An overview of time-to-event analysis for dental researchers

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Introduction

Welcome to the tutorial "An overview of time-to-event analysis for dental researchers." The objective of this tutorial is to explain the foundational concepts of time-to-event analysis for an audience of dental researchers. After introducing some key terms, I will explain the essential concepts of time-to-event analysis using a data set from the dental research literature. See this link for the full text of the publication based on a time-to-event analysis of this data set (Jain et al. (2022)).

Word bank

We begin our exploration of time-to-event analysis by highlighting some key terms. Detailed definitions of these terms are provided in the Dictionary section. Notice that several of these words are part of the common vernacular, but have a particular meaning within the context of time-to-event analysis.

Terms	Brief definition
Observation	Unit of study
Time	Time since entry into study
Event	Occasion that marks the outcome
Censored	No event was observed
Survival time	Time elapsed until event/censored
Median survival time	Time when about half of observations had events
Nth year survival	Proportion of observations still 'alive' year N
Kaplan-Meier plot	Curves that tell the story
Hazard ratio	Measure for comparing proability of 'event'
Cox model	Tool that estimates hazard ratios

Extended example with dental data

In this extended example, we will analyze a data set with time-to-event information on a set of crown margin repairs. Over the course of 10+ years, 1,002 patients received a crown margin repair treatment at the University of Iowa Dental Clinic. Data were collected for each patient via chart review from electronic dental records. The details of data collection and inclusion/exclusion criteria are available in the original manuscript (Jain et al. (2022)).

Our objective for this tutorial will be to analyze how long the crown margin repairs lasted. Our observations are the 1,002 crown margin repairs (CMRs), each representing a unique patient. An 'event' is a documented re-intervention on the CMR (such as replacement or extraction). CMRs that are not documented as having events during the study timeframe are the censored observations. The survival time for each CMR is the time (in years) between the date that the patient received the CMR treatment and the last date that the CMR was documented in the data.

We are interested in studying how several factors impact the lifespan of these CMRs. The factors we study here include:

- Age: patient's age (years) [1]
- Sex: patient's sex
- Caries Risk Assessment (CRA): the caries risk of the tooth that received the CMR
- Tooth Type: Whether the CMR was placed on an anterior (A) or posterior (P) tooth
- Jaw: Whether the CMR was placed in the maxillar (Mx) or mandibule (Md)

- Repair material: The material used for the CMR
- Surfaces: The type of surface on which the CMR was done (Buccal, lingual, or other)
- Number of surfaces: How many surfaces were involved in the CMR
- Root canal treatment (RCT): Was the tooth receiving the CMR root canal treated?
- Crown type: The type of crown used for the CMR
- Clinic: The clinic in which the CMR was placed
- Provider: Whether the provider placing the CMR was a faculty member or a student

Prepare the data set

Descriptive analysis

Once I have verified that the data set is ready for analysis, I create a "Table 1" that summarizes each variable in the data set. In Table 1, numeric values (like Age) are summarized with their median and range (min, max) values. Categorial variables are summarized by their counts and percentages.

Table 1: Description of data

Characteristic	**N = 1,002**
Age (yrs)	75.00 (32.00, 104.00)
Unknown	445
Sex	
F	294.00 (52.88%)
M	262.00 (47.12%)
Unknown	446
CRA	
High Risk	159.00 (40.87%)
Not High Risk	230.00 (59.13%)
Unknown	613
Tooth type	
A	190.00 (19.04%)
P	808.00 (80.96%)
Unknown	4
Jaw	
Md	474.00 (47.31%)
Mx	528.00 (52.69%)
Repair material	
Amal	379.00 (37.86%)
GI	114.00 (11.39%)
RBC	92.00 (9.19%)
RMGI	416.00 (41.56%)
Unknown	1

[1] We treat a lot of geriatric patients in our clinics, so yes, there are some patients who are > 100 years old.

