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The Speed and Impact of a New Technology Diffusion in Organ Transplantation: A Case Study Approach[1]

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Abstract

A miracle in medical procedure, organ transplantation, has taken place in recent decades due to the diffusion of a new technology. The new technology refers to a family of the so-called immunosuppressive drugs. As a result, survival rates of major organ transplants have risen to a record-level of 80 to 90%.

This paper has four objectives. First, the speed of new technology diffusion is measured from the historical penetration ratio for the major immunosuppressive drugs. It took, on average, 6 to 8 years for new drugs to gain the 50% penetration ratio. Second, historical improvement patterns of survival rates for major organ transplants are analyzed by the use of both classical and kinked experience curves. The results indicate that kinked experience equations generated much steeper slopes. Third, the relationship between the increased penetration ratios of new drugs to the improved survival rates of organ transplants is analyzed. Overall, rapid diffusion of new drugs appears to have caused faster improvement of the survival rates. Finally, we forecast the future improvement of survival rates through 2030 by the use of kinked experience equations. Our forecast shows that nearly every type of transplants will reach 90% or higher survival rates by 2020.

Keywords: Technology Diffusion, Organ Transplantations, Immunosuppressive Agents, Experience Curve
JEL Codes: I10, O33

[1] Working Paper Series

1. Introduction to organ transplantation

Organ transplantation is the procedure by which organs are transferred from a donor to a recipient for the purpose of replacing the recipient's damaged or absent organ. "Organ and/or tissues that are transplanted within the same person's body are called autografts. Transplants that are performed between two subjects of the same species are called allograft. Allograft can either be from a living or deceased source"[2], according to Wikipedia [86]. Currently, the list of solid organs that are transplanted includes kidney, livers, hearts, lungs, pancreases, and intestines.

According to 2010 report by the Global Observatory on Donation and Transplantation [24], "approximately 100,900 solid organ transplants are performed each year: 69,300 kidney transplants (46% from living donors), 20,300 liver transplants (15% from living donors), 5,330 heart transplants, 3,330 lung transplants, 2,380 pancreas transplants and 260 small bowel transplants."[3]

However, the most comprehensive and accurate source of organ transplants data especially with respect to survival rates is the United Network of Organ Sharing (UNOS) Scientific Registry of Organ Transplantation in the U.S. The Scientific Registry transplant database tracks outcomes of all solid organ transplants performed since October, 1987. Therefore, this study has used data from the UNOS data base, and is thus limited to the transplantations in the United States only.

In the U.S., the vast majority of transplants were done in kidneys, livers, hearts, and lungs in that order. As shown in Table 1, the largest numbers of transplants were done in kidney with 10,216 from deceased donors and 6,428 from living donors in 2006. Next was a liver transplant with 5,836 from deceased and 286 from living donors. The numbers of heart transplants were 2,147 while lung transplants numbered 1,397 cases. The total number of transplants in the U.S. was 27,802 in 2006, representing about 27.6% of the total worldwide transplants.

Nearly all the organ transplants show a significant improvement during this time period. For example, 1-Year survival rate of lung transplant at 33.3% in 1987 improved to 83.2% by 2006, while 1-Year survival rate of deceased liver at 57.2% in 1987 improved to 83.1% by 2006. However, some other organs have shown only a modest or no improvement. For example, 80% survival rate in 1987 for heart transplant improved to only 87.4% by 2006, and 80.0% survival rate in 1990 for intestine transplant actually decreased to 69.5% by 2006. An in-depth analysis of these improvement patterns will be made later in this paper.

With a significant improvement of survival rates, transplantation has become the treatment of choice for many patients suffering from end-of-the state organ failure or complications arising from disease of specific organ.

Consequently, demands for organ transplants far surpass supply throughout the world. In the United States, the growth of transplantation is also limited by the number of organs available transplantation as well.

What factors are responsible for the improvement of survival rate of organ transplants? According to Humar et al. [35], the list will include superior immunosuppressant to treat and prevent organ rejection, refinement in surgical technique, better diagnostic test methods for monitoring patients, enhancement of organ procurement procedures, accurate detection of organ rejection, better understanding of the immune system in general and many others.

This paper is organized in the following six parts. First, a brief history of organ transplantation and immunosuppressive drugs will be presented to provide necessary background information. Second, the speed of new technology diffusion will be measured from the historical penetration ratios for the major new drugs. Third, past improvement patterns of survival rates for major organ transplants will be analyzed by the use of both classical and kinked experience curves. Forth, the relationship between the increased penetration ratios of new drugs to the improved survival rates of organ transplants will be studied to examine the impact of new technology. Fifth, we shall forecast future improvement of survival rates through 2030 by the use of kinked experience curve models. Final part will have a conclusion, limitations of this study, and suggested future research topics.

[2] Wikipedia, Organ Transplantation [86], http://en.wikipedia.org/w/index.php?title=Organ_transplantation&oldid=403840891

[3] Global observatory on donation and transplantation [24], pp.4

Table 1. The Number of Transplants by Types of Transplants for the Years from 1987 to 2006

Year	Number of Transplants											Total
	Living Kidney	Deceased Kidney	Living Liver	Deceased Liver	Heart	Lung	Heart Lung	Intestine	SPK[a]	PTA[b]	PAK[c]	
1987	399	1,629		313	350	6	9		29	5	2	2,742
1988	1,817	7,035		1,677	1,648	33	74		171	30	31	12,516
1989	1,901	6,717	2	2,149	1,676	93	67		333	28	30	12,996
1990	2,091	7,265	14	2,617	2,068	202	52	5	458	18	37	14,827
1991	2,395	7,234	22	2,872	2,103	401	51	12	451	35	35	15,611
1992	2,534	7,138	33	2,954	2,146	535	48	22	492	29	27	15,958
1993	2,851	7,442	36	3,329	2,270	660	60	33	659	42	57	17,439
1994	3,005	7,534	56	3,486	2,310	707	71	22	745	36	54	18,026
1995	3,389	7,598	53	3,770	2,336	846	69	43	910	36	67	19,117
1996	3,670	7,597	63	3,859	2,311	788	38	41	847	42	112	19,368
1997	3,928	7,634	86	3,924	2,252	908	62	60	841	63	130	19,888
1998	4,409	7,898	91	4,269	2,293	837	46	66	967	63	155	21,094
1999	4,688	7,916	251	4,337	2,136	863	51	67	930	98	218	21,555
2000	5,468	7,958	399	4,384	2,161	940	46	77	908	99	301	22,741
2001	6,013	8,069	520	4,453	2,169	1,034	27	112	886	109	302	23,694
2002	6,227	8,287	361	4,692	2,108	1,028	32	103	902	128	374	24,242
2003	6,458	8,388	319	5,040	2,024	1,065	28	109	866	104	344	24,745
2004	6,638	9,029	322	5,449	1,959	1,153	38	145	880	120	419	26,152
2005	6,567	9,512	318	5,667	2,059	1,402	34	161	895	127	342	27,084
2006	6,428	10,216	286	5,836	2,147	1,397	31	161	914	94	292	27,802
Total	80,876	152,096	3,232	75,077	40,526	14,898	934	1,239	14,084	1,306	3,329	387,597

Notes: [a] SPK - Simultaneous Kidney Pancreas, [b] PTA - Pancreas Transplant Alone, [c] PAK - Pancreas After Kidney
Source: [57] Table 5.11c, 5.11d, 6.11, 7.11, 8.11a, 8.11b, 9.11a, 9.11b, 10.11, 11.11, 12.11a, 13.11

Table 2. Unadjusted 1-Year Graft Survival Rates by Types of Organ Transplants for the Years from 1987 to 2006

Year	Unadjusted One-Year Graft Survival Rates											
	Living Kidney	Deceased Kidney	Living Liver	Deceased Liver	Heart	Lung	Heart Lung	Intestine	SPK-KG[a]	SPK-PG[b]	PTA[c]	PAK[d]
1987	88.70%	76.10%		57.20%	80.00%	33.30%	44.40%		79.30%	65.50%	40.00%	100.00%
1988	88.70%	75.70%		64.30%	80.70%	42.40%	51.40%		81.90%	72.40%	53.30%	48.40%
1989	90.80%	78.30%	100.00%	64.00%	81.80%	57.00%	53.70%		85.30%	77.30%	46.40%	53.30%
1990	91.30%	80.00%	71.40%	67.60%	82.80%	70.30%	67.30%	80.00%	77.70%	69.80%	44.40%	51.40%
1991	93.00%	83.40%	63.60%	70.30%	80.80%	67.60%	62.70%	91.70%	85.40%	80.90%	51.40%	48.60%
1992	91.60%	83.50%	81.80%	72.00%	81.40%	68.70%	64.60%	68.20%	83.90%	78.90%	72.40%	55.60%
1993	91.80%	82.90%	83.30%	73.80%	81.70%	75.30%	70.00%	48.50%	85.10%	78.10%	44.60%	50.90%
1994	92.60%	84.30%	64.30%	76.40%	83.50%	74.30%	66.20%	59.10%	85.80%	80.50%	66.00%	70.40%
1995	92.50%	85.80%	73.60%	77.70%	83.90%	75.40%	76.80%	58.10%	89.50%	82.20%	63.90%	70.10%
1996	93.60%	87.30%	84.10%	76.30%	84.80%	70.50%	63.20%	61.00%	89.70%	83.80%	71.00%	67.60%
1997	94.10%	88.50%	84.90%	78.60%	84.70%	75.60%	59.70%	53.30%	92.00%	85.00%	67.90%	73.60%
1998	94.70%	88.80%	70.30%	79.90%	85.00%	75.30%	54.30%	50.00%	91.30%	83.10%	77.80%	72.20%
1999	94.50%	88.00%	74.10%	79.60%	83.20%	75.70%	56.90%	49.30%	91.70%	83.00%	82.50%	80.00%
2000	94.20%	87.90%	77.70%	80.70%	85.20%	77.10%	63.00%	68.80%	92.70%	83.60%	74.50%	73.30%
2001	94.40%	88.90%	80.20%	80.40%	85.30%	77.30%	74.10%	61.40%	91.80%	84.80%	77.60%	82.30%
2002	95.00%	89.00%	80.10%	82.30%	86.10%	80.60%	62.50%	69.90%	91.90%	86.30%	80.00%	77.30%
2003	95.40%	89.10%	84.00%	81.70%	87.40%	82.70%	50.00%	77.10%	92.40%	85.90%	68.10%	77.60%
2004	95.10%	90.00%	84.20%	83.00%	87.50%	84.20%	73.70%	77.20%	92.70%	85.20%	74.60%	78.30%
2005	95.20%	90.10%	84.00%	81.50%	86.90%	81.20%	76.50%	73.30%	93.50%	87.40%	85.70%	76.80%
2006	96.20%	90.60%	85.70%	83.10%	87.40%	83.20%	70.70%	69.50%	92.00%	84.20%	75.30%	77.60%

Notes: [a] SPK-KG - Simultaneous Kidney Pancreas-Kidney Graft, [b] SPK-PG - Simultaneous Kidney Pancreas-Pancreas Graft, [c] PTA - Pancreas Transplant Alone, [d] PAK - Pancreas After Kidney
Source: [57] Table 5.11c, 5.11d, 6.11, 7.11, 8.11a, 8.11b, 9.11a, 9.11b, 10.11, 11.11, 12.11a, 13.11

2. A Brief History of Organ Transplant and Immunosuppression

The first experimental transplantation of a kidney between dogs was conducted by Dr. Üllman in Vienna in 1902. About ten years later, the surgical techniques used to join blood vessels known as vascular anastomosis was pioneered by a French surgeon, Alexis Carrel who claimed that the technical problem of transplantation was essentially solved. Carrel was awarded of the Nobel Prize in 1912. However, he also warned that "until some method was developed to prevent the rejection of organism against foreign tissues, there would be no clinical application of organ transplantation."[4]

It was not until 1954, when a kidney was transplanted from one healthy identical twin to his twin in Boston, which became the first successful transplant in the history. For this, Dr. Joseph E. Murray later received the Nobel Prize in 1990.

Stimulated by this historic event, many more organ transplants were attempted. One of the most notables was the first heart transplant by Dr. Christensen Barnard of South Africa in 1967. The first successful liver transplant was made by Dr. Thomas Starzl in Colorado during the same year of 1967.

However, the tendency of the immune system to attack the grafts impeded further success of organ transplants. The technical advance in surgery appears to have hit its limit. The world of organ transplantation was in desperate need of better drug therapies of immunosuppression.

The first major breakthrough came with the discovery of a new drug called azathioprine in 1962 which ushered the so-called Azathioprine Era (1962-1983). As a result, graft survival rate at 1-Year for kidney had moved up to around 50%, according to Helderman et al. [32].

Hitchings and Eliot of the Wellcome Laboratory won the Nobel Prize in 1988 for their pioneering work in developing azathioprine in the late 50's and early 60's. The use of azathioprine combined with another drug, corticosteroids, helped to continue a slow improvement in the survival rates during the 1960's and 1970's.

The Azathioprine Era also ended the so-called Experimental Era which began with Dr. Murray's successful kidney transplant for the identical twin. During the Experimental Era (1954-1962), transplant scientists were experimenting with immunosuppressive therapies as well as surgical techniques for engrafting other organs such as the liver as well as the heart (Helderman et al. [32]).

In 1983, the Cyclosporine Era (1983-1995) was ushered in by the discovery and clinical trials of cyclosporine, another major breakthrough drug. One-year graft survival rate of kidney has moved up from 70 percent to more than 80 percent as a result. During this period, transplantation in livers, pancreas, hearts, and even lungs have also achieved excellent outcome (Helderman et al. [32]).

