EARLY GRAFT FUNCTION AND CYCLOSPORIN

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In our studies to date, we have used patient and graft survival as the main end point. Although it is true that ultimately these measures are the most important, daily serum creatinine values obtained in the first month after transplantation may be a helpful indicator of long term function as will be shown here. They should also be of importance in measuring the effectiveness of various protocols of immunosuppression.

We attempt in this chapter to utilize early function data from a small subset of patients gathered from five different centers. As a trial, data was gathered, computer programs written, and cyclosporin dosages and levels were examined.

METHODS

Detailed daily data was collected for the first 60 days after transplantation from 539 patients at five centers for this trial. The patient population was selected as much as possible from transplants which were performed consecutively within a center and during the same time period (1981-1985) between centers so as to obtain a representative sample of most transplants being performed. The centers that participated in this trial were the University of Texas at Houston; University of Minnesota; University of California, San Francisco; University of Pittsburgh; and the University of Southern California. For this initial analysis the serum creatinine, cyclosporin serum levels, and cyclosporin, prednisone, Imuran, Solu-Medrol and ATG/ALG dosages were used. By cross-referencing these data with the transplant registry file, studies on patient survival and matching were done. Rejection episodes were either

indicated by the centers or retrospectively assigned on the basis of an increase in serum creatinine, use of Solu-Medrol, recycling of prednisone, use of ATG, increased cyclosporin dosage and biopsy results. Cases with questionable rejections were excluded from this portion of the study.

RESULTS

The results are presented in the following figures and legends.

Figure 1. The striking difference in serum creatinine values for cadaver transplants in comparison with living-related donors is shown in the first 20 days after transplantation. Much of the difference represents the effect of ischemic damage to kidneys from cadavers. It is interesting to note, however, that histocompatibility differences between the two haplotype-identical HLA-identical siblings and the one-haplotype-identical parental transplants show a difference in average serum creatinine values from the third day on. The serum creatinine values of cadaver donor transplants reach a level of 3 mg/dl around 20 days after transplantation, which is higher than that for parental or HLA-identical sibling donor transplants.

Figure 2. When cadaver donor transplants were divided into those who were clinically doing well (ranks A or B), and those who were clinically doing poorly (ranks C or D), at one year post transplant, retrospective analysis of average serum creatinine values shows that the two groups had started out quite differently and that the average serum creatinine was higher even at day five for those transplants that were classified as functioning poorly at one year. Patients having good transplant function with clinical ranks of A or B at one year had lower serum creatinine values immediately after transplantation with levels of about 2.0 mg/dl at one month. Patients with poorly functioning kidneys at one

year had, at one month, an average serum creatinine slightly over 3.0 mg/dl. We can conclude that serum creatinine values, even as early as the fifth day post transplantation, are different in patients who ultimately had better or worse kidney function.

Figure 3. Patients who had serum creatinine levels under 2.5 mg/dl on the fifth day after transplantation were shown here to have higher graft survival rates than patients who had serum creatinines of more than 2.5 mg/dl on the fifth day post transplant. Thus, survival as well as clinical ranks as shown in the previous figure, appears to be correlated with the early serum creatinine level in cadaver donor transplants.

Figure 4. The one year graft survival rate of cadaver donor transplants is given here in relation to the serum creatinine levels on each of the postoperative days indicated. Thus, the upper line shows the one year graft survival rate of patients who had a serum creatinine of 0-2.4 mg/dl on post transplant day 0 to day 20. It can be noted that those patients who had such low serum creatinine values during the first 20 days postoperatively had one year graft survival rates that were over 80%. However, those patients having less favorable serum creatinine values during the first 20 days post transplantation clearly had a lower one year graft survival rate. Those patients who had high serum creatinine levels of over 7.5 mg/dl in the early postoperative period tended to have good one year graft survival rates over 75%, but if high serum creatinine levels were obtained after the fifth postoperative day, the one year graft survival rate was low. The serum creatinine level after the sixth day correlated fairly well with the ultimate one year graft survival rate.

Figure 5. The average serum creatinine levels of patients who do

not experience rejection during the first 60 days is seen to be lower than those who did have a rejection as might be expected. Among those who do not experience rejection, the average serum creatinine level comes down to a level of 2.5 mg/dl at about the 20th day and to 2.0 mg/dl at about the 50th day.

Figure 6. The peak number of patients who experience a rejection is noted to be on the seventh day after transplantation. The majority of the first rejections occur within two weeks. When larger numbers of patients are available for study, this curve can be better defined.

Figure 7. Average serum creatinine levels of patients who receive transplants that are zero or one A,B antigen mismatched show a lower level than the average in patients who have two to four HLA-A,B antigens mismatched. In the better matched transplants average serum creatinines of 2.0 mg/dl are reached two weeks after transplantation.

Figure 8. Cadaver donor transplants that were mismatched for zero or one antigen in the B,DR loci had only a slightly lower serum creatinine level than patients who were mismatched for two to four B,DR antigens. Note the small number of patients available with zero or one B,DR mismatches.

Figure 9. Patients who were mismatched for zero, one or two DR antigens, had essentially the same average serum creatinine levels.

Figure 10. Among cadaver donor patients who had zero or one A,B,DR mismatch, the average serum creatinine levels were lower than those who had two to six antigens mismatched. Again, the number of well matched patients was low.

Figure 11. The average serum creatinine levels for patients who received cadaver donor transplants at four different centers were generally concordant. The data from center 4 was based on a small number of

patients (16) who tended to have a higher serum creatinine level during the first two weeks after transplantation. By one month, patients at all 4 centers had similar serum creatinine values.

Figure 12. The one year graft survival rates of patients at the four different centers did not correlate exactly with the early serum creatinine levels at the four centers (Fig. 11). Center 4, which had the highest serum creatinine levels, had the highest one year graft survival rate and center 3, which had the best serum creatinine levels, had the lowest one year graft survival rate. No conclusions can be drawn from the small numbers except to note that comparisons between centers may yield valuable information on the most effective protocols for treatment of patients.

Figure 13. The cumulative percent rejection rate for the 4 centers encompassed a fairly large range from 30% rejection at 50 days to about 60%. It would be of interest to correlate the rejection rate with one year survival, with function, and with immunosuppressive regimens. Protocols by which rejections, or at least conventionally recognized rejections, are not seen at all are the ideal. Here, 40% to 70% of patients are seen not to have any rejection in the first 50 days.

Figure 14. In the same four centers, a comparison of the average total daily cyclosporin dose was quite different. Center 2 used a distinctly higher early cyclosporin dose for the first 40 days after transplantation. Their one year graft survival rate was higher than in center 1 or 3 which had used lower initial cyclosporin doses. Certainly, this is only a measure of one factor involved in this complex procedure.

Figure 15. The average cyclosporin dose given during the first month after transplantation can be seen to be higher for the cadaver

donor transplants than living-related donor grafts. Despite the use of lower levels of cyclosporin, there was a greater lowering of the serum creatinine values in the living-related donor transplants than in the cadaver donor transplants (Fig. 1).

Figure 16. The average cyclosporin dosage given to patients did not appear to correlate with whether the patients had rejections or not. When the patients were divided into those who had rejected and those who did not, the average cyclosporin dosage was quite similar for the first 60 days. Further division of rejection patients resulted in some differenee as shown in the next figure.

Figure 17. Among patients with no rejection episodes, the cyclosporin dosages per day were as shown. These patients could not be distinguished in the first 10 days from those who had a rejection episode within the first 10 days. However, those who rejected in 11-60 days had a lower cyclosporin dosage in the first 10 days. It would seem from these relatively small numbers of patients that dosages of cyclosporin lower than a tapering of 18 mg/kg/day to 12 mg/kg/day by the 20th days results in more rejection after the first 10 days.

Figure 18. The average daily cyclosporin levels were plotted for patients who had rejections and those who did not. As shown here, the average cyclosporin level was slightly lower for those patients who had rejected than those who did not. There is a tendency to have increasing cyclosporin levels up to day 15.

Figure 19. The cyclosporin serum level on day 5 was associated with the serum creatinine values through the 15th postoperative day. That is, patients who had a low cyclosporin level 0-75 ng/ml on the 5th day had the lowest serum creatinine levels. Those patients who had high day 5 cyclosporin levels of more than 200 ng/ml had the highest serum creatinine levels. These relationships might be the opposite of what we might

expect if we assumed that higher levels would be associated with more effective immunosuppression. These findings appear to be more consistent with early cyclosporin toxicity within the first 15 days.

Figure 20. The cyclosporin level on day 5 is compared with eventual graft survival. Intermediate levels of 76 to 200 mg/ml had the highest one year graft survival rate while the lowest survival rate was associated with patients who had cyclosporin levels greater than 200 mg/ml on day 5. However, at three years post transplant, the differences were small.

DISCUSSION

The trial described here suggests that a great deal could be learned from multicenter analyses of daily data. Different immunosuppression protocols can be examined in detail and compared. We describe here only the simple first level analysis.

Even with these simple analyses, we were quite interested to see that, for example, serum creatinine values on the fifth day post transplant already distinguish between transplants from HLA-identical sibling donors, parental donors, and cadaver donors. The histocompatibility influence in transplants can be concluded to occur within five days after transplantation if these results are confirmed in larger numbers of patients. With the small numbers available for analysis, even HLA-A,B,DR matching in cadaver donor transplants seems to have an early effect on the serum creatinine levels.

A clear association with serum creatinine levels during the first month after transplantation and eventual outcome of transplants has been presented (Fig. 4). For example, two weeks after transplantation, if the serum creatinine is less than 2.4 mg/dl the one year survival rate was more than 80% whereas if it was more than 7.5 mg/dl, the one year transplant survival rate was under 30%. Intermediate serum creatinine

levels led to intermediate graft survival rates. Even one week after transplantation, there was already about a 30% one year graft survival rate difference between kidneys that had serum creatinine levels less than 2.4 mg/dl and more than 7.5 mg/dl.

It is interesting to see that the average serum creatinine within the first 30 days was different at different centers (Fig. 11). This can indicate the difference in quality of preservation or types of donors utilized for transplant as well as differences in early immunosuppression regimens. Within the four centers in the original trial, the average serum creatinine levels had reached similar levels in all four centers by 30 days. Use of higher cyclosporin dosages at one center (Fig. 14) did not result in lower creatinine values at that center or higher long-term graft survival rates. Obviously other factors must be taken into account.

When comparing between related donor transplants and cadaver donor grafts, total daily cyclosporin dosage was less for the living-related transplants. In spite of the reduced cyclosporin dosage, the serum creatinine levels dropped to lower values in living-related donor grafts.

There are many opinions on the value of cyclosporin levels. Retrospective analysis of the levels in relation to rejections showed that those patients without rejections tended to have slightly higher cyclosporin levels. Further analysis will be needed to take into account other factors.

We hoped by these studies to show the potential of using daily data gathered from many centers. Much of the problem rests in data entry, manipulation and analysis, which of course must be done with computers. Other analysis has been performed by Mickey (1) and new programs for

analysis are being developed.

SUMMARY

1. The average serum creatinine during the first 20 days after transplantation was lower in HLA-identical siblings than parental donor transplants suggesting a very early effect of histocompatibility.
2. In rather small numbers of patients, the daily average serum creatinine values were not different with DR mismatching and B,DR mismatching but were lower in the better matched transplants for the A,B loci and the A,B,DR loci.
3. The average serum creatinine values in the first 20 days after transplantation were correlated with the one year graft survival rates. Those patients with serum creatinines less than 2.4 mg/dl had one year graft survival rates of over 80% compared with those patients with serum creatinines above 7.5 mg/dl after the first week who had one year graft survival rates of over 30% less. Intermediate serum creatinine values yielded intermediate one year graft survival rates.
4. The cyclosporin dosage in the first month after transplantation varied considerably between the four centers studied here. These values were not necessarily correlated with the one year graft survival rate, average serum creatinines and the cumulative rejection rates in this preliminary examination.
5. Patients who rejected between 11 to 60 days post transplant had lower cyclosporin dosages than those who rejected early or who had no rejections.

