iSQoL2 package

Version 7.0 (2024/09/12)

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News for the version 7.0:

- Owing to the current R package "namespace" without binary version, users need to install **Rtools** on your computer to compile the source form into the binary version.
- Allow assigning a weight to each observation in the index cohort to estimate the confounder-adjusted survival function and the mean cost function. (Lo WC, Hu TH, Shih CY, Lin HH, Hwang JS (2024))
- The R packages "ff", "ffbase", "bit" and "fastmatch" are unnecessary.
- Update the abridged life tables for Taiwan from 1991 to 2023.

1. **Description**

The **iSQoL2** 7.0 is a free **R** package for Microsoft Windows. It is developed using the open source **R** software (version 4.4.1) and relies on seven R packages (**data.table, lokern**, **namespace**, **plotrix**, **rms**, **survival** and **tcltk**). To use **iSQoL2**, you need to install **R** and these **R** packages on your Windows computer. The following two sections describe how to install and start **iSQoL2** in **R**.

The **iSQoL2** provides the following functions:

(1) Major functions: The details are described in section 4.

  (A) To extrapolate with or without a confounder-adjusted lifetime survival function and to estimate life expectancy (LE) for an index cohort with a specific disease or condition.

  (B) To extrapolate with or without a confounder-adjusted mean cost function to obtain the expected lifetime cost (COST) for an index cohort when long-term records of subjects' medical expenditures are available.

  (C) To extrapolate the mean QoL function to obtain quality-adjusted life expectancy (QALE) for an index cohort. Note that a sample of repeated QoL measurements from subjects is required.

  The execution of the last two functions, (B) and (C), depends on the extrapolated survival function from (A). Therefore, the lifetime survival rate must be estimated before executing (B) and (C).

(2) Additional functions: Details are described in Section 5.

  It includes five additional functions listed below, each of which is executed based on the temporary output file of the major function.

  - To compare life expectancy (LE), the expected lifetime cost (COST) or quality-adjusted life expectancy (QALE) between two groups.
  - To compare the expected loss-of-LE or loss-of-QALE between two groups.
  - To calculate cost-effectiveness ratio (CER).
  - To calculate incremental cost-effectiveness ratio (ICER).
  - Plot multiple curves as follows:
    - Survival function, quality-adjusted survival function
    - Loss function of LE or QALE
    - Mean cost function

2. **How to install iSQoL2**

Please follow the steps below to install **iSQoL2** and the required **R** packages (**data.table**, **lokern**, **namespace**, **plotrix**, **rms, Hmisc, survival, tcltk**) with the binary version.

Step1. Check whether **R** (version ≥4.4.x for Windows) and **Rtools** (version 4.4) are already installed on your computer. If not, please download and install **R** and **Rtools** from https://cran.r-project.org/bin/windows/base/ and https://cran.r-project.org/bin/windows/Rtools/, respectively. Since the current **R** package "**namespace**" is only available in source form, you will need to use **Rtools** to build the binary version.

Step2. Download **iSQoL2_MyWork.zip** from http://sites.stat.sinica.edu.tw/isqol/ and unzip it into a folder on your computer (for example, "**C:/Project**").

Step3. Download the file "namespace_0.9.1.tar.gz", the source form of the package "namespace", from https://cran.r-project.org/src/contrib/Archive/namespace/ and save it into the directory "~/iSQoL2_MyWork/Rpackages".

Step4. Open the file "**C:/Project /iSQoL2_MyWork/Rpath.txt**" and update it with the correct the location of "**Rgui.exe**" (the execution file for starting R). To find the location, right-click the **R** icon on your desktop, click **Properties**, and check the **Target** field.

Step5. Double-click **C:/Project /iSQoL2_MyWork/Ropen.bat** to start **R**.

Step6. Execute the command **source('Start_iSQoL2.R')** in the **R** console to create the initial settings for **iSQoL2** and check whether the required R packages are installed on your computer. If any packages are missing, they will be automatically installed from http://cran.uk.r-project.org. An active internet connection is required for this step.

Step7. Quit **R** to complete the installation of **iSQoL2**.

After running the above steps, users will find a folder named ".iSQoL2" in their Documents directory, typically located at "C:/Users/.../Documents/.iSQoL2". This folder will have an initialization file named "InitialParameters.txt" and an "Example" folder with 8 sample data files (*.txt) and 3 input files (*.csv). The detailed descriptions of the file "InitialParameters.txt" are provided in Table 1. Users can modify the initialization parameters through the menu "**iSQoL2/Update initial parameters**". The files in the "Example" folder are listed below and described in section 4 for more details.

— 8 example data files:
  - Data files of the index cohort I: "AgeSurF120_1.txt", "CostF120_1.txt" and "QolF120_1.txt" are the first example data for estimating LE, COST and QALE, respectively.
  - Data files of the index cohort II: "AgeSurF120_2.txt", "CostF120_2.txt" and "QolF120_2.txt" are the second example data for estimating LE, COST and QALE,

respectively.

- "Qol_ref1.txt" and "Qol_ref2.txt" are the average QoL for each age-sex group of the general reference population for the first and second examples, respectively.

- 3 input files: Each input file contains filenames of example data and parameters for running the major function of **iSQoL2**. The files "inputS.csv", "inputC.csv" and "inputQ.csv" are the input file used to execute the estimation of LE, COST and QALE, respectively.

Table 1. The descriptions of the parameters file "InitialParameters.txt".

Parameter	**Description**
• ..OutDir = ""	• The output directory of the additional functions. The default is the user documents directory (typically located at "C:/Users/…/Documents/.iSQoL2").
• ..GraphType = 1	• File format for saving the current figure. Default is Portable Network Graphic (png) Format. ..GraphType = 1(png), 2(jpg), 3(jpeg), 4(tif), 5(tiff), 6(pdf), 7(wmf), 8(emf), 9(bmp), 10(ps), 11(eps)
• ..Xlab = "Time in months"	• Horizontal axis title of a plot.
• ..ConvertToCsv = FALSE	• Convert the output file "*.rds" to "*.csv".
• ..OneWindow = 1	• The value is 0 for using multiple graphics devices to display different plots while executing the major function. The default is 1, which uses a single graphics device. It is recommended to set the value to 1 when running on multiple datasets simultaneously.
• ..SMethod = 1	• The value is 1 or 2, respectively, for using Kaplan-Meier method or Weibull model to estimate survival function during follow-up time. Default is 1.
• ..n.knots = 5	• The number of knots in the restricted cubic spline (RCS) model used for the rolling extrapolation algorithm to estimate lifetime survival function. Default is 5.
• ..FirstN.Sdel = 6	• The data, excluding the first 6 (=..FirstN.Sdel) time points, are used for the first step in the rolling extrapolation algorithm.
• ..TransformType=1	• The type of transformation for the ratio ($W(t)=S_{ind}(t)/S_{ref}(t)$, $0 < W(t) < 1$) of the index's survival function (S_{ind}) to the reference's survival function (S_{ref}). There are two types listed below. The default is the first type. – ..TransformType is 1 for logit(.) transformation, i.e., using the relationship between logit[W(t)] and t to fit RCS model. – ..TransformType is 2 for -log(-log(.)) transformation, i.e., using the relationship between -log[-log(W(t))] and log(t) to fit the

	RCS model.
• ..SepHRef = 36	• The parameter is used to estimate the hazard function $h_H(t)$ of the healthy (virtual) reference group, which is available in version ≥ 6.0. Let $h_H(t) = h_G(t) - (DM + \varphi \times SD)$. DM is the average difference ($h_G(t) - h_I(t)$ over t=$F - ..\text{SepHRef} + 1$), ..., F, representing the hazard difference between the general reference and the index group. – ..SepHRef: Number of time points used to estimate DM. Default value is 36 months. – φ: The value is automatically estimated by **iSQoL2** such that $h_H(t)$ is less than $h_I(t)$. – $h_G(t)$ is the hazard function of the general reference group. – $h_I(t)$ is the hazard function of the index group.
• ..SetNoIPTW_S = FALSE	• TRUE (Forcefully set all weights to 1 for all observations to run the adjusted Kaplan-Meier estimator when the data file includes weights that are not equal to 1), FALSE (Depends on the weights in the data file.)
• ..SetNoIPTW_C = FALSE	• TRUE (Forcefully set all weights to 1 for all observations to run the mean cost function when the cost data file includes weights that are not equal to 1), FALSE (Depends on the weights in the data file.)
• ..DiscountFromT = -1	• Time (t^{th} month) to start discounting in estimating COST/QALE/LE. The value is a positive integer or -1. The default value is -1, which represents t = (1 + maximum follow-up time of the index cohort).

3. **How to start iSQoL2 on R**

Suppose you have installed **iSQoL2** in the directory, for example "C:/Project". Follow the following steps to start **iSQoL2** in R.

Step1. Make sure the path in the file "C:/Project/iSQoL2_MyWork/Rpath.txt" matches the location of **Rgui.exe**. If it does not, **R** will not start up successfully.

Step2. Click "C:/Project/iSQoL2_MyWork/Ropen.bat" to start **R**.

Step3. Execute the command **source("Start_iSQoL2.R")** in R console to create the **iSQoL2** menu, as shown in the figure below.

Step4. You can then click **Run** within the **iSQoL2** menu to start running the estimates of life expectancy, lifetime cost, quality-adjusted life expectancy and other command functions. All commands within the **iSQoL2** menu are described in Table 2.

Table 2. The command descriptions of **iSQoL2** menu.

