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CADAVERIC RENAL TRANSPLANTATION AT THE UNIVERSITY OF PITTSBURGH: A TWO AND ONE-HALF-YEAR EXPERIENCE WITH THE POINT SYSTEM

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Two critically important issues in kidney transplantation today concern the equitable distribution of organs and the optimization of immunosuppressive regimens. The present allocation system used by the United Network for Organ Sharing (UNOS) assigns points based on waiting time, antigen matching and PRA, and takes into account medical urgency and logistical factors. This point system is based on the program developed by and implemented at the University of Pittsburgh since 1 January 1986 (1). We recently discussed our early experience with this system and noted an important effect of immunosuppressive regimen on graft survival (2). Specifically, immunosuppression with cyclosporine, azathioprine, and prednisone was found to have better results than with cyclosporine and prednisone alone. This finding held in all patients and was seen in highly sensitized patients. This issue is particularly important in light of criticism that a system that gives preference to the most sensitized and longest waiting patients will lead to poorer graft survival (19). In this chapter, we describe the results of a 2-1/2 year experience with the point system and show further evidence for the superiority of three-drug over two-drug immunosuppression in this population.

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METHODS

Five hundred and forty-nine renal transplantations were performed at the University of Pittsburgh hospitals* between 1 January 1986 and 30 June 1988. Eight of the kidneys were from living-related donors and were excluded from analysis. Similarly excluded were 11 cases of cadaver kidney transplantation in conjunction with a liver or heart transplant. There were thus 530 consecutive cases available for analysis.

Case Material

Four hundred and sixty-three adults, whose mean age was 42.4 ± 12.8 years, received 483 transplants. The most common disease of the native kidneys was glomerulonephritis. One hundred of the adult recipients (22%) were diabetics, almost all Type I.

Forty-two children received 47 transplants; 28 were 10 to 18 years old and 14 were six months to nine years old.

Tissue Typing

The HLA typing for all donors and all recipients was carried out in an accredited laboratory in which all known Class 1 and Class 2 antigens can be measured. Anti-donor antibodies were systematically looked for, and crossmatches with current recipient sera were performed in every case.

Point Allocation System

The Pittsburgh allocation system ranks potential recipients of a given kidney on the basis of several factors (1). Waiting time, defined as beginning with the date of referral, can account for up to 10 points. Each Class 1 or Class 2 antigen match between donor and recipient accounts for two points, for a potential total of 12 if there is complete HLA identity. Every 10 percent of preformed antibody analysis (also called panel reactive antibody (PRA)) accounts for one point, for a potential total of 10 points if there are antibodies against all of the lymphocyte test panel (100% PRA). Finally, medical urgency or logistic factors can add points, although these are rarely used. Thus, the system gives priority to those who have waited the longest, those with the best antigen match, and those with the greatest degree of presensitization who have a negative crossmatch.

Operative Procedures

Renal transplantation was generally with the standard operation (3). In most cases, a Carrell patch of aorta containing the renal arterial orifice(s) was anastomosed to the external iliac artery. Ureteral reconstruction was with a nipple-tunnel technique (3) or with modifications of the extra-

vesical operation which has been attributed to Lich (4), but which was actually described and taught by Woodruff (5)*.

In the 1986-1987 period, the organs from all local donors, and from the majority of donors in distant centers, were removed with the technique developed for multiple organ harvest (7, 8). In our center, the presence of a long cold ischemia time has not had an adverse affect on ultimate outcome (9), although the need for early postoperative dialysis increases with time. Preservation for locally recovered organs has been with the University of Wisconsin (UW - Belzer) solution since November 1987. We have made a practice of reflushing imported kidneys, which have generally been flushed and stored with Collin's solution, with UW solution.

Immunosuppression

During 1986, all patients were managed initially with cyclosporine and prednisone. In 1987, just under half of the recipients were started on cyclosporine, azathioprine, and prednisone. In 1988, all patients were induced with the three-drug regimen. Variations of this triple-drug regimen were described in 1984 at the International Transplantation Society (10-12) or shortly after (13). Earlier, the combination of cyclosporine and azathioprine had been tested in primates by

*The historical development of extravesical implantation is annotated elsewhere (6).

Reitz et al (14) and synergism was demonstrated in rats and dogs by Squifflet et al (15). By the time of the 1986 meeting in Helsinki of the International Transplantation Society, more than a dozen papers describing the advantages of three-drug or four-drug therapy were presented.

OKT3 was used for steroid-resistant rejection episodes (16). In some highly sensitized patients or cases of multiple retransplantation, OKT3 was used for induction.

Statistical Methods

Actuarial patient and graft survivals were calculated for the two-year period. Statistical analysis was performed using BMPD Software; significance was assessed by the Mantel-Cox Test.

RESULTS

Patient Survival and Causes of Death

Five hundred and five patients received 530 kidneys. Overall actuarial patient survival at one and two years was 93 and 90% (Figure 1). Forty (7.7%) of the 505 recipients have died.

An effort was made to assign a single cause of failure (Table 1), realizing that before the time of death, multiple diagnoses almost invariably were applicable. However, an initial complication usually triggered a series of adverse consequences, often including infection as well as deterioration of the renal

graft if this had not already occurred. The combinations of deadly complications after renal transplantation and how these interrelate have been described in detail previously, long before the advent of cyclosporine (17).

In 80% of the cases, there had been difficulty in maintaining good renal graft function (Table 1), either early because of acute rejection, or later because of chronic rejection or other factors. Apart from this factor, the most common principal cause of the events leading to death was infection, usually caused by opportunistic organisms or viruses.

