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Depression and Non-adherence Predict Mortality in Hemodialysis Treated ESRD Patients

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Abstract

Background—The scientific evaluation of depression's impact on mortality in HD patients has yielded mixed results, with the more recent, more rigorous studies detecting a significant relationship.

Method—In this study 130 HD patients from an urban North American hospital were evaluated for depressive affect and then observed for up to 5 years.

Results—In a corrected Cox regression model, that held constant age, gender, dialysis vintage, illness severity and diabetic status, depressive affect emerged as a modest but significant predictor of mortality (relative risk = 1.05, 95% CI 1.01 – 1.08). When the subjects were divided according to depressive affect severity, those with severe depressive affect had significantly shorter time to death (beta = .452, p = .044). In a sub-group of 85 subjects, self-reported medication adherence was also predictive of mortality, with higher rates of non-adherence being associated with increased mortality risk.

Conclusion—This paper lends support to the burgeoning literature on depression and reduced survival in HD populations, as well as begins the investigation of understanding the underlying mechanisms.

Keywords

Epidemiology; Survival; Depression

Depression has been identified as the most common psychiatric comorbidity in patients with end stage renal disease (ESRD) (1), with its' prevalence estimated at 20% to 30% (2). Depression has been associated with adverse medical outcomes, including mortality, for a variety of illnesses including cardiovascular disease (CVD) (3,4), diabetes (5–7), and cancer (8). Given the high prevalence of depression and its potential impact on health outcomes, researchers have looked at depression's impact on survival in the ESRD population.

Investigations of the association between depression and mortality in ESRD patients receiving renal replacement therapy have produced mixed results (9). Early studies provided preliminary evidence that depression significantly predicts survival in hemodialysis (HD) patients, but these studies contained methodological limitations such as inadequate measurement of the construct and unrefined statistical analyses (10,11). Other studies failed to demonstrate an effect of depression on all-cause mortality in ESRD patients even when

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utilizing more valid measures of depression and more advanced statistical strategies that controlled for physical and demographic determinants of survival (12–14).

More recently evidence has begun to accumulate to suggest that time-varying measurement of depression may better predict survival than a single assessment. Kimmel Peterson and Weihs et al. (15) were the first to demonstrate that persistent depressive affect is a risk factor for mortality in hemodialysis patients. In this study, Kimmel et al. (15) found that baseline depressive affect was not sufficient to predict mortality in a fairly large sample of HD patients, however, repeated measurements of depressive affect did predict survival in a time-varying model adjusted for illness co-morbidity and severity. These important results have since been replicated in larger samples using both self-report and structured physician interviews as means of assessing depressive affect and depression diagnosis (16, 17). The findings have also been extended to more specifically predict cardiovascular disease events as well as all-cause mortality while controlling for a wide range of covariates (18).

While it appears that the duration of depression may affect survival in patients with ESRD, the impact of the severity of depression remains unclear. Early evidence suggests that severity of depression significantly predicts adverse health outcomes, with more severe depression being associated with increased risk for first hospitalization (19) and death (15). Given the ubiquity of untreated depression in the ESRD population and the gravity of the potential implications, further exploration is warranted to identify levels of depression that influence survival.

The impact of depression on survival may be mediated by various psychological and physiological factors. Treatment non-adherence represents one potential pathway through which depression may affect mortality in patients with late stage kidney disease. Depressive symptoms of low motivation, impaired concentration, and apathy can significantly interfere with patients' adherence to treatment for ESRD. Studies (20, 21) have indicated a relationship between depressive affect and both laboratory and behavioral markers of poor compliance in dialysis patients. Decreased behavioral compliance with the dialysis prescription has been correlated with increased depressive affect in prevalent hemodialysis patients (22, 23, 24, 25, 26). This supporting data is suggestive of a mediational model in which treatment non-adherence partially explains the association between depression and mortality.

In the current study, we explored the relationship between depressive affect and survival in a controlled, time-varying analysis. We examined the impact of depressive affect severity on mortality by dividing our sample into mild, moderate and severely depressed categories. Furthermore, as the relationship between depressive affect and mortality has been hypothesized to have various direct and indirect pathways including lack of self-care, we also tested whether self-reported medication adherence plays a predictive role in HD survival (2). It is possible that depressed mood leads to lack of adherence with specific aspects of the dialysis prescription, which may be the cause of the decreased survival.

