Index of coexisting disease and old age as predictors of survival in hemodialysis patients

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ABSTRACT

Objective: To identify the factors that may influence survival in patients on chronic hemodialysis at a private hospital in Brazil. Methods: In this study, 99 patients in the CDE (Hemodialysis Unit of Hospital Albert Einstein) undergoing chronic hemodialysis for at least 3 months were evaluated retrospectively over the period from February 2000 to October 2006. The following patient characteristics were evaluated as possibly having an influence on survival: cause of chronic renal failure (with and without diabetes mellitus), sex, age, albumin levels, C-reactive protein (CRP), hemoglobin levels and ICED (Index of Coexisting Disease), an instrument to assess the presence and severity of comorbidities. Statistical analysis: Survival curves were calculated by the Kaplan-Meyer method and the differences between the curves were evaluated by a log-rank test. Results: The mean age of patients was 63.14 ± 16.18 years, 34% of them were female and 40% of them presented diabetes mellitus as the cause of chronic renal failure. Mean albumin and hemoglobin levels on admission were 3.44 ± 0.58 g/dl and 10.55 ± 1.51 g/dl, respectively, and median CRP level was 9.55 g/dl. The distribution of patients by ICED was mild (25%), moderate (36%) and severe (38%). Thirty-three (33%) patients died, 24 (24%) underwent renal transplantation, 5 (5%) were transferred to another dialysis unit, 36 (36%) continued dialysis treatment and 1 (1%) recovered renal function. One-year survival was 80% and the median survival period was 42.34 months (95% CI: 28.06-54.84). In univariate analysis, the following variables were associated with survival of patients: CRP levels on admission (RR: 1.39; 95% CI: 1.04-1.85; p = 0.026), age (RR: 1.049; 95% CI: 1.017-1.082; p = 0.028) and the level of ICED 3 compared with the level of ICED 1 (RR: 9.25; 95% CI: 1.23-69.48; p = 0.03). In multivariate analysis, the following variables were associated with survival of patients: age (p = 0.0025) and severe ICED compared with mild ICED (p = 0.0341). Conclusion: The factors associated with survival of patients were advanced age and severity of comorbidities. The utilization of ICED enables stratifying the dialysis patients according to severity of their comorbidities and it is useful to identify the patients with a greater risk of death and hospitalization, as well as to aid in the forecast of and optimization of resources necessary for their treatment.

Keywords: Dialysis/adverse effects; Survival analysis; Age effect

RESUMO

Objetivo: Identificar os fatores que podem influenciar a sobrevida dos pacientes em programa crônico de hemodiálise em um hospital
privado do Brasil. **Métodos:** Neste estudo, foram avaliados, retrospectivamente, 99 pacientes do Centro de Diálise Einstein (CDE), Unidade de Hemodiálise do Hospital Israelita Albert Einstein, que estiveram em programa crônico de hemodiálise por pelo menos três meses, no período de fevereiro de 2000 a outubro de 2006. As características dos pacientes que foram avaliadas quanto à possível influência na sobrevida foram: causa da insuficiência renal cardíaca (IRC) (com e sem diabetes mellitus), sexo, idade, níveis de albúmina, proteína C reativa (PCR), hemoglobina e o Índice de Doença Coexistente ou Index of Coexisting Disease – ICED (instrumento que avalia a presença e a severidade das comorbidades) da admissão. **Análise estatística:** As curvas de sobrevida foram calculadas segundo o método de Kaplan-Meier e as diferenças entre as curvas foram avaliadas pelo teste log-rank. **Resultados:** A média de idade dos pacientes foi de 63,14 ± 16,18 anos, 34% deles eram do sexo feminino e 40% apresentavam DM como causa da IRC. Os níveis médios de albúmina e hemoglobina na admissão foram 3,44 ± 0,58 g/dl e 10,55 ± 1,51 g/dl respectivamente, e a mediana dos níveis de PCR foi 9,55 g/dl. A distribuição dos pacientes de acordo com o nível de ICED na admissão foi: 25 (25%) pacientes apresentavam ICED leve, 36 (36%) apresentaram ICED moderado e 38 (38%) apresentavam ICED grave. Trinta e três pacientes (33%) foram a óbito, 24 (24%) foram submetidos a transplante renal, 5 (5%) foram transferidos para outra unidade de diálise, 36 (36%) continuaram em hemodiálise e 1 (1%) paciente recuperou a função renal. A sobrevida em um ano foi de 80% e a mediana da sobrevida dos pacientes foi de 42,34 meses (IC 95%: 28,06-54,84). Na análise univariada, os fatores que influenciaram a sobrevida dos pacientes foram o nível de PCR na admissão (RR = 1,39; IC 95%: 1,04-1,85; p = 0,026), a idade do paciente (RR = 1,049; IC 95%: 1,017-1,082; p = 0,028) e o nível de ICED 3 em relação ao nível de ICED 1 (RR = 9,25; IC 95%: 1,23-69,48; p = 0,03). Na análise multivariada, os fatores que estiveram associados à sobrevida foram a idade (p = 0,0025) e o ICED grave em relação ao ICED leve (p = 0,0341). **Conclusão:** Os fatores que estiveram associados à sobrevida dos pacientes foram a idade avançada e a gravidade das comorbidades. A utilização do ICED possibilita a estratificação dos pacientes em diálise quanto à gravidade de suas comorbidades e serve para identificar aqueles com maior risco de óbito e de internação, assim como auxilia na previsão e otimização dos recursos que serão necessários para o tratamento desses pacientes.