The second principal cause of death (nine patients) was cardiovascular disease. Gastrointestinal disease was also an important cause of death, with two lethal colonic perforations, two cases of severe upper gastrointestinal hemorrhage requiring emergency operations, and one case of liver failure (Table 1). A lymphoma caused the death of one patient. If diagnosed in time, these lymphomas usually involute with discontinuance or lightening of immunosuppression (18). No deaths were caused by epithelial malignancies in the 1986-88 recipients.

Miscellaneous causes of death included hemorrhage after a renal biopsy, a technical error in performing ureteroureteroneocystotomy, respiratory arrest during changing of a tracheostomy, a motor vehicle accident, and a respiratory arrest which may have been caused by an OKT3 infusion 12 hours earlier.

Graft Survival

Overall Graft Survival --- One- and two-year actuarial graft survival was 74 and 67% (Figure 1). Although a sophisticated examination of tissue typing was not part of this study, there was no obvious affect of tissue matching (Table 2). The incidence of current success was about the same with all levels of compatibility.

Because some of the patients received more than one graft during the 1986-88 study period, the actual number of patients represented by the 530 cadaveric transplantations was 505. Of these 505 patients, 465 (92%) are alive, and 379 (75%) are off dialysis (Table 3). Thus, a higher percentage of patients have a good result after renal transplantation than is indicated by actuarial graft survival.

Adults Versus Children --- Adults and children did not differ significantly in overall graft survival (Figure 2). Of the 42 pediatric recipients of 47 grafts four (9.5%) died, for a mortality that was similar to that in adults.

Primary Transplantation Versus Retransplantation --- The results in transplanting patients for the first time were slightly but not significantly better than the results of retransplantation (Figure 3).

Transplantation to "Clean" Versus Sensitized Patients --- Grafts in patients with a PRA less than 40% had a significantly ($p < .02$) better survival than in patients with a PRA greater

than 40% (Figure 4). This observation has been noted in most series.

Effect of Triple- Versus Double-Drug Immunosuppression

Beginning in January 1987, a subgroup of patients were treated with cyclosporine, azathioprine, and prednisone, and graft survival was found to be significantly better than with the cohort of patients receiving cyclosporine and steroids alone (2). Since January 1988, all patients have received triple-drug immunosuppression, and the initially favorable results have persisted. Actuarial one-year graft survival has been 83% in the triple therapy group and 70% in those receiving double therapy ($p < .0002$).

Adults Versus Children --- The advantage with triple-drug therapy was approximately the same whether the recipients were in the adult or pediatric population (Figure 6), although the numbers in the pediatric group were too small to show statistical significance.

Primary Transplantation Versus Retransplantation --- The advantage of triple-drug therapy was evident in recipients of primary grafts as well as in those undergoing retransplantation, and in the larger group of primary transplantations, the advantage was statistically significant ($p < .025$) (Figure 7). Actuarial one-year graft survival in primary transplantations on three-drug immunosuppression was 88%.

Low Versus High PRA --- Triple-drug therapy was advantageous for highly sensitized patients who have an actuarial one-year survival of 74%, compared to 58% under double-drug treatment. In contrast, patients with low PRA's have an actuarial one-year survival of 84% under triple-drug immunosuppression compared to 71% with double-drug treatment (Figure 8) ($p < .004$). Thus, triple-drug therapy has upgraded survival in both the favorable and immunologically unfavorable patient categories.

DISCUSSION

The equitable distribution of organs for transplantation is a matter of intense concern to the public as well as to health care providers. The point system (1) was designed to simplify recipient selection and to remove from the process the kind of bias against certain classes of potential recipients that could easily creep into an ad hoc system of patient selection. For example, there are no advantages or disadvantages for being old, afflicted by diseases of other organ systems, belonging to specific ethnic groups or religious persuasions, or being foreign-born.

One of the major criticisms of the point system (19) is a philosophic one: the goal of transplantation should be to maximize graft survival, and that the way to accomplish this is to transplant the "best" recipients, i.e., those who are young, healthy, and with low PRA's. The point system assures that

highly sensitized patients will come to transplantation. In our series, about 15% of patients had a PRA greater than 40%, connoting a poorer prognosis in all multi-center collections. Our earlier results with the point system demonstrated acceptable patient and graft survival, particularly in the group receiving three-drug immunosuppression. Our continued experience with three-drug immunosuppression has confirmed these improved results and should begin to address this criticism of the point system.

In the United States, and for the first time, the establishment of the United Network for Organ Sharing Kidney Transplant Registry will allow assessment of results after all of the cadaveric renal transplantations nationwide. From this data, analyses should begin to show if any of the factors used to compute points for the recipient scores will affect, either favorably or adversely, graft or patient life survival curves. Since our own experience with the point system precedes by almost two years that of all of the other centers which eventually were asked to adopt the system, some inkling of the implications of details of the point system will be watched for with interest in our patients. For example, a spectrum of donor-recipient matching is ensured by the point system, but so far, no major affect on the outcome has been identifiable as the result of extremely good or extremely poor compatibility or any permutations in between. The effect of age itself may prove to be important. In our own series, a high number of complications which would be expected in older patients were seen including

colonic perforations, and many lethal cardiovascular complications.

It will probably be several years before enough data can be collected on a nationwide basis to assess the effect of easy entry into candidacy for high-risk patients and equitable access to organs. If our experience is seen in other centers, the favorable patient and graft survival statistics should be reassuring, and the loss of organs will not be great.

SUMMARY

From 1 January 1986 to 30 July 1988, 530 consecutive cadaver kidney transplantations were performed with patient selection by a point system that took into account time waiting for an organ, donor-recipient matching, the degree of presensitization, and some less important factors. The effect of the system was to diminish judgmental factors in case selection which probably in the past had operated to the disadvantage of "undesirable" potential recipients including older ones. Primary one-year graft survival (74%) and graft survival after retransplantation (71%) were lower than in the earlier time. However, the results with triple-drug therapy using cyclosporine, azathioprine and prednisone demonstrate 88% one-year graft survival for primary graft recipients and 74% in highly sensitized patients, with a comparable patient mortality. These latter observations provide some assurance that the concepts of equitable access and

efficient utilization of a scarce resource are not mutually exclusive.

