Meta-analysis of time-to-event data

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Have you ever had to deal with time-to-event data while working on a systematic review?

Yes
No
Contents of the workshop

- Analysis of time-to-event data from a single trial
- Meta-analysis of (aggregate) time-to-event data
- Estimating $\ln(HR)$ and its variance
- Practical

Do not worry about equations highlighted in red – they are included for completeness but it is not essential to understand them.
Analysis of time-to-event (TTE) data from a single trial
Time-to-event data

- Arise when we measure the length of time between a starting point and the occurrence of some event

- Starting point:
  - date of diagnosis
  - date of surgery
  - date of randomisation (most appropriate in an RCT)

- Event:
  - death
  - recurrence of tumour
  - remission of a disease
Example for Patient A

Time to event = 730 days

Starting point
(e.g. Date of randomisation, 1\textsuperscript{st} January 2012)

Date of event
(e.g. Date of death, 31\textsuperscript{st} December 2013)
Censoring

• Event is often not observed on all subjects
• Reasons:
  -- drop-out
  -- the study ends before the event has occurred
• However, we do know how long they were followed up for without the event being observed
• Individuals for whom the event is not observed are called censored
Example for Patient B

Time to event = 365 days, observation would be censored

Starting point
(e.g. date of randomisation, 1st February 2012)

Date of censoring
(e.g. Date of study end, 31st January 2013)

Unknown date of event (e.g. Date of death)
Censoring

• Assume that censoring mechanism is independent of failure time mechanism (non-informative censoring)
Why special methods of analysis?

- Why not analyse the time to event as a **continuous** response variable?

- Assuming censored observations are uncensored will underestimate average survival time

- Ignoring censored observations is inefficient
Why special methods of analysis?

- Why not analyse the time to event as a **binary** response variable?
  
  - May be reasonable if...
    
      ✓ event is likely to occur very early on (e.g. acute liver failure)
      ✓ event is rare
      ✓ lengths of follow up are similar between patients
      ✓ interested in whether event occurs at all rather than time to event
  
  - But if...
    
      ✗ an appreciable proportion of the patients do experience event
      ✗ event may take a considerable time
      ✗ Time taken for an event to occur is of interest.

  .. looking not only at *how many* patients had event, but also at *how long* after treatment the event occurred, gives a **more sensitive** assessment.
Kaplan-Meier curves

- Graphical display of the survival (time to event) function estimated from a set of data
- The curve starts at 1 (or 100%) at time 0. All patients are 'alive' or event free
- The curve steps down each time an event occurs, and so tails off towards 0
- Poor survival is reflected by a curve that drops relatively rapidly towards 0.
The Log rank test

- **The Log rank Test** is a simple statistical test to compare the time to event of two groups.

- It takes censoring into account, is non-parametric, and compares the groups over the whole time-period.
The Log rank test continued...

- The log rank test compares the total number of events observed with the number of events we would expect assuming that there is no group effect.

- If events occur in the sample at the time-points $t_1,...,t_k$, expected number of events $e_j$ at time $t_j$ in group A is:

  $$e_j = \text{no. at risk in group A at } t_j \times \frac{\text{no. of events in sample at } t_j}{\text{no. at risk in sample at } t_j}$$

- **Total number** of events expected for group A is:

  $$E_A = e_1 + e_2 + ... + e_k$$

- The logrank test looks at whether $E_A$ is significantly different to the observed number of events $O_A$ in group A. If it is, this provides evidence that group is associated with survival.
Cox proportional hazards (PH) regression model

• Most commonly used regression model
• The hazard is modelled with the equation:

\[ h(t) = h_0(t) \times \exp(b_1x_1 + b_2x_2 + \ldots + b_kx_k) \]

• So, we assume that the hazard function is partly described by an underlying hazard, and partly by the contribution of certain risk factors.
The hazard ratio

• The **hazard** is the chance that at any given moment, the event will occur, given that it hasn’t already done so.

• The **hazard ratio** (HR) is a measure of the relative hazard in two groups i.e. ratio of the hazard for one group compared to another.

