% Hispanics among survivors over 2 years (Table 4.1), and was consistent with the survival advantage of minorities.(21) However, after case-mix adjustment, the advantage for African Americans during early dialysis period disappeared. Similar to the all-cause mortality result, African Americans exhibited essentially the same pattern with CV mortality with practically no survival advantage over whites in early time periods, although a somewhat better survival in infection related morality. The observation that African Americans had somewhat lower CVC use than whites (data not shown) might explain the higher infection-related mortality in whites. Hispanics, too, showed better survival in infectious deaths analyses;

however, although whites had somewhat higher percentage of CHF history, Hispanics contributed to a higher percentage of patients with low serum albumin levels and CVC use similar to whites. Both hypoalbuminemia and CVC access are known to be associated with infectious events and death. It might be that, while Hispanics were more likely to develop infections, they might have been less likely to die from them. Another explanation as to why Hispanics and, to some extent, African Americans had higher rates of hypoalbuminemia but lower infection-related mortality could be that, for most of the minorities, low albumin levels may be more indicative of malnutrition than infection.(22)

An interesting finding was the seemingly paradoxical association between diabetes and lower mortality in the first months, which was previously reported by Bradbury et al.(3) The possible explanation may be that they were more likely to see a physician on regular basis compared to non-diabetics and therefore may have been better prepared for the transitional period of early dialysis therapy. However, this survival advantage mitigated and even reversed over time probably because non-diabetics who survived the transitional period might be healthier than patients with diabetes.

Among clinical predictors, type of the vascular access was exceptionally strongly associated with mortality across all studied periods but in particular during the first 90 days, including both among CV and infection related deaths. Although our finding is consistent with previous reports indicating that CVC was associated with higher mortality in hemodialysis patients (9-12), our study uniquely shows that the association of vascular access type with mortality is the strongest at the time of dialysis initiation and decreased over time, which suggests the importance of replacing CVC with a more permanent access within the first few weeks – if not days – of dialysis therapy. Our results are consistent with findings from the Dialysis Outcomes and Practice

Patterns Study (DOPPS) reporting higher mortality for patients with CVC access comparing to other types. That study found that US patients had 36% to 43% higher mortality risk due to wide spread use of CVC use compared to European countries and about 30% higher when compared to Japan. (23)

The resilient role of low serum albumin level in predicting high mortality of dialysis patient has been previously identified (3, 24, 25); this is verified in our current study. A 10-year cohort study from Japan reported that patients with serum albumin levels >3.8 g/dL consistently had better survival (24) We found 21% increase in mortality in the first 90 days per 0.2 g/dl lower serum albumin compared to 12% during the 12-24 month period. We found that infection-related and CV mortality rates were respectively 5-fold and 2-fold higher among patients with low serum albumin levels <3.5 g/dl compared to higher levels. We also found that, among patients with no history of CHF and hypoalbuminemia, the percentage of deaths related to infections was the highest especially during the first 6 months on dialysis (19% to 21%), while patients with history of CHF and serum albumin >3.5 g/dl accounted for only 8% of infection-related deaths in the first 3 months of dialysis treatment (Table 4.3). Although hypoalbuminemia was strongly associated with both CV and infection-related mortality, it seems that, among patients who died from CV disease, CHF, which is usually due to volume overload, could be responsible for the patient outcomes especially during the early months of the dialysis treatment. Patients with CHF had higher CV mortality than patients without it, and the highest CV mortality of 76% was observed during the first 3 months of dialysis treatment in patients with CHF and serum albumin >3.5g/dl.

In a recent study from UK Renal National Registry cohort , using several models for predicting the first 3-year survival of incident dialysis patients, older age, white race, diabetes mellitus and other primary causes of ESRD, history of cardiovascular disease and smoking were

predictive of increased mortality.(26) Among laboratory parameters, serum levels of albumin, hemoglobin, and calcium were also predictors of 2-year mortality. These findings are somewhat similar to our results. We found an elevated mortality risk for patients with serum level of hemoglobin less than 10g/ml with 58% increase during the first 3 month of dialysis treatment.

Our study should be qualified for including only DaVita patients rather than the entire national dialysis population. However, DaVita patients are likely good representatives of average ESRD patients. We purposely excluded the incident patients who initiated their first week of therapy elsewhere to mitigate selection bias. It can be argued that there could be differences between the patients who started dialysis at an inpatient vs. outpatient facility. Nevertheless, the annualized mortality in our cohort for the first 3 months was about 30%, which was consistent with mortality reported for US patients in the same period.(2) We had no reliable information about patient visiting nephrologists prior to dialysis initiation (80% missing values), which precluded examination of this potential predictor of early mortality.

4.6 Conclusion

Incident hemodialysis patients have the highest mortality during the first 6 months of dialysis therapy, in particular in the first 2 months, and cardiovascular disease is the most common causes of death. Use of CVC as vascular access and hypoalbuminemia <3.5 mg/dL each explains 1/3 of all deaths in the first 90 days. Hence, replacing or avoiding CVC and improving hypolabuminemia could theoretically reduce early dialysis death by 30%. These findings warrant imminent design of clinical trials to examine interventions to target imminent AV fistula placement and to increase serum albumin in order to reduce early death among incident dialysis patients. Low serum level of hemoglobin was responsible for 9% of the deaths in the first 3 month indicating an importance of proper anemia control in hemodialysis patients.

4.7 Tables for Chapter 4

Table 4.1. Comparing patient characteristics across selected morality periods of the first 24 months in 18,707 incident hemodialysis patients who started dialysis therapy during 07/01/2001-06/30/2006 in a DaVita clinic

	Patients who died during the first 24 months				**Survived >=2 years**	**p-value**
	1-3 mo	**4-6 mo**	**7-12 mo**	**13-24 mo**		
N	n=1,994	n=1,271	n=1,550	n=1,851	n=12,041	
Age	72±13	70±13	69±13	69±13	60±15	<.0001
Gender (% female)	45%	47%	47%	44%	44%	0.16
Diabetes mellitus (%)	50%	57%	58%	61%	53%	<.0001
Race (%)						
White	62%	57%	60%	58%	47%	<.0001
Black	20%	24%	21%	22%	27%	<.0001
Hispanic	12%	11%	11%	12%	15%	<.0001
Other	6%	8%	8%	8%	11%	<.0001
Primary insurance (%)						
Medicare	65%	68%	70%	69%	51%	<.0001
Medicaid	5%	7%	7%	4%	6%	0.06
Other	30%	25%	13%	12%	43%	<.0001
Marital Status (%)						
Married	49%	46%	47%	54%	54%	<.0001
Divorced	5%	7%	7%	6%	7%	0.21
Single	21%	22%	20%	21%	26%	<.0001
Widowed	25%	25%	26%	19%	13%	<.0001
Kt/V (dialysis dose)	1.36±0.4	1.41±0.4	1.42±0.4	1.40±0.4	1.39±0.4	0.01
Vascular Access						
Dialysis Catheter (%)	81%	74%	65%	58%	53%	<.0001
AVF	8%	12%	16%	21%	30%	<.0001
Graft	11%	14%	19%	21%	17%	<.0001
Co-morbid Conditions (%)						
AIDS	0.6%	1%	0.7%	0.7%	0.4%	0.02
Cancer	9%	8%	7%	6%	4%	<.0001
Atherosclerotic Heart Disease	32%	27%	28%	27%	17%	0.005
Heart Failure	41%	37%	35%	33%	20%	<.0001
Pulmonary Disease COPD	12%	8%	9%	8%	4%	<.0001
Cerebro-vascular disease CVA	11%	11%	10%	11%	6%	<.0001
History of Hypertension	73%	74%	75%	79%	81%	0.04

	Patients who died during the first 24 months				Survived >=2 years	p-value
	1-3 mo	**4-6 mo**	**7-12 mo**	**13-24 mo**		
Other Heart Diseases	%	10%	7%	7%	5%	<.0001
Non-ambulatory	10%	7%	5%	5%	2%	<.0001
Peripheral Vascular Disease PVD	17%	18%	17%	16%	9%	<.0001
HIV	0.8%	0.6%	1%	2%	0.3%	0.15
Smoker	4%	4%	5%	5%	4%	0.17
Serum levels						
Albumin (g/dL)	3.1±0.6	3.3±0.5	3.3±0.5	3.4±0.5	3.6±0.5	<.0001
Albumin (% <3.5 g/ml)	72%	63%	56%	48%	35%	<.0001
Creatinine (mg/dL)	5.6±2.4	5.6±2.3	5.7±2.5	5.6±2.3	6.6±2.7	<.0001
TIBC (mg/dL)	193±63	205±58	214±57	222±51	232±50	<.0001
Bicarbonate (mg/dL)	22.6±4	22.6±4	22.6±4	22.4±4	22.0±4	<.0001
Phosphorus (mg/dL)	4.9±1.7	5.0±1.6	5.0±1.5	5.1±1.5	5.3±1.4	<.0001
Calcium (mg/dL)	8.7±0.8	8.8±0.8	8.8±0.8	8.7±0.8	8.9±0.8	<.0001
Ferritin (ng/mL)	549±749	419±522	374±490	314±365	278±347	<.0001
ISAT (%)	24±15	23±11	23±11	23±11	23±10	0.01
ALKP (u/L)	151±149	135±106	123±82	116±832	109±78	<.0001
PTH (pg/dl)	349±340	381±365	407±417	411±373	469±419	<.0001
nPCR (g/kg/day)	0.88±0.3	0.84±0.3	0.85±0.3	0.86±0.3	0.88±0.3	<.0001
nPCR (% >1 g/kg/day)	27%	24%	24%	25%	27%	0.0400
Blood hemoglobin (g/dL)	10.5±1.5	10.7±1.4	10.8±1.4	10.9±1.4	11.0±1.4	<.0001
Hemoglobin (% <10 g/dl)	24%	31%	29%	25%	24%	<.0001
WBC (x10^3/□l)	9.5±5.6	8.3±3.1	8.2±3.1	7.9±2.9	7.7±2.5	<.0001
Lymphocyte (% of WBC)	14±7.6	16±7.1	17±7.1	18±7.2	19.±7.4	<.0001
EPO dose (units q HD)	9817±5844	9752±5231	9385±5040	9038±5155	9031±5081	<.0001
Paricalcitol dose (mcg./HD)	3.8±3.1	3.8±3.0	3.6±3.0	3.7±3.3	3.9±3.4	0.07
BMI (kg/m2)	25.7±9	25.5±7	26.1±7	26.4±7	28.2±7	<.0001
eGFR (ml/min)	11.4±5	10.9±4	10.8±5	10.8±5	9.6±3	<.0001
eGFR (% >10)	39%	52%	58%	51%	39%	<.0001
eGFR (% >15)	10%	16%	18%	16%	10%	<.0001

Table 4.2. Case-mix adjusted death hazard ratios for the association between mortality at different time periods and individual predictors for incident hemodialysis patients in18,707 incident hemodialysis patients. Note that deaths and person-times before and/or after each period are censored

	<3 mo	**4-<6 mo**	**7-<12 mo**	**13-<24 mo**
Predictor	HR 95% CL	HR 95% CL	HR 95% CL	HR 95% CL
Age (decades)	1.50 *(1.43-1.56)*	1.44 *(1.35-1.54)*	1.32 *(1.26-1.38)*	1.33 *(1.28-1.39)*
Gender (female vs. male)	1.00 *(0.90-1.11)*	0.95 *(0.83-1.09)*	0.89 *(0.79-1.01)*	0.95 *(0.85-1.05)*
Diabetes mellitus	0.86 *(0.78-0.94)*	0.95 *(0.84-1.07)*	1.03 *(0.93-1.15)*	1.11 *(1.00-1.23)*
Race				
Whites vs. Blacks	1.12 *(0.97-1.28)*	1.01 *(0.86-1.18)*	1.33 *(1.16-1.52)*	1.29 *(1.14-1.46)*
Whites vs. Hispanics	1.09 *(0.94-1.27)*	1.24 *(1.02-1.52)*	1.53 *(1.23-1.85)*	1.33 *(1.14-1.56)*
Whites vs. Others	1.40 *(1.15-1.70)*	1.18 *(0.93-1.49)*	1.43 *(1.17-1.75)*	1.48 *(1.23-1.77)*
Health Insurance				
Medicaid vs. Medicare	1.48 *(1.17-1.87)*	1.74 *(1.32-2.29)*	1.68 *(1.30-2.18)*	1.07 *(0.84-1.37)*
Other vs. Medicare	1.10 *(0.93-1.31)*	0.90 *(0.77-1.05)*	0.78 *(0.66-0.91)*	0.78 *(0.69-0.89)*
Marital status				
Divorced vs. Married	0.90 *(0.60-1.33)*	1.09 *(0.67-1.80)*	1.15 *(0.69-1.92)*	0.86 *(0.60-1.25)*
Single vs. married	1.39 *(1.16-1.65)*	1.33 *(1.10-1.60)*	1.19 *(0.94-1.51)*	1.08 *(0.88-1.34)*
Widowed vs. Married	1.12 *(0.87-1.45)*	1.25 *(0.83-1.88)*	1.46 *(1,08-1.97)*	1.00 *(0.82-1.21)*
KTV (0.2↓)	0.92 *(0.88-0.96)*	0.96 *(0.93-1.00)*	0.99 *(0.92-1.03)*	0.98 *(0.95-1.01)*
Vascular access				
CVC vs. AVF	2.99 *(2.49-3.59)*	2.46 *(1.89-3.20)*	2.06 *(1.76-2.40)*	1.63 *(1.39-1.91)*
CVC vs. Graft	2.48 *(1.94-3.17)*	1.84 *(1.40-2.40)*	1.43 *(1.21-1.69)*	1.34 *(1.15-1.55)*
CVC vs. AVF+Graft	2.66 *(2.27-3.11)*	2.22 *(1.81-2.72)*	1.80 *(1.53-2.12)*	1.52 *(1.37-1.69)*
BMI (2kg/m2)	0.92 *(0.90-0.94)*	0.93 *(0.91-0.95)*	0.94 *(0.92-0.96)*	0.92 *(0.91-0.94)*
Co-morbidities				
Cardiac disorders				
Atherosclerotic Heart D	1.09 *(0.97-1.23)*	0.96 *(0.83-1.11)*	1.04 *(0.92-1.18)*	1.05 *(0.93-1.18)*
Heart Failure	1.31 *(1.11-1.54)*	1.36 *(1.20-1.55)*	1.29 *(1.15-1.45)*	1.33 *(1.19-1.48)*
Other cardiac disease	1.23 *(1.05-1.44)*	1.45 *(1.20-1.76)*	1.02 *(0.83-1.25)*	1.00 *(0.82-1.22)*
Vascular/Pulmonary				
CVA	1.07 *(0.92-1.24)*	1.09 *(0.91-1.31)*	1.08 *(0.91-1.28)*	1.27 *(1.09-1.48)*
PVD	1.11 *(0.98-1.27)*	1.27 *(1.08-1.49)*	1.28 *(1.10-1.49)*	1.16 *(1.01-1.33)*
COPD	1.43 *(1.23-1.67)*	1.02 *(0.82-1.27)*	1.14 *(0.94-1.37)*	1.13 *(0.95-1.36)*
Other co-morbidities				

	<3 mo	**4-<6 mo**	**7-<12 mo**	**13-<24 mo**
Predictor	HR 95% CL	HR 95% CL	HR 95% CL	HR 95% CL
Cancer	1.31 *(1.11-1.54)*	1.36 *(1.11-1.67)*	1.30 *(1.06-1.60)*	1.15 *(0.95-1.40)*
Non-ambulatory	2.01 *(1.70-2.38)*	1.73 *(1.38-2.18)*	1.46 *(1.15-1.84)*	1.66 *(1.33-2.09)*
Smoking	0.93 *(0.73-1.18)*	1.13 *(0.86-1.50)*	1.29 *(1.02-1.63)*	1.14 *(0.91-1.43)*
Hypertension	0.74 *(0.67-0.82)*	0.72 *(0.63-0.82)*	0.71 *(0.63-0.80)*	0.82 *(0.73-0.92)*
Lab parameters				
Albumin (0.2g/dl ↓)*	1.21 *(1.18-1.24)*	1.17 *(1.15-1.20)*	1.15 *(1.13-1.18)*	1.12 *(1.10-1.14)*
Albumin <3.5 g/ml*	2.56 *(2.30-2.84)*	2.04 *(1.81-2.31)*	1.89 *(1.70-2.10)*	1.59 *(1.44-1.75)*
Hemoglobin (1 g/dl ↓)*	1.24 *(1.20-1.28)*	1.13 *(1.09-1.18)*	1.07 *(1.03-1.11)*	1.05 *(1.01-1.08)*
Hemoglobin <10 g/ml	1.58 *(1.33-1.74)*	1.37 *(1.21-1.55)*	1.25 *(1.11-1.49)*	1.11 *(0.99-1.24)*
Creatinine (mg/dl ↓)*	1.03 *(1.01-1.06)*	1.04 *(1.01-1.07)*	1.03 *(1.00-1.05)*	1.05 *(1.03-1.08)*
Ca (mg/dl)*	1.14 *(1.07-1.22)*	1.09 *(1.00-1.18)*	1.11 *(1.04-1.19)*	1.03 *(0.97-1.09)*
Phosphorous (mg/dl)*	1.06 *(1.02-1.10)*	1.03 *(0.99-1.08)*	1.04 *(1.00-1.09)*	1.01 *(0.97-1.05)*
nPCR (0.2g/kg/day)	1.08 *(1.03-1.13)*	0.94 *(0.89-1.00)*	0.93 *(0.89-0.97)*	0.96 *(0.92-1.00)*
nPCR >1.0 g/kg/day	1.21 *(1.06-1.38)*	0.96 *(0.8-1.14)*	0.89 *(0.74-1.07)*	0.99 *(0.87-1.13)*
WBC (5000/HPF ↑)	1.52 *(1.45-1.59)*	1.26 *(1.15-1.39)*	1.26 *(1.16-1.37)*	1.14 *(1.04-1.25)*
Lym (10%)*	1.87 *(1.70-2.05)*	1.42 *(1.31-1.55)*	1.33 *(1.24-1.44)*	1.17 *(1.09-1.26)*
TIBC (50g/dl)*	1.51 *(1.43-1.59)*	1.40 *(1.31-1.49)*	1.30 *(1.22-1.38)*	1.20 *(1.14-1.26)*
Ferritin (500*ng/dl)	1.24 *(1.20-1.28)*	1.23 *(1.18-1.29)*	1.27 *(1.21-1.33)*	1.20 *(1.14-1.28)*
PTH (100pg/ml)	0.96 *(0.94-0.97)*	0.97 *(0.95-0.99)*	0.99 *(0.97-1.01)*	0.99 *(0.97-1.01)*
ISAT (10%)	1.09 *(1.05-1.13)*	1.05 *(0.99-1.11)*	1.02 *(0.98-1.08)*	1.07 *(1.02-1.13)*
eGFR (each 1 inc)	1.03 *(1.02-1.04)*	1.01 *(1.00-1.03)*	1.01 *(1.00-1.03)*	1.03 *(1.02-1.04)*
eGFR >10	1.29 *(1.17-1.42)*	1.20 *(1.07-1.35)*	1.04 *(0.94-1.16)*	1.11 *(0.97-1.28)*
eGFR >15	1.43 *(1.27-1.60)*	1.09 *(0.93-1.28)*	1.29 *(1.12-1.48)*	1.02 *(0.83-1.24)*