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FIGURE LEGENDS

Figure 1 Patient and graft survival for 1986-1987.

Figure 2 Pediatric and adult graft survival for 1986-1987.

Figure 3 Primary and retransplant graft survival for 1986-1987.

Figure 4 Graft survival for PRA less than and greater than 40%.

Figure 5 Graft survival for two- and three-drug immunosuppression.

Figure 6 Pediatric and adult graft survival with two- and three-drug immunosuppression.

Figure 7 Primary and retransplant graft survival with two- and three-drug immunosuppression.

Figure 8 Graft survival for PRA less than and greater than 40% with two- and three-drug immunosuppression.

TABLE 1 CAUSES OF DEATH AFTER RENAL TRANSPLANTATION

CAUSE OF DEATH	GRAFT FUNCTIONING	GRAFT REMOVED OR NON-FUNCTIONING	TOTAL
INFECTION	1	14	15
CARDIOVASCULAR	4	5	9
GASTROINTESTINAL	1	4	5
RESPIRATORY	0	2	2
MALIGNACY	0	1	1
TECHNICAL	0	1	1
MISCELLANEOUS (D.I.C., MULTIPLE ORGAN, FAILURE, HYPERKALEMA, BLEED AFTER BIOPSY, MOTOR VEHICLE ACCIDENT)	2	3	5
UNKNOWN	0	2	2
	8(20%)	32(80%)	40

TABLE 2 MATCHING IN 418 CASES, IN WHICH THERE WAS ADEQUATE DONOR AND RECIPIENT TYPING. KIDNEY FUNCTION HAS BEEN FROM 4–30 MONTHS.

# ANTIGENS MATCHED	FUNCTIONING / TOTAL	
6	4 / 6	(67%)
5	3 / 5	(60%)
4	14 / 19	(74%)
3	47 / 69	(68%)
2	96 / 128	(75%)
1	117 / 157	(75%)
0	66 / 103	(64%)
	347 / 487	(71%)

TABLE 3 FATE OF 505 RECIPIENTS OF 530 GRAFTS

ALIVE	465 (92.1%)
OFF DIALYSIS	379 (75.1%)
ON DIALYSIS	86 (17.0%)
DEAD	40 (7.9%)