6. Although firm conclusions cannot be drawn from the small numbers of patients included in this study we hope the potential value of this type of analysis is shown.

REFERENCES

1. Mickey MR, Berne MV, Kahan BD, Salvatierra O, Starzl TE, Terasaki PI. HLA Matching assessed from early function. Transplant Proc; In press.

FIGURE 1

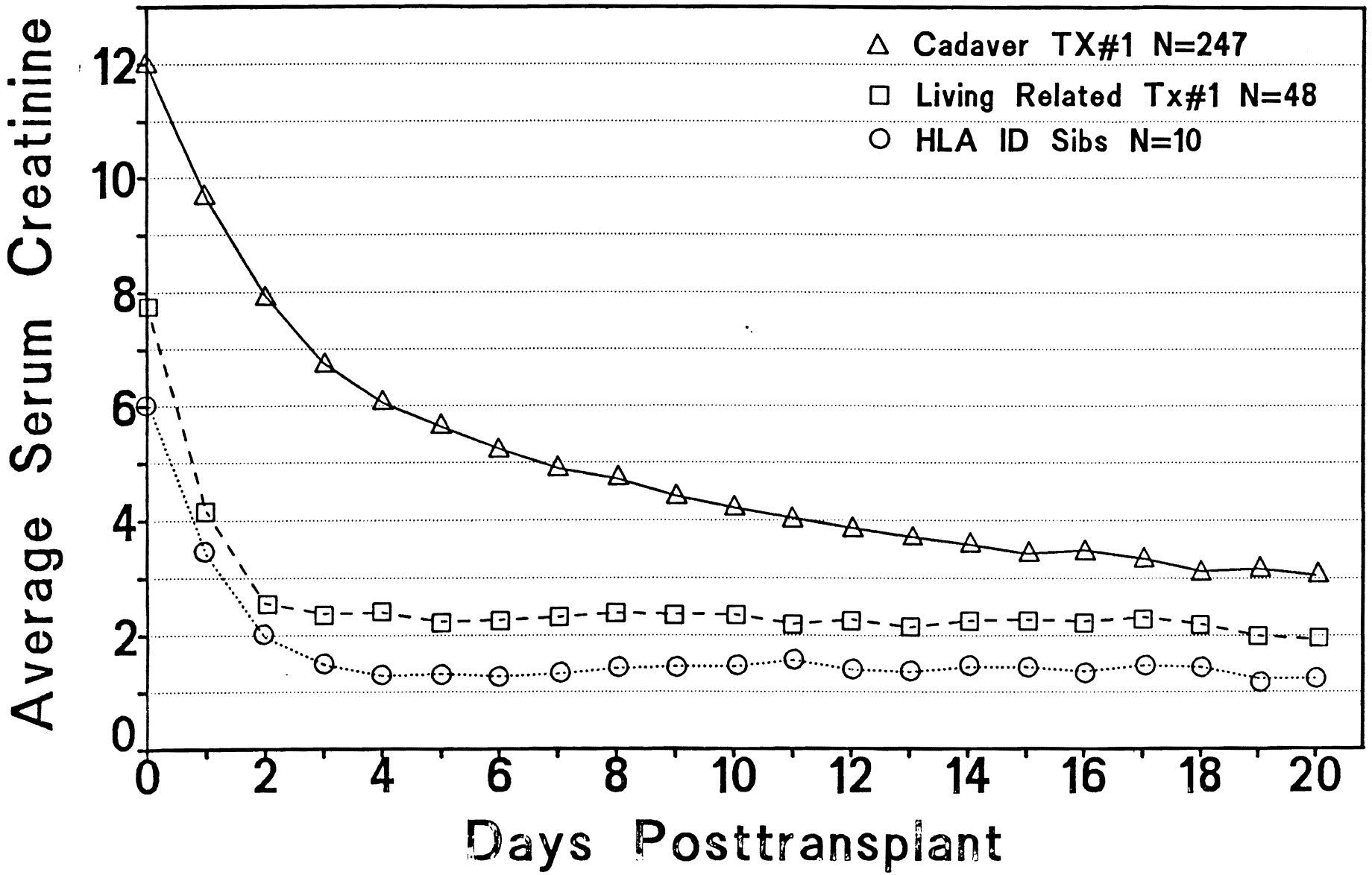

Average Serum Creatinine
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
16
18
20
Days Posttransplant
Cadaver TX#1 N=247
Living Related Tx#1 N=48
HLA ID Sibs N=10

FIGURE 2

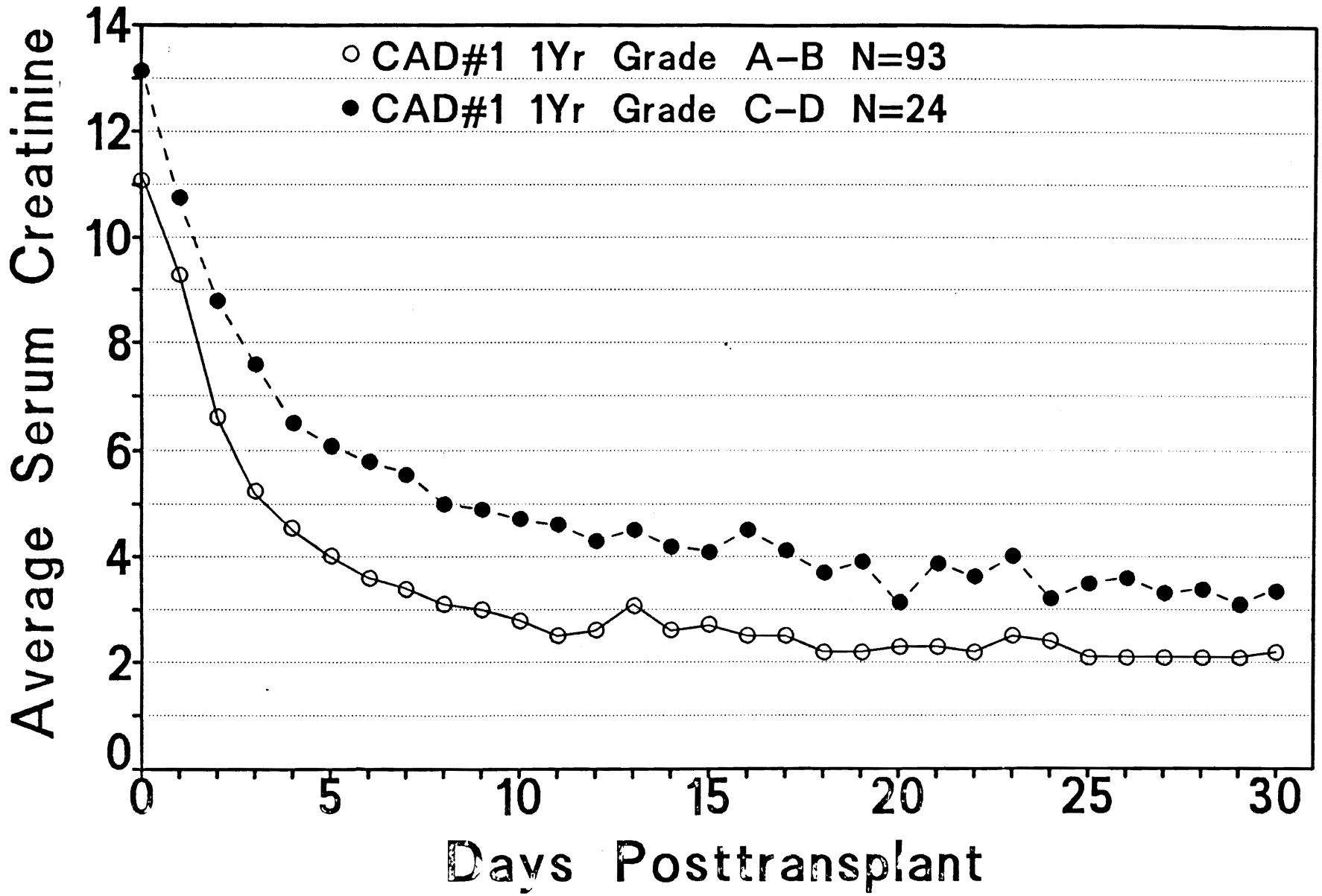

CAD#1 1Yr Grade A-B N=93
CAD#1 1Yr Grade C-D N=24
Average Serum Creatinine
0
2
4
6
8
10
12
14
0
5
10
15
20
25
30
Days Posttransplant

FIGURE 3

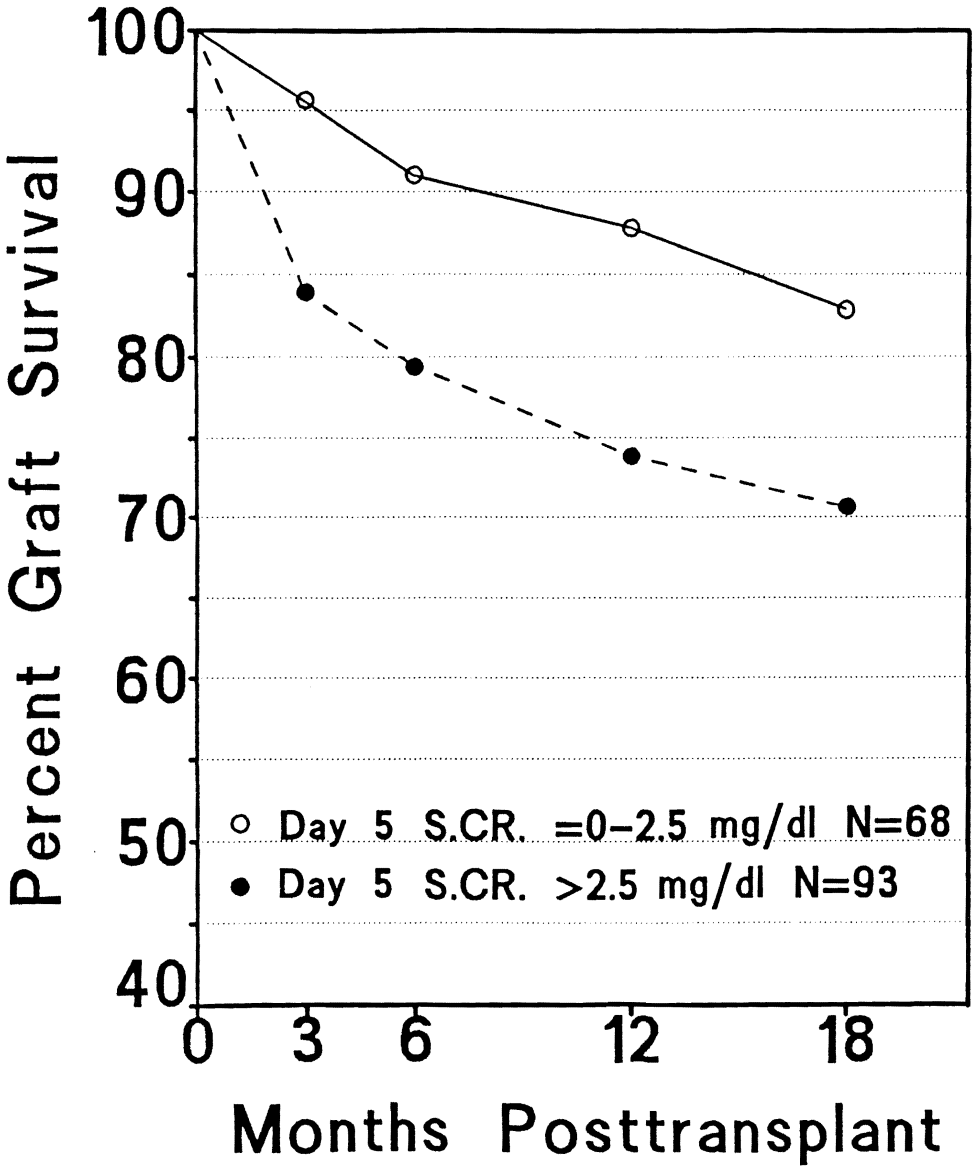

100
90
80
70
60
50
40
Percent Graft Survival
Day 5 S.CR. =0–2.5 mg/dl N=68
Day 5 S.CR. >2.5 mg/dl N=93
0
3
6
12
18
Months Posttransplant