* Indicates decrease per unit change of serum level of laboratory parameter

Table 4.3. Case-mix adjusted death hazard ratios (95% confidence interval (CI)) for the association between CV and infection-related mortality at different time periods and several individual predictors for incident hemodialysis patients in18,707 incident hemodialysis patients; note that deaths and person-times before and/or after each period are censored

	Deaths 0-3 months	Deaths 4-6months	Deaths 7-12months	Deaths 13-24months
Predictor Outcome1: CV mortality Outcome 2: Infectious mortality	HR 95% CI	HR 95% CI	HR 95% CI	HR 95% CI
Whites vs. Blacks				
CV mortality	1.14 *(0.92 - 1.41)*	1.02 *(0.81 - 1.30)*	1.20 *(0.94 - 1.54)*	1.46 *(1.18 - 180)*
Infectious mortality	1.26 *(0.85 - 1.89)*	1.28 *(0.84 - 1.96)*	1.70 *(1.12 - 2.58)*	1.20 *(0.85 - 1.70)*
Whites vs. Hispanics				
CV mortality	1.28 *(0.98 - 1.66)*	1.16 *(0.84 - 1.62)*	1.75 *(1.28 - 2.39)*	1.60 *(1.22 - 2.10)*
Infectious mortality	0.91 *(0.60 - 1.37)*	1.38 *(0.42 - 2.33)*	3.43 *(1.76 - 6.69)*	1.58 *(0.96 - 2.62)*
Heart Failure				
CV mortality	1.68 *(1.41 - 1.99)*	1.74 *(1.42 - 2.14)*	1.86 *(1.53 -2.24)*	1.43 *(1.20 - 1.71)*
Infectious mortality	1.56 *(1.14 - 2.14)*	1.76 *(1.24 - 2.50)*	1.17 *(0.80 - 1.70)*	1.69 *(1.24 - 2.31)*
CVC vs. AVF+Graft				
CV mortality	2.45 *(1.74 - 3.44)*	2.09 *(1.57 - 2.80)*	1.58 *(1.31 - 1.93)*	1.59 *(1.30 - 1.97)*
Infectious mortality	3.32 *(2.14 - 5.16)*	4.03 *(2.66 - 6.09)*	2.23 *(1.50 - 3.32)*	1.74 *(1.23 - 2.47)*
Albumin <3.5 vs. >3.5				
CV mortality	2.15 *(1.81 - 2.55)*	1.89 *(1.54 - 2.33)*	1.83 *(1.53 - 2.19)*	1.80 *(1.53 - 2.11)*
Infectious mortality	4.92 *(3.45 - 7.00)*	3.21 *(2.23 - 4.62)*	2.34 *(1.65 - 3.30)*	1.48 *(1.09 - 2.01)*

CVC - central venous catheter; AVF - arteriovenous fistula; graft – arteriovenous graft

4.8 Figures for Chapter 4

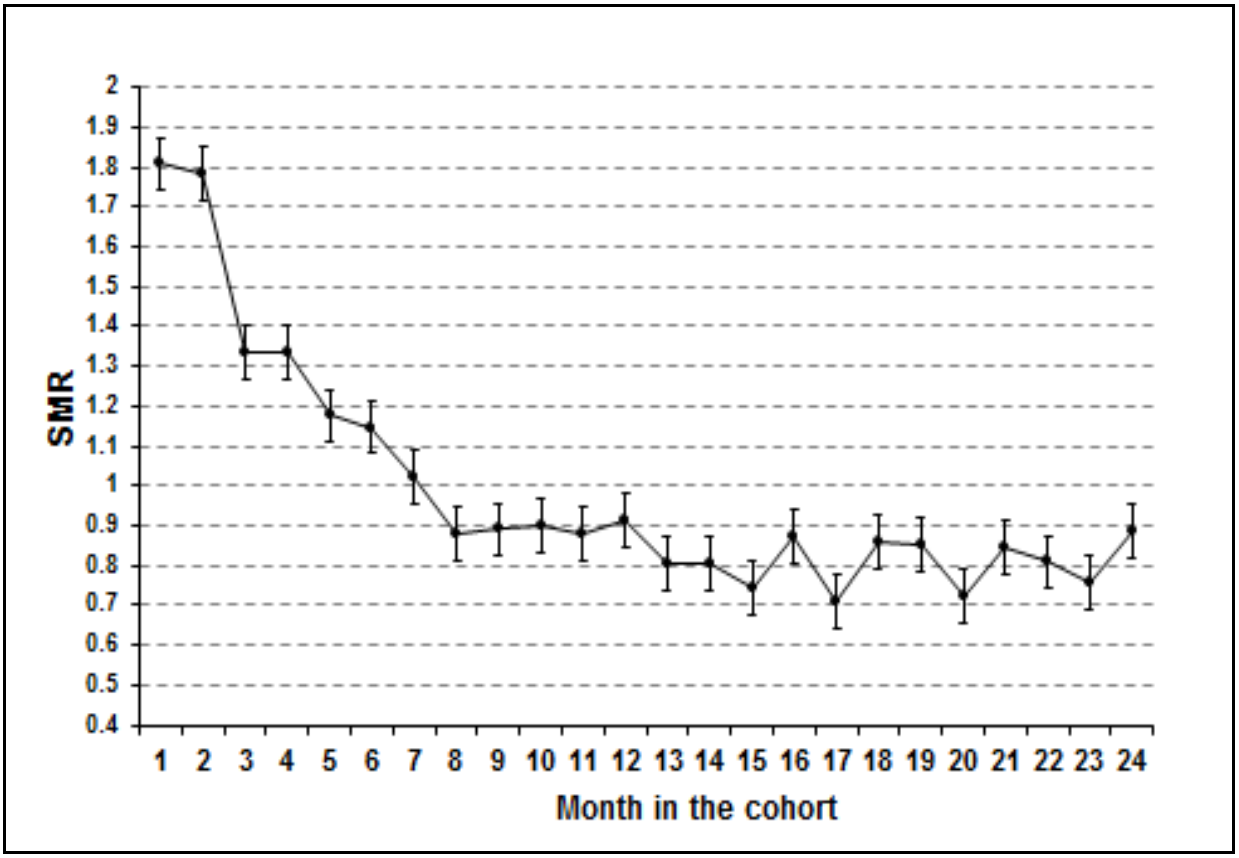

Figure 4.1. Monthly standardized mortality ratios (SMRs) during the first 2 years for the incident dialysis pts (n=18,707). SMRs are standardized by age, gender, diabetes, and race using the reference cohort of 57,456 hemodialysis patients who started DaVita cohort within 30 days after starting dialysis treatment

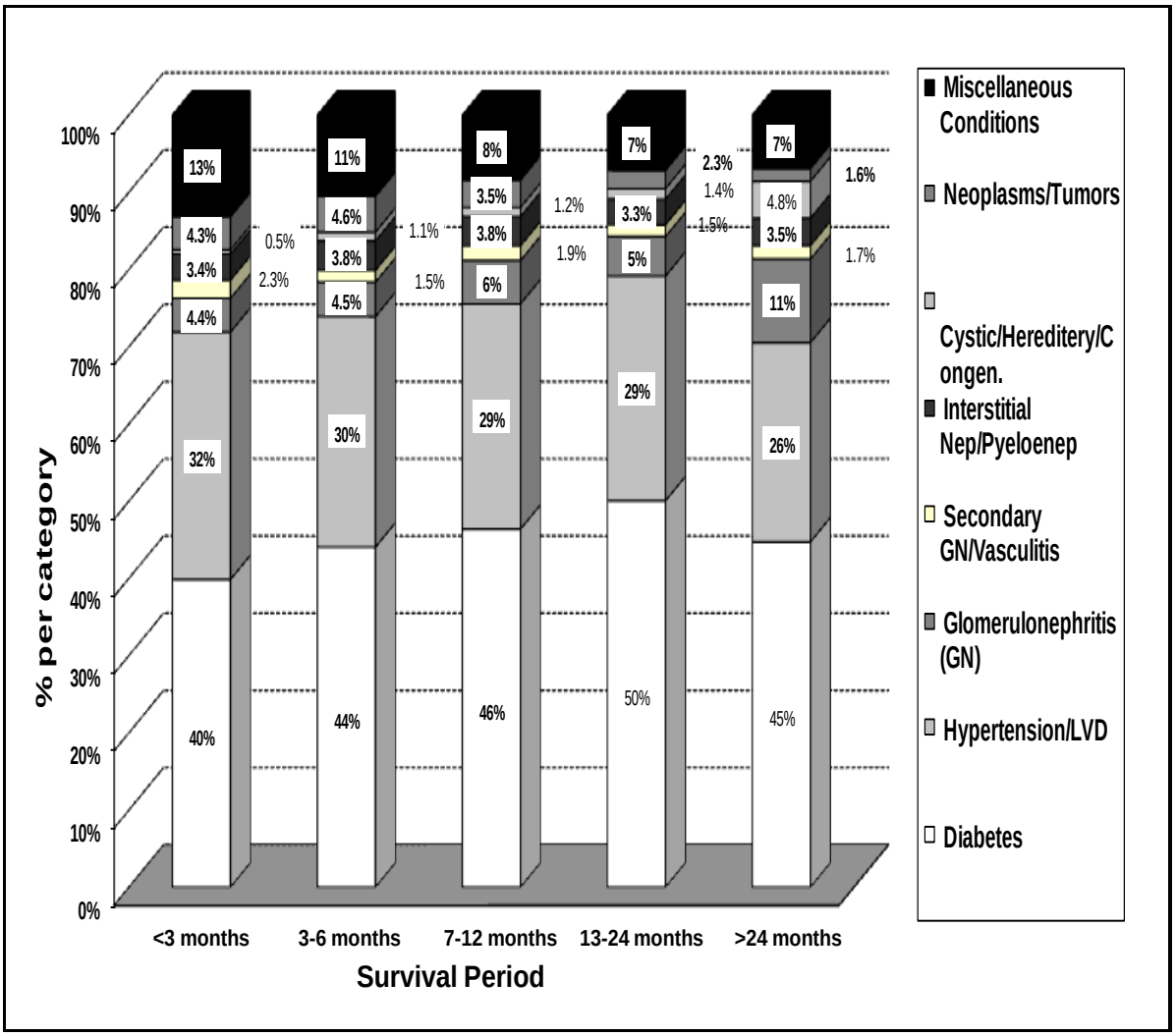

Figure 4.2. Primary causes of ESRD for incident hemodialysis patients who died within 24 months after dialysis initiation from 5 year DaVita Cohort 07/01-06/06; N= 6,507 compared to survivors (N total=17,871)

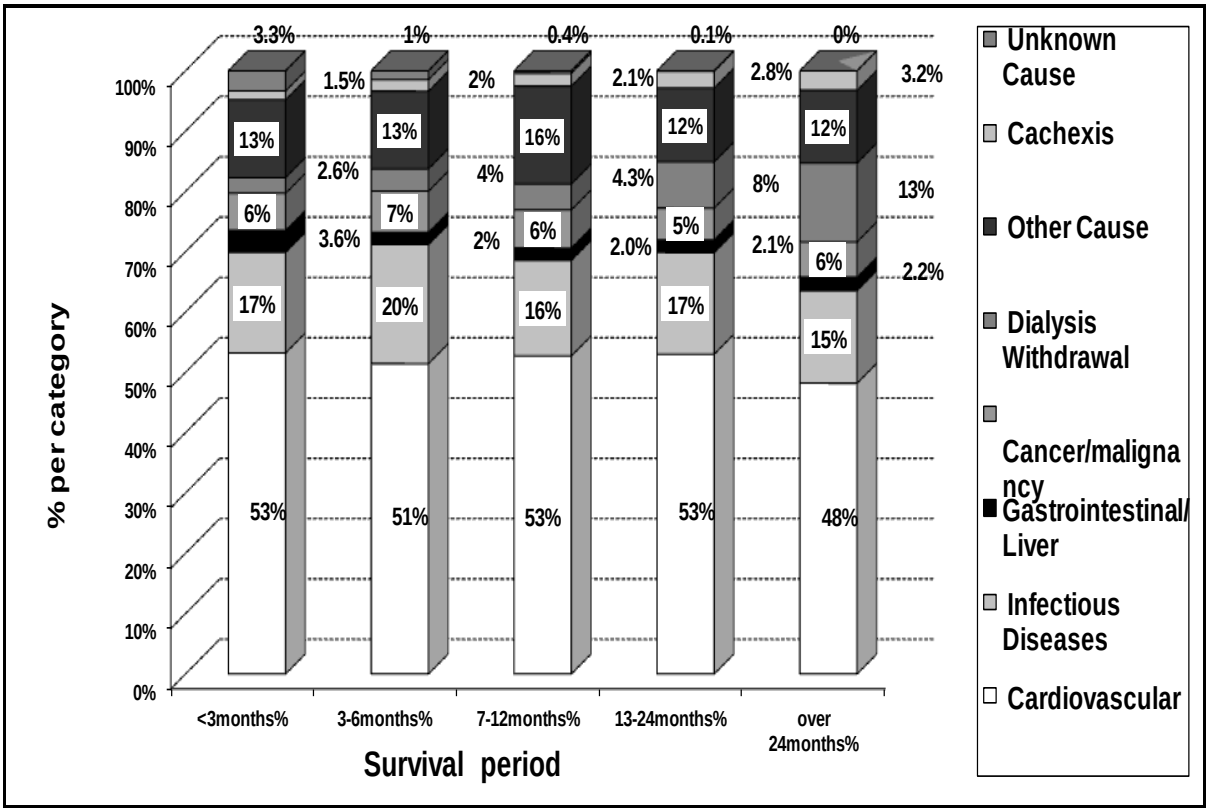

Figure 4.3. Causes of death by the mortality periods for incident hemodialysis patients from 5 year DaVita cohort, excluding pts with missing causes of death; N=6,867 (2,236 cases with no documented cause of death were excluded)

4.9 Supplemental Materials for Chapter 4

Table 4.1S. Characteristics of the incident hemodialysis patients who started dialysis therapy during 07/01/2001 and 06/30/2006 in a DaVita dialysis clinic

Population Characteristics	All patients in study cohort	Referent cohort*
N	N=18,707	N=58,453
Age	63±15	63±16
Gender (% female)	45%	45%
Diabetes mellitus (%)	54%	60%
Race (%)		
White	51%	48%
Black	25%	28%
Hispanic	14%	15%
Other	10%	9%
Primary insurance (%)		
Medicare	57%	60%
Medicaid	6%	7%
Other	37%	33%
Marital Status (%)		
Married	52%	49%
Divorced	7%	8%
Single	25%	27%
Widowed	16%	16%
Kt/V (dialysis dose)	1.40±0.4	1.41±0.2
Vascular Access		
Dialysis Catheter (CVC, %)	58%	78%
AV Fistula	25%	11%
AV Graft	17%	11%
Comorbid Conditions (%)		
AIDS	0.50%	6%
HIV serology positive	0.90%	1%
Cancer	5%	6%
Atherosclerotic Heart Disease	21%	23%
Heart Failure	26%	32%
Pulmonary Disease (COPD)	6%	8%
Cerebro-vascular disease (CVA)	8%	8%
History of Hypertension	79%	80%
Other Heart Diseases	6%	8%
Non-ambulatory	4%	5%
Peripheral Vascular Disease	12%	13%
Smoker +	4%	5%

Population Characteristics	All patients in study cohort	Referent cohort*
Serum levels		
Albumin (g/dL)	3.5±0.5	3.4±0.5
Creatinine (mg/dL)	6.2±2.6	6.3±2.7
TIBC (mg/dL)	223±54	217±52
Bicarbonate (mg/dL)	22.2±4	23.1±3
Phosphorus (mg/dL)	5.2±1.5	5.1±1.4
Calcium (mg/dL)	8.8±0.8	8.8±0.8
Ferritin (ng/mL)	328±439	368±468
nPCR (g/kg/day)	0.87±0.3	0.84±0.3
Blood hemoglobin (g/dL)	10.9±1.4	10.8±1.4
WBC (x10^3/□l)	8.0±3.0	8.4±3.2
Lymphocyte (% of WBC)	18±7.6	17±7.4
ISAT (%)	23±11	22±10
ALKP (u/L)	118±92	121±94
PHT (pg/dl)	435±403	462±411
Other relevant variables		
EPO dose (units q HD)	9198±5190	9979±4992
Paricalcitol dose (mcg q HD)	3.9±3	3.4±3
BMI (kg/m^2)	27.4±8	27.1±7
eGFR (ml/min)	10.1±3	9.9±4

* The population was used as a reference group for calculating SMRs

Table 4.2S. Population attributable fraction (95% confidence interval) for selected comorbid conditions and vascular access type in 18,707 incident hemodialysis during 07/1/2001-06/30/2006, indicating proportion of deaths that could have been theoretically prevented if the given risk factor or condition were not present.

	deaths within 3 month	deaths within 12 months	deaths within 24 months	deaths within 60 months
CVC dialysis access	0.34 *(0.17-0.54)*	0.28 *(0.14-0.41)*	0.23 *(0.12-0.32)*	0.19 *(0.14-0.24)*
Serum albumin <3.5 g/dl	0.33 *(0.19-0.45)*	0.26 *(0.20-0.33)*	0.23 *(0.18-0.28)*	0.20 *(0.16-0.24)*
Hemoglobin <10 g/dl*	0.09 *(0.04-0.13)*	0.06 *(0.03-0.09)*	0.05 *(0.03-0.07)*	0.04 *(0.03-0.06)*
Comorbid states				
ASHD	0.04 *(0.00-0.08)*	0.03 *(0.00-0.05)*	0.02 *(0.00-0.04)*	0.02 *(0.01-0.04)*
Cancer	0.01 *(-0.01-0.02)*	0.01 *(0.00-0.02)*	0.01 *(0.00-0.02)*	0.01 *(0.00-0.02)*
CHF	0.10 *(0.04-0.14)*	0.09 *(0.06-0.12)*	0.09 *(0.07-0.11)*	0.08 *(0.06-0.10)*
COPD	0.03 *(0.01-0.06)*	0.02 *(0.00-0.03)*	0.01 *(0.00-0.02)*	0.01 *(0.00-0.02)*
CVA	0.01 *(-0.01-0.02)*	0.01 *(0.00-0.02)*	0.01 *(0.00-0.02)*	0.01 *(0.00-0.02)*
PVD	0.01 *(-0.01-0.04)*	0.02 *(0.01-0.04)*	0.02 *(0.01-0.03)*	0.01 *(0.00-0.02)*
Non-ambulatory	0.03 *(0.01-0.05)*	0.02 *(0.01-0.03)*	0.02 *(0.01-0.03)*	0.02 *(0.01-0.03)*

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Chapter 5 Nutritional predictors of early mortality in incident hemodialysis patients

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5.1 Abstract

Background: Low serum albumin concentration and low dietary protein intake are associated with protein-energy wasting (PEW) and higher mortality in maintenance hemodialysis patients. The role of these nutritional markers is less clear in clinical outcomes of the first several months of dialysis therapy, where mortality is exceptionally high.