Suppose that we wish to compare Treatment group relative to Control:

\[ HR = \frac{\text{Hazard Trt}}{\text{Hazard Ctrl}} \]

- \( 0 < HR < 1 \) Trt group are at a decreased hazard compared to control.
- \( HR = 1 \) The hazard is the same for both groups.
- \( HR > 1 \) Trt group are at an increased hazard compared to control.

A HR of 0.5 means a *halving* of hazard
A HR of 2 means a *doubling* of hazard
What is the likely HR (treatment/control) for the outcome Overall Survival in this example?

![Survival Time vs. Survival Probability](image)

- **HR > 1**
- **HR = 1**
- **HR < 1**
Meta-analysis of time-to-event (TTE) data
Meta-analysis of TTE data

- For $K$ trials, and for each trial, $i=1,2..K$, an estimate of the log hazard ratio $\ln(HR_i)$ and its variance $\text{var}(\ln(HR_i))$ are available.
- An estimate of the log hazard ratio and variance pooled across trials can be calculated:

\[
\ln(HR) = \frac{\sum_{i=1}^{K} \ln(HR_i)}{\frac{1}{\sum_{i=1}^{K} \text{var}[\ln(HR_i)]}}
\]

\[
\text{var}[\ln(HR)] = \left[ \frac{\sum_{i=1}^{K} \frac{1}{\text{var}[\ln(HR_i)]}}{1} \right]^{-1}
\]
Meta-analysis of TTE data

• In practice pooling can be done using software eg.
  – Review Manager generic inverse variance
  – Stata ‘metan’ command
  – R ‘meta’ command

• BUT, reviewers need to obtain estimates of lnHR and standard error from each study to input

\[ \text{Standard error} = \sqrt{\text{Variance}} \]
Enter estimate of log(hazard ratio) and standard error (SE) from each study.

Revman calculates study HR and CI as well as pooled HR and CI.

Revman creates forest plot.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>study 1</td>
<td>-0.02</td>
<td>0.22</td>
<td>9.9%</td>
<td>0.98 [0.64, 1.51]</td>
</tr>
<tr>
<td>study 2</td>
<td>-0.17</td>
<td>0.21</td>
<td>10.9%</td>
<td>0.84 [0.56, 1.27]</td>
</tr>
<tr>
<td>study 3</td>
<td>-0.24</td>
<td>0.14</td>
<td>24.5%</td>
<td>0.79 [0.60, 1.03]</td>
</tr>
<tr>
<td>study 4</td>
<td>-0.12</td>
<td>0.15</td>
<td>21.3%</td>
<td>0.89 [0.66, 1.19]</td>
</tr>
<tr>
<td>study 5</td>
<td>-0.21</td>
<td>0.12</td>
<td>33.3%</td>
<td>0.81 [0.64, 1.03]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.84 [0.73, 0.96]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.93, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.52 (P = 0.01)
Meta-analysis of TTE data

Problem: In practice the HR and variance may not be available

Efficacy

The median survival was 14.5 months (range 3.2–30.5) for GEM CCRT patients compared with 6.7 months (range 4.6–18.1 months) for 5-FU CCRT patients ($p = 0.027$; Fig. 1). The 1- and 2-year survival rate was 56% and 15% for GEM CCRT compared with 31% and 0% for 5-FU CCRT, respectively. All deaths were cancer related.
Logrank and multivariate analyses were frequently reported at most only as P-values [(63/84 (75%)) and 22/47 (47%)]
Review of survival analysis