It was suggested by Helderman et al. [32] that the "Interregnum Period" began around 1995 "marked by a flurry of new drug development and clinical research."[5] They have pointed out an important shift away from the use of both azathioprine and cyclosporine toward newer drugs, mycophenolate mofetil and tacrolimus. They have also suggested that immunosuppression strategy may be adopting "mix and match therapeutic options available for specific characteristics of each recipient and organ" rather than "the one-size-fits-all approach."[6]

Whereas data used by Helderman et al. [32] in their article covered the period from 1987 through 2001, we will attempt to examine these newer trends by using data available through 2006 in this paper.

Immunosuppressive drugs inhibit or prevent activity of the immune system in order to prevent future rejection of transplanted organs and tissues. The success of organ transplantations is highly dependent on the effectiveness of immunosuppressive drugs to suppress recipient immune response to the foreign organ. In fact, transplant patients require lifelong immunosuppressive therapy to prevent this rejection. All of these drugs have very negative side-effects that include a high risk of opportunistic infection and malignancies from over-immunosuppression. Therefore, a major goal becomes that of discovering the optimal balance of therapy such that there is effective prevention of allograft rejection, while drug-related adverse effects are minimized.

In general, there are five basic categories of immunosuppressive drugs used in organ transplantation.

They are: (1) calcineurine inhibitors such as cyclosporine or tacrolimus, (2) antiproliferative agents such as azathioprine, mycophenolate mofetil, or sirolimus, (3) corticosteroids such as prednisone or methylprednisolone, (4) monoclonal antibodies, and (5) polyclonal antibodies.

Very briefly, calcineurin inhibitors block the message that causes rejection, while antiproliferative agents prevent the immune cells from multiplying (WebMD [80]). Corticosteroids act on the immune system by blocking the production of substances that trigger allergic and inflammatory actions. However, they also impede the function of white blood cells that can yield a side effect of increased risk to infection.

Monoclonal antibodies also block the growth of immune cells, while polyclonal antibodies temporarily deplete the body's immune cells. These five agents are often combined to serve three different purposes of inductive therapy, maintenance therapy and episodic therapy.

Inductive therapy, which is administered just before and after transplantation, uses high doses of monoclonal antibodies together with corticosteroids, polyclonal antibodies, and/or antiproliferative agents.

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4 Morris [52], pp.2
5 Helderman et al. [32], pp. 51
6 Helderman et al. [32], pp. 51

Maintenance therapy, on the other hand, will need to be administered for the rest of lifetime of the recipient. The classic triple combination includes low dosages of a calcineurine inhibitor, an antiproliferative agent, and a corticosteroid. The annual cost of the triple therapies can be as much as $25,000 per year with the substantial risk of side effects.

Despite the combined efforts of maintenance therapy, many transplanted organs do eventually fail. When such failure occurs, episodic therapy (treatment) relies on a high dose of corticosteroid to combat the rejection by severely depressing the immune system. Also, polyclonal and monoclonal antibodies or antiproliferative agent in high doses can be used as a rescue therapy.

Table 3 lists further details on the types of major drugs and their serious side effects as well as dosage information on these five immunosuppressive agents.

Table 3. Five Basic Categories of Immunosuppressive Agents in Transplantation

Category	Immunotherapy	Type	Side Effects	Route/Dose
Calcineurine Inhibitors	• *Primarily used for Maintenance Therapy*	• *Cyclosporine*	• Nephrotoxicity • Hypertension • Tremor • Coronary artery disease • Hirsutism • Gingival hyperplasia • Opportunistic infections • Malignancies • Hyperuricemia • Hepatoxicity • Hypertricosis	• Oral: 5-10 mg/kg/day • Intravenous: a third of the oral dose
		• *Tacrolimus*	• Nephrotoxicity • Hypertension • Hyperkalemia • Hypomagnesemia • Alopecia • Hyperglycemia • Opportunistic infections • Malignancies	• Oral: 0.15-0.3 mg/kg/day • Intravenous: 0.03 mg/kg/day
Antiproliferative Agents	• *Primarily used for Maintenance Therapy* • *Secondarily used for Inductive Therapy*	• *Azathioprine*	• Bone marrow depletion/suppression • Thrombocytopenia • Anemia • Pancreatitis • Hepatoxicity • Neoplasia	• Oral: 1-2 mg/kg/day • Intravenous: 1-2 mg/kg/day
		• *Mycophenolate Mofetil*	• Leucopenia • Thrombocytopenia • Nausea • Opportunistic infection • Malignancies • Gastrointestinal upsets	• Oral: 1~1.5 g twice a day • Intravenous: 1~1.5 g twice a day
		• *Sirolimus*	• Leucopenia • Thrombocytopenia • Hypercholesterolemia • Hypertriglyceridemia	• Oral: 2-5 mg/day
Corticosteroids	• *Primarily used for Episodic Therapy* • *Secondarily used for Maintenance Therapy and Inductive Therapy*	• *Prednisone* • *Methylprednisolone*	• Hypertension • Hyperlipidemia • Osteoporosis • Weight gain • A cushingoid appearance • Opportunistic infection • Glaucoma • Ulcer formation • Hyperglycemia	• Oral: 5-10 mg/day for maintenance • Intravenous: a high dose before, during, after transplant dose and taper schedule varies with organ
Monoclonal Antibodies	• Primarily used for Inductive Therapy • Secondarily used for Episodic Therapy	• Muromonab-CD3	• Acute clinical syndrome • Aseptic meningitis • Opportunistic infections • Lymphoma • Malignancies • Hypersensitivity reactions • HAMA reaction	• Intravenous: 5 mg/day for 7-14 days
		• Interleukin-2 Receptor Antagonist[a]	• Gastrointestinal disorders	• Intravenous: 20 mg 2 hours prior to transplant 20 mg 4 days after transplant
		• Daclizumab*	• Gastrointestinal disorders	• Intravenous: 1 mg/kg around the surgery every 14 days for 4 more doses
Polyclonal Antibodies	• Secondarily used for Inductive Therapy and Episodic Therapy	• Antithymocyte globulim-equine • Antithymocyte globulin-rabbit	• Leucopenia • Serum sickness • Antibody against foreign protein • Thrombocytopenia • Pruritis • Fever • Arthralgias • Opportunistic infections • Malignancies	• Intravenous: 10-20 mg/kg/day for up to 14 days (-euuine) 1.5 mg/kg/day for 7-14 days (-rabbit)

Notes: [a] Additional side effects specific to this drug are unknown due to the fact that the drug is still undergoing clinical trials
Source: [11], http://biomed.brown.edu/Courses/BI108/BI108_2004_Groups/Group04/Index.html

3. Speed of New Technology Diffusion

Diffusion is the spread of new technology across its potential market. Therefore, diffusion may be viewed as one of the three pillars on which the successful introduction of new technology takes place along with invention and innovation (Hall [28], Stoneman and Diederen [71]). Another well-known definition by Roger [61] states that diffusion is "the process by which an innovation is communicated over time among the members of a social system."[7] We will use the definition of diffusion speed as "the amount of time it takes to go from one penetration level to a higher level."[8]

Speed of diffusion, in general, is founded to be slow and variable (Rosenberg [62, 63]). For example, one of the early classical studies by Mansfield [45] discovered that the period from the date of the first use of technology to the date of the use of technology by 90% of potential users varies from five to fifty years.

A large number of studies on diffusion followed, resulting in many complex diffusion models and empirical applications, particularly in consumer durables and telecommunication areas (Meade and Islam [49], Sultan et al. [72], Bass [2, 3], Freiman [23], Desiraju et al. [19]).

For diffusion studies on drugs, the classic study by Coleman et al. [16] was followed by a number of other studies (Berwick [5], Van den Blute and Lillien [77]). This study may be the first to measure the diffusion speed of immunosuppressive drugs.

In contrast to complex diffusion models used for industrial and consumer products, drug diffusion study can be conducted by using relatively simple models for the following reasons. The new drug diffusion is usually preceded by a long period of incubation due to comprehensive clinical trials required for regulatory approval. Thus, once the new approved drug begins its diffusion, the original formula will remain unchanged during the diffusion cycle. In other words, one need not be concerned with continuous improvement issues from user-producer interactions that often occur with industrial and consumer products. Another simplifying factor may be that the key decision-makers in the new drug diffusion are doctors who prescribe the new drug for their patients, rather than patients themselves. These doctors are more likely to be influenced by the leading practice of major medical centers. Also, the accuracy of diffusion data available is likely to be higher.

We shall limit the scope of our analysis on the new and the old drugs used for maintenance therapy only. Furthermore, among the classic triple combination drugs used for maintenance therapy, we will focus on calcineurine inhibitors and antiproliferative agents only where significant changes did take place in the type of drugs used. As for the type of transplantation, we will concentrate on the four most frequent types of transplantations of kidney, liver, heart, and lung.

As has been mentioned earlier, the first major breakthrough occurred with the discovery of azathioprime (AZA) in 1962, which is an antiproliferative agent. FDA approved AZA for the use in organ transplants in 1968. It was demonstrated that the combination of AZA and corticosteroid had additive and synergistic effects, and this double therapy approach soon became the standard of therapy worldwide (Smith [68]).

However, when a new antiproliferative drug known as mycophenolate mofetil (MMF) got its FDA approval in 1994, the new drug MMF began to replace the old drug, AZA. MMF is "a useful alternative to AZA when AZA toxicity precludes use"[9], although "the exact role of MMF as AZA has yet to be conclusively established."[10]

A similar event took place in the case of calcineurine inhibitors. The first "miracle" drug of cyclosporine (CsA) was discovered at Sandoz, a Swiss pharmaceutical company in 1971. However, FDA approval was not gained until 1983. "It was the first immunosuppressant that noted selectively to suppress t-cell immunity, thus changing "many of the risk factors associated with AZA."[11]

However, a new replacement drug known as tacrolimus (TAC) was discovered at Fuzisawa Pharmaceuticals of Japan in 1984, and gained FDA approval in 1994. "It has very similar immunosuppressive properties to CsA but is 10 to 100 times more potent on a per gram basis."[12]

It has been indicated that "clinical outcome is better" with TCA over CsA, but "long term outcome has not been improved to the same extent."[13]

Penetration ratios of the new drugs versus the old drugs were available during the period from 1993 through 2007 from the OPTN[14]/SRTR[15] 2003 [56] and 2008 [57] annual reports by types of transplantations. We have shown these ratios in Fig. 1 through 4 for both calcineurin inhibitors and antiproliferative agents.

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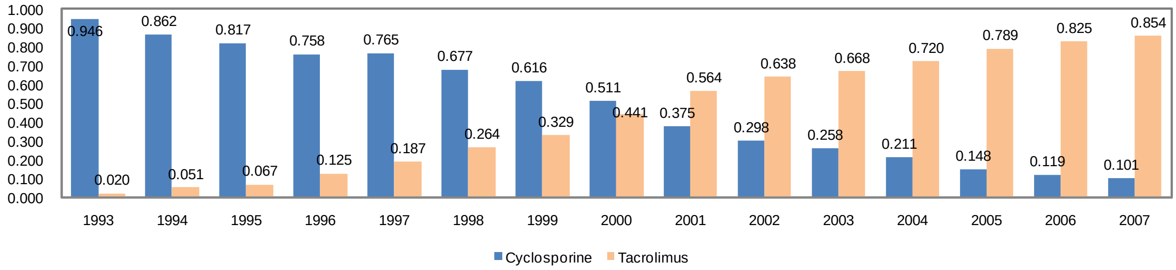
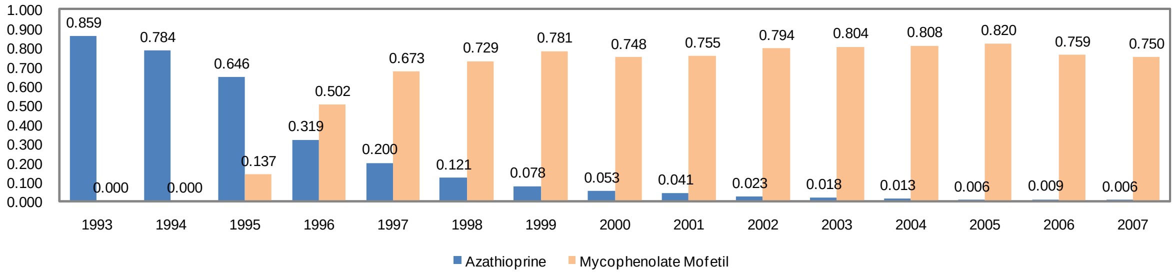
[7] Rogers [61], pp. 35
[8] Van den Blute [77], pp. 367
[9] Wikipedia [85], Mycophennolate mofetil, http://en.wikipedia.org/w/index.php?title=Mycophenolate_mofetil&oldid=398590846
[10] Wikipedia [84], Mycophenolic acid, http://en.wikipedia.org/w/index.php?title=Mycophenolic_acid&oldid=402502255
[11] Upton [75], http://www.world-of-fungi.org/Mostly_Medical/Harriet_Upton/Harriet_Upton.htm
[12] U.S. Department of Health and Human Services [74], Transplantation – History of Transplantation, http://www.niaid.nih.gov/topics/transplant/pages/history.aspx
[13] Wikipedia [87], Tacrolimus, http://en.wikipedia.org/w/index.php?title=Tacrolimus&oldid=402629202
[14] Organ Procurement and Transplantation Network
[15] Scientific Registry of Transplant Recipients

Fig. 1. Trends in Kidney Transplants Maintenance Immunosuppression Prior to Discharge, 1993-2007