UNIVERSITY OF PITTSBURGH
KIDNEY TRANSPLANTATION
SURVIVAL: PATIENT, GRAFT 1986 – 1988

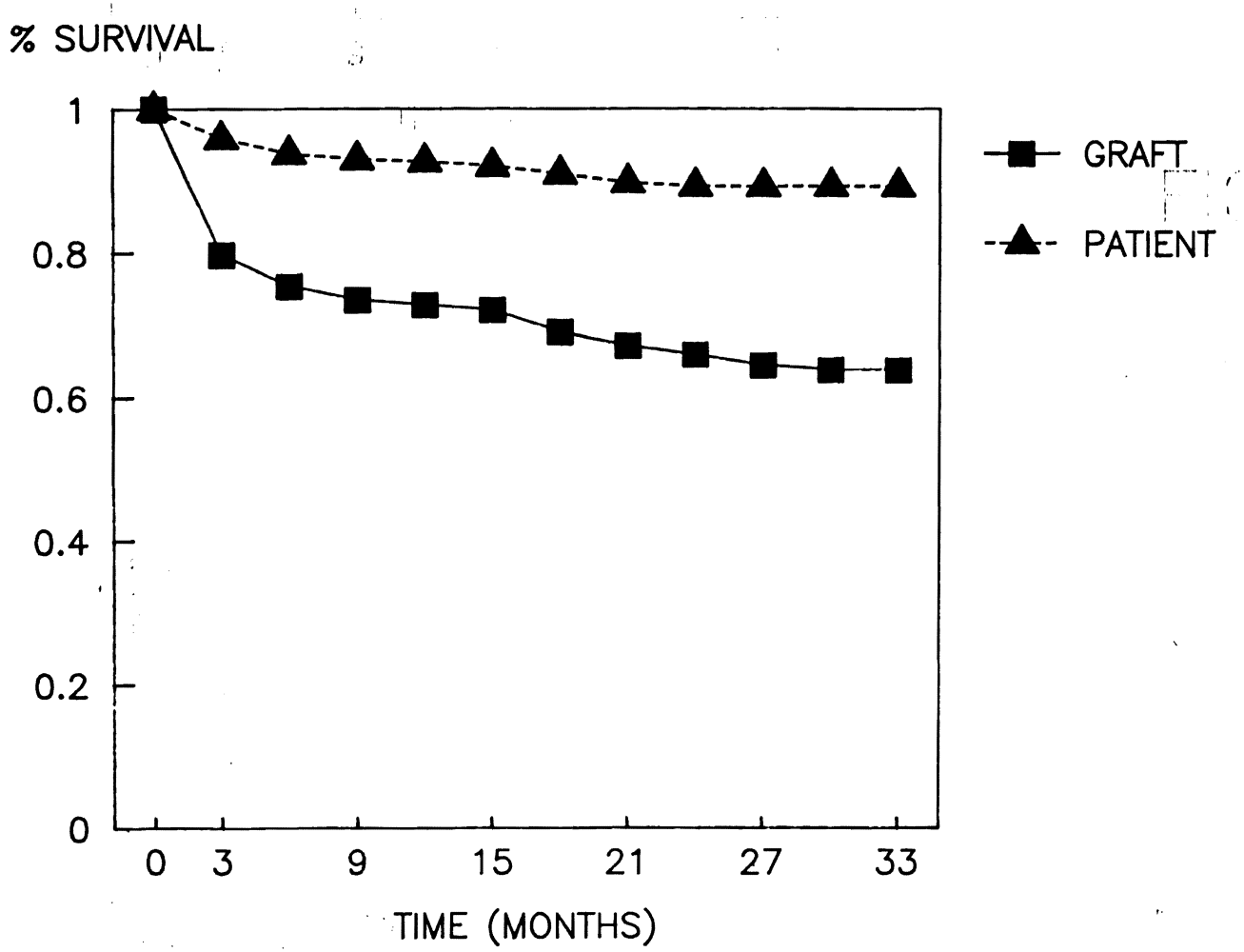

FIGURE 1

UNIVERSITY OF PITTSBURGH
KIDNEY TRANSPLANTATION
PEDIATRIC vs ADULT SURVIVAL

