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# Kidney Transplant: Survival Analysis and Prognostic Factors after 10 Years of Follow-Up

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**Abstract:** The aim of this work is to analyse recipient and graft survival after kidney transplant in a three-year cohort and to identify predictive factors with up to 10 years of follow-up. Methods: retrospective consecutive cohort study of 250 kidney transplant recipients operated between 2010 and 2012. Multiorganic transplants and both dead-donor and living-donor transplants were included. Data were collected from electronic health records. A survival analysis was conducted using the Kaplan-Meier method and a Cox proportional-hazards multivariate model. Results: mean follow-up was 8.1 ± 3.2 years. Graft survival at 2, 5 and 10 years was 89.0%, 85.1% and 78.4% respectively. The multivariate model identified the following risk factors for graft loss: diabetic nephropathy (HR 3.2 CI95% [1.1–9.4]), delayed graft function (3.8 [2.0–7.4]), chronic kidney rejection (3.7 [1.2–11.4]), and early surgical complications (2.6 [1.4–5.1]). Conversely, combined transplant was found to be a protective factor for graft loss (0.1 [0.0–0.5]). Recipient patient survival was 94.3%, 90.0% and 76.6% at 2, 5 and 10 years respectively. The model identified the following mortality risk factors: older recipient age (1.1 [1.1–1.2]), combined transplant (7.6 [1.7–34.5]) and opportunistic infections (2.6 [1.3–5.0]). Conclusions: 10-year recipient and graft survival were 76.6% and 78.4% respectively. Main mortality risk factors were older recipient age, opportunistic infections and multiorganic transplant. Main graft loss risk factors were diabetic nephropathy, delayed graft function, chronic kidney rejection and early surgical complications.

**Keywords:** graft survival; recipient patientsurvival; kidney transplant

**MSC:** 92C50



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## 1. Introduction

Kidney transplantation is the preferred renal replacement therapy for patients suffering from terminal chronic kidney disease. This is due to better survival outcomes compared to hemodialysis and peritoneal dialysis. Furthermore, it is associated with a better quality of life, fewer complications and a better cost-effectiveness ratio. Spain is the leading country worldwide in terms of kidney transplants per resident, with an annual average of 58 transplants per million and a progressive upward trend. According to the Spanish National Transplant Organisation data, 2.950 kidney transplants were performed in Spain. Of these, 115 were performed in La Fe University and Polytechnique Hospital [1–3].

During the last decade, there has been an increase in kidney transplant recipient survival, due to improvements in immunosuppressant therapy, surgical techniques and follow-up. Furthermore, the number of living-donor transplants has also increased. According to European series, 5-year global survival is approximately 92% for dead-donor

transplants and 95% for living-donor transplants. Regarding graft survival, this is estimated to be around 81% and 87% respectively [4].

In order to achieve the greatest transplant and recipient survival for transplant recipients and to adequately inform candidates of kidney transplant survival probability, it is highly important to know the main transplant loss and mortality risk factors. This will enable patients to be classified according to their individual risk of losing the transplant or dying, which will be useful as an aid in the decision process both for clinicians and patients (informed decision making).

Multiple mortality and graft -loss risk factors have been described in the scientific literature, including: donor and recipient ages, donor type (dead or living), recipient comorbidity (diabetes mellitus, obesity, hepatitis B virus infection, cardiovascular disease), aetiology of chronic kidney disease, type of renal replacement therapy, delayed graft function, perioperative complications, HLA incompatibility, BK polyomavirus infection and immunologic rejection. Nevertheless, disparity can be found between series, with the prognostic significance of some of these factors still controversial. This may be attributable to the small sample size of some cohorts, variability in follow-up, therapeutic changes or to the fact that most studies only analyse a few variables simultaneously [5–16]. Consequently, there is a greatneed to have updated data from recent cohorts with large sample size and long-lasting follow-up in order to plan treatment and follow-up strategies on an individual basis with the aim to optimise graft and recipient survival.

The main aim of this study was to analyse recipient and graft survival after kidney transplant in a three-year cohort and to identify the predictive factors of both in patients with at least 10 years of follow-up.

## 2. Materials and Methods

### *2.1. Study Design*

A retrospective, observational and analytical single cohort study of kidney transplant recipients was conducted. Multiorgan transplants and both dead-donor and living-donor transplants performed between January 2010 and December 2012 at La Fe University and Polytechnique Hospital were included consecutively. Only patients with a minimum follow-up of 10 years were recruited. Patients were followed up according to EAU Clinical practice guidelines. The only exclusion criteria were paediatric transplants (recipient younger than 16 years old). Our final sample size was 250 patients. The study was approved by our centre's Clinical Investigation Ethical Committee.

### *2.2. Data Collection*

Data were retrospectively collected by individualised review of clinical records and were introduced in a database specially designed for that purpose with Excel 2016 (Microsoft, Redmond, WA, USA).

