Associations of Depressive Symptoms and Pain with Dialysis Adherence, Health Resource Utilization, and Mortality in Patients Receiving Chronic Hemodialysis

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Abstract

Background and objectives Depressive symptoms and pain are common in patients receiving chronic hemodialysis, yet their effect on dialysis adherence, health resource utilization, and mortality is not fully understood. This study sought to characterize the longitudinal associations of these symptoms with dialysis adherence, emergency department (ED) visits, hospitalizations, and mortality.

Design, setting, participants, & measurements As part of a trial comparing symptom management strategies in patients receiving chronic hemodialysis, this study prospectively assessed depressive symptoms using the Patient Health Questionnaire 9, and pain using the Short-Form McGill Pain Questionnaire, monthly between 2009 and 2011. This study used negative binomial, Poisson, and proportional hazards regression to analyze the longitudinal associations of depressive symptoms and pain, scaled based on 5-point increments in symptom scores, with missed and abbreviated hemodialysis treatments, ED visits, hospitalizations, and mortality, respectively.

Results Among 286 patients, moderate-to-severe depressive symptoms were identified on 788 of 4452 (18%) assessments and pain was reported on 3537 of 4459 (79%) assessments. Depressive symptoms were independently associated with missed (incident rate ratio [IRR], 1.21; 95% confidence interval [95% CI], 1.10 to 1.33) and abbreviated (IRR, 1.08; 95% CI, 1.03 to 1.14) hemodialysis treatments, ED visits (IRR, 1.24; 95% CI, 1.12 to 1.37), hospitalizations (IRR, 1.19; 95% CI, 1.10 to 1.30), and mortality (IRR, 1.40; 95% CI, 1.11 to 1.77). Pain was independently associated with abbreviated hemodialysis treatments (IRR, 1.03; 95% CI, 1.01 to 1.06) and hospitalizations (IRR, 1.05; 95% CI, 1.00 to 1.10). Severe pain was independently associated with abbreviated hemodialysis treatments (IRR, 1.16; 95% CI, 1.06 to 1.28), ED visits (IRR, 1.58; 95% CI, 1.28 to 1.94), and hospitalizations (IRR, 1.22; 95% CI, 1.03 to 1.45), but not mortality (hazard ratio, 1.71; 95% CI, 0.81 to 2.96).

Conclusions Depressive symptoms and pain are independently associated with dialysis nonadherence and health services utilization. Depressive symptoms are also associated with mortality. Interventions to alleviate these symptoms have the potential to reduce costs and improve patient-centered outcomes.

Introduction

Patients receiving chronic hemodialysis experience many symptoms, of which depression and pain are particularly common and potentially treatable (1–6). Past studies demonstrate that depression and pain are present in approximately 20% and 50%, respectively, of patients receiving chronic hemodialysis, and both are strongly associated with impaired health-related quality of life. This has led to efforts to elucidate their associations with other adverse outcomes, including mortality (1,2,7–14). As part of the Dialysis Outcomes and Practice Patterns Study, Lopes et al. demonstrated that among patients on chronic hemodialysis, depression was independently associated with increased mortality and hospitalization (15). Several other studies reported similar associations as well as lower medication and dietary adherence among patients on chronic hemodialysis with depression (16–24). Considerably less is known about the associations of pain with clinical outcomes, although a recent study found that interdialytic pain was associated with increased mortality (25).

These studies suggest that depression and pain are associated with important patient-centered outcomes in the chronic hemodialysis population. However, most prior studies utilized a single baseline assessment of depression and pain, rather than serial longitudinal measurements. Both the presence and severity of these symptoms likely fluctuate considerably. Longer intervals between their measurement and the assessment of plausibly related clinical outcomes reduce the likelihood of confirming an independent (and potentially causal) association. In this study, which involved a secondary
analysis of clinical trial data, we sought to evaluate the independent associations of depressive symptoms and pain, assessed prospectively on a monthly basis, with dialysis adherence, emergency department (ED) visits, hospitalizations, and mortality.

