Depressive Affect and Hospitalization Risk in Incident Hemodialysis Patients

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Abstract

Background and objectives Recent studies demonstrated an association between depressive affect and higher mortality risk in incident hemodialysis patients. This study sought to determine whether an association also exists with hospitalization risk.

Design, setting, participants, & measurements All 8776 adult incident hemodialysis patients with Medical Outcomes Study Short Form 36 survey results treated in Fresenius Medical Care North America facilities in 2006 were followed for 1 year from the date of survey, and all hospitalization events lasting ≥24 hours were tracked. A depressive affect score was derived from responses to two Medical Outcomes Study Short Form 36 questions (“down in the dumps” and “downhearted and blue”). A high depressive affect score corresponded with an average response of “some of the time” or more frequent occurrence. Cox and Poisson models were constructed to determine associations of depressive affect scores with risk for first hospitalization and risk for hospitalization events, as well as total days spent in the hospital, respectively.

Results Incident patients with high depressive affect score made up 41% of the cohort and had a median (interquartile range) hospitalization event rate of one (0, 3) and 4 (0, 15) total hospital days; the values for patients with low depressive affect scores were one (0, 2) event and 2 (0, 11) days, respectively. For high-scoring patients, the adjusted hazard ratio for first hospitalization was 1.12 (1.04, 1.20). When multiple hospital events were considered, the adjusted risk ratio was 1.13 (1.02, 1.25) and the corresponding risk ratio for total hospital days was 1.20 (1.07, 1.35). High depressive affect score was generally associated with lower physical and mental component scores, but these covariates were adjusted for in the models.

Conclusions Depressive affect in incident hemodialysis patients was associated with higher risk of hospitalization and more hospital days. Future studies are needed to investigate the effect of therapeutic interventions to address depressive affect in this high-risk population.


Introduction

Depression is common in patients with ESRD, and affected patients are twice as likely as those without depression to die or require hospitalization within 1 year of this diagnosis (1). Furthermore, in addition to having greater mortality risk, depressed patients report poorer quality of life (2). Recent studies have also demonstrated an association between depressive affect, manifested by depressive symptoms, with higher mortality among patients with ESRD (3–7). Depressive symptoms and associated outcomes have been assessed by self-report using two questions within the Medical Outcomes Study Short Form 36 (SF-36) (4,5). Compared with physician-diagnosed depression, responses indicating a frequency of occurrence of at least “a good bit of the time” for the question “Have you felt so down in the dumps nothing could cheer you up?” had 74.2% agreement; 73.6% agreement was reported with the question “Have you felt downhearted and blue?” (4)

Incident hemodialysis (HD) patients exhibit the highest rates of morbidity and mortality, and the potential role of depressive affect in exacerbating risk remains a concern (1,5). Although not necessarily diagnostic of clinical depression, elicited responses representative for depressive affect can indicate a depressive state among this patient population. In this study, we measured the prevalence of depressive affect among an incident HD population using two questions from the SF-36 within their first 120 days of dialysis. We derived the “depression score” by combining the responses to the two survey questions associated with frequency of feeling “down in the dumps” and “downhearted and blue” (5). The mean score of these questions were used to represent depressive affect and determine the association between depressive affect and the number of hospitalization events, as well as hospital days, during a 1-year follow-up period.

Materials and Methods

Study Sample

The source population included 41,585 adult (age≥18 years) patients undergoing in-center HD at Fresenius
Medical Care North America (FMCNA) facilities between January 1, and December 31, 2006, with SF-36 survey results. The study sample consisted of 8776 patients (21% of 41,585 period prevalent patients) who were surveyed as incident patients (i.e., within the first 120 days of the first long-term dialysis session). Patient demographic characteristics and laboratory results were obtained from the FMCNA Knowledge Center data warehouse, which consolidates information from the facility-specific dialysis information systems (8). Baseline characteristics were tabulated as means±SDs for continuous variables and percentages for categorical variables. Consistent with the long history of quality improvement initiatives at FMCNA, this retrospective, observational analysis of healthcare data posed no additional risk to patients. As such, neither IRB review nor informed consent were obtained, since FMCNA did not deem them necessary in that these activities are a normal part of FMCNA quality improvement activities and health care operations. Additionally, all results have been presented as aggregated information that cannot be linked back to individual patients.