- Cyclosporine vs. Tacrolimus for Calcineurin Inhibitor Use



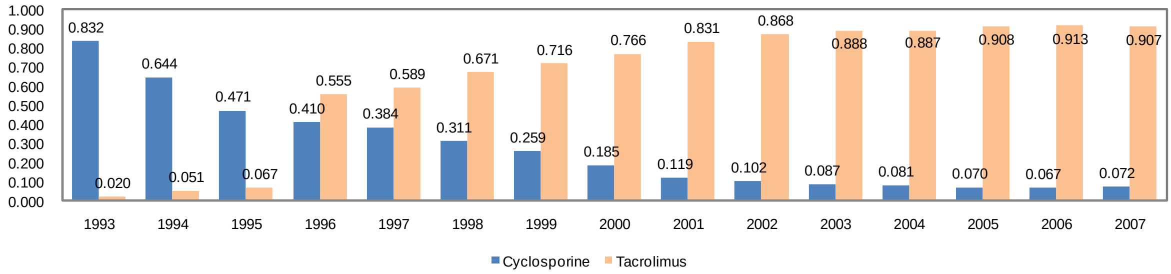
- Azathioprine vs. Mycophenolate Mofetil for Antimetabolite Use



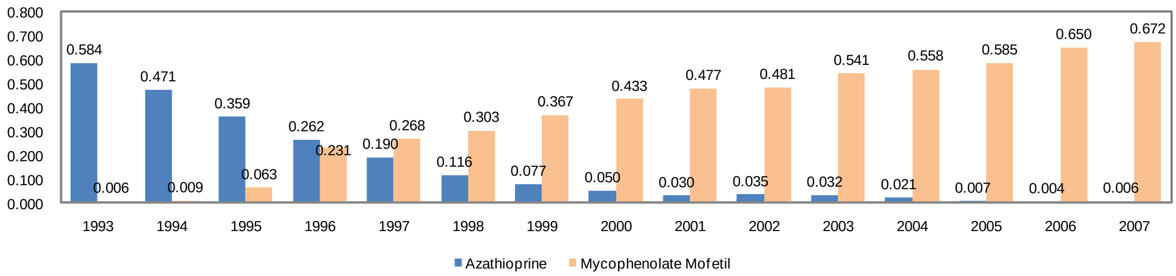
Source: [56] Table 5.6b, [57] Table 5.6e

Fig. 2. Trends in Liver Transplants Maintenance Immunosuppression Prior to Discharge, 1993-2007

- Cyclosporine vs. Tacrolimus for Calcineurin Inhibitor Use



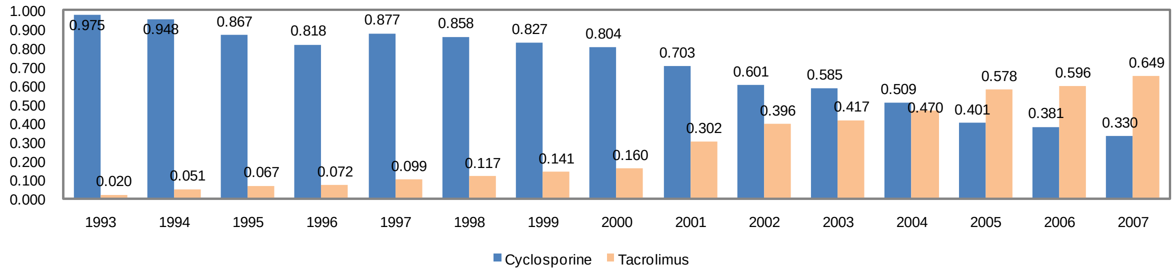
- Azathioprine vs. Mycophenolate Mofetil for Antimetabolite Use



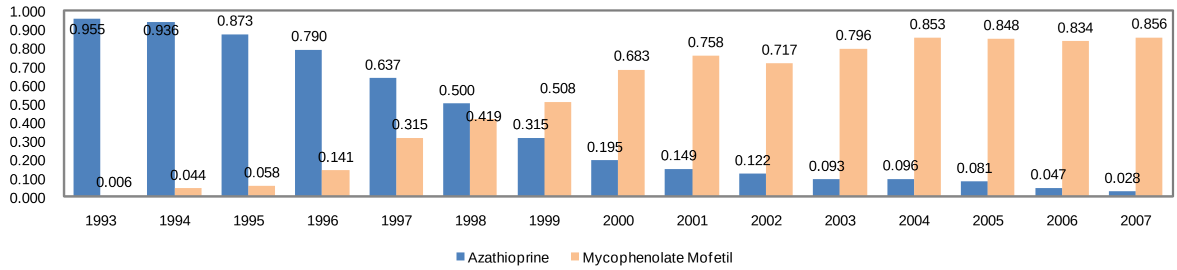
Source: [56] Table 9.6b, [57] Table 9.6e

Fig. 3. Trends in Heart Transplants Maintenance Immunosuppression Prior to Discharge, 1993-2007

- Cyclosporine vs. Tacrolimus for Calcineurin Inhibitor Use



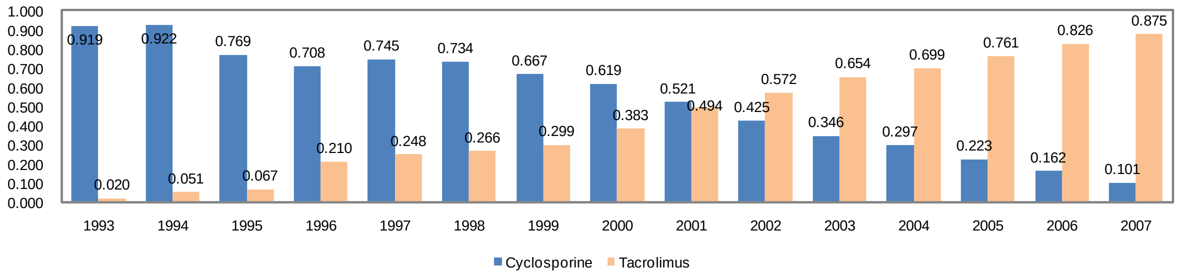
- Azathioprine vs. Mycophenolate Mofetil for Antimetabolite Use



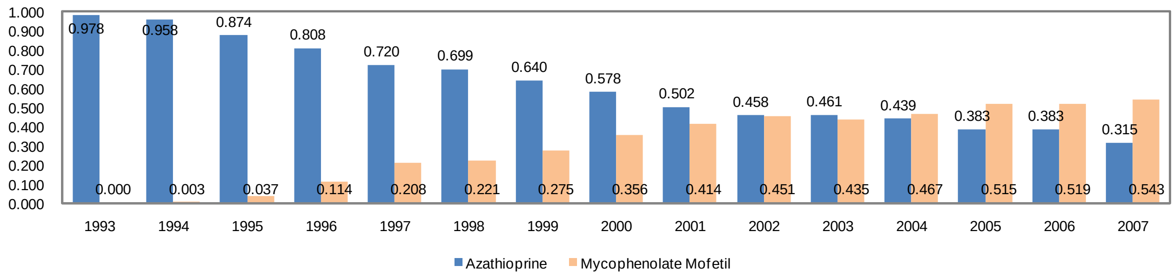
Source: [56] Table 11.6b, [57] Table 11.6e

Fig. 4. Trends in Lung Transplants Maintenance Immunosuppression Prior to Discharge, 1993-2007

- Cyclosporine vs. Tacrolimus for Calcineurin Inhibitor Use



- Azathioprine vs. Mycophenolate Mofetil for Antimetabolite Use



Source: [56] Table 12.6b, [57] Table 12.6e

For example, in 1993, 94.6% of kidney recipients were administered CsA and only 2% received TCA, but by 2007, the penetration ratio of TCA increased to 85.4% with only 10.1% of the recipients still receiving CsA. Similarly, in 1993, 85.9% of the kidney recipients received AZA, but by 2007, only 0.6% of the recipients were using AZA, as shown in Fig. 1.

For the historical analysis of diffusion speed, we will use the lower level of 0% or near 0% to the higher level of no less than 50% (Mansfield [46]). The penetration level of 50% is assumed to qualify the new drug as having established itself as the drug of choice.

How long did it take the new MMF to surpass the old AZA by gaining a minimum of 50% penetration ratio? Table 4 shows that the diffusion speed varies by types of transplants. For example, in case of lung transplant it took 10 years to reach 50% penetration, whereas kidney transplant took only 1 year to reach the same 50%. However, on average, it took MMF 6 years to gain 50% penetration ratio and 2.5 years to gain 25% penetration ratio, beginning the averaged year of 1994.8 with zero penetration ratio. Therefore, TAC reached 50% penetration ratio by the year of 2000.8.

As for the new drug of TCA, Table 5 shows that for example, in the case of heart transplant it took 12 years to reach 50% penetration, whereas liver transplant took only 3 years to reach the same 50%. However, on average, TCA took 8 years to gain 50% penetration ratio and 5.25 years to gain 25% penetration ratio from the beginning of 1993 with 2% penetration ratio. Therefore, MMF reached the penetration ratio of 50% by the year of 2001. In summary, it is remarkable that these two new drugs, on average, have become the drug of choice by nearly the same year of 2001 when they both have surpassed 50% penetration ratio.

How well the dynamic diffusion process of these drugs could have been explained by the use of analytical models? To answer this question, we tried the simple Fisher-Pry logistic substitution model. The results shown in Table 6 and Fig. 5 and 6 indicate that the model provided a very good fit to the historical penetration ratios. R^2s for the eight equations calculated for TAC and MMF ranged from 0.733 to 0.989 with the averaged R^2 of 0.92. This suggested that Fisher-Pry logistic substitution may be used to predict the speed of penetration for newer drugs that may appear in the future.

Table 4. Diffusion Speed of Mycophenolate Mefetil for Transplants by the Year of Penetration level of 1%, 25% and 50%

Year of % / Organ Transplant	Year of 1% (a)	Year of 25% (b)	Time 1% to 25% (b-a)	Year of 50% (c)	Time 1% to 50% (c-a)	Time 25% to 50% (c-b)
Liver	1995	1997	2	2003	8	6
Lung	1995	1999	4	2005	10	6
Kidney	1995	1996	1	1996	1	0
Heart	1994	1997	3	1999	5	2
Average	**1994.8**	**1997.3**	**2.50**	**2000.8**	**6.00**	**3.50**

Source: [56] Table 5.6b, 9.6b, 11.6b, 12.6b, [57] Table 5.6e, 9.6e, 11.6e, 12.6e

Table 5. Diffusion Speed of Tcrolimus for Transplants by the Year of Penetration level of 1%, 25% and 50%

Year of % / Organ Transplant	Year of 1% (a)	Year of 25% (b)	Time 1% to 25% (b-a)	Year of 50% (c)	Time 1% to 50% (c-a)	Time 25% to 50% (c-b)
Liver	1993	1996	3	1996	3	0
Lung	1993	1998	5	2002	9	4
Kidney	1993	1998	5	2001	8	3
Heart	1993	2001	8	2005	12	4
Average	**1993.0**	**1998.3**	**5.25**	**2001.0**	**8.00**	**2.75**

Source: [56] Table 5.6b, 9.6b, 11.6b, 12.6b, [57] Table 5.6e, 9.6e, 11.6e, 12.6e

Table 6. Historical Analysis of Penetration Ratios of New Immunosuppressive Drugs during the Period from 1993 to 2007 by Fisher-Pry Substitution

Type of Transplant	Drug	Fisher-Pry Model[c]	
		Equation	R^2
Kidney	TAC[a]	f / (1 - f) = exp { 0.3565 (t - 2000.935) }	0.989
	MMF[b]	f / (1 - f) = exp { 0.3812 (t - 1997.264) }	0.733
Liver	TAC[a]	f / (1 - f) = exp { 0.5132 (t - 1997.121) }	0.904
	MMF[b]	f / (1 - f) = exp { 0.2190 (t - 2002.567) }	0.917
Heart	TAC[a]	f / (1 - f) = exp { 0.2947 (t - 2004.349) }	0.982
	MMF[b]	f / (1 - f) = exp { 0.4199 (t - 1999.187) }	0.953
Lung	TAC[a]	f / (1 - f) = exp { 0.3289 (t - 2001.226) }	0.989
	MMF[b]	f / (1 - f) = exp { 0.2018 (t - 2004.557) }	0.893
Average			0.920

Notes
[a] TAC - Tacrolimus, [b] MMF - Mycophenolate Mefetil,
[c] Fisher-Pry Substitution Model: $f/(1-f) = \exp\{a(t-t_0)\}$
f: Fraction of applications in which the new drugs has been substituted for the old
t: Year
t_0: Time for 50% substitution
a: Control shape
Source: [22]

Fig. 5. Fisher-Pry Substitution Curves for Penetration Ratios of Tacrolimus for Organ Transplants

