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SURVIVAL ANALYSIS OF TIME-TO-EVENT DATA IN ORTHOPAEDIC SURGERY

CURRENT CONCEPTS

With an increasing incidence of orthopaedic procedures performed worldwide, the quantity of data collected, including "Big Data", is also rising. Widening indications for surgery, a growing number of implant options and variety of operative techniques, as well as an increasing need to demonstrate cost effectiveness, necessitate the use of robust analysis techniques to assess outcomes.

Traditionally, analysis of outcomes in orthopaedic surgery involves survival methods, where the outcome of interest is 'time to event', which is usually revision or re-operation. For arthroplasty, this represents the time from the date of insertion of the implant until the date on which the revision is performed and patients whose outcomes are not known or have died are censored. Revision is generally taken as the primary indicator of failure of a joint replacement. Although revision/re-operation is dependent on many factors, including the fitness for surgery of the patient, it provides a firm endpoint for analysis, particularly in epidemiological studies.

One of the strengths of survival analysis is the handling of incomplete data or follow-up. If an event is not seen within the timeframe observed or reported, there would be incomplete observations, known as censored events. 'Right' censoring is the most common and occurs either if a subject does not experience the event during the study period, is lost to follow-up or withdraws from the study. Death is another reason for censoring.

The 'risk set' at a specific time point is defined as the individuals/implants that at that time are at risk of experiencing the event (e.g. revision). These are the individuals that have survived up to that point and are those who may experience the outcome in question. An individual/implant will leave the risk set either by experiencing the event, or when they are censored.

The two main measures of interest in epidemiological studies are the risk of the event occurring (probability) and the rate of its occurrence (hazard).

NON-PARAMETRIC METHODS

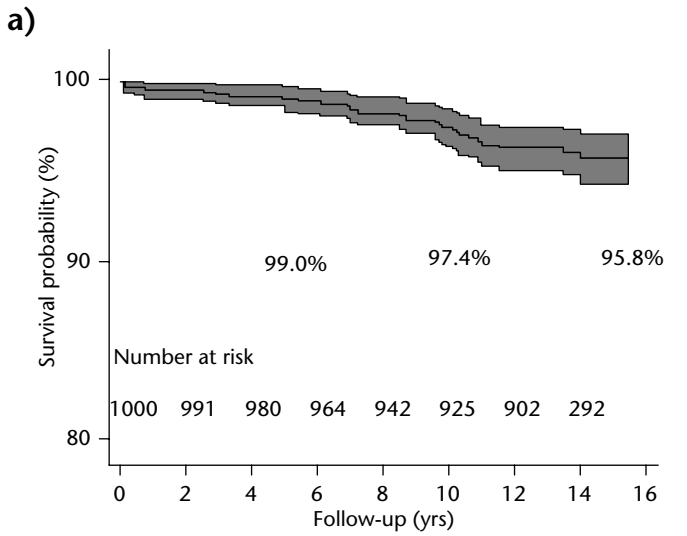
The Kaplan-Meier[1,2] and life table[3] are non-parametric and are the most frequently used methods in survivorship analysis of joint replacements. A key difference between the two is that life table methods do not require knowledge of the date of failure and therefore the probability of an event is calculated for fixed time points, not at the precise time an event occurs (Fig. 1).

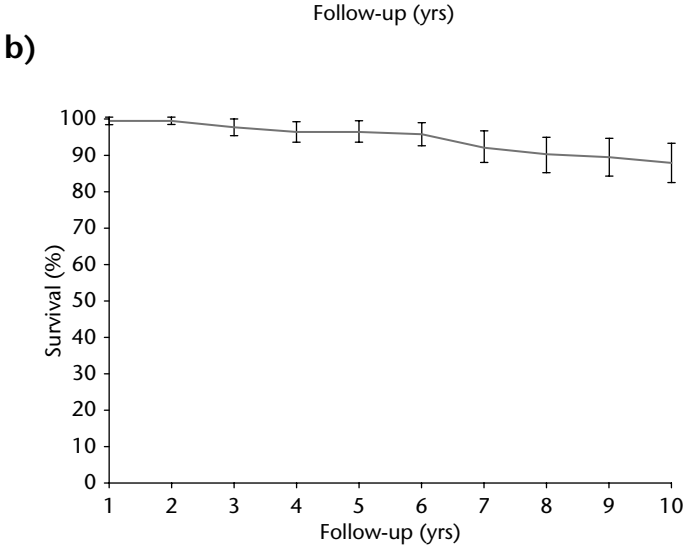
For Kaplan-Meier analysis, log-rank tests are used to compare survivorship between different groups, and the cumulative hazard function is often estimated non-parametrically using the Nelson-Aalen estimator.[4] The Kaplan-Meier model handles loss to follow-up data more completely than the life table method where follow-up is traditionally calculated on an actuarial year basis. The Kaplan-Meier analysis is normally plotted as a survival curve and is usually the preferred method for presenting long-term follow-up data where loss to follow-up can be a problem.

