

Kaplan–Meier Estimator

The Kaplan–Meier estimator is a **nonparametric** estimator which may be used to estimate the **survival distribution** function from **censored data**. The estimator may be obtained as the limiting case of the classical actuarial (**life table**) estimator, and it seems to have been first proposed by Böhmer [2]. It was, however, lost sight of by later researchers and not investigated further until the important paper by Kaplan & Meier [12] appeared. Today the estimator is usually named after these two authors, although sometimes it is denoted the product–limit estimator (*see* **Aalen–Johansen Estimator**). Below we describe the Kaplan–Meier estimator, illustrate its use in one particular case, and discuss estimation of the median and mean survival times. Furthermore, we show how the Kaplan–Meier estimator can be given as the product–integral of the **Nelson–Aalen estimator**, and indicate how this may be used to study its statistical properties. For almost four decades the Kaplan–Meier estimator has been one of the key statistical methods for analyzing censored survival data, and it is discussed in most textbooks on survival analysis. Rigorous derivations of the statistical properties of the estimator are provided in the books by Fleming & Harrington [7] and Andersen et al. [1]. In particular the latter presents formal proofs of almost all the results reviewed below as well as an extensive bibliography.

The Estimator and Confidence Intervals

Consider the survival data situation where we want to study the time to death (or some other event) for a homogeneous population with survival distribution function $S(t)$ representing the probability that an individual will be alive at time t . Assume that we have a sample of n individuals from this population. Our observation of the survival times for these individuals will typically be subject to right-censoring, meaning that for some individuals we only know that their true survival times exceed certain censoring times. The censoring is assumed to be independent in the sense that the additional knowledge of censorings before any time t does not alter the risk of failure at t . We denote by $t_1 < t_2 < \dots$ the times when deaths are observed and let d_j be the number of individuals who die at t_j .

The Kaplan–Meier estimator for the survival distribution function then takes the form

$$\hat{S}(t) = \prod_{t_j \leq t} \left(1 - \frac{d_j}{r_j}\right), \quad (1)$$

where r_j is the number of individuals at risk (i.e. alive and not censored: in the **risk set**) just prior to time t_j . If there are no censored observations, then (1) reduces to one minus the empirical distribution function. The variance of the Kaplan–Meier estimator is estimated by Greenwood’s formula:

$$\hat{\sigma}^2(t) = \hat{S}(t)^2 \sum_{t_j \leq t} \frac{d_j}{r_j(r_j - d_j)}. \quad (2)$$

In the case of no censoring, (2) reduces to $\hat{S}(t)[1 - \hat{S}(t)]/n$, the standard **binomial** variance estimator.

In large samples the Kaplan–Meier estimator, evaluated at a given time t , is approximately normally distributed so that a standard $100(1 - \alpha)\%$ confidence interval for $S(t)$ takes the form

$$\hat{S}(t) \pm z_{1-\alpha/2} \hat{\sigma}(t), \quad (3)$$

with $z_{1-\alpha/2}$ the $1 - \alpha/2$ fractile of the **standard normal** distribution. The approximation to the normal distribution is improved by using the log-minus-log transformation (*see* **Quantal Response Models**) giving the **confidence interval**

$$\hat{S}(t)^{\exp\{\pm z_{1-\alpha/2} \hat{\sigma}(t) / [\hat{S}(t) \ln \hat{S}(t)]\}}. \quad (4)$$

This interval is satisfactory for quite small sample sizes [3]. Confidence intervals with small-sample properties which are comparable with (4), or even slightly better, may be obtained by using the arcsine-square-root transformation [3] or by basing the confidence interval on the **likelihood ratio test** [5, Section 4.3; 16]. Note that all these confidence intervals should be given a pointwise interpretation. Simultaneous confidence bands for the survival distribution function are considered below.

