Is depression a risk factor for mortality in chronic hemodialysis patients?

Depressão seria um fator de risco para mortalidade entre pacientes em hemodiálise crônica?

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Abstract

Objective: The present study was conducted to assess the association between depressive symptomatology and mortality in chronic hemodialysis. **Method:** *A cohort of 40 patients was followed for a median period of 10.5 months. The Beck Depression Inventory was used to classify patients as exposed to depression (Beck Depression Inventory score ≥ 14) or not (Beck Depression Inventory < 14). Kaplan-Meier survival curves were used to compare the mortality rate between the two groups. The effects of potential confounding factors were adjusted using Cox proportional hazards model.* **Results:** *After 24 months of follow-up, survival rates were 39% for exposed and 95% for non-exposed patients (p = 0.029). The Cox proportional hazards model showed results similar to those of the bivariate analysis, indicating that depressive symptomatology tended to be associated with mortality (HR = 6.5, 95%CI: 0.8-55.6; p = 0.085). Other study variables, including age, concurrent systemic diseases, and biochemical markers, were not significantly associated with mortality. Exposed patients remained on dialysis longer and received kidney transplants less frequently (9% vs. 50% for non-exposed patients). When kidney transplantation was included in the Cox regression model, the hazard ratio of mortality for exposed as compared to non-exposed patients lost statistical significance (HR = 4.5; 95%CI: 0.5-40.0; p = 0.17).* **Conclusions:** *Our study suggests that the presence of depressive symptoms may act as an independent risk factor for mortality in chronic hemodialysis patients. However, this finding needs further investigations.*

Descriptors: Kidney failure; Renal dialysis; Proportional hazards model; Depression; Mortality

Resumo

Objetivo: Avaliar a associação entre depressão e óbito nos pacientes em hemodiálise crônica. **Método:** *Uma coorte de 40 pacientes foi acompanhada por um período mediano de 10,5 meses. A escala Beck Depression Inventory foi utilizada para classificar os pacientes como expostos à depressão (Beck Depression Inventory score ≥ 14) ou não expostos (Beck Depression Inventory < 14). Curvas de sobrevida, segundo o método de Kaplan-Meier, foram utilizadas para comparar a taxa de mortalidade entre os dois grupos. Os potenciais fatores de confusão foram ajustados por meio do modelo de riscos proporcionais de Cox.* **Resultados:** *Após 24 meses de seguimento, as taxas de sobrevida foram 39% para os pacientes expostos e 95% para os não-expostos (p = 0.029). O modelo de riscos proporcionais de Cox mostrou resultados semelhantes aos obtidos na análise bivariada, indicando que a sintomatologia depressiva tende a estar associada com mortalidade (HR = 6,5; IC95%: 0,8-55,6; p = 0,085). As outras variáveis estudadas, incluindo idade, doenças sistêmicas concomitantes e marcadores bioquímicos, não mostraram associações significativas com óbito. Pacientes expostos permaneceram mais tempo em hemodiálise e receberam menos transplante renal (9% vs. 50% para não-expostos). Quando o transplante renal foi incluído no modelo de riscos proporcionais de Cox, a razão de riscos de mortalidade para os pacientes expostos comparados com os não-expostos perdeu significância estatística (RR = 4,5; IC95%: 0,5-40,0; p = 0,17).* **Conclusões:** *Nosso estudo sugere que a presença de sintomas depressivos pode ser um fator de risco independente para óbito de pacientes em hemodiálise crônica. No entanto, este achado necessita ser mais investigado.*

Descritores: Falência renal; Diálise renal; Modelo de riscos proporcionais; Depressão; Mortalidade

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Introduction

Depressive symptoms are one of the most common psychological disturbances associated with physical illness, but they are often undetected and/or left untreated.[1,2] Depression may worsen disabilities, increase pain, reduce patient compliance, and affect prognosis.[2,3]

Depression is also generally accepted as the most common psychological problem encountered in patients with end-stage renal disease (ESRD).[4-6] Nevertheless, its prevalence and role in mediating survival in these patients are highly controversial.[7] While several studies with ESRD patients have shown an association between depression and mortality,[8,9] the opposite has also been reported,[10] and thus the question of whether or not depressive symptoms are independent predictors of mortality in ESRD patients remains. Therefore, the present study investigated the existence of an association between presence of depressive symptoms and mortality in a cohort of patients on chronic hemodialysis (HD).