Materials and Methods

Patient Population

This study used data collected from participants of the Symptom Management Involving End-Stage Renal Disease (SMILE) trial, a multicenter, randomized trial comparing two strategies (feedback to renal providers versus nurse-driven intervention) for the management of pain, depression, and sexual dysfunction in patients receiving chronic hemodialysis (26,27). The SMILE trial, which was conducted between 2009 and 2011, enrolled cognitively intact (Mini Cog score=3), English-speaking adults receiving outpatient hemodialysis at one of nine dialysis units in Western Pennsylvania. The institutional review boards of the University of Pittsburgh and the Veterans Affairs Pittsburgh Healthcare System as well as the Western Institutional Review Board approved the study and all patients provided informed consent.

Baseline Data Collection and Assessments of Depressive Symptoms and Pain

At baseline, we recorded participants’ age, race, sex, income, educational status, dialysis vintage, form of vascular access, and burden of comorbid illness (28). Beginning at the time of enrollment and continuing on a monthly basis for up to 24 months, we assessed patients’ depressive symptoms with the Patient Health Questionnaire-9 (PHQ-9) and pain with the Short-Form McGill Pain Questionnaire (SF-MPQ). Scores on the PHQ-9 range from 0 to 27, with higher scores denoting more severe depressive symptoms (29). The SF-MPQ includes 15 (11 sensory and 4 affective) descriptors of pain. A total pain score ranging from 0 to 45 is based on the sum of individual scores on the sensory and affective descriptors, which are each scored from 0 (no pain) to 3 (severe pain) (11,30).

Study Outcomes

The primary outcomes for the current analyses included dialysis adherence, ED visits, hospitalizations, and mortality, which we tracked monthly using patient and dialysis staff interviews and dialysis chart reviews. We considered two measures of dialysis adherence: missed treatments and abbreviated treatments. We defined missed treatments as scheduled dialysis treatments that patients missed each month unless they were on vacation or hospitalized. We defined abbreviated treatments as hemodialysis sessions each month that were shortened by at least 15 minutes by patient request. We defined ED visits based on patient self-report, because documentation of such events is commonly missing from dialysis charts. We defined hospitalizations as hospital admission for any cause and mortality as death from any cause or terminal withdrawal from dialysis at any time during the study.

Statistical Analyses

We used medians and interquartile ranges (IQRs) to report continuous variables and frequencies/proportions to describe categorical variables. For our primary analyses, we used negative binomial regression to model the association of depressive symptoms and pain with missed and abbreviated dialysis treatments and ED visits, and Poisson regression to model their associations with hospitalizations. Negative binomial and Poisson models allow for the analysis of count data while accounting for differential time at risk (or exposure) for the outcomes. Negative binomial regression relies on less restrictive assumptions about model variance. For dialysis adherence, we considered the number of dialysis treatments that should have been attended and completed as the exposure variable. For ED visits and hospitalizations, we used the patient-specific months of study follow-up as the exposure variable. We used a proportional hazards model with a smoothed hazard function based on cubic splines to analyze the associations of depressive symptoms and pain with mortality. Our primary analyses considered depressive symptoms and pain as continuous variables based on 5-point increments in symptom scores, utilizing the score at each monthly assessment as a predictor for outcomes that occurred subsequent to that assessment. Outcomes for each predictor continued to be tallied until the next symptom assessment was completed. We scaled the symptom scores such that 5-point increments on the PHQ-9 denote an increase in the level of depressive symptoms and likely reflect a clinically significant increase in SF-MPQ score. We performed secondary analyses considering depressive symptoms and pain as categorical predictors. We categorized PHQ-9 scores based on values ≥10, which denote the presence of moderate-to-severe depressive symptoms. We categorized pain as severe versus not severe based on the presence versus absence of a report of severe pain (score of 3) on any of the 15 pain descriptors on the SF-MPQ. Patients were considered censored at study end or withdrawal. All models included a random effect for the patients and all but the proportional hazards model included a linear effect of time. All models were adjusted for potentially confounding variables, identified a priori, including age, sex, race, employment, income, comorbid illness burden, time on dialysis, and type of vascular access. The analyses also included a fixed effect for the dialysis unit and an indicator variable for the dialysis schedule (Monday/Wednesday/Friday versus Tuesday/Thursday/Saturday) to account for the unit of randomization in the parent trial. In addition, because of the relationship between pain and depression, analyses for each symptom included the other symptom in the multivariable models. Because we recognized that there may be more complex temporal patterns in symptoms and outcomes, we also conducted multitrajectory analyses to identify and describe groups of patients with similar longitudinal patterns in symptom scores and study outcomes (31).