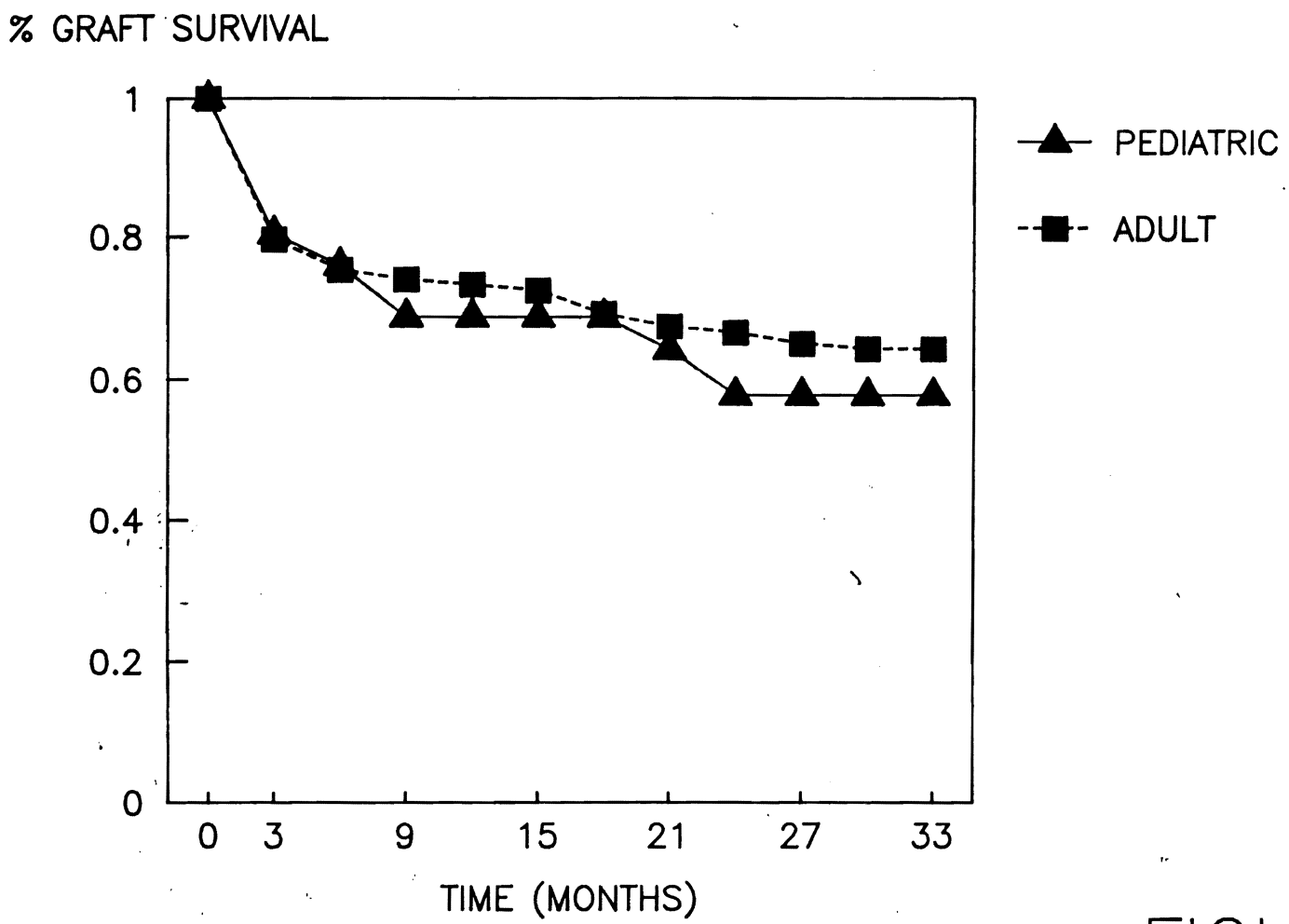

FIGURE 2

UNIVERSITY OF PITTSBURGH
KIDNEY TRANSPLANTATION
PRIMARY vs RETRANSPLANT SURVIVAL

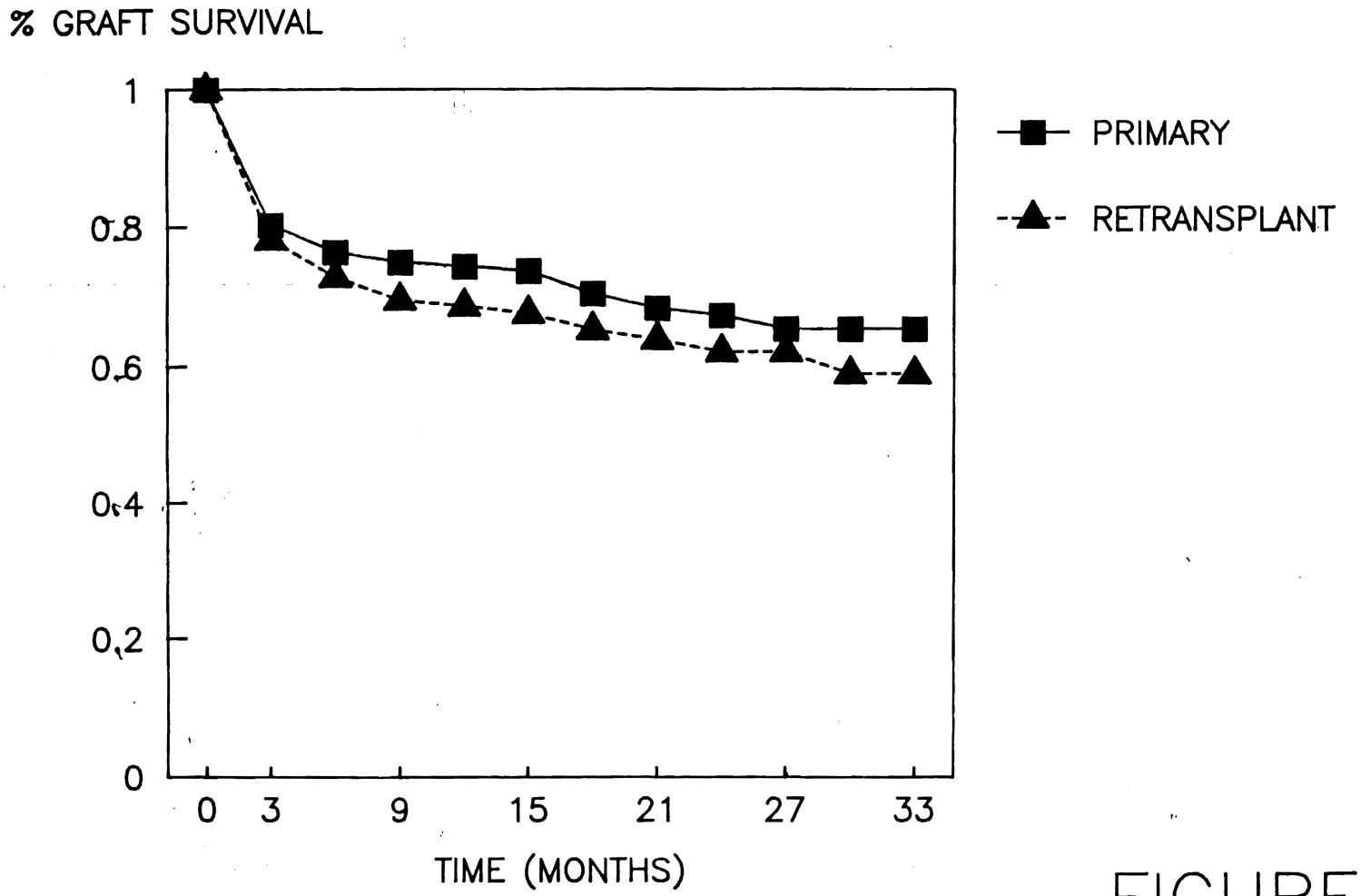

FIGURE 3

