An association between depressive symptoms and survival in incident dialysis patients

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Abstract

Background. Depression in end-stage renal disease patients is detrimental to quality of life, and is also associated with adverse clinical outcomes. The aim of this study was to examine whether depression symptoms in ‘incident dialysis’ patients predicted survival.

Methods. One hundred and sixty incident haemodialysis and peritoneal dialysis patients completed a self-report depression questionnaire (Beck Depression Inventory-II, BDI) at a point soon after dialysis initiation. Over the study period (May 2007–December 2009), patients were followed up with all-cause mortality recorded as the end point.

Results. The median follow-up time for the cohort was 511 days (min 47 days and max 1027 days). There were 27 deaths (16.9%). Depression symptoms were evaluated both as a continuous variable and using a defined cut-off for depressed patients (BDI ≥ 16). In a Cox proportional hazards model, adjusted for several covariates including albumin and extra renal comorbidity, depression score was an independent predictor of mortality (HR = 1.07, 95% CI 1.02–1.11, P = 0.002). In an additional adjusted model, a BDI score ≥ 16 was associated with a 2.7 times increase in the hazard for death (HR = 2.7, 95% CI 1.06–6.8, P = 0.037).

Conclusions. The severity of depression symptoms following the start of dialysis treatment is an independent predictor of survival. Further studies will be required to determine whether the treatment of depression would alter health-related outcomes, including survival.

Keywords: depression; end-stage renal disease (ESRD); incident; mortality; survival

Introduction

Depression is known to be one potentially modifiable risk factor that is associated with adverse outcomes including mortality and non-adherence among patients with physical illnesses. Indeed, there is considerable literature describing the association between depression and cardiac diseases and cardiovascular events [1–7]. This association may be of great importance in end-stage renal disease (ESRD) patients given the high incidence of both depression [8,9] and cardiac morbidity [10,11].

Accumulating evidence suggests that depression is elevated in ESRD as compared with general populations [9,12,13], and that depression predicts mortality in dialysis patients, after considering an array of demographic and clinical covariates [14–20]. For example, a recent study found that depression symptoms, as assessed by the Hospital and Anxiety Depression Scale (HADS), predicted 1-year survival in 101 established Dutch haemodialysis (HD) patients [17]. Analysis of the DOPPS data has found significant associations between baseline depression symptoms and mortality, albeit using rather unconventional methods of depression assessment [16]. More recently, others have used formal diagnostic approaches, and report a significant association between major depressive disorder (MDD) and mortality [20]. When treating depression symptoms in a time-varying analysis, Kimmel et al. [15] found a positive association between depression symptoms and mortality, yet failed to find an association between ‘baseline’ levels of depression and all-cause mortality. Other investigations have failed to find any association between depression and mortality in ESRD patients [21,22], which may be attributable to the various assessments of depression used, the statistical methods employed and the specific populations studied.

Depression soon after dialysis initiation is known to be significant [23], yet to our knowledge, the impact of depression symptoms during this early period upon survival has been the focus of only one previous study, which found that baseline depression symptoms failed to predict mortality [14]. Defining this potential relationship early on in the dialysis career may help target interventions to elevate mood and improve outcomes, before the manifestations of depression-related morbidity become apparent. In order to tend to this need, in the present study, depression symp-
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Depressive symptoms were assessed in newly initiating dialysis patients to evaluate whether they predicted short-term survival after considering identified covariates associated with premature death in ESRD patients.

Materials and methods

Design and patients

Incident dialysis patients (n = 160) from three UK NHS renal centres [Lister, n = 93 (rural hospital); Royal Free, n = 25 (inner London hospital); and Addenbrooke's, n = 42 (city hospital)] were recruited into the study at a point soon after dialysis initiation. Patients were eligible for inclusion if the following criteria were met: (i) ≤3 months on dialysis, (ii) no known significant visual or physical impairment that would prevent the completion of the questionnaires, (iii) fluency in verbal and written English language, (iv) not hospitalized at the time of assessment, and (v) no cognitive impairment as indicated by an age-adjusted score of <22 on the Mini-Mental State Examination [24]. The study was approved by an NHS research ethics committee.