Analysed variables were as follows: demographic and clinical characteristics of recipients (age at surgery, sex, previous HBV, HCV or HIV infection, arterial hypertension, diabetes mellitus, dyslipidemia, Body Mass Index (BMI), ABO blood group, aetiology of chronic kidney disease, type of previous renal replacement therapy, time in dialysis and number of previous kidney transplants); transplant and perioperative factors (multiorganic transplant, dead or living donor, induction immunosuppressant therapy, post-transplant immunosuppressant therapy, intraoperative or early postoperative surgical complications and early postoperative medical complications) and events during follow-up (late surgical complications, opportunistic infections, bacterial infections, cardiovascular events, tumours, acute rejection, chronic rejection, graft loss and death).

Early surgical complications were defined as those occurring 1 to 30 days after transplant, including: venous thrombosis, arterial thrombosis, haematoma, acute bleeding, haematuria, urinary fistula and evisceration. As late surgical complications (more than 30 days after transplant) we included: ureteral stenosis, renal lithiasis, renal artery stenosis, lymphocele, arteriovenous fistula, pseudoaneurysm, vesicoureteral reflux or incisional

hernia. Delayed graft function, the need for postoperative dialysis and immunological rejection during postoperative hospital admission were considered as early medical postoperative complications. As opportunistic infections we included: systemic HSV, HZV, CMV, BK polyomavirus, parvovirus, Leishmania and Candida infection. The main outcome variables were death and graft loss, with the latter was defined as the need for restarting dialysis, transplantectomy, retransplantation. or death from renal cause.

### *2.3. Statistical Analysis*

For descriptive statistics we used absolute and relative frequencies for qualitative variables; and central tendency (mean) and dispersion (standard deviation and 95% confidence interval) measures for quantitative variables. Age was considered as a continuous variable, while the other independent variables were treated as categorical variables. Our dependent variables for the study were the survival time for both graft loss and all cause mortality, and were treated as continuous variables.

We conducted a survival analysis using the Kaplan-Meier method and a Cox proportional-hazards multivariate model to identify predictive factors for both recipient survival and graft survival. A $p$-value $< 0.05$ was considered as statistically significant. For the Cox proportional hazards models, the proportionality assumption was tested and the variables were considered independent.

The results of the Kaplan.Meier models are displayed with the corresponding survivability curves. For the Cox proportional hazard models, the hazard ratio are presented with the corresponding 95% confidence intervals and $p$-values, as well as information on model fit.

Three predictive models were consecutively created according to Cox proportional-hazards multivariate model for each of the two mentioned outcome variables (recipient and graft survival). In the first, all potentially predictive variables initially collected were included. Following this, a second model was designed including a reduced combination of variables that were selected based on their high clinical relevance. Finally, the third model was built containing only those variables that had been found to have a statistically significant association with outcomes in the first and second models.

Statistical analysis was performed using SPSS®v20 (IBM, Armonk, New York, NY, USA) and Rv3.6.1 (R Development Core Team).

## 3. Results

A total of 250 patients were included with a mean follow-up of 8.1 $\pm$ 3.2 years. Mean age at surgery was 52.3 $\pm$ 14.0 years. Most cases were kidney-only (non multiple), living-donor transplants. A total of 29 patients (11.6%) received a combined transplant: 23 (9.2%) kidney-pancreas and 6 (2.4%) kidney-liver. Only in 15 cases (6.0%) did the graft come from living donors and in 23 (9.2%) the surgery was a retransplant (second or successive). Descriptive analysis of main analysed variables is shown in Table 1.

Incidence of intraoperative complications, medical and surgical postoperative complications, graft loss, death and other events occurring during follow-up is shown in Table 2.

The actuarial probability of recipient survival was 94.3% at 2 years, 90.0% at 5 years and 76.6% at 10 years. The actuarial survival function is shown in Figure 1.

The three Cox proportional hazard models were adjusted. Using the latter model, we identified the following mortality risk factors: older recipient age at surgery slightly increased the risk with each year significantly (HR 1.1 CI 95% [1.1–1.2]), combined transplants pose more than 7.5 times increase in mortality risk compared to those receiving a single transplant (HR 7.6 CI 95% [1.7–34.5]) and opportunistic infections more than doubled the risk to the patient (HR 2.6 CI 95% [1.3–5.0]) in the data studied. The three models described above are shown in Figures 2–4.

**Table 1.** Descriptive analysis ofthe main characteristics of the study population, including demographical, comorbidity, aetiology and renal replacement therapy.

| **Demographic Variables** | **n (%)** |
|---|---|
| Age at transplant in years [$\mu \pm$ SD] | $52.3 \pm 14.0$ |
| Sex | |
| Female | 86 (34.4) |
| Male | 164 (65.6) |
| **Comorbidity** | **n (%)** |
| Arterial Hypertension | 215 (86.0) |
| Diabetes Mellitus | 52 (20.8) |
| Obesity | 38 (15.2) |
| Dyslipidemia | 148 (59.2) |
| Hepatitis B Virus Infection | 7 (2.8) |
| Hepatitis C Virus Infection | 7 (2.8) |
| **Aetiology of Chronic Kidney Disease** | |
| Glomerular Nephropathy | 57 (22.8) |
| Diabetic nephropathy | 38 (12.2) |
| Autosomal Dominant Polycystic Kidney Disease | 34 (13.6) |
| Unknown | 62 (24.8) |
| **Renal Replacement Therapy** | |
| **Type** [1] | |
| Haemodialysis | 159 (64.1) |
| Peritoneal dialysis | 48 (19.4) |
| Both | 34 (13.7) |
| Pre-dialysis | 7 (2.8) |
| **Mean time (years) in replacement therapy [$\mu \pm$ SD]** | $4.4 \pm 4.2$ |

[1] 2 lost values for type of renal replacement therapy.

