CHAPTER 1

Evolution of Graft Survival in Kidney Transplantation: An Analysis of the OPTN/UNOS Renal Transplant Registry

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INTRODUCTION

Now that major barriers of the early years have been successfully overcome, renal transplantation has become a widely accepted treatment for end-stage renal disease (1). It is well established that renal transplantation confers a significant survival advantage over maintenance dialysis (2). In addition, after graft loss, the risk of mortality remarkably increases compared to patients with a well-functioning graft (3). Therefore, it is extremely important to quantify the success achieved in transplantation and to identify risk factors associated with inferior graft survival.

In the early 90s, investigators assumed that the reduction of early acute rejection rates would translate into improved graft survival (4, 5). Indeed, short-term graft survival improved substantially. Whereas the one-year graft survival for deceased donor (DD) transplants was 79% in 1988, it exceeded 90% in 2010. However, with the accumulation of sufficient data regarding renal transplantation, it became evident that long-term graft survival has improved little in the past decades (6, 7). Many different factors acting in concert might have contributed to this phenomenon. The purpose of this chapter was to re-evaluate the risk factors affecting long-term graft survival in the United States by analyzing the most recent data provided by the United Network for Organ Sharing (UNOS).

METHODS

Statistical analyses were performed using STATA/MP v. 10.0 (StataCorp, College Station, TX). Graft survival rates were estimated using Kaplan-Meier analysis, and statistical comparisons of survival curves were done by log-rank test. Parametric continuous data were analyzed by Student t-test. A p-value of <0.05 was considered significant. The mean survival time (MST) was defined as the intersection point of the Kaplan-Meier curve with the 50% survival threshold.

RESULTS

Patient population demographics

A total of 271,827 kidney recipients transplanted between January 1988 and August 2010 were analyzed. Retransplants (21,539), multi-organ transplants (17,290), and foreign transplants (75) were excluded. Among the primary, kidney-only, US transplants, 94,521 (34%) were living-donor (LD) transplants and 177,306 were deceased-donor (DD) transplants including 21,539 (8%) expanded criteria donor (ECD) transplants. Forty percent (108,071) were female and 46% (123,344) were younger than 45 years at transplantation. The demographics grouped by year of transplantation are displayed in Table 1.

Evolution of graft survival

Between 1988 and 2010, graft survival at 6 and 12 months post-transplant increased by approximately...
**Table 1. Demographic changes grouped by year of transplantation.**

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* Only 3-year period

10% for DD and LD transplants (Fig. 1). Taking this early improvement into account, no additional long-term graft survival rate improvement was evident for DD recipients and long-term graft survival for LD recipients shows a loss of the early improvement by 8, 10 and 12 years post-transplant (Fig. 2).

The MST for DD transplants increased from 7.9 to 9.2 years between the periods 1988-1995 and 1996-2009, whereas the MST for LD transplants decreased slightly from 14.2 to 13.8 years (Fig. 3).
Figure 2.

A

DD

- 1988 - 1991 (n=23,220)
- 1992 - 1995 (n=25,694)
- 1996 - 1999 (n=28,696)
- 2000 - 2003 (n=31,903)

B

LD

- 1988 - 1991 (n=5,987)
- 1992 - 1995 (n=9,368)
- 1996 - 1999 (n=14,706)
- 2000 - 2003 (n=22,792)

Figure 3.

A

p<0.001

B

p<0.001

DD

LD

era 1988-1995 (n=63,298)
era 1996-2009 (n=152,938)

era 1988-1995 (n=20,017)
era 1996-2009 (n=83,335)
When limiting the analysis to recipients with a 'low-risk constellation' for transplantation (recipient and donor age below 45 years), the MST of the grafts (DD and LD) modestly improved from 11.8 to 13.6 years between the two periods (Fig. 4).

![Figure 4. Graph showing graft survival over time for recipients and donor age < 45 years.](image)

**Non-immunologic factors affecting graft survival**

**Type of donation: DD versus LD**

The total number of kidney transplants doubled between 1993 (n=8,576) and 2009 (n=16,774) including a 3-fold increase in LD transplantations (Fig. 5A). The overall graft survival was substantially higher for recipients of LD transplants than recipients of DD transplants. The MST of LD grafts (14.0 yrs) differed significantly from the MST (8.6 yrs) for DD grafts (Fig. 5B).