Patients and method

A prospective cohort study was carried out from August 1996 to October 1999 to investigate the association between exposure to depressive symptoms (independent variable) and mortality (dependent variable) in ambulatory HD patients. All participants, present at the dialysis site, fulfilling the inclusion criteria and signing an informed consent form were included. The study was approved by the Research and Ethics Committee at Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Brazil.

From a total of 124 patients identified, 84 were excluded due to the following reasons: 31 for refusal, blindness, illiteracy, age below 15 years old, Mini-Mental State Examination[11] (MMSE score < 18), and 53 which were in HD for a period longer than 6 months. Therefore, we assembled a sample of 40 patients to be included in this study. Patients were evaluated at the beginning of their second HD session of the week using the Beck Depression Inventory (BDI),[12] which is often used to assess depression in patients with ESRD.[7,13-17]

BDI questionnaires were handed to them by medical students specifically trained to use this scale. Routine laboratory tests, including serum hemoglobin, hematocrit, albumin, creatinine, and Kt/V estimation, were performed in order to determine the clinical status of patients and the efficacy of HD, and to rule out the presence of disorders such as anemia and malnutrition, whose symptoms are similar to those of depression. In addition, since the usual complaints reported by ESDR patients[7,18] are also similar to the somatic symptoms that are used to diagnose depression, a second evaluation was performed using the Cognitive Depression Index (CDI) to reduce the possible confounding effect of medical illness on the somatic components of depression as measured in the BDI.[7,12,18] The CDI is a 15-item subscale of the BDI.

Patients were divided into two groups according to the results of the BDI. Since the median BDI score for the entire group was 14, patients with a BDI score ≥ 14 were considered as exposed to depressive symptoms, and patients with a BDI score < 14 were considered as not exposed, although it is known that many of the latter may also present depressive symptoms. Patients were followed for a period ranging from 3 to 38 months. The primary endpoint analyzed was mortality while on HD. Patients who were transferred to another center, who began continuous ambulatory peritoneal dialysis (CAPD), or who received a kidney transplant were censored at the moment that event occurred. Patients were not on antidepressants during the study.

With a fixed sample size of 40 patients the study attained a statistical power of 80% ($\beta = 0.20$) to detected a hazard ratio (HR) ≥ 5.0 with a significance level of 5%. In the statistical analysis, mean and standard deviation (SD) were used for quantitative variables with normal (Gaussian) distribution, and median and interquartile range (p25-p75) for ordinal qualitative variables and quantitative variables with non-Gaussian distribution. The categorical variables were presented as frequencies and percentages. Data analysis included the use of Student's t, Mann-Whitney's U, and chi-square tests. In addition, Kaplan-Meier curves were used to evaluate survival, followed by the log-rank test to compare the groups. The Cox proportional hazards model was used to assess the effect of confounding factors. Significance level (α) was set at 0.05. Data were analyzed using SPSS for Windows version 11.0.