THE COX PROPORTIONAL HAZARDS MODEL

A common method for regression analysis to assess the effect of different covariates on the hazard function (or rate of revision) is the Cox proportional hazards (PH) model.[7] The key assumption of the Cox model is proportional hazards. This implies that the hazard ratio remains constant during the course of follow-up and can be reported as a single number, i.e. the relative risk of revision due to a risk factor (such as diabetes) is constant, no matter the exposure time. From this assumption, it follows that an increase or decrease between any of the groups is constant over time.

The Cox PH model is a semi-parametric method. For single-event survivorship analysis (e.g. event = revision surgery), there is a direct association between the hazard and survival functions, therefore the Cox PH model is able to determine the effect of individual covariates on survival.[8] However, in large population-based data, the assumption of proportional hazards may not always be reasonable as the effect of a covariate on the





Figures 1a and 1b. Examples of Kaplan-Meier and life table graphs for survival analysis.

a) Reproduced with permission from: Kaplan-Meier survival analysis with 95% confidence intervals shown. Reproduced with permission from **Daniel J, Pradhan C, Ziaee H, Pynsent PB, McMinn DJ.** Results of Birmingham hip resurfacing at 12 to 15 years: a single-surgeon series. *Bone Joint J* 2014;96-B:1298-1306. b) Reproduced with permission from **Emerson RH, Alnachoukati O, Barrington J, Ennin K.** The results of Oxford unicompartmental knee arthroplasty in the United States: a mean ten-year survival analysis. *Bone Joint J* 2016; 98-B(10 Supple B):34-40.

hazard may vary with time. For example, the relative probability of revision after cementless *versus* cemented hip arthroplasty may be higher in the early period after implantation but not necessarily at five years. There are methods of testing the proportional hazards assumption, including graphical techniques such as plotting the 'Schoenfeld residuals' against time (Fig. 2).[9] Each individual for each covariate in the model has a separate residual, and when plotting scaled residuals against time, the slope should be zero if the proportional hazards assumption is accurate. However, there are sophisticated methods for introducing time-variable effects of covariates into a Cox regression model.

A crucial disadvantage of using the Cox PH model in large database studies is that despite allowing a comparison in hazard for individuals based on covariates (hazard ratio), it does not provide an estimate of the underlying baseline hazard which is needed to understand the process of the condition.

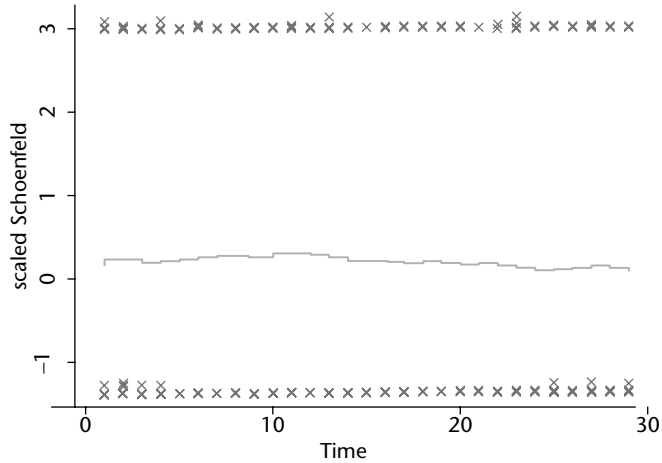


Fig. 2 Example of plot for scaled Schoenfeld residuals against time using a Cox PH model.

COMPETING RISKS

In survivorship analysis, competing risks are present when an individual or implant is at risk of more than one mutually exclusive event, for example, revision surgery and death where death is considered to be a competing risk. The occurrence of a competing event may prevent the event of interest from occurring. By censoring individuals who have died at the time of analysis, this alters the probability of the event of interest by changing the number of individuals at risk. Put simply, patients who have died are assumed to have had the same risk of having the event of interest had they not died. It has been shown that Kaplan-Meier survivorship analysis overestimates the risk of revision arthroplasty.[10]

It is logical to perform an analysis that takes into account competing risks. In arthroplasty registry studies, competing risks analysis has been adopted by a few.[11-14] In such studies, the competing risk of death has been accounted for. However, the statistical techniques can be expanded to account for multiple competing risks. For example, when the event of interest is revision due to aseptic loosening, death and revision for other indications are both competing risks.

Much of the competing risks methodology has been developed from cancer survival models where death for any cause other than cancer is a competing risk. However, the same methodology can be applied to arthroplasty and other orthopaedic time-to-event data.

There are different approaches to competing risk modelling. The first is to model the cause-specific hazards (hazard of failure due to the event of interest given that the subject is still alive at time t) and transform these to determine the cumulative incidence. A second approach is to model the cumulative incidence function directly through a method proposed by Fine and Gray.[15]

Both non-parametric and semi-parametric approaches to competing risks have been used in some arthroplasty registry studies,[11,12] but a flexible parametric model which avoids the assumption of proportional hazards and provides a model that can easily incorporate time-dependent effects are, thus far, not widely utilised in orthopaedic studies.

In conclusion, there are advancing approaches to survival analysis in orthopaedics. It is important to have an understanding of techniques and what their limitations are when interpreting the results, particularly the results of larger epidemiological studies. Also critical is the need to adopt appropriate methodology to provide the most accurate estimate of the

risk of an event for different groups of patients and implants – there is no 'one size fits all' method.

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