

# Package ‘MetaSurv’

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**Type** Package

**Title** Meta-analysis of a single survival curve using the multivariate methodology of DerSimonian and Laird.

**Version** 0.4

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**Description** This package contains functions to assess a summary survival curve from survival probabilities and number of at-risk patients collected at various points in time in various studies, and to test the between-strata heterogeneity.

**License** GPL (>=2)

**LazyLoad** yes

**Depends** mvtnorm, survival

**Imports** mvtnorm, survival

**URL** [www.r-project.org](http://www.r-project.org), [www.divat.fr](http://www.divat.fr)

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MetaSurv-package	<i>Meta-analysis of a single survival curve using the multivariate DerSimonian and Laird methodology.</i>
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## Description

This package contains functions to assess a summary survival curve from survival probabilities and number of at-risk patients collected at various points in time in various studies, and to test the between-strata heterogeneity.

## Details

This package contains functions to assess a summary survival curve from survival probabilities and number of at-risk patients collected at various points in time in various studies. The multivariate DerSimonian and Laird methodology is applied to obtain the pooled estimates assuming random effects. The user enters the survival probabilities and the numbers of at-risk patients at the points in time selected by the user. The package computes the summary survival curve, the Q-statistic for heterogeneity, the I-squared and H index for heterogeneity, the mean and median (if possible) survival times from the summary survival curve. The categorical study-level factor can be explored as heterogeneity factor. The summary survival curve is computed in each stratum and the between-strata heterogeneity is tested.

Package:	MetaSurv
Type:	Package
Version:	0.4
Date:	2014-06-30
License:	GPL (>=2)
LazyLoad:	yes

msurv	Estimation of the summary survival curve from the survival rates and the numbers of at-risk individuals extracted from studies of a meta-analysis.
FTR.data	Summary survival curve from aggregated survival data of a meta-analysis and comparisons between strata of studies.
DataExample	The data extracted from a meta-analysis by Cabibbo et al.
Divat	Survival data extracted from the DIVAT cohort.

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## References

Combescure C., Foucher Y. and Jackson D. The multivariate DerSimonian and Laird's methodology applied to meta-analysis of survival curves. Manuscript submitted.

Cabibbo, G., et al., A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology*, 2010. 51(4): p. 1274-83.

Ladriere, M and Foucher, Y and Legendre, C and Kamar, N and Garrigue, V and Morelon, E and Kessler, M and Soullillou, JP and Giral M. The western europe cohort of kidney transplanted recipients - the DIVAT network. *Clinical transplants*; 2010:460-461.

### See Also

URL: <http://www.divat.fr>

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DataExample

*The data extracted from a meta-analysis by Cabibbo et al.*

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### Description

Data were extracted from the studies included in the meta-analysis by Cabibbo et al. which aimed to assess the survival rate in untreated patients with hepatocellular carcinoma.

### Usage

```
data(DataExample)
```

### Format

A data frame with with the 8 following variables (columns).

**Study** This numeric vector represents number of the study.

**FirstAuthor** This vector represents the name of the first author.

**YearPub** This numeric vector represents the publication year.

**Time** This numeric vector represents the times for which the survival rates are collected in years.

**Survival** This numeric vector represents the survival rates for each value of Time

**NbRisk** This numeric vector represents the number of at-risk patients for each value of Time

**Location** This factor indicates the location of the study (Asia, North Amercia or Europe)

**Design** This factor indicates if the study is monocentric ou multicentric.

### Details

The survival probabilities were extracted from the published survival curves each month during the first six months and then by step of three months. The pictures of the curves were digitalized using the R package ReadImage and the probabilities were extracted using the package digitize proposed by Poisot. The numbers of at-risk patients for each interval of time were derived from the numbers of at-risk patients reported in the studies, and using the methods of Parmar or Williamson to account for censorship. Studies have different length of follow-up. For each study, survival probabilities and the numbers of at-risk patients were collected at all points in time before the end of follow-up.

## References

- Combesure C., Foucher Y. and Jackson D. The multivariate DerSimonian and Laird's methodology applied to meta-analysis of survival curves. Manuscript submitted.
- Cabibbo, G., et al., A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology*, 2010. 51(4): p. 1274-83.
- Poisot, T., The digitize Package: Extracting Numerical Data from Scatter-plots. *The R Journal*, 2011. 3(1): p. 25-26.
- Parmar, M.K., V. Torri, and L. Stewart, Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*, 1998. 17(24): p. 2815-34
- Williamson, P.R., et al., Aggregate data meta-analysis with time-to-event outcomes. *Stat Med*, 2002. 21(22): p. 3337-51.

## Examples

```
data(DataExample)
Times <- DataExample$Time
Survival <- DataExample$Survival
Study <- DataExample$Study

plot(Times, Survival, type="n",
      ylim=c(0,1), xlab="Time",ylab="Survival")

for (i in unique(sort(Study)))
{
  lines(Times[Study==i], Survival[Study==i], type="l", col="grey")
  points(max(Times[Study==i]),
         Survival[Study==i & Times == max( Times[Study==i])], pch=15)
}
```

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Divat

*Survival data extracted from the DIVAT cohort*

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## Description

Data were extracted from the DIVAT cohort. According to this data set, patient and graft survival can be computed for each hospital.