Right-censoring is not the only kind of data incompleteness in survival analysis. Often, e.g. in epidemiologic applications, individuals are not followed from time zero (in the relevant time scale, typically age), but only from a later entry time (conditional on survival until this entry time). Thus, in addition to right-censoring, the survival data are subject to left truncation. For such data we may, in

principle at least still use the Kaplan–Meier estimator (1) and estimate its variance by (2). The number at risk, r_j , is now the number of individuals who have entered the study before time t_j and are still in the study just prior to t_j . However, for left-truncated data the numbers at risk, r_j , will often be low for small values of t_j . This will result in estimates $\hat{S}(t)$ which have large sampling errors and which therefore may be of little practical use. What can be usefully estimated in such situations is the conditional survival distribution function, $S(t|t_0) = S(t)/S(t_0)$, representing the probability of survival to time t given that an individual is alive at time $t_0 < t$. It may be useful to estimate such conditional distribution functions for several values of t_0 (at which there are reasonable numbers at risk), there being nothing canonical about any particular value. The estimation is performed as described earlier, the only modification being that the product in (1) and the sum in (2) are restricted to those t_j for which $t_0 < t_j \leq t$.

An Illustration

As an illustration we use data from a randomized clinical trial for patients with histologically verified liver cirrhosis. Patients were recruited from several hospitals in Copenhagen between 1962 and 1969 and were followed until death, lost to follow-up, or until the closing date of the study, October 1, 1974. The time variable of interest is time since entry into the study. Patients are right censored if alive on October 1, 1974, or if lost to follow-up before that date.

We consider only the 138 placebo-treated male patients. Their median age at entry was 57 years, while the lower and upper quartiles were 51 and 66 years, respectively. Of the 138 patients, 88 died during the study. The Kaplan–Meier estimate of the survival distribution function for these patients is shown in Figure 1 with 95% confidence intervals computed according to (4). From the figure we see, for example, that the five years survival probability is estimated as 43.0% with a 95% confidence interval from 34.0% to 51.9%, while the estimated 10 years survival probability is 18.4% with a confidence interval from 9.7% to 29.3%. We return to the liver cirrhosis example below in connection with median and mean survival times and simultaneous confidence bands. A further discussion and analy-

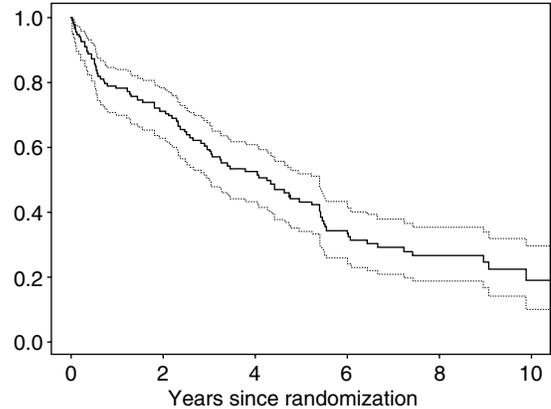


Figure 1 Kaplan–Meier estimate of the survival distribution function for 138 placebo-treated male patients with liver cirrhosis with 95% log-minus-log-transformed confidence intervals

sis of the data are given by Schlichting et al. [15]. The data were also used for illustrative purposes by Andersen et al. [1].

Median Survival Time and Related Quantities

The use of the Kaplan–Meier estimator is not restricted to estimating survival probabilities for given times t . It may also be used to estimate fractiles such as the **median survival time** and related quantities like the interquartile range (*see Quantiles*).