Follow-up
Hospitalization events (>24 hours) and total hospital days were tracked for up to 1 year from the date of SF-36 survey. Before each HD treatment, trained clinical staff inquire whether the patient had received medical care since the last treatment in the facility in order to elicit information regarding potential emergency department visits, hospitalization, physician visits, and admissions for clinical procedures. In addition, nursing staff review the patient roster daily to ensure that all treatments provided were matched to all treatments scheduled. Absences were documented and the reason for any absence entered into the electronic dialysis information systems as follows: missed without treatment provided elsewhere, hospitalized, died, recovered kidney function, underwent transplantation, or transferred to another facility. Hospitalized patients have their admission and discharge dates documented. Patients who died or withdrew from dialysis therapy, recovered kidney function, received a kidney transplant, or left the FMCNA system during the 1-year follow-up contributed person-time at risk but were censored on their discharge date.

SF-36 Questions Associated with Depressive Symptoms
The SF-36 has five mental health (MH) domain items, designed to determine the frequency of (1) being nervous, (2) being down in the dumps, (3) feeling calm and peaceful, (4) feeling downhearted and blue, and (5) being happy. Consistent with the literature, we used two of these five (9) as indicators of depressive affect:

MH 2: Have you felt so down in the dumps nothing could cheer you up? (i.e., “Dumps”)

MH 4: Have you felt downhearted and blue? (i.e., “Blue”)

Both items used a 6-point choice of responses: 1=all of the time, 2=most of the time, 3=a good bit of the time, 4=some of the time, 5=a little of the time, or 6=none of the time.

We used the same derivation of depressive affect score as in our prior report (5). Briefly, the initial step was to reverse the item scores so that the higher value represents having more frequent depressive symptoms:

\[
MH_{2\text{, reversed}} = 7 - MH2 \\
MH_{4\text{, reversed}} = 7 - MH4
\]

Then the revised “depression score” was defined as:

\[
\text{depression score} = \frac{MH_{2\text{, reversed}} + MH_{4\text{, reversed}}}{2}
\]

In the equation, depressive affect score represents the mean of reversed MH 2 and MH 4 responses. Thus, depressive affect score is a continuous variable ranging from one to six (higher score is worse). In our analysis, we categorized patients into two levels of depressive affect: level 1, “unlikely to be depressed,” if the score was ≤2 and level 2, “more likely to be depressed,” if the score was >2. This cutoff divided the patient cohort into two large comparable groups.

Statistical Analyses
Poisson regression models (10) were used to study the association between depressive affect and the total number of hospitalization events. To account for different exposure time for each patient, the model was offset by exposure-time in months. To minimize the extent to which data were skewed, a log link was implemented for the Poisson regression. With the log link, the Poisson model will produce risk ratio (RR), the ratio of the mean hospitalization rate for depressive affect level 2 versus level 1, with level 1 used as the reference. Poisson regression models were also constructed to determine the association between depressive affect and the total number of hospital days. Three Poisson models were constructed to determine an association between depressive affect and each outcome (hospitalization event and hospital days). Model 1 was unadjusted; model 2 was adjusted for physical component score (PCS), mental component score (MCS) modified to exclude five MH items, and the three MH items other than the two depressive affect items; and model 3 was further adjusted for age, sex, race, diabetes, albumin, creatinine, hemoglobin, calcium, phosphorus, and transferrin saturation.

Following analytic convention, time to first hospitalization was analyzed using the Kaplan–Meier method (11) to produce estimated probabilities of first hospitalization stratified by two depressive affect levels. Furthermore, with use of Cox proportional hazards models (12) (with a sequence of models 1–3 as above), the hazard ratio (HR) for first hospitalization during the 1-year follow-up was derived for depressive affect level 2 versus level 1. Association of hospitalization with general PCS and MCS was also assessed for comparison. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC).

Results
Among 8776 patients studied, 5178 (59%) were unlikely to be depressed (level 1 depressive affect), while 3598 (41%) were more likely to be depressed (level 2 depressive affect). For the level 1 group, the depressive affect score averaged 1.4±0.4, consistent with the presence of depressive symptoms.
between “none of the time” and “a little of the time” (Table 1). For the level 2 group, the depressive affect score averaged 3.4±0.9, consistent with the presence of depressive symptoms between “some of the time” and “a good bit of the time.” Overall, 66.4% of patients had at least one hospital admission in level 2, compared with 61% for level 1 (P<0.001). Between level 1 and level 2 depressive affect, 13.2% and 16.9% of patients, respectively, were eventually censored for death/withdrawal, 3.1% and 3.4% for discharge due to recovery of kidney function, and 23.5% and 22.9% for receiving a kidney transplant during the 1-year follow-up period.