FIGURE 4

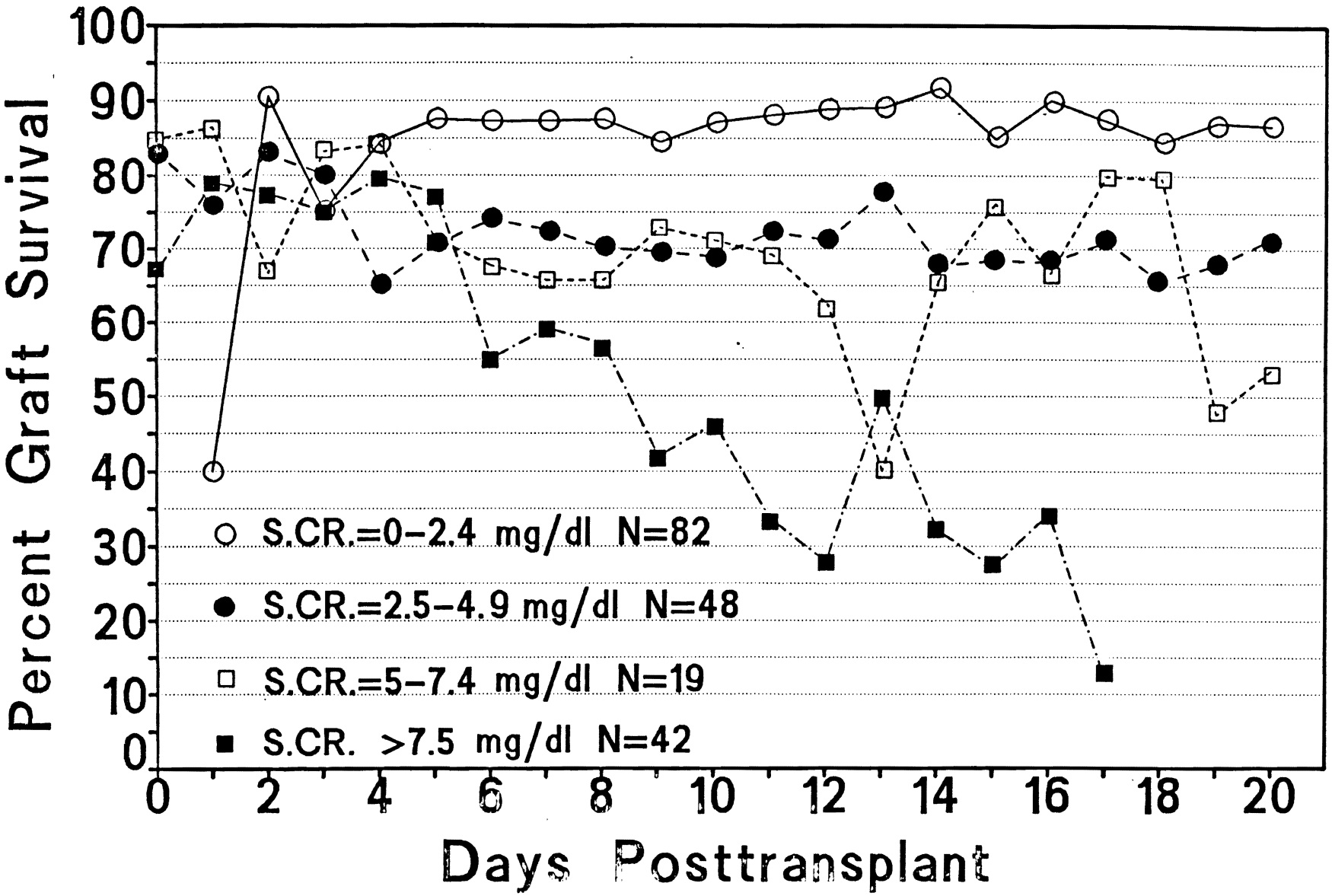

Percent Graft Survival
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
Days Posttransplant
S.CR.=0-2.4 mg/dl N=82
S.CR.=2.5-4.9 mg/dl N=48
S.CR.=5-7.4 mg/dl N=19
S.CR. >7.5 mg/dl N=42

FIGURE 5

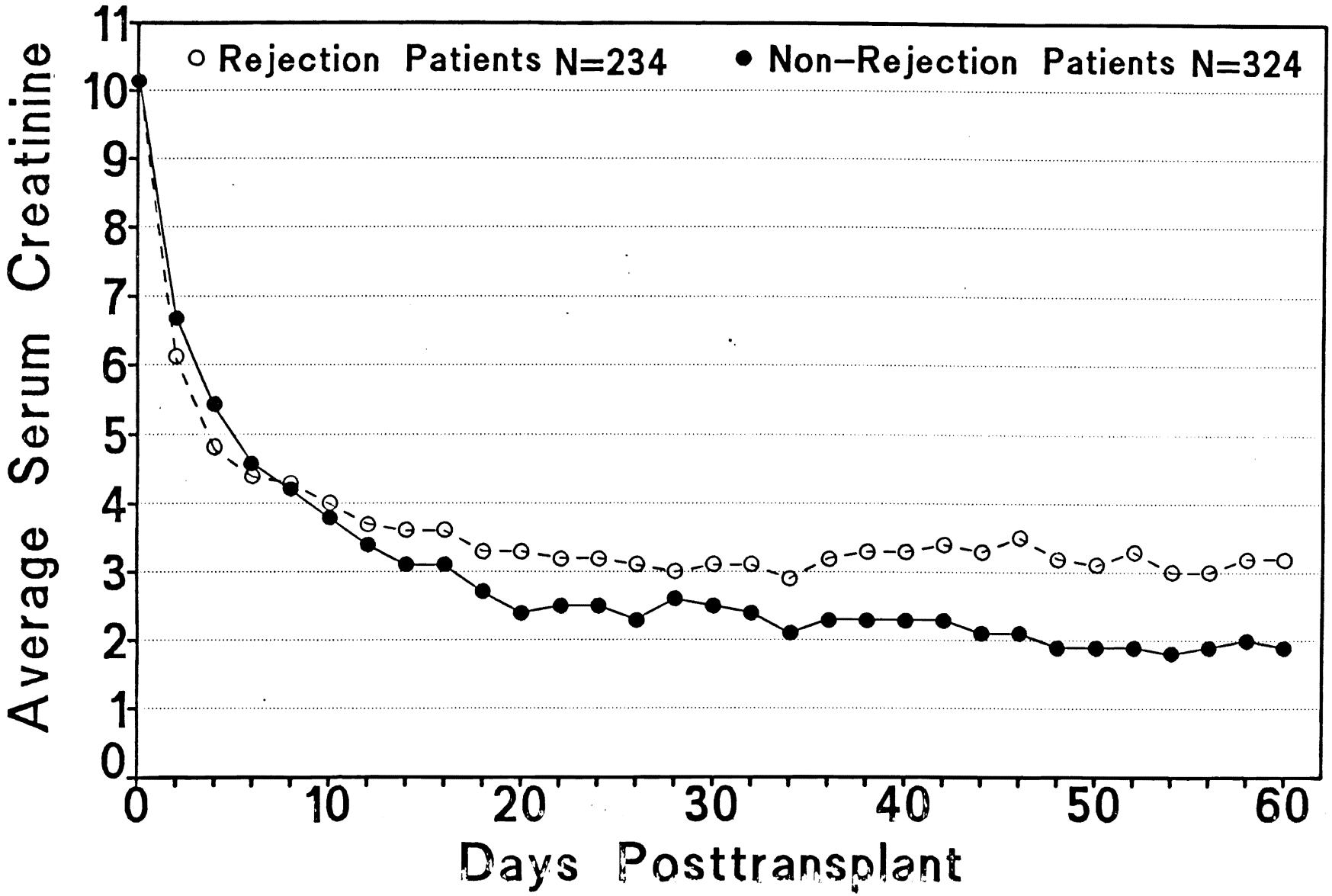

Average Serum Creatinine
11
10
9
8
7
6
5
4
3
2
1
0
Rejection Patients N=234
Non-Rejection Patients N=324
0
10
20
30
40
50
60
Days Posttransplant

FIGURE 6

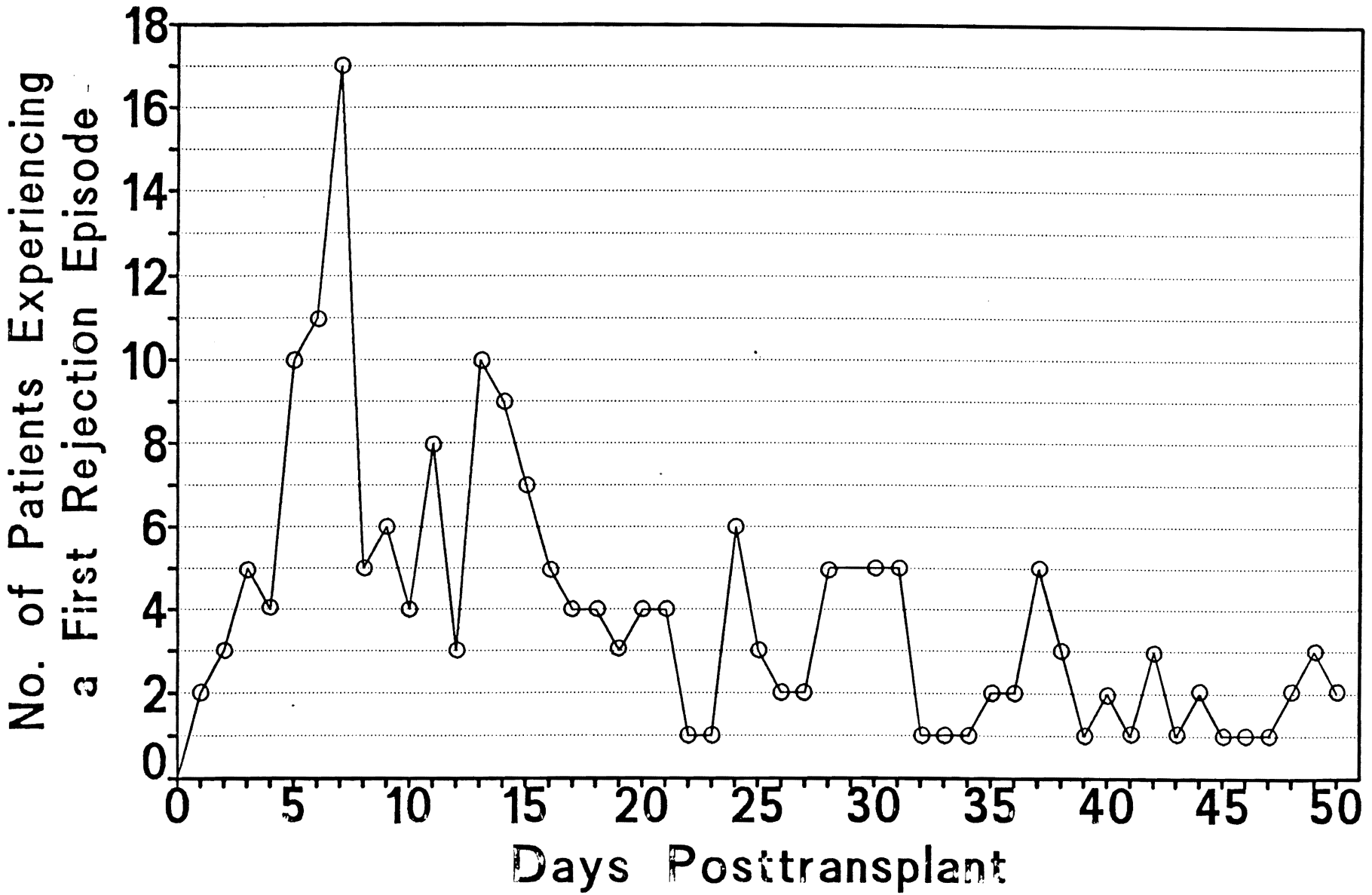

No. of Patients Experiencing a First Rejection Episode
18
16
14
12
10
8
6
4
2
0
0
5
10
15
20
25
30
35
40
45
50
Days Posttransplant