For our primary and secondary analyses, we report our findings using incident rate ratios (IRRs) with corresponding 95% confidence intervals (95% CIs). Estimated IRRs denote the effect per 5-point increase in symptom scores on study outcomes for the primary analyses and the effect of having moderate-to-severe depressive symptoms versus not having moderate-to-severe depressive symptoms and having severe pain versus not having severe pain for the secondary analyses that considered the symptom predictors as categorical variables. The results of the multitrajectory analyses are
strictly descriptive. All analyses were conducted using SAS 9.3 (Cary, NC) and Stata 12 (College Station, TX) software.

**Results**

**Study Population**

Of the 288 patients enrolled in the SMILE trial, 286 (99%) completed at least one depression or pain assessment and were included in our analyses. Patients’ median age was 64 years (IQR, 56, 73), 40% were African American, 56% were men, and 52% had diabetes (Table 1). We followed patients for a median of 557 days (IQR, 330, 721).

**Depressive Symptoms and Pain**

Patients completed a median of 16 (IQR, 9, 23) and a collective total of 4452 monthly PHQ-9 assessments, with moderate-to-severe depressive symptoms reported on 788 (18%). Seventy-three patients (25.5%) reported moderate-to-severe depressive symptoms (PHQ-9 score ≥10) at baseline, 141 (49.5%) reported moderate-to-severe depressive symptoms on at least one assessment, and 27 (9.4%) reported moderate-to-severe depressive symptoms on ≥75% of their assessments.

Patients completed a median of 16 (IQR, 9, 23) and a collective total of 4459 monthly SF-MPQ assessments, with pain reported on 3537 (79%). When present, the maximum level of pain reported on any of the 15 pain descriptors was mild on 1053 (30%), moderate on 1323 (37%), and severe on 1161 (33%). Severe pain was reported by 100 patients (35%) at baseline, 204 (71.3%) on at least one assessment, and 38 (13.3%) on ≥75% of their assessments. For the majority of monthly assessments (93%), both symptoms were assessed. Rarely (2%), symptoms were collected ≥2 months apart.

**Outcome Events**

Patients missed a total of 1424 (2%) hemodialysis sessions. The median percentage of missed sessions was 0.4 (IQR, 0, 2) per patient, whereas 60 patients (21%) missed an average of at least three sessions annually. Patients abbreviated a total of 5221 (9%) hemodialysis sessions. The median percentage of abbreviated sessions was 4 (IQR, 1, 10) per patient, whereas 76 patients (27%) abbreviated an average of at least 12 sessions annually. Patients visited the ED on 580 occasions with a median number of ED visits annually of 1.2 (IQR, 0, 3) per patient. There were a total of 919 hospitalizations. The median number of hospitalizations per patient annually was 1.6 (IQR, 1.5, 3.4). Sixty-two patients (22%) died or terminally withdrew from dialysis during the course of the study (Table 2).

**Associations of Depressive Symptoms with Study Outcomes**

In unadjusted analyses, each 5-point increment in the PHQ-9 score was associated with missed and abbreviated hemodialysis sessions, ED visits, hospitalizations, and mortality (Table 3). In multivariable analyses, depressive symptoms were independently associated with missed (IRR, 1.21; 95% CI, 1.10 to 1.33) and abbreviated (IRR, 1.08; 95% CI, 1.03 to 1.14) hemodialysis treatments, ED visits (IRR, 1.24; 95% CI, 1.12 to 1.37), hospitalizations (IRR, 1.19; 95% CI, 1.10 to 1.30), and mortality (IRR, 1.40; 95% CI, 1.11 to 1.77) (Table 3). However, the relationship with abbreviated hemodialysis sessions was not completely linear, with the strongest association occurring for changes in the lower end of the PHQ-9 scoring range (data not shown).