Command	**Description**
Run:	*Major functions of **iSQoL2**. The execution details are described in Section 4.*
• (A) Survival extrapolation and LE	• To estimate the extrapolated lifetime survival function and obtain LE. The temporary output file (*.rds) generated by this execution will be used for running (B), (C), and functions in the "**Additional functions**" menu and the "**Discount for LE/QALE/COST**" menu.
• (B) COST	• Use the estimated lifetime survival function to extrapolate the mean cost function and estimate COST. The temporary output file (*.rds) generated by this execution is required for running functions in the "**Additional functions**" menu and the "**Discount for LE/QALE/COST**" menu.
• (C) QALE	• Use the estimated lifetime survival function to extrapolate the mean QoL function and estimate QALE. The temporary output file (*.rds) generated by this execution is required for running functions in the "**Additional functions**" menu and the "**Discount for LE/QALE/COST**" menu.
Additional functions:	*The commands are applications based on the temporary output file (*.rds) generated by the major function ((A) or (B) or (C)). Details are described in Section 5.*
• Comparison of LE/QALE/COST	• Compare LE, COST or QALE over a given time period between two groups. It is necessary to provide the temporary output files (*.rds) from (A) or (B) or (C) for both groups.

• Comparison of the loss of LE/QALE	• Compare the loss of LE or QALE over a given time period between two groups. It is necessary to provide the temporary output files (*.rds) from (A) or (C) for both groups.
• CER	• Calculate the cost-effectiveness ratio (CER). It is necessary to provide the temporary output files (*.rds) from either (B) and (A) or (B) and (C).
• ICER	• Calculate the incremental cost-effectiveness ratio (ICER) between two groups. It is necessary to provide the temporary output files (*.rds) from either (B) and (A) or (B) and (C).
• Plot multiple curves	• Plot multiple curves for – survival function or quality-adjusted survival function – loss function of LE or QALE – mean cost function
Discount for LE/QALE/COST	• Use the given annual discount rate(s) to discount LE, QALE or COST. It is necessary to provide the temporary output files (*.rds) generated from (A), (C) or (B).
Close Graphics:	Close all graphics devices if there are too many open devices in **R** console.
Update Initial Parameters:	Update the parameters described in Table 1. To change any parameter value, click on it to edit and update the parameter settings.
Help:	Open ‘iSQoL2Help.pdf’ to get the **iSQoL2** manual.

4. **How to execute the major function**

4.1. **How to execute the estimation of life expectancy (LE)**

The following steps provide step-by-step guide on how to execute the extrapolation of survival function beyond the follow-up time and the estimation of LE. See Hwang et al., 2017 for details.

Notation:

- F_s: The maximum follow-up time from the onset.
- F: The last month before starting the extrapolation of survival function, where $F \leq F_s$.
- L: The time at which the extrapolation ends, where $F \leq F_s \leq L$. When $L = F_s$, the **iSQoL2** does not execute the rolling extrapolation algorithm.
- W(t): The ratio of the index's survival function ($S_{ind}(t)$) to the reference's survival function ($S_{ref}(t)$). $S_{ref}(t)$ is the general reference's survival function. If the index's survival function is greater than the general reference's survival, the **iSQoL2** system will replace the reference's survival function $S_{ref}(t)$ with the healthy function $S_{ref}(t) \times e^{\delta t}$.
- H: The number of time points (in months) in the last segment of the Restricted Cubic Spline (RCS) model used to fit the transformation of W(t).

Step1. **Prepare your data files with tab-delimited or space-delimited text format and save them in UTF-8 without BOM.**

Suggest you use notepad++ to edit these files. The files are described below.

- **Survival, age and sex file**:
  - Six columns without specifying column names.
    - 1st column: The onset year (A.D.) of the index cohort.
    - 2nd column: The onset age (year) of the index cohort.
    - 3rd column: The gender code is 1 for male and 0 for female.
    - 4th column: The survival time, defined as the duration from onset to death or the last known alive status, a positive real value in months for the index cohort. The maximum follow-up time is denoted as F_s.
    - 5th column: The status indicator is 0 for a censored case (alive at the end of follow-up) and 1 for a completed case (dead during the F_s-month follow-up).
    - 6th column: When biased estimators of survival function are due to confounding factors between groups, weights should be used to estimate the adjusted survival function. The purpose is to create a pseudo-population in which the distributions of the confounding factors are similar between groups. It is recommend that weights are given using inverse-probability of

treatment weighting (IPTW) method. If the column is omitted, the system will assign equal weight to all individuals in the index cohort. For more details, please refer to Xie J. and Liu C. (2005).

  - The first three columns are used to generate the survival times of the reference population, which is matched by the onset year, onset age and gender of the index cohort.
  - The last three columns are used to estimate the survival function of the index cohort during the follow-up period using either Kaplan-Meier or weighted Kaplan-Meier methods.
  - Two example files, named "AgeSurF120_1.txt" and "AgeSurF120_2.txt", contain data for 5,000 individuals with 120-month follow-up, and are located in the directory "C:/Users/.../Documents/.iSQoL2/Example". Both datasets have 5 columns and assign equal weight to all individuals in the index cohort.

- **Create a directory containing annual life table files**: These files are used to create the survival function of the reference population, which assists the index cohort in the extrapolation of survival function.
  - First, create a folder and put the annual life table files in it.
  - The annual life table files should be in the format of "&&****.txt". The "&&" represents two English letters, and "****" is the 4-digit year (A.D.). For example, "TW1999.txt".
  - Each file has 3 columns with no specified column names. The 1st column is age in years, and the 2nd and 3rd columns are the probabilities of death within one year for male and female, respectively.
  - When the death rate of a 110-year-old is missing, it is assumed to be 1.
  - The system will use these files to generate survival times for 100,000 individuals in the reference population, matched by the onset year, onset age and gender of the index cohort.
  - For example, the abridged life tables of Taiwan from 1991-2023 are included in the folder "C:/Project/iSQoL2_MyWork/Rpackages/iSQoL2/LifetableTW".

Step2. **Create an input file in EXCEL and save it as a CSV file with comma-separated values.** The CSV file specifies the input data files and parameters for executing the extrapolation of survival function for the index cohort. It contains 7 columns and at least 2 rows, as described below:

- Two or more rows:
  - 1st row: the column names.
  - 2nd row, 3rd row, etc.: The data files and execution parameters for the first index

cohort, the second index cohort, and so on.

- 7 columns:
  - 1st column: Number (*NB*) of bootstrap samples for estimating standard error of LE. The value must be an integer greater than or equal to 30. By default, it is set to 100.
  - 2nd column: The parameter, *F* ($F \leq F_s$), is the last month (since onset) before starting the rolling extrapolation algorithm. By default, *F* is set to F_s.
  - 3rd column: The parameter *L* is the time of ending the extrapolation. The value must be an integer greater than or equal to *F*. In other words, the rolling extrapolation algorithm will predict survival rate at times $F+1, F+2, \ldots., L$. When the survival rate at time *L* approaches 0.005 or is less than 0.005, *L* is considered suitable.
  - 4th column: The parameter *H* is the number of time points in the last segment of the restricted cubic spline (RCS) model used to fit the transformation of the ratio ($W(t)=S_{ind}(t)/S_{ref}(t)$). In other words, the transformation of W(t) for $(F-H+1) \leq t \leq F$, is restricted to a straight line. The default value is set to 12. The *H* is often between 12 and 24.
  - 5th column: The directory for saving the annual life table files prepared in Step 1. If the value is empty, it is regarded as "C:/Project/iSQoL2_MyWork/Rpackages/iSQoL2/LifetableTW" (the abridged life tables of Taiwan).
  - 6th column: The file with full path contains onset year, onset age, gender and survival data of the index cohort, as prepared in Step 1.
  - 7th column: The output directory is used for saving temporary output files and graph files. Note that the directories specified in each row must be different for each index cohorts.
- An example file named "InputS.csv" is located at "C:/Users/…/Documents/.iSQoL2/Example/InputS.csv". It contains three rows: the first row shows the column names, and two datasets will be executed. The settings for each column are described below.
  - *NB* (Number of bootstrap samples) = 100.
  - *F* (the last month before starting extrapolation) = 120 months.
  - *L* (Time of ending extrapolation) = 618 months.
  - *H* (Number of months beyond the last knot) = 12.
  - The fifth column is the abridged life tables of Taiwan area in the directory.
  - The sixth column contains two filenames for age-sex and survival data of the index cohort: "C:/Users/…/Documents/.iSQoL2/Example/AgeSurF120_1.txt" and "C:/Users/…/Documents/.iSQoL2/Example/AgeSurF120_2.txt". The first file

contains 5columns, and the second file contains 6 columns. Both files assign an equal weight of 1 to all observations.

- Output directory: "C:/Users/…/Documents/.iSQoL2/Example/Out1S" and "C:/Users/…/Documents/.iSQoL2/Example/Out2S".

Step3. **Begin extrapolating survival function and estimate life expectancy**.

