

Restricted Mean Survival Time and Confidence Intervals by Empirical Likelihood Ratio

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Abstract

Recently, an increasing number of researchers propose to use restricted mean survival time (RMST) to evaluate medical treatment outcomes when the proportional hazards assumption is in doubt. Using the empirical likelihood ratio for the Kaplan-Meier mean, we show how the statistical analysis for the RMST and difference/ratio of two RMSTs can be obtained. Examples are given using R software and package `emplik`.¹ We argue that the confidence intervals produced with this new method has several intrinsic advantages over the current method implemented in R package `survRM2`. A simulation is also included.

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Key Words and Phrases: Nuisance parameter, Profile Empirical likelihood, Wilks Confidence interval.

1 Introduction

When the proportional hazards assumption is in doubt, many researchers propose to use the restricted mean survival time (RMST) as a measure to evaluate/compare treatments with right censored data. Many papers appeared recently [1], [2], [3], [4], [5] to name a few, developing the theory and illustrating the usefulness of the new statistic. The nonparametric RMST estimator, $\widehat{\text{RMST}}$, used by the above papers are all defined by integrated Kaplan-Meier estimator [6]. Tests and confidence intervals of RMST proposed are of the Wald type. To construct a 95% confidence interval, you first estimate the asymptotic variance of $\widehat{\text{RMST}}$ and form the confidence interval by $\widehat{\text{RMST}} \pm 1.96$ (estimated standard deviation). A more sophisticated analysis may apply a transformation before constructing the confidence interval. Software to do these calculations are available, for example, in the R package `survRM2` [7].

Since the Kaplan-Meier estimator is a nonparametric maximum likelihood estimator (NPMLE), the $\widehat{\text{RMST}}$ proposed in the above papers is also a NPMLE. There are several well known methods to construct confidence intervals based on MLEs or likelihood functions, see for example [8]. We propose and illustrate here the Wilks method of testing and constructing confidence intervals for the RMST (also the difference/ratio of two RMSTs). In the paper [8], the Wilks method is recommended over the Wald method. What is new here is that the parametric likelihood function is replaced by a nonparametric (empirical) likelihood, and the observed data are right censored. For discussion of empirical likelihood method see [9], [11].

When sample size goes to infinite, the Wilks and the Wald confidence intervals are equivalent. However, for smaller samples Wilks intervals are often better. It is a generally accepted fact that the Wilks confidence intervals have several advantages over the Wald confidence intervals, see section 3 of [8] and

¹The computation in this paper are obtained with R package `emplik` version 1.0-4.3

additional references there. The disadvantage they mentioned for Wilks is the computational difficulty. But with ever faster computers, innovative algorithms [12], [13], and publicly available software, this is much less of a problem nowadays.

We list here briefly the advantages of Wilks over Wald: 1). The Wilks confidence intervals are not necessary symmetric about the MLE, rather, it tries to reflect the skewness of the given data. 2). The Wilks confidence intervals are always within the parameter space, while a Wald confidence interval of a probability can include negative values, for example. 3). Once we obtained the Wilks confidence interval for a parameter θ , $[a, b]$ (say), the Wilks confidence interval for $g(\theta)$ is just $[g(a), g(b)]$ (assuming g is increasing). 4). There is no need to figuring out the variance of the MLE/NPMLE and estimate it.

The confidence intervals for survival probability based on the Kaplan-Meier estimator in SAS `proc lifetest` is Wald based. It offers several options of transformation: linear, log, logit, log-log, and arcsine-sqrt. This is partly due to an attempt of correcting 2) above. But there is no clear consciences on what is the best transformation. R package `survival` offers similar options. If we use the Wilks method, these are non-issues. For the RMST problem at hand, the package `survRM2` used a log transformation when working on the ratio of two RMSTs, but did not use any transformation when working with the difference of two RMSTs. In one of the above papers, they commented that it is not clear what transformation should be used on the difference of two RMSTs. We do not have to worry about transformation on the parameter when apply the Wilks method. It automatically applied the best transformation without we knowing it, so to speak.

2 Empirical Likelihood Ratio Test

In survival analysis, many parameters of interest can be expressed as an integral with respect to the underlying survival function. Its natural estimator is then the same integral by replacing the unknown survival function with the Kaplan-Meier estimator, $\hat{F}_{km}(t)$. If this is the case, then we can perform a test and find its Wilks confidence interval by using the empirical likelihood ratio. The theoretical base of the empirical likelihood ratio tests and subsequent test-based confidence intervals are the following theorem.

Suppose $X_1, \dots, X_n \sim F$ are i.i.d. lifetimes. However they are subject to censoring and we only observe $T_i = \min(X_i, C_i)$, $\delta_i = I[X_i \leq C_i]$, where C_i are censoring times. In addition, we assume the censoring is noninformative.

