Donor and Recipient Characteristics

Causes of death and mortality risk factors

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Abstract

Background. Patient death continues to be a leading cause of renal transplant failure. This mortality is mainly due to cardiovascular, infectious and tumoural diseases. The aim of our study was to analyse the evolution of the mortality and its causes after renal transplantation (RT).

Methods. We studied 3365 adult renal transplant recipients, surviving at least 1 year, and transplanted in Spain in the years 1990, 1994 and 1998. Risk factors for all-cause and specific-cause mortality were analysed employing simple and multivariate Cox regression.

Results. 300 patients (8.9%) died after the first post-transplantation year. The follow-up was shorter (maximum 2.5 years) in recipients transplanted in 1998. When we consider an identical follow-up (2.5 years) for all patients, we did not find statistical differences in mortality rates or its causes, in the three analysed periods. Cardiovascular diseases (CVDs) and neoplasia were the most frequent causes of death. Mortality was higher for males and patients > 60 years. Renal function, evaluated by creatinine level or proteinuria range at 3 months and its increase in the first year post-transplantation were significant factors associated with high risk for cardiovascular and infectious death.

Conclusions. During the last decade, in Spain, the mortality after RT (2.5 years follow-up) remains stable. Recipient age (> 60 years), male gender and renal function in the first year were associated with higher risk of death, especially for CVD.

Keywords: chronic allograft nephropathy; kidney transplant; patient survival; post-transplant mortality risk; transplant deaths

Introduction

Improved immunosuppressive therapy and management strategies in renal transplantation (RT) have increased allograft and patient survival during the past decade [1,2]. In spite of this, mortality rates in RT were many fold that of the healthy population according to UNOS Scientific Renal Registry data [3]; however, it is lower in transplanted patients, when they are compared with patients on dialysis awaiting transplantation or patients not included on the waiting list [2].

Death with graft function is a common cause of graft loss and cardiovascular disease (CVD) is the predominant reported cause [4]. Other frequent causes of death are malignancies and infectious diseases.

We analyse transplant mortality between 1990 and 1998, its causes and risk factors in Spain, as a part of the Study of Risk Factors for Chronic Allograft Nephropathy.

Subjects and methods

We studied 3365 RT, all adults (male 63%), surviving at least 1 year, who underwent transplantation in Spain in the years 1990, 1994 and 1998. We analysed all- and specific-cause mortality, including cardiovascular, tumoural, infectious, hepatic, unknown and others.

Risk factors for all-cause mortality were assessed by means of simple and multiple Cox regression. Only those variables showing a significant effect in the simple logistic regression were considered for the multiple regression analysis. Multiple regression analyses was adjusted for year of transplant and centre effect.

Risk factors for specific-cause mortality were also analysed employing Cox regression. In the multiple regression analyses only year of transplant was included as an adjustment variable, because no deaths had been observed in some of the centres and so numerical problems would have arose when fitting the model. Results are expressed in terms of mortality rates.
Comparison of mortality rate and causes of death between years of transplantation

In this study 300 patients (8.9%) died after the first post-transplantation year. Table 1 shows the number and percentage of deaths for each year of transplantation, and for the total period. Different causes of death are also included.

Patients transplanted in 1998 have a maximum follow-up of 2.5 years, which is shorter than patients transplanted in 1990 or 1994. When we consider an identical follow-up (2.5 years) for all patients, we did not find significant statistical differences in mortality rates (Table 2), and in its causes. The mean time to death for different causes analysed was similar ($P = 0.2957$).