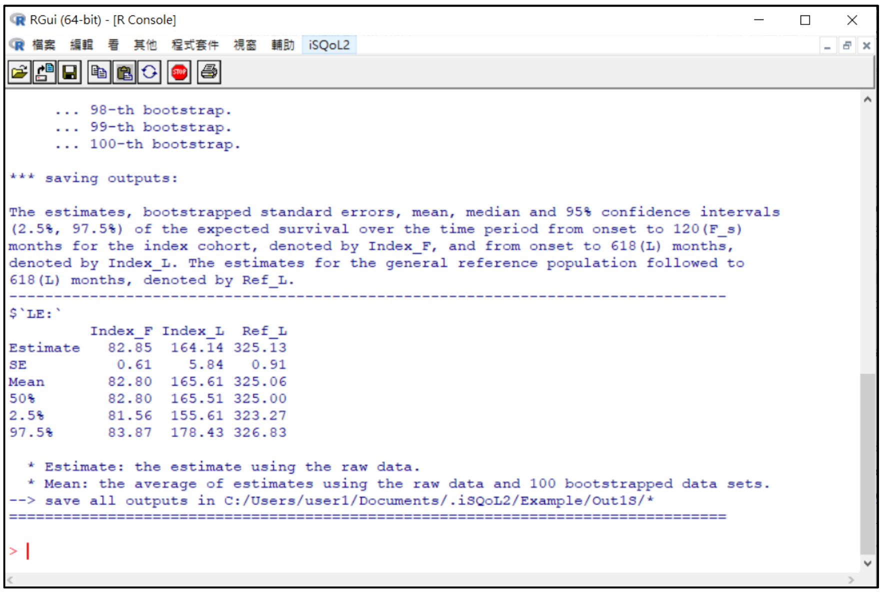
(3.1) Click [**iSQoL2/Run/(A) survival extrapolation and LE**] menu to select an input file ("InputS.csv") to start the execution. Note that if the program unexpectedly stops executing, it may be due to the increase in the transformation of W(t) with *t* during the last few months of *F*. Therefore, we suggest using a smaller value for *F* (e.g., *F* - 6) and re-running the step.

(3.2) After the execution is finished, a text output and four figures are shown in **R** console (depending on the parameter settings, the graphics device may display only the last output figure). These outputs are saved in the output directory specified in the input file and are described below.

- A text output: (*_sy.txt)

  The contents shown as Table 4.1.1 include the estimates, bootstrapped standard errors, bootstrapped means, bootstrapped medians, and 95% bootstrap confidence intervals of LE from onset to F_S (Index_F) and to *L* (Index_L) for the index cohort. The results also include the estimates for the general reference population from onset to *L* (Ref_L).

Table 4.1.1 The text output of the estimated LE is shown in **R** console.



```
     ... 98-th bootstrap.
     ... 99-th bootstrap.
     ... 100-th bootstrap.

*** saving outputs:

The estimates, bootstrapped standard errors, mean, median and 95% confidence intervals
(2.5%, 97.5%) of the expected survival over the time period from onset to 120(F_s)
months for the index cohort, denoted by Index_F, and from onset to 618(L) months,
denoted by Index_L. The estimates for the general reference population followed to
618(L) months, denoted by Ref_L.
--------------------------------------------------------------------------------
$`LE:`
         Index_F Index_L  Ref_L
Estimate   82.85  164.14 325.13
SE          0.61    5.84   0.91
Mean       82.80  165.61 325.06
50%        82.80  165.51 325.00
2.5%       81.56  155.61 323.27
97.5%      83.87  178.43 326.83

  * Estimate: the estimate using the raw data.
  * Mean: the average of estimates using the raw data and 100 bootstrapped data sets.
--> save all outputs in C:/Users/user1/Documents/.iSQoL2/Example/Out1S/*
================================================================================

> |
```

- Figures:
  - SurvF.*: The estimated survival probability of the index cohort and the

general reference population from onset to F_s.

  - TransformationWF.*: The figure includes two lines: the transformation of W(t) from onset to F_s and the prediction curve of the restricted cubic spline (RCS) regression model. If the index's survival function is greater than that of the general reference, the denominator of W(t) is the healthy (virtual) reference's survival function.
  - LogitWL.*: The transformation of W(t) from onset to the given L. If the index's survival function is larger than that of the general reference, the denominator of W(t) is the healthy (virtual) reference's survival function.
  - TransformationWL.*: The figure includes the extrapolated survival probability of the index cohort and the generated survival probability of the general reference population from onset to the given L.
- A temporary file:
  - The output file named "SurvivalOnly.rds" is a serialized object containing a list of **R** objects, including (NB+1) estimated survival functions of the index cohort and the general reference population, and so on. User can use the command "readRDS" to load it in **R**. Note that this file will be necessary for executing COST (Section 4.2), QALE (Section 4.3), additional functions (Section 5) and the discount for LE/QALE/COST (Section 6).

4.2. **How to execute the estimation of lifetime cost (COST)**

The following steps provide a detailed guide on how to execute the extrapolation of the mean cost function and the estimation of COST for the index cohort. The method uses the estimated survival rate from onset (t=0) to the end of the extrapolation (t=L) to extrapolate the mean cost function. The estimation of COST is then calculated using the extrapolated survival function and the extrapolated mean cost function. Therefore, you need to estimate LE before estimating COST. See Hwang et al., 2017 for details.

Notation:

- F_c: The maximum observed time for the costs of the index cohort since onset.
- F: The last month before starting extrapolation of the mean cost function, $F \leq F_c$.
- L: The time at which the extrapolation ends, $F \leq F_c \leq L$. The parameter is determined by the input value of L for the estimating LE.
- K and B: The parameters are used for extrapolating the mean cost function of the index cohort.

Step1. **Prepare your data files with tab-delimited or space-delimited text format and save them in UTF-8 without BOM**.

Suggest using notepad++ to edit these files. The files are described below.

- **Cost file**:

  The file has (F_c +3) columns and no column names.

  - 1st column: When biased estimators of the mean function are due to confounding factors between groups, weights should be used to estimate the mean cost function. The purpose and method for estimating these weights are described in Section 4.1. If no confounding factors are considered, all value in the first column are set to 1.
  - 2nd column: The value represents the survival time from onset to the time at which the subject died during the F_c-month period. For censored subjects, input the time with -1.
  - 3rd to the last column: Monthly accumulated cost per subject at each month from the onset to F_c. The costs at t=0, 1, 2, …, F_c are recorded in the third, fourth, …, (F_c +3)th columns, respectively. Each row indicates a subject's monthly costs. Note three things:

    (a) When a subject has no medical cost in any 1-month period, the monthly cost is set to 0.

    (b) The cost values beyond death or loss of follow-up are set to -1.

    (c) Total costs associated with the onset event before the onset can be summed into the cost at onset (recorded in the third column). If a subject had no additional cost records before onset, set the value to 0 in the third column.

- The example file named "costF120.txt" is saved in the directory "C:/Users/…/ Documents/.iSQoL2/Example". It contains the monthly costs for 5000 individuals over a period of F_c =120 months.

- **A temporary output file of the estimated LE**:

  The temporary file named "SurvivalOnly.rds" is an output file described in Section 4.1.

  - The example file is "C:/Users/…/Documents/.iSQoL2/Example/Out1S/Temporary/SurvivalOnly.rds".

Step2. **Create an input file in EXCEL and save it as a CSV file with comma-separated values**.

The CSV file contains data filenames and parameters used to estimate lifetime cost. It has 7 columns and 2 or more rows. The descriptions are as follows:

- Two or more rows:
  - 1st row: the column names.
  - 2nd row, 3rd row, ...: Filenames of data files and the input parameters for the first index cohort, the second index cohort, and so on.
- 7 columns:
  - 1st column: Number (*NB*) of bootstrap samples used to estimate the standard error of lifetime cost. The value is an integer greater than or equal to 30. The default value is set to 100.
  - 2nd column: The parameter *F* represents the last month before starting to extrapolate the mean cost function. Set *F* to F_c as the default value.
  - 3rd and 4th column: The parameters K and B are used to calculate the average costs $\overline{C_k}$ at $k = 0, 1, \dots, K, K^+$ months for extrapolating the mean cost function. The average costs $\overline{C_k}$ are calculated by the observed costs of subjects who died or alive during the $(F - B + 1)^{\text{th}}$ to F^{th} months. The value of B is a positive integer, and K can be -1 or 0 or a positive integer. When K=-1, the extrapolated mean cost function is assumed to be constant over time. Set K=12 and B=12 as the default values.
  - 5th column: Cost filename with full path for the index cohort.
  - 6th column: The output directory of estimating LE, as described in Section 4.1.
  - 7th column: The output directory is used for saving temporary output files and graph files. Note that the directories specified in each row must be different for each index cohorts.
- An example file located at "C:/Users/…/Documents/.iSQoL2/Example/InputC.csv" contains three rows: the first row lists the column names, and the second and third rows contain the specified data filenames and parameters for estimating lifetime

COST. The settings for each column are described below.

- *NB* (Number of bootstrap samples) = 100 for both data sets.
- Set *F* = F_c =120 months for both data sets.
- The parameters *K*=12 and *B*=12 for both data sets.
- The filenames for the cost data are "C:/Users/…/Documents/.iSQoL2/Example /costF120_1.txt" and "C:/Users/…/Documents/.iSQoL2/Example /costF120_2.txt".
- The Two output directories for estimating LE are "C:/Users/…/Documents/.iSQoL2/Example/Out1S" and "C:/Users/…/Documents/.iSQoL2/Example/Out2S".
- The output directories for saving the executed outputs are "C:/Users/…/ Documents/.iSQoL2/Example/Out1C" and "C:/Users/…/ Documents/.iSQoL2/Example/Out2C".

Step3. **Start extrapolating the mean cost function to obtain the lifetime COST**.