FIGURE 7

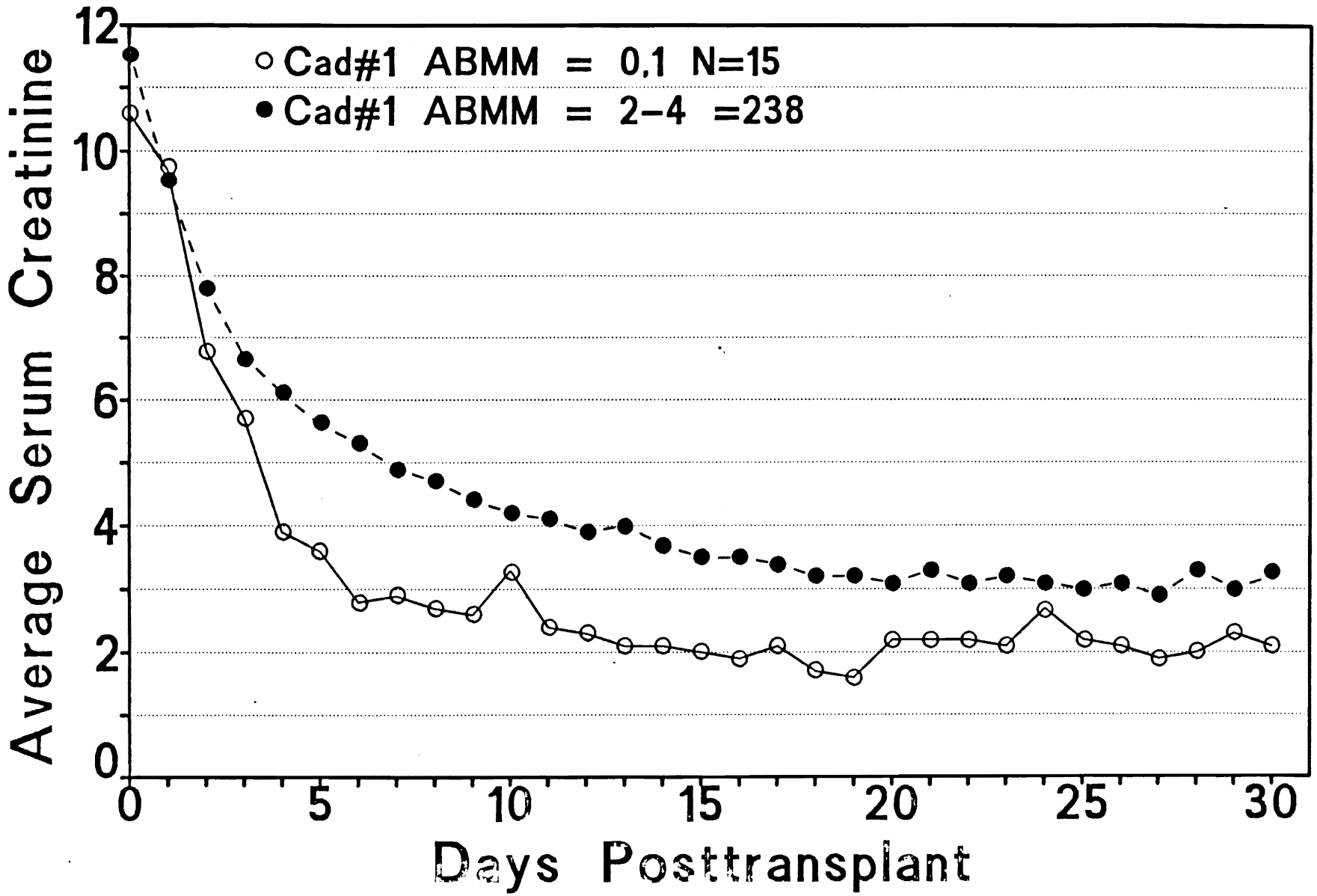

Cad#1 ABMM = 0,1 N=15
Cad#1 ABMM = 2-4 =238
Average Serum Creatinine
0
2
4
6
8
10
12
0
5
10
15
20
25
30
Days Posttransplant

FIGURE 8

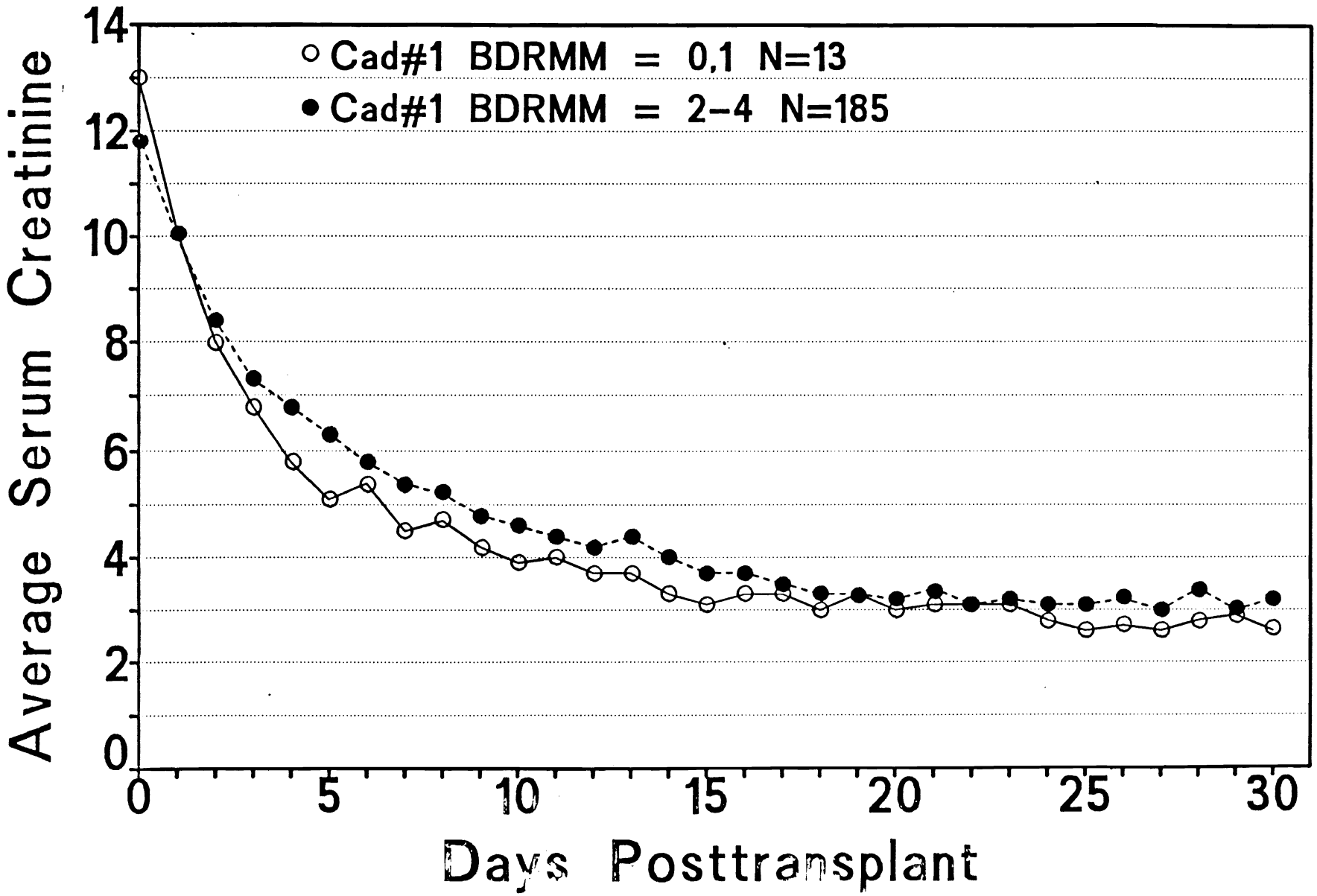

Cad#1 BDRMM = 0,1 N=13
Cad#1 BDRMM = 2-4 N=185
Average Serum Creatinine
0
2
4
6
8
10
12
14
0
5
10
15
20
25
30
Days Posttransplant