Results

Table 1 presents demographic and clinical information concerning the entire group and exposed and non-exposed patients. For the entire group, median time on HD was 1.6 month (0.7-3.6) at first interview. The maximum follow-up was 38 months (3.2 years), and median follow-up was 10.5 months (4.6-21.8). The mean BDI score (± SD) for the entire group was 16.2 ± 10.6, which

Table 1 - Demographic features of chronic hemodialysis patients with and without depressive symptoms

Characteristics	Entire group n = 40	Exposed* n = 22	Non-exposed† n = 18	p
Age, years	54.5 ± 15.1	59.1 ± 13.5	48.9 ± 15.4	0.032‡
Sex, n (%) male	29 (72.5)	14 (63.6)	15 (83.3)	0.286§
Color, n (%) white	35 (87.5)	18 (81.8)	17 (94.4)	0.355§
Marital status, n (%) married	23 (57.5)	15 (68.2)	8 (44.4)	0.234§
Education, n (%) high school/university level	19 (47.5)	10 (45.5)	9 (50.0)	0.975§
Economically active, n (%)	14 (35)	6 (27.3)	8 (44.4)	0.424§
Diabetes mellitus, n (%)	10 (25)	7 (31.8)	3 (16.7)	0.464§
Arterial hypertension, n (%)	21 (52.5)	11 (50.0)	10 (55.6)	0.726§
Beck depression inventory score	14.0 (8.3-20.5)			
Hepatitis C, n (%)	3 (8)	2 (9.1)	1 (5.6)	0.999§
Hematocrit, n (%)	26.8 ± 3.9	26.8 ± 4.2	26.8 ± 3.5	0.997‡
Hemoglobin, g/dl	8.8 ± 1.3	8.73 ± 1.4	8.8 ± 1.2	0.955‡
Serum albumin, g/dl	4.0 ± 0.4	4.1 ± 0.5	3.9 ± 0.3	0.310‡
Kt/V	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	0.650‡
Duration of renal disease, months	18.0 (5.0-60.0)	21.8 (6-30)	12 (6-48)	0.704**
Follow-up, months	10.5 (4.6-21.8)	14.7 (4.4-23.8)	8.2 (4.7-12.5)	0.348

Data are presented as number (percentage), mean ± standard deviation, or median (interquartile range, 25th-75th percentile)
*Beck Depression Inventory score ≥ 14; † Beck Depression Inventory score < 14; ‡ Student's t test; § Chi-square test;
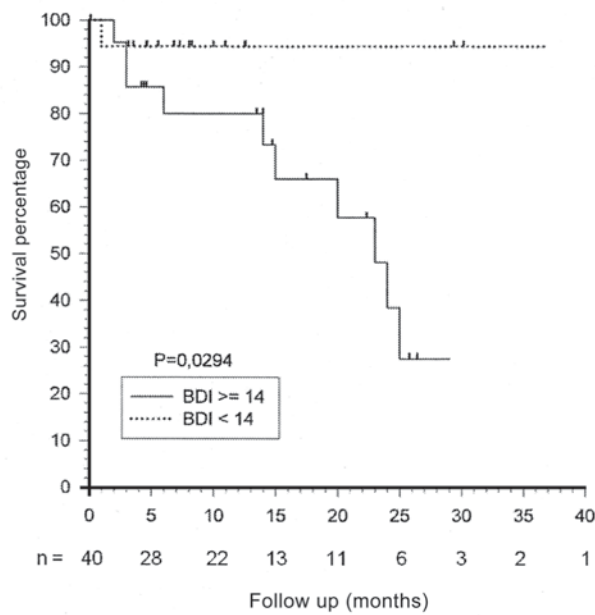**Mann-Whitney`s II test

Figure 1 - Survival curve comparing the exposed (BDI ≥ 14) and the non-exposed (BDI < 14) groups. (|) Censored observations.

falls within the range of mild to moderate depression.[12,16] The median score (p25-p75) was 14 (8.3-20.5).

The patients were divided into two groups: 22 were considered as exposed to depressive symptoms (BDI ≥ 14), and 18 as not exposed (BDI < 14). Median follow-up for exposed patients was 14.7 months, and for non-exposed patients, 8.2 months (p = 0.348). Among non-exposed patients nine (50%) were sent to renal transplantation, two (11%) died, and seven (39%) remained on HD. On the other hand, among exposed patients two (9%) had renal transplantation, 11 died (50%), and nine (41%) remained on HD.

