SURVIVORSHIP ANALYSIS OF HEART TRANSPLANT DATA

BY

BRUCE W. TURNBULL and BYRON W. BROWN, JR.

TECHNICAL REPORT NO. 34
OCTOBER 4, 1972

PREPARED UNDER THE AUSPICES
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1. **Introduction**

The purpose of this paper is to investigate in some detail the question of whether the Stanford Heart Transplant Program has prolonged lifetimes in the patients receiving new hearts. Since the transplantations are not done on a randomized basis, the data constitute what has been called by Wold (1966) an observational study. Furthermore, the control group to be used as a basis for comparing survival experience among transplanted patients is not at all clear.

In previous publications, both the Houston group (Mesner, et al., 1969) and the Stanford group (Clark, et al., 1971) used as the control group those patients selected for surgery who did not receive a heart. Gail (1972) pointed out that this was not a fair control group since the principal reason a transplant candidate does not receive a heart is that he dies before a donor can be found. The analyses presented in this paper were developed to take care of this bias, so as to provide a fair assessment of the extension of lifetime effected through heart transplantation.

It should be emphasized here that the following evaluation and discussion is addressed specifically to the question of survival itself. Questions of the quality of life, ethics, psychological aspects, cost, and so forth, are ignored. Further, early and recent patient experience has been aggregated in this paper, with no attempt to detect trends in time.
The Stanford Heart Transplantation Program is continuing at present, with 1-3 operations per month. However, this paper presents and analyzes the data only to the closing date of April 13, 1972. Further results are available and analyses continue, but all the alternative analyses discussed in this paper have not been done in detail for any single, more recent, closing date.

Certain details of the Program are relevant to the following discussions. For each patient entering the Program there is a well-defined conference date on which he is designated officially as a heart transplant candidate. This selection means that it has been determined that he is gravely ill, that he will very likely benefit from a new heart, and that he and his family have consented and seem up to the trial. A donor is then sought and the patient, given survival, receives a heart, usually within a matter of weeks, though occasionally it has taken a month or more.

A very few candidates have survived for a time before transplant, shown noteworthy improvement, and then been "deselected." For our purposes these were considered to be continuing candidates till death or closing date for analysis. As will be seen, one long surviving deselected candidate is a critical factor in the evaluation of the Stanford data.

In the following sections, we first present the data and our notation. In the third section we present two nonparametric methods of evaluating the data. In the fourth section we present three parametric approaches to the problem. In the fifth section we discuss the results, draw our conclusions and make our recommendations.
2. Data and Notation

For each patient in the program we let $t_1$ be his date of acceptance and $t_2$ be the date "last seen" which is either his date of death or the closing date for purposes of analysis (April 13, 1972) if still alive. Also, if the patient received a transplant, then let $t_3$ denote the date of the operation, where of course $t_1 \leq t_3 \leq t_2$. For a patient who did not receive a transplant let $X = t_2 - t_1$ be his survival time in days from date of acceptance. We label the cases such that $X_1, \ldots, X_n$ represent the survival times of those who have died and $X_{n+1}, \ldots, X_N$ represent the times of those still alive. For the group of patients who did receive transplants let $Y = t_3 - t_1$ denote their waiting time for a heart and $Z = t_2 - t_3$ denote their survival time from date of operation. Again we label the variables such that $(Y_j, Z_j), 1 \leq j \leq m$ represent those who have died and $(Y_j, Z_j), m+1 \leq j \leq M$ represent those still living. Note that throughout the entire paper (except section 3.2) subscript $i$ refers to non-transplant, subscript $j$ to transplant. For this study $n = 23, N = 26, m = 26$ and $M = 42$. Thus the total number of cases under study is $N + M = 68$. The data are listed in Table 1.