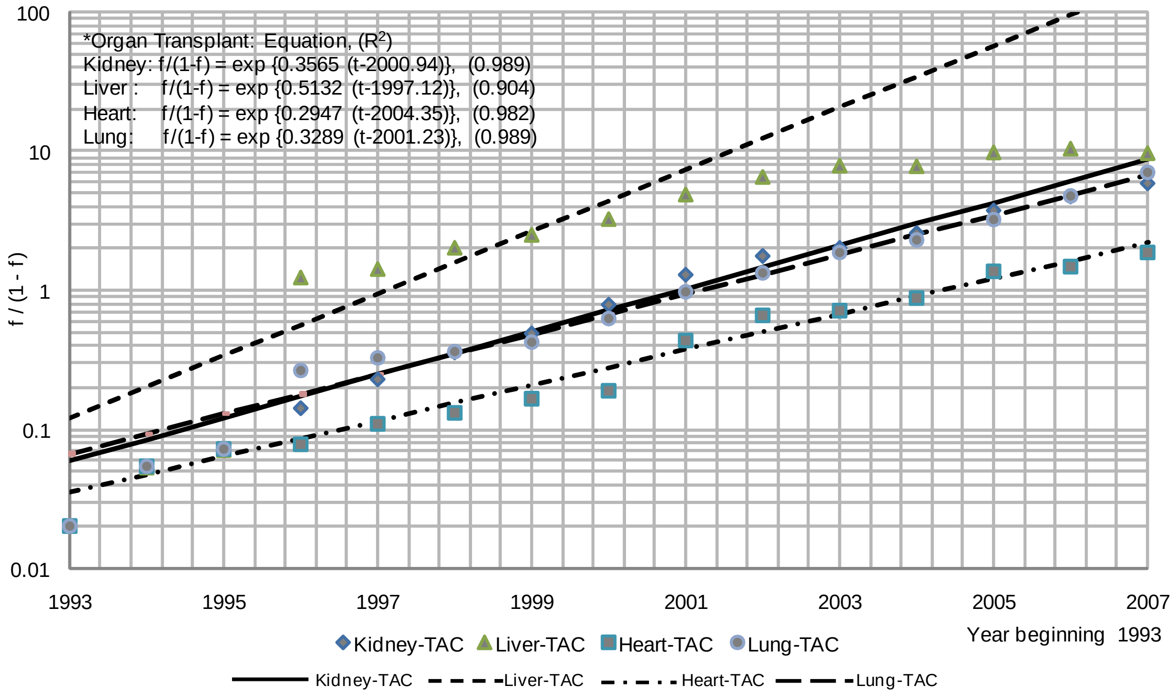
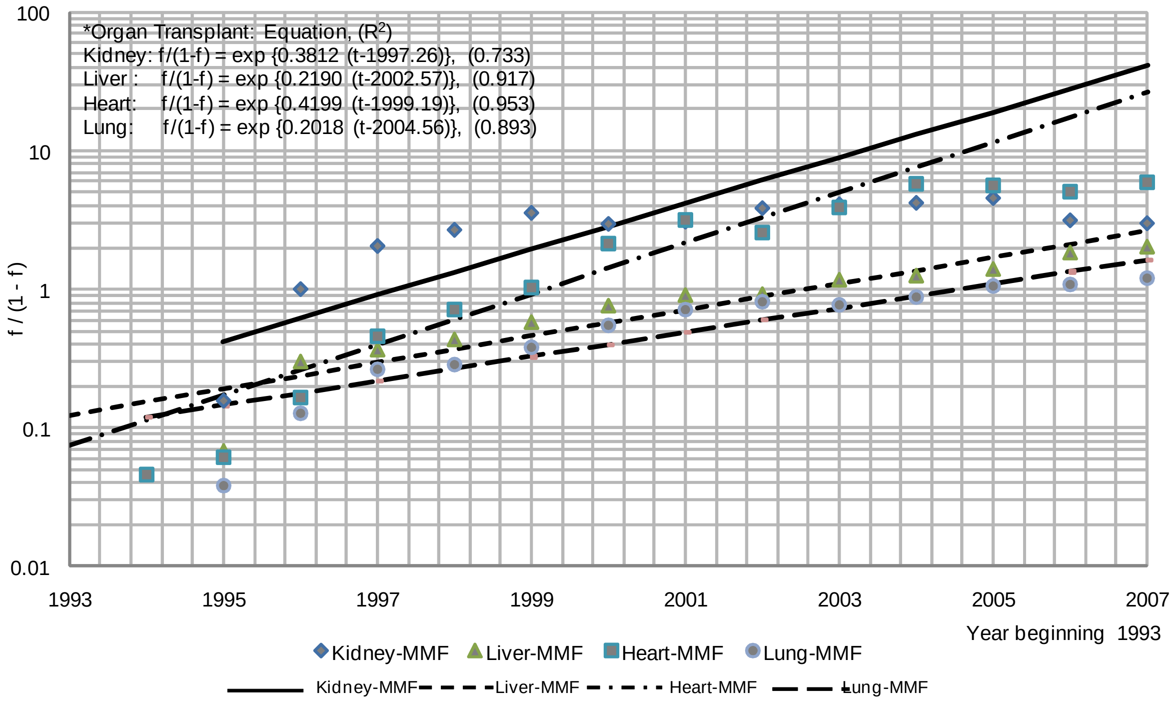


Fig. 6. Fisher-Pry Substitution Curves for Penetration Ratios of Mycophenolate Mefetil for Organ Transplants



4. Historical Analysis of Graft Survival Rates by the Use of Experience Curve

Now that we have analyzed the diffusion speed of the new drugs of TAC and MMF replacing the old drugs CsA and AZA which took place during the 1990's, we will proceed to examine the historical improvement of the survival rates of organ transplantation. Upon understanding the improvement pattern of survival rates, it may be possible to highlight the impact of technology diffusion of immunosuppressive drugs to the improved survival rate of transplantation. For the analytical model, we have adopted the experience curve. There are several reasons for this selection.

First, there is a large body of literatures to document that improvement of success rate of many medical practices, particularly surgical procedures, may be explained by the principle of past learning and experience (Lipscomb [44], Halm et al. [29], Bach et al. [1], Schrag et al. [66, 67], Birkmeyer et al. [7], Earle et al. [21], Hassan et al. [31], Hellinger [33], Begg and Scardino [4], Vickers et al. [79], Meehan and Georgeson [50], Tekkis et al. [73], Kaul et al. [38], Poon et al. [58], Yohannes et al. [91]). In short, the central idea is that practice can make it perfect.

Second, the pharmaceutical process of drug efficacy such as TAC, MMF and the multiple side-effects of individual drugs is extremely complex. Therefore, linking the impact of individual drug directly to the improvement of survival rate will be extremely difficult, if not impossible (Roberts et al. [60], Woodroffe et al. [88], Kramer et al. [42], Mayer et al. [47], Jain et al. [36, 37], Knoll and Bell [40], Remuzzi et al. [59], Buck [12])

Third, the combination regime of three types of drugs administered often in the maintenance therapy creates interaction among these drugs which generates variable results among individual recipient.

Fourth, there are also other immunosuppressive agents which are administered for induction and episodic therapy, which will influence the survival rate of transplantation.

Finally, continuous improvement in other factors such as surgical technique (Lee [43]), diagnostic test, organ procurement, etc. will also influence the survival rate of transplants, as well. In an experience curve analysis, all of these influencing factors are assumed to be represented by the past experience factor which is measured by the cumulative number of transplant operations.

More specifically, experience curve relates the rate of improvement in survival rate as a dependant variable and the rate of increase in the cumulative number of transplantations as an independent variable. Thus, the difficulty of directly assessing the impact of an individual drug to survival rate is thus by-passed.

The use of experience curve will enable us to test the first hypothesis as to whether a given percentage improvement of survival rate is associated with a given percentage increase in the number of transplantations. If so, the experience curve will also enable us to test the second hypothesis as to whether the rapid penetration of the new drugs that took place in the 1990s' may have resulted in a higher percentage improvement of survival rate during the similar time period.

The first hypothesis will be tested by the use of classical experience curve, while the second hypothesis will be tested by the use of kinked experience curve.

4.1. Application of the Classical Experience Curve

Our experience curve analysis will be made on the six categories of most frequent types of transplant operations. They are 1) kidney transplants from living donors, 2) kidney transplants from deceased donors, 3) liver transplants from living donors, 4) liver transplants from deceased donors, 5) heart transplants, and finally 6) lung transplants.

The 2008 OPTN SRTR annual report [57] provides unadjusted graft survival rates for these types of transplants by the year of transplant from 1987 to 2006 at 3-Month, 1-Year, 3-Year, 5-Year, and 10-Year intervals. For example, Table 7 presents this data on kidney transplants from deceased donors.

Our analysis will be made on 1-Year survival data as a short-term measure and 5-Year survival data as a long-term measure. For example, Table 7 shows that 8,287 transplants done in 2002 have its survival rate of 89% after one year, but the survival rate will decrease to 67.9% after the elapse of 5 years. Similarly, 8,388 kidney transplants done in 2003 has its survival rate of 89.1% after one year, but the survival rate after 5 year is not yet available in the 2008 annual report [57].

In our classical experience curve analysis, a dependent variable becomes failure rate instead of survival rate, while an independent variable is the cumulative number of transplants from the first year of transplants, namely 1987 through 2006.

More specifically, for the classical experience curve:

$$y(x_t) = y(x_1)x_t^{-b} \qquad (1)$$

where $t = 1,2,3, \cdots\cdots T$

x_t = cumulative organ transplants through year t

b = experience slope

$y(x_t)$ = failure rate at cumulative organ transplants through year t

$y(x_1)$ = failure rate at cumulative organ transplants through year 1

When both y and x in equation (1) are converted into logarithmic function, the relationship between the two variables becomes linear. Thus, a given percentage change in cumulative number of transplants will generate a constant percentage reduction in failure rate.

Table 8 and Fig. 7 and 8 show the results of 1-Year failure rates from the classical experience curve analysis on the six types of transplants. For example, 1-Year failure rate of kidney transplant from living donors has its experience slope estimated at 85.5% with R^2 of 0.853. This means that every time the cumulative number of transplants doubles or increases by 100%, the failure rate per transplant will decrease to 85.5%. The estimated experience slopes range from the maximum of 84.26% for kidney transplant from deceased donors to the minimum of 92.92% for liver transplant from living donors. The averaged slope for these six types of transplants is 88.7% with the averaged R^2 of 0.747.

Table 7. Unadjusted Graft Survival Rates of Kidney Transplants from Deceased Donors by the Year of Transplants at 3 Months, 1 Year, 3 Years, 5 Years and 10 Years

Year	Number of Transplants	Survival rate				
		3 Months	1 Year	3 Years	5 Years	10 Years
1987	1,629	83.40%	76.10%	63.40%	53.30%	34.20%
1988	7,035	82.80%	75.70%	63.60%	53.90%	34.30%
1989	6,717	84.80%	78.30%	66.50%	57.10%	35.70%
1990	7,265	86.20%	80.00%	68.80%	58.60%	37.00%
1991	7,234	95.20%	83.40%	72.70%	61.50%	38.10%
1992	7,138	89.00%	83.50%	72.60%	61.30%	36.60%
1993	7,442	88.60%	82.90%	71.90%	61.30%	38.50%
1994	7,534	89.80%	84.30%	73.70%	62.00%	38.30%
1995	7,598	91.10%	85.80%	75.40%	63.90%	40.80%
1996	7,597	92.00%	87.30%	77.00%	65.10%	41.20%
1997	7,634	93.20%	88.50%	77.50%	66.10%	42.00%
1998	7,898	93.50%	88.80%	78.20%	66.90%	+
1999	7,916	93.10%	88.00%	77.80%	67.00%	+
2000	7,958	93.40%	87.90%	77.10%	66.00%	+
2001	8,069	94.00%	88.90%	78.40%	67.30%	+
2002	8,287	93.80%	89.00%	78.20%	67.90%	+
2003	8,388	94.10%	89.10%	78.50%	+	+
2004	9,029	94.70%	90.00%	79.30%	+	+
2005	9,512	95.00%	90.10%	+	+	+
2006	10,216	95.10%	90.60%	+	+	+

Notes: (+) - Values not determined due to insufficient follow-up
Source: [57] Table 5.11b

Table 8. Historical Analysis of 1-Year Graft Failure Rates of Transplants Administered during the Period from 1987 to 2006 by the Classical Experience

Type of Transplant	Experience Curve			
	Equation[a]	Slope(%)	SE[b]	R^2
Living Kidney	$y = 0.50\ x^{-0.21}$	85.50	0.12	0.85
Deceased Kidney	$y = 2.02\ x^{-0.25}$	84.26	0.12	0.84
Living Liver	$y = 0.40\ x^{-0.11}$	92.92	0.27	0.31
Deceased Liver	$y = 1.56\ x^{-0.19}$	87.54	0.08	0.92
Heart	$y = 0.42\ x^{-0.10}$	93.11	0.09	0.65
Lung	$y = 0.97\ x^{-0.17}$	88.88	0.12	0.91
Average		88.70	0.13	0.75

Notes

[a] Experience curve equation y: 1-Year graft failure rate per transplant, x: Cumulative number of transplants

[b] SE: Standard Error

Fig. 7. Classical Experience Curves for 1-Year Failure Rates of Living Liver, Deceased Liver and Lung Transplants

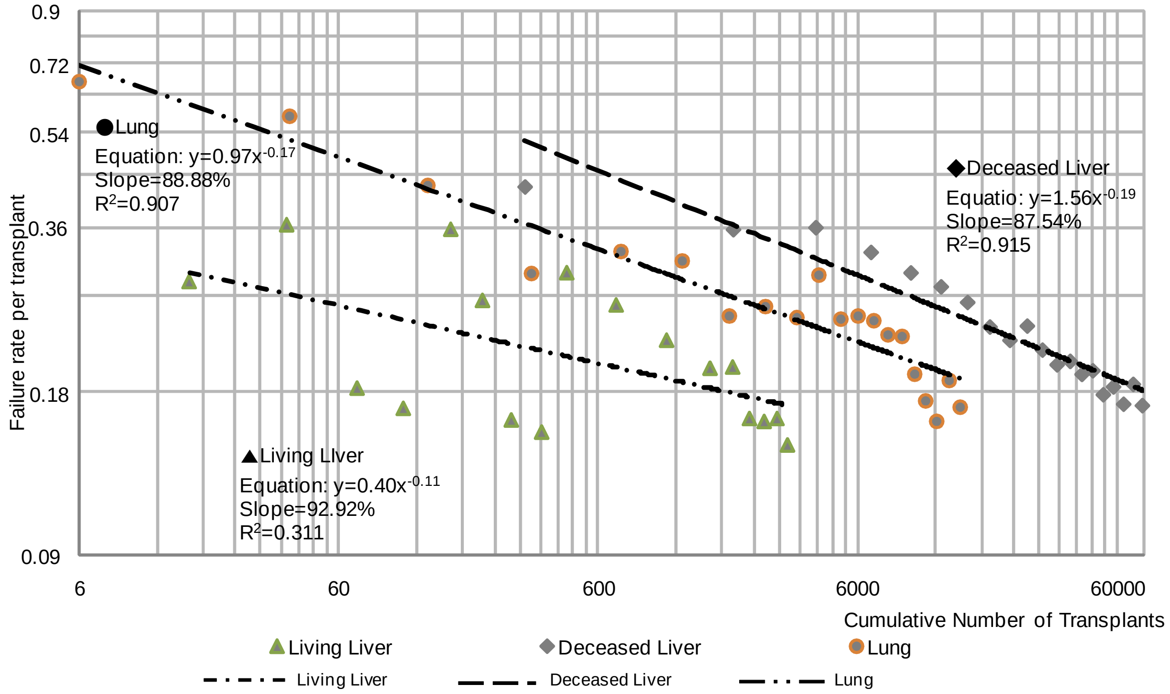


Fig. 8. Classical Experience Curves for 1-Year Failure Rates of Living Kidney, Deceased Kidney and Heart Transplants