Consider the p th fractile, ξ_p , of the cumulative distribution function $F(t) = 1 - S(t)$, and assume that $F(t)$ has a positive density function $f(t) = F'(t) = -S'(t)$ in a neighborhood of ξ_p . Then ξ_p is uniquely determined by the relation $F(\xi_p) = p$, or equivalently, $S(\xi_p) = 1 - p$. The Kaplan–Meier estimator is a step function and hence does not necessarily attain the value $1 - p$. Therefore a similar relation cannot be used to define the estimator $\hat{\xi}_p$ of the p th fractile. Rather, we define $\hat{\xi}_p$ to be the smallest value of t for which $\hat{S}(t) \leq 1 - p$, i.e. the time t where $\hat{S}(t)$ jumps from a value greater than $1 - p$ to a value less than or equal to $1 - p$. In large samples $\hat{\xi}_p$ is approximately normally distributed with a variance that may be estimated by

$$\widehat{\text{var}}(\hat{\xi}_p) = \frac{(1 - p)^2 \hat{\sigma}^2(\hat{\xi}_p)}{[\hat{f}(\hat{\xi}_p) \hat{S}(\hat{\xi}_p)]^2}. \quad (5)$$

Here $\hat{f}(t)$ is an estimator for the density function $f(t) = -S'(t)$ (see **Density Estimation**). One may, for example, use

$$\hat{f}(t) = \frac{1}{2b} [\hat{S}(t-b) - \hat{S}(t+b)] \quad (6)$$

for a suitable bandwidth b (corresponding to a kernel function estimator with uniform kernel). Furthermore, for $p < q$, $\hat{\xi}_p$ and $\hat{\xi}_q$ are approximately binnormally distributed, and their correlation may be estimated by

$$\widehat{\text{corr}}(\hat{\xi}_p, \hat{\xi}_q) = \frac{\hat{\sigma}(\hat{\xi}_p)\hat{S}(\hat{\xi}_q)}{\hat{\sigma}(\hat{\xi}_q)\hat{S}(\hat{\xi}_p)}. \quad (7)$$

Note that $\hat{S}(\hat{\xi}_p)$ in (5) and (7) is equal to or only slightly less than $1 - p$, and that (5) could have been simplified if we had used this approximate equality. We have chosen not to do so since then $\hat{S}(\hat{\xi}_p)$ in (5) and (7) cancels with the same factor in $\hat{\sigma}(\hat{\xi}_p)$; cf. (2).

The above results may be used in the usual way to determine approximate confidence intervals, e.g. for the median survival time $\xi_{0.50}$ and the interquartile range $\xi_{0.75} - \xi_{0.25}$, as illustrated below. For the purpose of determining a confidence interval for a quantile (fractile) like the median it is, however, better to apply the approach of Brookmeyer & Crowley [4]. For the p th fractile one then uses as a confidence interval all hypothesized values ξ_p^0 of ξ_p which are not rejected when testing the null hypothesis $\xi_p = \xi_p^0$ against the alternate hypothesis $\xi_p \neq \xi_p^0$ at the α level (see **Hypothesis Testing**). Such test-based confidence intervals can be read directly from the lower and upper confidence limits for the survival distribution function in exactly the same manner as $\hat{\xi}_p$ can be read from the Kaplan–Meier curve itself (see **Median Survival Time**).

For the liver cirrhosis data an estimate of the median survival time is 4.27 years (standard error 0.66 years), while the lower and upper quartiles are estimated as 1.46 years (0.35 years) and 8.97 years (1.13 years), respectively, with an estimated correlation of 0.28. In these computations the bandwidth $b = 1$ year was used in (6). An estimate of the interquartile range of the survival distribution function is $8.97 - 1.46 = 7.51$ years, with standard error $(0.35^2 + 1.13^2 - 2 \times 0.35 \times 1.13 \times 0.28)^{1/2} = 1.09$ years. From this an approximate 95% confidence interval for the median survival time is $4.27 \pm 1.96 \times 0.66$, i.e. from 2.98 to 5.56 years, while 95%

confidence limits for the interquartile range are from 5.37 to 9.65 years. For the median survival time it is, as mentioned earlier, better to read the confidence limits directly from the pointwise confidence intervals for the survival distribution function given in Figure 1. This gives 95% confidence limits for the median survival time from 3.02 years to 5.41 years. Note that no estimate of the density function is needed here.