3. Nonparametric methods

3.1 Actuarial Prediction Test

In this analysis, we first estimate the distribution of the survival time ($T$ say) of all patients entering the study if none were to receive a transplant. We apply the product-limit (PL) method of Kaplan and Meier (1958) using the observations $\{X_i : 1 \leq i \leq n\}$ and treating $\{X_i : n + 1 \leq i \leq N\}$, $\{Y_j : 1 \leq j \leq M\}$ as losses or
right-censored data. Let $t_1^r \leq t_2^r \leq \ldots \leq t_{N+M}^r$ be the ordered values of the pooled $\{X_i\}$ and $\{Y_j\}$. Then the maximum likelihood estimate of the survivorship function $S(t) = \text{Prob}[T > t]$ for $t > 0$ is given by:

$$ \hat{S}(t) = \prod_{r \in R(t)} \frac{[(N+M-r)/(N+M+1-r)]}{}, $$(3.1)

where $R(t)$ is the set of those positive integers for which $t_r^r \leq t$ and $t_r^r$ corresponds to one of the $\{X_i; 1 \leq i \leq n\}$ i.e. a death and not a loss. An estimate of the variance of $\hat{S}(t)$ is given by:

$$ \hat{V}[\hat{S}(t)] = \hat{S}^2(t) \sum_{r \in R(t)} \frac{[(N+M-r)(N+M+1-r)]}{-1}. $$(3.2)

(See Kaplan and Meier (1958, Section 2)). $\hat{S}(t)$ is plotted in Figure 1.

Note that the use of the transplant patient data, $\{Y_j\}$, as losses at the time of transplant, in the estimation of $S(t)$, eliminates a serious bias, contained in the previous papers (Messner, et al., (1969), Clark, et al., (1971)), and pointed out by Gail (1972).

We now proceed to construct a test of the null hypothesis, $H_0$, that heart transplantation has no effect on the survival rate.

Consider only patients who received transplants. For patient $j$ in this group define $V_j = 1$ if he is still alive on the date of analysis and 0 otherwise. Then the conditional probability that patient $j$ would survive to April 13, 1972 (a total of $\bar{U}_j$ days, say, after date of acceptance), given that he survived to the day of transplant, is equal to the conditional expected value of $V_j$, Under the null hypothesis this is given by the ratio $S(\bar{U}_j)/S(Y_j) = P_j$, say.
In calculating values of \( S(t) \) from the Kaplan-Meier function shown in Figure 1, values were interpolated from the dotted line rather than the step function; this yields slightly smaller \( P_j \). The total expected number alive on April 13, 1972 under \( H_0 \) is \( \sum_{j=1}^{M} P_j \). The observed number alive is simply \( M-m = 16 \). Substituting the estimated values of \( S(t) \) in the expression for \( \{P_j\} \) and using the binomial estimate \( \sum_{j=1}^{M} P_j (1-P_j) \) for the variance of \( \sum_{j=1}^{M} V_j \) we have that the statistic

\[
    z = \frac{(M-m) - \sum_{j=1}^{M} P_j}{\sqrt{\sum_{j=1}^{M} P_j (1-P_j)}}
\]  

has approximately a standard normal distribution. On computing \( z \) we obtain a value of \( z = \frac{16 - 14.2}{\sqrt{8.03}} = 0.64 \), with a one-tail normal area of \( P = 26 \) percent.

Thus, what has appeared to be a remarkable number of survivals (16), especially long term survivals, in the Stanford Program, seems to be little more than what might be expected (14.2), as predicted actuarially from pre-transplant survival experience among patients selected for survival.

This analysis can be faulted in several respects, however. First, of course, it is a nonparametric analysis and does not take best advantage of the quantitatively measured survival times by converting them to binary variables indicating survival or death at the closing date. Second, the choice of date for the conversion need not be the closing date. Other dates such as the six month survival may be tried.
The third, and most critical fault in this analysis, is that the
$F_j$, estimated actuarially from pre-transplant experience, are taken
to be exact in calculating the test statistic, $z$. In fact, the
Kaplan-Meier survivorship curve for these data is extremely unstable
past 90 days because few patients survive so long without receiving a
new heart. One patient, whose clinical course improved after selec-
tion, was deselected. He is responsible for the Kaplan-Meier curve
remaining at about 25 percent. If he is removed from the analysis,
the expected number of survivals is markedly lowered (to about 10)
and the calculated value of $z$ is highly significant.