**Descritores:** Diálise/efeitos adversos; Análise de sobrevida; Efeito idade

**INTRODUCTION**

In Brazil, according to data from the census carried out by the Brazilian Society of Nephrology, there were 70,872 patients undergoing dialysis in January 2006. The number of patients on dialysis has been increasing every day and the current prevalence in Brazil is 383 patients per million inhabitants (pmi), and ten years ago this number was around 190 patients per million inhabitants. However, this prevalence is still one third of that found in the USA, suggesting that there are still many more undiagnosed or untreated cases in Brazil.

Although some evidences suggest that the mortality rate among incident patients undergoing dialysis has decreased in the last years (improved treatment), the survival of patients undergoing dialysis is still a worrisome issue, since it is approximately 80% after the first year of treatment. In Brazil, mortality rate was 13% per year, in 2005. The main causes of death in dialysis patients are of cardiovascular and infectious nature.

The risk factors that most influence the mortality of dialysis patients are old age, diabetes mellitus (DM) as the cause of chronic renal failure (CRF) and the presence of associated disease in addition to the renal problem(1). Patients presenting diabetic nephropathy had a 20% survival in five years(2). Elderly patients with vascular disease represented the population undergoing dialysis that showed the worst prognosis and a five-year survival rate of only 15%. In some countries, dialysis is not offered as treatment option for elderly patients with CRF(3). These factors, in addition to being associated with a higher mortality rate, are related with worse quality of life, higher rate of hospitalization and higher utilization of resources(4). It is estimated that the cost of treatment per patient-year undergoing hemodialysis is roughly US$ 8,000 for the Brazilian government and around US$ 13,500 per patient-year for those who have a private health plan(5).

Other factors that determine survival of dialysis patients, such as demographic factors (ethnicity), socioeconomic level, health-related habits (smoking, alcohol use and drug abuse, exposure to communicable diseases) and factors related to the dialysis treatment itself, such as late indication and referral to dialysis treatment, inadequate dialysis dose, noncompliance to treatment, in addition to laboratory abnormalities during the dialysis treatment, such as hypoalbuminemia, inflammation, and anemia, among others.

**OBJECTIVE**

To identify the factors that may have an influence over the survival of patients undergoing a chronic hemodialysis program in a private hospital in Brazil.

**METHODS**

In this study, all patients of Einstein Dialysis Center (CDE) at the Hemodialysis Unit of Hospital Israelita Albert Einstein, undergoing a chronic hemodialysis program for at least three months, were evaluated in the period from February 2000 to October 2006.

All patients admitted to this dialysis unit were routinely evaluated by examinations in the first week of treatment and they assessed for the presence of comorbidities by means of the Index of Coexisting Disease (ICED)(6), an instrument that is applied up to the end of first month of admission. In patients undergoing dialysis, comorbidity...
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has been defined as any concomitant medical condition, except for complications related to the dialysis treatment (for example, problems related with vascular access).

ICED is the result of two indexes, the index of physical impairment (IPI) which evaluates 11 physical conditions graded according to severity (score 0-2) and the index of disease severity (IDS) which rates, according to severity, 19 medical conditions or comorbidities (score 0-3). Overall, 160 items are evaluated by ICED. The severity level evaluated in the IDS is defined according to the presence of symptoms, functional capacity and need of medications or hospitalizations. For full use of the IDS it is necessary to verify the data in patient files, whereas for the IPI, only good knowledge of the patient’s physical condition is required. The final ICED result is obtained through a specific algorhythm based on the higher scores obtained in IPI and IDS scales (Figure 1). There are four ICED levels, from 0 to 3: level 0 is considered normal and level 3 is considered severe. At the CDE, the ICED takes 30 minutes to be fully filled out by a nephrologist. It is worth mentioning that the medical staff of the CDE translated this original version of the scale from English to Portuguese.