The mean dialysis vintage at the time of survey of this incident HD cohort was 47±33 days (median, 49 days; range, 0–120 days), likely prompted by an automated reminder on day 45 for patient care staff to obtain the survey. Vintage days between the two depressive affect groups on the date of survey were similar (Table 1). The average age as of the SF-36 survey date for level 2 was 61.4±14.8 years, 1.5 years younger than in the level 1 patients, whose average age was 62.9±15.1 (P<0.001). The level 2 group had a higher proportion of men (47.7% versus 44.1%; P=0.001) and Hispanics (15.8% versus 10.4%; P<0.0001) but similar racial distribution and prevalence of diabetes. The level 2 group also had a lower mean PCS (30.9±9.1 versus 32.8±10.7) and a lower mean MCS (37.9±9.1 versus 35.7±8.8).

The level 2 group had more hospitalization events (1.8±2.3 versus 1.5±2.0) as well as more hospital days (11.4±18.4 versus 9.1±16.3) during the 1-year follow-up than the level 1 group (all significant at P<0.001) (Table 2). A PCS and an MCS higher by 1 SD were significantly (P<0.001) associated with 23% (95% confidence limit [95% CL], 20% to 26%) and 11% (95% CL, 7% to 14%) fewer mean hospitalization events, respectively. The mean percentage of hospital days was 29% (95% CL, 26% to 33%; P<0.001) lower for PCS and 11% (95% CL, 8% to 15%; P<0.001) lower for MCS.

For hospitalization events, the unadjusted Poisson model yielded an RR of 1.25 (95% CL, 1.16 to 1.35; P<0.001) for level 2 versus level 1 depressive affect (Table 3). The corresponding RRs were 1.10 (95% CL, 1.01 to 1.21; P=0.03) from adjusted model 2 and 1.13 (95% CL, 1.02 to 1.25; P=0.02) for model 3. For hospital days, the unadjusted Poisson model yielded an RR of 1.31 (95% CL, 1.16 to 1.35; P<0.001) for model 3. For hospital days, the unadjusted Poisson model yielded an RR of 1.31 (95% CL, 1.16 to 1.35; P<0.001) for model 3. For hospital days, the unadjusted Poisson model yielded an RR of 1.31 (95% CL, 1.16 to 1.35; P<0.001) for model 3.
The mean time to first hospitalization differed significantly between groups: 201 ± 2.4 days for level 2 versus 223 ± 1.8 days for level 1 (6.6 ± 0.08 versus 7.3 ± 0.06 months, respectively; log-rank P < 0.001) (Figure 1). By the end of the 1-year follow-up period, the survival probability (i.e., not hospitalized) was 0.34 versus 0.39 for level 2 versus level 1 depressive affect, respectively. The Cox proportional hazards models for time to first hospitalization (Table 3) yielded similar results; higher depressive affect score had an unadjusted HR of 1.18 (95% CL, 1.12 to 1.25; P < 0.001), with HRs of 1.10 (95% CL, 1.03 to 1.18; P = 0.003) from model 2 and 1.12 (95% CL, 1.04 to 1.20; P = 0.003) from model 3.

**Discussion**

These study results demonstrated that increased severity of depressive affect in patients new to HD was significantly associated with more hospitalization events, more hospital days, and shorter time to first hospitalization during the first year of dialysis. Within 1 year from the SF-36 survey, patients with greater depressive affect had a 13% greater likelihood of being hospitalized and 20% more hospital days after adjustment for age, sex, race, diabetes, SF-36 component scores, and laboratory measurements (model 3). These data are consistent with our earlier work describing depressive symptoms as a significant risk factor for mortality in the early dialysis treatment period (5). This study’s important contribution to the scientific literature is that it extends the association between depressive affect and hospitalization beyond established (i.e., prevalent) dialysis patients and into patients new to dialysis therapy. While prior work has associated depression in HD patients to hospitalization risk (13), the mechanisms by which such linkage occurs are likely multifactorial and may vary depending on the type of hospitalization. For example, self-reported depressive symptoms, independent of and additive to CKD, are a risk factor for hospitalization in older patients newly diagnosed with heart failure (14). Heart failure and other fluid overload conditions are