UNIVERSITY OF PITTSBURGH KIDNEY TRANSPLANTATION SURVIVAL: PRA < and > 40%

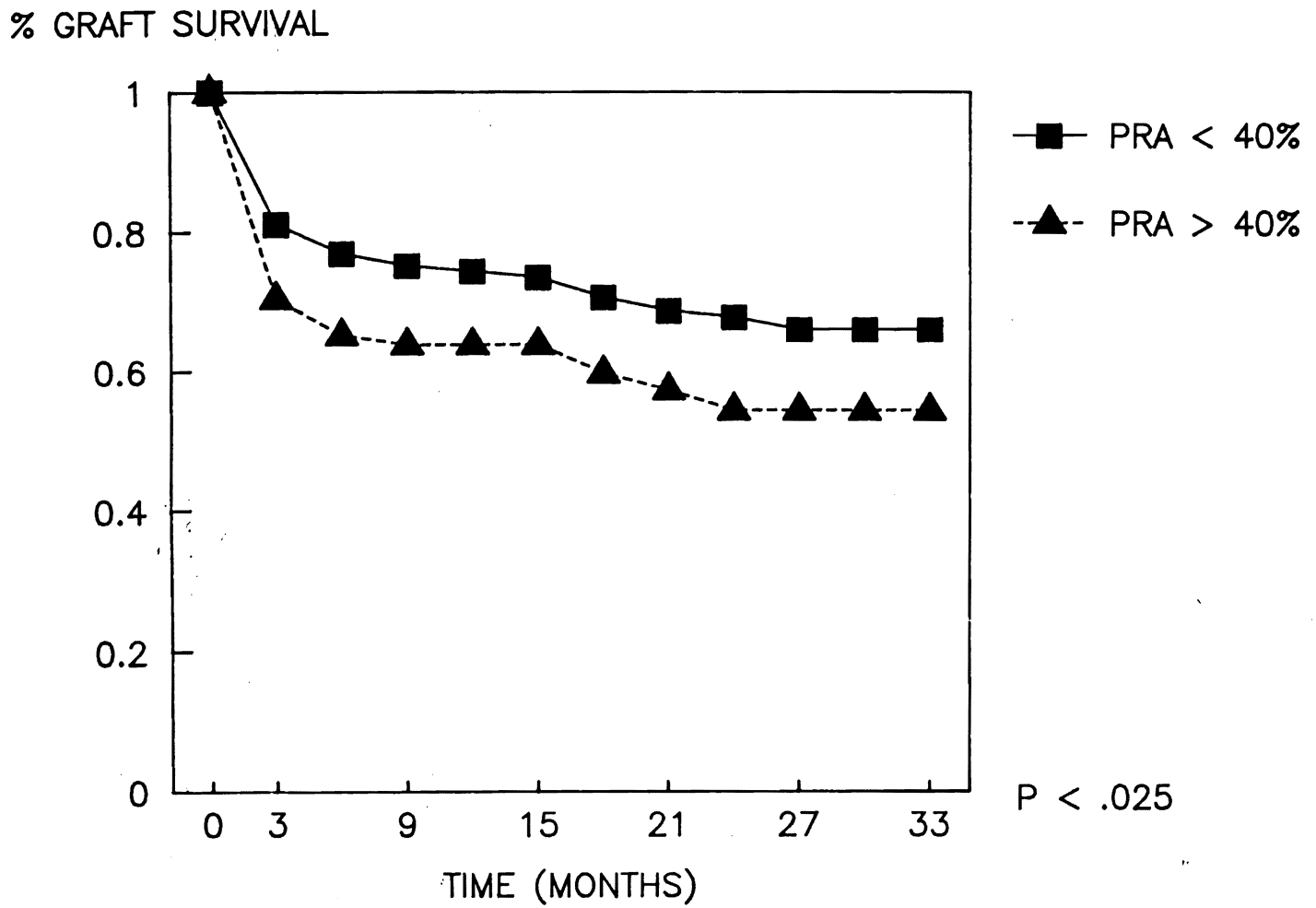

FIGURE 4

UNIVERSITY OF PITTSBURGH KIDNEY TRANSPLANTATION IMMUNOSUPPRESSION

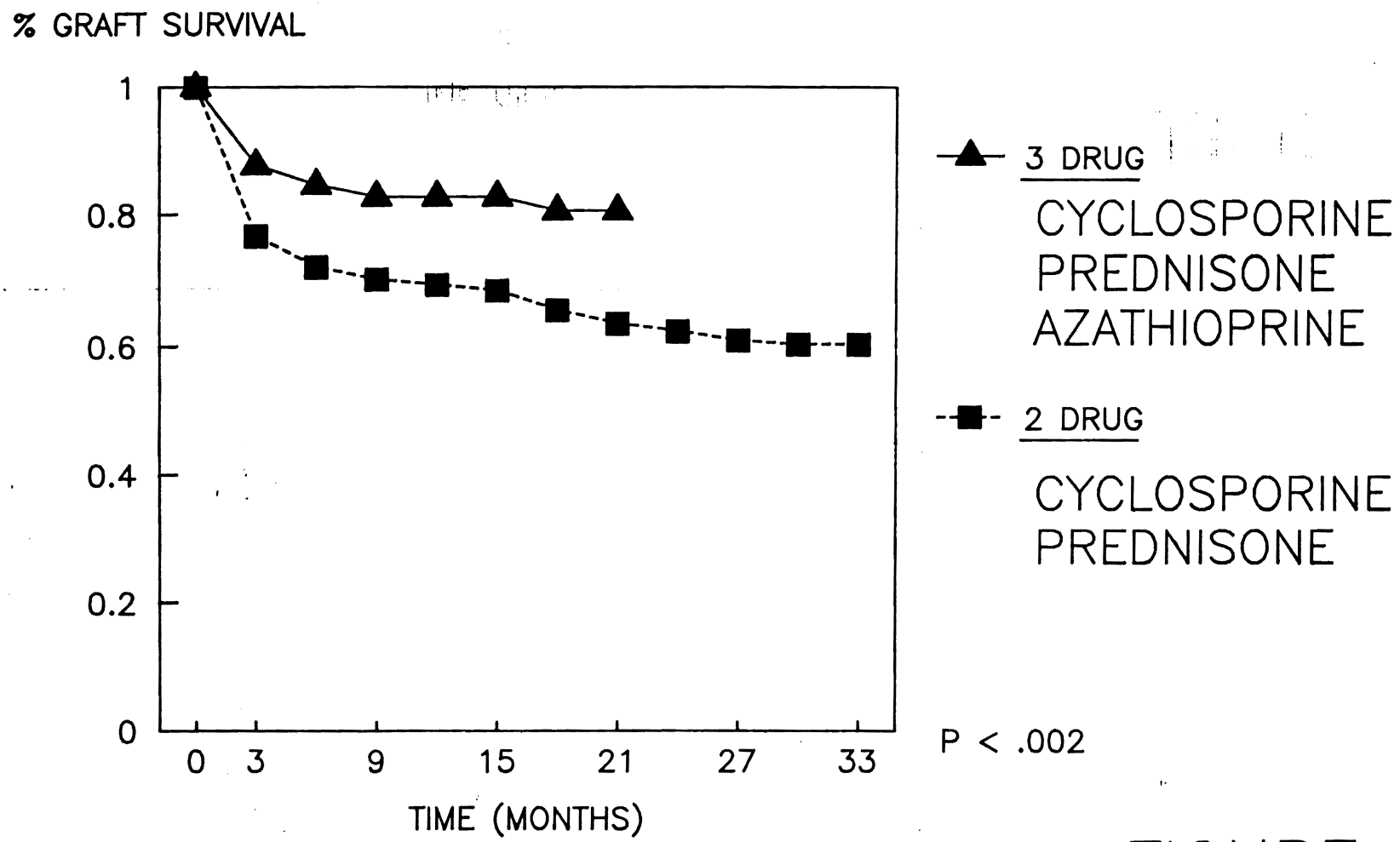