Table 1: Description of data *(continued)*

Characteristic	N = 1,002
Surfaces	
B	403.00 (40.22%)
L	214.00 (21.36%)
Other	385.00 (38.42%)
Number of surfaces	
1	724.00 (72.26%)
2	278.00 (27.74%)
Root canal treated?	
No RCT	648.00 (65.06%)
RCT	348.00 (34.94%)
Unknown	6
Crown type	
C	55.00 (5.51%)
Other	384.00 (38.44%)
PFM	560.00 (56.06%)
Unknown	3
Clinic	
FAMD	440.00 (43.91%)
FDDAU	80.00 (7.98%)
FGP	181.00 (18.06%)
OPER	112.00 (11.18%)
Other	46.00 (4.59%)
PROS	65.00 (6.49%)
SPEC	78.00 (7.78%)
Provider	
faculty	356.00 (35.53%)
student	646.00 (64.47%)
Status	
Censored	673.00 (67.17%)
Event	329.00 (32.83%)
Time	1.92 (0.00, 12.12)

[1] Median (Range); n (%)

Timeline chart

To illustrate the stories of specific patients, I drew a timeline chart (some people call this type of graph a “swimlane diagram”). This kind of diagram lets us put a loupe on our data and see what is going on for an individual patient.

The timeline chart tells the stories of five patients from the CMR study. Patient 438 had a CMR repair that lasted for more than six years. During those six years, the patient had dental visits at the UI Dental Clinic, and so the researchers could verify that the patient’s CMR was intact. After those 6+ years, we do not know what happened to this patient - there is no more data available for that person’s CMR. Perhaps this person moved out of town, or started going to another clinic. In this case, Patient 438 is counted as ‘censored’, meaning this person’s CMR did not need a re-intervention during the time that the patient was part of the study. Similarly, Patient 359 and Patient 1 are also censored, meaning that neither of their CMRs needed a re-intervention during the time of the study. Patient 17 has a censoring mark (the dark circle) at time 0 - this means that Patient 17 received a CMR treatment from the UI Dental Clinic during the time that the