Theorem 1 (Empirical Likelihood Theorem for the Kaplan-Meier Integral) Let $(T_1, \delta_1), \dots, (T_n, \delta_n)$ be n pairs of i.i.d. right censored observations. Suppose $g(t)$ is a given function such that the asymptotic variance of the Kaplan-Meier mean $\int g(t)d\hat{F}_{km}(t)$ is positive and finite:

$$0 < \text{AsyVar} [\sqrt{n} \int g(t)d\hat{F}_{km}(t)] < \infty .$$

Then, under null hypothesis $H_0 : \int g(t)dF(t) = \mu$, we have,

$$-2 \log R(\mu) = -2 \log \frac{\sup_{F: \text{satisfy } H_0} EL(F)}{EL(F = \hat{F}_{km})} \xrightarrow{\mathcal{D}} \chi_1^2 \quad \text{as } n \rightarrow \infty,$$

where $EL(F)$ is the empirical likelihood for F based on the n right censored data:

$$EL(F) = \prod_{i=1}^n [\Delta F(t_i)]^{\delta_i} [1 - F(t_i)]^{1-\delta_i} .$$

PROOF: See [11] Theorem 23 for a proof with a vector g . An easier to read version for univariate g and continuous F can be found in the appendix.

A direct consequence of the Theorem 1 is that the p -value for testing $H_0 : \int g(t)dF(t) = \mu$ vs. $H_a : \int g(t)dF(t) \neq \mu$ can be computed as $P(\chi_1^2 > -2\log R(\mu))$ for large samples; where we denote by χ_1^2 a chi square random variable with one degree of freedom. If we can test (obtain p -values) for various simple hypotheses by empirical likelihood ratio, then we will be able to construct a confidence interval:

$$95\% \text{ confidence interval} = \{\mu \mid -2 \log R(\mu) \leq \chi_1^2(0.95)\}.$$

In words, the confidence interval/region consist of those values of the parameter μ that the simple hypothesis cannot be rejected. Those intervals are called Wilks confidence intervals.

The calculation of the log empirical likelihood ratio in the above theorem was studied in [12] and [13]. The actual calculation in this paper is implemented in the R package `emplik`.

3 Restricted Mean Survival Time

When the largest survival time in a sample is right censored, the Kaplan-Meier estimator is non-uniquely defined beyond the last observed time. Thus the mean survival time estimator based on the Kaplan-Meier estimator is also non-uniquely defined. Some authors define the Kaplan-Meier to be zero beyond the largest censored observation in this case. We shall also take this convention.

The restricted mean survival time is used often in the comparison of cancer treatments when the proportional hazards assumption is in doubt. The idea is to compare the mean survival only on a limited time horizon, like 0 to 85 years, etc. By definition, the (true) RMST is

$$\mu(\tau) = \int_0^\tau 1 - F(s)ds$$

where τ is a pre-specified restriction time. We notice $\mu(\infty)$ is the ordinary mean value. After an integration by parts we can rewrite the true RMST as

$$\mu(\tau) = \int_0^\infty \min(s, \tau) dF(s).$$

An obvious estimate of the RMST is to replace $F(s)$ by the Kaplan-Meier $\hat{F}_{km}(s)$, so the estimate becomes (assume we always have Kaplan-Meier taking the value zero beyond the largest observation, which is the case for the Kaplan-Meier estimator in the package `emplik`)

$$\hat{\mu}(\tau) = \int_0^\infty \min(s, \tau) d\hat{F}_{km}(s).$$

The discussion above show that if we identify $g(t) = \min(t, \tau)$ then the empirical likelihood theorem in section 2 leads to a likelihood ratio test and a Wilks confidence interval for RMST.

For more discussions and references of RMST, in addition to the references mentioned in the introduction, please see the R package `survRM2`. Unlike the R package `survRM2` which is specifically made to do statistical inferences for the RMST, the R package we are going to use, `emplik`, is made for empirical likelihood ratio type analysis in general. Therefore some simple auxiliary functions need to be defined for the specific analysis of RMST. We illustrate those in the following examples.

Example 1. We use the data set `kidney` from the R package `KMsurv` to illustrate our method. The data set contains 119 cases of kidney dialysis patient and their catheter infection time is recorded. The maximum time recorded is 28.5 month. We pre-select the time restriction $\tau = 20$ (months). Suppose we are trying to test the hypothesis $H_0: \mu(20) = 15$ vs. $H_a : \mu(20) \neq 15$.

The actual R code and calculation is in Appendix. We see that the p -value of the test is 0.1125004. The existing function from the package `emplik` we used is `e1.cen.EM2`. The newly defined (one-line) function for testing RMST is `RMSTfun`.

Next, we try to construct the 95% Wilks confidence interval for RMST. This is accomplished by the function `findUL` from the package `emplik`, which in turn, requires a function that returns log likelihood in testing a hypothesis about `theta`. Therefore we need to define the (new) wrapper function `myfun8`. See Appendix for details.