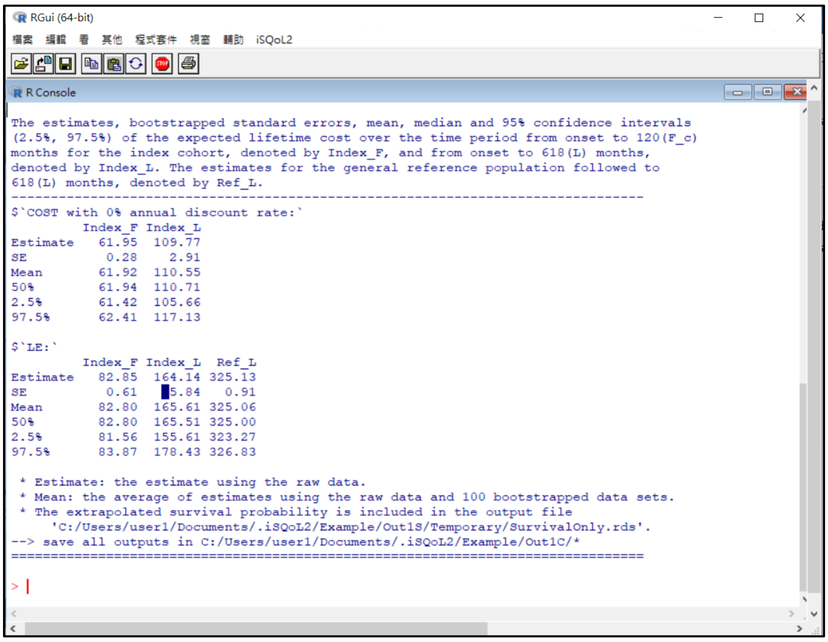
(3.1.) Click the [**iSQoL2/Run/(B) COST**] menu to select the input file "InputC.csv" to start the execution.

(3.2.) When the execution is finished, a text output and figures are shown in **R** console, and all output files are saved in the output directory specified in "InputC.csv". These outputs, saved in the specified output directory, are described below:

- A text output: (*_sy.txt)
  The results shown in Table 4.2.1 contain the estimates, bootstrapped standard errors, bootstrapped means, bootstrapped medians and 95% bootstrap confidence intervals for the expected cost from onset to the given *F* and from the onset to the end of extrapolation (*L*) for the index cohort. The results also provide the estimates of LE specified in the sixth column of the "InputC.csv" file.
- Figures:
  - CjB*K*.*: The average cost in *K* months prior to death and the average cost of subjects who won’t die within *K* months, for the given *K* and *B*.
    For example, the figure is shown as Figure 4.2.1(A) for (*B*, *K*) = (12, 12). It is saved to a file named "CjB12K12.tiff", and its values are saved in the third row of the file "CjB12K12.txt", estimated using the raw data. The values estimated using the the bootstrapped data sets are recorded starting from the fourth row of the file "CjB12K12.txt".
  - MeanCostF.*: The mean cost function over time from onset to *F* (the previous month before starting extrapolation) is plotted as Figure 4.2.1(B).
  - MeanCostE.*: The mean cost function over time from onset to the end of extrapolation (*L*) is plotted as Figure 4.2.1(C).
- A temporary file:

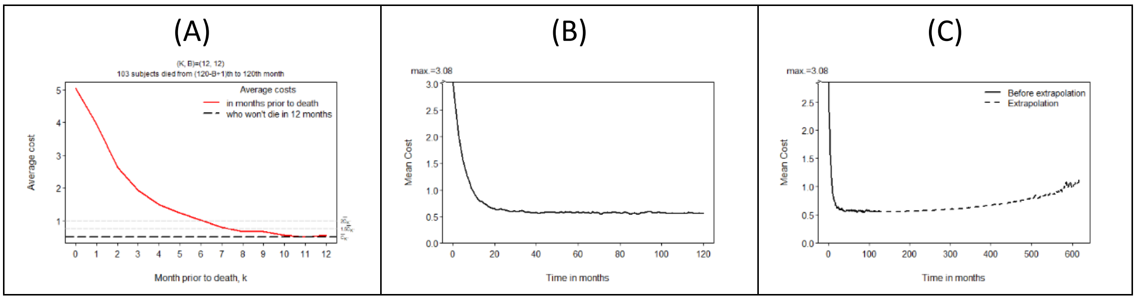
- The output file named "CostRate0.rds" is saved in the specified folder named "Temporary". It is a serialized object containing a list of **R** object, including (*NB*+1) estimated mean cost functions and survival-weighted mean cost functions from onset to the end of extrapolation for the index cohort, and so on. This file will be used for the execution of Section 5 and 6.

Table 4.2.1 The text output for estimating lifetime cost is shown in **R** console.



```
The estimates, bootstrapped standard errors, mean, median and 95% confidence intervals
(2.5%, 97.5%) of the expected lifetime cost over the time period from onset to 120(F_c)
months for the index cohort, denoted by Index_F, and from onset to 618(L) months,
denoted by Index_L. The estimates for the general reference population followed to
618(L) months, denoted by Ref_L.
--------------------------------------------------------------------------------
$`COST with 0% annual discount rate:`
         Index_F Index_L
Estimate   61.95  109.77
SE          0.28    2.91
Mean       61.92  110.55
50%        61.94  110.71
2.5%       61.42  105.66
97.5%      62.41  117.13

$`LE:`
         Index_F Index_L  Ref_L
Estimate   82.85  164.14 325.13
SE          0.61    5.84   0.91
Mean       82.80  165.61 325.06
50%        82.80  165.51 325.00
2.5%       81.56  155.61 323.27
97.5%      83.87  178.43 326.83

 * Estimate: the estimate using the raw data.
 * Mean: the average of estimates using the raw data and 100 bootstrapped data sets.
 * The extrapolated survival probability is included in the output file
     'C:/Users/user1/Documents/.iSQoL2/Example/Out1S/Temporary/SurvivalOnly.rds'.
--> save all outputs in C:/Users/user1/Documents/.iSQoL2/Example/Out1C/*
================================================================================

> 
```

Figure 4.2.1 The output figures after executing the lifetime cost estimation.



4.3. **How to execute the estimation of quality-adjusted life expectancy**

The following steps provide a step-by-step instruction on how to execute the extrapolation of the mean QoL function to estimate QALE (quality-adjusted life expectancy). See Chung et al., 2020 for details.

This method uses the survival rate from onset (t=0) to the end of extrapolation (t=L) to extrapolate the mean QoL function, and then estimate the quality-adjusted life expectancy using both the survival rate and the mean QoL function. Therefore, the temporary output file "SurvivalOnly.rds", as described in Section 4.1, is required before executing the QALE estimation.

Notation:

- F_q: The maximum assessment time of QoL data.
- L: The time at which extrapolation ends, where $F_q \leq L$.
- b: The bandwidth of the kernel smoothing function used to estimate the mean QoL function from the diagnosis time to the maximum assessment time.
- K and B: Parameters for extrapolating the mean QoL function.
- F_b (=F): The month before starting extrapolation, equal to (100-b)th percentile of all assessment times of QoL data.

Step1. **Prepare your data files with tab-delimited or space-delimited text format and save them in UTF-8 without BOM**.

- **QoL data file for an index cohort**:

  The file contains five columns with column names recorded in the first row. The definition for each column are descripted below:

  - 1st column: ID number for each individual with QoL measurements of a sample from the index cohort. The values are positive integer.
  - 2nd column: The survival time (i.e. month from onset to death or last known alive) for each individual in the index cohort.
  - 3rd column: Status indicator at the end of follow-up time, where 0 denotes a censored case (alive) and 1 denotes a completed case (dead).
  - 4th column: Time (≥ 0, month) from onset to the assessment time of the QoL data. Each individual in the sample has one or more assessment time points from onset to the end of follow-up time. The maximum assessment time is denoted F_q.
  - 5th column: QoL value at the assessment time, within the closed interval [0, 1]. Each individual has one or more QoL scores from onset to the end of follow-up.

  Two example files are "QolF120_1.txt" and "QolF120_2.txt", saved in "C:/Users/…/

Documents/.iSQoL2/Example". Each individual has one or more QoL scores in both data sets. The column name for QoL recorded in the 5th column is "QoL1".

- **QoL data file for the general reference population**:

  The file contains three columns, with the column names listed in the first row. Each row consists of sex, age and average QoL of the age-sex group for the general reference population. The definitions of each column are described below:

  - 1st column: Gender code of the general reference population, where 1 represents male and 0 represents female.
  - 2nd column: Age (year) for the general reference group.
  - 3rd column: Average QoL utility (e.g., EQ-5D) for each age-sex group. The column name must match the name of the 5th column in QoL data file of the index cohort.

  Note: When the same average QoL is assumed for all age-sex groups in the general reference population, set the values of the first and second columns in the second row to -1, and input the average QoL in the 3rd column.

  Two example files are "qol_ref1.txt" and "qol_ref2.txt":

  - The first file has one QoL measurements named "QoL1"; all individuals in the general reference have the same average QoL score of 0.9 for "QoL1".
  - The second file also has one QoL measurement named "QoL1", but each age-sex group has a different average QoL score.

- **Onset year, age and sex data file for the index cohort:**

  The file contains onset year, age and sex data, as described in the first three columns of the data files in Section 4.1. This data is used to generate QoL scores for the general reference population, matched by onset year, age and gender for the index cohort. If you use this file as the input data file (e.g., "AgeSurF120_1.txt" or "AgeSurF120_2.txt") in Section 4.1, the system will automatically load the first three columns from it. Otherwise, you will need to create a new data file that contains only the onset year, age and sex data for the index cohort.

  Note: When the general reference population assumes the same average QoL for all age-sex groups, this file is not required. For example, if the general reference population’s QoL data file is set to "qol_ref1.txt", this data file for the index cohort is not needed.

- **A temporary output file of executing LE**:

  Temporary file named "SurvivalOnly.rds" is an output file generated from the execution in Section 4.1.

  - For example:
    "C:/Users/…/Documents/.iSQoL2/Example/Out1S/Temporary/SurvivalOnly.rds".

Step2. **Create an input file in EXCEL and save it as a CSV file with comma-separated values**.
The CSV file contains data filenames and parameters for preparing the estimation of QALE. It contains 10 columns and at least 2 rows.