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**Table 2. Summary of outcomes (n=8776)**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Level 1 (n=5178; 59%)</th>
<th>Level 2 (n=3598; 41%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hospitalization events</td>
<td>1.5±2.0</td>
<td>1.8±2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of hospital stays (d)</td>
<td>9.1±16.3</td>
<td>11.3±18.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of hospitalization events</td>
<td>1 (0, 2)</td>
<td>1 (0, 3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of hospital stays (d)</td>
<td>2 (0, 11)</td>
<td>4 (0, 15)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values expressed with a plus/minus sign are the mean ± SD. Values expressed with ranges in parentheses are the median (interquartile range).

**Table 3. Association of total hospitalization events, hospitalized days, and time to first hospitalization with depressive affect for incident hemodialysis patients in 2006**

<table>
<thead>
<tr>
<th>Dependent Variable per Model</th>
<th>Rate/Hazard Ratio for Level 2 versus Level 1 (95% CL)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poisson regression with logarithmic link function and offset with exposure time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hospitalization events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.25 (1.16 to 1.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.10 (1.01 to 1.21)</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.13 (1.02 to 1.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total hospitalized days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.31 (1.2 to 1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.15 (1.03 to 1.27)</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.20 (1.07 to 1.35)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cox proportional hazards regression for time to first hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to first hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.18 (1.12 to 1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.10 (1.03 to 1.18)</td>
<td>0.003</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.12 (1.04 to 1.20)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Rate ratios are given for Poisson regression; hazard ratios are given for Cox regression. Category for depressive affect: level 1 = less likely depressed, score 1–2; level 2 = potentially depressed, score 2–6. Model 1 was unadjusted. Model 2 was adjusted for physical composite score, mental composite score with mental health items removed, and three remaining mental health items. Model 3 was additionally adjusted for hemodialysis vintage ≤ 90 days (incidence) versus > 90 days (prevalence), age, sex, race, diabetes, albumin, creatinine, hemoglobin, calcium, phosphorus, and transferrin saturation. 95% CL, 95% confidence limit.
common in HD patients and tend to recur, with use of healthcare resources recently estimated to cost Medicare $6372 per hospitalization episode and $266 million annually (15). Depressive affect can directly influence poor adherence to diet and fluid regimens (16). Furthermore, chemical brain alterations in depressed patients may affect cognitive dysfunction (which may manifest as poor adherence) (17), and cognitive dysfunction has been associated with depressive affect in HD patients (18). Poor adherence may also extend to missed HD treatments, which has been associated with greater risk for hospitalization from not just cardiovascular causes but all-causes as well (19,20). Poor adherence may also extend to medication adherence and dietary considerations (including anorexia) leading to malnutrition, both of which have been associated with increased hospitalization and mortality risk in this population (21–24).

In addition to nonadherence and other behavioral components (alcohol, smoking, decreased physical activity) linked to depression, biologic mechanisms linking depression to coronary artery disease have been proposed (25). Abnormal platelet function and reactivity are more prevalent in depressed patients (26), which may be mediated through serotonin imbalance (27). Dysregulation of the hypothalamic-pituitary-adrenal axis in depressed states may also play a role, particularly with regard to effect on stress responses, either biochemically with inflammatory cytokine imbalances or clinically through abnormalities of BP and heart rate (28–30). Furthermore, autonomic nervous system dysfunction may accompany depression, further exacerbating BP and heart rate dysregulation and potentially manifesting with reduced heart rate variability and cardiac baroreflexes that may further aggravate cardiovascular morbidity (31–33). While inflammation and autonomic dysfunction are not uncommon in patients undergoing HD (34,35), depression may represent an aggravating factor toward greater morbidity.