Demographic, clinical and laboratory variables upon admission to dialysis, which are necessary for this study and for filling ICED, were recovered from patient records, electronic records at the CDE and through Medtrack (a software used at the Hospital Israelita Albert Einstein, where the results of examinations and event dates were analyzed).

Statistical analysis

Univariate analyses according to the Cox proportional hazard model were determined for all variables involved - both continuous and categorical.

The Cox multiple regression model was established to identify the independent factors associated with patient survival. Variables with a p value < 0.25 in the Cox univariate analysis and variables with p ≥ 0.25 but with clinical importance according to medical literature were included in the multivariate analysis which used the backward procedure to select variables. A p value < 0.05 was used as the permanence criterion of variables in this procedure.

Due to its asymmetrical distribution, the continuous variable CRP was transformed according to the natural logarithm before statistical analyses. Survival curves were calculated for categorical variables according to Kaplan-Meier method and the differences between the curves were evaluated with the log-rank test.

All significance probabilities (p values) presented are bilateral and values below 0.05 are considered statistically significant. The software SAS 9.1 (Statistical Analysis System, Cary, NC, USA) was used for statistical analysis of data.

The characteristics of patients evaluated in this study as to their possible influence on survival of hemodialysis patients were: cause of CRF (diabetes mellitus and non-diabetes mellitus), sex, age, albumin levels, C-reactive protein (CRP), hemoglobin and ICED at admission.

RESULTS

This study included 99 patients with mean age of 63.14±16.18 years; 34% of patients were female and 40% of patients presented diabetes mellitus as the cause of CRF. Median follow-up time of all patients was 13.03 months (minimum of 3 and maximum of 68 months).

Most patients underwent three dialysis sessions per week with a low-flow polysulfone dialyzer.

Mean levels of albumin and hemoglobin at admission were 3.44 ± 0.58 g/dl and 10.55 ± 1.51 g/dl, respectively, and the median CRP level was 9.55 g/dl (minimum: 0.30 – maximum: 205 g/dl).

Patient distribution according to ICED level upon admission was: 25 (25%) patients presented mild ICED, 36 (36%) presented moderate ICED and 38 (38%) presented severe ICED. Chart 1 shows the demographic data of patients and their outcomes according to severity level of ICED.

Of a total of 99 patients, 33 (33%) died, 24 (24%) underwent renal transplantation, 5 (5%) were transferred to another Dialysis Unit, 36 (36%) remained in hemodialysis and one patient (1%) recovered renal function and returned to conservative treatment. Among those who were transferred, there were no deaths in the first three months following the transference. Median time of follow-up in patients who were alive was 13.73 months (minimum: 3 – maximum: 68 months).

The ICED distribution of 24 patients who underwent renal transplantation was: mild level, 15 (62.5%) patients, moderate level, 8 (33.3%) patients and severe level, one (4.2%) patient. Most transplanted patients presented mild ICED upon admission (Chart 1).
One-year survival was approximately 80% and the median survival of patients was 42.34 months (95% CI: 28.06-54.84) (Figure 2).

In the univariate analysis, the factors that influenced patient survival included CRP level on admission (RR = 1.39; 95% CI: 1.04-1.85; p = 0.026), patient age (RR = 1.049; 95% CI: 1.017-1.082; p = 0.028) and the level of ICED 3 compared with the level of ICED 1 (RR = 9.25; 95% CI: 1.23-69.48; p = 0.03) (Table 1). Other variables, such as albumin and hemoglobin levels, sex and cause of CRF did not influence patient survival (Figure 3-7).

In the multivariate analysis, the factors associated with patient survival included age (p = 0.0025) and severe ICED compared with mild ICED (p = 0.0341). As to the impact of age, for every 10-year increase in age, the risk of death increased 69.2% (RR: 1.69; 95% CI: 1.20-2.39), adjusted for the effect of severe ICED. Regarding the ICED, the risk of death for patients with severe ICED is 2.3 times higher than the risk of death for patients with mild ICED (p = 0.0025), with 95% CI: 1.06-5.03, adjusted for the age effect (Table 2).

Of a total of 25 patients with mild ICED, one (4%) patient died; among 36 (28%) patients with moderate ICED, 10 patients died and among 38 patients with severe ICED, 22 (58%) patients died. Most patients who died presented severe ICED. Median survival of patients with severe ICED was 26.97 months and median survival of patients with moderate ICED was 51 months (Figure 3).