~52% of trials reported an estimate of hazard ratio
Meta-analysis of TTE data

STATISTICS IN MEDICINE

EXTRACTING SUMMARY STATISTICS TO PERFORM META-ANALYSES OF THE PUBLISHED LITERATURE FOR SURVIVAL ENDPOINTS

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SUMMARY

Meta-analyses aim to provide a full and comprehensive summary of related studies which have addressed a similar question. When the studies involve time to event (survival-type) data the most appropriate statistics to use are the log hazard ratio and its variance. However, these are not always explicitly presented for each study. In this paper a number of methods of extracting estimates of these statistics in a variety of situations are presented. Use of these methods should improve the efficiency and reliability of meta-analyses of the published literature with survival-type endpoints. © 1998 John Wiley & Sons, Ltd.
1. Direct method – observed and log rank expected events

\[
\ln(HR_i) = \ln\left(\frac{O_{ri}/E_{ri}}{O_{ci}/E_{ci}}\right) \quad \text{var}(\ln(HR_i)) = \left(\frac{1}{E_{ri}}\right) + \left(\frac{1}{E_{ci}}\right)
\]  

\[
\ln(HR_i) = \left(\frac{O_{ri} - E_{ri}}{V_{ri}}\right) \quad \text{var}(\ln(HR_i)) = \frac{1}{V_{ri}}
\]

\(O_{ri}\) = observed number of events in the research group;  
\(O_{ci}\) = observed number of events in the control group;  
\(E_{ri}\) = logrank expected number of events in the treated group;  
\(E_{ci}\) = logrank expected number of events in the control group; and  
\(1/V_{ri}\) = Mantel–Haenszel variance of the log hazard ratio.
Example 1

From equation (2)

\[
\ln(HR) = - \frac{14.0}{40.7} = -0.34
\]

\[
\text{var(lnHR)} = \frac{1}{40.7} = 0.02
\]

\[
\text{SE(ln(HR))} = \sqrt{0.02} = 0.16
\]

HR (95% CI): 0.71 (0.52 to 0.97)
2. Direct - Cox model

Report may present results (coefficients) from the Cox regression model.

Direct estimate of $\ln HR$ and its variance (or standard error) can then be used.

Warning! Log Rank HRs (example 1) and Cox HRs may not be compatible for meta-analysis. For example – Cox HRs may be adjusted for other variables: age, sex, severity of disease etc.
3. Direct - HR with confidence interval

\[ \text{var}(\ln(HR_i)) = \left[ \frac{UPPCI_i - LOWCI_i}{2\Phi^{-1}(1 - \alpha_i/2)} \right]^2 \]  

Where UPPCI\(_i\) and LOWCI\(_i\) are the upper and lower confidence limits for \( \ln(HR_i) \)

\( \Phi \) is the cumulative distribution function of the Normal distribution and
\( \Phi^{-1}\left(1 - \frac{\alpha_i}{2}\right) = 1.96 \) for 95\% CI intervals
Example 2

Randomized Phase III Study of 5-Fluorouracil Continuous Infusion vs. Sequential Methotrexate and 5-Fluorouracil Therapy in Far Advanced Gastric Cancer with Peritoneal Metastasis (JCOG0106)

Efficacy

At the time of primary analysis (December 2008), 224 events had been recorded among 237 enrolled patients (Fig. 2-A). The median follow-up time for 237 patients was 10.1 months (range 0.6–40.3). The median overall survival was 9.4 (95% CI 7.6–10.8) months in patients assigned to the 5-FUci arm, and 10.6 (8.8–12.0) months in patients assigned to the MF arm. The MF arm was not superior to the 5-FUci arm [HR 0.94 (95% CI 0.72–1.22); one-sided $P = 0.31$].

_Jpn J Clin Oncol_ 2013;43(10)972–980
Example 2 continued

HR = 0.94 95% CI : (0.72 to 1.22)

\[ \ln(HR) = \ln(0.94) = -0.06 \]

From equation (3)

\[ \text{var}(\ln(HR)) = \left( \frac{\ln(1.22) - \ln(0.72)}{2 \times 1.96} \right)^2 = 0.017 \]

\[ SE(\ln(HR)) = \sqrt{0.017} = 0.13 \]
Enter estimate of log(hazard ratio) and standard error (SE) from each study

Revman calculates study HR and CI as well as pooled HR and CI

Revman creates forest plot
4. Indirect method - P-value

Report may provide \textit{p-value} from log rank test and information about number of events and number of patients in each group.