When considered as a categorical value in unadjusted analyses, moderate-to-severe depressive symptoms were associated with missed hemodialysis treatments, ED visits, and hospitalizations (Table 3). In multivariable analyses, moderate-to-severe depressive symptoms were independently associated with missed hemodialysis treatments (IRR, 1.27; 95% CI, 1.06 to 1.53) and hospitalizations (IRR, 1.43; 95% CI, 1.17 to 1.75) (Table 3). Moderate to severe depressive symptoms were not associated with mortality in unadjusted or multivariable models (Table 3).

**Associations of Pain with Study Outcomes**

In unadjusted analyses, each 5-point increment in the SF-MPQ score was associated with abbreviated hemodialysis treatments, ED visits, hospitalizations, and mortality (Table 4). In multivariable analyses, pain was independently associated with abbreviated hemodialysis sessions (IRR, 1.03; 95% CI, 1.01 to 1.06) and hospitalizations (IRR, 1.05; 95% CI, 1.00 to 1.07) (Table 4). In multivariable analyses, pain was independently associated with mortality (IRR, 1.02; 95% CI, 1.00 to 1.04) (Table 4).
When considered as a categorical variable in unadjusted models, severe pain was associated with missed and abbreviated hemodialysis treatments, ED visits, hospitalizations, and mortality. In multivariable analyses, severe pain remained independently associated with abbreviated hemodialysis treatments (IRR, 1.16; 95% CI, 1.06 to 1.28), ED visits (IRR, 1.58; 95% CI, 1.28 to 1.94), and hospitalizations (IRR, 1.22; 95% CI, 1.03 to 1.45), but not with mortality (IRR, 1.71; 95% CI, 0.81 to 2.96) (Table 4).

### Multitrajectory Analyses

For each dialysis adherence outcome, multitrajectory analyses identified two groups of patients with similar patterns of longitudinal symptoms and adherence. Patients with a higher longitudinal burden of depressive symptoms and pain over the course of the study (group 2) consistently had more missed and abbreviated hemodialysis sessions than those with low symptom burden (Figure 1). More complex inter-relationships between symptoms and outcomes were observed for the remaining outcomes, with five distinct groups observed for each outcome (Figure 2). Specifically, patients with moderate-to-severe depressive symptoms and/or pain (groups 3–5) had more ED visits than those with less severe symptoms (Figure 2A). Patients with low depressive symptom and pain scores (groups 1 and 2) were least likely to be hospitalized, whereas those with either more severe depressive symptoms or more severe pain (groups 3 and 4) were most likely to be hospitalized (Figure 2B). Patients with moderate average symptom scores (group 3) and patients with consistently high depressive symptoms with moderate or severe pain symptoms (groups 4 and 5) were the most likely to die during the study (Figure 2C).

### Discussion

In patients on chronic hemodialysis, depressive symptoms and pain, specifically severe pain, are independently associated with dialysis nonadherence, ED visits, and hospitalizations. These findings underscore the potential clinical significance of these symptoms and highlight the strong need to investigate the effect of symptom-alleviating interventions on dialysis adherence, healthcare utilization, and patient-centered outcomes.

A recent meta-analysis by Farrokhi et al., which included 31 studies and >67,000 patients on chronic dialysis, found that depression was independently associated with mortality (adjusted hazard ratio, 1.45; 95% CI, 1.27 to 1.65) (32). Three studies that performed sequential measurements of depression (two assessments in one study and semiannual assessments in two studies) also demonstrated an association of depression with mortality (hazard ratio, 1.66; 95% CI, 1.22 to 2.19). These studies that performed sequential measurements of depression also demonstrated an association of depression with mortality (hazard ratio, 1.66; 95% CI, 1.22 to 2.19).