![Figure 5. Graphs showing number of transplants and graft survival.](image)
Type of DD donor: standard criteria DD donor (SCD) versus expanded criteria donor (ECD) (era 1994-2010)

The policy of expanded criteria donor (ECD) was developed to increase utilization rates of available kidneys and to improve the kidney allocation process. Since 1994, the frequency of ECD constantly increased reaching the peak of 1,791 transplants in 2009. However, as previously reported (8), transplants from ECD were associated with a higher risk of graft loss compared to recipients of SCD transplants (MST: 6.0 vs 9.6 years, respectively, Fig 6).

Delayed graft function (DGF)

The rate of DGF declined from 22% in 1988-1991 to 16% in 2008-2010 (Table 1). The MST for recipients with DGF was remarkably lower compared to the recipients without DGF (Fig. 7). For recipients of DD transplants, the MST decreased from 9.7 to 6 years with DGF and the MST of living transplants declined from 14.5 to 7.5 years. Importantly, the main impact on graft survival occurred within the first year post-transplant, and in the following post-transplant years, the difference in survival remained stable around 20-25%.
DGF and cold ischemia time in recipients of DD kidneys

One important predictor for DGF was cold ischemia time (CIT). Over the evaluation period from 1988 to 2010, the mean CIT declined from 25 ±11 hours to 17 ±11 hours for recipients of DD transplants. However, the overall mean CIT was significantly higher in recipients with DGF (21 ±12 hrs) than in recipients without DGF (13 ±11 hrs) (Fig. 8).

Age of recipient

The recipient’s age was also an important factor influencing graft survival. For DD graft recipients, MST decreased from 10.5 (for age group <29) and 9.3 years (for age group 30-59) to 6.6 years for those over age 60 (Fig. 9A). This observation is likely due to higher rates of cardiovascular morbidity and mortality in recipients over age 60. Even more impressive was the decline in MST in the setting of living donation (MST: 19 yrs for age group <29, 14.3 yrs for age group 30-59, and 9 yrs for age group > 60) (Fig. 9B).
Race: black versus non-black

When separating the population into black and non-black recipients, the MST for DD grafts was 6.7 years for black recipients and 9.7 years for non-black recipients (Fig. 10A). For LD grafts, the difference in MST was more remarkable: 15.2 years for non-black recipients and 9.8 years for black recipients (Fig. 10B).

Non-compliance

Non-compliance as a contributory cause of graft loss was seldom reported during the first 10 years of the OPTN/UNOS Registry. During 2004-2007, 6-7% of graft losses were reportedly due in part to non-compliance. Since 2006 the incidence of grafts lost due to non-compliance decreased from 7% to 1.7% (Fig. 11A). The majority of these graft losses occur in the pre-adolescent (10-14 yrs) and adolescent (15-18 yrs) age groups (Fig. 11B).
Primary disease causing end-stage renal disease

When looking at primary renal diseases with the highest frequencies among transplant recipients, diabetes appeared as the leading cause followed by hypertension, polycystic kidney disease, chronic glomerulonephritis (not further specified), focal segmental glomerulosclerosis (FSGS), IgA nephropathy, and systemic lupus erythematosus (SLE). Three groups were identified according to their risk of graft failure (Fig 12): i) IgA nephropathy and polycystic kidney disease had the best MST with 12.5 (DD) and 20.0 years (LD), ii) FSGS, chronic glomerulonephritis, and SLE displayed slightly inferior MST with 9.7 (DD) and 16.4 (LD) years, and iii) hypertensive and diabetic nephropathy had markedly shorter MST with 7 (DD) and 10.5 years (LD). Importantly, the 2 leading primary diseases showed the poorest outcomes.

![Figure 12](image_url)

Diabetes mellitus as primary disease

When grouping the population into recipients with diabetes mellitus versus recipients without diabetes mellitus, the MST of DD grafts was lower (6.8 yrs) for diabetic recipients compared to 9.5 years for non-diabetic recipients (Fig. 13A). The difference in MST was more impressive in the LD setting: 10.1 years for diabetic recipients versus 16.3 years for non-diabetic recipients (Fig. 13B).
**Immunologic factors affecting graft survival**

**Acute rejection within 6 and 12 months post-transplant**

The rate of acute rejection within 12 months post-transplant substantially decreased from 22.0% in 1988 to 3.5% in 2009 (Fig. 14).