Method

Participants

Participants were recruited from the dialysis center of Downstate Medical Center in Brooklyn, New York from 2005 to 2007. The study was approved by the institutional review board. Dialysis patients were approached while receiving HD. To be included in the study individuals had to be a hemodialysis patient for more than 3 months, over the age of 18, and have sufficient English fluency and eyesight to complete the questionnaires. Patients who expressed an interest in participating were informed about the study and then provided

informed consent. Participants were given a packet of paper and pencil questionnaires regarding their current psychological functioning and other demographic information. A portion of this sample was described earlier (1), in which 85 patients in the dialysis center were approached with 73 agreeing to participate; 70 of these 73 completed the assessment. No data are available on the other 11 people who refused to participate. Two of the three who did not complete the assessment had been hospitalized. Following this initial wave, an additional ninety-seven dialysis patients were approached, 85 of whom completed the measures with informed consent, as part of larger study exploring the role of coping styles in HD patients. Of the second wave participants, 25 had already participated in Time 1, and were therefore excluded from these analyses. In total, 130 unique hemodialysis subjects were included.

Measures

The Beck Depression Inventory-II (BDI) is a 21-item self-report instrument with high scores (range 0–63) reflecting the presence and severity of depressed mood. It is a reliable and well-validated measure of depressive symptomatology in both clinical and nonclinical samples (20). The BDI has been used extensively in ESRD populations (14, 15, 21–23).

The Medication Therapy Adherence Scale (ITAS-M) is a modified version of the Immunosuppressive Adherence Scale (24), which is a valid and reliable instrument that measures patients' self-reported adherence to medication. The only modification we used was to expand the phrasing to refer to all medications, not simply immunosuppressive medications. The ITAS-M assesses how often individuals forget to take their medication as well as their carelessness with taking their medication in the past 3 months. There are four questions measuring adherence, each scored by percentages of non-adherence. Higher score reflect greater adherence. The ITAS has been shown to have acceptable reliability and validity in organ donation (24) and has been used in HD populations (25).

Age, disease severity (2 or more hospitalizations in the last year) and the presence of diabetes mellitus were extracted from medical records. Additionally, the nearest laboratory data following assessment were recorded including urea reduction ratio (URR), serum albumin and calcium phosphate product (CaPh). These laboratory values were selected because they are standard measures of dialysis adequacy and nutritional status and they are easily collected at each dialysis session.

The survival time for each patient was determined by the number of days between that individual's study evaluation and the end of the study observation period or date of death. Survival status was confirmed using the Social Security Death Index for each patient enrolled in the study. The Social Security Death Index is a database of death records created by the United States Social Security Administration.

Data Analysis

T-tests and chi-square analyses were used to compare baseline differences between those who survived the observation period and those who died. Cox proportional hazards regression was performed to predict the mortality hazard associated with baseline level of depressive affect, controlling for the effects of variation in age, time on dialysis, gender, illness severity and diabetic status. Relative risk was also calculated. The instantaneous relative risk of an event, at a given time, compares the likelihood for an individual with an increase of 1 in the value of the covariate compared with another individual, given both individuals are the same on all other covariates.

Survival analyses were then conducted using Cox's proportional hazards regression models. Survival statistics were calculated with SPSS 18.0 (SPSS, Chicago 2010). Cumulative survival estimates were plotted against time for three levels of depression: BDI levels less than 15 (no/mild symptoms), 15 to 24 (moderate levels), and 24 or greater (severe levels).

In a related analysis, in which the relationship between non-adherence and survival was examined, the same Cox regression model used for the BDI was utilized. However, adherence was substituted for depressive affect in the third step. The alpha level of tests of survival was 0.05. For the final analysis a modified Cox regression model was used to assess the mediating effect of non-adherence on the relationship between depressive affect and survival. In this modified model, age and diabetic status were entered in the first step, depressive affect was entered in the second step and adherence was entered in the final step.

Results

In the full sample, 130 hemodialysis patients were followed from 33 to 60 months after initial evaluation. By the end of the observation period, 38 subjects (29%) had died. Baseline descriptives of the population can be found in Table 1. The sample was 58% female and the average age was 57 ± 13.6 years. The sample was 84% African/Caribbean American and 48% had been born in this country. The average length of time on hemodialysis was 54 ± 54 months. Laboratory values were within target parameters. Mean depression score, as measured by the Beck Depression Inventory, was 12.6 ± 10.2 , suggesting non-clinical elevation in depressed mood.