Because of these several faults in the actuarial prediction test,
several other analyses were done and these are presented in succeed-
ing sections.

3.2 A Pseudo-permutation Test

In most situations, permutation tests are available as a means of
analysis, although they are not often used. Cox and Kempthorne (1963)
have described an application of a permutation test to survival data.
Here, because of the observational nature of the data, as opposed to
experimental nature, a permutation test is not available, and in this
section we describe what we call a "pseudo-permutation test."

Suppose that for all 69 cases we could observe a survival time $X$
$= t_0 - t_1$ and a waiting time to transplant $Y$. (Of course, we
cannot observe \( Y \) for a patient who has not received a transplant—we would only know that \( Y \) was greater than \( X \).) Under the null hypothesis, the \( X \)'s are independently and identically distributed, and so are the \( Y \)'s. A test could be constructed by considering all random pairings of the \( Y \)'s and \( X \)'s and calculating the permutation distribution of the statistic \( Z = \frac{1}{v} \sum_{i=1}^{68} \max(X_i - Y_i, 0) \) where \( v \) is the number of \( i \) such that \( X_i - Y_i > 0 \). Thus \( Z \) is a measure of the post-transplant survival. We would then reject \( H_0 \) if the actual observed value of \( Z \) lay in the tail of the permutation distribution of \( Z \).

Since the \( Y_i \) are not all known, these were randomly generated from the estimate of their distribution function obtained by the method of Kaplan and Meier, this time treating the \( \{Y_j : 1 \leq j \leq M\} \) as observations and the \( \{X_i : 1 \leq i \leq N\} \) as losses. For this reason we call this test a "pseudo-permutation test." Also, instead of considering all permutations, 1,000 permutations were generated at random (each permutation involving a new generation of \( Y \)'s also). The observed value of \( Z \) was 280.69 and of the 1,000 generated values, \( \frac{234}{1000} \) were greater than \( Z \), yielding an estimate of the one-tail significance level of \( P = \frac{234}{1000} = 23 \) percent.

4. **Parametric Models**

In order to make the best use of the scanty data available, especially concerning long term survival without transplant, it was felt that a parametric approach would be more appropriate. In this section we propose three parametric models to describe the pre-transplant survivorship function, namely an exponential, a mixture of two
exponentials, and a Pareto. This last can be shown to represent a continuous mixture of exponentials. The unknown parameters for each of the three models will be estimated from the data by the method of maximum likelihood (the most applicable method when censored data are present).

We shall consider alternatives to the null hypothesis in which the hazard function for each patient receiving a new heart is changed by an unknown constant factor $\tau$, and $\tau$ will also be estimated by the method of maximum likelihood. Of course, we do not really believe that cardiac transplantation changes the hazard rates in this way, but certainly if $\tau$ is significantly different from one, then the null hypothesis of no effect can be rejected. Furthermore, whether the hazard is reduced or increased will be indicated by whether $\tau$ is less or greater than one. If we conclude that $\tau$ is not significantly different from one, then this does not rule out some other possible departure from the null hypothesis.

4.1 The Exponential Model

In the first model we assume that every candidate entering the program has a constant hazard rate or risk $\theta_1$. This means an exponential survival curve with mean $1/\theta_1$ days. After the transplant, the constant hazard rate is $\theta_2 = \tau\theta_1$.

By the memoryless property of the exponential distribution, we have that the survival time $Z$ from date of operation for a transplanted patient is independent of the time $Y$ that the patient waited. Hence for this model there is no possibility of selection bias of the kind Gail (1972) hypothesized, and the only reason for using all
patients to get an estimate of the pre-transplant risk, $\theta_1$, is to bolster the sample size and improve the reliability of the estimate.