Methods: In a cohort of 17,445 incident hemodialysis, we examined variation in serum albumin and the normalized protein catabolic rate (nPCR), a surrogate of dietary intake, and quarterly mortality in the first 2 years of dialysis therapy. Cox proportional hazard models were fitted to estimate the association between mortality and combined albumin/nPCR categories for eight quarters. We investigated the associations between mortality and baseline and subsequent serum albumin levels per cohort quarter as well as changes in albumin and nPCR over time.

Results: Patients were 64+/-15 years old (mean+/-SD) and included 45% women, 24% African Americans, and 58% diabetics. Correlations between quarterly albumin and nPCR varied from 0.18 to 0.25. Serum albumin <3.5g/dl was consistently associated with high mortality as was nPCR<1 (except for qtr1). Low albumin and nPCR greater than 0.2 g/dL or g/kg/d were associated with increased risk of death. Quarterly rise in nPCR (>+0.2 g/kg/day) exhibited a reversal of changing impact on mortality from the 2nd to the last quarter.

Conclusions: Low albumin and nPCR are associated with mortality. A rapid rise in nPCR by the end of the second year may indicate PEW.

Index Words: Incident hemodialysis patients, mortality predictor, serum levels of albumin, serum levels of nPCR

5.2 Introduction

Albumin and normalized protein nitrogen appearance (nPNA also called nPCR) are important indicators of nutritional status in dialysis patients.

Several factors may contribute to low levels of albumin in dialysis patients such as urinary or dialytic albumin loss, inadequate dietary intake and inflammation [1]. Albumin concentration is associated with nPCR (a nutritional marker in dialysis patients) as well as with several other proteins such as acute phase proteins (APPs), C-reactive protein (CRP), α1 acid glycoprotein (α1AG) [2-5]. A dialysis session can affect protein metabolism due to losses in substrate as well as an increase in the net protein catabolism as an artifact of dialysis process. During a single dialysis session about 6-12g of amino acids are lost. It was reported that after an HD session the ribosome content of mussels decreased indicating decrease in protein synthesis, which in turn could be caused by amino acid loss during HD [6].

The relationship between low serum level of albumin and inflammation may be due to inflammation either decreasing albumin synthesis or increasing albumin fractional catabolic rate (FCR). [2]

A retrospective cohort study—the Dialysis Outcomes and Practice Patterns Study (DOPPS) in the US by Bradbury et al reported that 40% of patients who had albumin below 3.5 g/dl [7] had higher risk of death during the early period on dialysis. A 10-year cohort study reported increased risk of death in patients with serum albumin levels bellow 3.8g/dl by 5 fold compared to HD patients with 4.1g/dl. [8]

A prospective cohort study of 58,058 MHD patients by Kalantar-Zadeh et al showed that a drop in serum albumin over 6 months was associated with increased all-cause and cardiovascular

mortality. An estimated Population Attributable Fraction (PAF) of death for MHD patients with albumin level lower than 3.8g/dl was 19% indicating that about 10,000 deaths each year hypothetically could be prevented in the US by interventions aimed to rise serum albumin levels over 3.8g/dl [9].

A Meta analysis of 38 studies with total number of 265,330 patients showed the inverse relationship between albumin levels and all-cause mortality (HR=0.70; 0.64-0.78) as well as with CV mortality (HR=0.87; 0.79-0.96) [10].

A study by Shinaberger et al of 53,933 hemodialysis patients showed the association between the normalized protein nitrogen appearance (nPNA also called nPCR) and survival in MHD patients. Patients with daily protein intake of 1-1.4 g/kg/d had better survival, while a decrease in daily protein intake by 0.2 g/kg/day during the first 6 months was associated with increased risk of death in the following 18 months [11].

A case-crossover study in which dialysis patients were randomly assigned to receive in-center protein supplements showed significant increase in both albumin (from 3.49 to 3.52 mg/dl; p=0.035) and nPCR (from 1.05 to 1.16g/kg/d; p=0.007) in a group that received supplements, and significant decrease in both parameters (3.35 to 3.19 p=0.014 in albumin and 1.11 to 0.98 p=0.038 in nPCR) in the control group after 3-6 months of treatment, which continued dropping significantly in the control group [12]. The same study noted a trend in reduction in hospital admonitions and the length of hospital stay in a group that received supplements.

A review study by Dukkipati et al concluded that the intradialytic parenteral nutrition (IDPN) and intravenous infusion of essential nutrients during hemodialysis treatments had good

safety profile and could potentially improve protein and energy status and decrease a risk of protein energy wasting (PEW) [13].

A study of 64 dialysis patients enrolled in National Institute of Health Sponsored Hemodialysis (HEMO) study, found a positive correlation between serum levels of albumin and nPCR (0.208 p=0.034) indicating an increase in albumin synthesis after increase in nPCR (usually increases after dietary protein intake) [2].

Nutrition of patients with ESRD is an important factor and contributes largely to their survival. Poor nutrition can contribute to the malnutrition-inflammation syndrome (MIS). Loss of nutrients trough dialysis, poor appetite, and weight loss are common problems for patients receiving RRT [14]. Therefore, it is important to have a balanced diet with substantial amounts of protein, vitamins, and minerals. A nutritional status of dialysis patients can play a crucial role in their survival especially in the transitional time period right after initiation of dialysis treatment.

We hypothesized that a combination of serum albumin and nPNA levels may be predictive of mortality in dialysis patients in the first 24 months after dialysis initiation. Higher levels of albumin and nPNA could represent better nutritional status and less inflammation in ESRDS patients. Patients with serum levels of albumin above 3.5 g/dl and nPNA levels above 1.00 g/kg/day may have better survival during the first two years of dialysis and an increase in albumin and nPNA may improve patient's survival during the same time period.

5.3 Methods

5.3a Sources of Data, Study Population and Follow-up

We examined a cohort of incident hemodialysis patients who started the first week of hemodialysis treatment from July 01, 2001, to June 30, 2006 at one of DaVita's dialysis centers. Patients who used peritoneal dialysis modality at any given time were excluded.

We combined information from DaVita databases with data from USRDS using a unique patient identifier. Demographic and lab data as well as dates for starting dialysis treatment and enrolling in DaVita cohort were taken from DaVita sources. United States Renal Data System (USRDS) databases were used to corroborate the information about the dates of the events including death and transplantation, and co-morbidities at the start of dialysis therapy. Dialysis modality and laboratory data prior to the dialysis treatment were verified as well.[15] To examine the patterns of survival in the first 2 years among patients with different albumin and nPCR serum levels, quarterly lab measurements up to 8 quarters were used. Patients were followed for up to 5 years (1,830 days) or until death, kidney transplantation, or the end of the follow-up. Person-time was obtained by calculating the difference between the dates of the first ever hemodialysis treatment at one of the DaVita clinics and the end of follow-up or other censoring events.

All the quarterly laboratory measurements were converted into cohort-quarters where the first quarter represented the baseline measurements at the time of dialysis initiation rather than a calendar time of entry into a DaVita cohort.

5.3b Alb and nPCR as predictors of mortality

We examined the associations between the morality at each of first eight quarters on dialysis and combined levels of serum albumin and nPCR for the same quarters for which we created the following combined categories: 1) Albumin >3,5 g/dl *nPCR >=1g/kg/day; 2) Albumin

>3.5 g/dl * nPCR <1g/kg/day; 3) Albumin <3.5 g/dl * nPCR >= 1g/kg/day; 4) Albumin <3.5 g/dl * nPCR <1 g/kg/day.

The choice of these categories was justified as follows: since serum albumin was a marker of both nutrition and inflammation status, we tried to separate these two effects by combining albumin with nPRC which represented dietary protein intake. Patients with high nPCR but low serum albumin would likely have adequate nutrition and low albumin would indicate inflammation; patients with low nPCR and albumin over 3.5g/dl may have inadequate nutritional status but perhaps were less likely to have inflammation, while patients with low values for both parameters could be malnourished and have an inflammation, and patients with higher values for both parameters were more likely to have neither of the two conditions.

Additionally, we examined the associations between mortality and albumin and nPCR as separate predictors during the first 8 quarters on dialysis. We chose the same combined categories for serum albumin (comparing mortality for patients with <3.5 g/dL vs. >=3.5 g/dL), and nPCR (>=1 g/kg/day vs. <1 g/kg/day) for each of eight quarters.

Finally, we calculated the differences between the measurements taken during each of the quarters and the prior quarter for qtrs 2-8 for serum levels of albumin and nPCR. We then created "change categories" for both lab parameters where change between -0.2 g/dl to 0.2g/dl for albumin and -0.2g/kg/day to 0.2g/kg/day were considered stable, while decrease in over 0.2 units was defined as a decrease in laboratory parameter and increase in over 0.2 units was defined as an increase in the parameter.

All blood samples were drawn using standardized procedure and transported to the Central DaVita Laboratory located in Deland, FL usually within 24 hours. Blood or serum levels of

albumin and creatinine were measured monthly. Estimated prescribed dialysis treatment dose, known as Kt/V (single pool) [16] and protein intake known as normalized protein catabolic rate (nPCR)[11] were obtained using urea dynamic equations. All measurements were averaged over each calendar quarter (up to 13 weeks) to calculate one single value for each laboratory parameter per each patient per quarter. Most of these laboratory measurements (albumin, creatinine, phosphorus, calcium, bicarbonate, TIBC, WBC, lymphocyte, ferritin, and nPCR) and body mass index (BMI) may reflect the nutritional and/or inflammatory status of dialysis patients, they are referred to as the "malnutrition-inflammation cachexia syndrome" (MICS) throughout this study.[14]

5.3.c Statistical Analyses

Descriptive analyses were conducted to examine the population characteristics across four combined albumin/nPCR categories. We also calculated mean serum levels of albumin and nPCR for each quarter on dialysis and at baseline separately for patients who died during a quarter and for those who survived.

We examined correlations between serum levels of albumin and nPCR by calculating adjusted correlation coefficients adjusting for post-dialysis weight and creatinine for each of 8 quarters.

We also examined the associations between the risk of death during each of 8 quarters and the continuous values of serum albumin and separately of nPCR. We rescaled the units for both serum levels of albumin and nPCR by defining biologically and clinically meaningful increments of 0.2 g/dl for albumin and 0.2 g/kg/day for nPCR. The results of these two analyses are presented in the online supplement.

We fitted Cox proportional hazard models to examine the associations between the survival during each of the first eight quarters of dialysis treatment and either combined Alb/nPCR categories, categories for change or separate Alb or nPCR predictors. *Case–mix adjustment* was used in all of survival analyses which included adjustment for age, gender, four mutually exclusive race/ethnicity categories (African Americans, Hispanics, non-Hispanic whites, and others), primary insurance (Medicare, Medicaid, and other), marital status (married, single, divorced, widowed), dialysis vascular access, i.e., central venous catheter (CVC), arteriovenous fistula (AVF), or arteriovenous graft (AVG); dialysis dose (single pool Kt/V), diabetes mellitus as well as 11 additional co-morbid conditions including atherosclerosis, congestive heart failure (CHF), other cardiac conditions, cerebrovascular disease (CVA), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), cancer, hypertension, inability to ambulate, and smoking status; and entry calendar quarter for secular trend. All the models starting from quarter 2 were also adjusted for the baseline levels of albumin and nPCR. *Fully adjusted models*, which included adjusted all of the above, as well as 10 above-mentioned laboratory surrogates of the MICS and BMI were fitted in addition to the case-mix analysis. (Results did not differ substantially and are not presented). Additionally, we fitted the models that had an interaction term between Alb and nPCR, however it did not change our results and the p-values for the interaction were over 0.05 in all models.

All the analyses were conducted by using SAS 9.3 software (SAS Inc., NC).

5.4 Results

From 1 July 2001 to 30 June 2006, a total of 82,566 patients started hemodialysis treatment at a DaVita dialysis clinic within the first 90 days of therapy initiation. After excluding patients younger than 18 (n=637), incident peritoneal dialysis patients or those who switched modality at any given time (n=4,763), hemodialysis patients with missing person-time (n=6), hemodialysis patients who initiated the first week of dialysis therapy outside of a DaVita clinic (n=58,453) 18,707 incident hemodialysis patients remained. These patients had received at least one treatment of the first therapy week in a DaVita clinic and had remained in DaVita throughout the entire first 90 days or until death or transplantation. During the first 24 months, 6,666 patients died (36% or 30 deaths per 100 person years) and 1,399 received a kidney transplant.

Furthermore, patients with missing values for the serum levels of albumin and nPCR for all their time in cohort (n=1,262) were excluded and a total of 17,445 was used in the analyses. 2-year death rate remained 36% (6,325 deaths) among patients included in the analysis and was 27% (431 deaths) among patients that were excluded due to missing all ALB and nPCR measurements.

The mean age for the patients in the study was 64 years of age, 45% where females, 24% were African Americans, and 58% were diabetics. At baseline, mean serum level of albumin was 3.49 g/dl and mean nPCR level was 0.87g/kg/day with 44% of patients having serum albumin levels less than 3.5g/dl and 73% having nPCR less than 1g/kg/day.

Table 5.1 shows demographic characteristics by the combined serum albumin and nPCR categories at baseline (N=13,740). There racial distribution differed between the groups (53% of whites and 19% of blacks in reference group vs. 48% whites and 27% blacks in the group with Alb<3.5g/dl and nPCR <1g/kg/day), as well as type of vascular access (47% catheter use in the

reference group vs. 69% in the Alb<3.5g/dl and nPCR <1g/kg/day), % of patients with diabetes (54% in reference group vs. 66% in the Alb<3.5g/dl and nPCR <1g/kg/day), and baseline serum levels of creatinine (7.2 vs. 5.6 respectively).

Tables 5.1S.A and B examined the mean serum levels of albumin and nPCR for each of 8 quarters in the cohort by survival status at the end of the quarter. We also looked at the baseline ALB and nPCR values for the same patients and calculated the differences between the means for quarterly and baseline values for each group (**Figure 5.1**). We observed a steady increase in mean levels of serum albumin and somewhat moderate increase in nPCR levels over time among patients who were alive by the end of the quarter, while among those who died, mean albumin levels were lower compared to baseline measurements.

Correlations between serum albumin and nPCR were examined for each quarter with correlation coefficients varying from 0.18 to 0.25($p<0.0001$) (Scattered plots presented in on-line supplement **Figure 5.1S**). Previously reported correlations for albumin and nPCR varied from 0.06 to 0.26. [2, 5, 11, 17, 18]

In all of the analyzes we consistently observed an association between low serum level of nPCR and improved survival during the first 3 months of dialysis treatment which reversed after the first quarter.

Table 5.2 and Figure 5.2 present the case-mix adjusted death hazard ratios for the eight quarters on dialysis for combined categories for albumin and nPCR with (Alb>3.5g/dl nPCR>1g/kg/day as a reference group). Patients with serum albumin levels less than 3.5 g/dl had substantial increase in mortality especially after 3rd quarter (4-5 fold) regardless of nPCR values. In comparison, nPCR seemed to have little effect and did not depend on serum levels of albumin.

Additionally, we examined change in serum levels of albumin and nPCR from the prior quarter to the quarter of interest defining any increase or decrease by less than 0.2 units as no change **(Table 5.3, Figure 5.3)**. We examined change in mean levels of albumin and nPCR from the prior quarter to the quarter of interest separately for patients who survived until the end of quarter and those who died during it. We found that among patients who died during each of the quarter mean values for serum level of albumin always decreased from the prior quarter. However for surviving patients the mean for serum albumin practically did not change (**Figure 5.3A)**. For changes in mean serum levels of nPCR we observed increase in all patients from the previous quarter (higher in surviving patients) for the first 9 months of treatment with some decrease in patients who died during later quarters with no change in survivors (**Figure 5.3B)**.

We observed strong (over 3 fold increase) consistent association between decrease in serum albumin levels over 02 g/dl and mortality while increase in ALB level over 0.2 g/dl had showed only moderate survival advantage (**Figure 5.3C)**. Interestingly, the association between change in nPCR and mortality was not consistent over time. We observed that while decline in nPCR was associated with increase in mortality (although not as strong as decrease in albumin) increase in serum level of nPCR over 0.2g/kg/day was protective only during first 6 months after which it showed no survival advantage and became strongly associated with mortality by the end of second year with HR=2.77 (1.74 - 4.41) (**Figure 5.3D)**.

Finally, we examined the change from the previous quarter in the combined serum levels of ALB and nPCR (**Table 5.4**). We observed the highest increase in risk of death when both ALB and nPCR decreased over 0.2g/dl and 0.2g/kg/day respectively. As in the separate change analysis, we observed an increase in the risk of death during the last quarter among the patients with increased levels of nPCR, especially evident when serum level of albumin decreased for over 0.2g/dl.

A separate analysis of serum levels of albumin and nPCR presented in **Table 5.2S** and **Figure 5.2S** indicates that an increase in Alb and nPCR were both associated with lower mortality. However, the association was much stronger for albumin. Here, we present all-cause mortality analysis. The associations between infectious, cardio-vascular mortality and serum albumin (<3.5g/dl vs.>3.5g/dl) for this population were described elsewhere.

5.5 Discussion

Low serum albumin in dialysis patients is known to be associated with both malnutrition and inflammation [5, 19] while nPCR is mostly associated with dietary protein intake [11]. The links between low appetite and inflammation[20] as well as between inflammation, anemia and malnutrition were reported previously.[21] According to previous reports, Alb and nPCR were determined to be independent predictors of mortality in MHD patients.[18] In our study, we attempted to separate those effects by creating 4 combined Alb and nPCR categories and examining all-cause mortality for different categories over the first 8 quarters of dialysis treatment.