Few baseline characteristics differed significantly in a simple comparison of those who died over the course of the observation period to those that survived. Gender (chi-square = .564), length of time on dialysis ($p=.565$), URR ($p=.692$), CaPh ($p=.426$), Albumin ($p=.642$), and BDI ($p=.124$) scores were all not significantly different. Only age ($t(129) = 4.34, p<.000$) and diabetic status (chi-square = 11.17, $p=.002$) were significantly different at baseline with older subjects and diabetics being more likely to die.

To examine the relationship between depressive affect and time to death, a Cox regression analysis was utilized. Subject's age and gender (step 1), dialysis vintage, diabetic status, and disease severity (step 2) were held constant, while the relationship between depressive affect (step 3) and mortality was explored. Subject's age emerged as a significant predictor of mortality ($\beta = .058, p < .001$) while gender was non-significant ($\beta = -.142, p=.674$). Dialysis vintage ($\beta = .003, p=.286$) disease severity ($\beta = -.035, p=.921$) and diabetic status ($\beta = -.681, p=.055$) were all not significant. Depression score emerged as being a significant predictor ($\beta = .043, p=.020$) of mortality. The relative risk for depression was 1.05 (95% CI 1.01 – 1.08).

In a follow-up analysis, subjects were divided into depression severity categories. Subjects ($n=76$) with no/mild depression (scoring below a 15 on the BDI) were placed in one group, subjects ($n=42$) with moderate depression (15–24 on the BDI) were in a second category and subjects ($n=16$) with severe depression (>24 on the BDI) were in the third category. A similar Cox regression was run in which age, dialysis vintage and laboratory parameters were entered as separate steps. In this regression, the trichotomized BDI emerged as a significant predictor ($\beta = .452, p=.044$). The survival function for this analysis is presented in Figure 1.

Eighty-five subjects (65%) were asked to complete a self-report assessment of their medication adherence. Demographic characteristics of this sub-group are displayed in Table 1. Of these 85 subjects, 68 (80%) were still alive at the end of the observation period. The sample was largely compliant with their medication prescriptions, with 42% reporting

perfect or nearly perfect adherence. Only 13% reported a substantial problem with medication adherence. As in the depression analysis, a similar Cox regression model was used to examine the effect of self-reported adherence on mortality. While controlling for age ($\beta = .035$, $p = .089$) and gender ($\beta = -.126$, $p = .808$) in the first step, dialysis vintage ($\beta = .009$, $p = .074$), diabetic status ($\beta = -1.517$, $p = .019$) and disease severity ($\beta = -.122$, $p = .819$) in the second step, self-reported adherence emerged as a significant predictor ($\beta = -.205$, $p = .030$) of mortality. The relative risk of improved adherence was .815 (95% CI .677 – .980), meaning that being more adherent was protective against mortality.

To test the potential mediating effect of adherence on the relationship between depressive affect and mortality in the sub-sample of 85 participants, a modified Cox regression model controlling for age ($\beta = .040$, $p = 1.04$) and diabetic status ($\beta = -.962$, $p = .382$) was used. Depression score was entered in the second step and self-reported adherence was entered in the third step. When entered into the model together, neither depressive affect ($\beta = .029$, $p = .271$) nor adherence ($\beta = -.159$, $p = .094$) was found to be significantly associated with mortality. This loss of significance is likely due to the high correlation between depressive affect and adherence ($r = -.488$, $p = .000$).

Conclusions

In this paper we examined the relationship between depressive affect and survival in 130 incident urban ESRD patients on HD. While there have been mixed results in the literature of depression's effect on survival in HD populations, this study followed the methodological suggestions of Kimmel et al. (15) and utilized a Cox regression model, a validated measure of depressive affect, and corrected for age and illness parameters. In our corrected model depressive affect emerged as a significant predictor of mortality. In this model for every point increase on the BDI, with all other covariates held equal there was a 5% increased chance of mortality across the study observation duration. For a one standard deviation increase in BDI score (10.2) there would be a 51% increased chance of mortality over a 5-year period.