By the end of three years 40 patients had been admitted to the trial, 21 in the treated group and 19 in the control. Seventeen of the controls and six of the treated patients died before six months. All but one patient died within two years. No patient withdrew from the trial or was lost to follow-up. Survival in the treated and control patients was compared by the log-rank test recommended by Peto \textit{et al.}\textsuperscript{1} As shown in the figure, the median survival of the treated patients was 44 weeks and that of the controls nine weeks, a highly significant difference (\(p = 0.00006\)).
4. p-value (balanced randomisation)

\[(O_{ri} - E_{ri}) = 1/2 \times \sqrt{O_i \times \Phi^{-1}(1 - p_i/2)}. \quad V_{ri} \approx O_i/4\]

\[V_{ri} \approx O_{ri}O_{ci}/O_i. \quad \text{ } \quad O_{ri} - E_{ri} = \sqrt{O_{ri}O_{ci}/O_i} \times \Phi^{-1}\left(1 - \frac{p_i}{2}\right)\]

- Assumes equal numbers in the two groups
- \(p_i\) is the reported (two sided) \textbf{p-value} associated with the Mantel-Haenszel version of the logrank statistic
- \(\Phi\) is the cumulative distribution function of the Normal distribution
- \(O_i\) is the \textbf{total observed number of events} across both groups
4. p-value (unequal randomisation)

\[
V_{ri} \approx \frac{O_{ri}R_{ri}R_{ci}}{(R_{ri} + R_{ci})^2} \quad O_{ri} - E_{ri} = \frac{\sqrt{(O_{ri}R_{ri}R_{ci})}}{(R_{ri} + R_{ci})} \times \Phi^{-1}\left(1 - \frac{p_{i}}{2}\right)
\]
Then to obtain $\ln HR$ and variance (balanced or unequal randomisation)

$$\ln(HR_i) = \left(\frac{O_{ri} - E_{ri}}{V_{ri}}\right)$$

$$\text{var}(\ln(HR_i)) = 1/V_{ri}$$

$O_{ri}$ = observed number of events in the research group;
$O_{ci}$ = observed number of events in the control group;
$E_{ri}$ = logrank expected number of events in the treated group;
$E_{ci}$ = logrank expected number of events in the control group; and
$1/V_{ri}$ = Mantel–Haenszel variance of the log hazard ratio.
4. Indirect method: P-value

Report may provide p-value from logrank test and information about number of events and number of patients in each group.

By the end of three years 40 patients had been admitted to the trial, 21 in the treated group and 19 in the control. Seventeen of the controls and six of the treated patients died before six months. All but one patient died within two years. No patient withdrew from the trial or was lost to follow-up. Survival in the treated and control patients was compared by the log-rank test recommended by Peto et al. As shown in the figure, the median survival of the treated patients was 44 weeks and that of the controls nine weeks, a highly significant difference (p = 0.00006).
Example 3 continued

\[ P = 0.00006 \quad Rr = 21 \quad R_c = 19 \quad O_i = 39 \]

From equation (6):

\[ V = \frac{39 \times 21 \times 19}{(19+21)^2} = 9.7 \quad O - E = \sqrt{\frac{39 \times 21 \times 19}{19+21}} \times 4.01 = 12.5 \]

HR (95% CI): 3.63 (1.94 to 6.8)

From equation (2)

\[ \ln(HR) = \frac{12.5}{9.7} = 1.29 \quad \text{var}(\ln(HR)) = \frac{1}{9.7} = 0.10 \]

\[ SE(\ln(HR)) = \sqrt{0.10} = 0.32 \]
5. Indirect Method: Published survival curves

What is the approximate chance of surviving to 60 weeks if treated?