### Table 1. Mortality rate and cause of death between years of transplantation

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th></th>
<th>1994</th>
<th></th>
<th>1998</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N$</td>
<td>%</td>
<td>$N$</td>
<td>%</td>
<td>$N$</td>
<td>%</td>
<td>$N$</td>
<td>%</td>
</tr>
<tr>
<td>Deaths</td>
<td>139</td>
<td>16.9</td>
<td>118</td>
<td>11.0</td>
<td>43</td>
<td>2.9</td>
<td>300</td>
<td>8.9</td>
</tr>
<tr>
<td>Deaths due to CVD</td>
<td>41</td>
<td>5.0</td>
<td>33</td>
<td>3.1</td>
<td>10</td>
<td>0.7</td>
<td>84</td>
<td>2.5</td>
</tr>
<tr>
<td>Deaths due to neoplasia</td>
<td>25</td>
<td>3.0</td>
<td>27</td>
<td>2.5</td>
<td>13</td>
<td>0.9</td>
<td>65</td>
<td>1.9</td>
</tr>
<tr>
<td>Deaths due to infectious disease</td>
<td>12</td>
<td>1.5</td>
<td>17</td>
<td>1.6</td>
<td>8</td>
<td>0.5</td>
<td>37</td>
<td>1.1</td>
</tr>
<tr>
<td>Deaths due to chronic liver disease</td>
<td>9</td>
<td>1.1</td>
<td>5</td>
<td>0.5</td>
<td>2</td>
<td>0.1</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>Deaths due to other causes</td>
<td>41</td>
<td>5.0</td>
<td>30</td>
<td>2.8</td>
<td>7</td>
<td>0.5</td>
<td>78</td>
<td>2.3</td>
</tr>
<tr>
<td>Cause not stated</td>
<td>11</td>
<td>1.3</td>
<td>6</td>
<td>0.6</td>
<td>3</td>
<td>0.2</td>
<td>20</td>
<td>0.6</td>
</tr>
</tbody>
</table>

### Table 2. Survival (2.5 years) by year of transplantation (simple Cox regression)

<table>
<thead>
<tr>
<th>Year of transplantation</th>
<th>RR</th>
<th>CI 95%</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1990</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>1.288</td>
<td>(0.847, 1.960)</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>0.836</td>
<td>(0.544, 1.283)</td>
</tr>
</tbody>
</table>

Note: results were obtained from a Cox regression analysis. Significance level was 0.05 for all statistical tests.

### Results

#### Comparison of mortality rate and causes of death between years of transplantation

In this study 300 patients (8.9%) died after the first post-transplantation year. Table 1 shows the number and percentage of deaths for each year of transplantation, and for the total period. Different causes of death are also included.

Patients transplanted in 1998 have a maximum follow-up of 2.5 years, which is shorter than patients transplanted in 1990 or 1994. When we consider an identical follow-up (2.5 years) for all patients, we did not find significant statistical differences in mortality rates (Table 2), and in its causes. The mean time to death for different causes analysed was similar ($P = 0.2957$).

#### All-causes mortality risk factors

Results of the multiple Cox regression analysis are provided in Table 3. This analysis shows that recipient age >60 years, non-trauma as cause of donor death, the creatinine level at 3 months (mg/dl), the creatinine increase (from 3 months to 1 year), proteinuria at 3 months and proteinuria increase in the first year were significantly associated with a higher risk of mortality.

#### Specific-causes mortality risk factors

The results from simple Cox regression are not shown for any group. We only present here results from multiple regression analysis.

**CVDs mortality risk factors.** It appears that male gender [relative risk (RR) = 2.11, $P = 0.0086$] recipient age > 60 years (RR = 3.88, $P < 0.0001$), creatinine at 3 months (RR = 1.74, $P < 0.0001$), proteinuria at 3 months (RR = 1.38, $P = 0.0049$), proteinuria increase in the first year (RR = 1.24, $P = 0.0327$) and triglycerides at 3 months (RR = 1.27, $P < 0.0001$) were significantly associated with cardiovascular mortality.

**Infectious diseases mortality risk factors.** Multiple Cox regression analysis shows that recipients older than 60 years (RR = 3.45, $P = 0.0008$), azathioprine immunosuppressive therapy during the first year post-transplantation and the creatinine level at 3 months (RR = 1.62, $P = 0.0141$) were significantly associated with infectious mortality.

**Neoplasia mortality risk factors.** The results shows that recipients older than 60 years at transplantation (RR = 3.23, $P < 0.0001$) and, surprisingly, cold ischaemia time > 24 h (RR = 1.88, $P < 0.0001$) were associated with a higher malignancy-related death.