We see the 95% confidence interval for $\mu(20)$ is $[14.71036, 17.38996]$. The `step` input of the function `findUL` is the initial search step size from the MLE. We set the option `step=1` in `findUL`. Ideally, the step should be similar to 1/2 of the standard deviation of the MLE. A wide range of step sizes should work. A step too small makes the calculation slower, while a step too large can whack the calculation.

The input MLE in the `findUL` is supposed to be the MLE of the parameter that we are trying to find its confidence interval. In our case it is the MLE of RMST. But it does not have to be very accurate, a ballpark value will work. Here we used 15. May be 16 is better choice. But the final confidence interval is the same.

A good indication that everything is OK, is in the output `Lvalue` and `Uvalue`. They both should be equal to $\chi^2(1 - \alpha)$. Since the default confidence level is 95%, thus in the above example they have value close to $3.84 = \chi_1^2(0.95)$.

If you want a 90% confidence interval (or other levels), you can add an input `level=2.705543` (that is chi square 90% percentile: `qchisq(0.9, df=1)`) to the function `findUL`:

```
findUL(step=1, fun=myfun8, MLE=16, level=2.705543, x=kidney$time, d=kidney$delta)
```

If we are dealing with only right censored data (as in the Kaplan-Meier estimator), a much faster version of the calculation (replacing `el.cen.EM2`) is available in the package `kmc`, function `kmc.solve`, see [13]. But the package `kmc` is not as mature/stable as `emplik`, reflected in its version number, and short history.

Notice `el.cen.EM2` can also deal with data that have both right censor and left censor; `kmc.solve` can only deal with right censored data.

The smallest observation fed into `kmc.solve` must be an uncensored one. If you do have some censored observations that are smaller than any observed death, simply delete them. It is easy to show that those smallest censored observations do not carry any information in nonparametric modeling. Last, the `kmc.solve` only tests the mean equal to zero, so if you want to test other mean values, you need to first subtract it in the definition of the function.

By using the R package `kmc` to test the RMST, we get the same result but the speed is vastly improved. See appendix. We caution that the code in `kmc` is less stable.

4 Difference/Ratio of two Restricted Mean Survival Times

It is possible to formulate and prove a similar empirical likelihood theorem for the difference of two Kaplan-Meier means when dealing with two independent right censored samples and another one for the ratio. However, we shall take a simpler and more general approach here. We first introduce an extra (nuisance) parameter so that under the new null hypothesis of two parameters, the log empirical likelihood ratio for the two-samples are completely separate. This makes the calculation of the log empirical likelihood for two-sample easier: it is the sum of the two one-sample log empirical likelihood ratio. In addition, Theorem 1 in section 2 applies to each of them, leading to an asymptotic distribution of $\chi_1^2 + \chi_1^2 = \chi_2^2$ by independence. The last step is to profile out the nuisance parameter we introduced in the first place.

To profile out the nuisance parameter is a common approach in parametric likelihood ratio analysis. The fact that it is also valid for empirical likelihood is of no surprise. See Owen [9] Chapter 3. The novelty here is that we artificially introduced the nuisance parameter, only to be profiled out later.

Theorem 2 (Profile Empirical Likelihood) Suppose θ, ν are two parameters with true values denoted by θ_0, ν_0 , and the empirical likelihood ratio $-2 \log R(\theta_0, \nu_0) \rightarrow \chi_2^2$ in distribution. Then, under mild regularity conditions, the profile log empirical likelihood ratio: $-2 \log \max_{\nu} R(\theta_0, \nu)$ has asymptotic χ_1^2 distribution.

PROOF: See [10] Corollary 5 for proof and exact conditions needed. Those smoothness conditions on the estimating functions are obviously satisfied here.

4.1 Difference of two RMSTs

Here we try to find the confidence interval for the difference of two RMSTs from two independent samples.

Let us first look at the testing of $H_0 : \mu_1(\tau) - \mu_2(\tau) = \theta$. After introducing a nuisance parameter $r = \text{RMST}$ of sample 1, the null hypothesis about θ and r , $H_{01} : \mu_1(\tau) = r, \mu_1(\tau) - \mu_2(\tau) = \theta$, is equivalent to $H_{02} : \mu_1(\tau) = r, \mu_2(\tau) = r - \theta$. This H_{02} is two separate hypotheses about each of the sample; it can be solved one by one. The joint log likelihood is just the sum of the two (one sample) log empirical likelihoods.

Example 2 We use data from a study of treatments (D-penicillamine verses placebo) for primary biliary cirrhosis conducted at Mayo clinic to illustrate our method. In order to compare the results to those of R package `survRM2`, we use exactly the same data cases as theirs. There were 184 subjects in the treatment group, and 182 subjects in the placebo group. The censoring percentage is 41% for treatment group and 39% for placebo group, with maximum observed time of 4556 and 4523 (days) respectively.