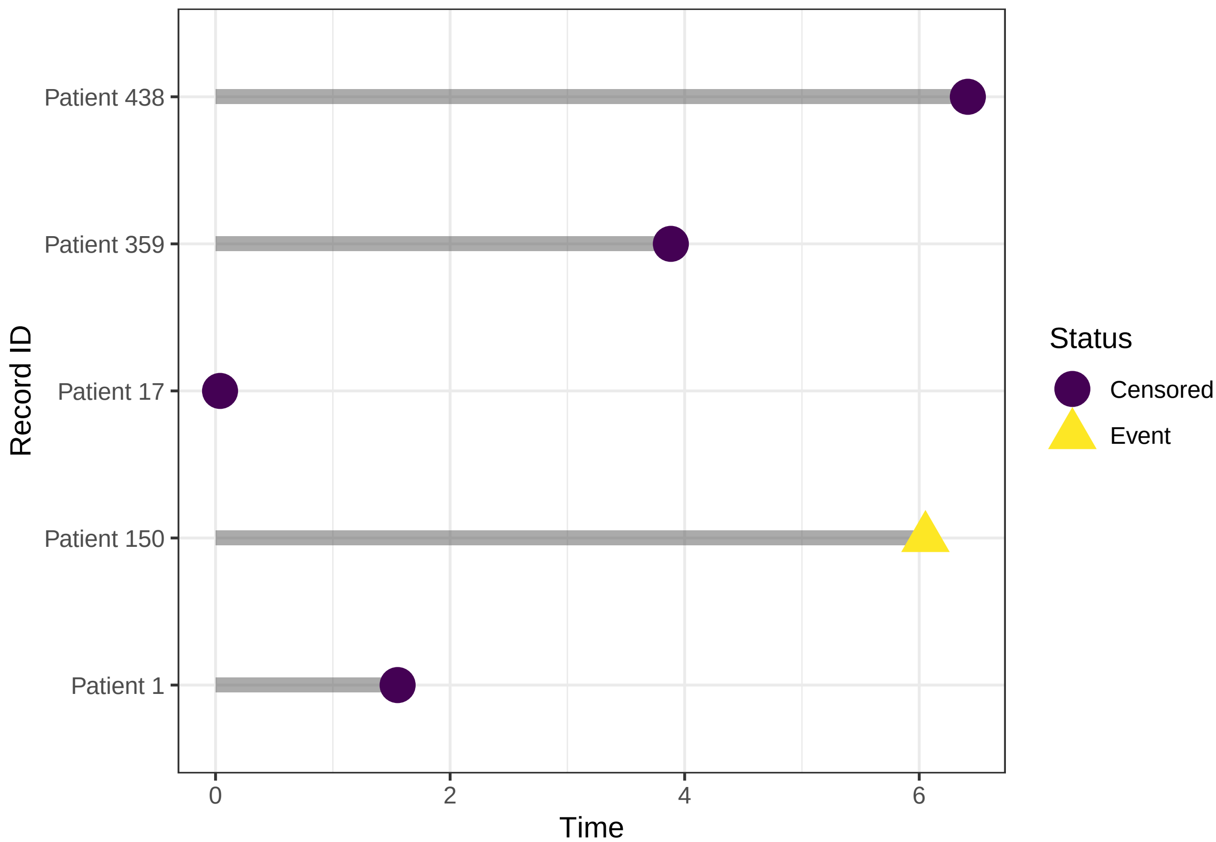


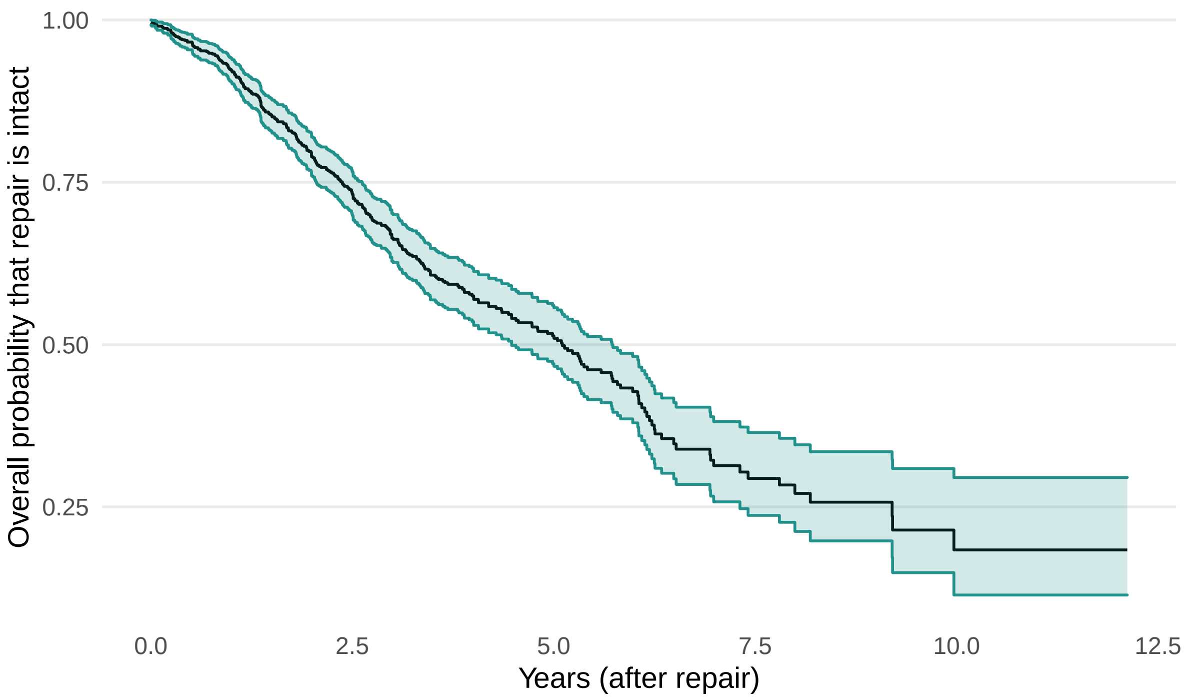
Figure 1: Timeline chart

researchers were collecting data, but never returned to that clinic again. The researchers at UI do not have any information about Patient 17 beyond the CMR treatment, and so this patient is 'censored at baseline.'

Patient 150 is the only patient in the timeline chart that has an 'event' marker, indicating that this patient's CMR needed a re-intervention after six years. Maybe this patient needed an extraction, or the teeth involved in the CMR required treatment for caries. This falls within the definition of 'event' that the researchers chose before analyzing the data for this study.

Kaplan-Meier plot

To get an idea of the overall trajectory of the time that the crown margin repairs are lasting, a create a Kaplan-Meier (KM) plot. As time goes on, there are fewer repairs upon which to draw estimates, so our estimates become more uncertain at later years. To visualize this uncertainty, we can add confidence intervals to the plots. A risk table provides details to supplement the general pattern illustrated in the KM plot.



At Risk	1002	421	140	30	6	0
Events	4	188	285	323	329	329

Figure 2: Kaplan-Meier plot

Whereas the timeline chart illustrated the stories of individual patients, the KM plot communicates the overarching story of the entire group of patients. The vertical ('y') axis of the KM plot shows the proportion (fraction) of CMRs that have **not** yet required a re-intervention. This value can be interpreted as the probability that a repair is intact. The horizontal ('x') axis shows time, where year 0 is the time that patients received the CMR treatments. The black line that looks like a staircase is the KM curve, representing the KM estimates of survival probability at each time. The colored area around that black line represents the 95% confidence interval.