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**DISCUSSION**

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Table 1. Results of Cox univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>-0.046</td>
<td>0.376</td>
<td>0.955</td>
<td>0.456 - 1.997</td>
<td>0.901</td>
</tr>
<tr>
<td>Age</td>
<td>0.04762</td>
<td>0.015</td>
<td>1.049</td>
<td>1.017 - 1.082</td>
<td>0.002*</td>
</tr>
<tr>
<td>Cause of CRF</td>
<td>0.441</td>
<td>0.362</td>
<td>1.555</td>
<td>0.764 - 3.166</td>
<td>0.223</td>
</tr>
<tr>
<td>ICED 2x1</td>
<td>1.363</td>
<td>1.054</td>
<td>3.91</td>
<td>0.49 - 30.90</td>
<td>0.196</td>
</tr>
<tr>
<td>ICED 3x1</td>
<td>2.224</td>
<td>1.028</td>
<td>9.25</td>
<td>1.23 - 69.48</td>
<td>0.030*</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.107</td>
<td>0.384</td>
<td>0.898</td>
<td>0.423 - 1.908</td>
<td>0.779</td>
</tr>
<tr>
<td>LN (CRP)</td>
<td>0.329</td>
<td>0.147</td>
<td>1.39</td>
<td>1.040 - 1.857</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

*p < 0.05 was considered statistically significant

Table 2. Factors that influenced survival of dialysis patients – multivariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICED 3 versus ICED 1</td>
<td>0.840</td>
<td>0.396</td>
<td>2.32</td>
<td>1.06 - 5.03</td>
<td>0.034*</td>
</tr>
<tr>
<td>Age (for each 10-year increment)</td>
<td>0.529</td>
<td>0.175</td>
<td>1.69</td>
<td>1.20 - 2.39</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*p < 0.05 was considered statistically significant
had demonstrated an association with patient survival in previous investigations, but in this study those variables were not associated with mortality, such as the cause of CRF (DM or non-DM), sex, and albumin and hemoglobin levels. The CRP levels in univariate analysis were associated with survival, in accordance with data from the medical literature. CRF is associated with a chronic inflammatory status characterized by increased levels of pro-inflammatory cytokines. In dialysis patients, increased CRP levels are related to hypoalbuminemia, malnutrition, erythropoietin resistance, increased risk of cardiovascular events and a higher mortality rate\(^{10}\).

The survival in our population of dialysis patients was similar to that found in dialysis units in the USA. In the last three decades, patients starting dialysis in the USA have been more clinically and socially complex. Most of them are older patients with diabetes and multiple comorbidities. These features differ from those found in dialysis units accredited by the Brazilian Unified Health System, which currently correspond to 95% of the dialysis units in Brazil, where the age group of patients is lower, i.e., only 25% of dialysis patients are ≥ 65 years old and only 25% of patients have diabetes according to the census published by the Brazilian Society of Nephrology, in 2006. At the CDE, the mean age of our patients was approximately 63 years and at least 40% of them suffered from diabetes mellitus. It should be pointed out that there were no black patients in our dialysis unit. These patients present a higher frequency of CRF due to both genetic factors and socioeconomic issues that prevent the access to healthcare services.

Several instruments have been used to assess the associated diseases in dialysis patients. The Charlson comorbidity index (CCI) is a generic index developed for inpatients; the Index of Coexisting Diseases (ICED) is a generic index that was adapted for dialysis patients; Davies and Wright-Khan indexes were both developed specifically for the population undergoing dialysis\(^{7,8}\).

Previous studies using these questionnaires showed an association between the presence of associated diseases and morbidity and mortality rates in dialysis patients. Curiously, as early as 1992, Nicolucci et al. reported the impact of comorbid conditions in the survival of dialysis patients. These authors showed that patients with severe ICED had a three-fold risk of death compared with patients with mild ICED\(^{11}\), a result that was quite similar to that found in our population.

Miskulin et al. compared the four instruments, Charlson, Davies, Wright-Khan and ICED, in a population of 1779 hemodialysis patients and they observed that ICED showed a higher discriminatory power than other indexes to predict patients who would die within one year. The ICED differed from other indexes for its capacity to characterize disease severity and not only assess the presence of conditions; additionally, the ICED aggregates the assessment of the index of physical impairment (IPI), which has been an important prognostic factor in dialysis patients\(^{7}\). The IPI approaches another dimension in the context of comorbidities and it can indirectly reflect (by means of a physical limitation) a symptomatic disease, a disease of difficult control or a disease in an advanced stage. Difficulty walking, for example, may result both from an ischemic heart disease or congestive heart failure or a peripheral vascular disease or even a respiratory disease. The ICED, in this study, showed less accuracy when the analyses of other prognostic variables were added such as age, albumin, cause of CRF and ethnicity\(^{7}\). Therefore, when comparing the outcomes obtained in large studies with different types of treatment, when comparing the quality of treatment offered in the different dialysis units and when making a clinical decision, it is necessary to analyze a combination of prognostic factors for survival.