Clinical parameters

In addition to demographic factors, baseline clinical data were recorded from electronic medical records including primary ESRD diagnosis, smoking status, blood haemoglobin, serum albumin and C-reactive protein (CRP), and sessional Kt/V. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine concentrations at the time of dialysis initiation, using the modified MDRD equation [25]. Depression history was recorded, where depressive disorders were listed in the medical problem list in the patients’ medical records. Anti-depressant use at the time of assessment from medical notes was also recorded. The path to dialysis was defined as either ‘planned’ or ‘unplanned’. Planned starters were defined as those with known stage 5 CKD who saw a nephrologist at least once within 90 days pre-initiation. Unplanned starters were those who had no contact with a nephrologist within 90 days pre-dialysis including some who may have been seen before this 90-day period.

Co-morbidity and functional performance

Co-morbidity was assessed from medical notes using the method described by Davies et al. [26] by a consultant nephrologist blinded to the Beck Depression Inventory-II (BDI) scores. One point for each of the following conditions was assigned: ischaemic heart disease (defined as prior myocardial infarction, angina or ischaemic changes on ECG), left ventricular dysfunction (defined as clinical evidence of pulmonary oedema not due to errors in fluid balance, or history of congestive heart failure), peripheral vascular disease (includes distal aortic, lower extremity and cerebrovascular disease), malignancy, diabetes, collagen vascular disease, and other significant pathology. The patients were grouped according to the number of co-morbidities [26]: none (score of 0), medium (score of 1–2) and high (score of 3 or more). Functional performance was assessed by the Karnofsky Performance Status (KPS) [27]. Patients’ functional status was defined according to dependency based upon their KPS score, where a score ≥70 reflects independence and <70 dependency.

Depression assessment

Depression symptoms were assessed via the BDI-II [28,29]. The BDI is a self-report depression questionnaire designed to assess the severity of depressive symptoms. The BDI consists of 21 items, which are each rated upon a four-point scale (0–3) indicating the frequency or severity of a particular depressive symptom (scores range from 0 to 63). The accuracy of the BDI (BDI-I and BDI-II) for use within the ESRD population has been demonstrated [30–35]. Although the BDI relies upon a continuous scale, cut-off values can be employed to indicate significant depressive symptoms. While the BDI cannot be used to diagnose clinical cases of depression, cut-off scores ranging from ≥14 to 16 compare well with diagnostic assessments in dialysis patients [30–34]. We have previously shown that employing a BDI-II ≥16 compares well with diagnostic measures among

UK dialysis patients [34]. This definition was employed in the present study to define patients with significant depressive symptoms. In the present analysis, the term ‘depression’ or ‘depressed’ refers to patients with significant depression symptoms (BDI ≥16) and not a clinical diagnosis.

Outcome assessment

All-cause mortality was the outcome measure over the study period (May 2007–December 2009), which was ascertained by active surveillance through the renal clinics by a local consultant nephrologist, who verified the date of death. Time zero in the survival models was taken at the time patients completed the BDI assessment. Patients were censored if they received a transplant, were lost to follow-up, recovered renal function, or were still alive at the end of follow-up.

Statistical analysis

The demographic, clinical and BDI data were described by the use of means (standard deviation), medians (interquartile range, IQR) and proportions. Group comparisons [differences between depressed (BDI ≥16) and non-depressed (BDI <16)] were assessed via parametric and, where appropriate, non-parametric inferential statistics including independent t-tests, Mann–Whitney U-tests, and chi-square analysis (Pearson’s and Fisher’s exact test where appropriate).