At year 0, all patients have a CMR intact, and so the proportion on the vertical axis is at 1. We say that the probability of having an intact CMR at year 0 is 100%. As time moves onward (from left to right), some patients start to need re-interventions. At each re-intervention, the KM curve drops down, giving it the 'staircase' appearance. The downward path of the KM curve illstrates that the probability of a CMR being intact is decreasing over time. By year 5, about half of the CMRs have required re-interventions. By year 10, the probability of a repair being intact is less than 25%.

Simultaneous with the downward path of the KM curve is the widening of the colored area. In the first two years, the colored area keeps tightly around the KM curve; however, by year 10 the colored area is quite widespread. This illustrates that as more CMRs require re-interventions, there is increasing uncertainty about the Kaplan-Meier estimate of survival probability. Generalizing beyond our example, confidence intervals typically get wider over time, reflecting the uncertainty in the KM survival probability estimation.

The risk table beneath the KM plot is lined up with the horizontal axis, indicating that the risk table information is also dependent on time. At each time point, the risk table shows two values: the number of CMRs 'at risk' at that time (top number), and the number of CMRs that have had 'events' up to that time (bottom number). "At risk" means the number of observations which have 1) not yet had an event and 2) have not yet been censored. "Events" indicates the total number of observations that have had events up to a specific time.

At year 0, all 1,002 CMRs are at risk. We do notice that four CMRs are marked as having events in year 0 - at first, this does not make clinical sense. Such a data phenomena is often a sign of a bookeeping issue, and that is the case here. For these four individuals, the researcher doing the chart review/data extraction should go back and read the clinical notes to determine the best way to document what happened to the patients represented by these four CMRs. In a typical time-to-event analysis, the number of events at the baseline time is 0.

Moving forward in time, we see that at 2.5 years there are 188 CMRs which have already required re-interventions. A total of 421 of our initial 1,002 CMRs are still at risk at this time, meaning we are still collecting data from the patients with these CMRs and none of them have required a re-intervention yet. Notice that 188 + 421 does not add up to 1,002 – the other 393 CMRs are neither at risk nor have they required re-intervention, which means they have been *censored* by year 2.5.

By year 12.5, there are no more observations at risk, meaning that all the CMRs have either been censored or required re-interventions.

Analysis

Median survival

In most time-to-event analyses, the authors report the median survival time. This is defined as the time by which approximately half of all the observations have had an event. For our CMR example, the median survival time is the number of years by which approximately half of the CMRs required a re-intervention.

Keep in mind: The median survival time is **not** just the median of all the survival time values. When we are talking about median survival, we have to account for the fact that some repairs are censored – only events that happen during our study can tell us something definitive about survival time! The Kaplan-Meier method for calculating median survival takes censoring into account. [2]

Table 2: Median survival time

Median survival time	95% CI (lower)	95% CI (upper)
5.11	4.48	5.72

The table above shows that the median survival time for the CMRs was about 5.1 years, with a 95% confidence interval of 4.48 - 5.72 years. Looking back at our KM plot, this estimate makes sense - we observed that the KM curve was at about 0.5 on the vertical axis at the year = 5 mark.

[2] I chose to do this calculation in 'R' with the 'survfit' function from the 'survival' package.

Nth year survival

We are also often interested to estiamte the survival probability of a repair making it ___ number of years. Below is a table that shows estimates of 1 year, 3 year, and 5 year survival for our CMRs.

Table 3: 1, 3, and 5 year survival

Time	Number at risk	Number of events	Probability of survival	Standard Error	95% CI (lower)	95% CI (upper)
1	690	64	0.923	0.009	0.904	0.941
3	342	161	0.664	0.019	0.628	0.702
5	140	60	0.513	0.023	0.471	0.560

Plot 3 year survival probability and median survival time

To show the difference between estimating ___ year survival and estimating the median survival time, I can illustrate how these two measurements align with our KM plot. In the plot below, I show the median survival time and 3 year survival measurements with colored lines. The arrows on the colored lines show where the researcher would start to estimate each of these measurements. For median survival, one begins with survival probability (on the vertical axis). For 3 year survival, one begins with time (on the horizontal axis).

To keep this illustration from being too visually 'busy', I will leave off the confidence intervals.