- 5%
- 30%
- 70%
5. Indirect Method: Published survival curves

1. Estimating numbers at risk

2. Incorporating numbers at risk
Survival curves

Step 1 - For each trial split the time-axis into T non-overlapping time intervals – chosen to limit number of events within any time interval

Step 2 - For each arm and each time point, read off the corresponding survival probability

Step 3 onwards: use these probabilities together with number at risk, number censored and extent of follow up time to estimate the hazard ratio in each interval and overall (see Appendix for methods)
Survival curves

TIME TO PROGRESSION

GEM+CDDP

0.95
0.78
0.65
0.42
0.39
0.24
Fmin and Fmax (Parmar method)

Accrual period

Date first patient randomised

Date last patient randomised

Date last patient follow-up

Fmin

Fmax
Fmin and Fmax (Parmar method)

1. Censoring tick marks on Kaplan-Meier curve
Assume first tick mark = Fmin, last tick mark = Fmax

2. Median follow-up and accrual period
Fmin = median follow-up - half the accrual period
Fmax = median follow-up + half the accrual period

3. Date of analysis and accrual period
Fmin = date of analysis - final date of accrual
Fmax = date of analysis - first date of accrual

4. Date of submission and accrual period
Fmin = (date of submission – 6 months) - final date of accrual
Fmax = (date of submission – 6 months) - first date of accrual

Tierney et al
Trials 2007
8:16
Additional information about numbers at risk should be used whenever provided in trial report

Cuts out some of the steps of Parmar et al estimating numbers at risk
Survival curves - Zero events

- Difficulties whenever estimated number of events within an interval on either arms is zero
- Replace zero by a small number of events $10^{-6}$ in that interval
- Best estimate of the total number of events and overall variance in each arm
- Preferable to concatenating time intervals
Practical methods for incorporating summary time-to-event data into meta-analysis
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## Data Extraction

Table 1: Suggested data collection form completed with data extracted from the report of the example trial in bladder cancer [6]

<table>
<thead>
<tr>
<th>Trial Reference: BA06</th>
<th>(Chemotherapy)</th>
<th>(No chemotherapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation ratio (e.g. 1:1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patients randomised</td>
<td>491</td>
<td>485</td>
</tr>
<tr>
<td>Patients analysed</td>
<td>491</td>
<td>485</td>
</tr>
<tr>
<td>Observed events</td>
<td>229</td>
<td>256</td>
</tr>
<tr>
<td>Logrank expected events</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hazard ratio, confidence interval (&amp; level e.g. 95%)</td>
<td>Not reported</td>
<td>0.85, CI 0.71 to 1.02 (95%)</td>
</tr>
<tr>
<td>Logrank variance</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Logrank observed minus-expected events</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hazard ratio and confidence interval (&amp; level e.g. 95%) or standard error or variance from adjusted or unadjusted Cox</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Test statistic, 2-sided p-value to 2 significant figures (&amp; test used e.g. logrank, Mantel-Haenszel or Cox)</td>
<td>Not reported, 0.075 (logrank)</td>
<td></td>
</tr>
<tr>
<td>Advantage to research or control?</td>
<td>Research</td>
<td></td>
</tr>
<tr>
<td>Actuarial or Kaplan Meier curves reported?</td>
<td>Yes, Kaplan Meier</td>
<td>Yes</td>
</tr>
<tr>
<td>Numbers at risk reported</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Follow-up details</td>
<td>Min = 14 months, Max = 82 months (Estimated from recruitment of 69 months, 11/9 – 7/95 and median follow-up of 48 months)</td>
<td></td>
</tr>
</tbody>
</table>

Tierney et al 2007
HR calculations spreadsheet

- Spreadsheet to facilitate the estimation of hazard ratios from published summary statistics or data extracted from Kaplan-Meier curves.

http://www.biomedcentral.com/content-supplementary/1745-6215-8-16-S1.xls

For the trial of Gemcitabine in combination with Oxaliplatin for pancreatic cancer (Louvet et al 2005), please complete the data extraction sheet as far as possible for the outcomes (i) Overall Survival and (ii) Progression Free Survival

Enter data into the excel spreadsheet available from

http://www.biomedcentral.com/content/supplementary/1745-6215-8-16-S1.xls

Find the estimate of lnHR and SE for each outcome in this study
Conclusions

• Time to event outcomes are important in medical research
• Hazard Ratio is the preferred treatment effect measure
• Be clear about outcome definition
• Indirect estimates may be reliable depending on level of information given, quality of graphics.
• Make life easier by using developed software.
• Always specify where logHRs and its variance have come from in your review (direct or indirect).
• IPD has many advantages which should be considered carefully
References