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### Table 2. Frequency of study outcomes

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Missed hemodialysis sessions</strong></td>
<td></td>
</tr>
<tr>
<td>Sessions missed</td>
<td>1424 (2)</td>
</tr>
<tr>
<td>Sessions missed (%)</td>
<td>0.4 (0, 2)</td>
</tr>
<tr>
<td>Missed average of ≥3 sessions/yr</td>
<td>60 (21)</td>
</tr>
<tr>
<td><strong>Abbreviated hemodialysis sessions</strong></td>
<td></td>
</tr>
<tr>
<td>Sessions abbreviated</td>
<td>5221 (9)</td>
</tr>
<tr>
<td>Sessions abbreviated per patient (%)</td>
<td>4 (1, 10)</td>
</tr>
<tr>
<td>Abbreviated average of ≥12 sessions/yr</td>
<td>76 (27)</td>
</tr>
<tr>
<td><strong>Emergency department visits</strong></td>
<td></td>
</tr>
<tr>
<td>Total visits</td>
<td>580</td>
</tr>
<tr>
<td>Annual visits per patient</td>
<td>1.2 (0, 3)</td>
</tr>
<tr>
<td><strong>Hospitalizations</strong></td>
<td></td>
</tr>
<tr>
<td>Total hospitalizations</td>
<td>919</td>
</tr>
<tr>
<td>Annual hospitalizations per patient</td>
<td>1.6 (1.5, 3.4)</td>
</tr>
<tr>
<td>Death or terminal withdrawal</td>
<td>62 (22)</td>
</tr>
</tbody>
</table>

Data are presented as the n (%) or the median (interquartile range).

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### Table 3. Association of depressive symptoms with study outcomes

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>Depressive Symptoms as Continuous Variable</th>
<th>Depressive Symptoms as Categorical Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted Association</td>
<td>Adjusted Association</td>
</tr>
<tr>
<td>Missed hemodialysis</td>
<td>1.25 (1.14 to 1.38)</td>
<td>1.21 (1.10 to 1.33)</td>
</tr>
<tr>
<td>Abbreviated hemodialysis</td>
<td>1.09 (1.03 to 1.15)</td>
<td>1.08 (1.03 to 1.14)</td>
</tr>
<tr>
<td>Emergency department visits</td>
<td>1.25 (1.13 to 1.37)</td>
<td>1.24 (1.12 to 1.37)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1.23 (1.14 to 1.34)</td>
<td>1.19 (1.10 to 1.30)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.36 (1.12 to 1.65)</td>
<td>1.40 (1.11 to 1.77)</td>
</tr>
</tbody>
</table>

Data denote the incident rate ratio (95% confidence interval).

*aEstimated effects are per 5-point increase in the Patient Health Questionnaire-9 score.

*bModels adjusted for age, sex, Charlson Comorbidity Index score, black race, time on dialysis, catheter (versus arteriovenous fistula or graft), employment, income, low health literacy, dialysis schedule (Tuesday/Thursday/Saturday versus Monday/Wednesday/Friday), and study site.
measurement and mortality assessment. Thus, our findings, which minimized the interval between symptom assessments, indicate that nearly half of all patients reported moderate-to-severe depressive symptoms on at least one assessment, yet <10% reported moderate-to-severe depressive symptoms on at least 75% of monthly assessments. Moreover, longer intervals between the measurement of depressive symptoms and assessment of mortality reduce the likelihood of confirming an independent association. Our patients completed a median of 16 monthly symptom assessments, which minimized the interval between symptom measurement and mortality assessment. Thus, our findings strengthen the likelihood of an independent (and potentially causal) association of depressive symptoms with mortality, and confirm the strong need to evaluate the effect of antidepressant therapy on this outcome.