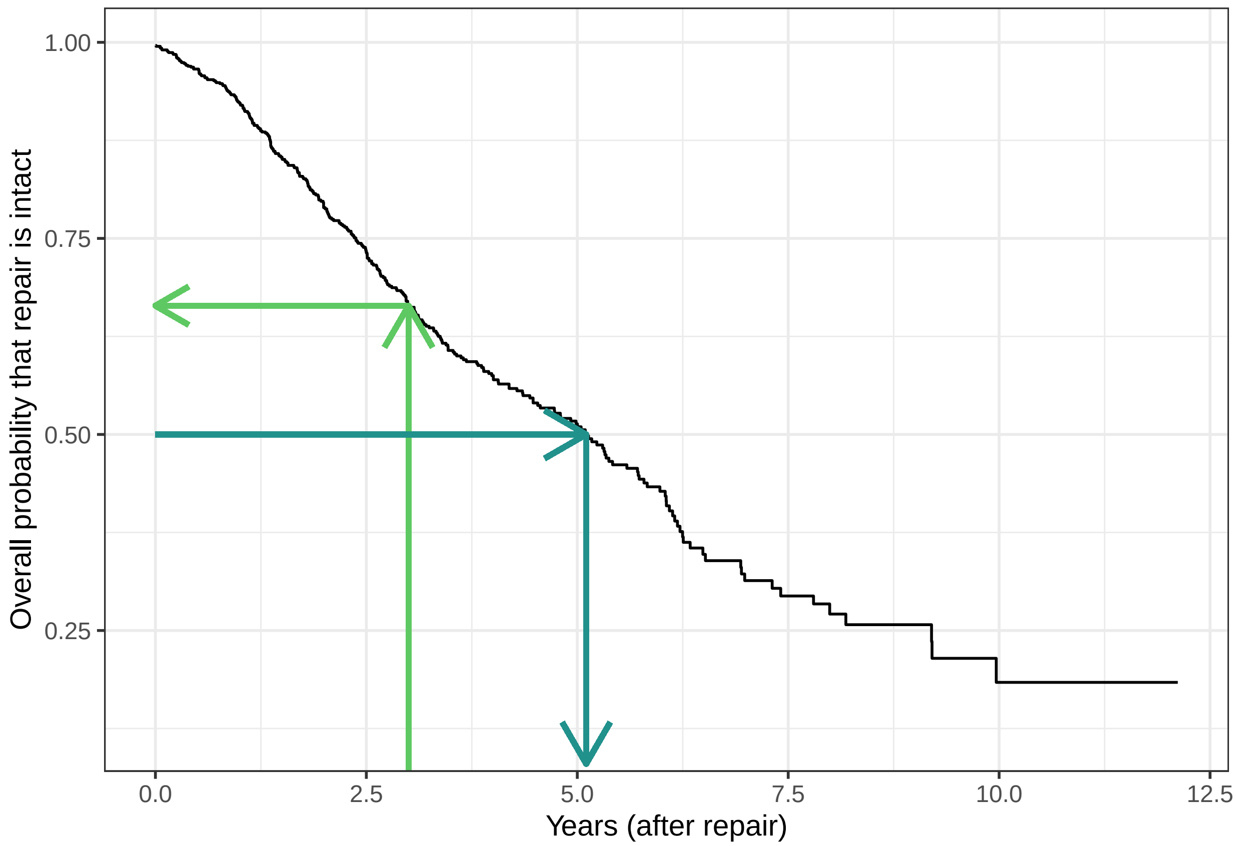


Figure 3: Median survival v. 3-year survival

Comparing groups

Up to this point, we have been studying a Kaplan-Meier plot that describes the entire data set (all crown margin repairs). In practice, the objective is often to compare two subgroups from within the data set – for instance, suppose we are interested in comparing how well crown margin repairs lasted between the root canal treated (RCT) and non-RCT groups. The plot below draws two Kaplan-Meier survival curves – one for each of these subgroups. We notice that across time, the curve representing the RCT teeth is consistently below the curve representing the non-RCT teeth. This indicates that the curve for the RCT teeth is *dropping (decreasing) faster*, illustrating that the crown margin repairs done on RCT treated teeth do not last as long as the repairs done on non-RCT teeth.

In addition to the curves in this graph, we also see the confidence intervals at each time point illustrated by the shaded area around each curve. The yellow and purple tinted areas overlap with each other quite a bit, which symbolizes that the difference between crown margin repairs done on RCT teeth and non-RCT teeth is subtle – the repairs last only slightly longer on the non-RCT teeth.

