Depression in Chronic Kidney Disease

Michele Fabrazzo and Rosa Maria De Santo*

Depression is the most frequent psychiatric problem in patients with chronic renal disease and may predict patient outcome and mortality. Depression is linked to stressful life characterized by many losses and by dependence, which even may lead to suicide. Despite the large number of patients with chronic kidney disease and the economic burden they represent, only a few of these patients receive adequate diagnosis and therapy. Diagnostic and Statistical Manual of Mental Disorders-IV criteria for major depression may help in differentiating symptoms of uremia and depression. Pharmacotherapy is available and antidepressants (tricyclic antidepressants and selective serotonin re-uptake inhibitors) have been used successfully in various studies. Finally, there is a need for further well-designed, longitudinal, survival studies to clarify the relationship better between depression and the different stages of renal dysfunction.

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The term depression usually is used to indicate an acute affective experience, a consequence of a physical disease or a medication-induced problem, a primary psychiatric syndrome or a symptom present in other psychiatric disorders. Depression is a pathologic condition that can affect 7% to 15% of men and 13% to 18% of women.1 In the general population, more than 1 in 8 people request treatment for depression during their lifetime: more than 60% of depressed patients initially consult their general practitioner and a small percentage are referred to a psychiatrist or psychiatric service, and only 30% to 50% of patients are diagnosed with depression.1 Depressed patients have a low quality of life, a worsening of their physical condition, and loss of role within the family and workplace even greater than patients with other chronic diseases. Moreover, depression may place a significant economic burden on patients, their family, and on the health care system. In the United States, affective disorders comprise 3.3% of national health care resource costs and 54% is related to treatment of the illness or disorder, an 8.1% cost for the impact on productivity and a 28.9% cost because of the increased mortality.1

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Problematic Aspects of Depression

Arieti,2 in 1978, already differentiated a physiologic condition, which can be called a normal sadness, from what is considered major depression. The boundaries of these 2 conditions are not well defined, they probably are quantitative or qualitative different states of mood. From this respect, the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) defines major depression according to different criteria (Table 1).

Therefore, in contrast with normal sadness, a depressed mood may not be associated with real adverse events and if losses are reported, they are grossly exaggerated, anticipated, or imagined. Major depression can be extremely painful, persistent, and pervasive, resisting all attempts to change by encouragement or reasoning. It commonly is associated with worthlessness, low self-esteem, sustained self-deprecation, and feelings of guilt and death wishes. It frequently escalates over time and impacts on interpersonal relations and daily functioning. More frequently than in normal sadness, rhythm disturbances and hormonal dysregulation may be recognized. Besides the symptomatologic criterion, major depression diagnosis, according to the DSM-IV, also is based on chronologic, functional, and exclusion criteria (Table 1). Major depression can be qualified further by the presence of melancholic features3 (Table 2), which corresponds to the classic concept of endogenous depression, whose outcome is...
independent of stressful events, whereas melancholic major depression also can be preceded by such events.

According to DSM-IV, affective, cognitive, somatic, and a psychomotor cluster of symptoms may be recognized in major depression.

The Prevalence and Diagnosis of Depression in Uremia

No large-scale, well-designed, epidemiologic studies in patients with renal diseases have been conducted. In 1993, however, 8.9% of dialyzed patients needed hospitalization because of psychiatric problems. 4

According to Kimmel laboratory, 4-14 patients with end-stage renal disease (ESRD) carry the risk for high frequency of moderate depression, which seems to be the most important clinical psychiatric complications in these patients.

In ESRD patients, previous studies have reported a variable prevalence of depression. In fact, a 0% prevalence of depression in the study by Wright et al15 and Glassman and Siegel16 was found, whereas Klein et al17 identified only a 15% rate of depressed patients. In the study by Foster et al18 and Smith et al,19 a 47% prevalence was reported. Moreover, 100% of patients had depression in the study by Reichsman and Levy.20

The reported variability of the prevalence of depression can be a result of different methodologic problems: earlier studies lack information on comorbidities, dialysis delivery/efficacy, undefined behavioral compliance, and psychosocial factors. Kimmel et al21 reported a total of 15,701 of 176,368 patients undergoing hemodialysis and peritoneal dialysis (8.9% of the total) who required hospitalization for depression. The rate per 10,000 patient-years was 74 for hemodialysis patients and 64 for peritoneal dialysis patients. The duration of hospitalization averaged 12.7 days for hemodialysis patients and 11.2 for peritoneal dialysis patients. In patients older than 65 years with chronic renal failure, the rate of depression and affective disorders was 90%. In addition, patients dialyzed for 1 year or more were more prone to hospitalization, which might be the end result of “initial denial or because early hopes of reversibility have not been fulfilled.”