The likelihood function is given by:

$$
L = \prod_{i=1}^{n} \theta_1 e^{-\theta_1 X_i} \prod_{k=n+1}^{N} e^{-\theta_1 X_k} \prod_{j=1}^{m} \theta_2 e^{-\theta_2 Y_j} \prod_{j=1}^{Z_j} \prod_{j=1}^{M} (\theta_1 y_j + \theta_2 Z_j).
$$

The log likelihood, $L^*$, is:

$$
L^* = n \log \theta_1 + m \log \theta_2 - \theta_1 [\Sigma_{i=1}^{N} X_i] - \theta_2 \Sigma_{j=1}^{M} Y_j - \theta_2 \Sigma_{j=1}^{M} Z_j.
$$

Differentiating $L^*$ with respect to $\theta_1$ and $\theta_2$ and setting the derivatives equal to zero, we obtain the maximum likelihood estimates:

$$
\hat{\theta}_1 = \frac{n}{\Sigma_{i=1}^{N} X_i + \Sigma_{j=1}^{M} Y_j} \quad \text{and} \quad \hat{\theta}_2 = \frac{M}{\Sigma_{j=1}^{M} Z_j}.
$$

(4.1)

(4.2)

By inverting the matrix of second derivatives of $L^*$, we find that $\hat{\theta}_1$ and $\hat{\theta}_2$ are uncorrelated and that asymptotically unbiased variance estimates of $\hat{\theta}_1$ and $\hat{\theta}_2$ are given by $\hat{\sigma}^2_{\theta_1/n}$ and $\hat{\sigma}^2_{\theta_2/m}$ respectively.

The calculated values were as follows:

$$
\hat{\theta}_1 = 7.24 \times 10^{-3} \quad \text{s.d.}(\hat{\theta}_1) = 1.51 \times 10^{-3}
$$

$$
\hat{\theta}_2 = 2.20 \times 10^{-3} \quad \text{s.d.}(\hat{\theta}_2) = 0.43 \times 10^{-3}
$$
Also, by the invariance property of maximum likelihood estimates and Taylor’s series approximations for the standard deviation, we have:

\[ \hat{\tau} = \frac{\hat{\theta}_2}{\hat{\theta}_1} = 0.30 \]

\[ \text{s.d.}(\hat{\tau}) = \frac{\hat{\theta}_2}{\hat{\theta}_1} \left( \frac{1}{n} + \frac{1}{m} \right)^{1/2} = 0.09. \]

We see that \( \hat{\tau} \) is significantly different from one (\( P < .001 \)). Also, \( \hat{\theta}_2 - \hat{\theta}_1 \) is significantly different from zero (\( P < .005 \)).

Under the model, the data support the hypothesis that cardiac transplantation significantly reduces the hazard rate for patients in the program, the reduction being estimated at 70 percent.

4.2 A Mixture of Two Exponentials

In Section 3.1 it was noted that the actuarial prediction approach was very sensitive to the long time survival of one of the deselected patients. In fact, this patient was the difference between a non-significant and a strongly significant result. In the method of Section 4.1, the influence of the deselected patient is suppressed. This method attaches the same pre-transplant hazard rate to all patients and averages all pre-transplant experience to estimate this rate. Post-transplant data does not influence the pre-transplant estimate.

The serious disagreement between the two approaches to evaluation of the evidence suggests that the exponential model be modified. We assume that there are two "types" or populations of accepted candidates. A proportion \( 1-c \) (\( 0 \leq c \leq 1 \)) of the patients are "regular"
and all have constant hazard rate $\theta$; the remainder are "hardy" patients and have a constant hazard rate $\varphi$ where $\varphi < \theta$. Thus, we are assuming that the survival time distribution of all patients entering the program has density:

$$(1-c)e^{-\theta t} + ce^{-\varphi t}, \quad (t \geq 0). \quad (4.3)$$

(Note that if we set $\varphi = 0$ then $c$ represents a "cure rate" and the model is similar to that first considered by Boag (1949) for lognormal distributions.)