Mean Survival Time

Owing to right-censoring, in most survival studies it will not be possible to obtain reliable estimates for the mean survival time $\mu = \int_0^\infty tf(t) dt = \int_0^\infty S(t) dt$ (see **Life Expectancy**). This is one important reason why, in survival analysis, the median is a more useful measure of location than the mean. What may be usefully estimated from right-censored survival data is the expected time lived in a given interval $[0, t]$, i.e. $\mu_t = \int_0^t S(u) du$. This is estimated by

$$\hat{\mu}_t = \int_0^t \hat{S}(u) du,$$

the area below the Kaplan–Meier curve between 0 and t . Such an estimate may be of interest in its own right, or it may be compared with a similar population-based estimate to assess the expected number of years lost up to time t for a group of patients. In large samples, $\hat{\mu}_t$ is approximately normally distributed with a variance that may be estimated by

$$\widehat{\text{var}}(\hat{\mu}_t) = \sum_{t_j \leq t} \frac{(\hat{\mu}_t - \hat{\mu}_{t_j})^2 d_j}{r_j(r_j - d_j)},$$

a result which may be used to give approximate confidence limits for μ_t . By letting t tend to infinity, the above results may be extended to the estimation of the mean μ itself [8]. However, the conditions (mainly on the censoring) needed for such an extension to be valid are usually not met in practice.

In the liver cirrhosis study no patient was followed for more than 13 years, making the estimation of the mean survival time impossible. We may, however, estimate the expected number of years lived up to a given time t . In particular, estimates for the expected number of years lived up to 5 years and 10 years after

the start of the study are 3.29 years (standard error 0.17 years) and 4.73 years (0.33 years), respectively.

Redistribute-to-the-right Algorithm and Self-consistency

We mentioned earlier the relationship between the Kaplan–Meier estimator and the empirical distribution function in the case of no censoring. The redistribute-to-the-right algorithm and the concept of self-consistency, both due to Efron [6], further illustrate this relation.

For notational convenience we assume that there are no ties, and we denote by $t_1^0 < t_2^0 < \dots < t_n^0$ the ordered times of deaths and censorings combined. The redistribute-to-the-right algorithm is as follows. First, we construct the ordinary empirical (survival) distribution function which places probability mass $1/n$ at each of the observed times t_j^0 . If $t_{j_1}^0$ is the smallest t_j^0 that corresponds to a censored observation, then we remove its mass and redistribute it equally among the $n - j_1$ time-points to the right of it. Then, if $t_{j_2}^0$ is the second smallest censored observation, we remove its mass, which will be $1/n + 1/[n(n - j_1)]$, and redistribute it equally among the $n - j_2$ time-points to its right, etc. This algorithm will converge in a finite number of steps to the Kaplan–Meier estimator (1) (with the modification that it is set equal to zero after t_n^0 also when this last time-point corresponds to a censored observation).

A self-consistent estimator $\tilde{S}(t)$ for the survival distribution function equals $1/n$ times an estimate for the number of individuals who survive time t . More precisely,

$$\tilde{S}(t) = \frac{1}{n} \left[\#(t_j^0 > t) + \sum_{t_j^0 \leq t} a_j(t) \right], \quad (8)$$

where $a_j(t) = \tilde{S}(t)/\tilde{S}(t_j^0)$ if the observation at t_j^0 corresponds to a censored observation, and $a_j(t) = 0$ if it corresponds to an observed death. It turns out that the Kaplan–Meier estimator (modified as just indicated) is the unique self-consistent estimator. Turnbull [17] (see **Turnbull Estimator**) used the idea of self-consistency to derive an iterative procedure (a version of the **EM algorithm**) for estimating the survival distribution function nonparametrically from arbitrarily

grouped, censored, and truncated data, while Gill [9] showed that the self-consistency equation, (8), may be interpreted as a generalized score equation.