- Two or more rows:
  - 1st row: Column names for each column.
  - 2nd row, 3rd row, etc.: Filenames of data files and input parameters for the first index cohort, the second index cohort, and so on.
- 10 columns:
  - 1st column: Number (*NB*) of bootstrap samples for estimating the standard error of QALE. The value should be an integer greater than or equal to 30. Set 100 as the default value.
  - 2nd column: The parameter is called "bandwidth" and denoted "*b*". It specifies the width of the kernel smoothing function used to estimate the mean QoL function from the diagnosis time to the maximum assessment time (F_q). It is a percentage value (%), usually between 1 and 5.
  - 3rd and 4th column: The parameters *K* and *B* are for extrapolating the mean QoL function. The defaults are K =12 and B = 36. If the extrapolated mean QoL is assumed to be constant over time, set *K* to -1.
  - 5th column: The mean QoL for the dead individuals in the index cohort. The default value is 0.
  - 6th column: The filename with the full path records the QoL scores of the index cohort.
  - 7th column: The filename with full path records the average QoL scores for each age-sex group in the general reference population.
  - 8th column: The filename with full path records the onset year, age and sex data of the index cohort. If the filename in the 7th column indicates that the average QoL is the same for each age-sex group in the general reference population, set the value in this column to blank.
  - 9th column: The output directory for the estimation of LE described in Section 4.1.
  - 10th column: The output directory for saving the text outputs and graphs of the estimated QALE. If the input file (InputC.csv) has two or more rows, specify different directories for each row in the column.
- An example file "C:/Users/…/Documents/.iSQoL2/Example/InputQ.csv" contains three rows, indicating that two data sets will be executed:
  - The first data set is assumed to have the same average QoL for the general

reference individuals, so the value in the 8th column of the second row is set to blank.

- The second data set has different average QoL for each age-sex group in the general reference population, so the value in the 8th column of the third row must be provided the filename that records the onset year, age and sex data of the index cohort.

Step3. **Start to extrapolate mean QoL function and estimate QALE**

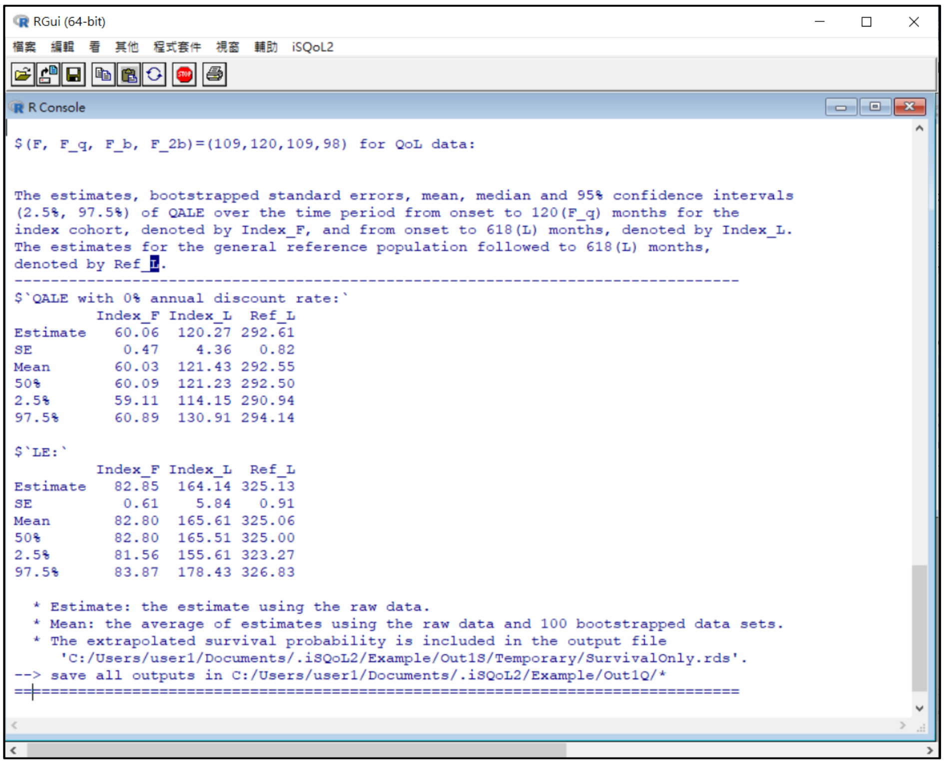
(3.1.) Edit the input file "C:/Users/…/.iSQoL2/Example/InputQ.csv" to update *b*, *B* and *K* with suitable values if necessary. For example, replace *K* with 8 for the first data set.

(3.2.) Click [**iSQoL2/Run/(C) QALE**] menu to select the input file "InputQ.csv" to start the execution.

(3.3.) After finishing the execution, a text output, figures and a temporary file named *.rds will be shown in the **R** console and saved in the output directory specified in the last column of the file "InputQ.csv".

- A text output:
  The results, shown in Table 4.3.1, contain the estimates, bootstrapped standard errors, mean, medians and 95% confidence intervals of QALE from onset to F_q and *L* for the index cohort. The results also include estimates for the general reference population. The summary table is saved to a file named "*_sy.txt".

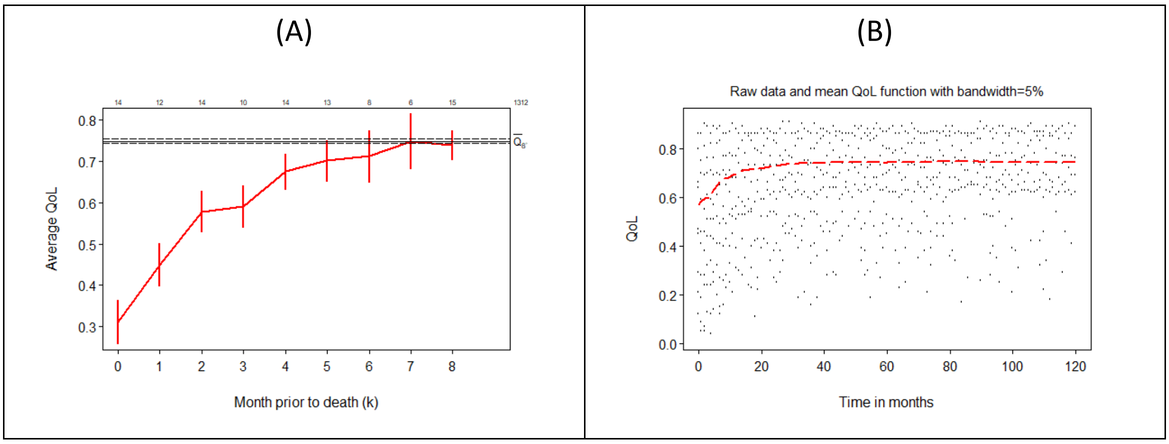
Figure 4.3.1 The text output of the estimated QALE is shown in the **R** console.



```
$(F, F_q, F_b, F_2b)=(109,120,109,98) for QoL data:


The estimates, bootstrapped standard errors, mean, median and 95% confidence intervals
(2.5%, 97.5%) of QALE over the time period from onset to 120(F_q) months for the
index cohort, denoted by Index_F, and from onset to 618(L) months, denoted by Index_L.
The estimates for the general reference population followed to 618(L) months,
denoted by Ref_L.
--------------------------------------------------------------------------------
$`QALE with 0% annual discount rate:`
         Index_F Index_L  Ref_L
Estimate   60.06  120.27 292.61
SE          0.47    4.36   0.82
Mean       60.03  121.43 292.55
50%        60.09  121.23 292.50
2.5%       59.11  114.15 290.94
97.5%      60.89  130.91 294.14

$`LE:`
         Index_F Index_L  Ref_L
Estimate   82.85  164.14 325.13
SE          0.61    5.84   0.91
Mean       82.80  165.61 325.06
50%        82.80  165.51 325.00
2.5%       81.56  155.61 323.27
97.5%      83.87  178.43 326.83

  * Estimate: the estimate using the raw data.
  * Mean: the average of estimates using the raw data and 100 bootstrapped data sets.
  * The extrapolated survival probability is included in the output file
     'C:/Users/user1/Documents/.iSQoL2/Example/Out1S/Temporary/SurvivalOnly.rds'.
--> save all outputs in C:/Users/user1/Documents/.iSQoL2/Example/Out1Q/*
================================================================================
```

- Figures:
  - *B*QK*.tiff: The average QoL in *K* months prior to death and the average QoL of subjects who won’t die within *K* months. For example, this figure is shown as Figure 4.3.2(A) for (*B*, *K*) = (36, 8).
  - *_MeanF.tiff: The mean QoL function with *b*=5% over time from onset to F_q (maximum assessment time) is plotted as Figure 4.3.2(B).
  - *_MeanE1.tiff: The mean QoL function over time from onset to the end of extrapolation for the index cohort is plotted as Figure 4.3.2(C).
  - *_MeanE2.tiff: The mean QoL functions over time from onset to the end of extrapolation for both the index cohort and the general reference population are plotted as Figure 4.3.2(D).
  - *_E1.tiff: The figure, shown as Figure 4.3.2(E), includes the survival function, mean QoL function and the quality-adjusted survival function over time from onset to the end of extrapolation for the index cohort.
  - *_E2.tiff: The figure, shown as Figure 4.3.2(F), includes the quality-adjusted survival functions over time from onset to the end of extrapolation for both the index cohort and the general reference population.
- A temporary file:
  - A file named "QAS_*.rds" is saved in the "Temporary" folder of the specified output directory. It is a serialized object that contains a list of **R** objects, including the extrapolated quality-adjusted survival function for the index cohort and the general reference population, and so on. This file will be necessary for the execution of Section 5 and 6.