Kaplan–Meier plots, with log-rank tests, were constructed to examine differences in survival (recorded in days) between groups. Survival was described in terms of the cumulative proportion (standard error, SE) of patients surviving 18 months (540 days) post-dialysis initiation. Cox proportional hazards models were constructed to examine the association between depression symptoms (BDI) and survival in both unadjusted and adjusted models. Adjusted survival models controlled for the following covariates: serum albumin levels, blood haemoglobin levels, path to dialysis, Davies comorbidity score, log CRP, and KPS <70. CRP was transformed due to a skewed distribution. These covariates were selected due to their univariate association with either survival or depression. Two sets of models were evaluated, one in which depression was treated as a continuous variable (i.e. total BDI scores) and the other where depression was treated as a categorical variable (employing a BDI ≥16 to define depressed patients). All data were analysed in SPSS version 17.0.

Results

Patient characteristics

Two hundred and twenty-one initiating dialysis patients who were eligible for the study were approached. One hundred and sixty patients gave consent and completed the baseline measures (consent rate = 72.4%). Participants (n = 160) and non-participants (n = 61) did not differ significantly with regard to age (t[219] = 0.19, P = 0.233), sex (X²[1,221] = 1.62, P = 0.20), treatment modality (X²[1,221] = 0.99, P = 0.32), or renal centre (X²[2,221] = 4.4, P = 0.11). A summary of demographic and clinical data is shown in Table 1. The mean age of the incident cohort was 57.4 (±16.0) years. The majority of patients were male (67.5%), white (90.6%) and receiving haemodialysis (82.5%). The median dialysis vintage at the time of assessment was 30.5 days (min 1 and max 90 days, IQR = 35.8). The mean BDI score was 12.0 (SD = 8.7). Approximately one in four patients (25.6%) scored ≥16 on the BDI suggesting significant depressive symptoms. A documented history of depression as indicated from medical records was evident in 15% of the sample. Seventeen patients (10.6%) were on anti-depressants. As expected, there was a strong association between a positive depressive history and current anti-depressant use (P < 0.001).
Comparisons between depressed (BDI ≥16) and non-depressed (BDI <16) patients

The differences between depressed (BDI ≥16) and non-depressed patients (BDI <16) with regard to baseline demographic and clinical factors are shown in Table 1. Depressed patients (BDI ≥16) were significantly younger and were more likely to have an unplanned entry to dialysis, as compared with non-depressed patients (BDI <16, see Table 1). In addition, depression (BDI ≥16 vs. BDI <16) was significantly associated with dependent physical functioning (i.e. KPS <70) and with a depressive history, yet was not associated with current anti-depressant use (P = 0.33).

There was no association between depression and renal centre (χ²[1,160] = 3.6, P = 0.163), or between depression and Davies co-morbidity (χ²[2,160] = 4.1, P = 0.129). Similarly, the mean BDI scores did not differ significantly across the three Davies co-morbidity groups (F[2,159] = 1.7, P = 0.183).

Correlates of the BDI

The BDI scores correlated with the KPS score (Spearman’s rho = 0.462, P < 0.01) and age (r = -0.260, P < 0.01). The BDI scores failed to correlate with albumin (r = -0.081, P = 0.309), haemoglobin (r = -0.03, P = 0.730), CRP (Spearman’s rho = 0.06, P = 0.418), eGFR (r = 0.019, P = 0.811) and dialysis vintage (r = 0.05, P = 0.496).

Survival analysis

The patients were followed up for a median of 511 days (min 47 and max 1027 days), during which there were 27 deaths (16.9%). Over the study period, 4 patients recovered renal function, 14 were transferred to other dialysis units (lost to follow-up) and 14 were transplanted. Although censoring for transplantation is informed censoring, patients who went on to have a transplant did have comparable BDI scores as compared with those who did not receive a transplant (P = 0.246).

Two patients died within 90 days of dialysis initiation, and all survived at least 30 days. The cumulative survival at 1 year post-dialysis initiation was 87.7% (SE = 0.03) and at 18 months 85.9% (SE = 0.03). No patients discontinued dialysis therapy.