Here we take the restriction time $\tau = 10 \text{ years} = 3652.5 \text{ days}$.

For a simple test of hypothesis $H_0 : \mu_1(3652.5) - \mu_2(3652.5) = 0$ we can do, after defining the functions `RMSTdiff` and `ThetafunD`, the following to obtain the p -value.

```
ThetafunD(theta=0, x1=pbxX1, d1=pbcd1, x2=pbxX2, d2=pbcd2)
```

We omit the output to save space.

Next we find a 95% confidence interval for the difference $\mu_1(3652.5) - \mu_2(3652.5)$. See appendix for the R code and output.

Clearly this coding consists of three blocks. The first block is the `RMSTdiff` function, which introduced a nuisance parameter (RMST of sample one, `r`) to make the calculation of the empirical likelihood easier. It then computes the log likelihood ratio from each sample and returns the summation.

The second block, `ThetafunD`, is to profile out the nuisance parameter `r`. It is a wrapper for the R function `optimize`. Two points of caution: in some cases, the log likelihood ratio from the first bloc may not be smooth [however, for the RMST function here, it is smooth]. An example of a non-smooth log likelihood is the testing of quantile/medians. If that is the case, we have to use an exhaustive search or `optimize` will have to be applied after some smoothing. Another point is the lower and upper bound of the search. This must take into account the value and approximate confidence interval for the nuisance parameter. Here the nuisance parameter is RMST of sample 1. It has value approximate 2612 and (95%) confidence interval approximately 2400 to 2815. This makes us use the lower = 1500 days and upper = 3100 days. When in doubt, a larger range can be used. The drawback is the search will be slower.

The third block is the `findUL` function to construct confidence interval. Here we know roughly the width of the final confidence interval should be at least 400 days. So we use `step = 100`. The final 95% confidence interval of the difference, `RMST1 - RMST2` is: $[-340.4272, 243.4025]$. Please note this is in terms of days. To compare to the results from `survRM2` we need to convert them to the years, which is $[-340.4272/365.25, 243.4025/365.25] = [-0.9320389, 0.6663997]$ (years). As a comparison, the Wald confidence interval from the R package `survRM2` example is $[-0.939, 0.665]$. Our confidence interval is shorter and is not symmetric about the MLE ($= -0.137$). As discussed in section 1, the advantage of Wilks confidence intervals should be more profound over Wald if the distribution of $\hat{\mu}_1(\tau) - \hat{\mu}_2(\tau)$ is

more skewed.

4.2 Ratio of two RMSTs

We now try to find the confidence interval for the ratio of two RMSTs from two independent samples.

Example 3 Using the same data from the section 4.1 example 2, we first consider testing $H_0 : \mu_1(\tau)/\mu_2(\tau) = \theta$. Here we introduced an extra nuisance parameter $r =$ the RMST of sample 2. The new null hypothesis before profiling is $H_{02} : \mu_2(\tau) = r, \mu_1(\tau) = r\theta$.

The R code and sample output is in Appendix.

Again, there are three steps: (1) find the log empirical likelihood ratio for testing H_{02} by `RMSTratio`. (2) profile the nuisance parameter r out (producing a p-value for testing H_0). (3) find the confidence interval using `findUL`.

The nuisance parameter in the difference of two RMSTs case is RMST1, and here the nuisance parameter is RMST2. However, the two RMSTs are not too far apart and the range [1500, 3100] is wide enough so that it works for both case in the `optimize` function in step 2.

The true MLE of θ here is not 1, but it is close enough. We therefore take the input `MLE=1` in `findUL` function. A reasonable choice of the `step` input in `findUL` function for ratio is anywhere between 0.1 and 0.2. Please note this is the 95% confidence interval for the ratio of RMST1/RMST2. In this case it is [0.8782903, 1.09761]. This is almost the same as the interval given by the R package `survRM2`: [0.878, 1.096].

One nice property of the confidence interval obtained here is that for the confidence interval of the reciprocal of the ratio above, RMST2/RMST1, is just [1/1.09761, 1/0.8782903] due to invariance.

5 Simulation

We have conducted a small simulation to show the empirical likelihood test, although an asymptotic test, performs pretty well for moderate sample sizes. In table 1 for both samples the lifetimes X_i are generated from a Weibull distribution with shape parameter 0.9 and scale parameter 12.7. The censoring times C_i are generated from a uniform (0, 12.5) distribution.