Again one can assume that after transplantation the hazard rates $\theta$ and $\varphi$ are multiplied by the same constant factor $\tau$, write down the likelihood function, and maximize it by numerical methods, since the four likelihood equations cannot be solved explicitly. However, this model suggests the more realistic model of the next section, and we pursued this more appealing model, though we believe both models would yield the same insights.

4.3 The Pareto Model: An Empirical Bayes Approach

In this third parametric model we again assume that each candidate prior to transplant has a constant force of mortality or hazard, $\theta$. However, it is reasonable to assume that $\theta$ varies from patient to patient and is in fact a random variable with some prior probability distribution. Denote this random variable by $\Theta$. Recall that $T$ denoted the lifetime of a candidate from date of acceptance to death if no transplant were performed. Thus the conditional density of $T$ given $\Theta$ is
\[ f_{T|\theta}(t|\theta) = \theta e^{-\theta t} \quad (t \geq 0). \quad (4.4) \]

For \( \theta \), it is convenient to take the prior distribution to have a gamma density i.e.

\[ f_{\theta}(\theta) = \frac{\lambda}{\Gamma(p)} (\lambda\theta)^{p-1} e^{-\lambda\theta} \quad (4.5) \]

where, following the empirical Bayes method, \( p \) and \( \lambda \) will be estimated from the data. Note that the gamma distributions form a "rich" class of prior distributions for \( \theta \).

The marginal density of \( T \) is given by

\[ f_T(t) = \int_{0}^{\infty} f_{T|\theta}(t|\theta)f_{\theta}(\theta)d\theta = \frac{p\lambda^p}{(\lambda+t)^{p+1}} \]

and so \( T \) has a Pareto distribution. It should be remarked here that the two previous models may also be considered in this way where \( \theta \) has respectively a prior one point or two point distribution.

The Pareto model can be considered as the continuous mixture of infinitely many exponential distributions and has previously been used to describe response time distributions in a variety of situations (see, for example, Maguire, Pearson and Wynn (1952); Anscombe (1961); Massy, Montgomery and Morrison (1970); and Fox and Kraemer (1971)).

As before, we consider alternatives to the null hypothesis where transplantation changes each patient constant risk by an unknown constant factor \( \tau (>0) \) which is common to all patients. The likelihood function is given by:
\[ L = \prod_{i=1}^{n} \int_{\theta_i}^{\infty} e^{-\theta_i X_i} f_\theta(\theta_i) d\theta_i \]
\[ \cdot \prod_{i=n+1}^{N} e^{-\theta_i X_i} f_\theta(\theta_i) d\theta_i \]
\[ \cdot \prod_{j=1}^{m} (\tau \theta_j) e^{-\theta_j (Y_j + TZ_j)} f_\theta(\theta_j) d\theta_j \]
\[ \cdot \prod_{j=m+1}^{M} e^{-\theta_j (Y_j + TZ_j)} f_\theta(\theta_j) d\theta_j. \]

Here we have integrated out the variables \( \{\theta_i\} \) using the prior density \( f_\theta \) given by (4.5). This is called a Type II likelihood by Good (1965, page 35).