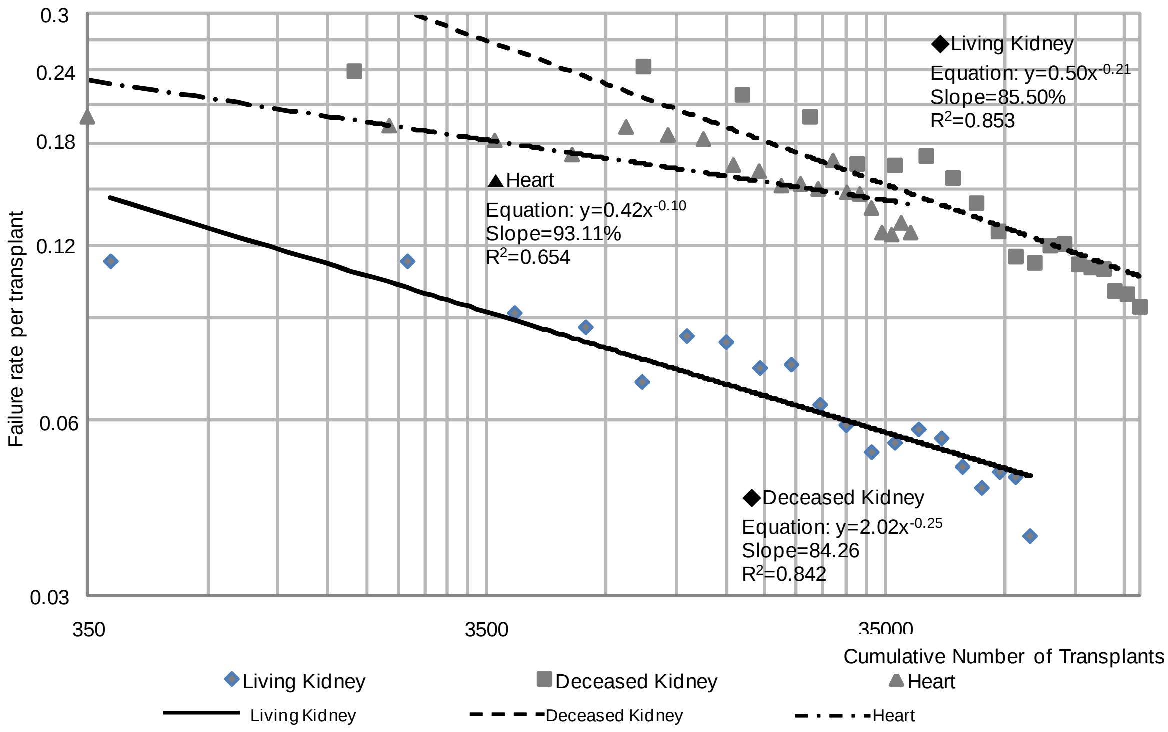


Table 9 and Fig. 9 and 10 show the results of 5-Year failure rates from the classical experience curve analysis on the same six types of transplants. For example, 5-Year failure rate of the same kidney transplant from living donors covering the time period from 1987 to 2002 has its experience slope of 93.63%, lower than 85.5% slope for the 1-Year case with R^2 of 0.902. As expected, the averaged slope for these six types of transplants is 94.38%, again lower than the averaged slope of 88.7% for 1-Year case with the averaged R^2 of 0.742.

Table 9. Historical Analysis of 5-Year Graft Failure Rates of Transplants Administered during the Period from 1987 to 2002 by the Classical Experience

Type of Transplant	Experience Curve			
	Equation[a]	Slope(%)	SE[b]	R^2
Living Kidney	$y = 0.56\ x^{-0.10}$	93.63	0.04	0.90
Deceased Kidney	$y = 1.08\ x^{-0.10}$	93.24	0.05	0.86
Living Liver	$y = 0.41\ x^{-0.04}$	97.06	0.26	0.06
Deceased Liver	$y = 1.08\ x^{-0.11}$	92.79	0.04	0.93
Heart	$y = 0.63\ x^{-0.08}$	94.87	0.05	0.77
Lung	$y = 1.06\ x^{-0.08}$	94.67	0.05	0.93
Average		94.38	0.08	0.74

Notes
[a] Experience curve equation y: 5-Year graft failure rate per transplant, x: Cumulative number of transplants
[b] SE: Standard Error

Fig. 9. Classical Experience Curves for 5-Year Failure Rates of Living Liver, Deceased Liver and Lung Transplants

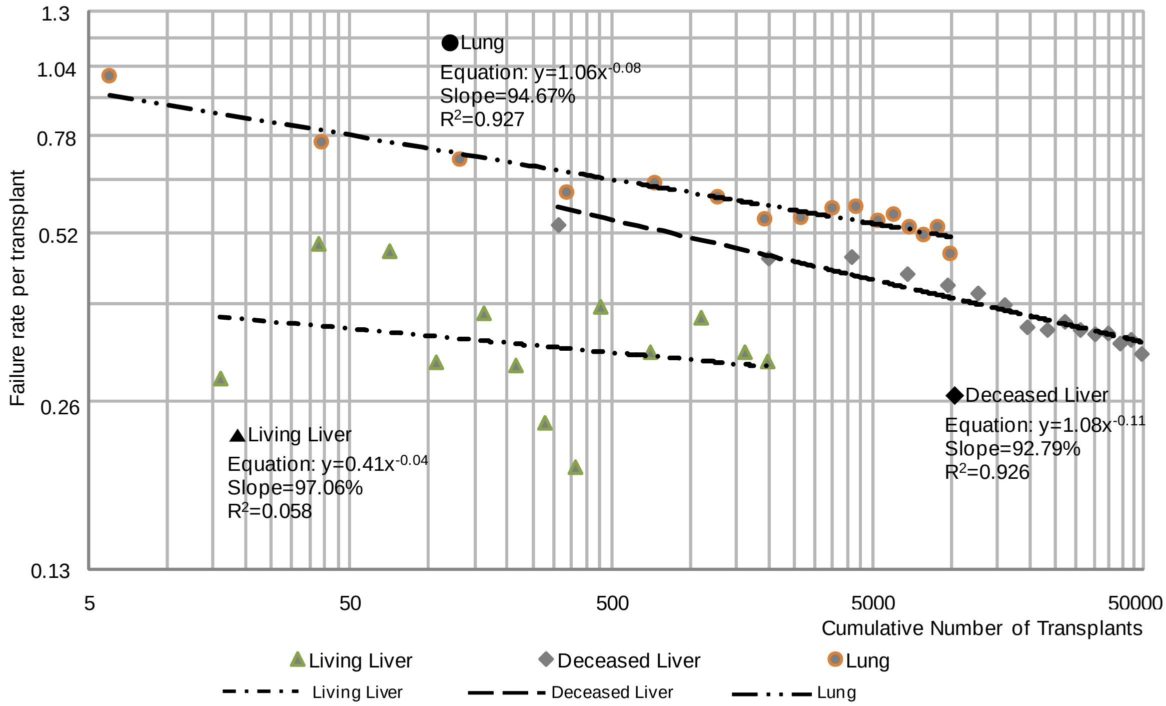


Fig. 10. Classical Experience Curves for 5-Year Failure Rates of Living Kidney, Deceased Kidney and Heart Transplants

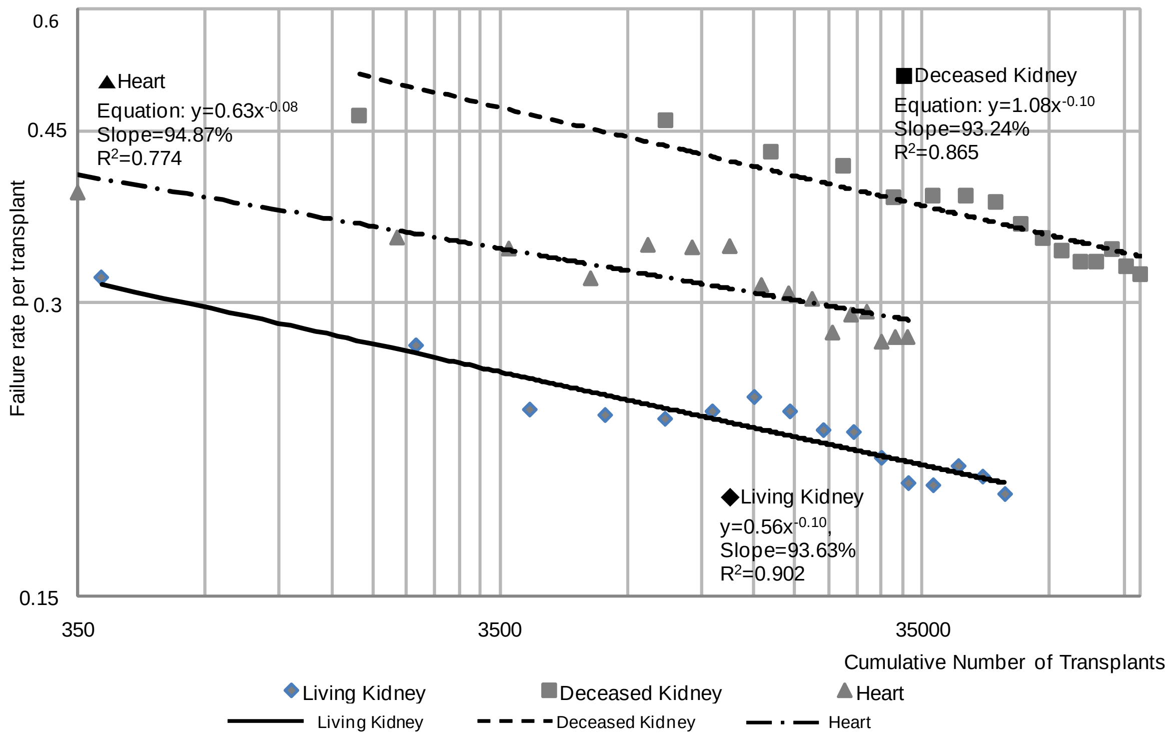
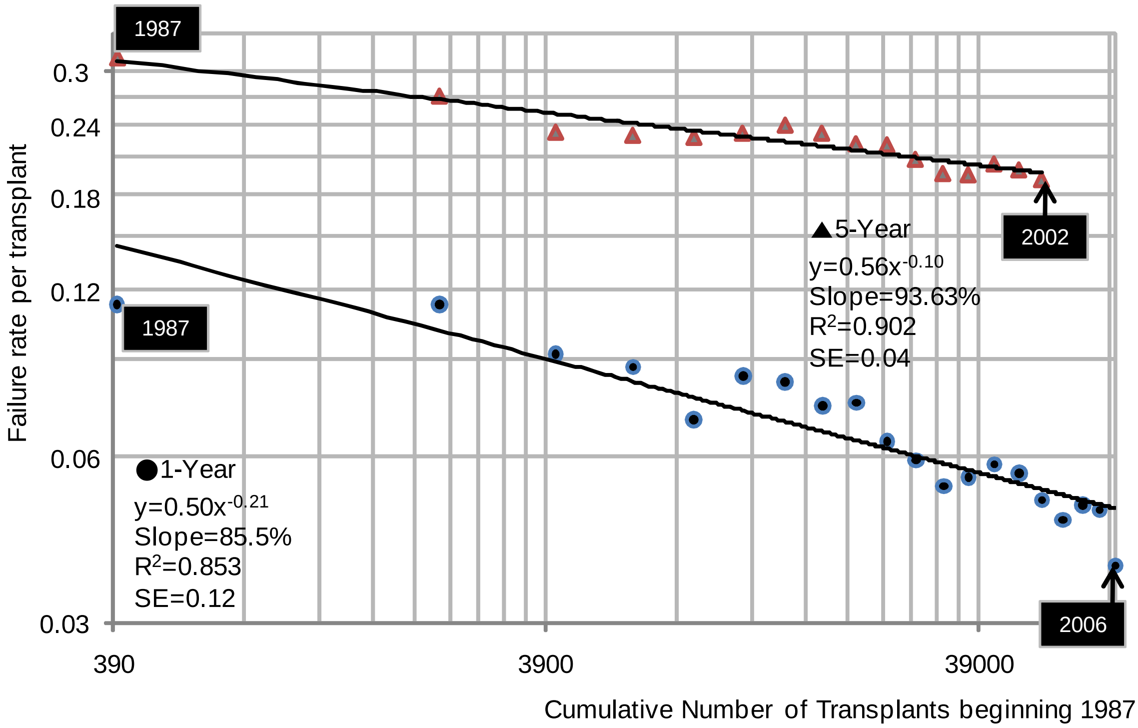


Fig. 11 shows these two experience curves of 1-Year and 5-Year failure rates together for graphic comparison. For kidney transplant from living donors, both 1-Year and 5-Year failure rates continued their declines. However, the rate of the decline for the 1-Year failure rates is greater than the case of the 5-Year failure rates.