FIGURE 9

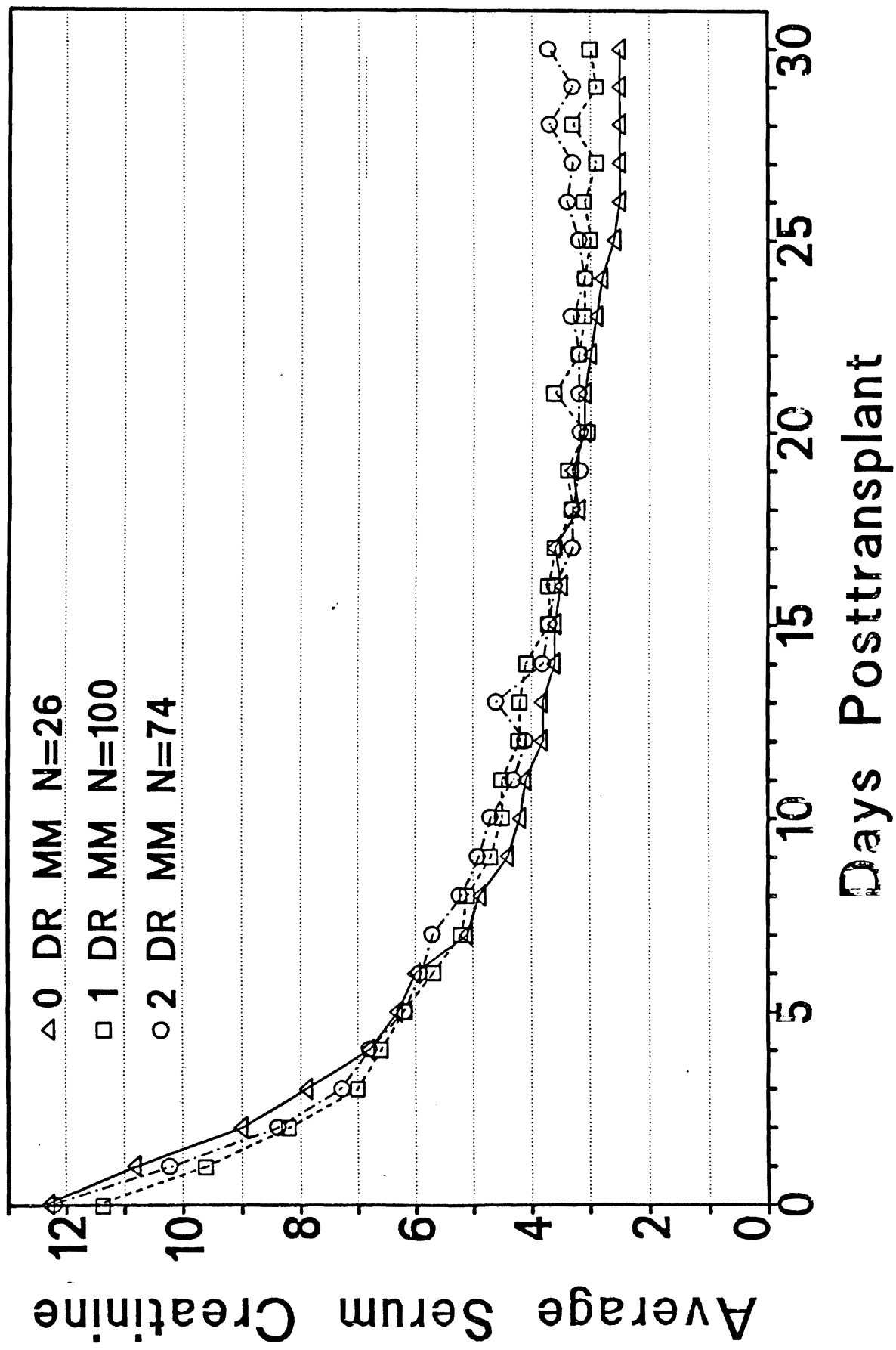

Average Serum Creatinine
12
10
8
6
4
2
0
0
5
10
15
20
25
30
Days Posttransplant
△0 DR MM N=26
□1 DR MM N=100
○2 DR MM N=74

FIGURE 10

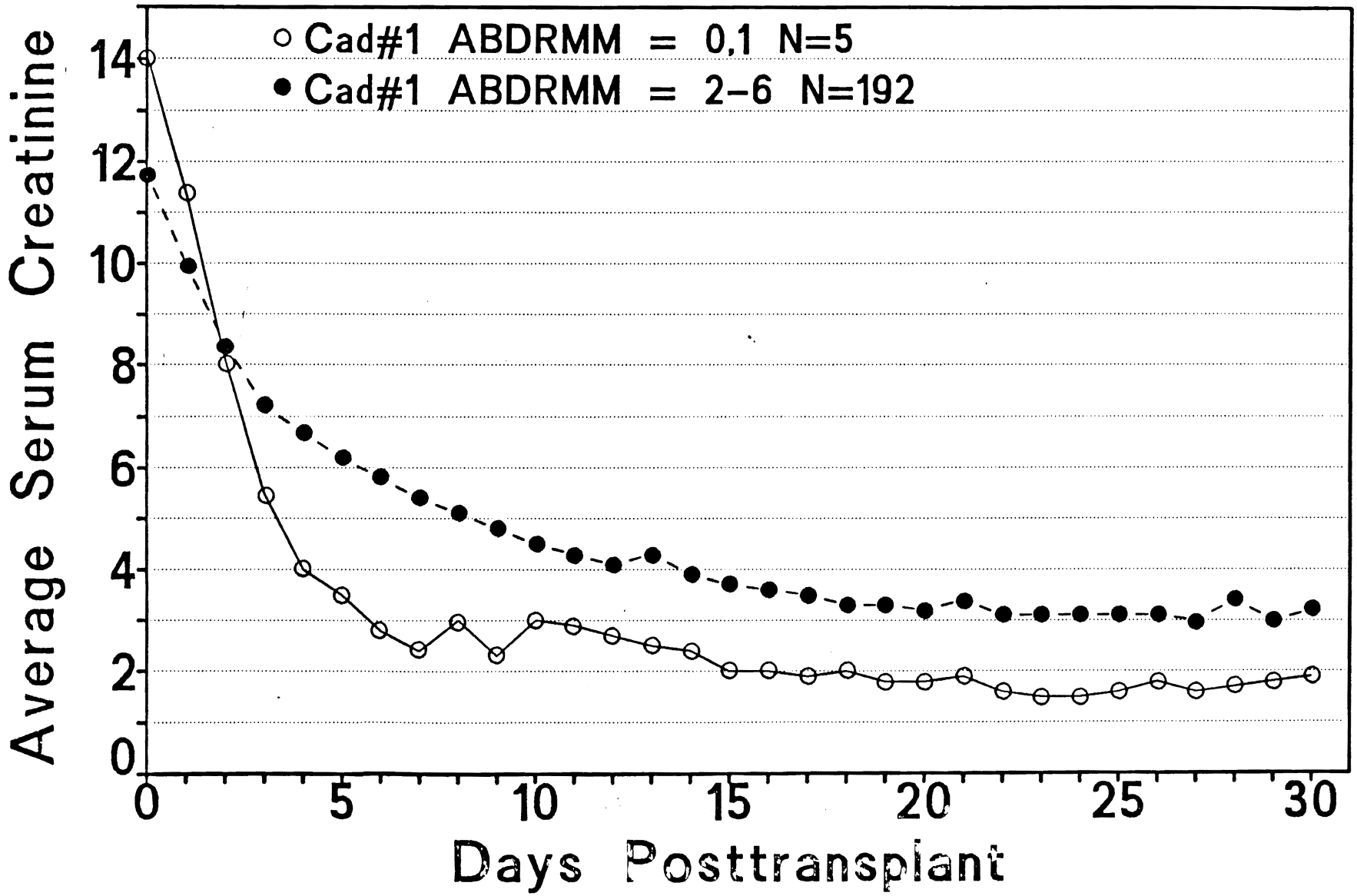

Cad#1 ABDRMM = 0,1 N=5
Cad#1 ABDRMM = 2-6 N=192
Average Serum Creatinine
0
2
4
6
8
10
12
14
0
5
10
15
20
25
30
Days Posttransplant

FIGURE 11

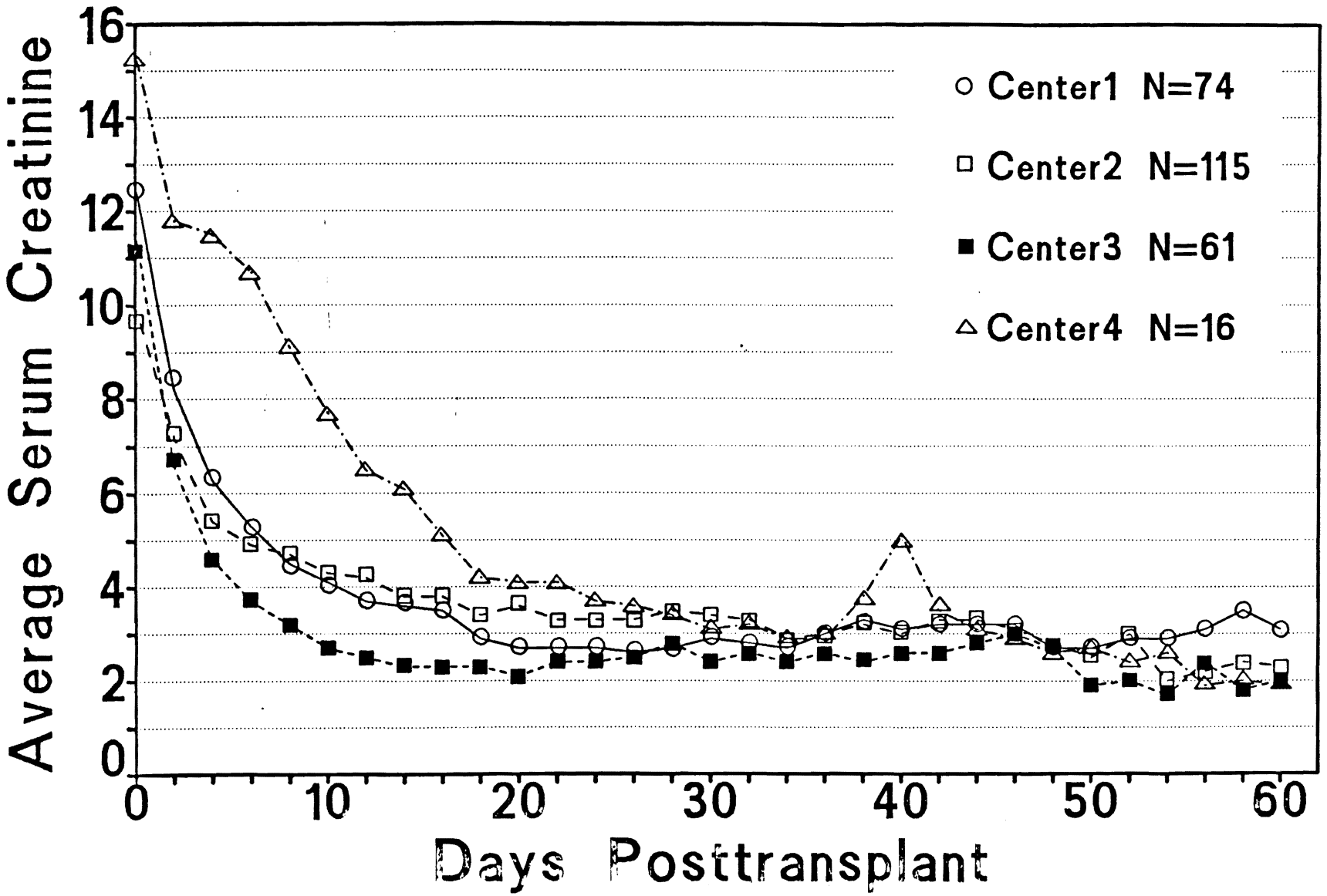

Average Serum Creatinine
16
14
12
10
8
6
4
2
0
0
10
20
30
40
50
60
Days Posttransplant
Center1 N=74
Center2 N=115
Center3 N=61
Center4 N=16