## Usage

```
data(Divat)
```

## Format

A data frame with the 3 following variables (columns).

**hospital** This numeric vector represents the hospital in which the kidney transplantation was performed. Six hospitals were included.

**time** For right censored data, this numeric vector represents the follow up time (in days). When the event is observed, this numeric vector represents the exact time-to-event.

**status** This indicator describes the end of the follow-up. The status equals 0 for right censored data and 1 if the event is observed.

## Details

The data were extracted from the prospective multicentric DIVAT cohort ([www.divat.fr](http://www.divat.fr)). Patients transplanted between 2000 and 2012 in 6 French centers were included. Only adult patients receiving a single kidney transplant and treated by Calcineurin inhibitors and Mycophenolate Mofetil for maintenance therapy after transplantation were considered. In parallel, patients who received multi-organ transplantation were excluded from the study. 6,48 adult renal transplant recipients were included. The time-to-event under interest is the time between the kidney transplantation and the graft failure, i.e. the first event between the return in dialysis or the death of the patient with functional kidney.

## References

Combescur C., Foucher Y. and Jackson D. The multivariate DerSimonian and Laird's methodology applied to meta-analysis of survival curves. Manuscript submitted.

Ladriere, M and Foucher, Y and Legendre, C and Kamar, N and Garrigue, V and Morelon, E and Kessler, M and Soullillou, JP and Giral M. The western europe cohort of kidney transplanted recipients - the DIVAT network. *Clinical transplants*; 2010:460-461.

## Examples

```
data(Divat)

divat.surv <- survfit(Surv(time/365.24, status) ~ hospital, data = Divat)

plot(divat.surv, lty = 1:6, col=1:6, lwd=2, mark.time=FALSE,
      xlab="Post transplantation time (days)", ylab="Patient and graft survival")
```

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msurv

*Summary survival curve from aggregated survival data of a meta-analysis*

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## Description

Estimation of the summary survival curve from the survival rates and the numbers of at-risk individuals extracted from studies of a meta-analysis.

## Usage

```
msurv(study, time, n.risk, surv.rate, confidence)
```

## Arguments

study	A numeric vector with the numbering of the studies included in the meta-analysis. The numbering of a study is repeated for each survival probabilities extracted from this study.
time	A numeric vector with the time at which the survival probabilities are collected.
n.risk	A numeric vector with the number of at-risk patients in the study for each value of the time.

surv.rate	A numeric vector with the survival rates collected per study for each value of time.
confidence	A text argument indicating the method to calculate the 95% confidence interval of the summary survival probabilities: "Greenwood" or "MonteCarlo".

### Details

The survival probabilities have to be extracted at the same set of points in time for all studies. Missing data are not allowed. The studies included in the meta-analysis can have different length of follow-up. For a study ending after the time  $t$ , all survival probabilities until  $t$  have to be entered in data. The data are sorted by study and by time. The conditional survival probabilities are arc-sine transformed and thus pooled assuming fixed effects or random effects. A correction of 0.25 is applied to the arc-sine transformation. For random effects, the multivariate methodology of DerSimonian and Laird is applied and the between-study covariances are accounted. The summary survival probabilities are obtained by the product of the pooled conditional survival probabilities. The mean and median survival times are derived from the summary survival curve assuming a linear interpolation of the survival between the points.

### Value

verif.data	A data frame in which the first column (study) correspond to the number of the study and the second column (check) equals 1 if the time of collection for this study respects the other times for the other studies and 0 otherwise. Remember that the times of survival rates have to be identical between studies. The end of each study can be different. If at least one study did not respect this format, the other arguments values are non-attributed (NA).
summary.fixed	A matrix containing the summarized survival probabilities assuming fixed effects. The first column contains the time at which the summary survivals are computed. The second column contains the estimations of the summary survival probabilities. The third and fourth columns contain the lower and the upper bound of the 95% confidence interval, computed by either the Greenwood or the Monte Carlo approach as specified by the user.
median.fixed	A numerical vector containing the estimated median survival time computed from the summary survival curve assuming fixed effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.
mean.fixed	A numerical vector containing the estimated mean survival time computed from the summary survival curve assuming fixed effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.
heterogeneity	A numerical vector containing the value of the Q statistic for the heterogeneity, the H index and the I-squared index (in percentage).
summary.random	A matrix containing the summarized survival probabilities assuming random effects. The first column contains the time at which the summary survivals are computed. The second column contains the estimations of the summary survival probabilities. The third and fourth columns contain the lower and the upper bound of the 95% confidence interval around the summary survival probabilities, computed by either the Greenwood or the Monte Carlo approach as specified by the user.
median.random	A numerical vector containing the estimated median survival time computed from the summary survival curve assuming random effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.

mean.random      A numerical vector containing the estimated mean survival time computed from the summary survival curve assuming random effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.

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### References

Combescure C., Foucher Y. and Jackson D. The multivariate DerSimonian and Laird's methodology applied to meta-analysis of survival curves. Manuscript submitted.