Fig. 11. Graphic Comparison of Classical Experience Curves for 1-Year and 5-Year Failure Rates of Kidney Transplant from Living Donors



Notice that time period represents the year for which transplants were performed. For example, 5-Year failure rate in 1987 refers to transplants performed in 1987 whose failure was reported 5 years afterward in 1992.

4.2. Applications of the Kinked Experience Curve

Is it possible to observe change in reduction ratio from one time segment to another time segment during the study period?

Changes in improvement of learning rates over time have been observed by Boston Consulting Group [8] when they suggested the kinked experience price slope as a function of the product life cycle. Some energy modeling groups also used "kinked" (piece-wise linear) learning curves, with successively lower learning rates at more mature development stages (McDonald and Schrattenholzer [48], Rossiter and Kouvaritakis [64], Nakicenovic and Victor [53]). More recently, van Sark [78] has summarized the three empirical kinked price slopes which show higher, not lower, learning rates during the later stages in photovoltaic, ethanol and wind technologies.

Weiss et al. [82] reported the kinked experience curve analysis on the energy consumption rates of five major home appliances in two successive time periods, before and after the introduction of an energy policy in the Netherlands. The results show significantly higher learning slopes for the later time period. For example, the learning slope of 17% for refrigerators during the first time period of 1964 to 1994 had increased to 49% during the second period of 1995 to 2008. More recently, Chang and Lee [14, 15] have found kinked experience slopes from the cases of road fatalities rates as well as suicide rates for large number of countries.

Although the case of more than one kinked curve is theoretically possible, we are unaware of any reported empirical cases of multiple kinked curves. Unless the history of failure rates of transplants to be studied displays a multiple kinked pattern, we will limit our analysis to a single kinked curve analysis.

We are ready to specify the kinked experience curve as follows:

For kinked experience curve:

$$y(x_t) = y(x_1)x_t^{-b_1} \qquad (2)$$

where $t = 1,2,3, \cdots\cdots k\text{-}1$

b_1 = experience slope for equation (2)

Equation (2) is for the time period from 1987 through one year before the kinked year.

$$y(x_t) = y(x_k)x_t^{-b_2} \qquad (3)$$

where $t = k, k+1, \cdots\cdots T$

$y(x_k)$ = failure rate at cumulative organ transplants through year k

b_2 = experience slope for equation (3)

Equation (3) is for the time period from the kinked year through 2006 for 1-Year failure rate and through 2002 for 5-Year failure rate.

The kinked year will vary by types of transplants. However, it is important that x_2, cumulative number of transplants be always counted from 1987, the beginning year of our study period.

Table 10 and Fig. 12 and 13 show the results of 1-Year failure rates from the kinked experience curve analysis on the same six types of transplants. For example, 1-Year failure rates of kidney transplant from living donors has its first experience slope of 88.7% from 1987 to 2000 and its kinked (2nd) experience slope of 68.3% from 2001 to 2006. The remaining five other types of transplants also show that all of the kinked slopes are steeper than the first slopes. The average of the first slope for the six types of transplants is 89.95% versus 73.53% as the averaged kinked slopes. And the averaged R^2 for the kinked equations is 0.78 in contrast to R^2 of 0.71 for the first equations. The differences between the first slopes and the kinked slopes were subjected to Newey-West t test. The results show that p values which are 1.5% or less, establishing their statistical significance. The kinked years range from 1996 through 2001 with the averaged kinked year of 1995.5.

Table 10. Historical Analysis of 1-Year Graft Failure Rates of Transplants Administered during the Period from 1987 to 2006 by the Kinked Experience

Type of Transplant	Kinked year	Time Period	Experience Curve				Newey-West t statistic		
			Equation[c]	Slope(%)	SE[d]	R^2	b_2-b_1	t-value	p-value
Living Kidney	2001	1987 ~ 2000 (1st[a])	$y = 0.37x^{-0.17}$	88.70	0.11	0.81	-0.38	-3.36	0.004
		2001 ~ 2006 (2nd[b])	$y = 20.85x^{-0.55}$	68.30	0.08	0.68			
Deceased Kidney	2001	1987 ~ 2000 (1st[a])	$y = 1.45x^{-0.21}$	86.33	0.13	0.78	-0.28	-4.30	0.001
		2001 ~ 2006 (2nd[b])	$y = 35.73x^{-0.50}$	70.86	0.02	0.91			
Living Liver	1998	1989 ~ 1997 (1st[a])	$y = 0.51x^{-0.17}$	88.64	0.34	0.26	-0.19	-2.79	0.015
		1998 ~ 2006 (2nd[b])	$y = 2.75x^{-0.36}$	77.92	0.05	0.96			
Deceased Liver	1996	1987 ~ 1995 (1st[a])	$y = 1.07x^{-0.15}$	90.44	0.08	0.86	-0.14	-4.52	<0.001
		1996 ~ 2006 (2nd[b])	$y = 4.03x^{-0.28}$	82.19	0.04	0.86			
Heart	2001	1987 ~ 2000 (1st[a])	$y = 0.31x^{-0.07}$	95.46	0.07	0.62	-0.42	-2.97	0.009
		2001 ~ 2006 (2nd[b])	$y = 20.52x^{-0.48}$	71.60	0.04	0.64			
Lung	2000	1987 ~ 1999 (1st[a])	$y = 0.88x^{-0.15}$	90.13	0.10	0.92	-0.36	-3.00	0.008
		2000 ~ 2006 (2nd[b])	$y = 21.35x^{-0.51}$	70.32	0.09	0.66			
Average of 1st Period	1999.2			89.95	0.14	0.71			
Average of 2nd Period				73.53	0.06	0.78			

Notes

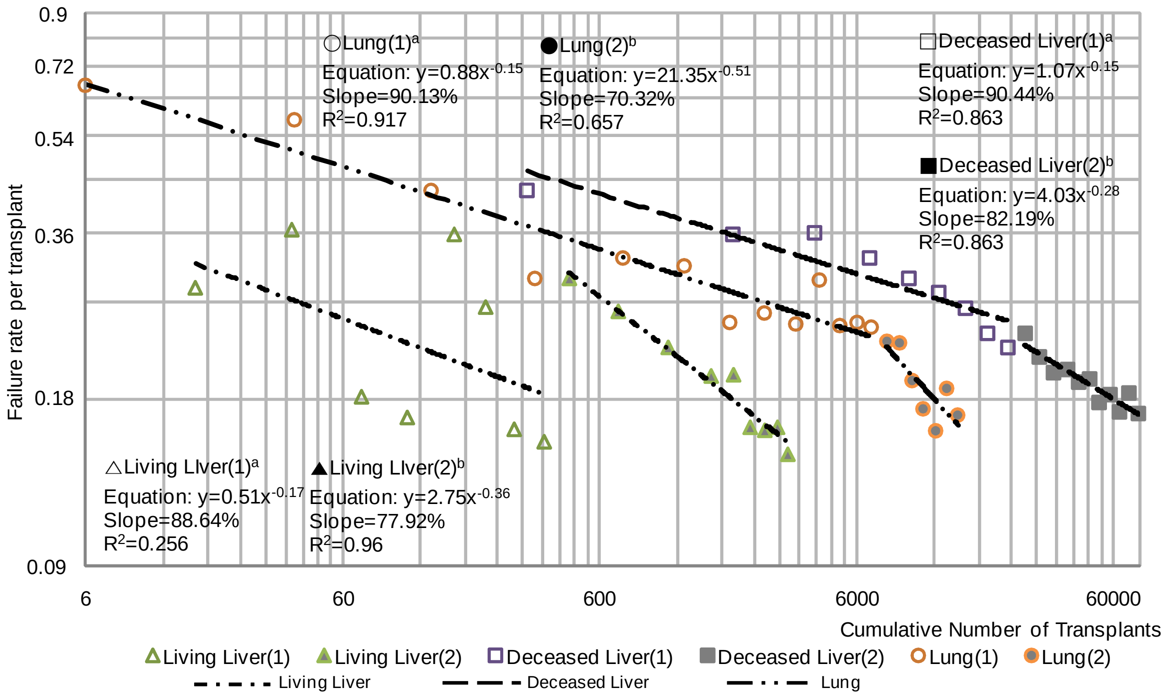
[a] 1st: 1st period of 1987-one year before the kinked year

[b] 2nd: 2nd period of the kinked year-2006

[c] Experience curve equation y: 1-Year graft failure rate per transplant, x: Cumulative number of transplant

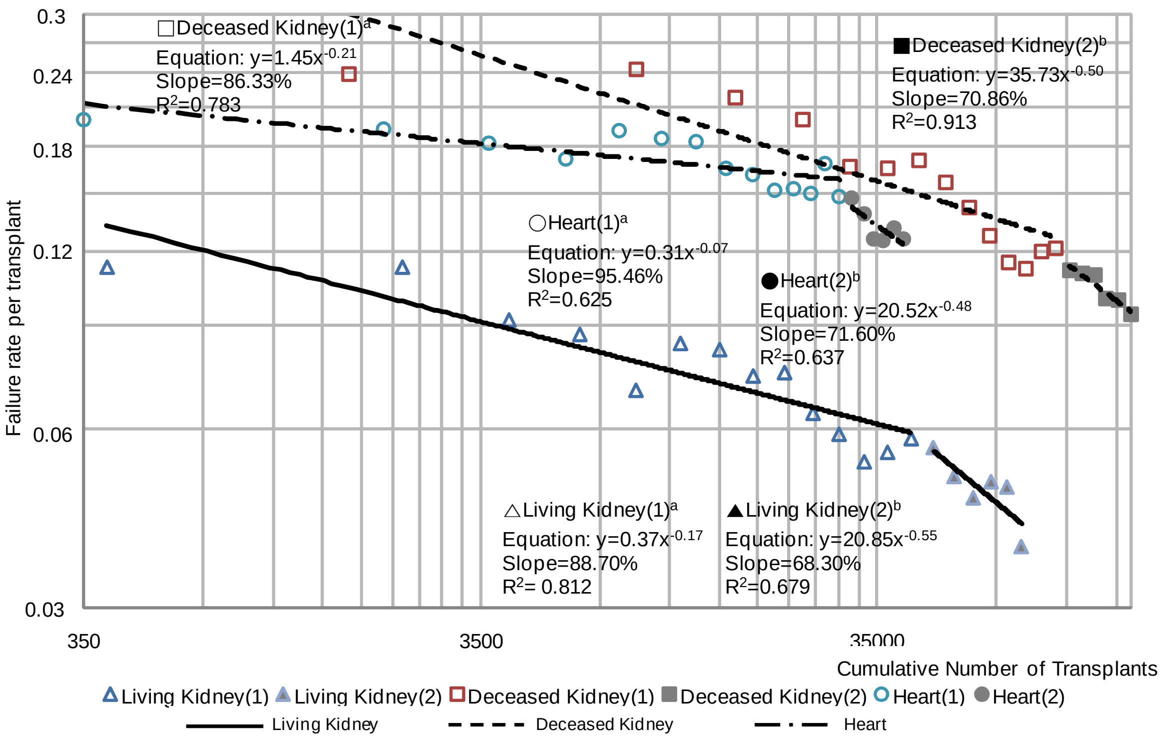
[d] SE: Standard Error

Fig. 12. Kinked Experience Curves for 1-Year Failure Rates of Living Liver, Deceased Liver and Lung Transplants



Notes
[a] (1) is 1st period of 1987-one year before the kinked year
[b] (2) is 2nd period of the kinked year -2006

Fig. 13. Kinked Experience Curves for 1-Year Failure Rates of Living Kidney, Deceased Kidney and Heart Transplants



Notes
[a] (1) is 1st period of 1987-one year before the kinked year
[b] (2) is 2nd period of the kinked year -2006

Table 11 and Fig. 14 and 15 show the results of 5-Year failure rates from the kinked experience curve. Again, 5-Year failure rates of kidney transplants from living donors has its first slope of 92.92% from 1987 to 1992 and its kinked slope of 89.32% from 1993 to 2002. With one exception of liver transplants from living donors, all other types of transplants have their kinked slopes which are steeper than the first slopes. The average of the first slope for the six types of transplants is 94.26% versus 89.06% as the averaged kinked slopes. And the averaged R^2 for the kinked equation is 0.8 in contrast to R^2 of 0.75 for the first equations. With the exception of liver transplant from living donors, differences between the first slopes and the kinked slopes were subjected to Newey-West t test. The results show that p values which are 2.3% or less, establishing their statistical significance. The kinked year ranges from 1990 for liver transplant from living donors to 1996 for lung transplants. The averaged kinked year is 1993.8.

Fig. 16 shows these two kinked experience curves of 1-Year and 5-Year failure rates together for graphic comparison. As explained above, we can verify both curves show kinked patterns with the kinked year of 2001 for 1-Year failure rate and 1993 for 5-Year failure rate. Again, kinked experience curve of 1-Year failure rates has steeper slope than 5-Year failure rates.