Psychiatric disorders may be unrecognized22 at the beginning of dialysis treatment or may be attributed incorrectly to uremia. In fact, depressed ESRD patients may complain of fatigue, irritability, apathy, anorexia, aches, sleep disorders, bowel disorders, incapacity to concentrate, decrease of appetite, and action tremor, which are usual for uremia but at the same time are similar to symptoms of depression. Only feelings of sadness, helplessness, hopelessness, guilt, presence of a death wish, and loss of libido should be considered as symptoms of depression.

Uremia-Associated Losses and Dependences as Causes of Depression

Several factors for depression can be identified in dialyzed patients. The most important are the feelings of loss3,11,22 and dependence (Table 3), a concept advanced in 1986 by Israel.22 Further concerns are about dietary constraints, time restrictions, functional limitations, loss of employment and loss of role in the dyad and workplace, change in sexual function, illness and medications effects, and fear of death.23 Moreover, dependence on the dialysis machine, the dialysis staff, and physicians also occurs.22-26

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Criteria for Major Depression According to DSM-IV</th>
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<tr>
<td><strong>Criteria</strong></td>
<td><strong>Symptomatologic criterion</strong></td>
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<td></td>
<td>At least 5 of the following symptoms:</td>
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<td>Depressed mood</td>
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<td>Markedly diminished interest or pleasure in all, or almost all, activities</td>
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<td>Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or a decrease or increase in appetite</td>
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<td>Insomnia or hypersomnia</td>
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<td>Psychomotor agitation or retardation</td>
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<td>Fatigue or loss of energy</td>
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<td>Feelings of worthlessness or excessive or inappropriate guilt</td>
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<td></td>
<td>Diminished ability to think or concentrate or indecisiveness</td>
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<td></td>
<td>Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan or a suicide attempt or a specific plan for committing suicide</td>
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<tr>
<td><strong>Chronologic criterion</strong></td>
<td>Depressive symptoms should last for at least 2 weeks</td>
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<tr>
<td><strong>Functional criterion</strong></td>
<td>Depressive symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning</td>
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<tr>
<td><strong>Exclusion criterion</strong></td>
<td>The symptoms are not caused by the direct physiologic effects of a substance (eg, drug abuse or medication) or a general medical condition (eg, hypothyroidism)</td>
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Data from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.3

<table>
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<tr>
<th>Table 2</th>
<th>Criteria for Major Depression With Melancholic Features According to DSM-IV</th>
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<tr>
<td></td>
<td>Lack of pleasure in all or almost all activities, or lack of reactivity to pleasurable stimuli</td>
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<td>Presence of at least 3 of the following</td>
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<td>A distinct quality of depressed mood</td>
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<td></td>
<td>Diurnal variation of mood</td>
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<td></td>
<td>Psychomotor retardation or agitation</td>
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<td></td>
<td>Loss of weight and appetite</td>
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<td></td>
<td>Feelings of excessive or inappropriate guilt</td>
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Data from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.3
Survival and Depression

Several studies\textsuperscript{15-17,19,20,27-36} have assessed the relationship between depression and mortality in hemodialysis patients, but the conclusions have been contradictory. Shulman et al\textsuperscript{37} followed-up a group of 64 patients for 10 years. At 10 years, patients with Beck Depression Inventory (BDI)\textsuperscript{38} scores of 14, in comparison with those with a BDI greater than 25, had a survival probability of 26% versus 10%, respectively. For BDI scores in the range of 14 to 24, the probability was nearly 16%. Although somatic items contributed disproportionately to BDI scores, they could not account for abnormally increased scores, and cognitive and emotional subscores paralleled changes in somatic scores. The BDI score correlated with a chronic dysphoric state present for years or months without remission in patients who previously were not depressed before dialysis. The BDI score was the most important predictor of survival. However, 30% of the patients had major depression as measured by interviews and 30% of patients had major depression by BDI scores.

Comorbid illnesses were associated with lower survival rates. Age, sex, and serum calcium level were independent significant associations with mortality after adjustment for BDI. The impact of depression was maximal in the first few years of dialysis. However, the study was performed when quantification of dialysis administration was not available.