Kaplan–Meier survival analysis: differences between categorical variables (log-rank test)

There was a significant difference in survival between depressed (BDI ≥16) and non-depressed (BDI <16) patients (P = 0.013, Figure 1). At 18 months, the cumulative survival (CS) in depressed patients was 74.9%...
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Depressed

No (BDI <16)

Yes (BDI ≥16)

p=0.013

Fig. 1. Kaplan–Meier survival function comparing depressed (BDI ≥16) and non-depressed (BDI <16) patients (with log-rank test).

(SE = 0.07) compared with 89.6% (SE = 0.03) in the non-depressed group. Patients scoring KPS >70, indicating independent functioning, survived significantly longer (CS at 18 months = 90.6%, SE = 0.03) as compared with those with a KPS ≤70 (CS at 18 months = 58.5%, SE = 0.11, P < 0.01).

Survival was not associated with any of the following factors: a documented depressive history (P = 0.474), treatment modality (P = 0.302), the use of anti-depressants (P = 0.08), gender (P = 0.486), smoking status (P = 0.423) or renal centre (P = 0.731). Survival had a marginal association with comorbidity, with patients identified as ‘severe’ having greater mortality (P = 0.06). In addition, there was an effect of the path to dialysis upon survival tending towards significance, with unplanned starters having shorter survival (P = 0.06).

Cox proportional hazards models

Clinical variables were initially evaluated in separate Cox survival models. Haemoglobin (HR = 0.82, 95% CI 0.69–0.96, P = 0.018), albumin (HR = 0.91, 95% CI 0.86–0.97, P = 0.002) and log CRP (HR = 2.1, 95% CI 1.52–2.89, P < 0.01) all predicted survival. Interestingly, age failed to predict survival (P = 0.151) over this follow-up. Furthermore, dialysis vintage (albeit short) was not associated with survival (P = 0.452). Accordingly, serum albumin levels, blood haemoglobin levels, path to dialysis, Davies comorbidity score, log CRP and KPS <70 were selected as initial covariates in multivariate models due to their univariate association with survival.

Multivariate survival analysis: Cox proportional hazards models

In unadjusted models, the BDI scores were significantly associated with mortality. A one-point increase in the BDI scores increased the hazard for death by 6% (see Table 2). In fully adjusted models, a one-point BDI increase was associated with a 7% increase in the hazard for death (controlling for serum albumin levels, blood haemoglobin levels, path to dialysis, Davies comorbidity score, log CRP and KPS <70). This equates to approximately twice the risk of death at any given time for a 1 standard deviation change in the BDI. Examination of the covariates revealed that Hb (HR = 0.78, 95% CI 0.62–0.97, P = 0.03) and log CRP (HR = 1.7, 95% CI 1.2–2.3, P = 0.002) also predicted survival. None of the other covariates predicted mortality including KPS score and albumin. A parsimonious model was assessed containing Hb, log CRP and the BDI scores. In this simplified model, log CRP (HR = 1.9, 95% CI 1.4–2.7, P < 0.001) and the BDI (HR = 1.06, 95% CI 1.02–1.1, P = 0.001) remained significant predictors of mortality.

The results were replicated after substituting the continuous BDI scores with a BDI ≥16 to categorize depressed patients (vs. non-depressed, BDI <16) in the survival models. In the fully adjusted model, patients with a BDI ≥16 had a 2.7 times the increase for the hazard for death, as compared with patients with a BDI <16 (P = 0.037, Table 2). Haemoglobin (HR = 0.76, 95% CI 0.60–0.96, P = 0.02) and log CRP (HR = 1.7, 95% CI 1.20–2.40, P = 0.001) also predicted survival. None of the other covariates predicted mortality.