Jackson D., White I.R. and Thompson S.G. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med*, 2010. 29(12): p.1282-97.

Jackson D., White I.R. and Riley R.D. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat Med*, 2012.

### Examples

```
# import and attach the data example
data(DataExample)

attach(DataExample)

# computation of the summary survivals

results<-msurv(Study, Time, NbRisk, Survival, confidence="Greenwood")
results

# plot the estimated summary survival curve against the extracted ones

RandomEffectSummary<- results$summary.random

plot(Time, Survival, type="n", col="grey", ylim=c(0,1),xlab="Time",
      ylab="Survival")

for (i in unique(sort(Study)))
{
  lines(Time[Study==i], Survival[Study==i], type="l", col="grey")
  points(max(Time[Study==i]),
         Survival[Study==i & Time==max(Time[Study==i])], pch=15)
}

lines(RandomEffectSummary[,1], RandomEffectSummary[,2], type="l",
      col="red", lwd=3)
points(RandomEffectSummary[,1], RandomEffectSummary[,3], type="l",
      col="red", lty=3, lwd=3)
points(RandomEffectSummary[,1], RandomEffectSummary[,4], type="l",
      col="red", lty=3, lwd=3)
```

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msurv.strata	<i>Summary survival curve from aggregated survival data of a meta-analysis and comparisons between strata of studies.</i>
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### Description

Estimation of the summary survival curve from the survival rates and the numbers of at-risk individuals extracted from studies of a meta-analysis and comparisons between strata of studies.

### Usage

```
msurv.strata(study, time, n.risk, surv.rate, confidence, strata)
```

### Arguments

study	A numeric vector with the numbering of the studies included in the meta-analysis. The numbering of a study is repeated for each survival probabilities extracted from this study.
time	A numeric vector with the time at which the survival probabilities are collected.
n.risk	A numeric vector with the number of at-risk patients in the study for each value of thr time.
surv.rate	A numeric vector with the survival rates collected per study for each value of time.
confidence	A text argument indicating the method to calculate the 95% confidence interval of the summary survival probabilities: "Greenwood" or "MonteCarlo".
strata	A factor designing the strata. Each stratum has to contain at least two studies.

### Details

The survival probabilities have to be extracted at the same set of points in time for all studies. Missing data are not allowed. The studies included in the meta-analysis can have different length of follow-up. For a study ending after the time t, all survival probabilities until t have to be entered in data. The data are sorted by study and by time. The conditional survival probabilities are arc-sine transformed and thus pooled assuming fixed effects or random effects. A correction of 0.25 is applied to the arc-sine transformation. For random effects, the multivariate methodology of DerSimonian and Laird is applied and the between-study covariances are accounted. The summary survival probabilities are obtained by the product of the pooled conditional survival probabilities. The mean and median survival times are derived from the summary survival curve assuming a linear interpolation of the survival between the points. The summary survival curve is assessed in each stratum. The duration of follow-up is the greatest duration for which each stratum contains at least two studies reporting the survival at this duration. The between-strata is assessed and tested.

### Value

verif.data	A data frame in which the first column (study) correspond to the number of the study and the second column (check) equals 1 if the time of collection for this study respects the other times for the other studies and 0 otherwise. Remember that the times of survival rates have to be identical between studies. The end of each study can be different. If at least one study did not respect this format, the other arguments values are non-attributed (NA).
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<code>summary.fixed</code>	A list of matrix. Each matrix contains the summarized survival probabilities assuming fixed effects. Each matrix provides the results for one stratum. The first column contains the time at which the summary survivals are computed. The second column contains the estimations of the summary survival probabilities. The third and fourth columns contain the lower and the upper bound of the 95% confidence interval, computed by either the Greenwood or the Monte Carlo approach as specified by the user. The last element of the list is the summary survival when all strata are pooled.
<code>summary.random</code>	A list object containing the summarized survival probabilities in each stratum assuming random effects. The results are presented similarly as <code>summary.fixed</code> .
<code>median.fixed</code>	A numerical vector containing the estimated median survival time computed from the summary survival curve assuming fixed effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.
<code>mean.fixed</code>	A numerical vector containing the estimated mean survival time computed from the summary survival curve assuming fixed effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.
<code>heterogeneity</code>	A numerical vector containing the value of the Q statistic for the heterogeneity, the H index and the I-squared index (in percentage).
<code>p.value</code>	The p-value of the test for the null hypothesis that the between-strata heterogeneity is null.

### Author(s)

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 C. Combescure <Christophe.Combescure@hcuge.ch>

### References

Combescure C., Foucher Y. and Jackson D. The multivariate DerSimonian and Laird's methodology applied to meta-analysis of survival curves. Manuscript submitted.  
 Jackson D., White I.R. and Thompson S.G. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med*, 2010. 29(12): p.1282-97.  
 Jackson D., White I.R. and Riley R.D. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat Med*, 2012.

### Examples

```
# import and attach the data example
data(DataExample)

attach(DataExample)

# computation of the summary survivals

results<-msurv.strata(study = Study, time = Time, n.risk = NbRisk,
  surv.rate = Survival, confidence="Greenwood", strata = Location)

results
```

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