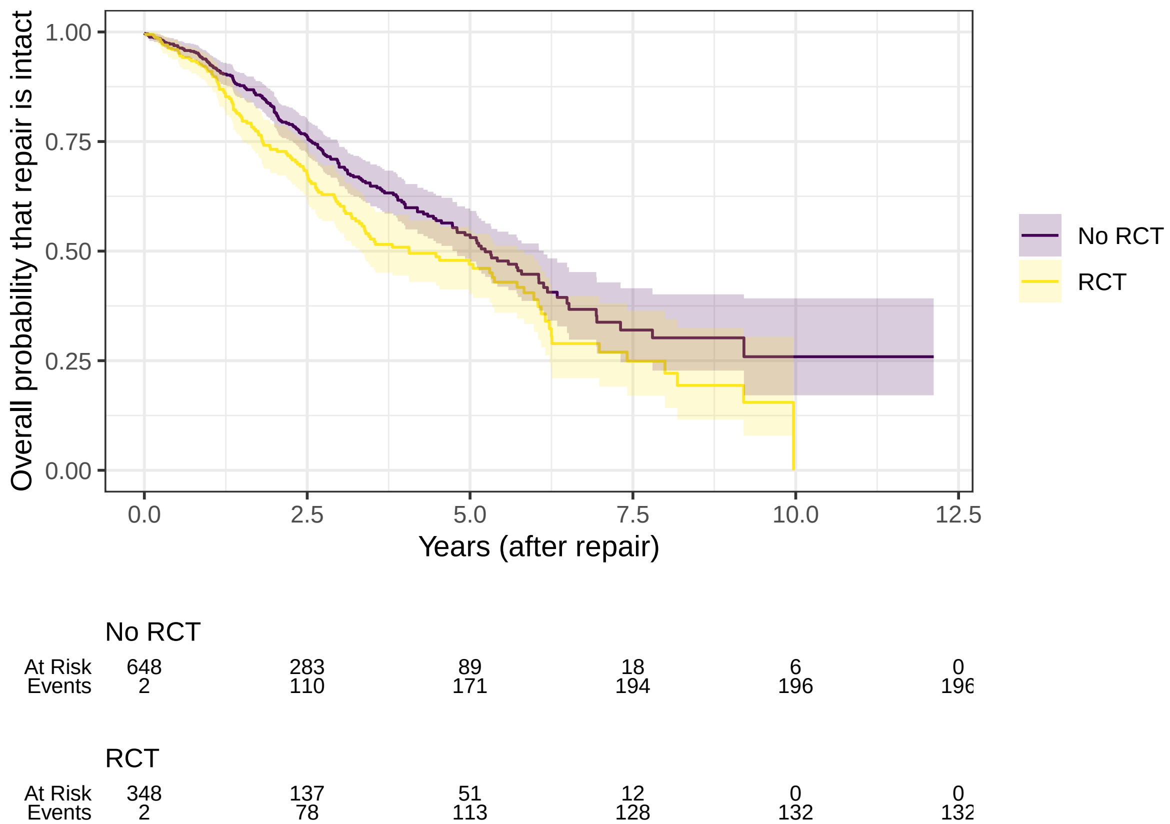
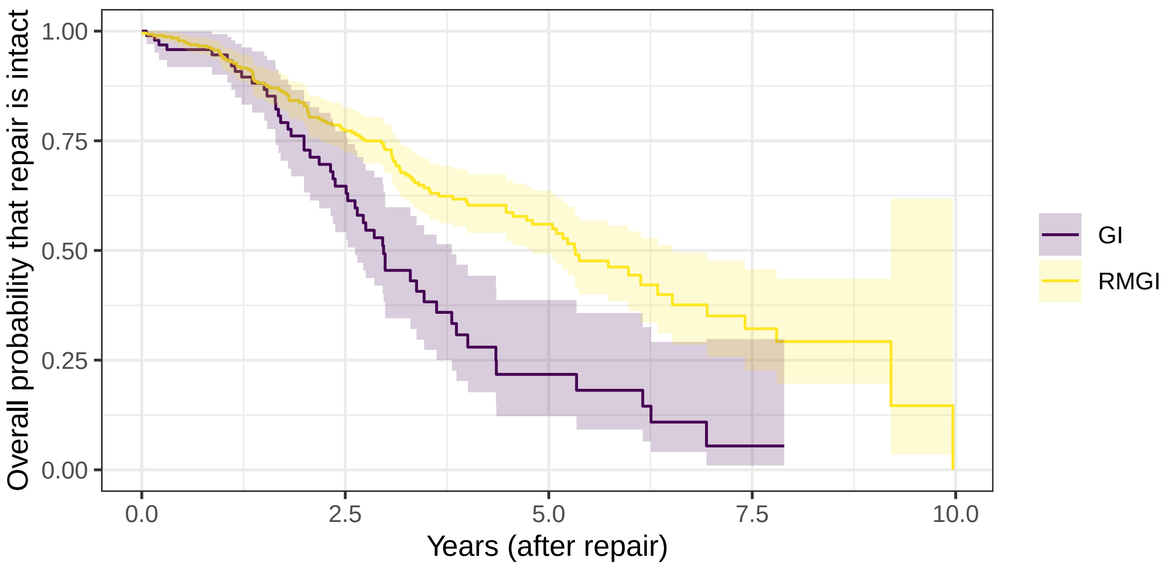