Simulated type I errors are based on 5000 runs. We have used the t-distribution calibration for empirical likelihood as suggested by Owen [9] equation (3.3): i.e., the $-2 \log R$ is deemed 5% significant if it is larger than $[qt(0.975, df = n1 + n2 - 2)]^2$, where $qt()$ denotes the quantile function of a student t-distribution.

sample sizes	restriction time	EL test (5%)	Wald test (5%)
25, 25	$\tau = 8$	5.74%	7.1%
25, 25	$\tau = 10$	6.12%	7.02%
30, 30	$\tau = 8$	5.30%	6.52%
30, 30	$\tau = 10$	5.73%	6.44%
40, 40	$\tau = 8$	5.30%	6.02%
40, 40	$\tau = 10$	5.36%	6.08%

Table 1. Nominal versus actual type I error for Empirical Likelihood (EL) test and Wald test.

The type I errors for empirical likelihood are slightly inflated compare to the nominal, but they are less profound than the results of asymptotic Wald test. Even without the t-distribution calibration, the EL test's type I error in sample sizes 30+30, $\tau = 8$ case would be 5.92% vs. Wald test 6.52%, and for 30+30, $\tau = 10$, 5.73% vs. Wald test 6.44%, etc.

For the same sample size, we see that when the restriction time are higher ($\tau = 10$), the type I errors (of both test) are less accurate than a lower restriction time ($\tau = 8$). This may due to the larger variance of Kaplan-Meier in the tail.

In table 1, the probability of an observation end up being uncensored and occurs before restriction time $\tau = 8$ ($\tau = 10$ respectively) is about 35.2% (37.2%). The probability of an observation being larger than $\tau = 8$ ($\tau = 10$) is about 18.6% (8.8%).

We used a Dell OptiPlex 9020 desktop computer with i7-4790 CPU for simulation. The computational time of a p-value for testing the difference of two RMSTs is about 1.1 seconds, for sample size (200, 200) using the empirical likelihood method; and about 0.9 second for sample size (50, 50). The Wald test is obtain using the R package `survRM2`, and is almost instant.

We also carried out another simulation in the un-equal sample size setup and included an alternative setting, where for the first sample the lifetimes are generated from a Weibull (1.9, 12.7) distribution and the rest remain the same as in table 1. In the alternative case, the error is “percent of nominal 95% confidence intervals NOT catching the true parameter value”.

sample sizes	restriction time	distributions	EL test (5%)	Wald test (5%)
35, 25	$\tau = 10$	H_0	6.04 %	6.51 %
35, 25	$\tau = 10$	H_A	6.12 %	6.83 %

Table 2. Nominal versus actual error.

We see the same improvements on the finite sample accuracy of the EL tests over the Wald tests.

6 Discussion

The empirical likelihood method avoids the need for calculating/estimating the variance of the RMST. Also, no transformation of the parameter needs to be considered. On the other hand, we are left with some optimization problems, which (at least in this case) can easily be solved by a computer. In this respect, it is similar to the bootstrap method: calculation/estimating the variance is replaced by computer algorithms. But the empirical likelihood method always gives you the same p-value testing a given null hypothesis while the bootstrap result varies depend on the random number generator and the number of bootstrap iterations.

The empirical likelihood method is highly recommended over Wald method when (1) the sample sizes are small to moderate; (2) the sampling distribution of the estimator, $\hat{\mu}_1(\tau) - \hat{\mu}_2(\tau)$, is skewed; (3) either a variance estimator is not available or there are several competing ones and no clear winner.

We would like to point out that the variance estimator used by R package `survRM2` [14] and by SAS `proc lifetest` [15] differ by a factor $m/(m - 1)$ where m is the total number of observed events before restriction time τ .

The restricted mean time lost (RMTL) is related to RMST: $RMTL = \tau - RMST$. The statistical analysis of RMTL and the difference of two RMTLs can be easily obtained from those for the RMST by simple arithmetic. The analysis for the ratio of two RMTLs can be similarly done by the same method illustrated in this paper. Notice that we have $RMTL(\tau) = \int_0^\infty \max(\tau - s, 0) dF(s)$. We need to replace the R function `RMSTfun` by `RMTLfun` defined by: `RMTLfun <- function(x) {pmax(600-x, 0) - 100}` for testing $RMTL = 100$, with $\tau = 600$, for example.

The empirical likelihood method can also be used to test the hypothesis of several RMSTs with different restriction times. This amounts to use several g 's to impose several constraints.