Additionally we examined the mean levels of the Alb and nPCR for each of quarter and compared them to the baseline measurements. The lowest serum levels for both lab parameters were recorded at the time of dialysis initiation. This can be due to a volume overload that many patients experience prior and shortly after starting renal-replacement therapy (RRT).[5] A study by Chandna et al observed a substantial drop in nPCR in CKD patients in the 3 months preceding initiation of dialysis.[17] It is recommended that CKD patients adhere to the low protein diet which could also contribute to low nPCR levels at baseline.[22] National Kidney Foundation's K/DOQI clinical practice guidelines recommend daily protein intake from 06-0.8g/kg/day for CKD patients but 1.2-1.3g/kg/day for MHD patients.[22] It was previously reported that nPCR could be increased in hemodalysis patients after 2 months of taking protein dietary

supplements.[23] In fact, among patients in our study, 73% had nPCR less than 1g/kg/day at the time of dialysis initiation but by the end of month 6 this number decreased to 50% and remained unchanged by the end of the 2nd year. This may explain the protective role of low nPCR in the first 3 months of dialysis treatment that we consistently observed in all our analyses. However, after the first quarter the association between low nPCR and mortality reversed with hazard ratios for all-cause mortality and nPCR changing from 0.8(0.67-0.95) during the first 3 months to 1.52 (1.31-1.76) from 4-6 months on dialysis when comparing patients with nPCR levels of less than 1g/kg/day to those with nPCR higher than 1g/kg/day.

We observed that the mean for serum level albumin increased with every quarter of dialysis treatment for patients who were alive at the end of the quarter but it was consistently lower comparing to the baseline for the patients who died. The fact that we observed an increase in the serum level of albumin for each consecutive quarter among surviving patients may suggest a survival advantage for the healthier patients who had higher serum albumin levels at baseline. However, while the mean level of ALB increased over time, it was higher among surviving patients but lower for patients who died during the quarter of interest while comparing to their own baseline values which may also indicate positive effect of dialysis treatment among survivors.

While examining mortality among 4 combined Alb and nPCR categories, we found that low albumin was associated with higher mortality independently of nPCR levels. Moreover, the weakest associations were observed during the time of dialysis initiation, and for all the analyses the strength of associations increased after 3-6 months.

The strong association between low levels of serum albumin and mortality was observed in all our models and was consistent for all 8 quarters. While our results were consistent with those previously reported [2,5,8,9] we were the first to examine the mortality patterns from quarter to

quarter. Importantly, survival advantage of higher and increasing albumin levels persisted over time.

Positive association between low level of nPCR and mortality was reported before[11] and was observed in our study although the strength was much lower compared to the effects of albumin. Chandna et al reported that low nPCR values at the time of starting dialysis treatment were predictive of elevated risk of death [17], which was observed in our study as well. However, unlike in their study, we observed an increase in mean values of nPCR over time especially after 3-6 months of dialysis treatment.

Examining changes in serum levels of albumin from the previous quarter to the next one for the first 8 quarters showed consistently strong association (over 3 fold for most quarters) between the risk of death and decrease albumin over 0.2g/dl, while increase was inversely associated with mortality. Although we are not aware of any studies examining mortality patterns and their association with changes in serum levels of albumin over time, the association between the change in ALB and mortality was shown previously either for the shorter follow-up or as cumulative measure. [24, 25]

As we examined changes in serum level of nPCR over time we found that decline in nPCR over 0.2g/kg/day within a 3 months period was associated with elevated risk of death. This was not surprising and the association was previously noted although not as pattern for over 2 years time period. [11, 24] The more surprising finding was that increase in nPCR over 0.2g/kg/day appeared to have protective effect only for the first 6-9 months after which it became uncertain until it showed strong positive association with mortality after 21st month of a follow-up. When adjusted for the change in Albumin the association remained (results are not shown). It was previously reported by Shinaberger et al that rapid increase in nPCR or nPCR over 1.4g/kg/day may be

associated with higher mortality which may be attributed to negative nitrogen balance, increase in catabolic rate during infection or inflammation.[11] The fact that in our study this effect became clearly visible only during the last quarter may indicate that the rapid increase in nPCR from quarter 7 to 8 in some patients can be due to increase in catabolic rate because of PEW that progresses as dialysis vintage increases. In fact, the mean level of creatinine for patients who died during qtr 8 after and had increase in nPCR for over 0.2g/kg/day was 7.7 mg/dl but it was 8.6 for patients from the same group who survived for at least to 24 months. Moreover, the mean weight for the same patients was 63kg compared to 76kg among those who had an increase in nPCR but survived. The change in weight from the previous quarter was -1.3 kg for those who died and had rapid increase in nPCR for the previous quarter, while surviving patients showed 0.5 kg weight gain for the same time period. When we examined combined changes in serum Albumin and nPCR it was evident that during the last quarter patients with decrease in nPCR level had the same elevated risk of death as patients with increased nPCR, which was especially evident in a group of patients with decreased serum level of ALB.

To our knowledge, this is one of the largest longitudinal studies of incident dialysis patients that attempted to look at the serum levels of albumin and nPCR over the first 24 months of dialysis treatment associated with mortality patterns. The novelty of our study is that we look separately and in great detail at each quarter examining the effects of serum levels of albumin and nPCR in an attempt to separate the effects of malnutrition and inflammation associated with low albumin. Unfortunately, we did not have information on C-reactive protein (CRP) levels for our cohort which could potentially help us to account for inflammation with greater certainty as the CRP's role a marker of inflammation is well established as is its association with low serum levels of

albumin in MHD patients. [3-5] Neither had we information about dietary practices, hence the protein or caloric intake, of the patients enrolled.

5.6 Conclusion

Low quarterly serum albumin levels were strongly associated with an increase in all-cause mortality in incident hemodialysis patients during the first 24 months of dialysis treatment. It appeared to be a strong predictor of mortality regardless of levels of nPCR. Moreover, decline in serum level of albumin over 0.2g/dl from the prior quarter was also a strong predictor of mortality.

Quarterly serum levels of nPCR lower than 1g/kg/day were associated with increased risk of death except for the first 3 months of dialysis treatment. Although the strength of association was weaker, it too seemed to be independent of serum levels of albumin. Decrease in nPCR over 0.2g/kg/day was predictive of higher mortality which could indicate that maintaining a daily protein intake of 1-1.2 g/kg/day after initiation of dialysis treatment could be beneficial to hemodialysis patients.

An abrupt increase of 0.2g/kg/day or higher in serum level of nPCR after 21 months of dialysis treatment may however be an indicator of protein energy wasting process and such change should be viewed with caution especially if loss of weight and decline in serum creatinine occurs simultaneously. This should be especially carefully monitored in patients with rapid decline in serum albumin level combined with increase in nPCR. Dietary modifications increasing daily protein intake in this patient group may be necessary.

5.7 Tables for Chapter 5

Table 5.1. Patients' characteristics at baseline by combined low vs. high Alb and low vs. high nPCR (2x2=4) categories in the 5 year cohort (07/01-06/06) of 17,445 incident hemodialysis patients

Population Characteristics	**nPCR>1 ALB>3.5**	**nPCR<1 ALB>3.5**	**nPCR>1 ALB<3.5**	**nPCR<1 ALB<3.5**	**p**
N=13,740	***N=2,373***	***N=5,566***	***N=1,272***	***N=4,529***	
Age	63±15	63±16	65±15	64±15	<.0001
Gender (% female)	41%	43%	45%	49%	<.0001
Diabetes mellitus (%)	54%	51%	65%	66%	<.0001
Race (%)					
White	53%	55%	50%	48%	<.0001
Black	19%	26%	19%	27%	<.0001
Hispanic	15%	11%	18%	15%	<.0001
Other	12%	8%	13%	9%	<.0001
Primary insurance (%)					
Medicare	55%	56%	57%	60%	<.0001
Medicaid	5%	5%	6%	7%	<.0001
Other	40%	39%	37%	33%	<.0001
Marital Status (%)					
Married	57%	54%	57%	48%	<.0001
Divorced	8%	7%	5%	8%	<.0001
Single	21%	24%	20%	27%	<.0001
Widowed	14%	15%	18%	18%	<.0001
Kt/V (dialysis dose)	1.5±0.4	1.3±0.4	1.5±0.4	1.3±0.4	<.0001

Population Characteristics	**nPCR>1 ALB>3.5**	**nPCR<1 ALB>3.5**	**nPCR>1 ALB<3.5**	**nPCR<1 ALB<3.5**	**p**
N=13,740	***N=2,373***	***N=5,566***	***N=1,272***	***N=4,529***	
Vascular Access (%)					
Dialysis Catheter	47%	52%	63%	69%	<.0001
AVF	33%	30%	20%	15%	<.0001
Graft	20%	18%	17%	15%	0.0006
Co-morbid Conditions (%)					
Cancer	5%	5%	6%	6%	0.03
Atherosclerotic Heart Disease	19%	20%	22%	22%	0.06
Heart Failure	22%	22%	30%	29%	<.0001
Pulmonary Disease COPD	5%	6%	7%	6%	0.07
Cerebro-vascular disease CVA	7%	8%	8%	9%	0.02
History of Hypertension	80%	81%	77%	76%	<.0001
Other Heart Diseases	2%	2%	5%	5%	<.0001
Non-ambulatory	5%	6%	7%	7%	0.0003
Peripheral Vascular Disease PVD	10%	11%	14%	14%	<.0001
Smoker +	3%	5%	3%	5%	0.001
Serum levels					
Creatinine (mg/dL)	7.2±3	6.3±3	6.7±3	5.6±3	<.0001
TIBC (mg/dL)	246±49	241±47	210±50	199±52	<.0001
Bicarbonate (mg/dL)	21±4	22±3	21±4	23±3	<.0001
Phosphorus (mg/dL)	5.7±2	5.0±1	5.7±2	4.9±1	<.0001
Calcium (mg/dL)	9.0±1	9.1±1	8.6±1	8.6±1	<.0001
Ferritin (ng/mL)	283±363	258±313	416±529	374±500	<.0001

Population Characteristics	**nPCR>1 ALB>3.5**	**nPCR<1 ALB>3.5**	**nPCR>1 ALB<3.5**	**nPCR<1 ALB<3.5**	**p**
N=13,740	***N=2,373***	***N=5,566***	***N=1,272***	***N=4,529***	
Blood hemoglobin (g/dL)	11.2±1	11.2±1	10.6±1	10.7±1	<.0001
WBC (x10^3/□l)	7.7±3	7.5±3	8.9±4	8.2±3	<.0001
Lymphocyte (% of WBC)	18±7	19±7	15±7	17±8	<.0001
ISAT (%)	24±7	23±10	24±12	23±11	0.005
ALKP (u/L)	105±65	103±55	130±134	131±104	<.0001
PHT (pg/dl)	492±437	450±403	443±417	396±361	<.0001
Epogen dose (units/treatment)	8375±4537	8791±4572	9373±4647	10025±4992	<.0001
Zemplar dose (mcg/treatment)	4.1±4	4.0±3	4.0±3	3.7±3	0.02
BMI (kg/m2)	27±6	28 ±7	26±7	27±7	<.0001
eGFR (ml/min)	9.4±4	10.0±4	9.8±5	10.8±5	<.0001

Table 5.2. HR for the Case-Mix models looking at the morality for each of the first 8 qtrs on dialysis among combined nPCR and Alb measurements with Alb >3.5 and nPCR>1 as a reference category (HR=1) for incident HD patients from 5 year DaVita cohort 07/01-06/06

	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
QTR in cohort	**nPCR<1ALB>3.5***	**npcr>1ALB<3.5***	**nPCR<1ALB<3.5***
1-3 months (qtr1)	0.72 *(0.59 - 0.88)*	2.50 *(1.86 - 3.11)*	1.86 (1.54 - 2.25)
4-6 months (qtr2)	1.26 *(0.93 - 1.71)*	3.34 *(2.46 - 4.53)*	4.48 (3.40 - 5.89)
7-9 months (qtr3)	1.53 *(0.97 - 2.42)*	5.80 *(4.24 - 7.92)*	6.94 (5.07 - 9.50)
10-12 months (qtr4)	1.29 *(0.95 - 1.75)*	4.99 *(3.38 - 7.35)*	5.56 *(3.61 - 8.58)*
13-15 months (qtr5)	0.92 *(0.54 - 1.58)*	3.52 *(2.53 - 4.89)*	6.53 *(5.07 - 8.41)*
16-18 months (qtr6)	0.98 *(0.74 - 1.31)*	6.96 *(3.67 - 9.66)*	6.69 *(4.85 - 9.22)*
19-21 months (qtr7)	1.10 *(0.73 - 1.69)*	5.05 *(2.54 - 10.03)*	5.94 *(3.92 - 9.00)*
22-24 months (qtr8)	0.93 *(0.59 - 1.47)*	3.98 *(2.19 - 7.24)*	4.60 *(2.68 - 7.92)*

* nPCR>1 ALB>3.5= ref group (HR=1)

Table 5.3 . Hazard Ratios of death for the change in serum levels of ALB and nPCR from the prior quarter to the quarter of interest for the first 8 quarters of dialysis treatment for incident hemodialysis patients from5-year DaVita cohort; 07/01-06/06

	HR (95% CI)	**HR (95% C)**
QTR in cohort	**Δ ALB ↓over 0.2g/dl***	**Δ ALB ↑over 0.2 g/dl**
q2-q1	2.57 *(2.23 - 2.97)*	0.47 *(0.40 - 0.56)*
q3-q2	3.54 *(2.92 - 4.29)*	0.93 *(0.76 - 1.13)*
q4-q3	3.40 *(2.82 - 4.10)*	0.69 *(0.52 - 0.91)*
q5-q4	3.14 *(2.51 - 3.92)*	1.09 *(0.79- 1.52)*
q6-q5	3.40 *(2.73 - 4.24)*	0.71 *(0.52 - 0.99)*
q7-q6	3.57 *(2.84 - 4.49)*	0.88 *(0.62 - 1.27)*
q8-q7	3.81 *(2.92 -4.97)*	0.80 (0.52 -1.23)
QTR in cohort	**Δ nPCR ↓over 0.2g/kg/day***	**Δ nPCR ↑over 0.2 g/kg/day**
q2-q1	1.65 *(1.34 - 2.03)*	0.69 *(0.57 - 0.83)*
q3-q2	2.38 *(1.73 - 3.26)*	0.90 *(0.64 - 1.27)*
q4-q3	1.74 *(1.26 - 2.42)*	1.17 *(0.76 - 1.80)*
q5-q4	2.04 *(1.26 - 3.29)*	1.30 *(0.81 - 2.08)*
q6-q5	2.60 *(1.67 - 4.06)*	1.32 *(0.82 - 2.14)*
q7-q6	2.64 *(1.71 - 4.08)*	1.64 *(0.81 - 3.32)*
q8-q7	2.99 *(1.83 - 4.87)*	2.77 *(1.74 - 4.41)*

*** reference= no change (HR=1)**

Table 5.4. Hazard Ratios of death for the combined change in serum levels of ALB and nPCR from the prior quarter to the quarter of interest for the first 8 quarters of dialysis treatment for incident hemodialysis patients from5-year DaVita cohort; 07/01-06/06

	↓Alb; ↓nPCR	**↓Alb; no change nPCR**	**↓Alb; ↑nPCR**	**no change Alb; ↓nPCR**	**no change Alb and nPCR**	**no change Alb; ↑nPCR**	**↑Alb; ↓nPCR**	**↑Alb; no change nPCR**	**↑Alb; ↑nPCR**
q2-q1	3.16 *(2.20 - 4.54)*	3.07 *(2.30 - 4.09)*	2.91 *(2.11 - 4.01)*	1.37 *(0.90 - 2.11)*	1.00 *(1.00 - 1.00)*	0.99 *(0.77 - 1.29)*	0.57 *(0.33 - 1.00)*	0.60 *(0.49 - 0.73)*	0.45 *(0.31 - 0.65)*
q3-q2	5.92 *(3.90 - 8.98)*	3.37 *(2.56 - 4.45)*	4.27 *(2.65 - 6.87)*	1.21 *(0.66 - 2.23)*	1.00 *(1.00 - 1.00)*	1.12 *(0.71 - 1.75)*	1.75 *(0.97 - 3.16)*	0.88 *(0.60 - 1.30)*	0.64 *(0.46 - 0.89)*
q4-q3	4.58 *(3.17 - 6.60)*	3.84 *(2.83 - 5.21)*	4.00 *(2.40 - 6.59)*	1.11 *(0.72 - 1.72)*	1.00 *(1.00 - 1.00)*	1.18 *(0.80 - 1.74)*	0.66 *(0.25 - 1.75)*	0.87 *(0.60 - 1.25)*	0.89 *(0.60 - 1.34)*
q5-q4	5.43 *(3.31 - 8.91)*	3.01 *(2.17 - 4.18)*	3.38 *(1.61 - 7.11)*	1.22 *(0.54 - 2.79)*	1.00 *(1.00 - 1.00)*	1.48 *(0.94 - 2.33)*	0.50 *(0.13 - 2.00)*	0.62 *(0.37 - 1.03)*	0.89 *(0.41 - 1.92)*
q6-q5	4.53 *(2.77 - 7.41)*	3.41 *(2.34 - 4.97)*	4.21 *(1.43 - 12.42)*	1.79 *(0.75 - 4.21)*	1.00 *(1.00 - 1.00)*	1.32 *(0.68 - 2.53)*	0.80 *(0.16 - 4.07)*	0.64 *(0.40 - 1.01)*	1.00 *(0.44 - 2.27)*
q7-q6	4.48 *(2.57 - 7.81)*	2.98 *(2.12 - 4.20)*	10.48 *(5.02 - 21.87)*	1.58 *(0.99 - 2.52)*	1.00 *(1.00 - 1.00)*	0.97 *(0.47 - 1.99)*	0.58 *(0.09 - 3.68)*	0.87 *(0.51 - 1.54)*	0.94 *(0.29 - 3.04)*
q8-q7	11.0 *(6.75 - 17.99)*	3.51 *(2.23 - 5.54)*	11.4 *(6.02 - 21.69)*	1.89 *(0.72 - 4.95)*	1.00 *(1.00 - 1.00)*	3.11 *(2.03 - 4.76)*	0.38 *(0.02 - 7.08)*	1.10 *(0.56 - 2.15)*	2.27 *(0.70 - 7.34)*