Figure 4: Comparing RCT groups

As a second example of comparing Kaplan-Meier plots between groups, let us suppose that we are working in a materials science context, where we are interested in comparing crown margin repairs that were done with glass ionomer (GI) to repairs done resin-modified glass ionomer (RMGI). We see in the next figure that the survival curve representing the GI group is much lower than the curve for the RMGI group for all times after two years. We also see that the space between the two curves increases over time - the two curves are diverging. The confidence intervals do not overlap much at all after 2.5 years. These survival curves indicate that the crown margin repairs done with RMGI lasted notably longer than the repairs done with GI. There is evidence in this data set that the modification to GI makes a positive impact on the expected lifespan of crown margin repairs.

Cox model

Our final survival analysis tool for this tutorial is a Cox proportional hazards model. This model examines each of the variables (i.e. the independent variables) in relationship the time-to-event outcome.



GI

At Risk	114	39	6	1	0
Events	0	25	45	49	49

RMGI

At Risk	416	174	56	11	0
Events	2	62	98	112	115

Figure 5: Comparing repair materials

Table 4 summarizes the results of this Cox model using hazard ratios (HR), 95% confidence intervals (CI), and p-values. Hazard ratios (as defined in the Dictionary) indicate the multiplicative impact of an independent variable on the probability of survival. In the popular Cox regression model, the hazard ratio for an independent variable can be calculated by taking the model coefficient (i.e. the β value) for that independent variable and raising e to the power of that β value: $e^{\beta} = \text{HR}$. In Table 4, this step of *exponentiating* model coefficients has already been done. [3]

Let's calculate a hazard ratio

[3] To see what 'R' code I used to format the table this way, refer to the 'analysis.Rmd' files in the GitHub page for this tutorial.

Table 4: Cox model results

Characteristic	**HR**	**95% CI**	**p-value**
Age (yrs)	1.01	0.99, 1.03	0.4
Sex			
F			
M	1.18	0.79, 1.77	0.4
CR A			
High Risk			
Not High Risk	0.73	0.49, 1.11	0.14
Tooth type			
A			
P	1.84	0.96, 3.54	0.066
Jaw			
Md			
Mx	0.67	0.42, 1.07	0.093
Repair material			
Amal			
GI	2.59	1.29, 5.21	0.008
RBC	1.44	0.56, 3.68	0.4
RMGI	1.30	0.81, 2.09	0.3
Surfaces			
B			
L	1.28	0.72, 2.28	0.4
Other	1.54	0.89, 2.66	0.12
Number of surfaces			
1			
2	1.40	0.89, 2.20	0.15
Root canal treated?			
No RCT			
RCT	1.56	1.02, 2.38	0.040
Crown type			
C			
Other	1.06	0.38, 2.98	>0.9
PFM	0.98	0.36, 2.68	>0.9
Clinic			
FAMD			
FDDAU	1.82	0.97, 3.40	0.062
FGP	2.06	0.75, 5.66	0.2
OPER	0.90	0.50, 1.63	0.7
Other	1.18	0.47, 2.98	0.7
PROS	1.80	0.56, 5.81	0.3
SPEC	1.22	0.46, 3.19	0.7
Provider			
faculty			
student	1.88	0.89, 3.99	0.10