Appendix
Survival curves – Parmar et al

Step 3

From reading the manuscript, estimate the minimum ($F_{min}$) and maximum ($F_{max}$) follow-up of patients

- May be given directly
- Censoring tick marks on curves
- Estimated from dates of accrual and date of submission, or perhaps publication of the manuscript
Survival curves – Parmar et al

Time point
NAR at start of interval

\[ R(t_s) \]

Step 4 Research Group

Calculate Number at risk at start of interval

\[ R(t_s) = R(t - 1) - D(t - 1) \]

For first interval \( R(0) \) = number of patients analysed in the relevant treatment group
Survival curves – Parmar et al

Time point
NAR at start of interval
Censored during the interval

\[ C(t) = R(t_s) \left( \frac{1}{2} \frac{(t_e - t_s)}{(F_{max} - t_s)} \right) \]

Step 5  Research Group

If \( t_s \geq F_{min} \) and \( F_{min} \leq t_e \leq F_{max} \)
Calculate Number censored during first interval

If \( t_s < F_{min} \) and \( t_e < F_{min} \) number censored = 0
If \( t_s < F_{min} \) and \( F_{min} \leq t_e \leq F_{max} \) then set \( t_s = F_{min} \)
If \( t_s < F_{min} \) and \( t_e > F_{max} \) set \( t_s = F_{min} \) and \( t_e = F_{max} \)
If \( t_s > F_{min} \) and \( t_e > F_{max} \) set \( t_e = F_{max} \)
Survival curves – Parmar et al

Time point
NAR at start of interval
Censored during the interval
NAR during interval

Step 6  Research Group

Calculate Number at Risk during first interval

\[ R(t) = R(t_s) - C(t) \]
Survival curves – Parmar et al

Time point
NAR at start of interval
Censored during the interval
NAR during interval
Number of deaths during interval
Survival probability

\[ S(t_s) \quad S(t_e) \]

\[ C(t) \quad R(t) \quad D(t) \]

Step 7  Research Group

Calculate Number of deaths during first interval

\[ D(t) = R(t) \left\{ \frac{S(t_s) - S(t_e)}{S(t_s)} \right\} \]
Survival curves – Parmar et al

Time point
NAR at start of interval
Censored during the interval
NAR during interval
Number of deaths during interval
Survival probability

\[
\begin{align*}
\text{Time point} & \quad t_s & \quad t_e \\
R(t_s) & \\
C(t) & \\
R(t) & \\
D(t) & \\
S(t_s) & \\
S(t_e) & \\
\end{align*}
\]

Step 8  Control Group

Repeat step 4 -7 for the control group
Survival curves – Parmar et al

Step 9

Calculate ln(HR) and its variance for the first interval

\[
\ln(HR_i(t)) = \ln\left(\frac{D_{ri}(t)/R_{ri}(t)}{D_{ci}(t)/R_{ci}(t)}\right)
\]

\[
\text{var}[\ln(HR_i(t))] = \frac{1}{D_{ri}(t)} - \frac{1}{R_{ri}(t)} + \frac{1}{D_{ci}(t)} - \frac{1}{R_{ci}(t)}
\]

Step 10

Repeat steps 4-9 for all intervals
Survival curves – Parmar et al

Step 11

Calculate pooled log(HR) and its variance for the trial by combining estimates across all intervals

\[
\ln(\text{HR}_i) = \frac{\sum_{t=1}^{T} \ln(\text{HR}_i(t)) \cdot \frac{\text{var}[\ln(\text{HR}_i(t))] + 1}{\sum_{t=1}^{T} \text{var}[\ln(\text{HR}_i(t))]}}}{\sum_{t=1}^{T} \text{var}[\ln(\text{HR}_i(t))]} \\
\text{var}[\ln(\text{HR}_i)] = \left[ \sum_{t=1}^{T} \frac{1}{\text{var}[\ln(\text{HR}_i(t))]} \right]^{-1}
\]