5.8 Figures for Chapter 5

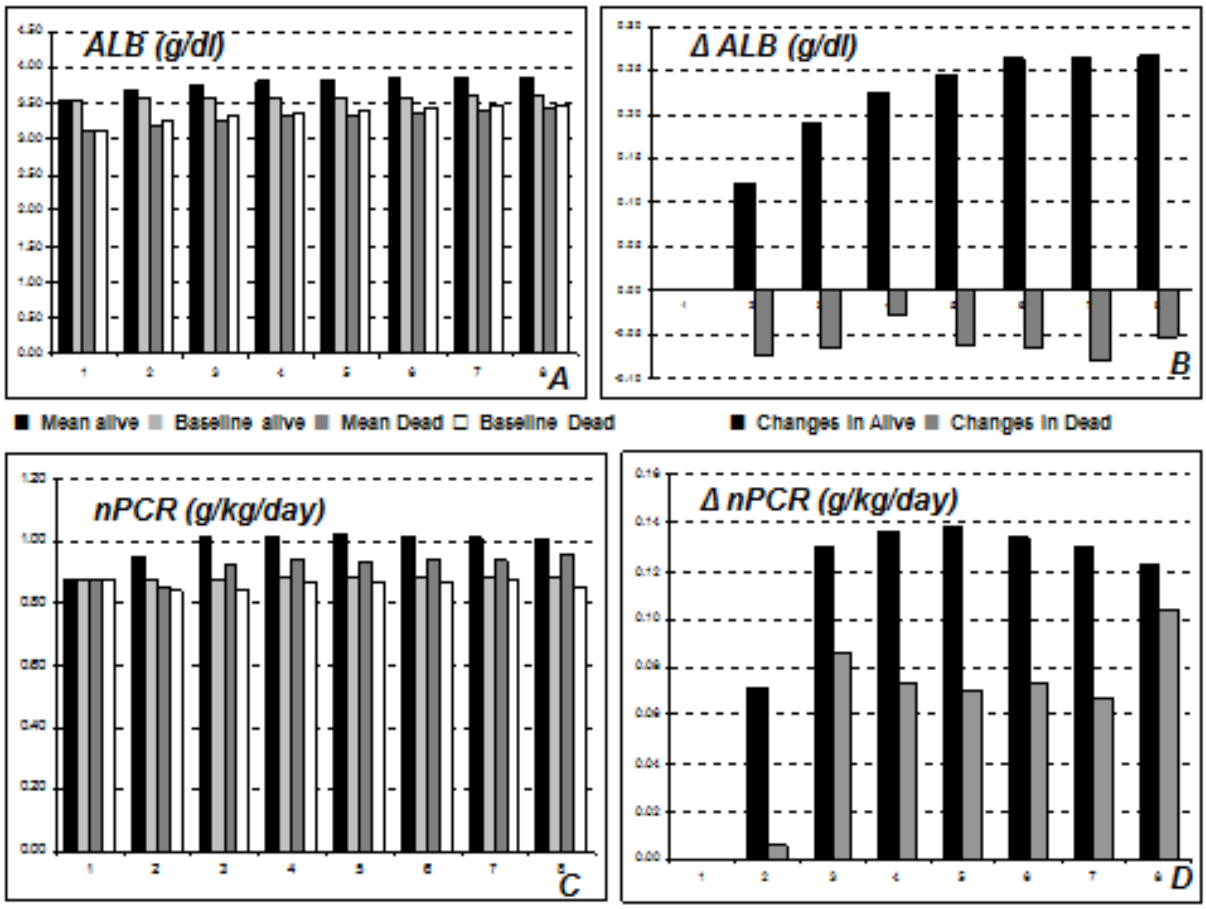

Figure 5.1. Mean serum levels of albumin and nPCR for each of the 8 quarters in cohort by survival by the end of the qtr comparing to mean baseline values for the same group and changes in means from baseline to each quarter by survival; N=17,745

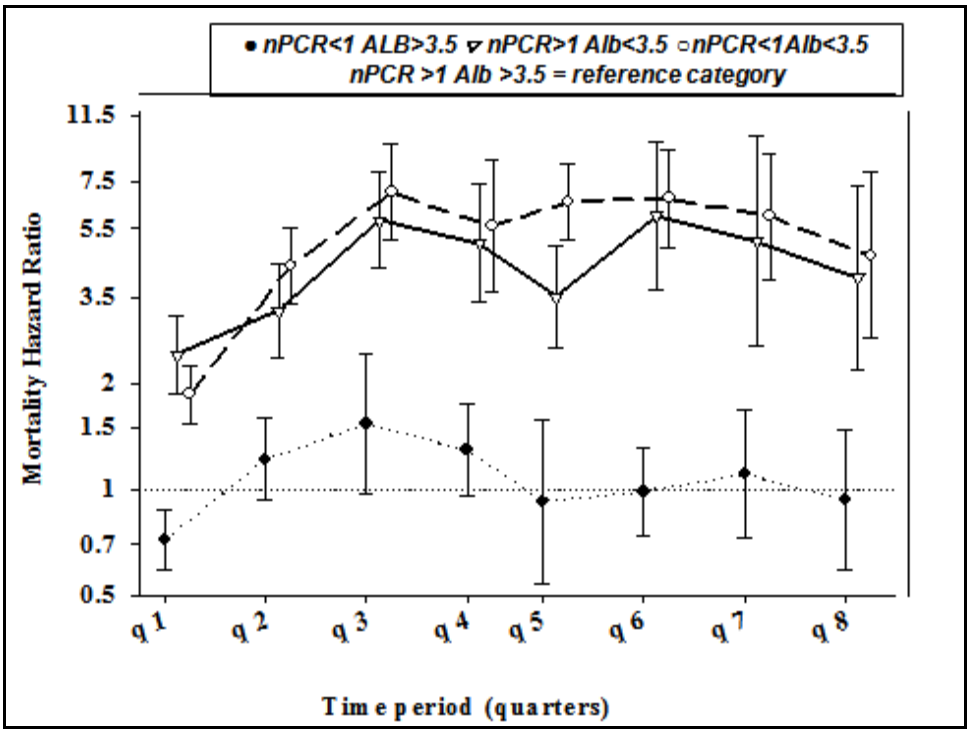

Figure 5.2. Hazard ratios of death comparing combined Alb/nPCR categories or the first 8 quarters (24 months) of dialysis treatment among incident hemodialysis patients from 5 year DaVita cohort; 07/01-06/06

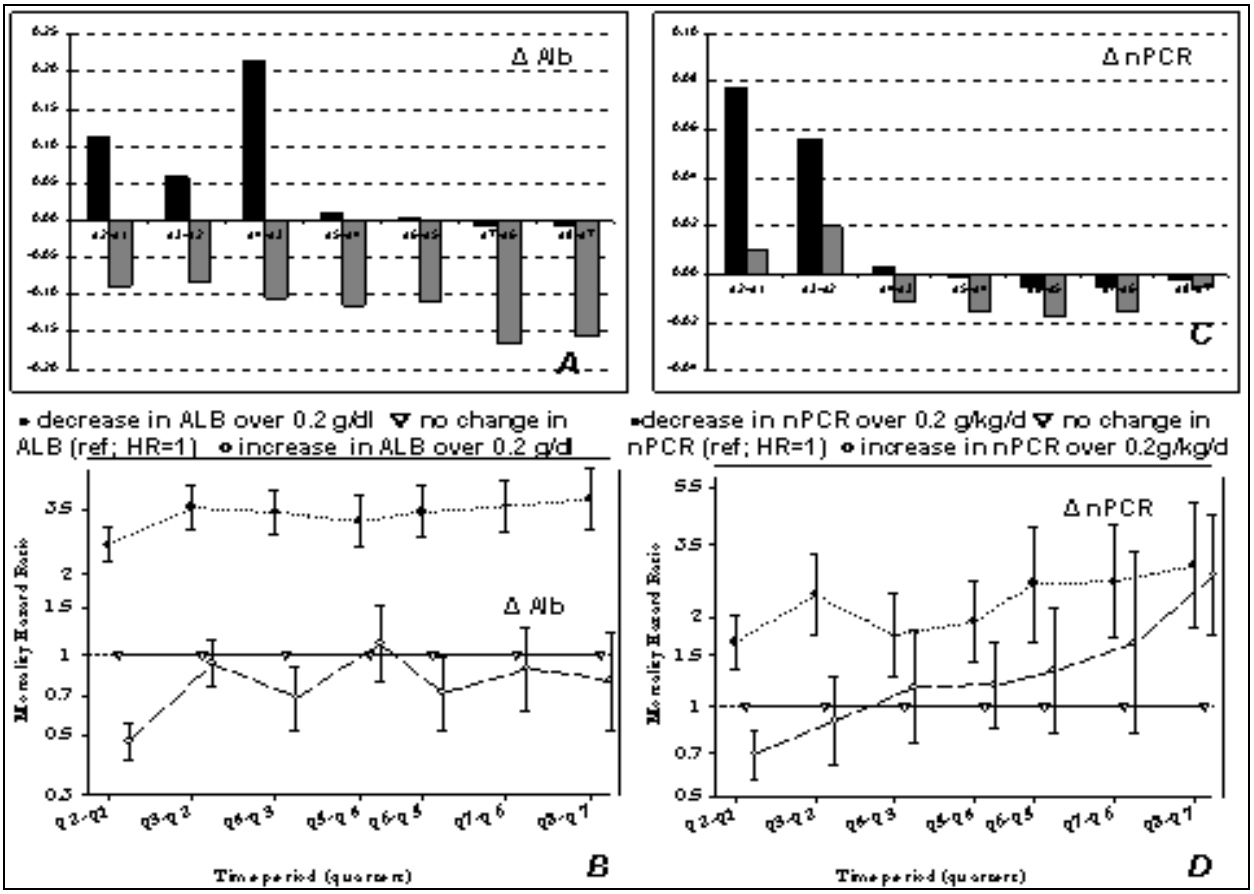

Figure 5.3. Change in the mean serum levels of ALB and nPCR from the previous quarter to the quarter of interest separately for alive (black) patients and those who died during the quarter (gray) (A, C) and Hazard Ratios of death comparing increase and decrease in serum levels to no change for incident dialysis patients from 5-year DaVita cohort; 07/01-06/06

5.9 Suggested on-line supplement

Table 5.1 S.A. Mean quarterly values for serum level albumin by survival status at the end of the quarter comparing to baseline serum levels of albumin among the same group of patients for incident dialysis patients from 5-year DaVita cohort; 07/01-06/06.

	Alive				Dead			
Quarter in cohort	N	Mean Alive	Baseline Mean	Δ for alive	N	Mean Dead	Baseline Mean	Δ for dead
1-3 months (qtr1)	14891	3.53±0.53	3.53±0.53	0.00	1825	3.11±0.57	3.11±0.57	0.00
4-6 months (qtr2)	12433	3.68±0.45	3.56±0.51	0.12	1003	3.19±0.55	3.26±0.52	-0.07
7-9 months (qtr3)	10819	3.76±0.42	3.57±0.51	0.19	565	3.28±0.54	3.34±0.51	-0.06
10-12 months (qtr4)	9769	3.81±0.41	3.58±0.50	0.23	499	3.33±0.52	3.36±0.51	-0.03
13-15 months (qtr5)	9030	3.83±0.40	3.59±0.50	0.25	383	3.34±0.57	3.40±0.52	-0.06
16-18 months (qtr6)	7870	3.85±0.39	3.59±0.50	0.26	319	3.37±0.53	3.44±0.49	-0.07
19-21 months (qtr7)	6850	3.86±0.39	3.59±0.50	0.26	265	3.40±0.58	3.48±0.49	-0.08
22-24 months (qtr8)	5929	3.86±0.38	3.60±0.49	0.27	240	3.41±0.53	3.46±0.50	-0.05

Table 5.1 S.B. Mean quarterly values for serum levels of nPCR by survival status at the end of the quarter comparing to baseline serum levels of nPCR among the same group of patients for incident dialysis patients from 5-year DaVita cohort; 07/01-06/06

	Alive				Dead			
Quarter in cohort	N	Mean Alive	Baseline Mean	Δ for alive	N	Mean Dead	Baseline Mean	Δ for dead
1-3 months (qtr1)	12582	0.87±0.26	0.87±0.26	0.00	1219	0.88±0.30	0.88±0.30	0.00
4-6 months (qtr2)	11324	0.95±0.26	0.88±0.26	0.07	904	0.85±0.25	0.84±0.25	0.01
7-9 months (qtr3)	9117	1.01±0.26	0.88±0.26	0.13	482	0.93±0.27	0.84±0.25	0.09
10-12 months (qtr4)	7618	1.02±0.25	0.88±0.26	0.14	394	0.94±0.27	0.87±0.28	0.07
13-15 months (qtr5)	6487	1.02±0.24	0.88±0.25	0.14	267	0.94±0.28	0.87±0.28	0.07
16-18 months (qtr6)	5528	1.02±0.24	0.88±0.25	0.13	220	0.94±0.26	0.86±0.24	0.07
19-21 months (qtr7)	4743	1.01±0.24	0.88±0.25	0.13	174	0.94±0.26	0.87±0.26	0.07
22-24 months (qtr8)	4047	1.01±0.24	0.89±0.25	0.12	170	0.96±0.29	0.85±0.23	0.10

Table 5.2S. Hazard ratios of death for the Albumin and nPCR examined separately for the first 8 quarters of dialysis among incident hemodialysis patients from 5-year DaVita cohort; 07/01-06/06

	HR (95% CI)	**HR (95% C)**
Time Period	**Abl >3.5 vs <3.5 (g/dl)**	**nPCR <1 vs. >1 (g/kg/day)**
1-3 months (qtr1)	2.49 *(2.23 - 2.77)*	0.80 *(0.67 - 0.95)*
4-6 months (qtr2)	3.33 *(2.78 - 3.92)*	1.52 *(1.31 - 1.76)*
7-9 months (qtr3)	4.40 *(3.62 - 5.33)*	1.56 *(1.28 - 1.90)*
10-12 months (qtr4)	4.12 *(3.43 - 4.95)*	1.45 *(1.17 - 1.81)*
13-15 months (qtr5)	4.97 *(3.97 - 6.23)*	1.58 *(1.26 - 1.98)*
16-18 months (qtr6)	5.51 *(4.21 - 7.20)*	1.33 *(0.96 - 1.84)*
19-21 months (qtr7)	4.74 *(3.66 - 6.15)*	1.33 (0.86 - 2.05)
22-24 months (qtr8)	4.87 *(3.71 - 6.40)*	1.19 *(0.90 - 1.57)*
	HR (95% CI)	**HR (95% C)**
QTR in cohort	**Alb (↓ by 0.2 g/dl)**	**nPCR (↓by 0.2 g/kg/day)**
1-3 months (qtr1)	1.21 *(1.19 - 1.23)*	0.92 *(0.87 - 0.98)*
4-6 months (qtr2)	1.46 *(1.41 - 1.51)*	1.31 *(1.21 - 1.41)*
7-9 months (qtr3)	1.48 *(1.43 - 1.53)*	1.27 *(1.16 - 1.38)*
10-12 months (qtr4)	1.42 *(1.38 - 1.47)*	1.21 *(1.11 - 1.30)*
13-15 months (qtr5)	1.48 *(1.43 - 1.53)*	1.26 *(1.11 - 1.42)*
16-18 months (qtr6)	1.49 *(1.43 - 1.56)*	1.28 *(1.11 - 1.48)*
19-21 months (qtr7)	1.47 *(1.40 - 1.54)*	1.23 *(1.04 - 1.47)*
22-24 months (qtr8)	1.49 *(1.42 - 1.56)*	1.13 *(0.98 - 1.29)*

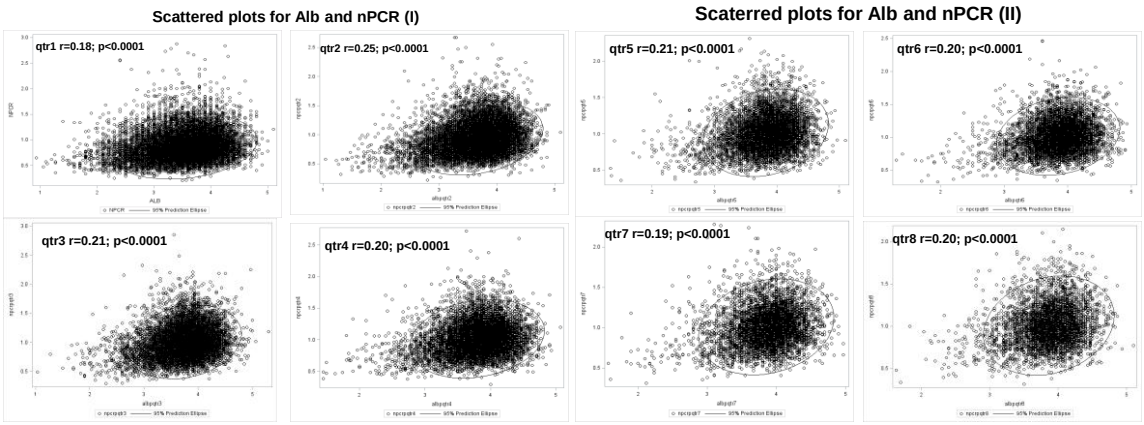

Figure 1S. Scattered plots examining correlation between quarterly serum level of albumin and nPCR for 8 quarters on dialysis.

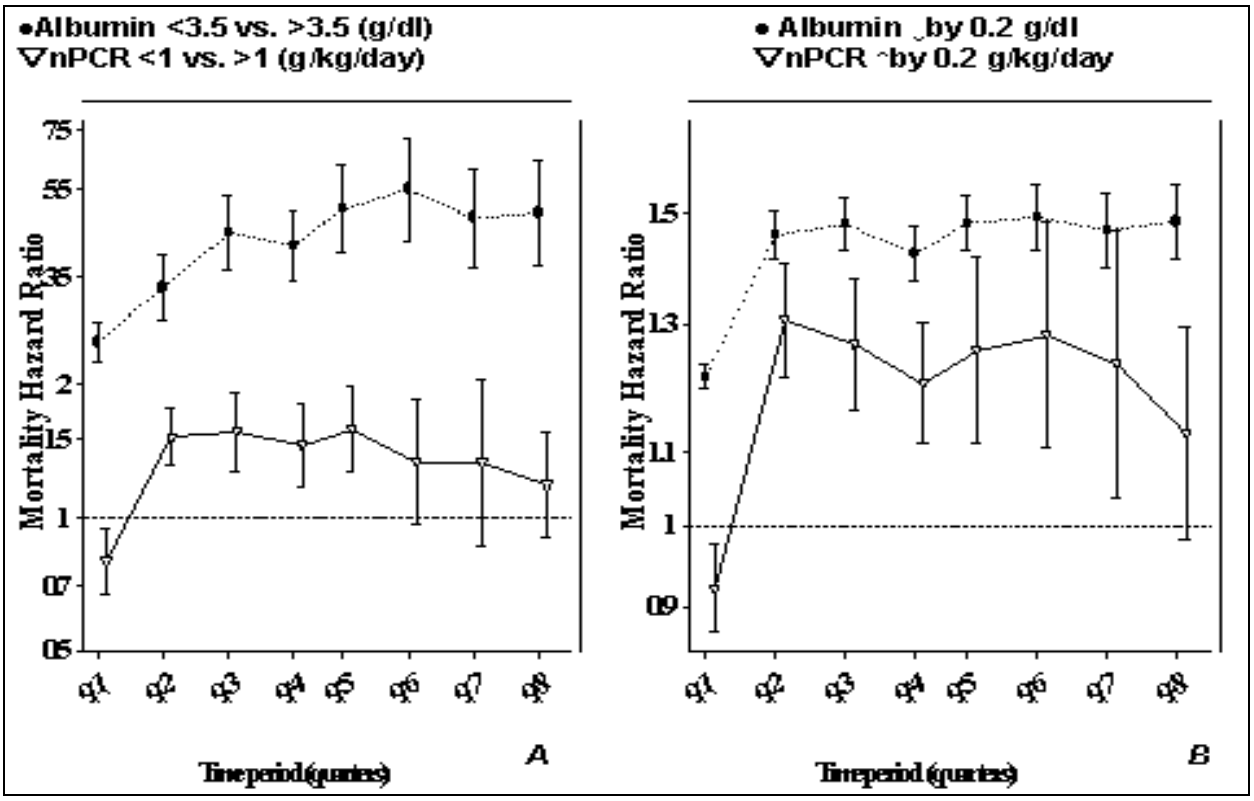

Figure 5.2S. Hazard ratios of death for the Alb and nPCR levels for the first 8 quarters examined separately for the incident hemodialysis patients from 5-year DaVita cohort; 07/01-06/06

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Chapter 6 Comparative Effect of Peritoneal versus Hemodialysis on Mortality in the First Two Years: A Marginal Structural Model Analysis

Authors:

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6.1 Abstract

Background: Previous research indicated the survival differences between hemodialysis (HD) and peritoneal dialysis (PD) modalities, especially during the first 2 years of dialysis treatment. Given the challenges of conducting randomized trials, differential rates of modality switch and transplantation and time-varying confounding in cohort data during early dialysis treatment, use of novel analytical techniques in contemporary observational cohorts can help examine the PD versus HD survival discrepancy.