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7 Appendix I. Example R code for calculation

R calculation for Example 1. Obtain p -value.

```
library(KMsurv)
library(emplik)
data(kidney)
RMSTfun <- function(x) {pmin(x, 20) - 15}
el.cen.EM2(x=kidney$time, d=kidney$delta, fun=RMSTfun, mu=0, maxit=50)

## $loglik
## [1] -131.105
##
## $times
## [1] 0.5 0.5 0.5 0.5 0.5 0.5 1.5 2.5 2.5 3.5 3.5 4.5 4.5 5.5 6.5 8.5 8.5
## [18] 9.5 10.5 11.5 15.5 15.5 16.5 18.5 23.5 26.5 28.5
##
## $prob
## [1] 0.01122308 0.01122308 0.01122308 0.01122308 0.01122308 0.01122308 0.01243132 0.01279473
## [9] 0.01279473 0.01381316 0.01381316 0.01533046 0.01533046 0.01599773 0.01746515 0.02043914
## [17] 0.02043914 0.02186346 0.02285866 0.02485554 0.03538362 0.03538362 0.03297763 0.03220609
## [25] 0.06200016 0.10114908 0.39333447
##
## $lam
## [1] 2.061926
##
## $iters
## [1] 50
##
## $'-2LLR'
## [1] 2.51874
##
## $Pval
## [1] 0.1125004
```

Construct confidence interval for Example 1.

```
myfun8 <- function(theta, x, d){
  el.cen.EM2(x,d,fun=function(t){pmin(t,20)-theta},mu=0,maxit=50)
}
findUL(step=1, fun=myfun8, MLE=15, x=kidney$time, d=kidney$delta)
## $Low
## [1] 14.71036
##
## $Up
## [1] 17.38996
##
## $FstepL
## [1] 6.103516e-05
##
## $FstepU
## [1] 6.103516e-05
##
## $Lvalue
## [1] 3.839861
##
```

```
## $Uvalue
## [1] 3.839985
```

Example 1 Calculation using R package `kmc` version 0.2-3. First, find the p -value.

```
library(KMsurv)
library(kmc)
data(kidney)

RMSTfun <- function(x) {pmin(x, 20) - 15}
kmc.solve(x=kidney$time, d=kidney$delta, g=list(RMSTfun))
```

Example 1 Using package `kmc` version 0.2-3 to Find the confidence interval:

```
myfun9 <- function(theta, x, d){
ff <- function(t){pmin(t, 20) - theta}
kmc.solve(x, d, g=list(ff) )
}
findUL(step=1, fun=myfun9, MLE=16, x=kidney$time, d=kidney$delta)

## $Low
## [1] 406.4569
##
## $Up
## [1] 535.4033
##
## $FstepL
## [1] 6.103516e-05
##
## $FstepU
## [1] 6.103516e-05
##
## $Lvalue
## [1] 3.84
##
## $Uvalue
## [1] 3.84
```

R code for example 2

```
myabc <- abc[1:312,]
abcX1 <- myabc$time[myabc$trt==1]
abcX2 <- myabc$time[myabc$trt==2]
abcD1 <- myabc$status[myabc$trt==1]
abcD2 <- myabc$status[myabc$trt==2]
abcd1 <- as.numeric(abcD1==2)
abcd2 <- as.numeric(abcD2==2)

RMSTdiff <- function(r, x1, d1, x2, d2, theta){
temp1 <- el.cen.EM2(x=x1, d=d1, fun=function(x){pmin(x, 3652.5)}, mu=r)
temp2 <- el.cen.EM2(x=x2, d=d2, fun=function(x){pmin(x, 3652.5)}, mu=r-theta)
return(temp1$"-2LLR" + temp2$"-2LLR")
}

ThetafunD <- function(theta, x1, d1, x2, d2) {
```

```

temp <- optimize(f=RMSTdiff, lower=1500, upper=3100,
                x1=x1, d1=d1, x2=x2, d2=d2, theta=theta)
cstar <- temp$minimum
val <- temp$objective
list("-2LLR"=val, cstar=cstar, Pval= 1-pchisq(val, df=1))
}

findUL(step=100, fun=ThetafunD, MLE=0, x1=pbX1, d1=pbcd1, x2=pbX2, d2=pbcd2)

## $Low
## [1] -340.4272
##
## $Up
## [1] 243.4025
##
## $FstepL
## [1] 1e-06
##
## $FstepU
## [1] 1e-06
##
## $Lvalue
## [1] 3.84
##
## $Uvalue
## [1] 3.84

```

R code and sample out put for Example 3.

```

RMSTratio <- function(r, x1, d1, x2, d2, theta){
temp1 <- el.cen.EM2(x=x1,d=d1,fun=function(x){pmin(x, 3652.5)},mu=r*theta)
temp2 <- el.cen.EM2(x=x2,d=d2,fun=function(x){pmin(x, 3652.5)},mu=r)
return(temp1$"-2LLR" + temp2$"-2LLR")
}

ThetafunR <- function(theta, x1, d1, x2, d2) {
temp <- optimize(f=RMSTratio, lower=1500, upper=3100,
                x1=x1, d1=d1, x2=x2, d2=d2, theta=theta)
cstar <- temp$minimum
val <- temp$objective
list("-2LLR"=val, cstar=cstar, Pval= 1-pchisq(val, df=1))
}

findUL(step=0.2, fun=ThetafunR, MLE=1, x1=pbX1, d1=pbcd1, x2=pbX2, d2=pbcd2)

## $Low
## [1] 0.87829
##
## $Up
## [1] 1.097608
##
## $FstepL
## [1] 6.103516e-05
##
## $FstepU
## [1] 6.103516e-05