Withdrawal From Dialysis/Suicide

Discontinuation of dialysis therapy in the years from 1991 to 1994 was responsible for 17.8% of the deaths occurring in 126,156 patients with ESRD.\textsuperscript{39} Levy\textsuperscript{40,41} pointed out that the rate of suicide in dialysis patients is 50 times higher than in the general population. Beder\textsuperscript{42} provided a profile of characteristics of patients likely to withdraw from treatment (Table 4) and showed that “hyperindependence and impulsivity carry a poor prognosis, as do denial of illness beyond the initial phase of dialysis and evidence of psychopathology.”

In a study with 716 dialysis patients followed-up for 20 years, dialysis withdrawal accounted for 18.5% of all deaths.\textsuperscript{43} Patients who stopped dialysis were older when starting dialysis, and 65.1% were 61 years of age and older. Cancer, malnutrition, catabolism, and dissatisfaction with life were associated with the decision to withdraw from dialysis. In addition, 50% of the patients had either diabetic nephropathy or atherosclerotic renal vascular disease.

In a study of the Michigan Dialysis Registry (4,753 white and 2,988 black patients), the problem of withdrawal was analyzed carefully and it was shown that it was higher in white patients. Age and diabetic nephropathy had a statistically significant joint effect. In female patients there were slightly lower rates of withdrawal.\textsuperscript{44} McKegney and Lange\textsuperscript{45} have made a case for the communication gap between patients and the dialysis staff. They believed that dialysis patients do not let the staff know that the quality of life provided by the machine is felt to be inadequate to continue to fight, and they also stressed the inadequacy of the dialysis staff in catching this condition. It also has been reported that over-optimism should be avoided by the nephrologist.

In addition to the problem of withdrawal there is the problem of suicide, which is not synonymous with withdrawal. In the

<table>
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<th>Table 3 Uremia-Associated Losses and Dependences</th>
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<tr>
<td><strong>Losses</strong></td>
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<tr>
<td>Loss of urinary function</td>
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<td>Loss of the capacity to concentrate</td>
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<td>Loss of work place</td>
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<td>Loss of the freedom to select or to find a job</td>
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<td>Loss of the capability to accept an exacting job</td>
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<td>Loss of role in the family</td>
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<td>Loss of family dynamics</td>
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<td>Loss of role in social relationships</td>
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<td>Loss of quality of life</td>
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<td>Loss of the sense of femininity</td>
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<td>Loss of menstruation</td>
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<td>Loss of the capability to have orgasm</td>
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<td>Loss of the sense of masculinity</td>
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<td>Loss of erectile function</td>
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<td>Loss of libido</td>
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<td>Loss of capability to set constructive goals</td>
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<td>Loss of good mood</td>
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<td>Loss of life expectancy</td>
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<td>Loss of the capability of practicing a sport</td>
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<td>Loss or limitations in mobility</td>
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<td>Loss of freedom in selecting foods</td>
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<td>Loss of freedom in selecting beverages</td>
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<td>Loss of body weight</td>
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<td>Loss of muscle mass</td>
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<td>Loss of body imaging</td>
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<td>Loss of skin color</td>
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<td>Loss of weight stability</td>
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<td>Loss of sleep hours</td>
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<td><strong>Dependences</strong></td>
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<td>On dialysis staff</td>
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<td>On physician</td>
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<td>On medications</td>
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<td>On family</td>
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<td>On a machine</td>
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<td>On dialysis shifts</td>
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<td>On dialysis calendar</td>
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<th>Table 4 Characteristics of Patients Likely to Withdraw From Dialysis</th>
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<tr>
<td><strong>Patients aged ≥60 years</strong></td>
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<tr>
<td>Depressed patients</td>
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<td>Anxious patients</td>
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<td>Patients with comorbid conditions</td>
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<td>Patients whose self-perception is one of being sick rather than well</td>
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<td>Patients facing imminent surgery</td>
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<td>Patients with dementia</td>
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<td>Patients on dialysis for more than 8 years</td>
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<tr>
<td>Sophisticated patient who tries to control everything</td>
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<td>Patients of higher economic status</td>
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<td>Patients in denial</td>
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<td>Impulsive hyperindependent patient</td>
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Data from Beder.\textsuperscript{42}
United States the rate of suicide among dialysis patients is 0.3 patients per 1,000 patients-years, whereas in the general population the rate is 0.12 per 1,000 person-years. There are many methods of suicide, the most frequent is the ingestion of a high quantity of foods containing potassium.46

**Suicide in ESRD Patients**

Although depression and dialysis withdrawal are relatively common in patients with ESRD, there have been few systematic studies of suicide in this population.