Discussion

The data from this multicentred incident cohort demonstrated that depression symptoms soon after the initiation of dialysis therapy are associated with mortality. While these findings support the data from previously published research [14,15,17,18,20], this is the first investigation to demonstrate that baseline levels of depression symptoms soon after patients initiate dialysis predict survival. Boulware et al. [14] were able to demonstrate that depression symptoms predicted survival over the initial 24 months of dialysis, but only when analysing depression symptoms as a time-varying variable. After evaluating baseline levels of depression, Boulware et al. were unable to find any association between depression and survival. This may be the result of using a brief depression assessment, whereas the present study employed the BDI, versions of which are more commonly used in the ESRD population. In addition, the findings described in our study were not dependent upon how the BDI scores were analysed, whether as a con-

Table 2. Association of depression symptoms with all-cause mortality in incident dialysis patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Type of analysis, HR (95% CI)</th>
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<tr>
<td></td>
<td>Crude</td>
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<tr>
<td>BDI ≥16*</td>
<td>1.06 (1.03–1.10), P = 0.001</td>
</tr>
<tr>
<td>BDI ≥16*</td>
<td>2.58 (1.19–5.63), P = 0.017</td>
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<sup>a</sup>Where reference category (1.0) was non-depressed (i.e. BDI <16).

<sup>b</sup>Adjusted for albumin, haemoglobin, path to dialysis, Davies co-morbidity, log CRP and KPS <70.
We found no association between depression and haemostatic and immune function. Hypoalbuminaemia explained by non-adherence to medical regimes, high risk. Others have proposed that the association is symptoms of illness; thus, depression may be a marker of assessment of depression in ESRD is confused with somatic mortality which may relate to the relatively short follow-up.

With regard to the prevalence of depression symptoms, approximately one in four of the patients in this study scored $\geq 16$ on the BDI, suggesting a potential for depression. This estimate conforms to previous data in incident dialysis patients, although others have suggested that the prevalence of depression may be somewhat higher following the start of dialysis. Of course, the potential for other psychiatric disorders including adjustment disorder may complicate the assessment of depression during this early stage of the patient's dialysis career.

Depression and extra-renal comorbidity may have a close relationship; thus, the finding that depression predicts mortality may indeed be potentially confounded by comorbidities. It may even be that the assessment of depression is a surrogate marker for comorbidity. Although our data, and that from earlier reports, suggest that the effect of depression is independent of comorbidity, the time-varying data of Boulware et al. suggest that increasing levels of comorbidity increase depression. In the present analysis, there was no evidence of any association between comorbidity and depression symptoms. Several other studies in dialysis patients have reported an association between depression and comorbidity; however, their findings are mixed. Different methods of assessing both depression and extra-renal comorbidity may underlie such contradictory findings. In this regard, the measurement of both depression and comorbidity requires specific empirical attention in this patient setting. Interestingly, it has been suggested that it is the interpretation of the illness (i.e. illness perception) rather than the illness per se that is associated with depression; thus, it may be more surprising that depression fails to correlate with extra-renal comorbidity. Furthermore, in the present analysis, comorbidity was only weakly associated with mortality which may relate to the relatively short follow-up.

The relationship between depression symptoms and mortality is undoubtedly complex. The measurement or assessment of depression in ESRD is confused with somatic symptoms of illness; thus, depression may be a marker of sub-threshold disease or comorbidities not deemed to be high risk. Others have proposed that the association is explained by non-adherence to medical regimes, maladaptive health behaviours, and changes in haemostatic and immune function. Hypoaalbuminaemia, a well-established risk factor for mortality in ESRD, has also been associated with depression in ESRD. We found no association between depression symptoms and serum albumin at the initiation of dialysis, although other studies have reported that depression predicts a decreasing trend in serum albumin over time. Furthermore, depression has potentially been linked to inflammation in ESRD patients, although the evidence is somewhat contradictory. Similarly, we found no association between CRP and depression, though we did not measure more specific markers of inflammation such as IL-6 and hsCRP. A potential pathway between depression and mortality implicates the triad of malnutrition, inflammation and atherosclerosis (MIA). There are close links between these in ESRD, and some preliminary evidence that depression could be involved in MIA syndrome.