```

```

##
## $Lvalue
## [1] 3.840018
##
## $Uvalue
## [1] 3.839883

```

8 Appendix II. Empirical Likelihood Theorem for Right Censored Data: Proof

We shall assume the underlying survival function $1 - F$ is continuous for easier reading. The feature of the distribution (or survival) function we are testing (mean value of $g(X)$) is specified by $\int g(t)dF(t)$, i.e. $H_0 : \int g(t)dF(t) = \mu$. So at a minimum we need to assume the asymptotic variance of this statistics, $AsyVar\sqrt{n}[\int g(t)d\hat{F}_{km}(t) - \mu]$, is finite. WLOG, we assume the true $\mu = 0$.

1st Step. The first major step is to re-write the asymptotic variance of Kaplan-Meier mean $\int g(t)d\hat{F}_{km}$. There are several equivalent expressions for the variance, but we shall focus on one that is given by Akritas (2000).

Assume F is continuous, we have

$$AsyVar[\sqrt{n} \int g(t)d\hat{F}_{km}(t)] = \int [g(t) - \bar{g}(t)]^2 \frac{dF(t)}{1 - G(t-)} \quad (1)$$

where G is the censoring distribution.

We call the attention of readers to the use of \bar{g} , the advanced time:

$$\bar{g}(s) = \frac{\int_{(s, \infty)} g(x)dF(x)}{1 - F(s)}. \quad (2)$$

Actually, we should probably write it as $\bar{g}_F(s)$ instead of $\bar{g}(s)$ since the definition uses F . The reference of the advanced time is Akritas (2000), Efron and Johnstone (1990). The nice thing about this variance formula (1) is that it allows us to use the Cauchy-Schwarz inequality to show some maximum result. After all, the empirical likelihood ratio is a “**maximum** likelihood ratio”.

2nd step Let us recall the Cauchy-schwarz inequality. The integral version of it is

$$\left[\int_A \xi(x)\eta(x)dv \right]^2 \leq \int_A \xi^2(x)w^2(x)dv \int_A \frac{\eta^2(x)}{w^2(x)}dv$$

here dv is a measure on the set A , w is positive. The max of left hand side is achieved if and only if $\xi w = \eta/w$ (a.s. dv), and easy to check, when this happens we have the equality holds.

We will be using the inequality with $\eta(x) = [g - \bar{g}]$; $\xi(x) = [f - \bar{f}]$; $w = \sqrt{1 - G_-}$ and $dv = dF$.

So, the actual inequality we shall use to find the maximum of empirical likelihood ratio is

$$\int \frac{[g - \bar{g}]^2}{1 - G_-} dF \geq \frac{[\int (f - \bar{f})(g - \bar{g})dF]^2}{\int [f - \bar{f}]^2 [1 - G_-] dF}.$$

We notice the left hand side of this inequality is the Asymptotic Variance of the Kaplan-Meier mean.

Another way to express the Cauchy-Schwarz inequality above is

$$\sup_f \frac{[\int (f - \bar{f})(g - \bar{g})dF]^2}{\int [f - \bar{f}]^2 [1 - G_-]dF} = \int \frac{[g - \bar{g}]^2}{1 - G_-} dF.$$

Or

$$\inf_f \frac{\int [f - \bar{f}]^2 [1 - G_-]dF}{[\int (f - \bar{f})(g - \bar{g})dF]^2} = \frac{1}{\int \frac{[g - \bar{g}]^2}{1 - G_-} dF}. \quad (3)$$

Third Step. Since the empirical likelihood ratio is defined via a constrained maximum, we first take care the constrain. We “arrange” (for lack of a better word) the constrained maximum into two components, a scalar λ and a function f , where the scalar takes care of the constraint and the arbitrary f will be maximized by Cauchy-Schwarz inequality.

Recall the log empirical likelihood ratio statistic is

$$-2 \log \frac{\max_{\int g dF=0} \prod_{\delta_i=1} \Delta F(t_i) \prod_{\delta_i=0} 1 - F(t_i)}{\prod_{\delta_i=1} \Delta \hat{F}_{km}(t_i) \prod_{\delta_i=0} 1 - \hat{F}_{km}(t_i)}. \quad (4)$$

Let us focus on the numerator of the above. The maximum is taken over all F that satisfy the constraint. We write the jumps of F to be maximized as

$$\Delta F(t_i) = \Delta \hat{F}_{km}(t_i) [1 - \lambda f(t_i)]. \quad (5)$$

This is to say that we only look at those F that are dominated by the Kaplan-Meier. This is just a tilt of the Kaplan-Meier in the **direction** f with **magnitude** λ . This will simplify the above expression, and before we go on we examine some of the requirements for f .