Survival after 24 months was 39% in exposed individuals, and 95% in non-exposed individuals (p = 0.029) (Figure 1). As shown in Table 1, age was the only potential confounding factor that was significantly different between the groups.

Table 2 - Bivariate analysis of association between selected factors and mortality in chronic hemodialysis patients

Variable	n	Mortality		HR	95%CI	p*
		f	%			
BDI						
≥ 14	22	11	50.0	4.5	1.1-17.7	0.029
< 14	18	2	11.1			
CDI†						
> 5	18	8	44.4	4.0	1.0-16.3	0.244
≤ 5	18	2	11.1			
Age						
≥ 50	23	10	43.5	2.5	0.8-7.6	0.999
< 50	17	3	17.6			
Arterial hypertension						
Present	21	6	28.6	0.8	0.3-1.9	0.130
Absent	19	7	36.8			
Diabetes mellitus						
Present	10	4	40.0	1.3	0.5-3.4	0.277
Absent	30	9	30.0			

f: frequency; HR: hazard ratio; CI: confidence interval; BDI: Beck Depression Inventory; CDI: Cognitive Depression Inventory
* Significance based on the logrank test; † Data missing in four cases

Table 2 shows the results of the bivariate analysis correlating several potential risk factors with occurrence of mortality. BDI scores ≥ 14 were associated to mortality (HR = 4.5), followed by CDI scores ≥ 5 (HR = 4.0). The other potential risk factors, including age, did not show important associations. A bivariate analysis of the relationship between mortality and the biochemical variables which express clinical status revealed that degree of anemia, nutrition, and efficacy of HD were not significantly different between those patients who survived and those who did not (Table 1).

After the adjustments for the effect of some potential confounding factors, such as age ≥ 50 years, hypertension, diabetes, and renal transplantation (Table 3) on the Cox regression model, patients with BDI scores ≥ 14 still showed an association with mortality, although this finding was not statistically significant.

The Present work has been approved by the Ethics Committee of Hospital São Lucas/PUCRS (number: 099/623).

Discussion

Depression is a frequent problem in HD patients.[2] Despite being underdiagnosed, it appears to exert an important influence on clinical outcomes. In accordance to Kimmel,[19] the prevalence of depression in dialysis patients ranged from zero to 100%, suggesting that the real extent of this problem in this population is unknown. Using the Hospital Anxiety and Depression Scale, morbid and borderline depression were present in 33 and 55%, respectively, of HD patients.[20] The present study was designed to investigate the association between the existence of depressive symptoms and mortality in chronic HD patients. For that, we employed a well-known instrument, the BDI, after exclusion of patients with cognitive deficit according to the MMSE. The BDI scores observed in our population (mean = 16.2 ± 10.6 and median = 14) fell within the range defined as mild depression by Beck et al.,[12] and were similar to the scores reported by other investigators.[21-23]

The choice of a cutoff of 14 for the BDI score was mainly related to obtaining two groups with similar samples sizes, in our case 18 (BDI < 14) and 22 (BDI ≥ 14). There was no intention to establish a particular level to be used for BDI. Instead, this choice was focused on creating two distinct groups, one with less intense depressive symptoms and the other with more intense symptoms. In the bivariate analysis, intensity of depressive symptoms as defined by BDI scores was associated with mortality. It should also be pointed out that, in the bivariate analysis, the CDI was also associated with mortality, although this finding did not reach statistical significance. In our study, CDI results were similar to BDI results. This is in agreement with a previous study,[24] which showed that on secondary analysis, BDI and CDI results were virtually identical overall. The same correlation between the BDI and the CDI was found in a study carried out in three large HD centers in the United States.[15]

The unexposed group presented a shorter follow-up because most (nine out of 18, 50%) of its patients had renal transplantation, and this is precisely one of the aspects we would like to point out. Depression may act as a surrogate marker of a more complex situation where several factors might be responsible for the occurrence of an undesirable outcome, such as remaining on HD or dying.[25] In this line of thought, depression