Product–Integral Representation and Relationship to the Nelson–Aalen Estimator

Usually one assumes that the survival distribution function $S(t)$ is absolute continuous with density function $f(t) = -S'(t)$, hazard rate function $\alpha(t) = f(t)/S(t)$, and cumulative hazard rate function $A(t) = \int_0^t \alpha(u) du$. However, the Kaplan–Meier estimator is discrete in nature, and the same applies to the Nelson–Aalen estimator for the cumulative hazard rate function. This makes it useful to be able to handle both discrete and continuous distributions within a unified framework. Let us therefore review how the survival distribution function $S(t)$ and the cumulative hazard rate function $A(t)$ are related for distributions which need neither to be continuous nor discrete. For such distributions

$$A(t) = - \int_0^t \frac{dS(u)}{S(u-)}, \quad (9)$$

where $S(t-)$ denotes the left-hand limit of the survival distribution function at t . For an absolute continuous distribution, (9) specializes to $A(t) = -\ln S(t) = \int_0^t \alpha(u) du$. For a discrete distribution it gives $A(t) = \sum_{u \leq t} \alpha_u$, where the discrete hazard, α_t , is the conditional probability of death exactly at time t given that death has not occurred earlier. To express the survival distribution function by the cumulative hazard rate function it is convenient to use the product–integral \mathcal{P} , defined as the limit of approximating finite products in a similar manner as the ordinary integral \int is defined as the limit of approximating finite sums (see **Product-integration**). With the use of the product–integral we may write

$$S(t) = \mathcal{P}_{u \leq t} [1 - dA(u)]. \quad (10)$$

For a continuous distribution, (10) specializes to the well-known relation $S(t) = \exp[-A(t)]$, while for a discrete distribution it takes the form $S(t) = \prod_{u \leq t} (1 - \alpha_u)$.

The Nelson–Aalen estimator for the cumulative hazard rate function is $\hat{A}(t) = \sum_{t_j \leq t} d_j/r_j$. This corresponds to a distribution with all probability mass

concentrated at the observed failure times and with discrete hazard $\hat{\alpha}_j = d_j/r_j$ at t_j . Using (10), the corresponding survival distribution function takes the form

$$\hat{S}(t) = \prod_{u \leq t} [1 - d\hat{A}(u)] = \prod_{t_j \leq t} (1 - \hat{\alpha}_j), \quad (11)$$

i.e. it is the Kaplan–Meier estimator (1). Thus the Kaplan–Meier and Nelson–Aalen estimators are related in exactly the same way as are the survival distribution function and the cumulative hazard rate function themselves. This fact is lost sight of when one considers the relations $A(t) = -\ln S(t)$ and $S(t) = \exp[-A(t)]$ which are only valid for the continuous case. In fact, the latter relations have led researchers to suggest the estimators $-\ln \hat{S}(t)$ and $\exp[-\hat{A}(t)]$ for the cumulative hazard rate function and the survival distribution function, respectively. The numerical differences between these two estimators and the Nelson–Aalen and Kaplan–Meier estimators will be of little importance in most cases. But the fact that the Nelson–Aalen and Kaplan–Meier estimators are related through (9) and (10) indicates that they are the canonical nonparametric estimators for the cumulative hazard rate function and the survival distribution function. This statement is supported by the fact that they may both be given a **nonparametric maximum likelihood** interpretation [11].

Martingale Representation and Statistical Properties

The product–integral formulation (11) of the Kaplan–Meier estimator shows its close relationship to the Nelson–Aalen estimator, and it is the key to the study of its statistical properties. In fact, these are closely related to those of the Nelson–Aalen estimator. We here indicate a few main steps and refer to Andersen et al. [1, Section IV.3] for a detailed account.