Shulman et al37 reported 7% of deaths by suicide (caused by an overdose of aspirin, bleeding through shunts, and gas from a motor vehicle) and 4.6% of all deaths by dietary non-compliance. In addition, the risk for suicide should be considered even higher than in the general population and comparable with that in patients with other severe chronic illnesses. Their conclusion was that depression has to be monitored in the early stages of chronic renal failure.

In Italy, De Stefano et al37 were unable to trace the rate of suicide even in dialyzed patients with depression.

**Therapy**

Levy et al21,48,49 and Kimmel et al7 recently have underlined that adequate primary care of patients with renal failure requires a knowledge of the major psychologic stresses, the diet, the procedure, the machine, the medications, and the relationship with the dialysis staff and the physicians. They advised optimization of dialysis therapy on the grounds of evidence-based medicine, which speaks for advanced technology of machine and membranes, the treatment of anemia, and the treatment of a calcium-phosphate imbalance. It also is extremely important for patients to start dialysis therapy on time. Late referral is associated with increased morbidity and mortality50-52 and with worse scores for depression in comparison with patients who receive early referral.53 This must be associated with prevention and psychiatric, psychologic, and psychosocial support. When necessary, pharmacologic treatment should be initiated.

There are many problems with the use of psychotropic drugs54,55 in renal failure. This is not only because of changes in pharmacodynamic and pharmacokinetic effects caused by loss of renal function. In fact, absorption is reduced, volume distribution is increased, and protein binding is reduced. The reduction in protein binding causes higher available drug levels.48 Finally, deacetylation, acetylation, hydroxylation, O-demethylation, N-demethylation, conjugation, and sulfoxidation may be reduced. In renal disease, the reduction in excretion of drugs is a function of the fraction removed by the kidneys and by the degree of renal function. Therefore, it always is important to know the most simple clinical indicator of renal function, which is the plasma creatinine concentration.29 Finally, the dialysis procedure per se may affect drug concentrations in plasma, but not in tissues, so that a rebound may occur after treatment.

Pharmacologic treatment of depression in renal disease is a topic receiving continuous input by everyday clinical practice.56 Antidepressants should be used and should be part of the armamentarium of every nephrologist. For Levy et al,21,46,49 the dosage should not be more than two thirds of the maximum dose reached in patients with normal renal function. Kimmel et al7 suggested that antidepressants should be used for any patients meeting DSM-IV criteria and should be used at a dosage providing the maximum reduction in symptoms with the minimum of side effects.

Patients with ESRD usually respond to pharmacotherapy with few medication side effects. Tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) have been used successfully in various studies.32,48,49,57,58 SSRIs, however, are associated with nausea, headache, insomnia, and nervousness. In the 1990s, TCAs were the drugs of choice, and some of them continue to be used such as nortryptiline. In fact, this drug has an anticholinergic effect, which is the lowest for the category and a favorable therapeutic window in the range of 50 to 150 ng/L. The use of antidepressants should be initiated only on the advice of a specialist, taking into account the possibility of drug interactions. The great majority of TCAs and SSRIs undergo extensive hepatic metabolism by the P-450 enzyme system.59 This can lead to active metabolites such as norfluoxetine and nortryptiline, and nonactive metabolites as in the case of fluvoxamine and sertraline. Among SSRIs, several studies pointed out the use of sertraline, bupropion, and nefazodone.37,58 In these studies, medication doses were titrated carefully by the psychiatric investigators who took into account the clinical response and the side effects. Their mean BDI scores at the completion of the study were well below baseline values and a dramatic improvement in depressive symptoms was observed. This stresses the importance for treating depression in dialyzed patients.

**Conclusions**

Depression is a common but underdiagnosed and understudied problem in ESRD patients. In multiple studies in patients with chronic medical illnesses, it has been shown to increase symptom burden, to lead to additive function impairment, to increase medical costs, and to impair self-care and adherence. The available data on chronic renal failure patients with significant medical comorbidities are not sufficient. Therefore, it is important that the assessment of depression should be included in routine patient evaluations. On the other hand, researchers in the field of renal diseases should learn to distinguish major depression from high levels of depressive affect. Finally, there is a need for well-designed, longitudinal, survival analyses to clarify the relationship between depression and different stages of renal dysfunction.

**Acknowledgment**

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