Performing the integrations we obtain:

\[ L = \prod_{i=1}^{n} \left( \frac{p \lambda^p}{(\lambda + X_i)^{p+1}} \right) \prod_{i=n+1}^{N} \left( \frac{\lambda}{\lambda + X_i} \right)^p \]
\[ \cdot \prod_{j=1}^{m} \left( \frac{\tau \lambda^p}{(\lambda + Y_j + TZ_j)^{p+1}} \right) \prod_{j=m+1}^{M} \left( \frac{\lambda}{\lambda + Y_j + TZ_j} \right)^p. \]

Thus, the log likelihood, \( L^* \), becomes:

\[ L^* = m \log \tau + (N+M)p \log \lambda + (m+n) \log p \]
\[ - (p+1) \sum_{i=1}^{n} \log(\lambda + X_i) - p \sum_{i=n+1}^{N} \log(\lambda + X_i) \]
\[ - (p+1) \sum_{j=1}^{m} \log(\lambda + Y_j + TZ_j) - p \sum_{j=m+1}^{M} \log(\lambda + Y_j + TZ_j) \]
To obtain the estimates \( \hat{p}, \hat{\lambda}, \hat{\tau}, \) \( L^* \) was maximized by three dimensional search, and the values were checked by direct calculation and by calculation of the partial derivatives. The results were:

\[
\hat{p} = 0.45, \quad \hat{\lambda} = 23, \quad \hat{\tau} = 0.86.
\]

By inverting the matrix of second derivatives, we can obtain an asymptotically unbiased estimate of the covariance matrix of \( \hat{p}, \hat{\lambda}, \) and \( \hat{\tau}, \) given by:

\[
\begin{pmatrix}
0.013 & 0.57 & -0.025 \\
47.1 & -0.61 & \\
& & 0.015
\end{pmatrix}
\]

Thus, we have: \( \text{s.d.}(\hat{p}) \doteq 0.115, \) \( \text{s.d.}(\hat{\lambda}) \doteq 6.86 \) and \( \text{s.d.}(\hat{\tau}) \doteq 0.39. \)

This analysis is in agreement with the nonparametric evaluations and in marked disagreement with the analysis based on the exponential model. The results indicate some reduction in hazard (14 percent), but nothing approaching statistical significance. In fact, this parametric empirical Bayes approach seems to attach even less weight to the evidence for transplantation than do the nonparametric approaches. The reason for this is that the Pareto model seems to take the several very long term survivals among the transplants into account, not so much by decreasing \( \tau, \) but by an increase in the variability of the pre-transplant expectation of survival. In other words, it attributes the longevity of some transplant patients to their lower initial risks \( (\hat{\eta}_i), \) rather than to any substantial overall reduction, \( \tau, \) in risk.
It should be noted that the survival curves for the exponential and nonparametric models are based only on pre-transplant information i.e. \( \{X_j, Y_j \mid 1 \leq i \leq N, 1 \leq j \leq M \} \). On the other hand, the empirical Bayes approach allows the post-transplant information \( \{Z_j \mid 1 \leq j \leq M \} \) to play a role in the estimation of the distribution of risks for all patients entering the program.

If one wants to estimate the pre-transplant survival curve using the Pareto model, without benefit of the post-transplant data, one can proceed as follows. The likelihood function for the pre-transplant "experience" only is:

\[
L = \prod_{i=1}^{n} \frac{p^\lambda}{(\lambda + X_i)^{p+1}} \prod_{i=n+1}^{N} \frac{\lambda^p}{(\lambda + X_i)^{p}} \prod_{j=1}^{M} \frac{\lambda_j^p}{(\lambda + Y_j)^{p}}.
\]

Setting \( \frac{\partial \log L}{\partial p} \) and \( \frac{\partial \log L}{\partial \lambda} \) equal to zero, we obtain

\[
\hat{p} = 0.47 \quad \hat{\lambda} = 24
\]

with standard deviations of 0.30 and 24.3, respectively, very close to the estimates obtained using all the data. Thus, the estimate of distribution of the initial risks for patients entering the program is virtually the same whether or not the experience of post-transplant patients is taken into account.