Let $J(t) = 1$ if there is at least one individual at risk just before time t ; $J(t) = 0$ otherwise. Furthermore, introduce $A^*(t) = \int_0^t J(u) dA(u)$, and let

$$S^*(t) = \prod_{u \leq t} [1 - dA^*(u)]. \quad (12)$$

We note that (12) is almost the same as $S(t)$ [cf. (10)] when there is only a small probability that there is

no one at risk at times $u \leq t$. By a general result for product–integrals (Duhamel’s equation), we may write

$$\frac{\hat{S}(t)}{S^*(t)} - 1 = - \int_0^t \frac{\hat{S}(u-)}{S^*(u)} d(\hat{A} - A^*)(u). \quad (13)$$

Here $\hat{A} - A^*$ is a square integrable martingale (see **Nelson–Aalen Estimator**). It follows that the right-hand side of (13) is a stochastic integral and hence itself a mean zero square integrable martingale. As a consequence of this, $E[\hat{S}(t)/S^*(t)] = 1$ for any given t , so the Kaplan–Meier estimator is almost **unbiased**. Furthermore, the predictable variation process of the martingale on the right-hand side of (13) may be used to arrive at an estimator for the variance of $\hat{S}(t)/S^*(t)$. From this, Greenwood’s formula (2) follows provided one adopts a general model, not necessarily continuous. Greenwood’s formula may also be derived through a standard **information** calculation starting with a binomial-type likelihood for such a general model.

A further consequence of (13) is that $\sqrt{(n)}(\hat{S} - S)/S$ is asymptotically equivalent to $-\sqrt{(n)}(\hat{A} - A)$ and therefore converges weakly to a mean zero Gaussian martingale. In particular, for a fixed t , the Kaplan–Meier estimator (1) is asymptotically normally distributed, a fact that was used in connection with the confidence intervals (3) and (4). Also, the asymptotic distributional results of the estimators for the median and mean survival times reviewed earlier are consequences of this weak convergence result.

Confidence Bands

The weak convergence of $\sqrt{(n)}(\hat{S} - S)/S$ to a mean zero Gaussian martingale also makes it possible to derive confidence bands for the survival distribution function, i.e. limits that contain $S(t)$ for all t in an interval $[\tau_1, \tau_2]$ with a prespecified probability. Two important types of such confidence bands are the equal precision bands [14] and the Hall–Wellner bands [10]. Borgan & Liestøl [3] derived transformed versions of these confidence bands and compared them with the nontransformed ones.

The standard and log-minus-log transformed equal precision bands are obtained by replacing $z_{1-\alpha/2}$ in (3) and (4) by $d_{1-\alpha}(\hat{c}_1, \hat{c}_2)$, the $1 - \alpha$ fractile in the distribution of the supremum of the absolute value

of a standardized Brownian bridge over the interval from \hat{c}_1 to \hat{c}_2 (see **Brownian Motion and Diffusion Processes**). Here

$$\hat{c}_i = \frac{n[\hat{\sigma}(\tau_i)/\hat{S}(\tau_i)]^2}{1 + n[\hat{\sigma}(\tau_i)/\hat{S}(\tau_i)]^2}, \quad i = 1, 2. \quad (14)$$

The fractile $d_{1-\alpha}(\hat{c}_1, \hat{c}_2)$ may be found (approximately) by solving (with respect to d) the following nonlinear equation:

$$\frac{4\phi(d)}{d} + \phi(d) \left(d - \frac{1}{d} \right) \ln \left[\frac{\hat{c}_2(1 - \hat{c}_1)}{\hat{c}_1(1 - \hat{c}_2)} \right] = \alpha,$$

with $\phi(d)$ the standard normal density. The equal precision bands require $0 < \hat{c}_1 < \hat{c}_2 < 1$, so they cannot be extended all the way down to $t = 0$. Typically, one will also omit the largest values of t .