### Table 3. Risk factors for death (multiple Cox regression)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR</th>
<th>CI 95%</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (ref. ‘&lt;60 years’)</td>
<td>4.120</td>
<td>(3.118, 5.445)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cause of death (ref. trauma)</td>
<td>1.303</td>
<td>(1.012, 1.679)</td>
<td>0.0401</td>
</tr>
<tr>
<td>Creatinine at 3 months (+1 mg/dl)</td>
<td>1.724</td>
<td>(1.442, 2.062)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine increase from 3 months to 1 year (+1 mg/dl)</td>
<td>1.609</td>
<td>(1.302, 1.988)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proteinuria at 3 months (+1 mg/dl)</td>
<td>1.304</td>
<td>(1.125, 1.511)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Proteinuria increase from 3 months to 1 year (+1 mg/dl)</td>
<td>1.156</td>
<td>(1.005, 1.330)</td>
<td>0.0427</td>
</tr>
<tr>
<td>Centre</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>–</td>
<td>–</td>
<td>0.4270</td>
</tr>
</tbody>
</table>

Results were obtained from a Cox regression analysis. Significance level was 0.05 for all statistical tests. Ref., reference.
**Chronic liver disease mortality risk factors.** In this group recipient age >60 years (RR = 4.32, \(P = 0.0096\)), the presence of HBsAg(+) (RR = 16.14, \(P < 0.0001\)) or HCV(+) (RR = 5.39, \(P = 0.0031\)) were associated with a high risk of mortality due to liver failure.

**Discussion**

One of the main limitations of this study originates from the fact that the number of deceased patients is fairly low (8.9%), especially in the category of infectious or hepatic diseases, which made their statistical analysis difficult. Furthermore, the maximum follow-up period for the patients transplanted in 1998 was only 2.5 years, which is shorter than the patients transplanted in 1990 or in 1994. Post-transplant mortality is dependent on age- and transplant-related factors. The latter are not very significant during the first months, but they are especially important 3–5 years post-transplant [3], an important reason for a long follow-up when patient survival is studied. Nevertheless, these limitations do not prevent certain conclusions to be drawn. First of all, when we consider the same follow-up (2.5 years) for all patients, the mortality rate and its causes remain stable. These results are different from other recent series [5,6], but the number of patients, the shorter follow-up and other methodological variables could explain these differences.

The second conclusion was that the most frequent death causes were CVD, malignancies and infectious disease. These findings support data previously obtained by others [3,4,7]. In this study, mortality was higher in older recipients (≥60 years) and male patients. The creatinine level and the range of proteinuria (and its increase in the first year post-transplantation) were associated with a higher risk of cardiovascular and infectious mortality, findings in line with other published studies [8,9]. Post-transplant atherogenic factors are traditional risk factors [10,12], and their early and aggressive control will allow a reduction of the mortality in the coming years. Other putative non-classical and uraemia-related factors have been proposed [8].

Malignancies and infectious-related mortality remain stable in the last decade, in spite of transplanting older recipients and the use of more powerful immunosuppressive therapy. These results are probably due to refinements in patient management, including reduction in corticosteroid dose, less use of anti-lymphocyte agents, more efficient anti-infectious drugs and, obviously, the improvement of diagnosis and treatment options [6]. In Europe the prevalence of cancer, after 10 years of RT, is 20–30% and it increases as the evolution period evolves. The RR of de novo cancer is three to five times higher than for the general population [13,14].

Only 5% of the patients died due to chronic liver disease, and this incidence is too low to obtain an adequate analysis. Mortality was higher in HBsAg(+) or HCVAb(+) recipients, a finding that must be analysed carefully, bearing in mind the low number of patients and other recent findings in larger series [15,16].

In conclusion, during the last decade, in Spain the mortality rate and causes of mortality remain stable. Our study also shows that renal function in the first year is associated with a high risk of CVD, the most important cause of death in this series.

We also consider that a longer follow-up, could permit us to obtain a better analysis about the evolution of the mortality in the last decade in our country.

**Conflict of interest statement.** None declared.

**References**