FIGURE 5

UNIVERSITY OF PITTSBURGH KIDNEY TRANSPLANTATION PEDIATRIC vs ADULT SURVIVAL

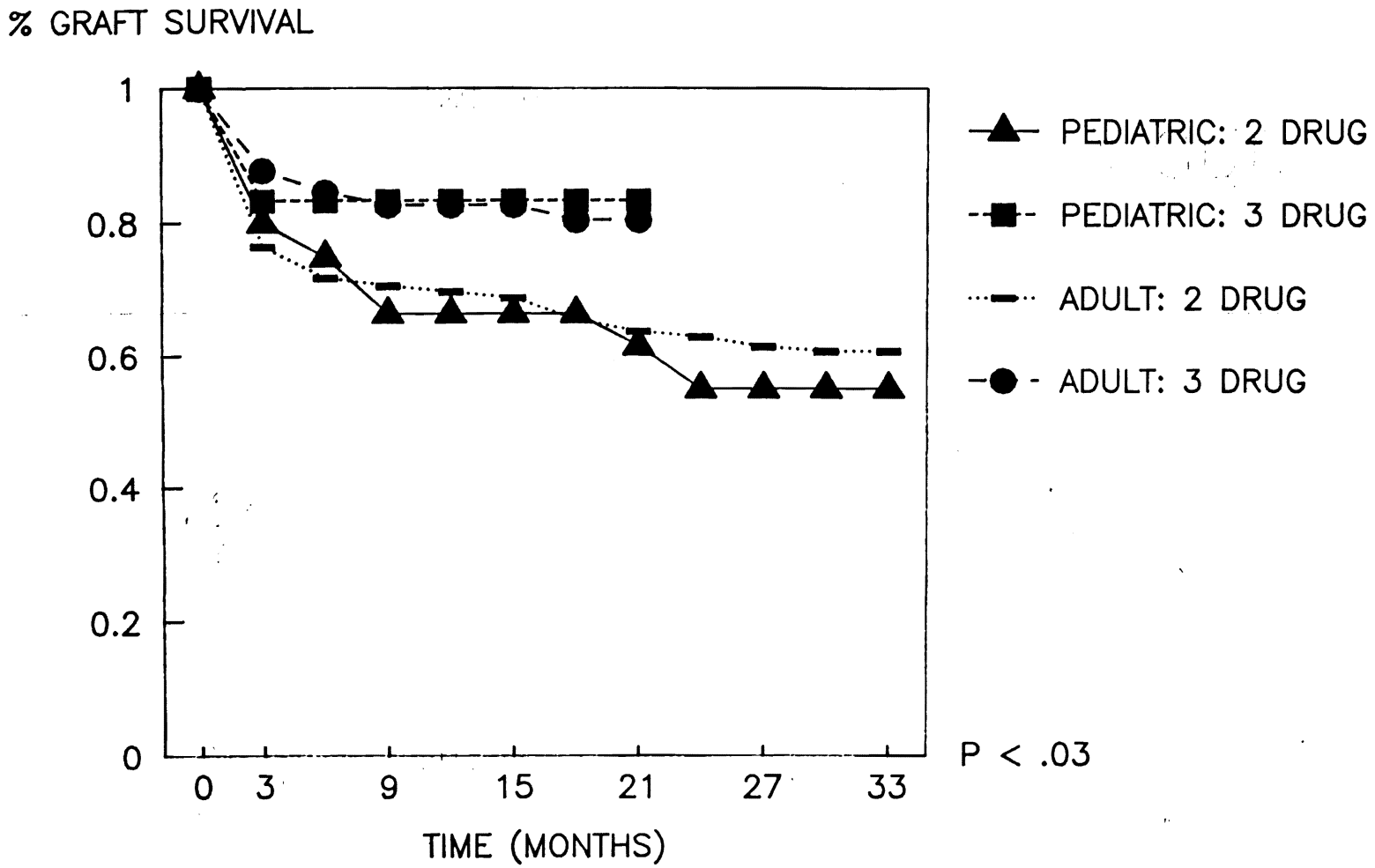

FIGURE 6

UNIVERSITY OF PITTSBURGH
KIDNEY TRANSPLANTATION