Past studies also demonstrated an association of baseline depression with risk of hospitalization (15,21,22,23). Our study extends these prior observations by documenting an independent relationship between time-varying depressive symptoms and hospitalization. We further elucidate the health services implications of depressive symptoms by demonstrating their independent association with ED visits. Hospitalizations, and to a considerably lesser extent ED visits, are significant contributors to healthcare costs. Annual Medicare expenditures on the ESRD program currently exceed $30 billion, of which, greater than one third is allocated for inpatient care (34). Studies in other populations, including patients with depression and acute coronary syndrome, demonstrate lower all-cause rehospitalization rates with antidepressant therapy (35). Whether there are similar effects of antidepressant therapy on hospitalization and health services utilization in patients on chronic hemodialysis is unknown, but this possibility clearly warrants investigation.

Depression has been associated with decreased adherence to prescribed medications and dietary restrictions in patients on chronic hemodialysis (17,23,24). However, a study by Kutner et al. of 170 patients found that depression, assessed at baseline, was not independently associated with abbreviated or missed dialysis treatments (17). Conversely, we found independent associations of time-varying depressive symptoms with abbreviated and missed dialysis sessions. More frequent symptom assessments leading to shorter intervals between these assessments and the evaluation of dialysis adherence likely explain these discordant findings. Small trials suggest that pharmacologic therapy reduces depressive symptomatology and that cognitive-behavioral therapy improves depression as well as adherence to medications and dietary and fluid restrictions among patients on chronic hemodialysis (36–41). Such therapies may offer a means to improve dialysis adherence and reduce the adverse outcomes associated with noncompliant behavior.

Considerably less is known about the association of pain with serious adverse outcomes among patients receiving chronic hemodialysis. We found that pain was independently associated with abbreviated hemodialysis sessions and hospitalizations (but not other study outcomes), whereas severe pain was independently associated with these outcomes as well as ED visits. These findings suggest that pain, beyond its importance to patients, has potentially significant implications for health resource utilization and costs. We did not identify an association of pain with mortality, which differs from the findings of a recent study by Harris et al. that demonstrated that interdialytic pain was associated with reduced survival (25). Differences in demographic and clinical characteristics and pain assessment methods across the two studies may account for the discordant findings. Whereas Harris et al. assessed pain at baseline, we performed serial monthly measurements of this symptom. Much like depressive symptoms, the presence and severity of pain likely fluctuate substantially due to comorbid illness burden, psychosocial circumstances, and treatment effects. Efforts to understand the independent relationship between pain and mortality may be strengthened by repeated measurements of this symptom over time.

### Table 4. Association of pain with study outcomes

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>Pain as Continuous Variable</th>
<th></th>
<th>Severe Pain as Categorical Variable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted Association</td>
<td>Adjusted Association</td>
<td>Unadjusted Association</td>
<td>Adjusted Association</td>
</tr>
<tr>
<td>Missed hemodialysis</td>
<td>1.04 (0.99 to 1.10)</td>
<td>1.00 (0.95 to 1.05)</td>
<td>1.26 (1.04 to 1.52)</td>
<td>1.11 (0.93 to 1.34)</td>
</tr>
<tr>
<td>Abbreviated hemodialysis</td>
<td>1.05 (1.02 to 1.08)</td>
<td>1.03 (1.01 to 1.06)</td>
<td>1.20 (1.09 to 1.33)</td>
<td>1.16 (1.06 to 1.28)</td>
</tr>
<tr>
<td>Emergency department visits</td>
<td>1.07 (1.02 to 1.13)</td>
<td>1.02 (0.97 to 1.08)</td>
<td>1.74 (1.42 to 2.13)</td>
<td>1.58 (1.28 to 1.94)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1.09 (1.04 to 1.13)</td>
<td>1.05 (1.00 to 1.10)</td>
<td>1.28 (1.08 to 1.50)</td>
<td>1.22 (1.03 to 1.45)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.16 (1.04 to 1.29)</td>
<td>1.11 (0.97 to 1.27)</td>
<td>1.93 (1.17 to 3.18)</td>
<td>1.71 (0.81 to 2.96)</td>
</tr>
</tbody>
</table>

Data denote the incident rate ratio (95% confidence interval).

*Estimated effects are per 5-point increase in the Short-Form McGill Pain Questionnaire score.