**Table 2.** Descriptive analysis of the frequency of the main complications recorded in the study population during follow-up.

| **Type of Complication** | **n (%)** |
|---|---|
| Intraoperative Complication | 31 (12.4) |
| Bleeding | 16 (6.4) |
| Thrombosis | 4 (1.6) |
| Early Surgical Complication | 81 (32.4) |
| Late Surgical Complication | 56 (22.4) |
| Acute Rejection | 42 (16.8) |
| Chronic Rejection | 15 (6.0) |
| Graft Delayed Function | 84 (33.6) |
| Opportunistic Infection | 90 (36.0) |
| Bacterial Infection | 164 (65.6) |
| Cardiovascular Event | 59 (23.6) |
| Tumour Diagnosis | 61 (24.4) |
| Urological Tumour | 15 (6.0) |
| Graft loss | 49 (19.6) |
| Death | 55 (22.0) |

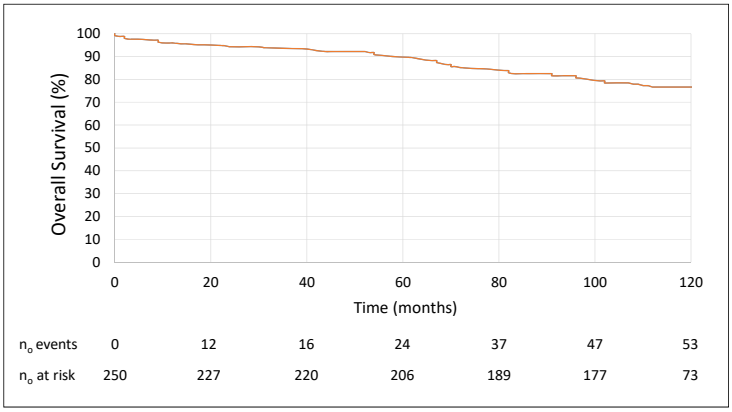


**Figure 1.** Overal Survival Curve (Kaplan-Meier method model).

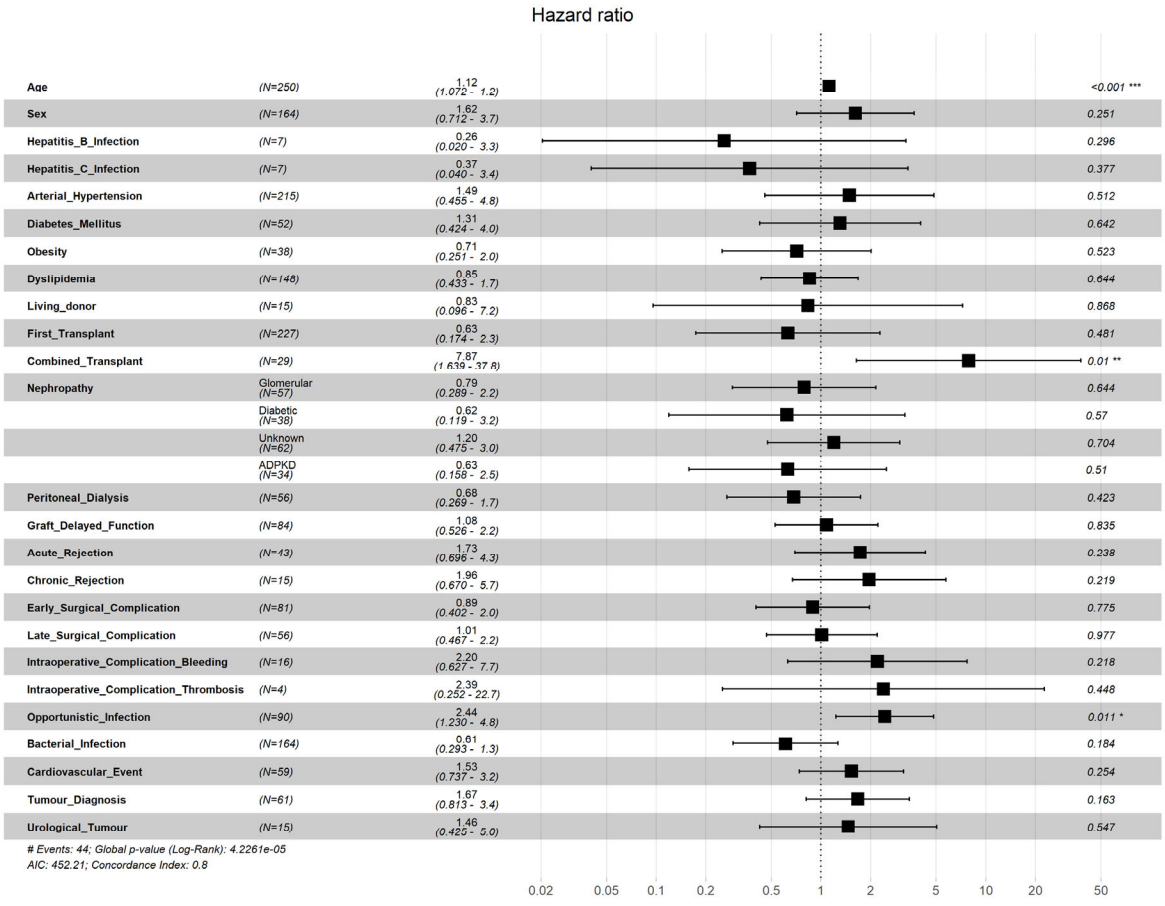


**Figure 2.** Results of the Cox proportional hazards model for overall survival, including the studied variables. * $p$-value < 0.05, ** $p$-value < 0.01, *** $p$-value < 0.001.

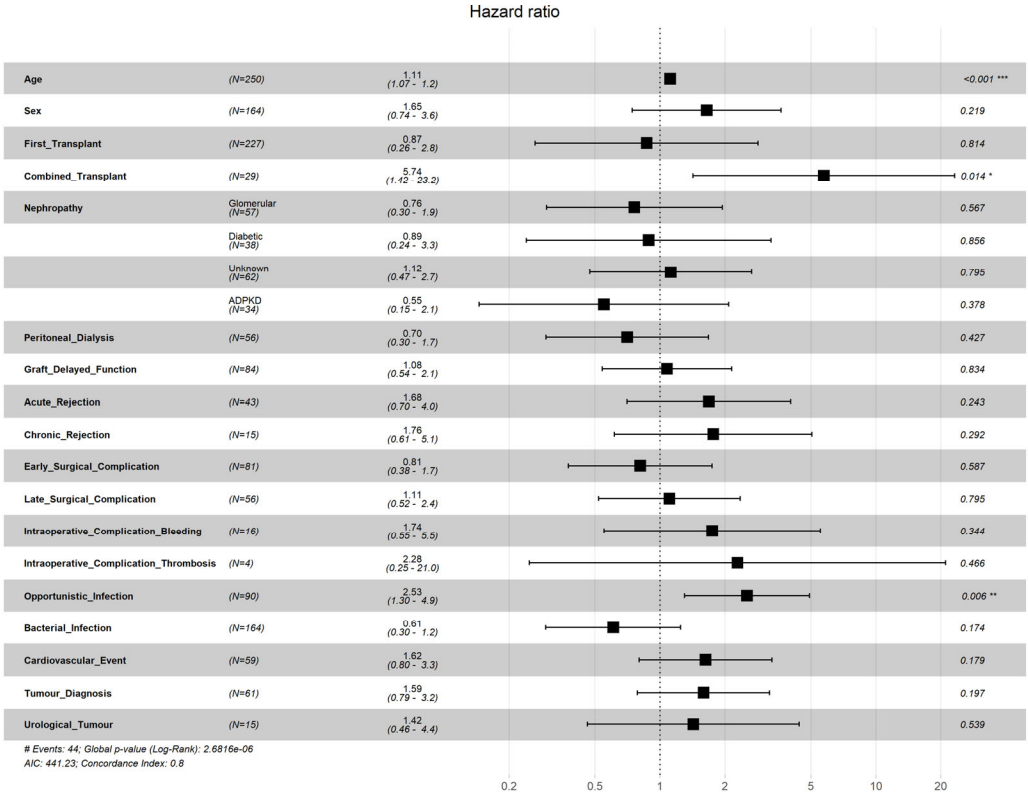


**Figure 3.** Results of the Cox proportional hazards model for overall survival, including the clinical selection of the studied variables. * $p$-value < 0.05, ** $p$-value < 0.01, *** $p$-value < 0.001.