PRIMARY AND RETRANSPLANT SURVIVAL

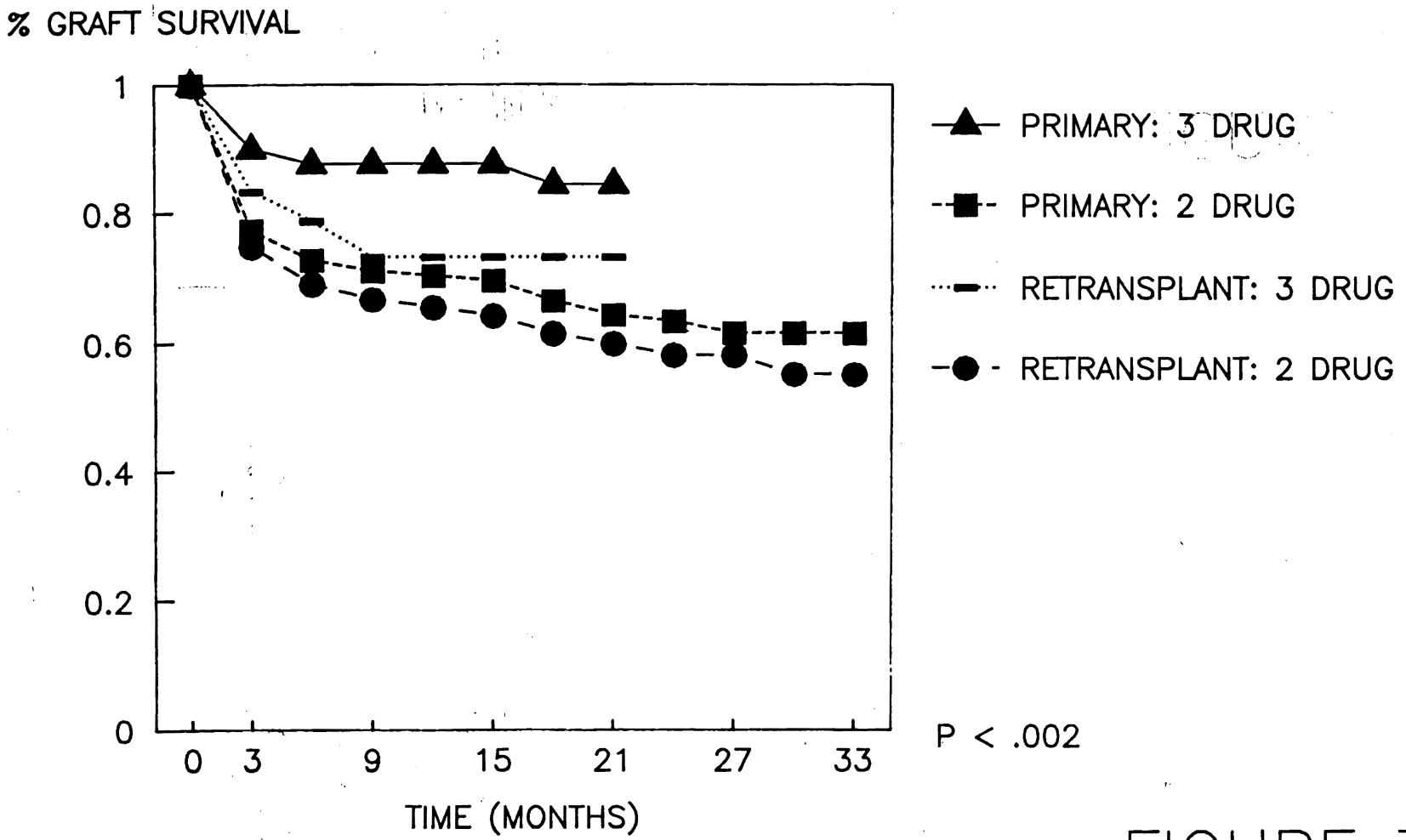

FIGURE 7

UNIVERSITY OF PITTSBURGH KIDNEY TRANSPLANTATION SURVIVAL: PRA < and > 40%

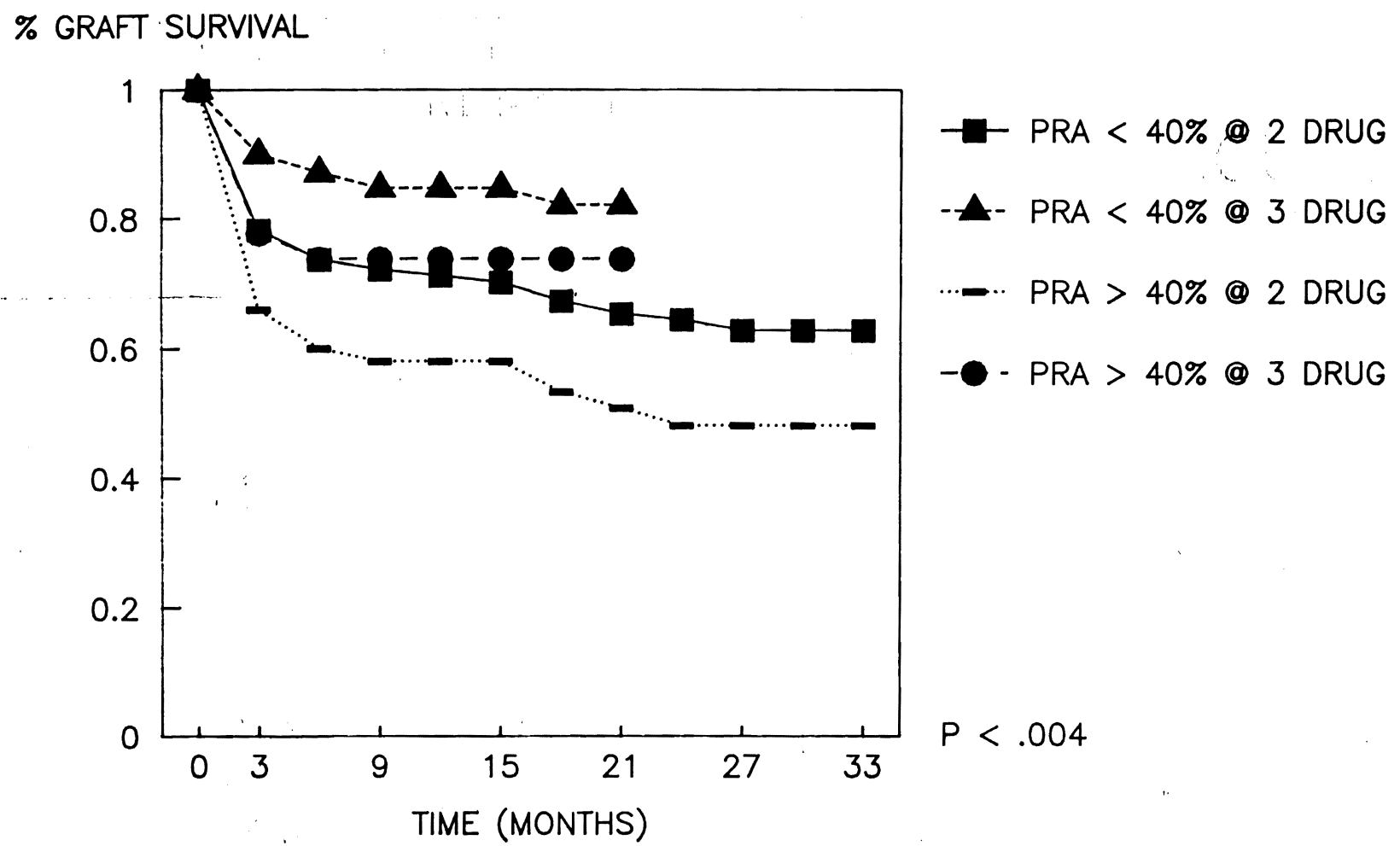

FIGURE 8