*Models adjusted for age, sex, Charlson Comorbidity Index score, black race, time on dialysis, catheter (versus arteriovenous fistula or graft), employment, income, low health literacy, dialysis schedule (Tuesday/Thursday/Saturday versus Monday/Wednesday/Friday), and study site.
Several studies have elucidated plausible mechanisms whereby depression might mediate increased mortality, including higher levels of inflammatory cytokines, catecholamines, and cortisol, as well as enhanced platelet aggregation and decreased patient engagement in healthy behaviors (42). Whether such mechanisms could link pain with serious adverse outcomes, including mortality among patients on chronic hemodialysis also warrants future study.

Our study has certain limitations. First, our patients were participants in a clinical trial of symptom management interventions, which may have affected their depressive symptoms, pain, and clinical outcomes. However, we observed clinically insignificant intervention effects on these symptoms that likely had no meaningful effect on their associations with clinical outcomes (26). Moreover, we adjusted our models in this study for the unit of randomization in the parent trial. Second, this study was conducted in a single geographic area, which may limit generalizability. Third, to assess depressive symptoms, we used the PHQ-9, which is not considered the “gold standard” tool for the diagnosis of major depression. Nonetheless, the PHQ-9 was previously validated in the chronic hemodialysis population (5,43). It is important to note that the level of depressive symptomatology, defined categorically, was not independently associated with mortality; this finding differs from most prior studies.

We believe this is related to the relatively low absolute number of mortality events in our study and the reduced statistical power with categorization of a predictor variable. Fourth, observational studies cannot establish causal associations and we are unable to determine potential mechanisms linking depressive symptoms and pain with adverse outcomes. Fifth, the longitudinal analyses presented simplify the potential associations between symptoms and outcomes. These analyses assume the same association over all assessments, with the exception of a linear change in outcomes over time and an overall estimate of the patient-specific tendency for each outcome. However, post hoc analyses that assessed for interactions between the symptoms, evaluated associations by type of pain, and included lagged symptom scores as predictors, random slopes over time for patients, or higher order effects of time did not change the associations we observed. Sixth, our assessment of ED visits relied on patient interviews and hence was potentially subject to recall bias. However, because of the frequency of such assessments, it is unlikely that patient recollection overestimated or underestimated this outcome. Nonetheless, because ED visits were captured by patient interview, it is possible that ED visits that occurred just before death were missed. Finally, the median percentage of missed dialysis treatments was low and may not represent clinically significant nonadherence.

Figure 1. Multitrajectory models: dialysis adherence. Predicted longitudinal trajectories of the mean SF-MPQ score, mean PHQ-9 score, and mean dialysis adherence by groups of patients with similar longitudinal patterns in pain, depressive symptoms, and dialysis adherence for missed (A) and abbreviated (B) dialysis sessions. PHQ-9, Patient Health Questionnaire-9; SF-MPQ, Short-Form McGill Pain Questionnaire.
Figure 2. | Multitrajectory models: ED visits, hospitalizations, and mortality. Predicted longitudinal trajectories of the mean SF-MPQ score, mean PHQ-9 score, and outcomes by groups of patients with similar longitudinal patterns of pain, depressive symptoms, and outcomes for ED visits (A), hospitalizations (B), and mortality (C). ED, emergency department.
In conclusion, among patients on chronic hemodialysis, depressive symptoms and pain are independently associated with dialysis nonadherence and health resource utilization, whereas depressive symptoms are also independently associated with mortality. The strength and validity of these findings are based on the serial longitudinal assessment of symptoms and outcomes. Moreover, our multitrajectory analyses demonstrate that there are groups of patients with consistent longitudinal patterns of depressive symptoms, pain, and adverse outcomes. Although there is no evidence at present that treating depressive symptoms or pain decreases health resource utilization or mortality, treatment can alleviate these bothersome symptoms. Focusing treatment and future research on patients with consistent longitudinal symptoms may improve the approach to and benefits of symptom alleviation. Considering the high costs, morbidity, and mortality of this chronically ill population, studies of antidepressant and analgesic interventions should evaluate their capacity to enhance dialysis compliance, reduce health resource utilization and costs, and improve survival.

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