Study Design: Cohort of incident dialysis patients with up to 5 years of follow-up receiving dialysis treatment at one of the DaVita outpatient facilities between 7/2001 and 6/2006.

Setting and Participants: On dialysis treatment day 90, there were 23,718 incident dialysis−22,360 HD and 1,358 PD−patients. Incident PD patients were younger, had less co-morbidity and were 9-times more likely to switch dialysis modality and 3-times more likely to receive kidney transplantation over the 2 year period, compared to HD patients. We used the casual models known as marginal structural models (MSM) to examine the survival differences between PD and HD over the first 24 months accounting for modality change, differential transplantation rates, and detailed time-varying laboratory measurements in DaVita dialysis patients.

Predictors: Dialysis modality on day 90 of treatment accounting for change during the first two years of treatment as well as for time-dependent confounders.

Outcomes: Mortality and dialysis modality during first two years of dialysis treatment.

Results: In MSM analyses, PD offered persistently greater survival independent of the known confounders including dialysis modality switch or transplant censorship with a PD-versus-HD death hazard ratio of 0.52 (95% confidence interval 0.34-0.80).

Limitations: Did not examine survival beyond 24 months.

Conclusions: PD was associated with 48% lower mortality over the first 2 years of therapy.

Key Words: Dialysis modality, peritoneal dialysis, marginal structural model, propensity score. Inverse probability weights, causal models

6.2 Introduction

The number of patients with end-stage kidney disease requiring maintenance dialysis treatment continues to increase.(1, 2) Therefore, the choice of dialysis modality has become an important decision, which not only affects the programs funding renal replacement therapy but also influences patients' quality of life and survival.(3) The most common choice of dialysis modality (>90%) in US has been hemodialysis (HD) despite the rising costs which increased from $64,000 per patient in 2003 to $82,285 in 2009. During the same period, the annual expenses for peritoneal dialysis (PD) patient had increased from $47,000 to $61,588.(3, 4) However, in 2008, only about 6% of all maintenance dialysis patients in the US received the less expensive PD modality.(5, 6) Obtaining best practice evidence on which modality is the best for a particular patient and for how long has been fraught with difficulties and mixed results.

Although the randomized controlled studies are the best way to compare the outcomes of different dialysis modalities, many patients when properly educated about their choices would not agree to randomization. As an example, a randomized controlled trial attempted in Netherlands in 1997-2000 was stopped prematurely due to insufficient enrolment.(7) We are aware of only one randomized controlled study to compare HD and PD currently underway in China, the results of which may not be available for some time.(8) Hence, PD-HD observational epidemiologic studies remain important.

Many observational studies comparing survival of PD and HD patients were conducted in the past several decades. Whereas some older studies reported a somewhat inferior outcome with PD compared to HD, most of the recent studies infer that with the improvement of PD techniques survival of PD patients equates or even surpasses that of HD patients.(6, 9) However, virtually all observational studies have had methodological limitations in addition to non-random assignment

of dialysis modality, such as suboptimal adjustment for differential modality switch over time (since PD patients are more likely to switch to HD than HD patients to switch to PD over time), inability to account for time-varying confounding by physiologic (laboratory) values which are both the results and determinants of dialysis treatment choices, and inappropriate adjustment for the differential longitudinal censorship of transplantation across modalities.(8) The latter may be a major challenge in such studies, especially since PD patients are much more likely to receive a kidney transplant during the first 2 years of dialysis therapy.

Marginal structural model (MSM) is a relatively novel statistical technique that allows estimating the effect of a given treatment using inverse-probability-of-treatment weighting to adjust for the time-varying confounding as happens over time with dialysis patients. With sufficient confounding control (an unverifiable assumption) and in absence of measurement error, MSM can yield estimates comparable to those achieved in randomized trials by simulating randomization in observational data.(10) In this study, we examined the comparative effect of PD versus HD with mortality during the first 2 years of dialysis treatment in a large, contemporary (2001-2007) and nationally representative cohort of incident dialysis patients with all laboratory data. We used MSM to account for transplant censorship, modality changes over time, and time-varying laboratory measures during each calendar quarter. We hypothesized that a choice of initial dialysis modality and a decision to switch from one modality to another affects survival of incident dialysis patients.

6.3 Methods

6.3.a Dialysis Patients

We linked the databases from the United States Renal Data System (USRDS) and DaVita, Inc., a large provider of dialysis treatment in the US, using unique patient identifiers, to identify a nationally representative cohort of incident dialysis patients. Dates of dialysis initiation, death, and transplantation were collected from the USRD as well as the information about co-morbidities and employment status at baseline. The DaVita database provided all other information about the patients who received dialysis in DaVita clinics between July 1, 2001 and June 30, 2006, and was followed until June 30, 2007. The date of enrollment in a DaVita clinic, dialysis treatment data and laboratory measurements during the cohort period were also extracted. Patients with a time gap >90 days between the first dialysis initiation at the USRDS and DaVita were excluded. From the DaVita dataset we also extracted the information about the calendar quarter in which each patient entered the cohort, quarter in which he/she reached Day 90 on dialysis, and the quarter where patient died or transplanted. Laboratory measurements were extracted and averaged for up to 20 calendar quarters. Information about demographic characteristics (age, race, gender, marital status, etc.) and insurance at baseline were also obtained.

A total of 59,062 incident maintenance dialysis patients were identified in DaVita dialysis clinics during the 6-year cohort (7/2001-6/2007). Limiting the cohort to patients with no missing data on dialysis modalities and the key predictors provided a population of 49,034 including 46,253 HD and 2,781 PD patients. We finally restricted the cohort to 23,718 incident dialysis patients including 22,360 HD and 1,358 PD patients, who initiated dialysis between July 1, 2001 and June 30, 2004, so that every patient could potentially stay in the cohort for at least 8 calendar quarters (2 years) with all laboratory data, i.e. until June 30, 2006.

6.3.b Modality Switch and Informative Censorship

Using USRDS records we were able to determine the duration of dialysis treatment and a status for each patient (death, transplant, changes in dialysis modality) during each of the 20 calendar quarters even if they transferred to a non-DaVita dialysis center. Hence, we assumed no loss to follow-up, and the only informative censoring event considered was kidney transplantation. For censored patients, we added days from the concluding quarter to its preceding quarter and counted any event that occurred (death or transplantation) as occurring in the latter quarter if patient contributed less than 45 days to the last calendar quarter. This was done to make cohort quarters more commensurate to quarters used in the conventional Cox analysis where person-time and not the calendar-time was used.

6.3.c Laboratory Measures

Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to a DaVita Laboratory in Deland, Florida, within 24 hrs. All laboratory values were measured by automated and standardized methods. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, albumin, creatinine, and total iron binding capacity (TIBC), were measured monthly. Serum ferritin was measured quarterly. Hemoglobin was measured weekly to bi-weekly. Normalized protein catabolic rate (nPCR), an estimation of daily protein intake, was measured monthly.

6.3.d Statistical Analyses

We created Kaplan-Meier (KM) survival curves to compare the survival between PD and HD patients after adjusting for age, gender, race, and diabetes. We also examined survival stratifying separately on diabetes and heart failure status and adjusting for age, gender and race. Additionally we compared survival between PD and HD patients separating those who never changed the initial modality from the patients who had at least one modality change during the cohort time.

The MSM using the inverse probability weights (IPW) was employed to determine the effects of dialysis modality on mortality during the first 2 years while accounting for the switches between the modalities during this time period as well as the time spent under each modality.(11, 12) Two logistic regressions were fitted to estimate the numerator and denominator of the inverse probability of treatment weights (IPTW). We used baseline covariates to predict the probability of dialysis modality at Day 90 on dialysis for the numerator and baseline and time dependent covariates that included history of dialysis modality (and laboratory parameters in models where laboratory data were included) to predict modality at any given quarter after Day 90 during the first 2 years of dialysis treatment for the denominator. The second set was for the inverse probability of censoring weights (IPCW) to account for the informative censoring from receiving a kidney transplant. These were fit using two similar logistic models, also including dialysis modality (in both numerator and denominator) and modality at the previous quarter (denominator) as predictors of receiving kidney transplantation at any given quarter after reaching Day 90 on dialysis.

We created three different models of IPWs using increasing number of covariates for estimation. For Model 1, the IPTWs were calculated using age at baseline and modality from the prior quarter as the time-dependent predictor. For Model 2, the IPTWs were calculated using age, gender, race (non-Hispanic Whites vs. others), and diabetes at baseline; and for Model 3 same as above with addition of baseline and time-dependent measurements for serum levels of albumin and hemoglobin, since they were considered important predictors that may be associated with choice of dialysis modality as well as mortality.(13, 14). IPCW were calculated similarly as above, but person-time starting from the time of dialysis initiation and dialysis modality for each quarter were added to the models as important predictors of transplantation. We then created stabilized IPW by

combining the two weights as described elsewhere.(12) Each stabilized IPW had a mean of around 1.

We used 3 levels of adjustment for all models: (1) IPW only adjusted models, (2) in order to overcome possible residual confounding from the variables already included in the IPWs, we further adjusted for baseline variables used to estimate IPWs 3) we also added the additional variables to the 3rd level of adjustment such as marital status, employment, baseline co-morbidities (COPD, cancer, hypertension, ability to ambulate), and baseline serum levels of ferritin, calcium, phosphorus, and nPCR. These additional predictors while important predictors of mortality were not good predictors of dialysis modality or transplantation.

We used stabilized IPWs to fit Cox, Poisson and logistic regressions to estimate causal hazard rations for association between dialysis modality and mortality during the 2nd to 7th cumulative quarters after reaching Day 90 of dialysis treatment, i.e., up to 24 months from the time of dialysis initiation. We performed additional analyses where we fitted conventional Cox proportional hazard models to compare the mortality patterns with the MSMs. All descriptive and multivariate statistics were performed with the SAS, version 9.2 (SAS Institute, Inc., Cary, NC).

6.4 Results

Table 6.1 shows patients' characteristic, co-morbidities and laboratory data upon dialysis initiation across modality status on Day 90, modality switch over time and transplantation status. Out of 23,718 incident dialysis patients, 1,629 were transplanted during their first two years of dialysis therapy including 1,385 HD and 244 PD patients, resulting in transplant rates of 6% and 18%, respectively. Among the HD patients at Day 90, 6% switched modality at least once during 2 years, whereas the modality switch rate was 57% among PD patients. As shown in Table 6.1,

patients who never changed modality and did not undergo transplant were older, more likely to be diabetic or to have atherosclerotic heart disease or heart failure. Patients who changed modality but received no transplant were similar in their characteristics although somewhat younger and had lower percentage of diabetes, atherosclerosis or heart failure. Patients who were transplanted regardless of modality changes were much younger and had less co-morbidity.

Case-mix adjusted Kaplan-Meier survival analyses are shown in **Figure 6.1**. PD patients had better survival than HD patients. The pattern remained unchanged after stratification on diabetes. PD patients without heart failure had the best survival followed by HD patients without heart failure. Examining separately patients with and without modality changes, those who changed dialysis modality at least once during 2 years had better survival than patients who did not. Nevertheless, HD patients without a modality change had slightly greater survival than their PD counterparts (see Figure 6.1). Conventional (non-MSM) survival analyses to estimate death hazard ratios of PD vs. HD modality are shown in **Table 6.2** and **Figures 6.2 and 6.3**. We fitted Cox proportional hazard model over 24 months comparing mortality of PD to HD patients. In additional sensitivity analyses we also performed Poisson and logistic regressions to estimate the relative risk and odds ratios of death, respectively, and the results were similar (data not shown). Non-MSM models indicated that despite a rather prominent survival advantage of PD during the first several months, PD superiority appeared to mitigate over time, so that among patients without any modality switches no survival advantage was noticeable by the completion of the 2 year observation period.

Table 6.3 and **Figure 6.4** show estimates of death hazard ratios for PD modality (with HD as reference) in the first 2 years of dialysis treatment using MSM and taking into account changes in modality over time and the differential censorship through transplantation. In all models PD

patients showed a greater survival during the first 2 years compared to HD patients. A noticeable difference between the conventional and MSM analyses was the persistence of the survival advantage of PD over the entire 2 year period with no mitigation trend of the summary estimates over time. In the IPW with baseline variables models adjusted for time-varying laboratory measures, PD offered 48% lower mortality, i.e., a death hazard ratio of 0.52 (95% CL 0.34-0.80) in Model 3 (see Table 6.3). **Table 6.4** and **Figure 6.5** show the same MSM-estimated death hazard ratios in the cohort of incident dialysis patients but stratified by diabetes status and age (<65 vs. >=65 years). In each subgroup we used the same adjustment levels as for the models that included all patients. The IPWs were calculated using the same baseline and time-dependent predictors that were used for Model 2. As observed in the MSM analyses of the entire cohort, PD patients had lower risk of death compared to HD with survival advantage of PD persisted consistently for up to 24 months after dialysis initiation.

6.5 Discussion

Examining a contemporary cohort of 23,718 incident dialysis patients including 22,360 HD and 1,358 PD patients on Day 90 of dialysis treatment, we found that incident PD patients were younger and had less co-morbidity than their HD counterparts. PD patients were 9-times more likely to switch dialysis modality over the 2 year period than the opposite switch among incident HD patients. During the same period PD patients were 3-times more likely to receive a kidney transplant. Comparing two modalities over the first 2 years of dialysis treatment, we found that in the causal MSM models, PD offered persistently greater survival independent of the known confounders including dialysis modality switch or transplant censorship, so that a 48% lower mortality was observed by the end of 2^{nd} year . These findings may have important clinical and

policy implications, given high mortality of HD patients in general and in particular during the first 2 years and given lower costs of PD.

Our study is one of a few using relatively novel causal modeling technique known as MSM. The reason for using these models was to try to validly handle time-varying confounding and selection bias from longitudinal censoring.(15) MSM uses IPWs to control for time-dependent confounders rather than including them in the model directly.(10, 16) By creating the counterfactual population using IPWs the covariate imbalances are mitigated substantially allowing a better estimate of the causal effects. (17) Another study by Mehrotra *et al* (18) used MSM techniques, but in the said study laboratory measurements over time were not available since the data were solely based on the USRDS dataset, whereas our current study used detailed laboratory data from the DaVita cohort. Hence, we uniquely accounted for time-varying laboratory measures at several levels in Model 3. Since MSMs produce causal estimates, the results of MSM analyses can be comparable to the randomized trials.(10) Even though the Netherlands trial of 1997-2000 was stopped due to insufficient enrolment,(7) the results obtained from only 38 patients indicated that PD patients had better overall 5 year survival. Death hazard ratio for HD patients vs. PD was 3.6 (95% CL: 0.8-15.4).(7) Although the study did not have enough power to reach meaningful conclusions the results were consistent with our findings based on MSM.

Our findings indicate that PD patients had significantly and persistently lower mortality risk during the entire first 2 years after dialysis initiation despite differential censorship of kidney transplantation with much higher rate among PD patients and despite higher likelihood of modality switch among PD patients. A study by Quinn et al attributes early survival advantage of PD patients to the fact that sicker patients without nephrologist referral are more likely to initiate HD which then could account for the higher mortality among HD patients during early dialysis

treatment. (19) While we did not have a reliable data on pre-dialysis nephrologists' visits our results of MSM did not show a significantly distinct pattern of early survival advantage in the first 6 to 12 months. In most MSM analyses a trend toward even better survival of PD was observed for up to 24 months.

Our findings are partially similar and partially in contrast to a study by van der Wal *et al*(14) who also used MSM to investigate dialysis modality differentials in Europe but did not account for modality changes over time. They found that, while PD patients did better during the first 3 months of dialysis treatment, their survival advantage decreased thereafter and HD patients had better survival during the entire 2nd year. We found that PD patients tend to change dialysis modality more often in the US. Moreover, while the absolute number of PD and HD patients changing modalities is similar, since the number of patients receiving PD is much lower (<10%) censoring patients at the time of first modality change most likely have much greater effect on PD comparing to HD especially during later time periods. Similar concerns are valid for much higher rate of transplantation among PD patients in the first 2 years, which practically deplete the PD cohort of its healthiest patients who would have otherwise survived much longer than the remainder of the cohort. Since persons who changed modalities or who underwent transplantation had significantly better survival comparing to those who did not, then naturally no advantage of PD could be detected if patients were censored at the time of switch or transplantation. Indeed we found that in non-MSM survival analyses PD patient survival was significantly less or even reversed by the end of the 2 years (Figures 6.1-6.3 and Table 6.2), whereas in MSM that effectively account for time-varying confounders a persistent PD survival was evident (Figures 6.4 and 6.5 and Tables 6.3 and 6.4). Comparing the results from MSMs to the conventional Cox models we observed that while the confidence limits largely overlapped, the survival differential of

PD increased slightly with vintage in MSMs was not evident in conventional analysis. This is not surprising given the ability of MSM to handle time-varying confounding and censoring unlike conventional analyses. A review article by Suarez *et al*(17) examined the publications in which MSM and conventional analysis were used and found that in 40% of the analyses the estimates differed by at least 40% and in 11% of the analyses the opposite results were reported when MSM vs. conventional models were compared.