Table 3 - Cox proportional hazards model describing the adjusted measures of association between selected factors and mortality in chronic hemodialysis patients

Variable	n	HR	95%CI	p
BDI ≥ 14	40	6.5[1]	0.8-55.0	0.085
BDI ≥ 14	29	5.4[2]	0.7-42.7	0.109
BDI ≥ 14	29	4.6[3]	0.5-40.0	0.170

HR: hazard ratio; CI: confidence interval; p: statistical significance; BDI: Beck Depression Inventory; [1]Cox model including BDI, age, arterial hypertension, and diabetes; [2]Cox model including only BDI in patients not submitted to renal transplantation; [3]Cox model including BDI, age, arterial hypertension, and diabetes in patients not submitted to renal transplantation.

should not be seen as a causal factor on its own but as an additional risk factor in a process which deserves further investigations to reveal the role several participants have.[26]

The Cox proportional hazards model including BDI, age, hypertension, and diabetes in patients not submitted to renal transplantation showed that depressive symptomatology tended to be associated with mortality. Increased intensity of depressive symptoms (BDI ≥ 14) stood out from the other factors, presenting an HR for mortality > 4.0 in HD patients, despite the loss of statistical significance and a wide confidence interval. Other risk factors, such as hemoglobin, hematocrit, and Kt/V, could not be included in the Cox model, because of the instability observed in HR estimates. This was probably due to the colinearity between the factors studied, and to the small sample size.

Unlike our study, two earlier investigations[13,27] reported associations between mortality and advanced age. Those studies considered age and depressive symptoms, measured by the BDI, to be important predictive factors of survival in home dialysis patients, and to be more precise than other demographic, organic, or biochemical variables. In another study, psychosocial factors together with demographic factors were more important than physiological variables in the determination of survival in HD patients.[28]

In the literature reviewed by us, both Smith et al.[29] and Kutner et al.[30] criticized studies which used psychological and/or social variables and relatively small samples to predict survival of patients with chronic renal disease. Kutner et al. also criticized studies which did not use survival analysis techniques.[30] These aspects are also dealt with in the classification of biases in psychiatric consultation-liaison research methodology.[31,32] In our prospective cohort study, we made use of a recognized survival analysis technique, the Cox proportional hazards model, to identify independent mortality risk factors. As recommended by Fletcher et al.,[33] the most direct way to study survival is to establish a cohort of patients at a specific moment (such as, for example, the beginning of treatment) and keep them under observation. Thus, we sought to control the possible distortions of the effect of different HD treatment periods, and standardized the moment of patient inclusion, opting for a maximum of 6 months of treatment, so that all patients would be either new cases, or in the initial treatment period. On the other hand, it is also important to acknowledge some of the limitations of this study: a single BDI evaluation, a small sample for the number of variables studied, a small proportion of women in the sample, and the loss of data referring to the CDI and serum albumin in four patients.

Our study suggests that an increased intensity of depressive symptoms is associated with mortality in HD patients, independently of other factors such as age, concurrent systemic disease, clinical variables and efficacy of dialysis treatment. As previously stated, we believe that our results do not necessarily demonstrate a causal relationship. Depression reduces compliance with dialysis treatment,[34] but this relationship may be multifactorial and dependent on a complex combination of several variables.[35] In some patients, clinical involvement may thus be more closely linked to mortality than are depressive symptoms. The examination of depressive symptoms thus becomes as important as efficient clinical control, as in the case of the patients included in this study.

According to the results of the present study, and given the simplicity of the BDI, which is self-administered and not time-consuming, it is suggested that the evaluation of depressive symptoms be incorporated into the routine of dialysis treatment. Future prospective studies with a larger sample and more frequent BDI evaluations – possibly every 6 months[5] – should be carried out to confirm our findings.

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