[1] HR = Hazard Ratio, CI = Confidence Interval

Dictionary

- **Observation**: The unit of study. These units could be people, as in the case of a clinical investigation where each unit of study is a patient. An observation could also be a dental implant, a set of dentures, or a plate of bacteria. Regardless of the research context, the observation is studied by the researcher for a specified amount of time. For each observation, there is a time of entry into the study and a time of last observation. In addition to these dates/times, information about the details of an observation are also recorded.
  - **Time**: The units of time that have passed since an observation's entry into the study. In time-to-event analysis, the date/time of entry into the study is labeled as 0, and the subsequent units of time (e.g. days, weeks, years) count forward from that starting time. For example, suppose the observations in my study are patients treated in a specific dental clinic, and I am recording time in years. If Patient A enters the study in 2018 and I study that patient until 2022, then I would call 2018 "year 0" and 2022 "year 3." Note that the time of entry into the study often differs among observations. Returning to our example, suppose Patient B enters my study in 2019. In this case, "time 0" for Patient B is 2019. When I make generalizations about all the patients in the study, I would reference "time 0", understanding that this is different calendar years for patients A and B.
  - **Event**: The occasion, occurrence, or sign related to the outcome of interest. Every scientific investigation should have an established research objective that informs the choice of an outcome. The choice of this outcome determines the choice of event for a time-to-event analysis. Suppose I want to compare different kinds of dentures to assess which ones are more durable (i.e. which dentures last the longest). In this case, I would need to define what it means for a denture to "last" - perhaps this means that the denture still fits well and does not require replacement. For this context, the outcome of interest could be the amount of time until replacement, and the "event" could be defined as replacement. The observations in the study would be dentures, and the goal would be to study the dentures over time and record the dates and details of those which require replacement. We would say that the dentures which need to be replaced are the 'observations which have an event.'
  - **Censored**: The state of observations which do **not** have an event recorded during the time of the study. We describe such observations as "being censored", as opposed to those observations which have events. Censoring can occur when an observation is lost to follow up or does not have an event before the end of a study. Suppose again that I am studying different kinds of dentures to compare their longevity. If a denture is still functioning at the time when I stop collecting data, then I would record this as a censored observation. If a denture is lost to follow up (meaning that the patient with the denture stops coming to my clinic after enrolling in the study), I would also mark that denture as censored. Notice that in both cases, I would not know how long the denture lasted. For all dentures in my study, the last time I collected data about a denture is the date at which I record that denture as 'being censored' or 'having an event'.
  - **Survival time**: The time elapsed from the time of entry into the study until the time of either an event or censoring. Consider a denture that I begin studying in 2013 and which needs a replacement in 2021. I would say this denture had an event, and it had a survival time of 8 years.
  - **Median survival time**: The time by which approximately half of all the observations in a study had experienced an event. For example, suppose I am studying 50 patients with full dentures, and the event of interest is replacing those dentures. If after 9 years, 25 of those dentures have been replaced, I would report 9 years as the median survival time.
  - **Nth year survival (e.g. 3 year survival)**: The proportion of observations that have **not** had an event after 'n' units of time (where 'n' can be any number). Back to the denture example, suppose I am interested in studying 10 year survival in a data set of 50 dentures. If after 10 years, 15 dentures (30% of 50) have still not been replaced and have not been censored, then I would report 10-year survival as 30%.
  - **Kaplan-Meier plot**: This name is a reference to the foundational publication by Kaplan and

Meier (1958) and the work generated from its ideas. In brief, Kaplan and Meier presented a method for working with data that has censoring. Kaplan-Meier plots are curves that can be used to illustrate the time-to-event phenomena over time. These plots represent both events and censored observations. We will examine some examples of these curves later in the tutorial.

  - **Hazard ratios**: A multiplicative factor used to compare the survival probability between groups. Suppose that in our denture example, we compare dentures made with material A to dentures made with material B. If we find that the hazard ratio for dentures made with material A is 2.5, then the data are showing that at any given time, those dentures made with material A are 2.5 times as likely to need replacement compared to dentures made with material B. Keep in mind that a hazard ratio of 1 means lack of association, a hazard ratio greater than 1 suggests an increased risk, and a hazard ratio below 1 suggests a smaller risk. Dawson, Blanchette, and Pihlstrom (2021) provide an extended explanation of this concept.
  - **Cox (proportional hazards) model**: This is a reference to the foundational publication by Cox (1972). In brief, Cox proposed a method for a regression-like analysis which is specially crafted for time-to-event data. The Cox regression model lets us make generalizations about the impact of independent variables on the outcome of interest using hazard ratios. We will see an example of this kind of model later in the tutorial.

Acknowledgements and further reading

- In my own time–to-event analyses work using `R`, I have often referred to a tutorial by Emily Zaboor (Zaboor (2022)).
- Clark et al. (2003) has published a series of tutorials which are more in-depth than what I provide here

References

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