As noted earlier, high prevalence of depression is associated with initiating dialysis treatment and, subsequently, poor outcomes in the ESRD population (2); however, many clinicians (including nephrologists) have not been comfortable diagnosing and managing depression (36). Screening for depressive affect makes sense for identifying patients at greater risk for depression, and managing patient’s depressive symptoms sooner may potentially reduce patient morbidity and hospitalizations. Reducing the burden of illness within this patient population is the ultimate health care goal; addressing depressive affect could decrease complications and potentially lead to cost savings in the health care system. This is clearly not trivial, as demonstrated for fluid overload and heart failure, among all other potentially actionable causes of hospitalization in the HD population.

Various treatments designed to reduce mortality in the HD population have been promoted, but proposals to manage depression in the general population, although a
public health priority, have not reached the same level of priority in dialysis patients. Some of these treatment strategies, such as antidepressant medications (37), changes in dialysis treatment schedules or alternative dialysis therapies (38), cognitive-behavioral therapy (CBT) (39), exercise programs (40), and stress reduction therapies (to include music or art) (41), have been reported to improve symptoms or reduce depressive episodes in patients with ESRD (40). Duarte et al. showed that CBT was effective: HD patients receiving group therapy showed significant improvements in the treatment of depression compared with the control group, who did not receive CBT (39). Another nondrug study by Cukor et al. supports using CBT treatment in HD patients, with a successful reduction in major depression disorder (42). Brown et al. studied patients with both asthma and major depression and determined that effective improvements of depression can help improve or reduce asthma symptoms (43). We await results from a pilot study that will use symptom-targeted therapy (44). However, no broad-based systematic study has been reported in incident HD patients, and prospective studies are needed to determine whether treatment of patients diagnosed with depressive affect will benefit from early screening and treatment.

The present study has many strengths, including a large sample size (n=8776) from a national population of incident HD patients and use of multivariable-adjusted models. However, it also has several limitations. First, this study is a retrospective analysis of observational data; such findings of associations are subject to residual confounding from unmeasured factors, such as socioeconomic status, comorbidity (e.g., cardiovascular disease burden), and health status (e.g., BP) and do not necessarily prove causation (i.e., that depressed affect is the cause of poor survival). Second, we used two questions on the SF-36 questionnaire to assess depressive affect, not the full depression mental health assessment. Third, we could assess risk only for responders to the SF-36 survey, not the entire cohort of incident patients who started HD in 2006. Fourth, while we found that age, sex, Hispanic ethnicity, albumin, and creatinine were associated with the depressive affect score, diabetes did not differ between groups, unlike in prior reports. It is possible that diabetes is primarily associated with severity of symptoms or tends to associate more strongly with a clinical diagnosis of depression. Fifth, we treated depressive affect as a baseline covariate, although dialysis initiation by itself could result in depressive symptoms related to loss of bodily function, self-worth, and need for adjustment to a different lifestyle. However, the mean vintage at the time of survey was 47 days (median, 49 days), as noted in the Results section, because an electronic reminder in the dialysis information systems prompts initiation of SF-36 surveys at vintage day 45 for all incident patients. This reminder bypasses the initial 30- to 45-day adjustment period to long-term dialysis treatment, as well as the potential presence of acute debilitating illnesses that accompany transition to long-term dialysis and may help mitigate the effect of the initial shock of requiring this therapy. Future studies should delineate how depressive affect evolves during the course of HD treatment.

In conclusion, this study establishes an association between depressive affect and hospitalization risk in incident HD patients. Its important contribution to the scientific literature is that it extends the association between depressive affect and hospitalization beyond established (i.e., prevalent) dialysis patients and into patients new to dialysis therapy. We posit that identifying and determining the level of depressive affect may allow for possible interventions to manage these patients’ depressive symptoms, thus potentially affecting the need for hospitalization and reducing the number of days spent in the hospital. More frequent hospitalization events and more hospital days affect our health care system, using valuable resources and personnel time, thus increasing overall costs to the system. Future studies are needed to investigate the effect of therapeutic interventions to address depressive affect, preferably in the form of prospective randomized trials.

Acknowledgments
We thank the dedicated social workers and clinical staff of Fresenius Medical Services for diligently collecting information that forms the basis of the epidemiological studies that we do.

Disclosures
All authors are employees of Fresenius Medical Care, North America. Part of this work was presented as a poster in the National Kidney Foundation 2012 Spring Clinical Meeting.

References

Received: February 5, 2014 Accepted: June 19, 2014
Published online ahead of print. Publication date available at www.cjasn.org.