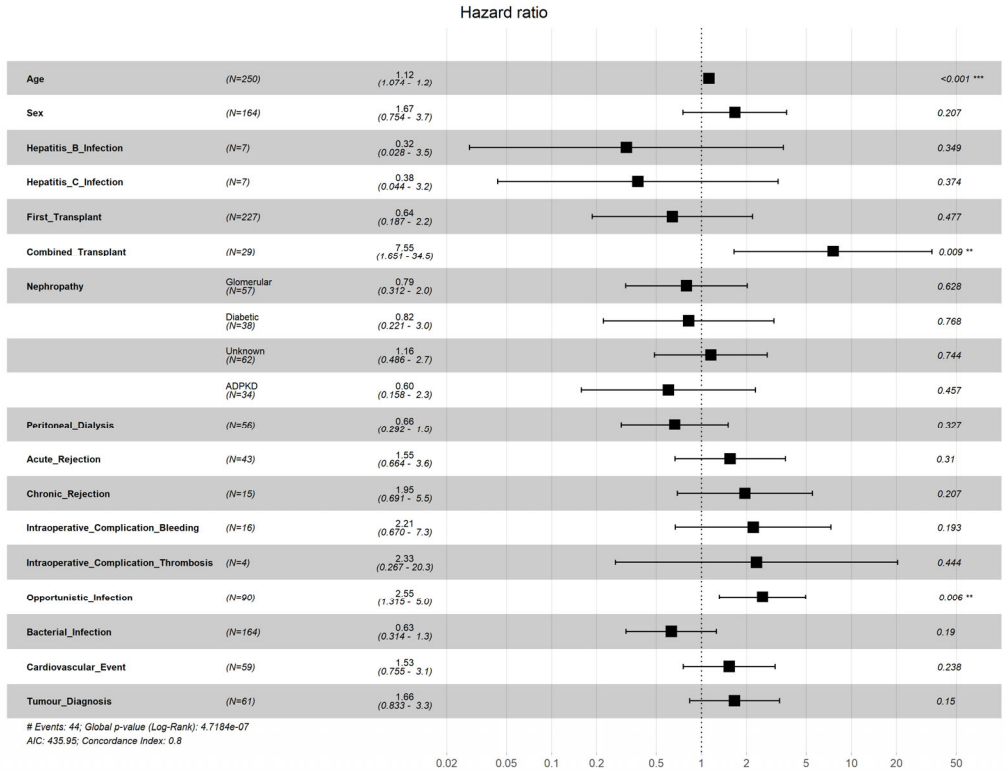


**Figure 4.** Results of the Cox proportional hazards model for overall survival, including the most significant studied variables. ** $p$-value < 0.01, *** $p$-value < 0.001.

The actuarial probability of graft survival was 89.0%, 85.1% and 78.4% at 2, 5 and 10 years respectively. Graft survival evolution during follow-up is shown in Figure 5.

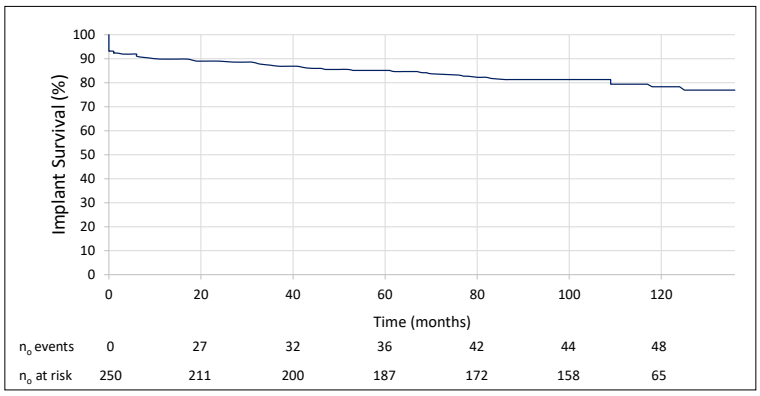


**Figure 5.** Graft Survival curve (Kaplan Meier method model).

Regarding recipient survival, three Cox proportional models were computed. The third model identified the following as risk factors for graft loss: diabetic nephropathy (HR 3.17 CI 95% [1.1–9.4]), delayed graft function (HR 3.8 CI 95% [2.0–7.4]), chronic kidney rejection (HR 3.7 CI 95% [1.2–11.4]), and early surgical complications (HR 2.6 CI 95% [1.4–5.1]). Conversely, combined transplant (kidney-pancreas and kidney-liver) was found to be a protective factor for graft loss (HR 0.1 CI 95% [0.0–0.5]). Other variables also identified as protective factors with this model were as follows: late surgical complications (HR 0.3 CI 95% [0.1–0.8] and tumour diagnosis during follow-up (HR 0.3 CI 95% [0.1–0.9]). These models and their results can be found in detail in Figures 6–8.