FIGURE 12

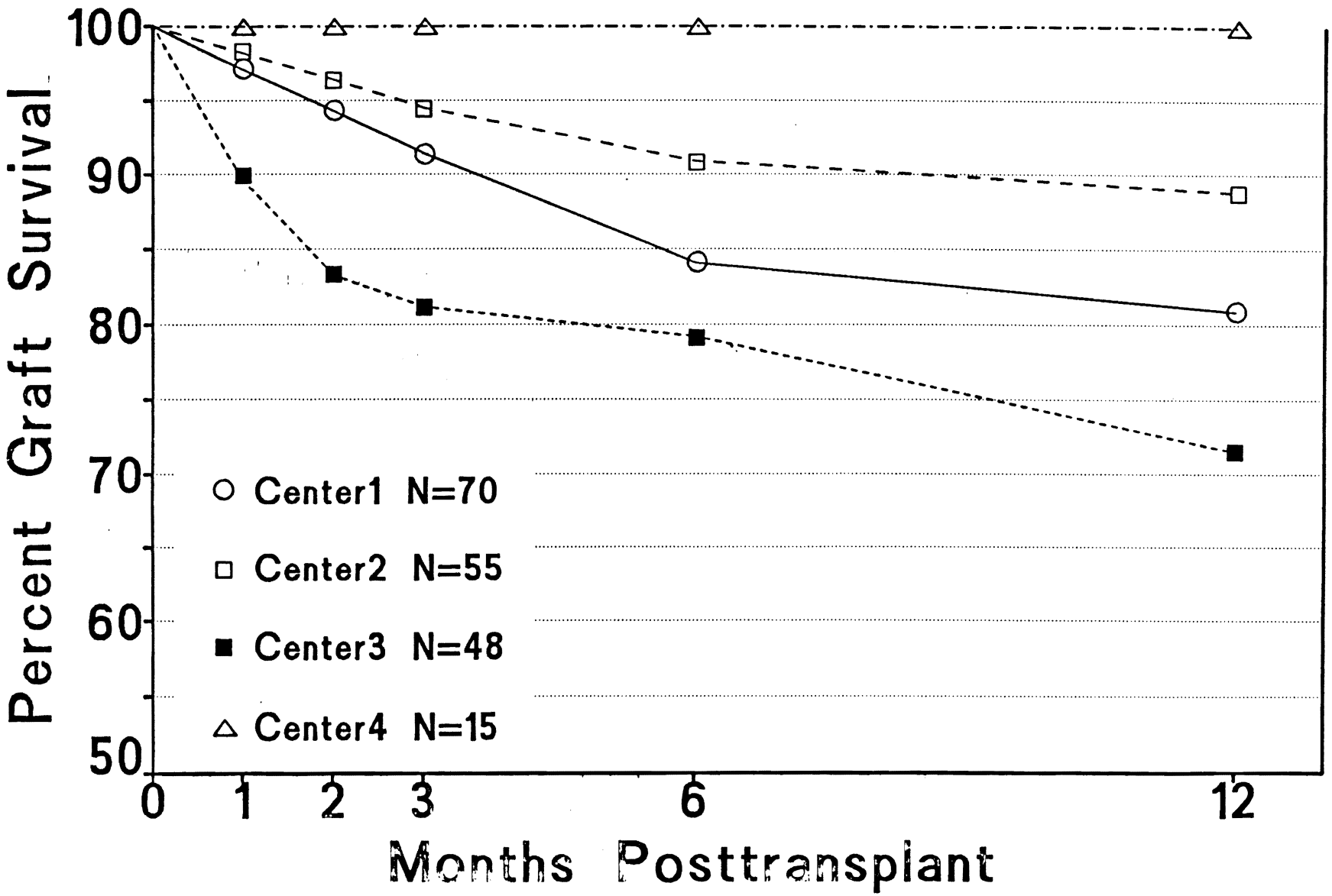

100
90
80
70
60
50
Percent Graft Survival
Center1 N=70
Center2 N=55
Center3 N=48
Center4 N=15
0
1
2
3
6
12
Months Posttransplant

FIGURE 13

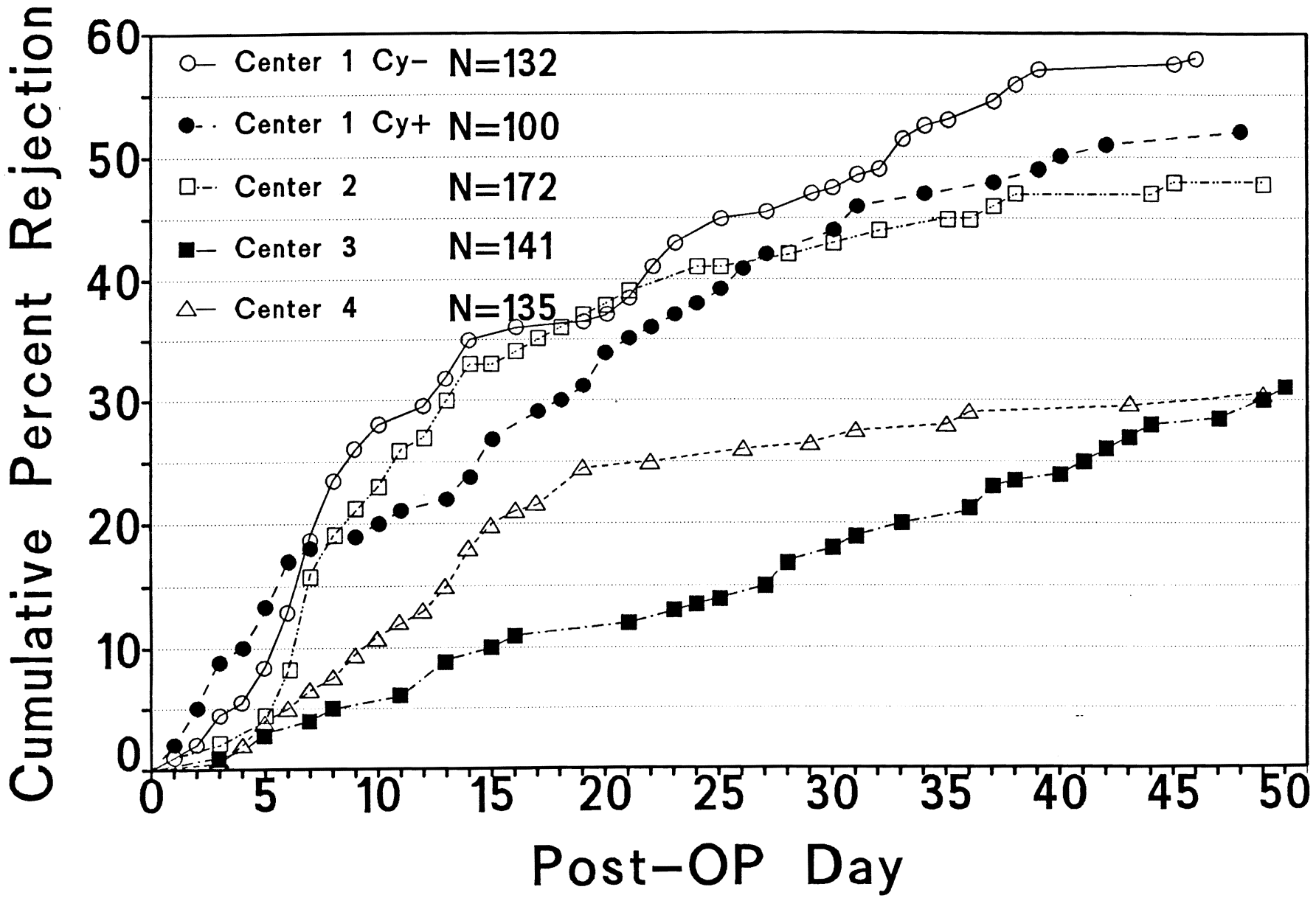

Cumulative Percent Rejection
60
50
40
30
20
10
0
Center 1 Cy- N=132
Center 1 Cy+ N=100
Center 2 N=172
Center 3 N=141
Center 4 N=135
0
5
10
15
20
25
30
35
40
45
50
Post-OP Day

FIGURE 14

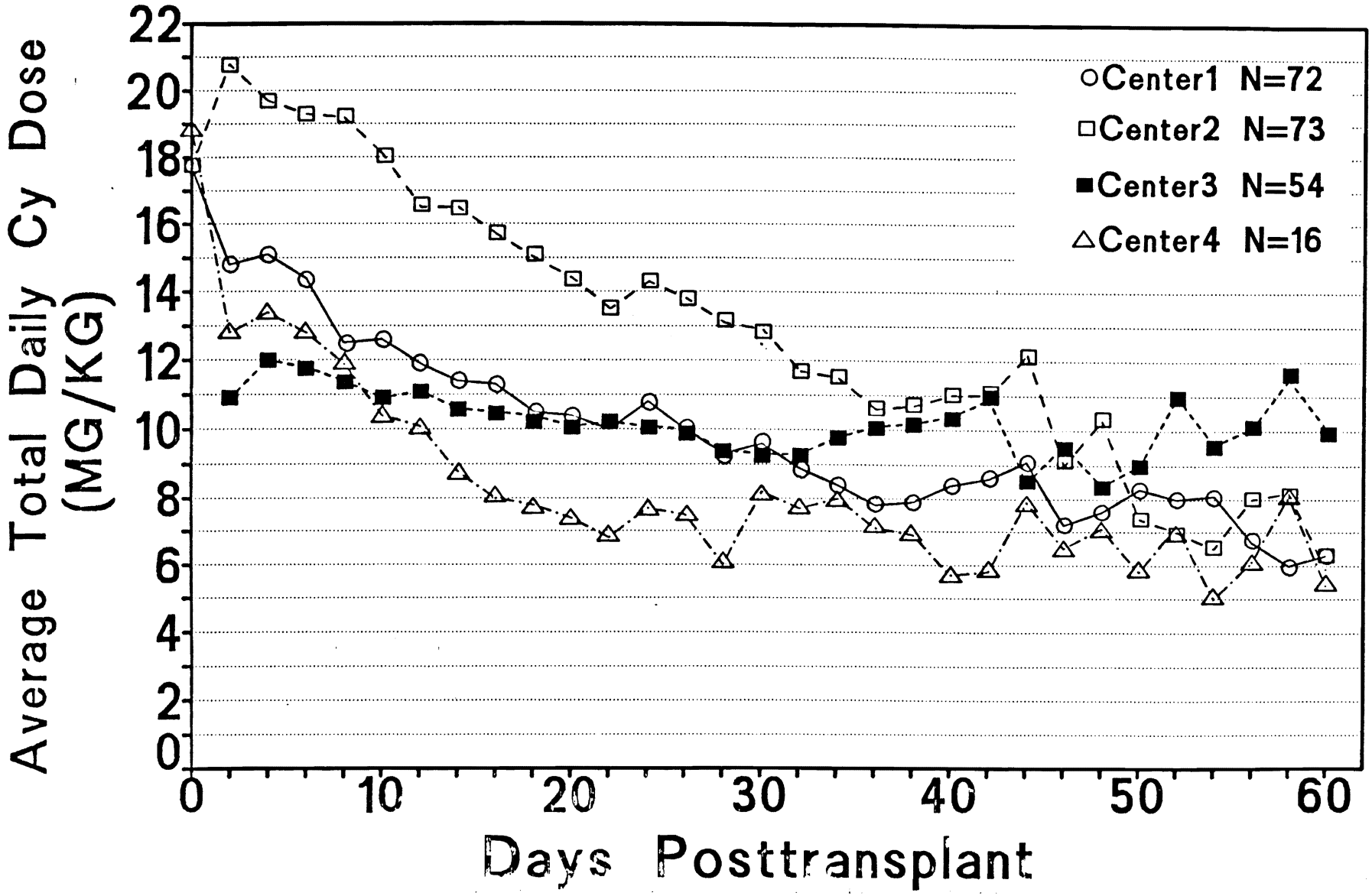

Average Total Daily Cy Dose (MG/KG)
22
20
18
16
14
12
10
8
6
4
2
0
0
10
20
30
40
50
60
Days Posttransplant
Center1 N=72
Center2 N=73
Center3 N=54
Center4 N=16

