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Original Investigation

Association Between Depression and Mortality in Patients Receiving Long-term Dialysis: A Systematic Review and Meta-analysis

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Background: We aimed to systematically review and analyze the association between depression and mortality risk in adults with kidney failure treated by long-term dialysis.

Study Design: A systematic review and meta-analysis of observational studies.

Setting & Population: Patients receiving long-term dialysis.

Selection Criteria for Studies: Searching MEDLINE, EMBASE, and PsycINFO, we identified studies examining the relationship between depression, measured as depressive symptoms or clinical diagnosis, and mortality.

Predictor: Depression status as determined by physician diagnosis or self-reported scales.

Outcomes: Pooled adjusted HR and OR of depression for all-cause mortality.

Results: 15 of 31 included studies showed a significant association between depression and mortality, including 5 of 6 studies with more than 6,000 participants. A significant link was established between the presence of depressive symptoms and mortality (HR, 1.51; 95% CI, 1.35-1.69; $I^2 = 40\%$) based on 12 studies reporting depressive symptoms using depression scales (N = 21,055; mean age, 57.6 years). After adjusting for potential publication bias, the presence of depressive symptoms remained a significant predictor of mortality (HR, 1.45; 95% CI, 1.27-1.65). In addition, combining across 6 studies reporting per-unit change in depression score (n = 7,857) resulted in a significant effect (HR per unit change in score, 1.04; 95% CI, 1.01-1.06; $I^2 = 74\%$).

Limitations: Depression or depressive symptoms were documented only from medical charts or a single self-report assessment. Included studies were heterogeneous because of variations in measurement methods, design, and analysis.

Conclusions: There is considerable between-study heterogeneity in reports of depressive symptoms in dialysis patients, likely caused by high variability in the way depressive symptoms are measured. However, the overall significant independent effect of depressive symptoms on survival of dialysis patients warrants studying the underlying mechanisms of this relationship and the potential benefits of interventions to improve depression on the outcomes.

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INDEX WORDS: Maintenance dialysis; end-stage renal disease; depression; death; depressive symptoms; dysthymia.

During recent years, more attention has been paid to nonrenal symptoms of end-stage renal disease (ESRD).[1,2] It is estimated that up to 39.3% of patients with ESRD have depressive symptoms.[3,4] Several factors contribute to the development of depressive symptoms, such as loss of the primary role in the family, decreased physical function, medications, and dietary restrictions.[2,5,6] Depressive symptoms, accompanied by a high burden of physical symptoms, are associated with poor adherence to treatment and loss of well-being in patients with ESRD.[1,2] Accordingly, depression has been suggested to be linked with mortality.

Earlier studies linking depression with mortality risk in patients with ESRD were inconclusive, whereas recent large studies have demonstrated an independent association between depression and mortality.[7-10] Nonetheless, there is considerable variation in the reported findings, in part due to differences in study design, statistical methodology, and the method used to ascertain depression. The objective of this systematic review is to evaluate the association between depression, measured as either depressive symptoms using depression scales or

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clinical diagnosis, and mortality of patients on long-term dialysis therapy.

METHODS

Criteria for Selection of Studies

All observational studies published in either abstract or full form that included an assessment of the ability of depressive symptoms or clinical depression to predict mortality were included. Studies were included if they recruited adult participants 18 years or older who were receiving dialysis (hemodialysis and peritoneal dialysis modalities) as a long-term renal replacement therapy. Non-English articles were considered for inclusion provided that an abstract in English was available.

Depression was defined as documentation of clinical depression (major depression, minor depression, or dysthymia) or depressive symptoms since the initiation of dialysis therapy in any of the following ways: (1) a diagnosis of depression based on structured clinical interviews validated against the *Diagnostic and Statistical Manual of Mental Disorders* or the *International Classification of Diseases* criteria, (2) measurement of depressive symptoms using a depression scale, (3) measurement of depressive symptoms by subscales of other questionnaires if validated as an indicator of depressive symptoms, and (4) any clinical record of the diagnosis of depression during the period after initiation of long-term dialysis therapy.

The primary outcome of interest was all-cause mortality after the initiation of dialysis therapy. Studies with assessment of the outcome less than 3 months or more than 10 years after depression measurement were not included, based on the assumption that mortality occurring either very early or late after the screening is unlikely to be related to depression.