Our second finding, that severe depressive affect (>24 on the BDI) had a dramatically different survival course than mild or moderate depressive affect, is novel. In Kimmel's paper they found survival differences for the mild to moderately depressed group in a similar but larger sample (15). However, they utilized multiple assessment points over time and it is possible that chronic low-level depressed mood predicts mortality, while a single assessment of mild to moderate depressed mood does not.

While regression modeling imposes directionality, it is possible that the observed relationship could more accurately reflect that people who are imminently dying feel depressed. It is interesting to note that the Cox regression lines in Figure 1 don't separate until 20 months, which means that the effect of the baseline depression did not begin to express itself in mortality rates for nearly two years post assessment. This pattern seems to support the predictive nature of depression on mortality.

The third finding of this paper is that self-reported medication adherence predicts survival. While this might seem intuitive, this is the first data to demonstrate this in an HD population. For each increase in a point on the ITAS-M, there was a 19% increase in survival over the 5-years course of the study period. This finding is a bit difficult to interpret as the ITAS-M utilizes an ordinal scale, but increased medication adherence is clearly protective.

This finding seems significant in and of itself, and in the context of understanding the mechanisms through which depression affects mortality. It has been suggested that there are a variety of direct and indirect pathways through which depression could negatively impact survival. An exploratory analysis examined the association between depressive affect and medication adherence and their combined impact on mortality. Once the variance in mortality due to depressive affect was accounted for, the relationship between adherence and survival was no longer evident. It is possible, that we were unable to establish a mediating effect of non-adherence as we were insufficiently powered due to a small sample size. The strong association between depression and adherence may also have contributed to the lack of statistical significance in the regression model. This high degree of colinearity between these two constructs suggest that non-adherence may be endemic to high levels of depressive affect. Given this preliminary evidence, future models investigating depression's deleterious effects should include measures of medication adherence.

This study had several methodological strengths in that it utilized a well-validated measure of depressive affect and focused on understudied, but over-represented minority populations. Additionally it utilized Cox regression methodology, which provides more power to the analytic strategy because it measures time to death and not simply the dichotomous outcome of death. Furthermore, unlike earlier studies, a corrected model was developed to account for known predictors of mortality. Although a more standardized assessment of comorbid illness may have offered a better control for comorbidity, the model did account for presence of diabetes, a highly prevalent comorbid condition for HD patients, as well as disease severity. The study sample was predominantly Black, and although minorities are understudied and overrepresented in the ESRD population, our sample was not demographically similar to the USRDS, which may affect the study's generalizability. The study was limited by a relatively small sample size and had few outcome events (38 deaths), making it possible that the models are overcorrected. This study did not utilize multiple measurements of depression over time as other studies have (15, 16), because that design addresses the longitudinal course of depression and outcome, as opposed to our goal, to investigate the relationship between a single depression assessment and survival. Furthermore, the cross-sectional design does not allow direct inference about the mechanism of the relationship between depression and survival. It is possible that depression is associated with other behavioral or medical variables that are the true cause of the association with mortality.

This study contributes to the support for depression's impact on survival in HD patients. While the relationship between depression and non-adherence and their impact on survival is not yet defined, further investigation is warranted. Future trials should look at mechanisms of this relationship as well as explore the effect of depression treatment on survival.

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Figure 1.
Cox Regression Survival Function Across Depression Severity

Table 1

Sample characteristics of the full sample and sub-sample

Parameter	Full Sample (n=130) Mean $\pm$ SD or %	Sub-sample (n=85) Mean $\pm$ SD or %
Female	58%	60%
Age (years)	57.6 $\pm$ 13.6	55.9 $\pm$ 13.2
Afro/Caaribbean American	84%	86%
Born in the U.S.	48%	49%
Currently Employed	17%	19%
Dialysis Vintage (months)	54.8 $\pm$ 54.3	48.0 $\pm$ 45.9
Diabetic	31%	35%
2 hospitalizations in last year	39%	45%
Urea Reduction Ratio	70.7 $\pm$ 10.5	69.8 $\pm$ 11.7
Calcium Phosphate Product	49.5 $\pm$ 15.8	49.2 $\pm$ 16.1
Serum Albumin g/dl	3.83 $\pm$.86	3.86 $\pm$.37
Beck Depression Inventory	12.6 $\pm$ 10.2	13.2 $\pm$ 10.5
Mild(<15)	55%	52%
Moderate (15–24)	32%	35%
Severe (>24)	13%	13%