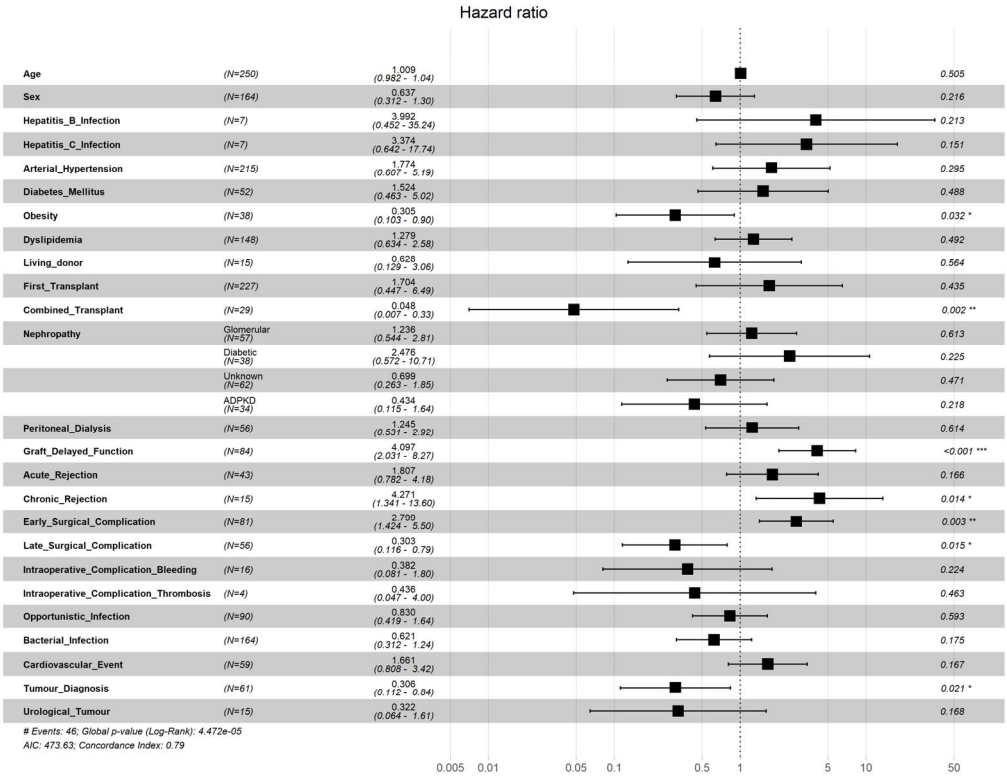


**Figure 6.** Results of the Cox proportional hazards model for graft survival, including the studied variables. * $p$-value < 0.05, ** $p$-value < 0.01, *** $p$-value < 0.001.

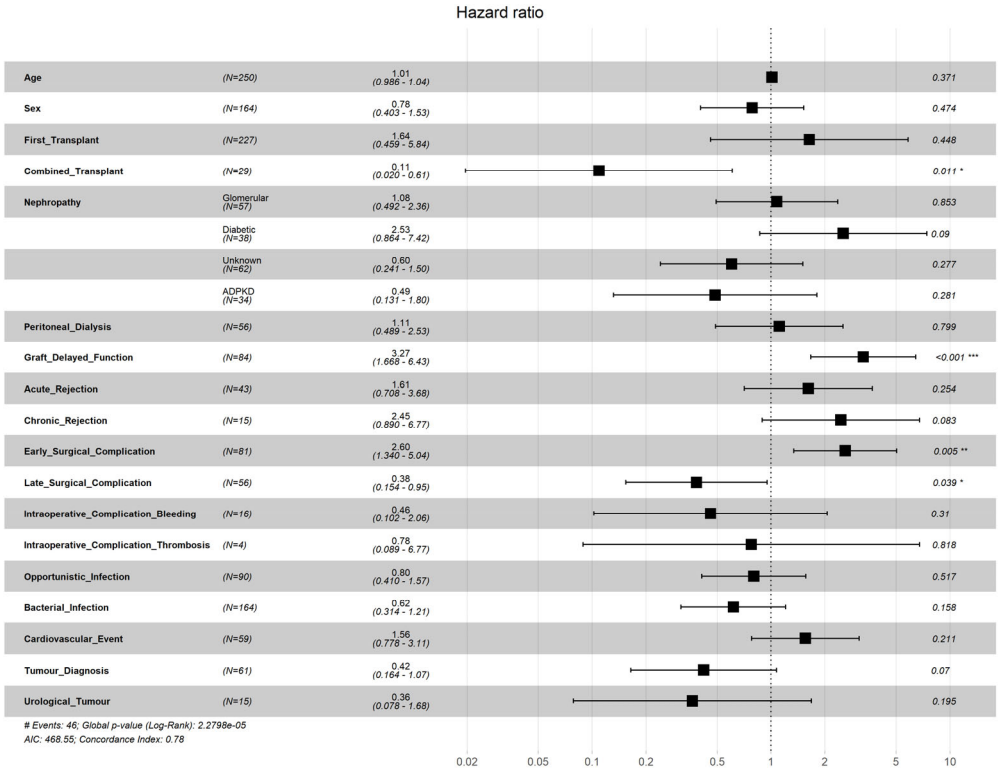


**Figure 7.** Results of the Cox proportional hazards model for graft survival, including the clinical selection of the studied variables. * $p$-value < 0.05, ** $p$-value < 0.01, *** $p$-value < 0.001.