Our findings also indicate that changes in modality during the first 2 years of dialysis may affect the survival patterns over time. Often a switch from PD to HD relates to the technique failure, while problems with vascular access, higher risk of cardio-vascular disease or personal preference are commonly cited when HD patients switch to PD.(20) In our study patients with the same transplantation status had similar characteristics regardless whether or not they changed an initial modality (Table 6.1). Therefore any differences in survival between the two modality groups can mostly be attributed to the changes in modality over the time of follow-up. This may indicate that change of dialysis modality may be considered as a practical option if a patient does not show improvement or becomes sicker over time. It is also consistent with the previously reported findings that patents who initiate dialysis with PD tend to do better in the first 24 months and especially during the first 3-6 months. (21)

Our study should be qualified for its observational, non-randomized, nature that is threatened by uncontrolled confounding (especially confounding by indication in this case), measurement errors and selection bias. We did not examine survival beyond 24 months after dialysis initiation. The strengths of our study include the contemporary cohort of dialysis patients from the entire US, inclusion of detailed laboratory measures that were processed in a single laboratory center, the statistical process of accounting for time-varying modality changes and

transplant censorship by using MSM , and detailed comparisons between the conventional models (including Cox, Poisson and propensity matched analyses) and novel MSM techniques.

6.6 Conclusion

Comparing survival of PD and HD among 23,718 incident dialysis patients during their first 2 years of dialysis treatment in contemporary (2001-2006) and nationally representative cohort using statistical techniques that accounts for time-varying confounding and differential censorships, we found that incident PD patients had 48% greater survival independent of known confounders. These findings, if further confirmed, may have important implications for the choice of dialysis modality and resource allocations in renal replacement therapy programs. Further research is needed to examine the effect of modality and its changes on the survival of dialysis patients over a longer time period.

6.7 Tables for Chapter 6

Table 6.1. Characteristics of 23,718 incident dialysis patients according to modality status at Day 90, modality switches over the first 2 years, and transplant status (Trp) in DaVita dialysis clinics from July 1, 2001 through June 30, 2006

Modality at Day 90	**Incident HD patients (n=22,360)**				**Incident PD patients (n=1,358)**			
Modality Switch Status	**Always HD**		**Switched HD to PD**		**Always PD**		**Switched PD to HD**	
Transplanted (Trp)	**not Trp**	**Trp**	**not Trp**	**Trp**	**not Trp**	**Trp**	**not Trp**	**Trp**
N	*N=19,884*	*N=1,292*	*N=1,091*	*N=93*	*N=419*	*N=167*	*N=695*	*N=77*
Age	64±15	48±14	55±15	44±15*	62±15	47±13	57±15	48±15*
Gender (% women)	46%	38%	43%	40%	48%	47%	47%	43%
Diabetes mellitus (%)	64%	43%	52%*	39%	59%	36%	57%	48%*
Race (%)								
Non-Hispanic White	43%	51%	51%	52%*	56%	64%	47%	56%*
Black	30%	19%	25%	20%*	16%	16%	23%	22%*
Hispanic	18%	18%	13%	14%*	13%	8.4%	18%	17%*
Asian	3%	5%	5%	11%*	7%	6%	5%	5%
Employment status (%)								
Retired	56%	25%	43%	24%*	56%	13%	43%	29%*
Employed	14%	49%	30%	43%*	26%	72%	36%	47%*
Unemployed	29%	26%	28%	33%*	18%	14%	20%	25%
Primary insurance (%)								
Medicare	63%	34%	53%	45%*	46%	22%	51%	39%*
Medicaid	7.6%	4.3%	5.3%	7.1%*	2.9%	1.3%	4.5%	1.3%*
Other	30%	62%	42%	49%*	52%	77%	44%	61%
Marital Status (%)								
Married	47%	60%	53%	59%*	66%	72%	61%	59%
Divorced	7.8%	7.3%	7.4%	6.4%	7.4%	6.0%	6.6%	4.3%
Single	27%	30%	28%	29%	15%	20%	22%	27%
Widowed	18%	2.8%	11%	4.3%*	11%	2.0%	10%	8.5%*
Comorbidities (%)								
AIDS	0.6%	0.1%	0.5%	0.1%	0.8%	0.1%	0.8%	0.1%
Atherosclerotic Heart	24%	10%	21%	16%*	23%	4%	17%	5%
Cancer	5%	2%	5%	3%*	4%	2%	4%	1%
Heart Failure	31%	12%	23%	8%*	21%	5%	17%	12%*

Modality at Day 90	**Incident HD patients (n=22,360)**				**Incident PD patients (n=1,358)**			
Modality Switch Status	**Always HD**		**Switched HD to PD**		**Always PD**		**Switched PD to HD**	
Transplanted (Trp)	**not Trp**	**Trp**	**not Trp**	**Trp**	**not Trp**	**Trp**	**not Trp**	**Trp**
N	*N=19,884*	*N=1,292*	*N=1,091*	*N=93*	*N=419*	*N=167*	*N=695*	*N=77*
COPD	7%	2%	5%	2%*	4%	0.6%	4%	1%
Cerebro-vascular	8%	2%	5%	2%*	7%	3%	6%	6%
HIV	0.9%	0.1%	2%	0.1%*	2%	0.1%	0.3%	0.1%
Hypertension	79%	79%	79%	76%	80%	75%	84%	79%
Non-ambulatory	4%	0.4%	2%	0.1%*	2%	0.1%	0.4%	1%
Other Heart Diseases	5%	2%	4%	0.1%*	6%	2%	3%	1%
PVD	13%	4%	10%	3%*	12%	4%	10.%	3%*
Smoker	5%	4%	5%	2%	4%	3%	6%	7%
BMI (kg/m2)	26.7±7.3	26.4±5.8	27.4±6.5	25.8±5.6*	26.3±5.6	25.6±3.7	26.8±6.1	27.5±6.9
Laboratory data								
nPCR (g/kg/day)	0.93±0.25	0.98±0.2	0.91±0.3	0.93±0.2*	0.80±0.3	0.88±0.2	0.91±0.3	0.74±0.3
albumin (g/dL)	3.6±0.5	3.8±0.4	3.7±0.5	3.9±0.4*	3.4±0.5	3.8±0.4	3.5±0.6	3.7±0.5*
creatinine (mg/dL)	6.8±2.7	9.1±3.0	7.4±3.2	9.1±3.7*	6.5±2.6	7.7±2.7	7.1±3.0	8.0±2.9*
ferritin (ng/mL)	361±409	270±261	343±422	277±233*	302±331	207±235	257±288	232±330 *
TIBC (mg/dL)	213±46	227±43	224±48	236±40*	243±52	257±47	247±49	250±49*
calcium(mg/ dL)	9.1±0.7	9.3±0.7	9.2±0.7	9.3±0.6*	9.1±0.7	9.3±0.7	9.1±0.7	9.5±0.8*
phosphorous (mg/dl)	5.4±1.4	5.9±1.3	5.5±1.5	5.6±1.2*	4.9±1.2	5.1±1.2	5.0±1.3	5.3±1.2*
intact PTH (pg/ml)	302±288	327±312	316±312	332±262*	301±256	348±331	369±318	381±384 *
hemoglobin (g/dL)	12.1±1.4	12.4±1.4	12.2±1.5	12.3±1.2*	12.3±1.5	12.6±1.4	12.3±1.4	12.6±1.4 *
WBC (x103/□l)	7.7±2.5	7.3±2.1	7.7±2.5	7.1±2.0*	7.9±3.5	7.2±2.1	7.4±2.3	7.6±2.3*
lymphocyte (%WBC)	20±7.6	22±7.6	20±7.5	21±7.0*	19±7.3	20±7.4	20±7.3	23±7.7*

p-values were calculated separately for HD and PD modalities;

p-values <0.05 are marked with *

Table 6.2. Death hazard ratios (HR) for dialysis modality (PD vs. HD) in incident dialysis patients using Cox analysis (n=23,718)

Survival period	Unadjusted	Adjusted for IPW predictors	Fully adjusted
Unmatched survival analyses			
9 months (2 qtrs)	0.43 *(0.33-0.53)*	0.52 *(0.41-0.66)*	0.58 *(0.48-0.73)*
12 months (3 qtrs)	0.45 *(0.37-0.54)*	0.56 *(0.41-0.67)*	0.62 *(0.51-0.75)*
15 months (4 qtrs)	0.54 *(0.44-0.60)*	0.63 *(0.54-0.74)*	0.70 *(0.59-0.62)*
18 months (5 qtrs)	0.56 *(0.49-0.65)*	0.69 *(0.60-0.79)*	0.75 *(0.65-0.87)*
21 months (6 qtrs)	0.61 *(0.54-0.70)*	0.75 *(0.66-0.85)*	0.81 *(0.71-0.92)*
24 months (7 qtrs)	0.61 *(0.54-0.69)*	0.75 *(0.66-0.84)*	0.81 *(0.72-0.92)*

*Months show time from dialysis initiation while quarters count starts from the quarter when patient reaches day 90 of dialysis treatment; ** All p values were less than 0.05

Table 6.3. Death hazard ratios (HR) for dialysis modality (PD vs. HD) in 23,718 incident dialysis patients using MSM taking into account changes in dialysis modality and transplant censorship in the first 2 years

	Death hazard ratios (HR) using MSM		
Survival period	**IPW adjusted**	**Doubly Robust (DR)**	**DR, plus additional adjusters**
Model 1			
9 months (2 qtrs)*	0.40 *(0.31-0.51)*	0.51 *(0.40-0.65)*	0.58 *(0.45-0.75)*
12 months (3 qtrs)	0.49 *(0.40-0.61)*	0.63 *(0.51-0.78)*	0.72 *(0.58-0.90)*
15 months (4 qtrs)	0.42 *(0.30-0.58)*	0.54 *(0.38-0.77)*	0.64 *(0.48-0.87)*
18 months (5 qtrs)	0.38 *(0.26-0.56)*	0.46 *(0.30-0.72)*	0.53 *(0.36-0.80)*
21 months (6 qtrs)	0.38 *(0.24-0.60)*	0.44 *(0.26-0.75)*	0.50 *(0.31-0.80)*
24 months (7 qtrs)	0.25 *(0.14-0.47)*	0.34 *(0.20-0.59)*	0.41 *(0.21-0.68)*
Model 2			
9 months (2 qtrs)	0.39 *(0.30-0.49)*	0.48 *(0.39-0.61)*	0.56 *(0.44-0.71)*
12 months (3 qtrs)	0.46 *(0.38-0.57)*	0.59 *(0.48-0.72)*	0.68 *(0.56-0.84)*
15 months (4 qtrs)	0.40 *(0.30-0.54)*	0.50 *(0.36-0.70)*	0.61 *(0.46-0.81)*
18 months (5 qtrs)	0.35 *(0.25-0.50)*	0.42 *(0.27-0.64)*	0.50 *(0.35-0.73)*
21 months (6 qtrs)	0.35 *(0.24-0.52)*	0.40 *(0.24-0.66)*	0.48 *(0.31-0.75)*
24 months (7 qtrs)	0.23 *(0.11-0.45)*	0.32 *(0.18-0.55)*	0.40 *(0.25-0.64)*
Model 3			
9 months (2 qtrs)	0.35 *(0.26-0.37)*	0.42 *(0.30-0.56)*	0.44 *(0.32-0.61)*
12 months (3 qtrs)	0.43 *(0.33-0.57)*	0.54 *(0.40-0.71)*	0.59 *(0.44-0.78)*
15 months (4 qtrs)	0.39 *(0.29-0.52)*	0.50 *(0.38-0.67)*	0.55 *(0.45-0.74)*
18 months (5 qtrs)	0.43 *(0.30-0.61)*	0.57 *(0.40-0.82)*	0.61 *(0.43-0.86)*
21 months (6 qtrs)	0.45 *(0.30-0.68)*	0.60 *(0.40-0.90)*	0.61 *(0.42-0.89)*
24 months (7 qtrs)	0.37 *(0.21-0.64)*	0.53 *(0.33-0.84)*	0.52 *(0.34-0.80)*

*Months show time from dialysis initiation while quarters count starts from the quarter when patient reaches day 90 of dialysis treatment; ** All p values were <0.05

Model 1: (age, baseline modality; time dependent modality (TD); stabilized IPW mean=1.06)

Model 2: (age, sex, race, DM baseline modality; time dependent modality; stabilized IPW mean=1.06)

Model 3: (IPW: age, sex, race, DM baseline modality, Alb, Hgb; TD modality, Alb, Hgb; stabilized IPW mean=1.29)

Model 1: IPTWs were calculated using age at baseline and modality from the prior quarter as the time-dependent predictor

Model 2: IPTWs were calculated using age, gender, race (non-Hispanic Whites vs. others), and diabetes at baseline

Model 3: Same as above with addition of baseline and time-dependent measurements for serum levels of albumin and hemoglobin.

IPCW were calculated similarly as above but person-time starting from the time of dialysis initiation and dialysis modality for each quarter was added to the models because they were important predictors of transplantation.

Table 6. 4. Death hazard ratios (HR) for dialysis modality (PD vs. HD) in 23,718 incident dialysis patients using MSM taking into account changes in dialysis modality and transplant censorship in the first 2 years stratifying on diabetes status and age

	Death hazard ratios (HR) using MSM		
Survival period	**IPW adjusted**	**Doubly Robust (DR)**	**DR, plus additional adjusters**
With Diabetes, N=14,539 (mean for stabilized IPWs= 1.07)			
9 months (2 qtrs)	0.48 *(0.36-0.65)*	0.56 *(0.42-0.76)*	0.62 *(0.48-0.84)*
12 months (3 qtrs)	0.61 *(0.47-0.79)*	0.73 *(0.57-0.94)*	0.81 *(0.63-1.05)*
15 months (4 qtrs)	0.47 *(0.33-0.66)*	0.55 *(0.37-0.83)*	0.66 *(0.47-0.92)*
18 months (5 qtrs)	0.37 *(0.24-0.58)*	0.38 *(0.21-0.58)*	0.46 *(0.26-0.77)*
21 months (6 qtrs)	0.37 *(0.22-0.61)*	0.34*(0.17-0.70)*	0.43 *(0.24-0.79)*
24 months (7 qtrs)	0.26 *(0.14-0.47)*	0.27 *(0.13-0.54)*	0.34 *(0.18-0.63)*
Without Diabetes, N=9,179 (mean for stabilized IPW= 0.97)			
9 months (2 qtrs)	0.29 *(0.20-0.43)*	0.39 *(0.26-0.58)*	0.49 *(0.33-0.72)*
12 months (3 qtrs)	0.31 *(0.21-0.43)*	0.42 *(0.29-0.60)*	0.51 *(0.36-0.74)*
15 months (4 qtrs)	0.38 *(0.27-0.54)*	0.50 *(0.35-0.73)*	0.60 *(0.41-0.88)*
18 months (5 qtrs)	0.38 *(0.28-0.52)*	0.52 *(0.37-0.72)*	0.60 *(0.43-0.85)*
21 months (6 qtrs)	0.39 *(0.29-0.51)*	0.52 *(0.39-0.71)*	0.62 *(0.45-0.84)*
24 months (7qtrs)	0.38 *(0.29-0.51)*	0.54 *(0.40-0.72)*	0.64 *(0.47-0.87)*
Age <=65 years, N=12,257 (mean for stabilized IPW=1.02)			
9 months (2 qtrs)	0.46 *(0.32-0.67)*	0.46 *(0.32-0.67)*	0.58 *(0.43-0.78)*
12 months (3 qtrs)	0.55 *(0.44-0.74)*	0.56 *(0.41-0.76)*	0.67 *(0.50-0.92)*
15 months (4 qtrs)	0.50 *(0.36-0.68)*	0.52 *(0.39-0.69)*	0.63 *(0.48-0.83)*
18 months (5 qtrs)	0.50 *(0.38-0.67)*	0.51 *(0.38-0.68)*	0.62 *(0.48-0.63)*
21 months (6 qtrs)	0.52 *(0.39-0.68)*	0.52 *(0.39-0.70)*	0.69 *(0.49-0.84)*
24 months (7 qtrs)	0.40 *(0.23-0.68)*	0.45 *(0.31-0.65)*	0.58 *(0.43-0.79)*
Age > 65years, N=11,445 (mean for stabilized IPWs=1.07)			
9 months (2 qtrs)	0.43 *(0.35-0.69)*	0.47 *(0.34-0.64)*	0.54 *(0.39-0.73)*
12 months (3 qtrs)	0.55 *(0.31-0.74)*	0.60 *(0.43-0.81)*	0.68 *(0.51-0.92)*
15 months (4 qtrs)	0.42 *(0.22-0.80)*	0.48 *(0.27-0.65)*	0.59 *(0.37-0.94)*
18 months (5 qtrs)	0.29 *(0.13-0.63)*	0.33 *(0.16-0.68)*	0.39 *(0.20-0.75)*
21 months (6 qtrs)	0.26 *(0.11-0.62)*	0.29 *(0.12-0.68)*	0.34 *(0.15-0.75)*
24 months (7 qtrs)	0.20 *(0.08-0.50)*	0.23 *(0.09-0.55)*	0.27 *(0.12-0.61)*

*Months show time from dialysis initiation while quarters count starts from the quarter when patient reaches day 90 of dialysis treatment;

** All p values were less than 0.05

Model 1 (age, sex, race, DM baseline modality; time dependent modality)

6.8 Figures for Chapter 6

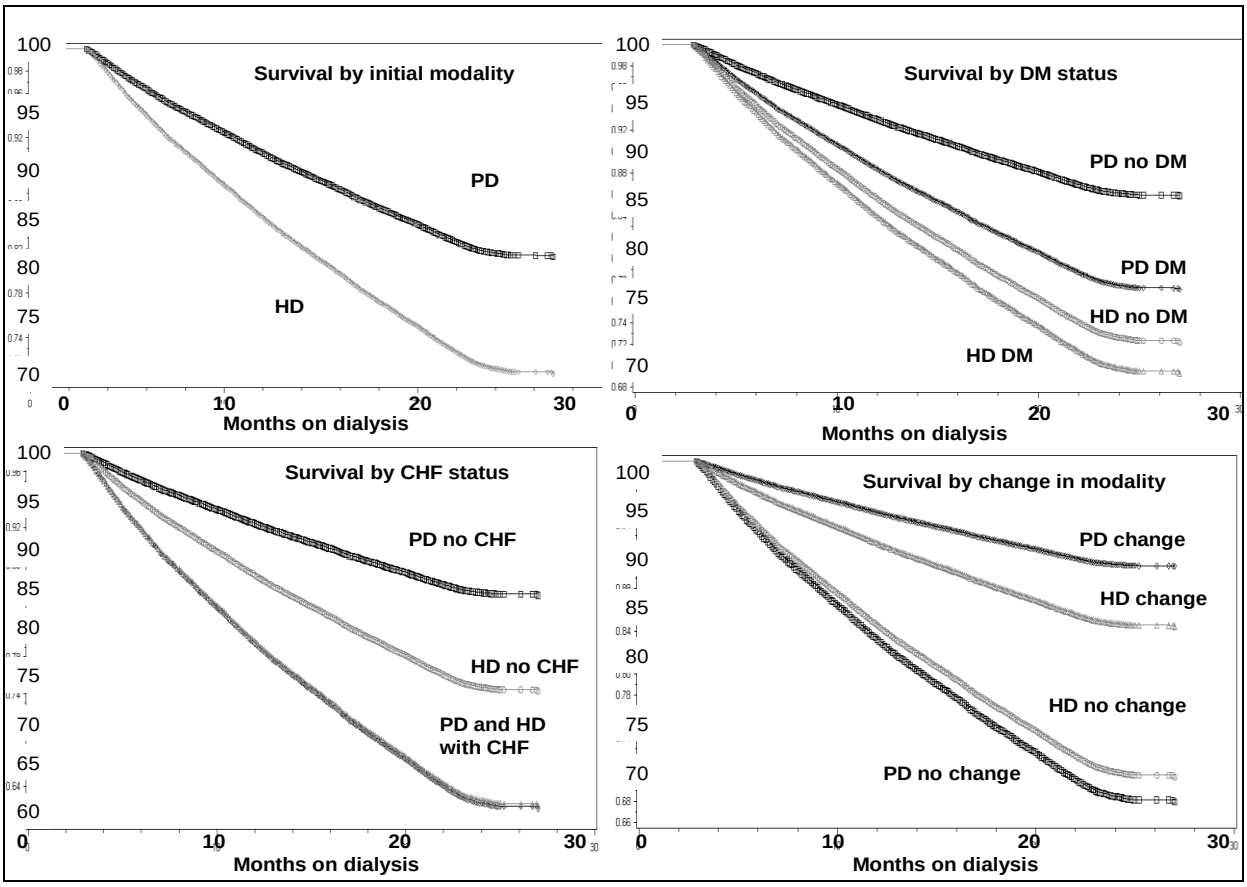

Figure 6.1. Kaplan-Meier survival curves adjusted for age, gender, race, and diabetes examining survival among PD and HD patients (modality is defined on Day 90) for incident dialysis patients, 7/2001-6/2006, n=23,718.