Table 11. Historical Analysis of 5-Year Graft Failure Rates of Transplants Administered during the Period from 1987 to 2006 by the Kinked Experience

Type of Transplant	Kinked year	Time Period	Experience Curve				Newey-West t statistic		
			Equation[c]	Slope(%)	SE[d]	R^2	b_2-b_1	t-value	p-value
Living Kidney	1993	1987 ~ 1992 (1st[a])	$y = 0.60\ x^{-0.11}$	92.92	0.04	0.93	-0.06	-2.60	0.023
		1993 ~ 2002 (2nd[b])	$y = 1.12\ x^{-0.16}$	89.32	0.03	0.88			
Deceased Kidney	1993	1987 ~ 1992 (1st[a])	$y = 0.77\ x^{-0.06}$	95.66	0.04	0.78	-0.13	-6.18	<0.001
		1993 ~ 2002 (2nd[b])	$y = 3.03\ x^{-0.19}$	87.48	0.02	0.91			
Living Liver	1998	1989 ~ 1997 (1st[a])	$y = 0.68\ x^{-0.16}$	89.56	0.30	0.28	0.04	0.40	0.695
		1998 ~ 2002 (2nd[b])	$y = 0.75\ x^{-0.12}$	92.27	0.08	0.48			
Deceased Liver	1990	1987 ~ 1989 (1st[a])	$y = 0.74\ x^{-0.06}$	96.19	0.03	0.90	-0.09	-8.02	<0.001
		1990 ~ 2002 (2nd[b])	$y = 1.63\ x^{-0.15}$	90.19	0.03	0.94			
Heart	1993	1987 ~ 1992 (1st[a])	$y = 0.50\ x^{-0.04}$	97.00	0.04	0.69	-0.16	-5.80	<0.001
		1993 ~ 2002 (2nd[b])	$y = 2.21\ x^{-0.20}$	86.93	0.03	0.85			
Lung	1996	1987 ~ 1995 (1st[a])	$y = 1.09\ x^{-0.09}$	94.21	0.05	0.93	-0.10	-4.04	0.002
		1996 ~ 2002 (2nd[b])	$y = 2.68\ x^{-0.18}$	88.15	0.03	0.76			
Average of 1st Period	1993.8			94.26	0.09	0.75			
Average of 2nd Period				89.06	0.04	0.80			

Notes

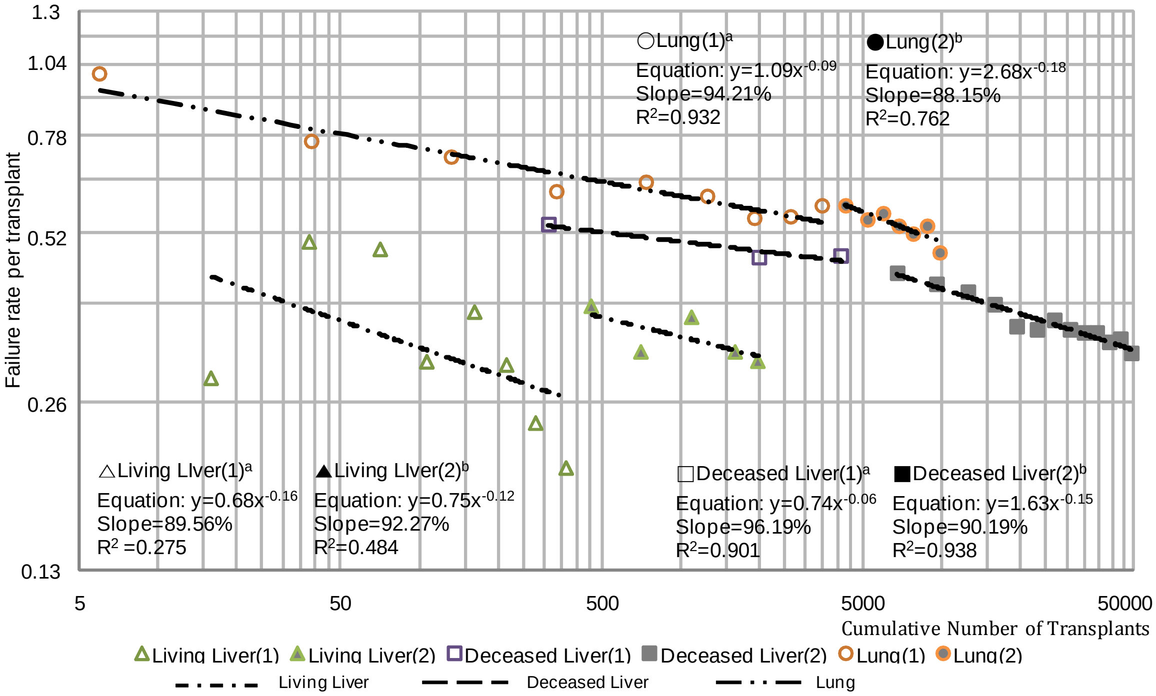
[a] 1st period of 1987-one year before the kinked year

[b] 2nd: 2nd period of the kinked year-2002

[c] Experience curve equation y: 5-Year graft failure rate per transplant, x: Cumulative number of transplant

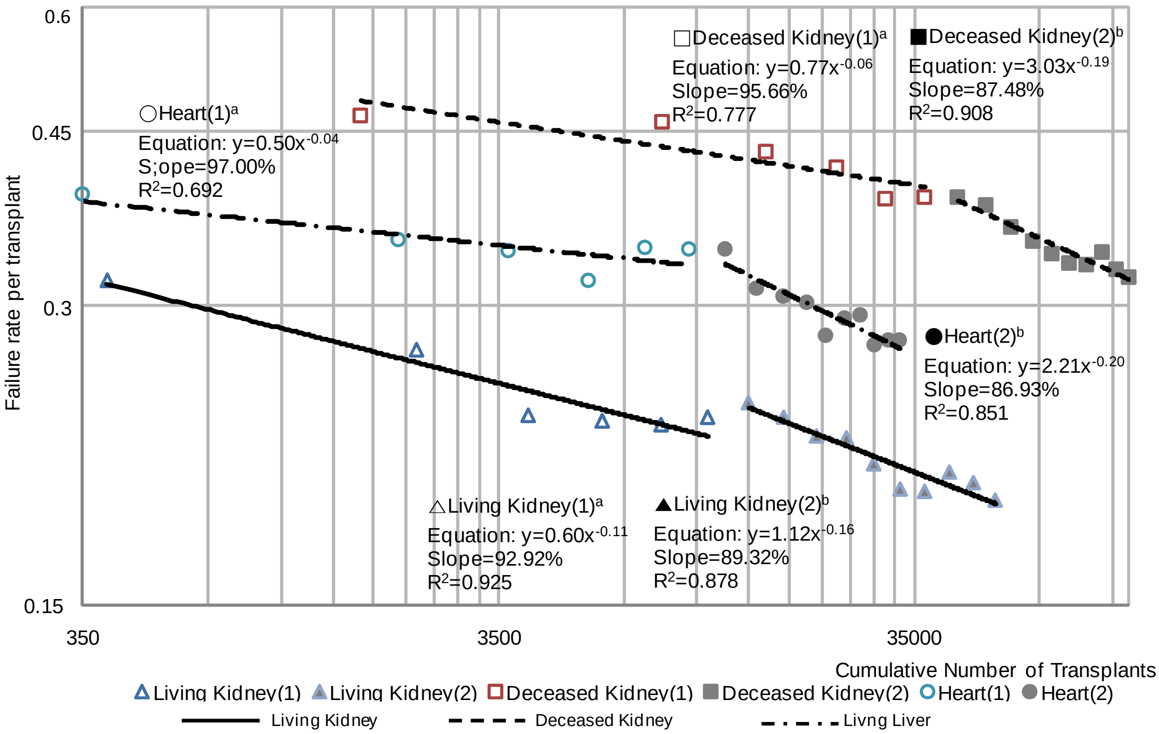
[d] SE: Standard Error

Fig. 14. Kinked Experience Curves for 5-Year Failure Rates of Living Liver, Deceased Liver and Lung Transplants



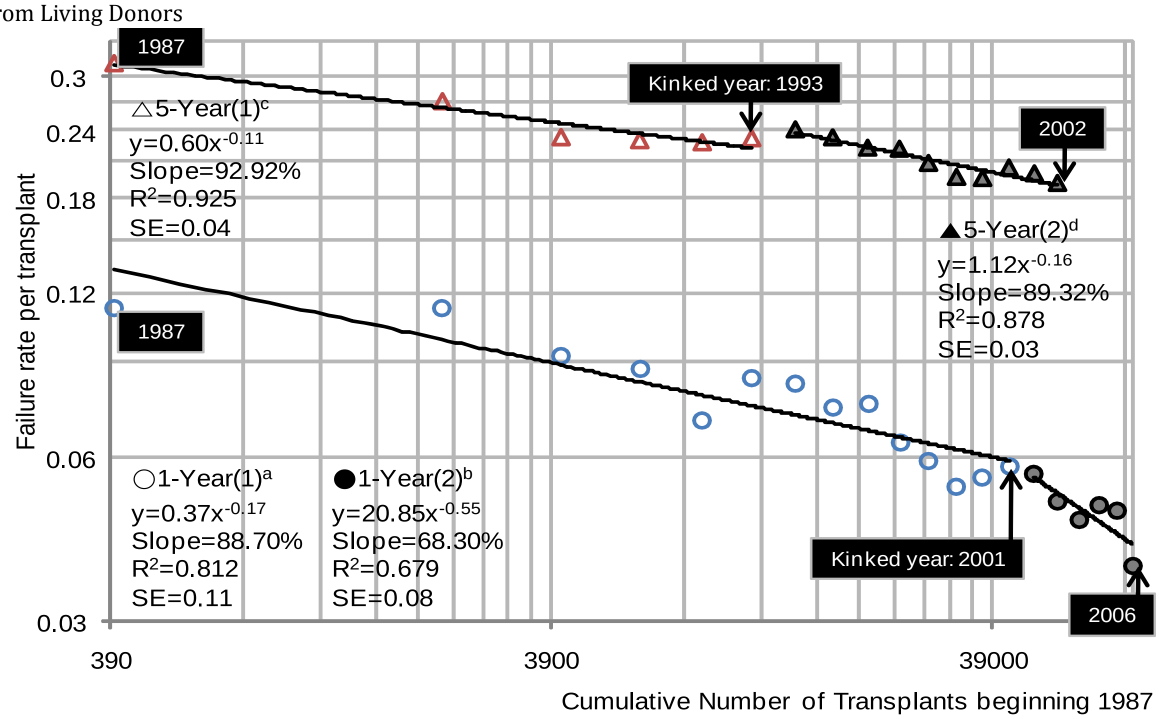
Notes
a (1) is 1st period of 1987-one year before the kinked year
b (2) is 2nd period of the kinked year -2002

Fig. 15. Kinked Experience Curves for 5-Year Failure Rates of Living Kidney, Deceased Kidney and Heart Transplants



Notes
a (1) is 1st period of 1987-one year before the kinked year
b (2) is 2nd period of the kinked year -2002

Fig. 16. Graphic Comparison of Kinked Experience Curves for 1-Year and 5-Year Failure Rates of Kidney Transplant from Living Donors



Notes

[a] 1-Year(1) is 1st period of 1987-one year before the kinked year

[b] 1-Year(2) is 2nd period of the kinked year -2006

[c] 5-Year(1) is 1st period of 1987-one year before the kinked year

[d] 5-Year(2) is 2nd period of the kinked year -2002

4.3. Choice between the Classical versus the Kinked as the Forecasting Model for Future Improvement Rates

Between the classical versus kinked equations, which should be selected for forecasting purpose? We compared the results from these two equations in terms of the slope, R^2, and standard error.

For example of 1-Year failure rates, as shown in Table 8 and 10, heart transplant shows the largest reduction of slope between the classical and the kinked experience curve. It has the classical experience slope of 93.11% with R^2 of 0.65 and the kinked (2nd) experience slope of 71.60% with R^2 of 0.64. The smallest reduction in slope appears in liver transplant from deceased donors. It has the classical experience slope of 87.54% with R^2 of 0.92 and the kinked experience slope of 82.19% with R^2 of 0.86. The remaining four other types of transplants also show that all of the kinked (2nd) curve slopes are steeper than the classical curve slopes. The average of the kinked (2nd) experience slopes for the six types of transplants is 73.53% versus 88.7% as the averaged classical experience slopes. And the averaged R^2 and standard error for the kinked (2nd) equations are 0.78 and 0.06 in contract to R^2 standard error of 0.75 and 0.13 for the classical equations.

In the case of 5-Year failure rates, all of types of transplants also show that all of the kinked (2nd) curve slopes are steeper than the classical curve slopes. The average of the kinked (2nd) experience slope for the six types of transplants is 89.06% versus 94.38% as the averaged classical experience slopes. And the averaged R^2 and standard error for the kinked (2nd) equations are 0.80 and 0.04 in contract to R^2 and standard error of 0.74 and 0.08 for the classical equations.

In summary, on average, the kinked (2nd) equations on every type of transplants generate higher R^2 and lower standard error which indicates better fit to the data than the classical ones for both 1-Year and 5-Year failure rates of transplants. Thus, we have chosen the kinked (2nd) equations to be better models that will be used in our forecast.

5. Comparison of the Kinked Years and the Surpassed Years for the New Drugs

Now we will attempt to provide some explanations as to why the kinked year may have occurred at those particular time periods. Is it possible that the replacement timing of new drugs over the old drugs may have caused kinked years to occur?

In order to examine this issue, we shall compare kinked years estimated from the kinked experience curve analysis to the years when the new drugs of TAC and MMF become the drug of choice. Notice that we shall assume that the drug of choice is established when the new drug usage surpasses 50% of the total population of the recipients (Mansfield [45, 46]).

More specifically, we subtract surpassed year from kinked year to obtain what we define as "time-gap", as shown in Table 12. For example, "time-gap" of TAC for 1-Year failure rates relating to living liver transplant is +2 year which is obtained from subtracting the surpassed year of 1996 from 1998 as the kinked year. For MMF for living liver transplant, "time-gap" is calculated as -5 years because the surpassed year of 2003 is subtracted from 1998 as the kinked year. And then we have averaged these two "time-gaps" of 2 years and -5 years to obtain "averaged-time-gap" of -1.5 years. We continued the same calculation for each of the 5 remaining types of transplants. The averaged "time-gaps" for TAC is -0.67 years, while the averaged "time-gaps" for MMF is -0.83 years. When we average these "averaged-time-gaps", we obtain -0.75 years. These results are calculated from 1-Year failure rates.