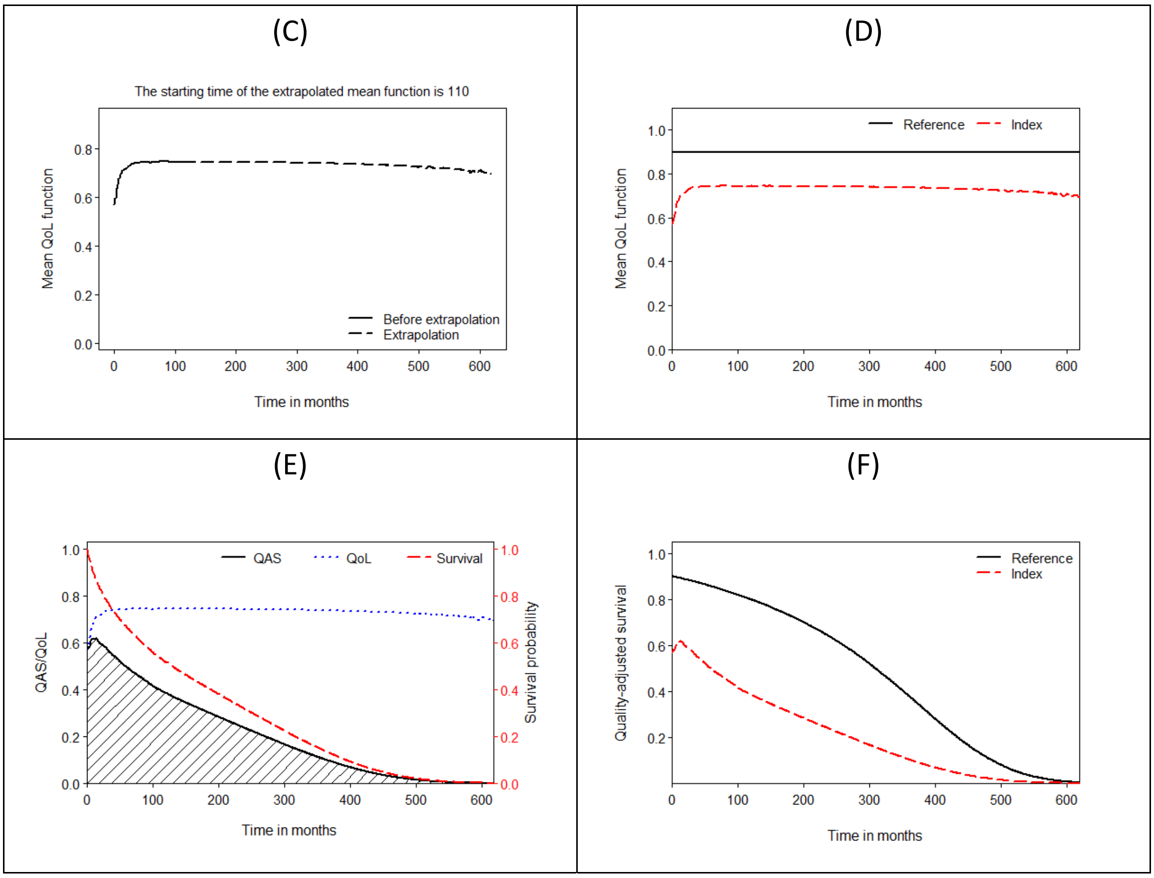
Figure 4.3.2 The output figures after executing the expected quality-adjusted life expectancy.



(A)

(B)

Figure 4.3.2 The output figures after executing the expected quality-adjusted life expectancy.



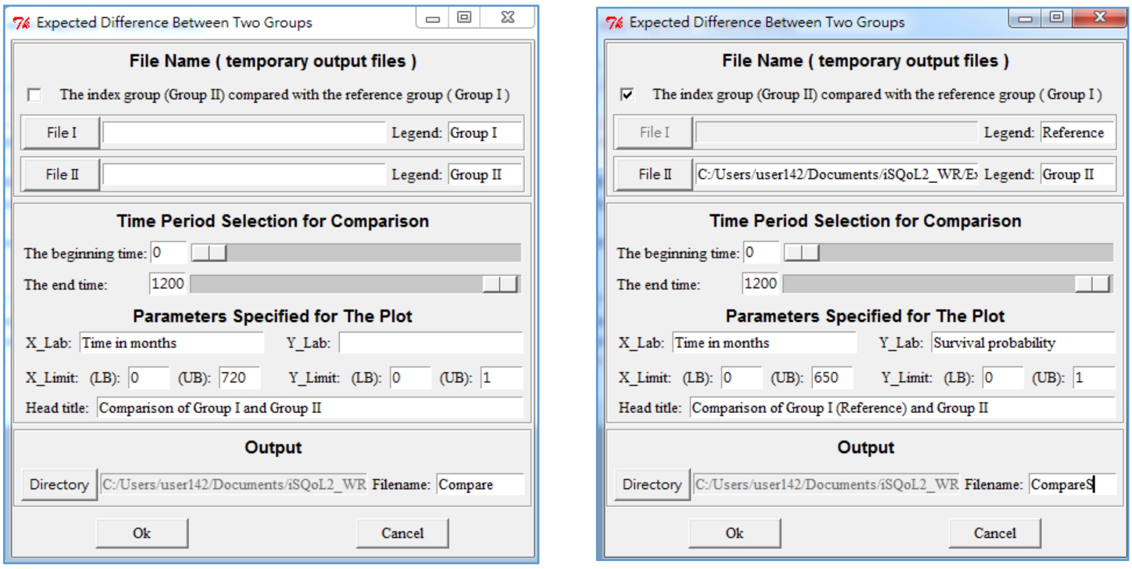
5. Additional functions

The following functions are executed based on a temporary output file (*.rds) from the major function. Before executing, you need to provide the temporary file (*.rds).

5.1 The expected difference of LE/QALE/COST between two groups

The function is used to compare the expected survival (expected cost/expected quality-adjusted survival) over a given time period between two groups. It also computes the expected years of life lost (EYLL) and the loss of QALE.

Figure 5.1 Input window for executing the expected difference between (A) two groups or (B) the index cohort and the general population.



(A)

☐ The index group (Group II) compared with the reference group (Group I)

File I Legend: Group I

File II Legend: Group II

The beginning time: 0

The end time: 1200

X_Lab: Time in months Y_Lab:

X_Limit: (LB): 0 (UB): 720 Y_Limit: (LB): 0 (UB): 1

Head title: Comparison of Group I and Group II

Directory C:/Users/user142/Documents/iSQoL2_WR Filename: Compare

(B)

☑ The index group (Group II) compared with the reference group (Group I)

File I Legend: Reference

File II C:/Users/user142/Documents/iSQoL2_WR/E: Legend: Group II

The beginning time: 0

The end time: 1200

X_Lab: Time in months Y_Lab: Survival probability

X_Limit: (LB): 0 (UB): 650 Y_Limit: (LB): 0 (UB): 1

Head title: Comparison of Group I (Reference) and Group II

Directory C:/Users/user142/Documents/iSQoL2_WR Filename: CompareS

The steps below describe how to run the function.

Step1. Click [**iSQoL2/Additional Functions/comparison of LE/QALE/COST**] to open the input window shown in Figure 5.1(A).

- Click the [**File I**] button and the [**File II**] button to select two temporary files named like "Survival*.rds" , "CostRate*.rds" or "QAS*.rds".
- If you tick the checkbox [**The index group (Group II) compared with the reference group (Group I)**] and select a temporary file (*.rds) for [**File II**], the result will be the expected difference between the index cohort and the general reference population.
- **To compute loss-of-LE (EYLL):** Tick the checkbox [**The index group (Group II) compared with the reference group (Group I)**]; click the [**File II**] button to select a temporary file named "Survival*.rds" as shown in Figure 5.1(B); set the beginning

time and end time to 0 and 1200, respectively.

- **To compute loss-of-QALE:** Tick the checkbox [**The index group (Group II) compared with the reference group (Group I)**]; click [**File II**] button to select a temporary file named "QAS*.rds" as Figure 5.1(B); set the beginning time and the end time as 0 and 1200 respectively.

Step2. Fill in all inputs and then click **Ok** to execute the estimation. The results will contain a summary of the estimates and a figure.

- The summary outputs in the **R** console will contain the expected difference, the bootstrapped standard error, p value of Z-test statistics, and percentile of the bootstrap estimates (in month-unit and year-unit). The outputs also provide the estimated LE/QALE/COST (month-unit and year-unit), which is the result of the major function for two groups. The results, shown as Table 5.1, will be shown in the **R** console and saved to a file specified in the input window.