Miskulin et al., in 2000, observed that the number and severity of comorbid conditions at treatment admission were significantly lower in patients who chose peritoneal dialysis as the initial dialysis modality as compared to patients who started with hemodialysis. The presence and severity of comorbidities, according to assessment by the ICED, was a strong predictor of the type of dialysis initially used; the more severe the associated disease, the lower the preference for peritoneal dialysis at the beginning of dialytic treatment\(^{9}\). Once again, we should point out the crucial importance of considering this feature of patients when comparing the survival of patients in these two treatment modalities.

The ICED was the only comorbidity index used in a multicenter study named HEMO. In this research, the patients were randomized into four groups according to the dose of dialysis offered and the dialyzer flow\(^{10}\). The study primary endpoint was mortality. The study results showed that important factors in patient survival included age, ethnicity, sex, diabetes mellitus and serum albumin. On the other hand, the high flow and the high dose of dialysis did not have an impact on the primary endpoint. The ICED was used in one thousand patients undergoing hemodialysis in this study and it showed that dialysis patients had multiple and severe comorbidities, i.e., 99% of patients had one or more medical conditions, while 61% of patients had one or more physical limitations. The proportion of patients according to the ICED of 0 to 3 was 0.2%, 34.9%, 31.2% and 33.7%, respectively. Similar to the findings at the CDE, most dialysis patients present moderate (2) and severe (3) comorbid conditions. In the HEMO study, the factors associated with the most
severe comorbidities were old age, diabetes mellitus, low schooling level, unemployment, low serum creatinine and longer time spent in dialysis. With this study, it was possible to confirm the ICED good reliability and reproducibility by the medical and nursing teams, since they were both prepared to fill out the ICED and agreed on the results found\(^{(4)}\). At the CDE, the nursing team has not been prepared yet to use this instrument.

Another study showed increased prevalence and severity of comorbidities during the follow-up of dialysis patients compared with the associated diseases found at admission, and the changes in the levels of ICED severity during the follow-up were also associated with higher mortality\(^{(5)}\).

The ICED was also used to evaluate the risk of hospitalizations. A company named Renaissance Health Care (RHC) which has contracts with individual health insurance plans to guide management and care of patients with renal disease requiring dialysis, used a variation of the ICED for patients undergoing dialysis in which variables with special relevance for dialytic patients were included (for example, age, diabetes control, serum levels of albumin and hemoglobin, etc.). In this variation of the ICED, patients were stratified into three levels: low, moderate and high. The ICED was applied at admission to dialysis treatment and every 90 days; patients were followed up for one year. High-risk patients presented a higher number of hospitalizations and mortality, and the changes in the levels of ICED during the period studied were also associated with changes in the risk of hospitalization and death. The main causes of hospitalization were a result of comorbid condition complications such as diabetes mellitus, cardiovascular disease, high blood pressure and peripheral vascular disease\(^{(1)}\).

In conclusion, the advantages related to the use of ICED are as follows: 1. it is an instrument that is able to evaluate fatal and non-fatal diseases and, consequently, predicts the survival and the use of resources such as hospitalizations, for example; 2. the ICED includes the severity level of diseases related to short-term survival and the use of resources; 3. the ICED includes the measurement of physical impairment, which is related to quality of life and the patient’s preferred treatment options; 4. information obtained through ICED is aggregated in a single variable, which allows a concise measurement of comorbidity in an individual or in a population; 5. changes in the levels of ICED classifications are more sensitive predictors of the endpoints than a point measurement\(^{(12)}\).

Among the ICED limitations, it was shown that the use of the four-level scale does not reveal the large amount of information collected through the ICED; in addition, it does not take into consideration the number of comorbidities that each patient presents and, due to the large number of topics, it is difficult to be used in dialysis units with many patients\(^{(6,12)}\).

**CONCLUSIONS**

The Einstein Dialysis Center was the first place in Brazil to use the ICED as an instrument to evaluate comorbidities in dialysis patients. We believe that a simplified form of this index, as a prognostic information equivalent to the ICED, makes this questionnaire more accessible to Dialysis Units, where there are several patients, thus allowing its regular use both upon admission and during the follow-up. Patient stratification regarding the presence and severity of their comorbidities allows us to evaluate them in terms of risk of death and other endpoints, such as hospitalizations and cost, and it also enables treatment adjustment and optimization.

**REFERENCES**