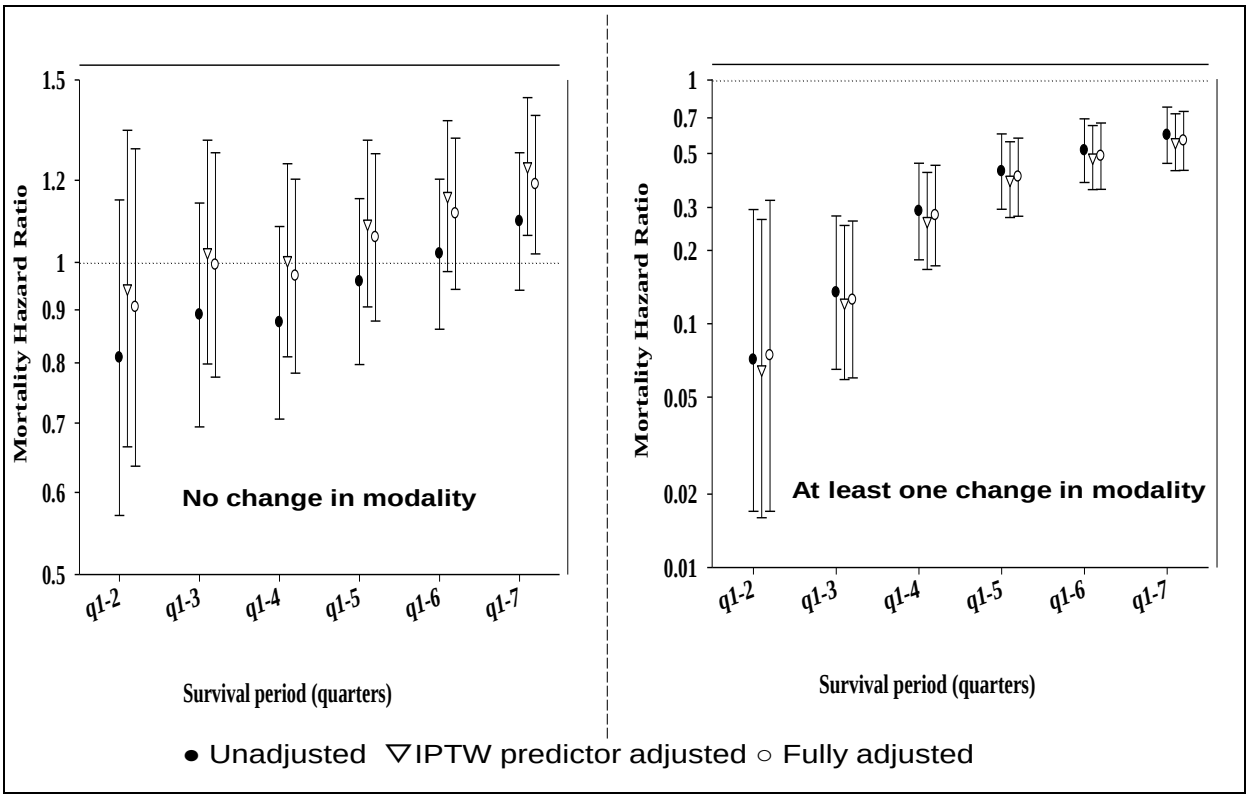

Figure 6.2. Cox model estimated associations between dialysis modality (PD vs. HD) and mortality among incident dialysis patients who never changed modalities (n=21,762, Left panel) and patients with at least one modality change over 2 years (n=1,956, Right panel)

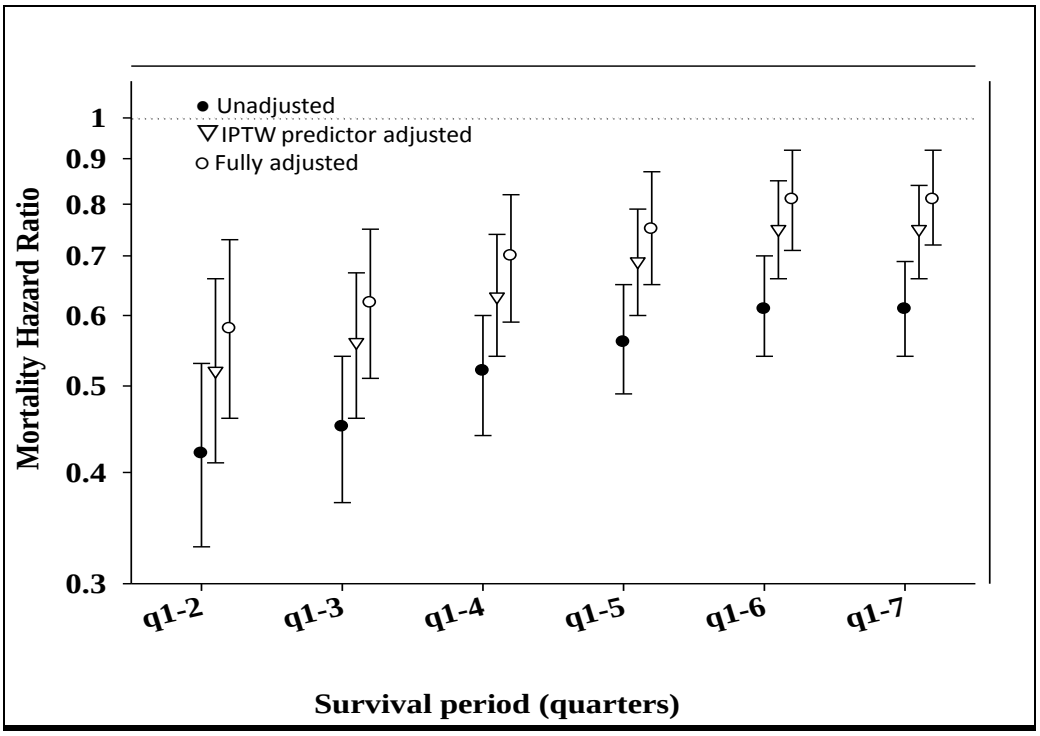

Figure 6.3. Death hazard ratios (HR) for dialysis modality (PD vs. HD) in incident dialysis patients using Cox models (n=23,718)

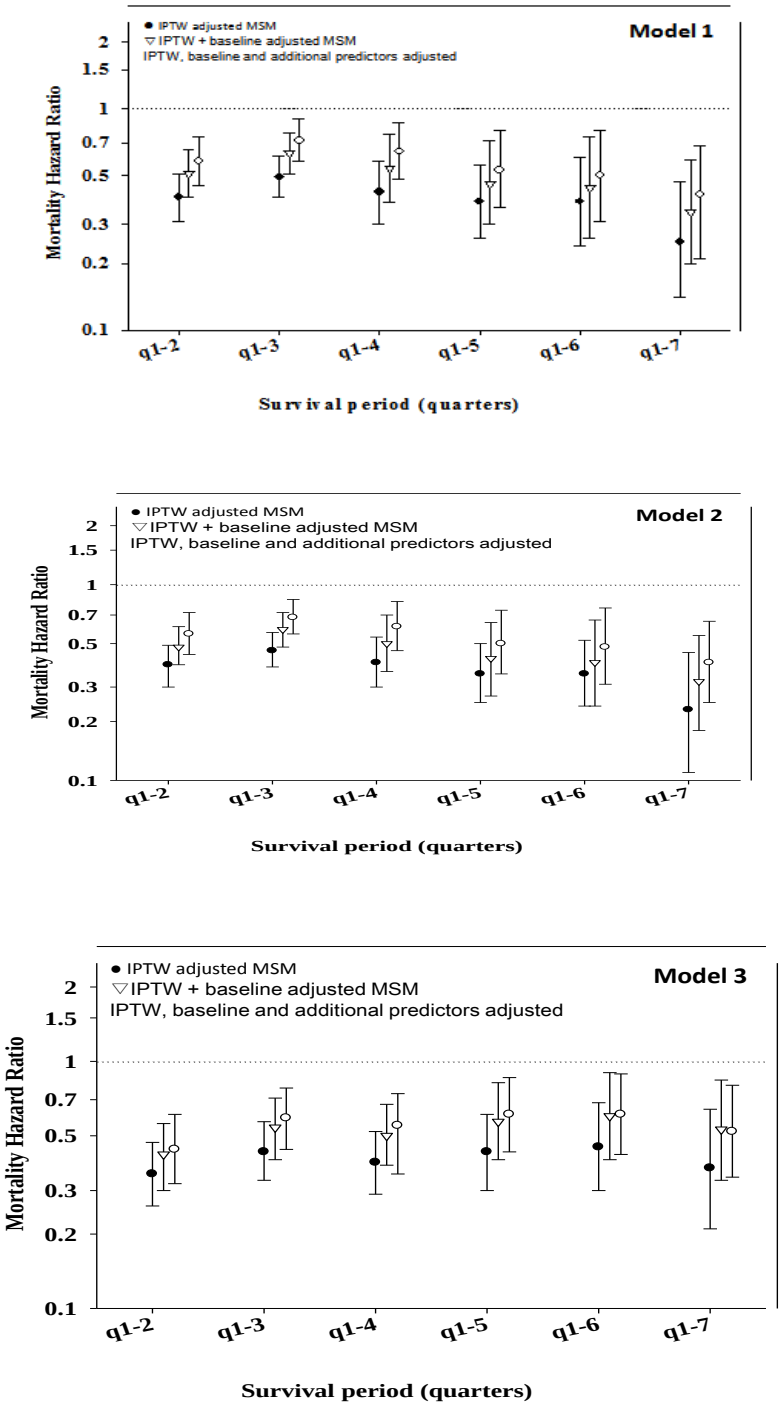

Figure 6.4. Death hazard ratios (HR) for dialysis modality (PD vs. HD) in 23,718 incident dialysis patients using MSM taking into account changes in dialysis modality and transplant censorship in the first 2 year

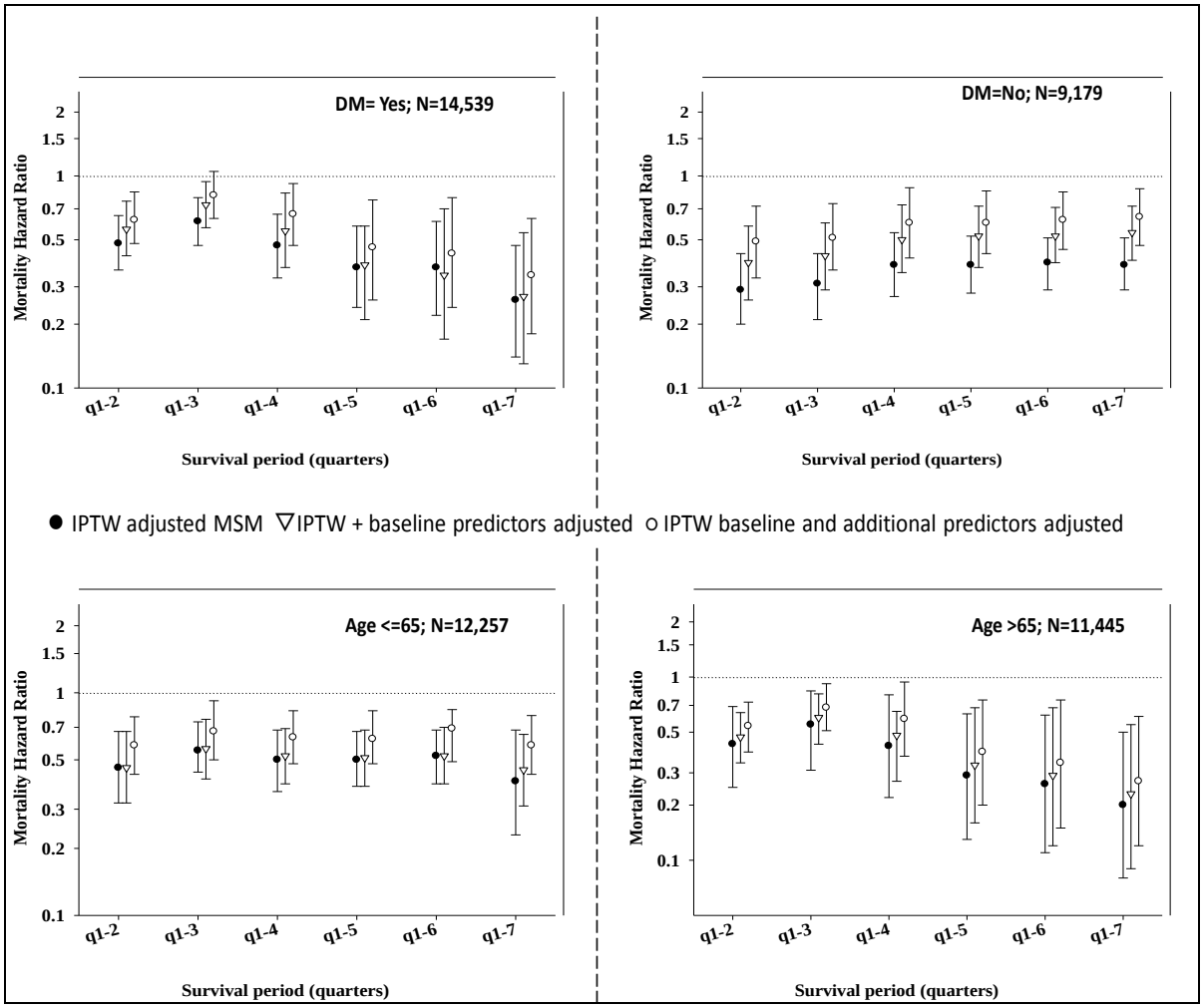

Figure 6.5. Death hazard ratios (HR) for dialysis modality (PD vs. HD) in 23,718 incident dialysis patients using MSM taking into account changes in dialysis modality and transplant censorship in the first 2 years stratifying on diabetes status and age

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Chapter 7 Concluding remarks

This study examined mortality in dialysis patients during the first 24 months after initiation of dialysis therapy in a contemporary cohort of dialysis patients from the entire US. The strengths of the study were inclusion of detailed laboratory measures that were processed in a single laboratory center, the statistical process of accounting for time-varying modality changes and transplant censorship by using MSM, and detailed comparisons between the conventional models (including Cox and Poisson) and novel methods.

Mortality was highest among hemodialysis patients during the first 1-4 months with Standardized Mortality Ratios 1.81 (1.74-1.88), 1.79 (1.72-1.86) during the first two months on dialysis. Use of central venous catheters at baseline was associated with both cardio-vascular and infectious disease mortality as was low serum albumin level. However, the associations for those two predictors were much stronger for infection related deaths compared to CV mortality, while CHF was associated with high CV mortality especially during first several months after dialysis initiation.

Use of CVC as vascular access and hypoalbuminemia <3.5 mg/dL at the time of dialysis initiation each explain over 30% of all deaths in the first 90 days. Hence, replacing or avoiding CVC and improving hypolabuminemia could theoretically decrease the number of deaths shortly after dialysis initiation by 30%.

In addition, low quarterly serum albumin levels as well as a decline in serum level of albumin over 0.2g/dl from the prior quarter were strongly associated with increase in all-cause mortality in incident hemodialysis patients during the first 24 months of dialysis. Quarterly

serum levels of nPCR lower than 1g/kg/day were also associated with increased risk of death except for the first 3 months of treatment. Both albumin and nPCR were strong predictors of mortality independently of each other. A decrease in nPCR over 0.2g/kg/day was predictive of higher mortality as well.

The only period at which an increase in nPCR level showed beneficial effect was from a first to a second quarter. After that positive change in nPCR over 0.2g/kg/day was not predictive of better survival in hemodialysis patients. Moreover, an abrupt increase of 0.2g/kg/day or higher in serum level of nPCR after 21 months of dialysis treatment was associated with higher risk of death and could be an indicator of protein energy wasting (PEW). Therefore, such an increase should be viewed with caution especially if loss of weight and decline in serum creatine occurs simultaneously. This should be especially carefully monitored in patients with rapid decline in serum albumin level combined with increase in nPCR. Dietary modifications such as increasing daily protein intake in this patient group may be necessary. Recommendations of maintaining a daily protein intake of 1-1.2 g/kg/day after initiation of dialysis treatment could be beneficial to all hemodialysis patients but especially to those with signs of PEW.

Choice of dialysis modality also seemed to play an important role in the 2 year survival of incident patients. Comparing the survival of PD and HD among incident dialysis patients during their first 24 months of dialysis treatment showed that incident PD patients had 48% greater survival independent of known confounders. These findings, if further confirmed, may have important implications on the choice of dialysis modality and resource allocations in renal replacement therapy programs. Additional findings indicated that patients who switched dialysis

modalities at least once had better survival compared to those who never did. Therefore, it may be desirable to switch modality in patients who do not show improvement over time.