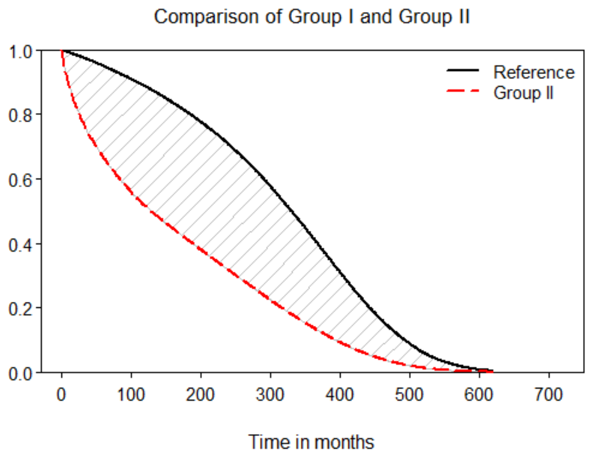
Table 5.1 Summary of the comparison of between LE in the index cohort and the general reference population.

```
The difference of the expected survival(Group I - Group II)
over the time period [0, 618] between two groups:
---------------------------------------------------------------------------
$`Difference:`
   Time_Period Estimate     SE z-statistic p-value    50%   2.5%  97.5%
  month: 0-618   160.99   5.90       27.29    0.00 159.74 146.74 168.92
  year: 0-51.5    13.42   0.49       27.29    0.00  13.31  12.23  14.08

$`The expected survival during time period [0, 618]:`
         Group1(month) Group2(month) Group1(year) Group2(year)
Estimate        325.13         164.1       27.094        13.68
SE                0.91           5.8        0.076         0.49
50%             325.00         165.5       27.083        13.79
2.5%            323.27         155.6       26.939        12.97
97.5%           326.83         178.4       27.235        14.87


$Inputs:
 ***              Group I: Reference (expected survival)
 ***             Group II: Group II (expected survival)
 ***               File I:
C:/Users/user1/Documents/.iSQoL2/Example/Out1S/Temporary/SurvivalOnly.
 ***              File II:
C:/Users/user1/Documents/.iSQoL2/Example/Out1S/Temporary/SurvivalOnly.
 ***        Extrapolation: 618 (Group I), 618 (Group II) months
 *** Number of bootstrap: 100 (Group I), 100 (Group II)
 ***              Outfile: C:/Users/user1/Documents/.iSQoL2/Compare.txt

Notes:
(1) Group I is the reference population. If the extrapolation time L is the end of life,
    the estimated EYLL (expected years of life lost) is 12.187 years (=146.25 months).
(2) Y-axis label: Survival function.
```

The results in Table 5.1, using Group II as the general reference group, show that the expected years of life lost (EYLL) is 12.17 years. Additionally, the estimated LE are 26.214 and 14.047 years for the general reference population and index cohort, respectively.

- Figure 5.2 shows two lifetime survival curves for the index cohort and the general reference population. It is presented in **R** graphics device and saved to a user-specified file.

Figure 5.2 The diagonal striped area between the survival cruves of the index cohort and the general reference population represents EYLL.



[Appendix 5.1] How to calculate the estimate of the expected difference

Let X_0 and Y_0 be the estimates calculated from the raw data of Group I and II, respectively. The bootstrapped estimates $(X_1, \ldots.., X_R)$ and $(Y_1, \ldots.., Y_R)$ are obtained from R bootstrapped data sets for Group I and Group II. The difference between the two groups is equal to $D_i = X_i - Y_i$, where i =0, 1, …, R . Thus, the values in Table 5.1 are described as follows.

- The "Estimate" is equal to D_0.
- The "SE" is the standard deviation of the estimates D_0, D_1, …, D_R.
- The "z-statistic" (calculated as "Estimate" divide by "SE") and the "p-value" are used to determine whether the difference is statistically significant.
- The 50%, 2.5% and 97.5% represent the 50th, 2.5 th and 97.5 th percentiles of the estimates D_0, D_1, …, D_R, respectively. The 2.5 th and 97.5 th percentiles is the lower and upper bounds of the 95% confidence interval.

5.2 Comparison of the loss of LE/QALE between two groups

The function is used to compare the loss of the expected survival (or quality-adjusted survival) over a given time period between two groups. If the comparison is from the diagnosis to the end of life, the estimated difference-in-difference is the difference of EYLL (or loss-of-QALE) between two groups (i.e. Difference = $EYLL_1 - EYLL_2$ = [loss-of-LE_1] – [loss-of-LE_2] or Difference = [loss-of-$QALE_1$] – [loss-of-$QALE_2$]).

Execution Steps:

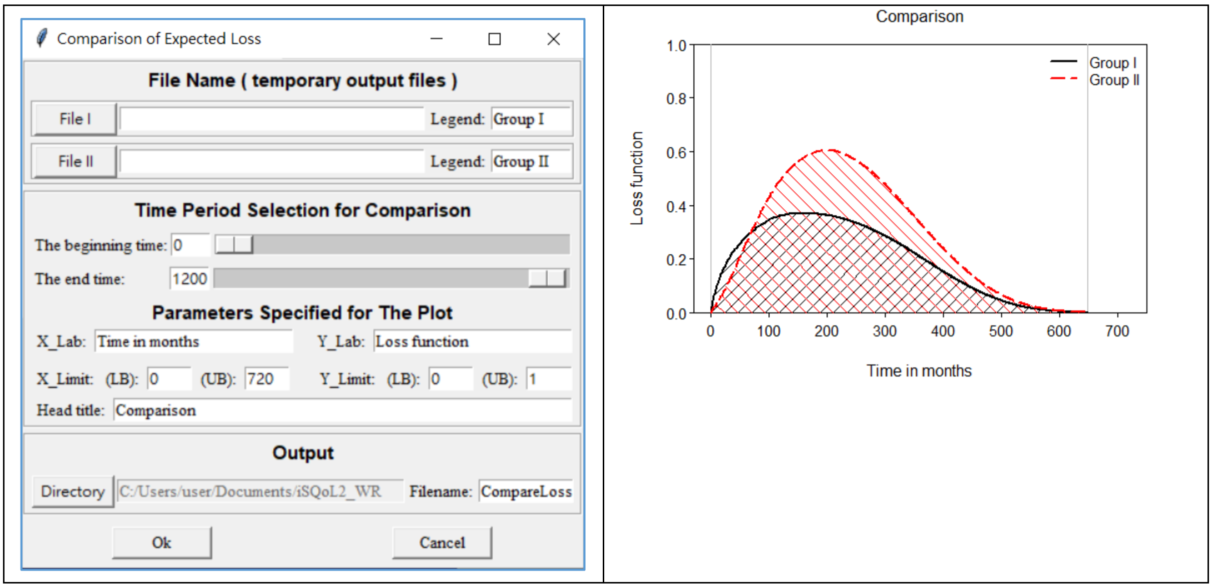
Step1. Click [**iSQoL2/Additional Functions/comparison of the loss of LE/QALE**] to open the input window shown on the left side of Figure 5.2.

Step2. Fill in all inputs in the input window:

- Select two temporary files named "Survival*.rds" (or "QAS*.rds") by clicking the [**File I**] button and the [**File II**] button.
- Set [**The beginning time**] and [**The end time**] to 0 and 1200, respectively. This setting calculates the difference in loss from the onset to the end of extrapolation.

Step3. Click **Ok** to get a figure and the estimates. The figure on the right side of Figure 5.2 shows two loss functions for Group I and II. The estimates (in both month and year units) include the difference, the bootstrapped standard error (S.E.) of the difference, and the 2.5th, 50th, and 97.5th percentiles of the bootstrapped differences. The results also provide the Z-test statistic and p-value to test whether the difference between two groups is statistically significant. Additionally, the results include the loss-of-LE (or loss-of-QALE) in both month and year units for the two groups.

Figure 5.2 The input window on the lief side for the comparing the loss-of-LE (or loss-of-QALE). The figure on the right side shows the two loss functions for the two groups.



Comparison of Expected Loss

File Name (temporary output files)

File I Legend: Group I

File II Legend: Group II

Time Period Selection for Comparison

The beginning time: 0

The end time: 1200

Parameters Specified for The Plot

X_Lab: Time in months Y_Lab: Loss function

X_Limit: (LB): 0 (UB): 720 Y_Limit: (LB): 0 (UB): 1

Head title: Comparison

Output

Directory C:/Users/user/Documents/iSQoL2_WR Filename: CompareLoss

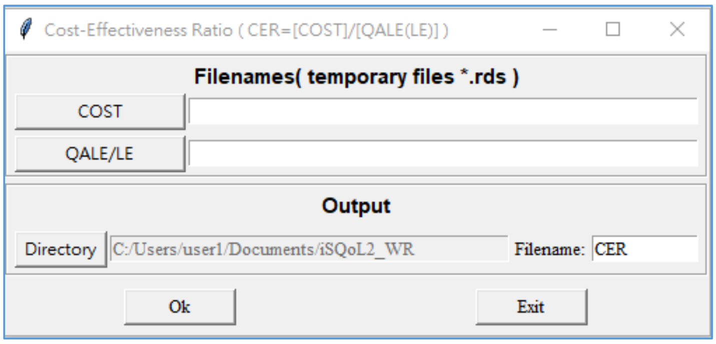
5.3 CER

The function calculates the cost-effectiveness ratio (CER), which is the ratio of COST to LE (or QALE). The results include the estimates of CER, the bootstrapped standard error (S.E.) of CER, and the 2.5th, 50th, and 97.5th percentiles of the bootstrapped CERs.

How to execute the function?

- Click [**iSQoL2/Additional Functions/CER**] to open the input window shown in Figure 5.3.
- Fill all inputs, then click **Ok** button to start the execution. Note the following:
  (1) Select a temporary file named "CostRate*.rds" by clicking the [**COST**] button.
  (2) Select a temporary file named "Survival*.rds" or "QAS*.rds" by clicking the [**QALE/LE**] button
- All results will be shown in the **R** console and saved to the file specified in the input window. The text outputs include the estimated CER, the bootstrapped S.E., and the 2.5th, 50th, and 97.5th percentiles of the bootstrapped CERs. (in both month and year units)

Figure 5.3 The input window for executing CER.