Transplant recipients who experienced acute rejection within 6 months post-transplant had reduced MST (7.8 years for DD and 12.5 years for LD) compared to the recipients without rejection episodes (10.2 years for DD and 15.4 years for LD) (Fig. 15). Accordingly, the MST was lower in those recipients with acute rejection within 12 months post-transplant (8.7 for DD and 12.9 years for LD) than in recipients without acute rejection (10.6 for DD and 15.8 years for LD) (Fig. 16).
Number of previous transplantations

The number of previous transplantations also affected graft outcome. As the number of previous transplants increased, the MST declined from 8.9 years for DD recipients with no previous transplants to 8.5 years for those with 1 or more previous transplant (Fig. 17A). Among LD recipients, the MST declined from 14.4 years (no previous transplantation) to 12.6 years (1 or more previous transplant) (Fig. 17B).

![Figure 17](image)

HLA compatibility

With higher degrees of HLA compatibility, the MST increased for both DD and LD transplants (Fig. 18). HLA-matched transplants (6 or 5 matches) showed the highest MST with 10.7 and 20.0 years for DD and LD, respectively whereas completely mismatched transplants had the lowest MST of 8.2 (DD) and 12.6 (LD) years. Surprisingly, HLA-matched transplants derived equally from LD and DD (13% vs 10%), and the mismatched transplants (0, 1, or 2 matches) were predominant among DD recipients.

![Figure 18](image)
Combining non-immunologic and immunologic factors

ECD recipients stratified by acute rejection within the first post-transplant year

ECD transplant recipient who experienced acute rejection within the first year post-transplant displayed inferior MST (6.2 years) when compared with ECD transplant recipients who were rejection-free (MST 8.0 years) (Fig. 19A). There was a 5-year difference in MST when comparing rejection-free SCD transplant recipients with ECD recipients who experienced acute rejection (data not shown).

When limiting the analysis to just ECD recipients over age 60, the MST further declined from 6.9 years for those without acute rejection to 5.2 years for those with acute rejection (Fig. 19B).

Diabetic transplant recipients stratified by acute rejection within the first post-transplant year

In concert, the risk factors diabetes and acute rejection decreased the MST of DD transplants from 11.7 years (no diabetes and no rejection) to 8.1 years (diabetic recipient but no rejection) and 6.9 years (diabetic recipient with rejection) (Fig. 20A)

For LD transplants, the MST declined from 18.3 years (no diabetes and no rejection) to 11.1 years (diabetic recipient but no rejection) and 9.1 years (diabetic recipient with rejection) (Fig. 20B).
DISCUSSION

It is evident that overall improvement in kidney allograft survival rates has been mainly due to a substantial reduction in early graft failures. Indeed, the one-year graft survival rate increased by 10% between 1988 and 2009, whereas longer-term survival reflected by the MST showed little improvement during this 22-year period. Multiple factors may have contributed to this complex phenomenon. Some of these factors were avoidable, others not. Given the imminent organ shortage and the growing waiting list of patients with multiple co-morbidities, most donor- and recipient-related factors (i.e. ECD kidneys, age and primary disease of recipient) are not avoidable.

ECD transplants

On one hand, some have criticized the use of marginal organs to overcome the organ shortage, arguing that it is at the expense of worse outcomes (9). Usually physicians recommend ECD transplants to elderly transplant candidates and elderly transplant candidates are likely to accept ECD transplants, especially if their prognosis on dialysis is poor (10). Thus, higher-risk kidneys are preferentially given to older candidates, and one could imagine that this high-risk population may impede improvement of long-term graft survival. On the other hand, the UNOS data show that the MST for DD transplants with lower risk (recipient age <45 years AND donor age < 45 years) increased by only two years between the era 1988-1995 and 1996-2009. Even more impressive was the observation that the MST for living donor transplants has not increased in the past 20 years (MST of approximately 14 years since 1988). Similar results were previously reported by Lamb, et al (11). Based on these findings, one could conclude that the lack in improvement is not exclusively due to increased utilization of ECD transplants. The fact that the transplant population with lowest risk revealed marginal improvement indicates that other factors than ‘donor-related parameters’ are decisive.