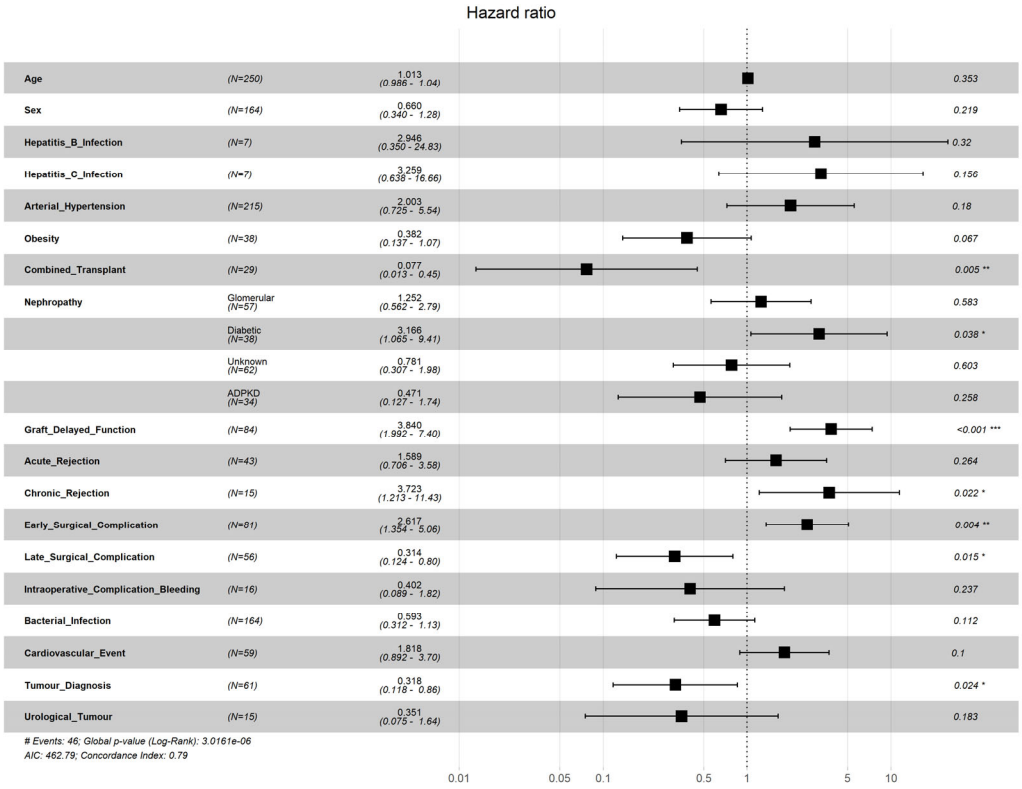


**Figure 8.** Results of the Cox proportional hazards model for graft survival, including the most significant studied variables. * $p$-value < 0.05, ** $p$-value < 0.01, *** $p$-value < 0.001.

## 4. Discussion

Kidney transplantation is the renal replacement therapy of choice for suitable patients, since it has been shown to have better survival and quality of life outcomes compared to other alternatives. In line with these findings, we have observed a high recipient survival rate in our cohort, similar to those described in the literature to date, such as Thereby a meta-analysis of 32 articles, published in 2016 by Querard et al. that reported a 5-year recipient survival of 78–86%, comparable but slightly lower than our 90% [2]. Nevertheless, it must be noted that this meta-analysis included American, European, Asian and Oceanic series, with noteworthy heterogeneity between them that could justify the observed differences. In fact, if we take only European series from the meta-analysis into account, the mean recipient survival is 85–90%, closer to our results. Likewise, our results are in agreement with the 2016 annual registry of the European Dialysis and Transplant Association that reported a survival of 87–94% [16]. Regarding of 10-year recipient survival, we calculated a rate of 76.6% in our cohort. However, it is complicated to compare this result with other authors, since few studies have been published in the last 20 years reporting a sufficiently follow-up.

On the other hand, we must keep in mind that an appreciable number of patients suffer from graft loss during follow-up for multiple reasons (immunologic rejection, chronic graft nephropathy, primary kidney disease relapse) and this loss may or may not lead to patient death. In this context, it is highly important to consider not only recipient survival, but also renal graft survival. With a 5-year graft survival of 85%, our results are among the most favourable within European series, which report a rate between 75% and 87% [2,6,16]. In the longer term (10 years), few studies are to be found in the literature, as is the case for recipient survival, although some authors have described 10-year graft survival rates similar to ours. Compared to our 78.4%, a Mexican group observed a survival rate of 80% [17] and an Irish group of 79% [18]. Conversely, there are also other articles such as the paper published by Gondos et al., that found a lower transplant survival, of around 56% [6].

With this aim we designed the present Cox proportional-hazards multivariate model. Through this model, we identified as mortality risk factors the older recipient age, combined transplants (kidney-pancreas and kidney-liver) and opportunistic infections. Comparing our results with available literature, we observe that both recipient age and opportunistic infections had been previously associated with lower survival. That is the case of Saucedo-Crespo et al., who in 2016 published a retrospective study which described a 13% decrease in 5-year survival for transplant recipients older than 70 years compared to younger recipients ($p < 0.01$) [19]. In relation to the impact of opportunistic infections, there is less evidence in the literature. However, some authors such as Gopalakrishnan et al. observed a reduction in survival for these patients (91.8% vs. 98.1%) but with only 1 year of follow-up [20]. On the other hand, we have not found any paper specifically analysing multiorgan transplant as a mortality risk factor. Nevertheless, it seems to be logical that multiorgan transplant recipients may have a higher risk of mortality not only because of their multiple comorbidities, but also because of the higher technical complexity of surgery and the higher risk of both intraoperative and postoperative complications. It may be disconcerting here to note that combined transplant works as a protective factor against graft loss in our sample. This paradoxical observation might be explained by the higher mortality rate observed in this group. Taking into account that patients who died of non specifically renal causes (comorbidity, surgical complications, liver or pancreas graft dysfunction) are considered as censored data in graft survival analysis, the higher mortality rate among multiorgan transplant recipients could lead to a shorter follow-up in this subgroup and, consequently, to a lower probability of observing the event as "graft loss".