C:/Users/user1/Documents/iSQoL2_WR

Filename: CER

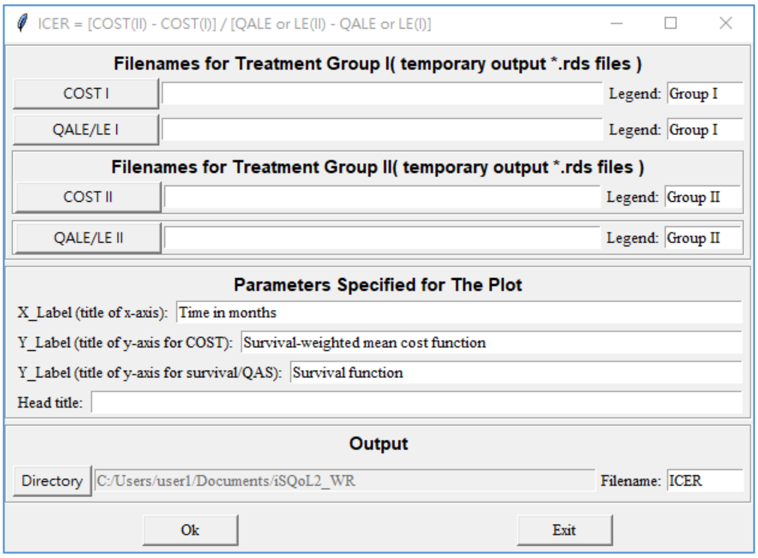
5.4 ICER

The function calculates the incremental cost-effectiveness ratio (ICER). ICER is defined as [Cost_2 - Cost_1]/[LE_2 - LE_1] or [Cost_2 - Cost_1]/[QALE_2 - QALE_1] for two groups. The execution results contain the estimate of ICER, the bootstrapped standard error (S.E.) of ICER, and the 2.5th, 50th, and 97.5th percentiles of the bootstrapped ICERs.

How to execute the function?

- Click [**iSQoL2/Additional Functions/ICER**] to open the input window as shown in Figure 5.4.
- Fill all inputs, then click the **Ok** button to start the execution. Note the following:
  - [**COST I**] and [**QALE/LE I**] are for the estimated lifetime cost and life expectancy (or the expected quality-adjusted survival) of the first index cohort, respectively. [**COST II**] and [**QALE/LE II**] are for the second index cohort.
  - Select a temporary file named "CostRate*.rds" by clicking the [**COST ***] button.
  - Select a temporary file named "Survival*.rds" or "QAS*.rds" by clicking the [**QALE/LE ***] button.
- The text outputs and two figures will be shown in the **R** console and saved to the file specified in the input window. The outputs include:
  - Text outputs: the estimated ICER, the bootstrapped S.E., and the 2.5th, 50th, and 97.5th percentiles of the bootstrapped ICERs. (in both month and year units)
  - Figures: One figure shows the survival functions (or quality-adjusted survival function) for the two groups, and the other figure shows the survival-weighted mean cost functions (the product of the survival function and the mean cost function) for two groups.

Figure 5.4 The nput window for executing ICER.



Legend: Group I

Legend: Group I

Legend: Group II

Legend: Group II

X_Label (title of x-axis): Time in months

Y_Label (title of y-axis for COST): Survival-weighted mean cost function

Y_Label (title of y-axis for survival/QAS): Survival function

Head title:

C:/Users/user1/Documents/iSQoL2_WR

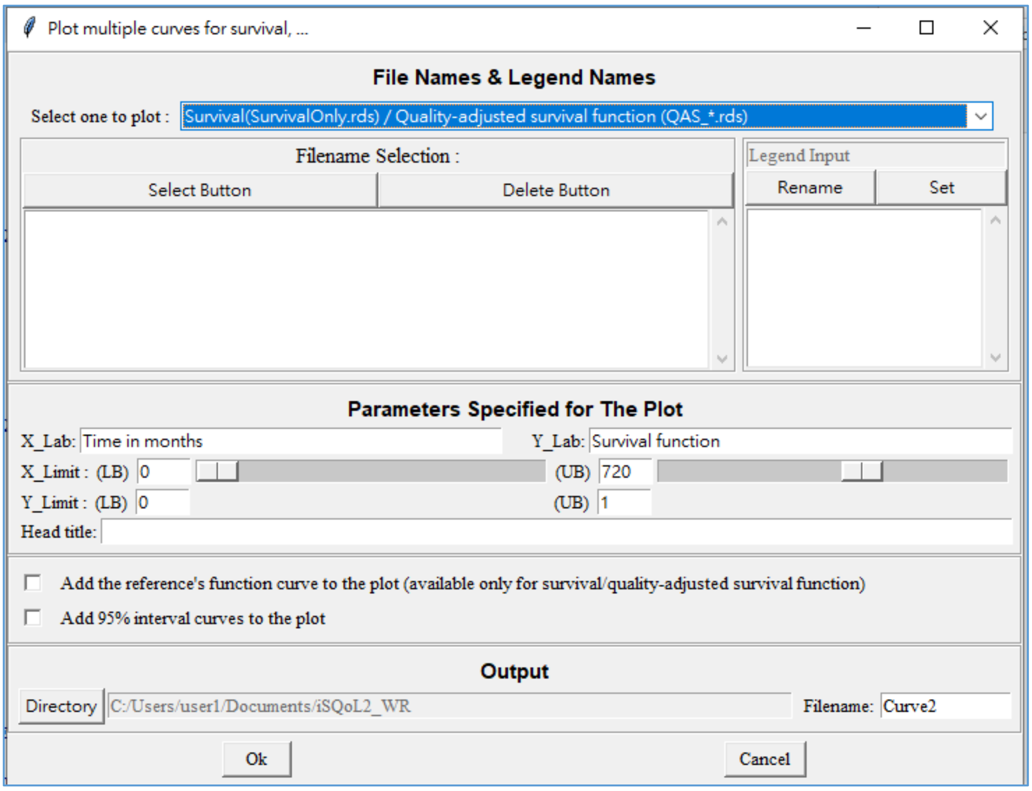
Filename: ICER

5.5 Plot multiple curves

The function is used to plot multiple curves in a graphics device. The curves can represent one of the following estimated functions:

- Survival functions
- Quality-adjusted survival functions
- The loss functions
- The mean cost functions

Figure 5.6 The input window for plotting multiple curves.



Select one to plot : Survival(SurvivalOnly.rds) / Quality-adjusted survival function (QAS_*.rds)

X_Lab: Time in months
Y_Lab: Survival function
X_Limit : (LB) 0 (UB) 720
Y_Limit : (LB) 0 (UB) 1
Head title:

☐ Add the reference's function curve to the plot (available only for survival/quality-adjusted survival function)
☐ Add 95% interval curves to the plot

Directory C:/Users/user1/Documents/iSQoL2_WR
Filename: Curve2

How to execute the function:

- Click [**iSQoL2/Additional Functions/plot multiple curves**] to open the input window shown in Figure 5.6.
- Choose a function to plot from [**Select one to plot**] menu.
- Click **Select Button** (or **Delete Button**) to select (or delete) one or more target files:
  - The left box contains temporary output files named *.rds.
  - The right box is used to show the legend for each selected file. To change a legend name, select it from the right box, click the **Rename** button to alter it, and then click the **Set** button to apply the change.

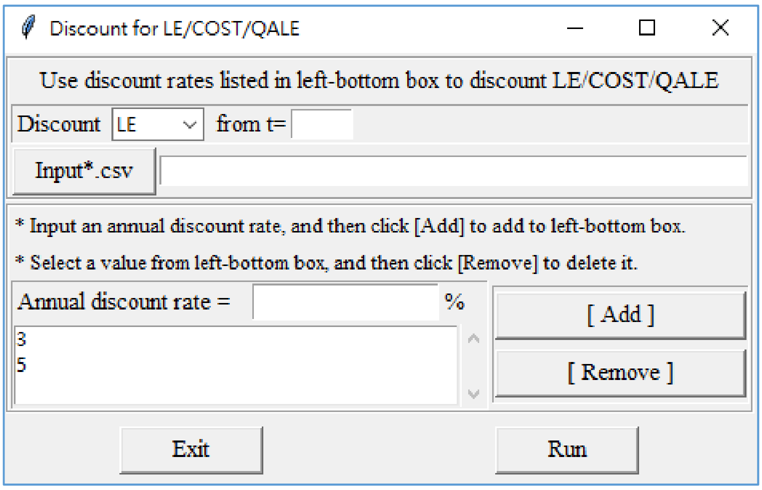
Note that:

- When the plot is shown in the **R** console, move the mouse cursor to the graphics coordinate to specify the legend location.
- If legend names are empty, no legend will appear in the plot.

— Fill in the other inputs and click the **Ok** button to start the execution. The text outputs and a figure will be shown in the **R** console and saved to the file specified in the input window.

6. Discount for LE/QALE/Cost

The command is used to discount LE, COST or QALE, which has been estimated in Section 4.1 or 4.2 or 4.3, respectively. Before running the command, you need to prepare an input file (Input*.csv) as described in Section 4. Then, click the [**iSQoL2/Discount for LE/QALE/COST**] menu to open the input window shown below.



Use discount rates listed in left-bottom box to discount LE/COST/QALE

Discount LE from t=

* Input an annual discount rate, and then click [Add] to add to left-bottom box.

* Select a value from left-bottom box, and then click [Remove] to delete it.

Annual discount rate = %

3
5

Next, follow these steps to execute the command:

(1) Select one of LE, QALE, COST for discounting.

(2) Input the starting time *t* (in months after onset) for discounting.

(3) Select the input file (Input*.csv) described in Step 2 of Section 4. Note that all estimates will be discounted using the same discount rate(s) for all data sets in Input*.csv.

(4) Add or remove annual discount rates in the left-bottom box:

- To add a rate:
  Input the annual discount rate and click [**Add**] to put it in the left-bottom box.
- To remove a rate:
  Select the annual discount rate in the left-bottom box and click [**Remove**] to delete it.

(5) Click [**Run**] to start the discounting LE/QALE/COST using the annual discount rate(s) listed in the left-bottom box.

The results contain the estimated LE/QALE/COST discounted according to the specified annual discount rate(s). These results will be shown on the **R** console and saved in the directory specified in the last column of Input*.csv. For each data set, there will be two output files with filenames in the format "&_Rate*_sy.txt" and "&_Rate*_#.rds".

7. Reference

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