FIGURE 15

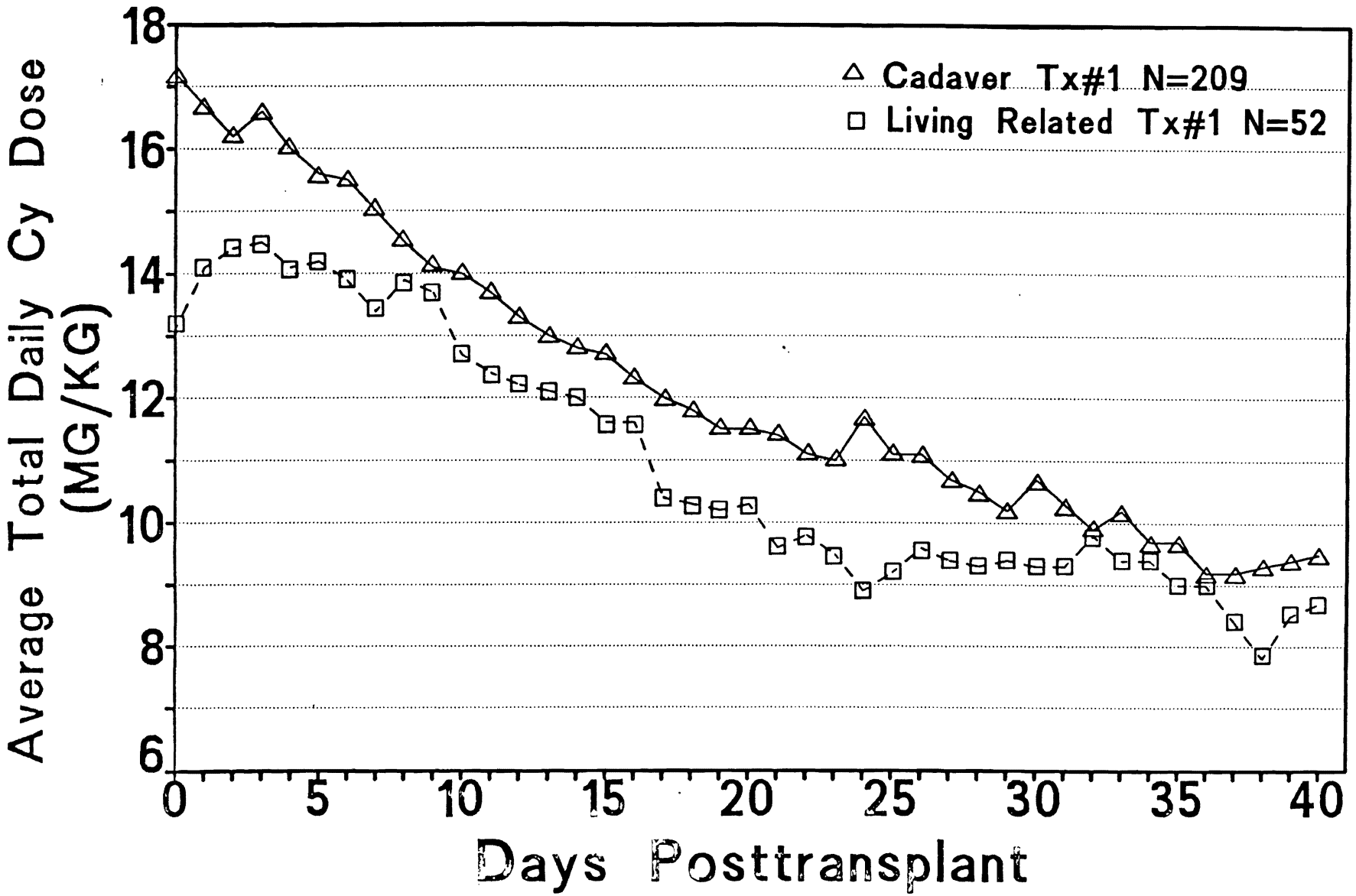

Average Total Daily Cy Dose (MG/KG)
18
16
14
12
10
8
6
0
5
10
15
20
25
30
35
40
Days Posttransplant
Cadaver Tx#1 N=209
Living Related Tx#1 N=52

FIGURE 16

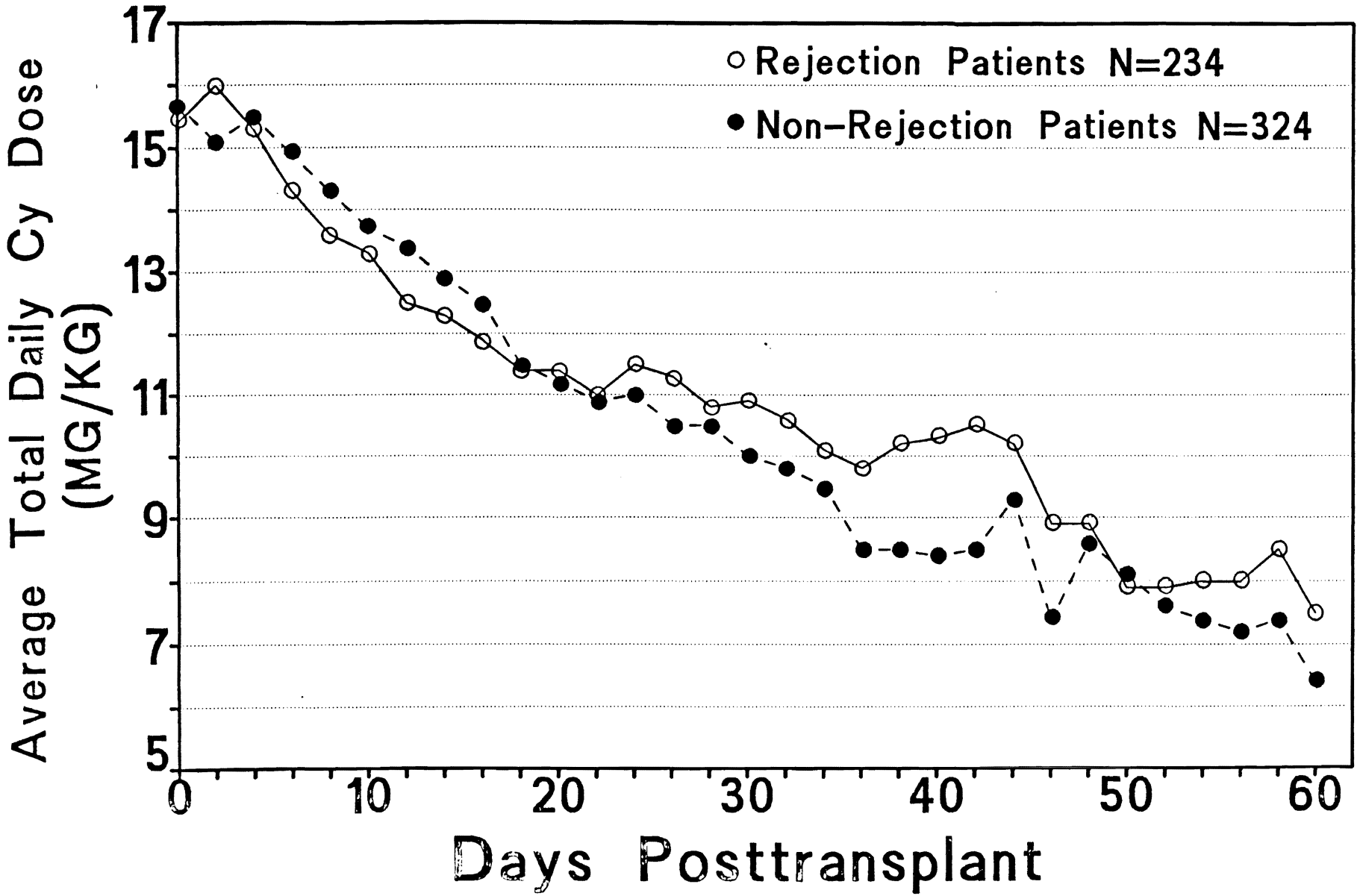

Average Total Daily Cy Dose (MG/KG)
17
15
13
11
9
7
5
0
10
20
30
40
50
60
Days Posttransplant
Rejection Patients N=234
Non-Rejection Patients N=324

FIGURE 17

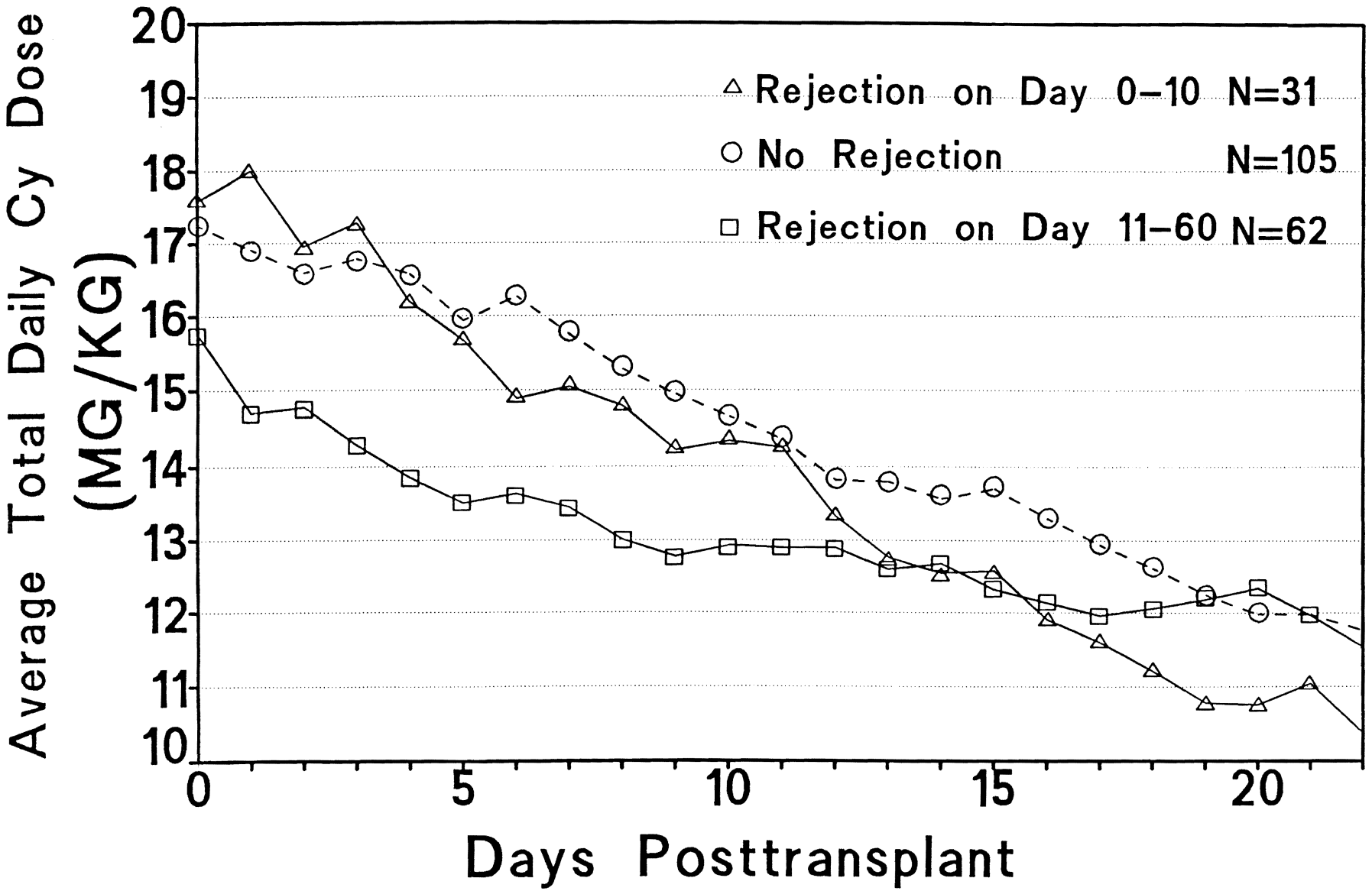

Average Total Daily Cy Dose (MG/KG)
20
19
18
17
16
15
14
13
12
11
10
0
5
10
15
20
Days Posttransplant
Rejection on Day 0–10 N=31
No Rejection N=105
Rejection on Day 11–60 N=62