The nontransformed Hall–Wellner band takes the form

$$\hat{S}(t) \pm n^{-1/2} e_{1-\alpha}(\hat{c}_1, \hat{c}_2) \left\{ 1 + n \left[\frac{\hat{\sigma}(t)}{\hat{S}(t)} \right]^2 \right\} \hat{S}(t). \quad (15)$$

Here $e_{1-\alpha}(\hat{c}_1, \hat{c}_2)$ is the $1 - \alpha$ fractile in the distribution of the supremum of the absolute value of a Brownian bridge over the interval from \hat{c}_1 to \hat{c}_2 ; cf. (14). For completely observed survival data the Hall–Wellner band reduces to the well-known Kolmogorov band $\hat{S}(t) \pm n^{-1/2} e_{1-\alpha}(\hat{c}_1, \hat{c}_2)$. For the band (15), one will often let $\tau_1 = 0$, in which case tables of $e_{1-\alpha}(\hat{c}_1, \hat{c}_2) = e_{1-\alpha}(0, \hat{c}_2)$ are given, for example by Koziol & Byar [13] and Hall & Wellner [10] for selected values of α and \hat{c}_2 . We note that (15) is obtained from (3) by substituting $n^{-1/2} e_{1-\alpha}(\hat{c}_1, \hat{c}_2) \{1 + n[\hat{\sigma}(t)/\hat{S}(t)]^2\} \hat{S}(t)$ for $z_{1-\alpha/2} \hat{\sigma}(t)$. The same substitution in (4) gives the log-minus-log transformed Hall–Wellner band. This transformed band requires $\hat{c}_1 > 0$, so it cannot be extended all the way down to $t = 0$. Owing to the approximation $e_{1-\alpha}(\hat{c}_1, \hat{c}_2) \approx e_{1-\alpha}(0, \hat{c}_2)$, the above-mentioned tables may also be used for the transformed bands when \hat{c}_1 is close to zero.

The nontransformed equal precision band tends to achieve too high error rates when the number of observations is low, and the use of transformed bands is recommended, even for samples of a hundred or more. The achieved error rates of the nontransformed Hall–Wellner band are fairly close to the nominal ones even in small samples, and the improvement

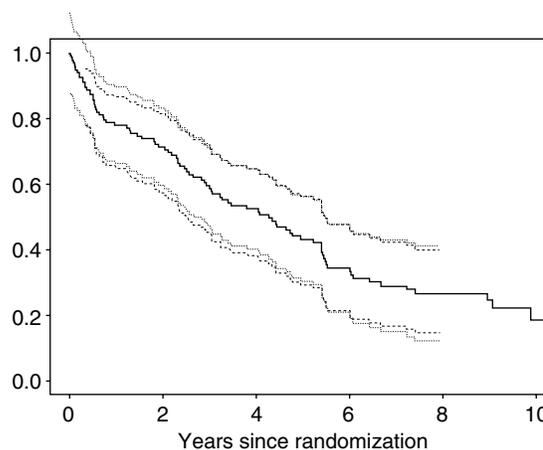


Figure 2 Kaplan–Meier estimate of the survival distribution function for 138 placebo-treated male patients with liver cirrhosis with 95% confidence bands: log-minus-log transformed equal precision band over the interval from 4 months to 8 years (---); Hall–Wellner band over the interval [0, 8] years (···)

obtained by using transformed bands is of less importance.

Figure 2 shows the Kaplan–Meier estimate for the liver cirrhosis data with 95% confidence bands. The bands shown are the log-minus-log transformed equal precision band over the interval from 4 months to 8 years and the nontransformed Hall–Wellner band valid from time zero to 8 years. Since $\tau_1 = 1/3$ year and $\tau_2 = 8$ years correspond to $\hat{c}_1 = 0.090$ and $\hat{c}_2 = 0.789$, the fractiles $d_{0.95}(\hat{c}_1, \hat{c}_2) = 2.99$ and $e_{0.95}(0, \hat{c}_2) = 1.36$ were used. It is seen that the equal precision band is narrower than the Hall–Wellner band both for low and high values of t , while the Hall–Wellner band is slightly narrower than the equal precision band for intermediate values.

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