Regarding other potential graft loss risk factors, it may seem contradictory from a clinical point of view that late surgical complications and tumour diagnosis during follow-up have been identified as protective factors in our cohort. This finding probably reflects an inherent bias associated with long-survival patients, since late surgical complications and tumour diagnosis occur late during follow-up and, therefore, only in patients with sufficiently long survival. Furthermore, long term immunosuppressant therapy is associated

with a higher incidence of tumours, which may explain why the development of tumours is a factor linked to long survival but not a predictor of better survival outcomes.

On the other hand, we identified the following factors as predictors of graft loss: diabetic nephropathy as the aetiology of chronic kidney disease, delayed graft function, chronic rejection and early surgical complications. In relation to diabetic nephropathy, we have found few papers specifically focusing on its prognostic implication in terms of graft survival since most of them analyse diabetes mellitus prevalence in general. In our cohort it has been shown to be a risk factor for graft loss compared to the other aetiologies of chronic kidney disease. This finding differs from other authors such as Noguchi et al., who reported a 5-year graft survival similar for diabetic nephropathy and other aetiologies [21].

Conversely, delayed graft function is a well-established graft loss risk factor. At this point our results coincide with the literature despite the heterogeneity in the definition of "delayed graft function" [22,23]. However, it must be mentioned that we have not found a statistically significant association with recipient survival that differs from the previously cited articles.

As we mentioned above, chronic kidney rejection also works as a risk factor for graft loss. It must be noted that we have not found available studies focusing on this specific prognostic factor, as most papers analyse acute rejection or do not specify the kind of rejection they are considering [24]. Over time, with improvements in immunosuppressant therapies, acute kidney rejection is being associated with decreasing graft loss rates [25].

Finally, development of early surgical complications, both urological, vascular and abdominal wall related, has been shown to be a negative prognostic factor in terms of graft survival. This association is noteworthy, since most previous studies have failed to demonstrate such a significant relation, such as in the case of Pillot et al. in their paper published in 2012 [26]. However, considering the different types of early surgical complications individually, vascular complications have previously been clearly associated with early graft loss [27].

Regarding methodology, it must be pointed out that our study has several strengths compared to most published series. On one hand, a systematic sampling of consecutive cases was carried out, including all adult patients receiving a kidney transplant in our centre from 2010 to 2012. Furthermore, both living-donor transplants and multiorgan transplants (kidney-liver and kidney-pancreas) were included. No patients were excluded, minimising the probability of selection bias. Moreover, we achieved a large sample size with a considerably long follow-up (mean follow-up 8.1 $\pm$ 3.2 years). Indeed, our follow-up is longer than those of most published studies, making it possible to analyse recipient and graft survival at 10 years. Such a long-term survival analysis is not easily found in the literature available to date.

The main limitations of this study are the retrospective design and the difficulty in collecting some variables (especially those related to donors due to reasons of confidentiality). Furthermore, the definition of some variables such as chronic rejection or graft delayed function are heterogeneous between different authors, making it difficult to compare outcomes.

## 5. Conclusions

Five and ten-year recipient survival was 90.0% and 76.6% respectively. The main mortality risk factors were older recipient age (HR 1.1), opportunistic infections (HR 2.6) and, with a greater impact, multiorganic transplant (HR 7.6).For graft loss, the five and ten-year survival was 85.1% and 78.4%. The main risk factors were diabetic nephropathy (HR 3.2), delayed graft function (HR 3.8), chronic kidney rejection (HR 3.7) and early surgical complications (HR 2.6).

Survival rates in our study cohort are comparable to those of other similar studies at five-year follow-up. In addition, information is available on an important cohort of patients up to ten years, allowing the study of the impact of long-term risk factors. The identification and management of these risk factors could lead to better survival values

in future patients, as well as improving the information available during the informed decision-making process.

**Author Contributions:** Conceptualization, Á.B.-R., F.Q.-F., F.G.-P., A.B-A.; Methodology, Á.B.-R., F.Q.-F., J.D.-C., D.V.-C.; Software, J.D.-C.; Validation, Á.B.-R., F.Q.-F., A.B.-A., M.R.-C.; Formal Analysis, J.D.-C., Á.B.-R., F.Q.-F.; Investigation, Á.B.-R., F.Q.-F.; Resources, Á.B.-R., F.Q.-F.; Data Curation, Á.B.-R., F.Q.-F., J.E.-V., D.J.C.-A.; Writing—Original Draft Preparation, Á.B.-R., F.Q.-F.; Writing—Review & Editing, Á.B.-R., F.Q.-F., A.B.-A., M.R.-C.; Visualization, Á.B.-R., F.Q.-F., D.V.-C.; Supervision, A.B.-A., M.R.-C., D.V.-C.; Project Administration, E.B.-R., A.B.-A.; Funding Acquisition, E.B.-R., A.B.-A. All authors have read and agreed to the published version of the manuscript.

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