Declining acute rejection rate but unchanged long-term survival

With the advent of potent immunosuppressive agents, the rate of early acute rejection impressively decreased and contributed to the improvement of short-term graft survival. It is astonishing and even paradoxical that long-term survival has been largely unaffected by this important progress. Based on this observation, one is tempted to conclude that reducing the rate of early acute rejections does not result in improved long-term survival. Furthermore, this questions the choice of acute rejection as a surrogate end-point for long-term survival in many studies (6). We can only speculate about the reason why there is a lack in long-term improvement. One possible explanation could be a higher rate of ongoing subclinical rejections despite a lowered rate of clinical rejections. This speculation is supported by a recently published study demonstrating that an induction treatment - consisting of polyclonal anti-T-lymphocyte globulin and intravenous immunoglobulins – significantly reduced clinical rejection episodes, but did not decrease subclinical rejections (12). At 3 and 6 months post-transplant the rate of subclinical antibody-mediated rejection was still 30% despite the use of an induction therapy. Now, the key question remains, whether ongoing subclinical rejection has an impact on long-term graft survival. Probably, yes. There is growing evidence demonstrating that subclinical rejections, both antibody- and cell-mediated, contribute to the development of transplant glomerulopathy, interstitial fibrosis and tubular atrophy (13, 14). Notably, in the study of El-Zoghby, et al, 23% of the graft losses were due to chronic immunologic injury that led to transplant glomerulopathy (15%) or interstitial fibrosis/tubular atrophy (8%). Therefore, one of the factors contributing to the lack of long-term improvement might be an ongoing immunologic process that is - even if subclinical - inadequately controlled. In this regard, a practical intervention to early diagnose subclinical rejections might be the implementation of protocol biopsies. This issue is vigorously debated in renal transplantation (15-18).
New immunosuppressive agents are required

Despite a variety of immunosuppressive agents that were developed in the last 3 decades, none has improved long-term survival. In this regard, many questions are still unanswered. Now that we are able to detect donor-specific antibodies (DSA) at very low-levels with high sensitivity, the question arises whether all detected DSA are pathogenic? Is it just a question of time and all DSA will become deleterious or are some DSA "protective" and should not be treated? How can we diagnose chronic antibody-mediated injury at an early stage and how can we stop it?

Given the fact that under the current immunosuppressive regimen, more than 80% of renal grafts show some degree of inflammation which is associated with inferior outcome (19-21), new ways of treatment approach are urgently needed. One novel treatment approach is the use of bortezomib which has the ability to deplete plasma cells (22-25). Whether this promising agent will translate into improved long-term graft survival, requires an extended follow-up with real, hard end-points.

Prevention and control of cardiovascular risk factors

Moving forward, we must also focus on the common cardio-vascular risk factors that affect long-term graft and patient survival. The increasing number of diabetic and hypertensive transplant recipients (20 and 40%, respectively, in 2010) is worrisome. Recently, Parekh, et al (26) reported that diabetes is an independent risk factor for DGF which in turn increases the need for early post-transplant dialysis. Several possible mechanisms were discussed, including increased ischemia-reperfusion injury, elevated markers of inflammation and enhanced oxidative stress. Even if the role of aggressive peri-operative glucose control is not yet definitively assessed, it is clear that preventing and controlling cardiovascular risk factors is indispensable to improving long-term outcomes.

CONCLUSION

While allograft survival reached almost the maximum at one year, optimizing long-term survival is still a major challenge in the 21st century. Some recipient and donor-related factors are not avoidable given the increasing number of polymorbid patients and the need to utilize ECD kidneys. Long-term improvement may depend upon early diagnosis and treatment of chronic allograft injury. This should be a valid incentive to develop efficacious immunosuppressive agents. Furthermore, avoiding risk factors that provoke cardiovascular diseases are the sine qua non for increased long-term graft survival.

SUMMARY

In summary, the analysis of more than 270,000 kidney transplants recipients who were transplanted between January 1988 and August 2010 showed the following important points:

Despite enormous progress in short-term graft survival in the last decades, long-term graft survival remained largely unchanged over the period from 1988 to 2010.

The marked decline in acute rejection episodes in the early transplantation period mainly contributed to the improvement of short-term graft survival.

The immunosuppressive agents that were introduced in the past 3 decades have not improved long-term graft survival.

Therefore, new treatment approaches are strongly required to prevent and treat chronic allograft injury especially caused by immunologic factors.

Avoiding and controlling risk factors that are responsible for cardiovascular diseases are the sine qua non for increased long-term graft survival.
REFERENCES


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