Identification of Studies

Search Strategy

Three online databases—MEDLINE (1948 to August 2012), EMBASE (1947 to August 2012), and PsycINFO (1806 to August 2012)—were searched using the text words "dialysis" OR "hemodialysis," "depression" OR "depressive," and "mortality" OR "survival" OR "death," as well as the vocabulary terms specific to each database. The OvidSP (Ovid Technologies Inc) was used to identify articles from the 3 indexing databases. No filters for language, publication status, or study design were applied (Item S1, available as online supplementary material). The search was performed using a specialist information manager–designed search strategy.

We also reviewed bibliographic information of pertinent review articles; proceedings of international conferences (World Congress of Nephrology, American Society of Nephrology Renal Week, and European Renal Association–European Dialysis and Transplant Association Congress; 2006 to August 2012); and dissertations (ProQuest; 1637-August 2012). Authors of abstracts were contacted for detailed data when possible.

Selection of Studies and Data Extraction

Search results were imported into EndNote X for Windows (Thomson Reuters), and duplications were excluded. Inclusive screening of titles was done by one author (F.F.) to exclude irrelevant records. Two authors (F.F. and N.A.) independently reviewed the refined list of records by screening titles and abstracts based on study design, participants, and the exposure and outcome of interest. Full texts of selected records were screened further. All full-text articles were assessed for eligibility by 2 authors (F.F. and N.A.), with discrepancies resolved through review by a third author (S.V.J.) and consensus. Two authors (F.F. and N.A.) independently extracted study characteristics and effect estimates. Double data entry into RevMan, version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration), was applied by creating and comparing 2 separate RevMan files. In case of missing data, the investigators contacted the authors.

Assessment of Risk of Bias in Included Studies

Data quality was appraised independently by 3 authors (F.F., N.A., and S.V.J.). A modified version of the Newcastle-Ottawa Scale[11] for cohort studies was used for quality appraisal (Item S2). We considered the clinical structured interview of all participants for diagnosis of depression as the highest level of ascertainment of exposure, and identification of depressive symptoms using a depression scale applied to all participants as acceptable. Studies with documentation of depression or depressive symptoms without assessment in selected groups did not meet ascertainment of exposure quality standard. Clinically important determinants for mortality for the Newcastle-Ottawa Scale comparability tool included age, diabetes, and cardiac disease. Because the mechanism for a potential link between depression and mortality is unclear, the minimum time required for observation was unknown. Clinically, it was thought that depression-related mechanisms most likely are long term (with the rare exception of suicide and dialysis therapy withdrawal), and the authors therefore agreed that the study would be considered to have met quality appraisal criteria if they had at least 1 year of follow-up. A maximum lost-to-follow-up rate $<10\%$ was acceptable (Item S2). Studies that met the criteria for representativeness of the exposed cohort ($\geq$3 criteria for selection, $\geq$1 for comparability, and $\geq$2 in the outcome sections) were considered low risk of bias.

Assessment of Effect Size and Heterogeneity

For data presented as a dichotomous variable (presence or absence of clinical depression and depressive symptom scores above or below a cutoff point), crude and adjusted hazard ratios (HRs) and/or odds ratios (ORs) were extracted. Studies reporting data presented as a continuous variable had HRs and ORs for each unit change in scores extracted. When risk estimates were not reported, crude ORs were calculated with 95% confidence intervals (CIs), if possible. Standard errors of the risk estimates were calculated using standard methods.

Between-study heterogeneity was investigated by χ^2 test ($P < 0.1$), and I^2 statistic was used to quantify its impact.[12]

Quantitative Synthesis

Data Synthesis

Eligible studies for quantitative data synthesis were imported into RevMan, version 5.1. Meta-analysis was done to estimate a summary measure of the ORs and HRs. The included studies were grouped based on the effect size (OR and HR) and measurement method of depression (dichotomized or continuous depression score and diagnosis of depression based on prospective structured interviews or review of medical charts) for separate meta-analyses. Studies reporting more than one effect size were included in all applicable groups. The generic inverse variance weighting method (DerSimonian and Laird[13]) was used to test the overall effect for reports of crude and adjusted estimates. The random-effects model was used as a conservative approach to summarize the findings.

Assessment of Publication Bias

The funnel plot was used to visualize potential publication bias. We used the trim-and-fill method to adjust the calculated effect sizes for publication bias.[14] R statistical software, version 2.15.1 (R Foundation for Statistical Computing), was used.