Since $\sum_{all} \Delta F(t_i)$ must be one, we must have $f(t_i)$ satisfy $\sum_{all} f(t_i) \Delta \hat{F}_{km}(t_i) = 0$.

Also the maximum require the constraint $\int g(t) dF(t) = 0$ (recall WLOG we assumed $\mu = 0$), this leads to an equation for the λ that satisfy

$$\lambda \sum_{all} g(t_i) f(t_i) d\hat{F}_{km}(t_i) = \sum_{all} g(t_i) d\hat{F}_{km}(t_i)$$

or we shall write the above as

$$\lambda A = gg,$$

where the definition of A and gg are defined by the above equation. Thus we have $\lambda = ggA^{-1}$.

Finally, (4) becomes

$$\begin{aligned} & -2 \log \max_{\int g dF=0} \prod_{\delta_i=1} [1 - \lambda f(t_i)] \frac{\prod_{\delta_i=0} \sum_{s>t_i} \Delta \hat{F}_{km}(s_j) [1 - \lambda f(s_j)]}{\prod_{\delta_i=0} 1 - \hat{F}_{km}(t_i)} \\ & = -2 \max_f \log \prod_{\delta_i=1} [1 - \lambda f(t_i)] \prod_{\delta_i=0} \frac{\sum_{s>t_i} \Delta \hat{F}_{km}(s_j) [1 - \lambda f(s_j)]}{1 - \hat{F}_{km}(t_i)}. \end{aligned}$$

Forth Step Here we calculate the derivatives and write out a Taylor expansion for

$$u(\lambda) = \log \prod_{\delta_i=1} [1 - \lambda f(t_i)] \prod_{\delta_i=0} \frac{\sum_{s>t_i} \Delta \hat{F}_{km}(s_j) [1 - \lambda f(s_j)]}{1 - \hat{F}_{km}(t_i)}.$$

$$u(\lambda) = u(0) + \lambda u'(0) + 1/2 \lambda u''(0) \lambda + \dots$$

Easy to check, $u(0) = \log(1) = 0$ and $u'(0) = 0$. (Without calculation, we can explain why $u'(0) = 0$: this log likelihood ratio $u(\lambda)$ achieves its maximum value 0 at $\lambda = 0$, therefore the derivative at $\lambda = 0$ must be 0.)

All then left to complete the above 3 term Taylor expansion is the calculation of $u''(0)$ which involves f . After this we can use Cauchy-Schwarz inequality of step 2 to find the maximum of u over f .

Long and tedious calculation show (see [11] for details)

$$u''(0)/n = - \sum [f - \bar{f}]^2 [1 - \hat{G}_{km}(t_i-)] \Delta \hat{F}_{km}(t_i) .$$

The Taylor expansion for the $-2 \log$ empirical likelihood ratio (before maximization) becomes

$$(\sqrt{n}\lambda) \frac{u''(0)}{n} (\sqrt{n}\lambda) + \dots = (\sqrt{n}gg) A^{-1} \frac{u''(0)}{n} A^{-1} (\sqrt{n}gg) + \dots .$$

Final Step is to use Cauchy-Schwarz to find the maximum of the middle part of above (which is the only place involving f)

$$A^{-1} \frac{u''(0)}{n} A^{-1} = \frac{\sum [f - \bar{f}]^2 [1 - \hat{G}_{km}(t_i-)] \Delta \hat{F}_{km}(t_i)}{[\sum g f \Delta \hat{F}_{km}(t_i)]^2} \quad (6)$$

and once we find the maximum achieved for this expression (6), the chi square limit is easy.

We recall the mean of f with respect to \hat{F}_{km} is zero, so we may rewrite the denominator of above as the square of covariance between f and g (under Kaplan-Meier measure). Therefore,

$$\sum g f \Delta \hat{F}_{km}(t_i) = \sum [g - \bar{g}] [f - \bar{f}] \Delta \hat{F}_{km}(t_i) .$$

Here we used a formula of covariance with advanced time, similar to the variance formula we discussed earlier. This equality is proved in [11], Lemma 26.

Now use (3) to see that the minimum of $-2 \times \log$ likelihood ratio over f is

$$(\sqrt{n}gg) \frac{1}{\int \frac{(g-\bar{g})^2}{1-\hat{G}_{km}(t-)} d\hat{F}_{km}(t)} (\sqrt{n}gg) + \dots .$$

This last expression, under null hypothesis, clearly has an asymptotic chi square distribution, with degree of freedom 1.

ADDITIONAL REFERENCE FOR THE APPENDIX:

Akritas, M. (2000). The central limit theorem under censoring. *Bernoulli* 6: 1109–1120.

Efron, B. and Johnstone, I. (1990). Fisher's information in terms of the hazard rate. *Ann. Statist.*, 18, 38–62.