Using \( \hat{p} \) and \( \hat{\lambda} \), one could now estimate \( \tau \) by a method of moments approach. If we knew the \( \{\theta_j\} \) we would use \( m/\sum_{j=1}^{M} \theta_j Z_j \) to estimate \( \tau \), however, since the \( \theta_j \) are unknown, we replace them by estimates \( \hat{\theta}_j = \hat{p}/(\hat{\lambda} + Y_j) \), since
\[
\mathbb{E}[\theta|T > \tau] = \frac{p}{\lambda + \tau}
\]
(4.6)

(using (4.4) and (4.5)). From this method we obtain

\[
\tilde{\tau} = \frac{m}{\sum_{j=1}^{M} \tilde{\theta}_j Z_j} = 0.22
\]

but since no estimate of the standard deviation of \( \tilde{\tau} \) is available, this estimate is not very useful. However, it does agree more closely with the estimate of \( \tau \) obtained under the exponential model.

It is also interesting to note that \( 1/\tilde{\sigma} \), the estimated mean survival time, is linear in the waiting time \( Y \) and this suggests that the method of Feigl and Zelen (1965) might be applicable, using the waiting time \( Y \) as the concomitant variable.

Note that \( \tilde{p} \) and \( \tilde{\lambda} \) agree very well with \( \hat{p} \) and \( \hat{\lambda} \), while \( \tilde{\tau} \) disagrees radically from the estimate \( \hat{\tau} \). We conclude that the several long term survivors among the patients receiving hearts do not change our estimate of the distribution of risks for patients accepted for the program. When we allow post-transplant experience to play a role in estimating these risks, the benefit of surgery is in doubt (\( \hat{\tau} \) not significantly different from one). However, if we ignore post-transplant experience in estimating pre-transplant risk for the individual patients, the empirical Bayes approach is forced to assign all early transplants something close to the mean prior risk, \( p/\lambda \), no matter how long they survive after transplant. Thus we might expect the results to be similar to those of the constant risk exponential model, and, indeed, we see that \( \tilde{\tau} \) is quite close to the estimate \( \hat{\tau} = 0.30 \) obtained in Section 3.1. In this case we had that \( \tau \) was significantly different from one and the benefits of surgery seemed quite apparent.
5. **Conclusion**

With regard to the single scientific question addressed in this paper—does cardiac transplantation at Stanford prolong life—our answer cannot be definitive. All evaluations suggest that it does. However, the long term survival of one deselected patient demonstrates the possibility that certain of the patients receiving hearts might have done well without a new heart. Any model allowing a broad spectrum of incoming risks, nonparametric or parametric, will acknowledge such possibilities and _will not_ reject the null hypothesis. Any model that assumes constant or nearly constant risks for most transplanted patients _will_ reject the null hypothesis. Without additional data on the long term prognosis for survival for the patient who does not receive a heart, the matter will remain in doubt.

On the basis of other considerations, such as the improved quality of life for the patient receiving a new heart, the continuation of the Stanford Program as a study without randomized controls seems justified, but the results reported here have stimulated renewed effort to obtain more useful data on prognosis.

6. **Acknowledgements**

We are indebted to the Stanford Heart Transplantation Program, and, in particular, to Dr. Eugene Dong, for asking us to carry out this analysis, for making the data available, and for his continuing interest and helpful comments. We are grateful to Professors Rupert Miller and Bradley Efron for their interest and comments; Mrs. Marie Hu carried out the extensive calculations on various sets of data over the past two years, using many approaches; her help is gratefully acknowledged.
7. References


Table 1

Survival Times and Times to Transplant for 69 Stanford Patients
(Closing Date: April 13, 1972)

<table>
<thead>
<tr>
<th>Nontransplant Patients</th>
<th>Transplant Patients</th>
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</thead>
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<td>( \frac{1}{Y} )</td>
</tr>
<tr>
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<td>( \frac{1}{Z} ) alive=a</td>
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<tr>
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\( \frac{1}{x} \) = days to death or closing date
\( \frac{1}{y} \) = days to transplant
\( \frac{1}{z} \) = days from transplant to death or closing date
\( 2/ \) = deseleced patients