Our study has some potential limitations to consider when evaluating the findings. Our end point of all-cause mortality prevents evaluation of any specific association between depression and CVD-related deaths, which would be of interest given the high prevalence of cardiac disease in the dialysis population. With regard to the censoring, it was decided to censor patients for transplantation because the clinical trajectory of the disease is altered following this outcome. Although this naturally introduced some bias, it should be noted that patients who went on to receive a transplant did have comparable BDI scores compared with those who did not. Hence, it seemed pragmatic to censor for this event. In addition, the analysis presented here was re-analysed with transplant uncensored. The results remained unchanged with depression, Hb, and log-CRP predicting survival.

Our measure of depression was not diagnostic; thus, replicating this study using a diagnostic approach would be of interest. However, we did employ a conventional depression severity measure (BDI), and used an adjusted cut-off score recommended for ESRD patients. It is envisaged that adopting a diagnostic approach would produce similar findings to the data shown here. Another consideration regards the heterogeneity in the timing of depression assessment post-dialysis initiation. However, we found no relationship between dialysis vintage and depression symptoms or between vintage and mortality, suggesting that the variation in vintage may not have unduly affected our findings. With regard to the consideration of depressive history and anti-depressant use, these were both recorded from medical charts. Given that depression is missed in this patient setting, the data collocated from medical charts may be inaccurate, probably under-representing cases of depressive episodes. In addition, treatments for depression other than anti-depressants were not recorded (e.g. psychotherapy), yet it is known that such treatments are rarely utilized in this population.

In conclusion, following dialysis initiation, efforts are made to correct ESRD-related problems including problems relating anaemia and bone and mineral metabolism. The data presented here indicate that the treatment of co-morbid depression symptoms during this early period may also be important. Indeed, several interventions including drug, cognitive behavioural therapy and exercise have shown promise for ameliorating depression in
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ESRD patients. However, the potential for treatment of depression to improve clinical outcomes in ESRD patients needs to be established. There is mixed evidence that treating depression has a positive impact on survival outcomes in other physical illnesses [53], even though treatment may have an important role in improving quality of life. This alone is sufficient to justify screening for and treatment of depression in ESRD, particularly after dialysis initiation. Increasing our understanding of the pathways between depression and mortality in ESRD may help to develop interventions to attenuate the risk of death, as well as to improve the psychological outlook of patients on dialysis.

Acknowledgements. This research was kindly supported by a Joint British Renal Society–Kidney Research UK Fellowship (BR5/KRUK). We thank Sam Norton (University of Hertfordshire) for comments on versions of this manuscript.

Conflict of interest statement. None declared.

References

The effect of diabetes on incidence and mortality in end-stage renal disease in Germany

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Abstract

Background. We aimed to examine the epidemiology and mortality risk of patients with incident end-stage renal disease (ESRD) in diabetic and non-diabetic individuals and to determine differences between sexes.

Methods. We used the claims data of a statutory health insurance company. Patients aged 30 years and older who started dialysis or had pre-emptive kidney transplantation between 1 April 2006 and 7 October 2008 were included. We estimated incidence rates of ESRD according to diabetes status, sex and age as well as relative and attributable risks due to diabetes. Using Cox regression, we studied survival and estimated time-dependent hazard ratios (HR).

Results. We included 623 patients with incident ESRD (n = 254 had diabetes); 477 (76.6%) were male, and the mean age was 66.5 years. Standardized to the German population, incidences of ESRD in patients with and without diabetes were 157.9 and 25.6 per 100 000 person-years respectively (6.2-fold increased risk). The impact of diabetes on mortality was time-dependent. Diabetics had an increased mortality risk after the first year. An interaction of diabetes with time (per additional year of follow-up) was found in the whole population (HR 2.01, 95% CI