We have repeated the same procedure for 5-Year failure rates for transplants and the results are shown in Table 13 which generates the "averaged-time-gaps" of -2.42 years in comparison to -0.75 years calculated in Table 12

In spite of substantial variation of the "time-gap" by the type of organ transplant, it is remarkable that the years when these new drugs have become established as the drug of choice appear to coincide with the kinked years in case of 1-Year failure rates. On the other hand, the kinked years occurred on average 2.42 years ahead of the surpassed years for the case of 5-Year failure rates.

Finally, the difference between the averaged kinked years from 1-Year failure rates versus the averaged surpassed years for TAC was subjected to Paired samples t test[16] to check whether the difference is statistically significant. As shown in Table 14, p value was calculated to be 0.465 which exceed the benchmark of 0.05. The result shows that the difference is not statistically significant.

We have repeated the same test for three other cases of 5-Year failure rates from TAC, 1-Year failure rates from MMF, and 5-Year failure rates from MMF. The results of these three tests also show that the difference between the kinked years and the surpassed years are not statistically significant, as shown in Table 14.

[16] Paired samples t test compares the means of two variables. It computes the difference between the two variables for each case, and tests to see if the average difference is significantly different from zero.

Table 12. Comparison of Kinked Years for 1-Year Failure Rates and the Surpassed Years for the New Drugs

Type of Transplnat	Kinked Year (a)	Surpassed Year of TAC[a] (b)	Time Gap (a-b)	Surpassed Year of MMF[b] (c)	Time Gap (a-c)	Averaged Time Gap [(a-b)+(a-c)]/2
Living Kidney	2001	2001	0	1996	5	2.50
Deceased Kidney	2001	2001	0	1996	5	2.50
Living Liver	1998	1996	2	2003	-5	-1.50
Deceased Liver	1996	1996	0	2003	-7	-3.50
Heart	2001	2005	-4	1999	2	-1.00
Lung	2000	2002	-2	2005	-5	-3.50
Average	1999.5	2000.2	-0.67	2000.3	-0.83	-0.75

Notes: [a] TAC - Tacrolimus, [b] MMF - Mycophenolate Mefetil

Table 13. Comparison of Kinked Years for 5-Year Failure Rates and the Surpassed Years for the New Drugs

Type of Transplant	Kinked Year[a] (a)	Surpassed Year of TAC[b] (b)	Time Gap (a-b)	Surpassed Year of MMF[c] (c)	Time Gap (a-c)	Averaged Time Gap [(a-b)+(a-c)]/2
Living Kidney	1997	2001	-4	1996	1	-1.50
Deceased Kidney	1997	2001	-4	1996	1	-1.50
Living Liver	2002	1996	6	2003	-1	2.50
Deceased Liver	1994	1996	-2	2003	-9	-5.50
Heart	1997	2005	-8	1999	-2	-5.00
Lung	2000	2002	-2	2005	-5	-3.50
Average	1997.8	2000.2	-2.33	2000.3	-2.50	-2.42

Notes: [a] Kinked years add 4 years to make them comparables to those kinked years estimated in Table 10, [b] TAC - Tacrolimus, [c] MMF - Mycophenolate Mefetil

Table 14. The Results of Paired Samples t Test for the Difference between Averaged Kinked Years versus Averaged Surpassed Years

Averaged Kinked Year		TAC[b]		MMF[c]	
		Averaged Surpassed Year	t-value (p-value)	Averaged Surpassed Year	t-value (p-value)
1-Year Failure Rates	1999.5	2000.2	-.791 (.465)	2000.3	-.374 (.724)
5-Year Failure Rates	1997.8		-1.234 (.272)		-1.576 (.176)

Notes

[a] Paired samples t test

Level of significance is 5%.

If the p-value is less than .05, there is a significant difference.

If the p-value is greater than .05, there is no significant difference.

[b] TAC - Tacrolimus, [c] MMF - Mycophenolate Mefetil

6. Forecast of future survival rates of organ transplants

Now we are ready to forecast future improvement of survival rates for the years of 2010, 2020, and 2030.

In order to forecast survival rates for the future, we have used our kinked (2nd) experience curve equations we had estimated earlier which are shown in Table 10. In addition, we need to estimate annual number of transplants from 2007 through 2030 so that we will have cumulative number of transplants through 2030. For this purpose, we have used both linear equations in Table 15 and logistic equations in Table 16 to forecast annual number of transplants for each of the six types of transplants. The assumption for the linear equations is that the number of transplants will increase linearly following the past trend. On the other hand, the assumption for the logistic equations of slowing down to approach the upper limit is used due to the expected shortage of donated organs in the future. Using these equations, we have projected the number of transplants for each year from 2007 through 2030. These yearly forecasted numbers of transplants are added to generate cumulative number of transplants for each type of transplants.

For example, according to the linear growth equation, the cumulative number of transplants for kidney from living donors is estimated to be 213,743 by 2020, and 347,142 by 2030. Using these cumulative numbers of transplants, it is now possible to forecast failure rates for the kidney transplant from living donors. By converting into survival rates, the 2030 survival rate of kidney from living donors is forecasted to be 98.13%.

To explain further, we used the kinked (2nd) experience equation, $Y=20.85x^{-0.55}$, together with the cumulative number of transplants, x, of 347,142, to generate the failure rate of 0.0187 (1.87%). And then survival rate 98.13% was calculated by subtracting failure rate from 100%.

We have repeated the same process to generate survival rates for each of 6 types of transplants. Annual number of transplants, cumulative number of transplants, and survival rates are summarized in Table 17.

Table 15. Summary of Linear Equations for Forecasting the Number of Transplants

Type of Transplant	Period		Forecasting Equation[a]	R^2
	Estimation	Forecasting		
Living Kidney	1987 ~ 2006	2007 ~ 2030	y = 320.78 x - 636400	0.970
Deceased Kidney	1987 ~ 2006	2007 ~ 2030	y = 141.62 x - 274894	0.827
Living Liver	1989 ~ 2006	2007 ~ 2030	y = 25.70 x - 51162	0.696
Deceased Liver	1987 ~ 2006	2007 ~ 2030	y = 225.92 x - 447304	0.927
Heart	1987 ~ 2006	2007 ~ 2030	y = 32.51 x - 62888	0.195
Lung	1987 ~ 2006	2007 ~ 2030	y = 68.45 x - 135921	0.935

Notes: [a] Forecasting equation (linear) y: The number of transplants, x: Year

Table 16. Summary of Logistic Equations for Forecasting the Number of Transplants

Type of Transplant	Period		Forecasting Equation[a]	R^2
	Estimation	Forecasting		
Living Kidney	1987 ~ 2006	2007 ~ 2030	y = 8018.6 / { 1+ exp [1.74 - 0.19 (x - 1987)] }	0.974
Deceased Kidney[b]	1987 ~ 2006	2007 ~ 2030	N/A	N/A
Living Liver	1989 ~ 2006	2007 ~ 2030	y = 360.8 / { 1+ exp [21.34 - 1.87 (x - 1989)] }	0.876
Deceased Liver	1988 ~ 2006	2007 ~ 2030	y = 7214.3 / { 1+ exp [0.99 - 0.12 (x - 1988)] }	0.969
Heart	1987 ~ 2006	2007 ~ 2030	y = 2155.9 / { 1+ exp [1.26 - 2.00 (x - 1987)] }	0.897
Lung	1987 ~ 2006	2007 ~ 2030	y = 1246.8 / { 1+ exp [2.08 - 0.29 (x - 1987)] }	0.918

Notes: Notes
[a] Forecasting equation (logistic) y: The number of transplants, x: Year
[b] Deceased Kidney is not applicable to the logistic equation.

Table 17. Forecast of 1-Year Annual Number of Transplants, Cumulative Number of Transplants and Survival Rates Through 2030

Linear Application

Type of Transplant	Year											
	2006 (Actual)			2010			2020			2030		
	A	B	C	A	B	C	A	B	C	A	B	C
Living Kidney	6,428	80,876	0.96	8,368	112,423	0.9652	11,576	213,743	0.9756	14,783	347,142	0.9813
Deceased Kidney	10,216	152,096	0.91	9,762	190,295	0.9150	11,178	295,706	0.9318	12,595	415,279	0.9424
Living Liver	286	3,232	0.86	501	5,082	0.8726	758	11,506	0.9051	1,015	20,500	0.9229
Deceased Liver	5,836	75,077	0.83	6,795	100,902	0.8456	9,054	181,280	0.8692	11,314	284,249	0.8848
Heart	2,147	40,526	0.87	2,465	50,191	0.8887	2,790	76,631	0.9093	3,115	106,322	0.9225
Lung	1,397	14,898	0.83	1,670	21,165	0.8645	2,354	41,626	0.9039	3,039	68,931	0.9256

Logistic Application

Type of Transplant	Year											
	2006 (Actual)			2010			2020			2030		
	A	B	C	A	B	C	A	B	C	A	B	C
Living Kidney	6,428	80,876	0.96	7,428	109,850	0.9648	7,920	187,505	0.9738	8,003	267,283	0.9784
Deceased Kidney[d]	10,216	152,096	0.91		N/A			N/A			N/A	
Living Liver	286	3,232	0.86	361	4,675	0.8687	361	8,283	0.8931	361	11,891	0.9062
Deceased Liver	5,836	75,077	0.83	6,150	98,963	0.8447	6,855	164,899	0.8656	7,101	235,028	0.8784
Heart	2,147	40,526	0.87	2,182	49,254	0.8877	2,182	71,075	0.9059	2,182	92,896	0.9173
Lung	1,397	14,898	0.83	1,235	19,807	0.8598	1,246	32,242	0.8906	1,247	44,708	0.9073

Notes

[a] Annual Number of Transplants: A, [b] Cumulative Number of Transplants: B, [c] Survival Rate: C

[d] Deceased Kidney is not applicable to the logistic equation.

As for the logistic growth equation, the cumulative number of transplants for kidney from living donors is estimated to be 187,505 by 2020, and 267,283 by 2030. We have applied the same procedure we used in the application of linear equation and calculated survival rate to be 97.84% that is slightly 0.29% lower than the survival rate from the linear equation we estimated earlier. There is one exception that kidney transplant from deceased donors does not fit to logistic equation. The survival rates for 5 remaining types of transplants are shown in Table 17.

Table 17 shows that in 2006 living kidney transplant had the best performance with 96% survival rate and the worst performance was from both deceased liver transplant and lung transplant with the same survival rate of 83%. Our forecast of future survival rate of living kidney transplant in 2030 is projected at 98.13% from 96% in 2006. The worst performance in 2030 will still be deceased liver transplant although the 2030 survival rate may reach 88.48% from 83% in 2006. All other remaining transplants are projected to have 90% or higher survival rates by 2020. Improvement will continue through 2030 at a much slower rate, however.

In the case of logistic growth model, the projected survival rates of transplants are very similar to those projected from the linear growth model. Future survival rate of living kidney transplant is forecasted at 97.84% from 96% in 2006. Again, the worst performance in 2030 will still be deceased liver transplant although the 2030 survival rate may reach 87.84% from 83% in 2006. All other remaining 4 transplants that fit to logistic equation have 90% or higher survival rates by 2020 and beyond.

In the comparison of the forecasted survival rate for each of 5 types of transplants between linear and logistic application, there appears to be no significant difference.

7. Summary and Conclusion

According to Mansfield [45, 46], diffusion speed of new technology to reach 90% of potential users varies from five to fifty years. Our study on the diffusion speed of immunosuppressive drugs is similar with the diffusion speed of 8 years for TAC and 6 years for MMF to reach the penetration ratio of 50%. Coincidentally, both TAC and MMF surpassed the penetration ratio of 50% at nearly the same year of 2001, while their starting points of the penetration were different as TAC began in 1993 and MMF began in the year of 1994 for liver, lung, kidney transplants and 1993 for heart transplant.

The results of our experience curve analysis on these 6 types of transplants are remarkable in that all six types of transplants show kinked patterns without exception. On average, R^2 and standard error estimated from the kinked models yielded better results than those estimated from the classical experience models for both 1-Year and 5-Year failure rates of transplants.

In comparing of the kinked years versus the surpassed years, they are closely matched. To explain, the averaged kinked year associated with 1-Year failure rates was nearly identical to the averaged surpassed year for new drugs. In the case of 5-Year failure rates, kinked years preceded the surpassed years by on the average of 2.42 years.

In summary, we have demonstrated that a constant percentage increase in cumulative number of transplant generates a constant percentage improvement in survival rates. Furthermore, diffusion of new technology in immunosuppressive drugs has caused faster improvement of survival rates of transplantations.

As for the forecast of future improvement in 1-Year survival rates, all six types of transplants will realize continuous improvement through 2020 and 2030. All six types of transplants with one exception of deceased liver transplant will reach 90% or higher survival rates by 2020. The best performance will be shown in living kidney transplant with 97.56% in 2020 from 96% in 2006. However, further improvement of survival rates through 2030 will become gradually smaller, as the survival rates approach the upper limit of 100%.

This study is subjected to a number of limitations. We have limited our analysis of new drugs to the two major types of calcineurine inhibitors and antiproliferative agents, leaving three other types of immunosuppressive drugs of corticosteroids, monoclonal antibodies, and polyclonal antibodies. We have also excluded the impact of both inductive and episodic therapy with immunosuppressive drugs.

Furthermore, a number of other influencing factors to improve survival rates such as continuous advances in surgical procedures, organ procurement procedures, diagnostic test methods, etc. have not been analyzed individually.

There are several suggested topics for future research. If information on survival rates from other countries is available, it will be possible to conduct cross-country study by using the same methodology from this study. Extension to this study is also possible by covering all the other types of transplants such as pancreas and intestine, etc. which are left out in this study.

The kinked experience equation may be applicable to other types of medical procedures which are subjected to rapid technological advances. For example, robotic surgery may be one such area for future application.

Finally, economic cost-benefit or benefit-risk analysis on the diffusion of new drugs may be another extension possible in the future.

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