FIGURE 18

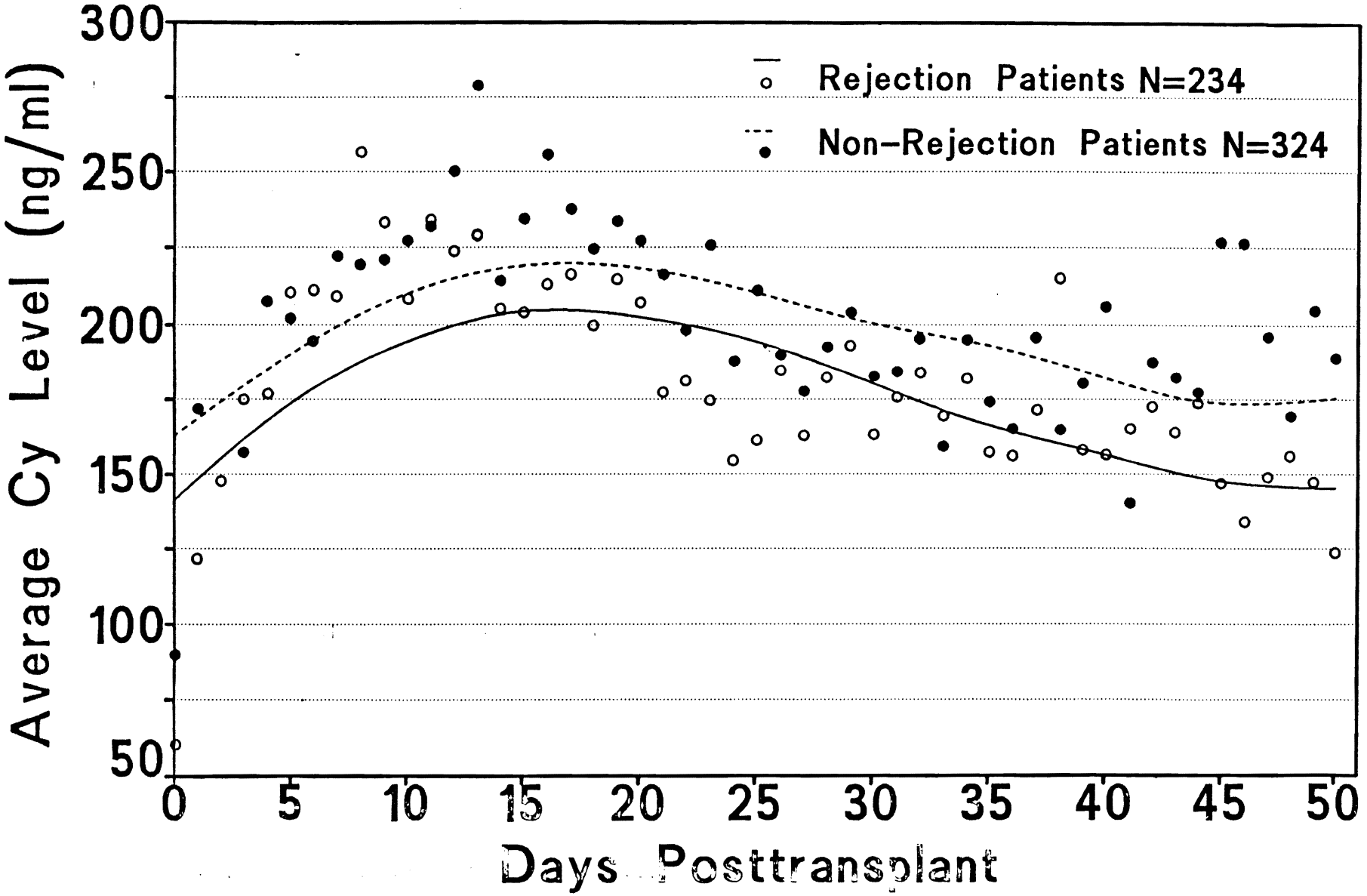

Rejection Patients N=234
Non-Rejection Patients N=324
Average Cy Level (ng/ml)
300
250
200
150
100
50
0
5
10
15
20
25
30
35
40
45
50
Days Posttransplant

FIGURE 19

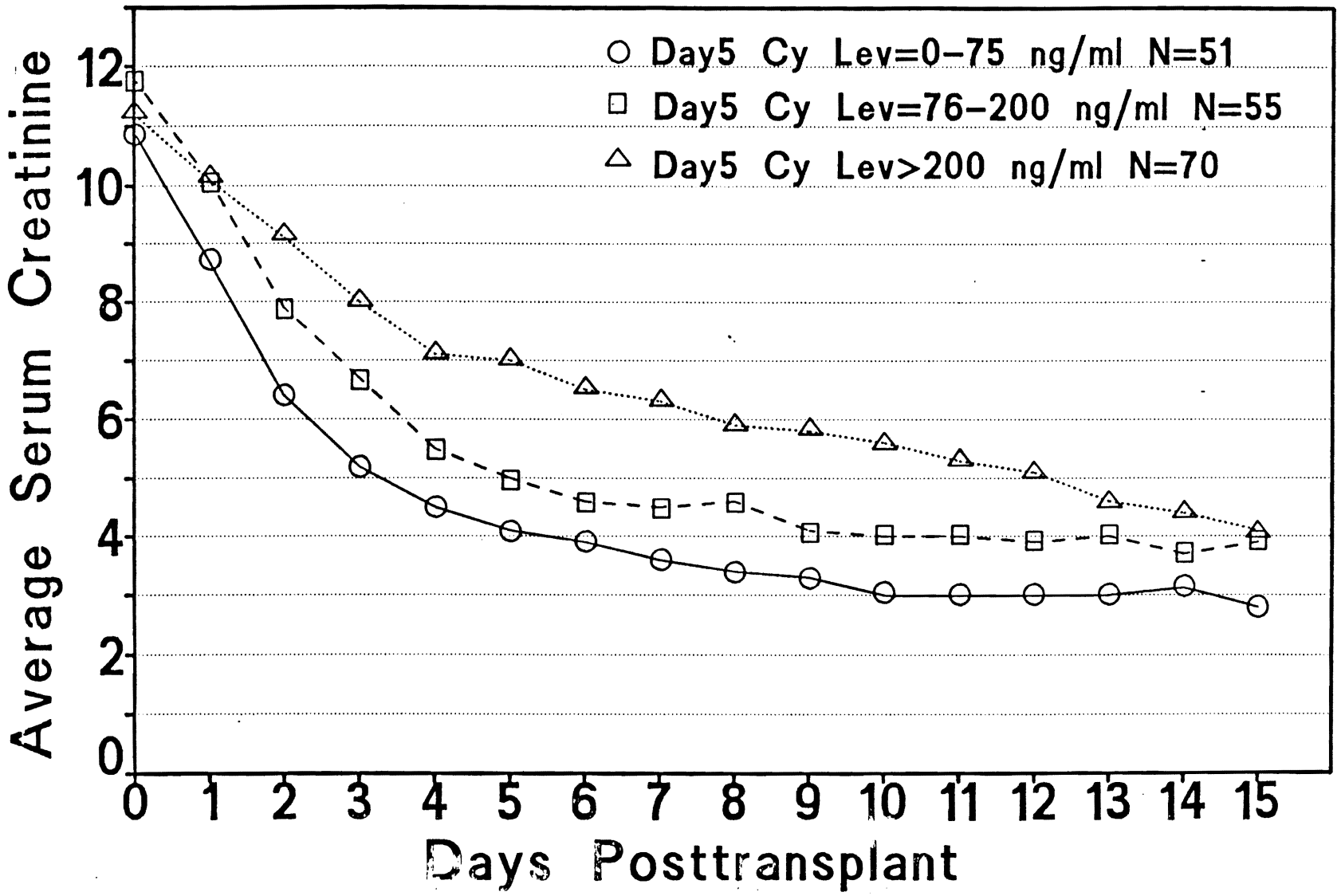
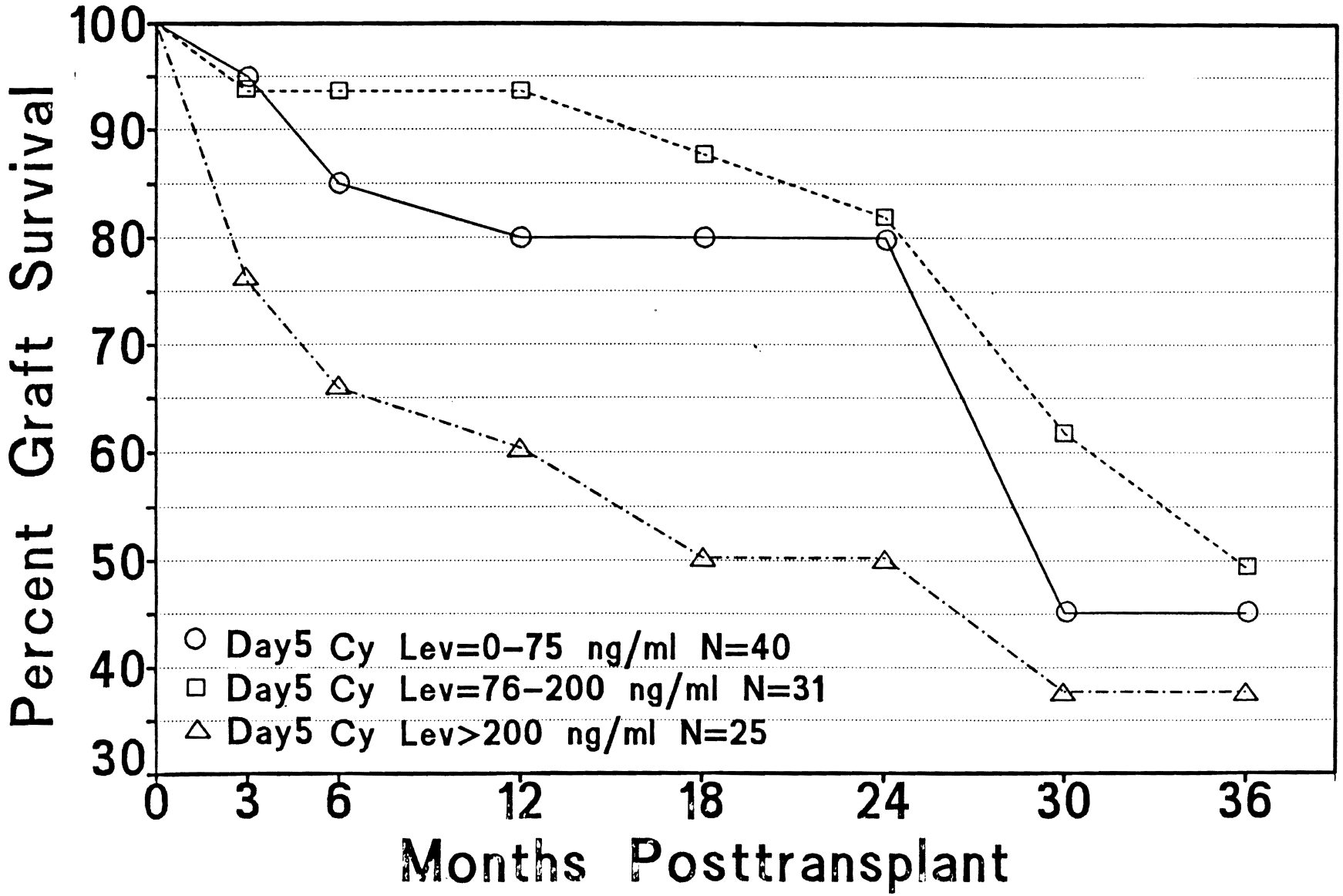

Day5 Cy Lev=0-75 ng/ml N=51
Day5 Cy Lev=76-200 ng/ml N=55
Day5 Cy Lev>200 ng/ml N=70
Average Serum Creatinine
0
2
4
6
8
10
12
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Days Posttransplant

FIGURE 20


Percent Graft Survival
100
90
80
70
60
50
40
30
0
3
6
12
18
24
30
36
Months Posttransplant
Day5 Cy Lev=0-75 ng/ml N=40
Day5 Cy Lev=76-200 ng/ml N=31
Day5 Cy Lev>200 ng/ml N=25