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No bias of ignored bilaterality when analysing the revision risk of knee prostheses: Analysis of a population based sample of 44,590 patients with 55,298 knee prostheses from the national Swedish Knee Arthroplasty Register

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Abstract

Background: The current practice of the Swedish Knee Register is not to take into consideration if one or both knees in a patient are subject to surgery when evaluating risk of revision after arthroplasty. Risk calculations are typically done by statistical methods, such as Kaplan-Meier analyses and Cox's proportional hazards models, that are based on the assumption that observed events are independent, and this is rarely appreciated. The purpose of this study was to investigate if ignoring bilateral operations when using these methods biases the results.

Methods: The bias of not taking bilateral operations into account was investigated by statistically analysing 55 298 prostheses in 44 590 patients, undergoing knee arthroplasty surgery in Sweden during 1985–1999, using traditional proportional hazards analysis, which assumes that all observations are independent, and a shared gamma frailty model, which allows patients to contribute repeated observations.

Results: The effect of neglecting bilateral prostheses is minute, possibly because bilateral prosthesis failure is a rare event.

Conclusion: We conclude that the revision risk of knee prostheses in general can be analysed without consideration for subject dependency, at least in study populations with a relatively low proportion of subjects having experienced bilateral revisions.

Background

The revision risk, or survival, of different prosthesis types are often evaluated using statistical methods as Kaplan-Meier analysis and Cox's proportional hazards model. These techniques are, however, based on the assumption that observed events are independent, and this is rarely appreciated. Bilateral prostheses are often included in study populations and subject-specific factors, physiolog-

ical or behavioural could be expected to play an important role for the lifetime of prostheses.

The purpose of this study is to investigate if the inclusion of patients with bilateral prostheses has practical consequences for the evaluation of knee prostheses.

Table 1: Age and sex of the studied population.

Factor	Females	Males
Age		
0 – 14	-	-
15 – 19	1	-
20 – 24	7	-
25 – 29	15	3
30 – 34	28	7
35 – 39	61	22
40 – 45	119	40
45 – 49	229	125
50 – 54	650	307
55 – 59	1 408	842
60 – 64	2 910	1 709
65 – 69	5 185	2 741
70 – 74	7 404	3 794
75 – 79	7 927	3 363
80 – 84	3 494	1 541
85 +	905	383
Total	29 713	14 877

Methods

The National Swedish Knee Arthroplasty Register

The Swedish Knee Arthroplasty Register, SKAR, has registered knee arthroplasties in Sweden since 1975 [1].

In this study all 44590 patients with osteoarthritis, OA, and rheumatoid arthritis, RA, operated on during 1985–1999 with either unicompartmental, UKA, or tricompartmental, TKA, knee arthroplasties were included in the study population. Their age and sex is presented in Table 1.

This study population was not, as generally is the case in clinical studies, defined for the purpose of a clinically relevant comparison but to ensure a substantial group of patients with two major types of implants for the specific purpose of analysing the effects of ignoring bilaterality.

33 882 patients had one prosthesis implanted and 10708 patients had had bilateral prostheses implanted. The total number of studied prostheses was thus 55298. In unilaterally operated patients 1 803 (5.3%) prostheses were revised while in bilaterally operated patients one and two prostheses were revised in 1 089 (5.1%) and 296 (1.4%) knees respectively.

Mean survival time was 60 (range: 0 – 287) months, and the cumulative five-year revision risk was 6.4%.

The majority of the implanted prostheses, 39759 or 71.9%, were TKA; 15539 or 28.1% were UKA. The crude cumulative five-year revision risk was 4.9% and 9.3% for TKA and UKA respectively.

Statistical methods

Lifetimes of prostheses are often analysed using the proportional hazards model. The time from a prosthesis implantation to its revision is studied using the instantaneous failure rate, or hazard, $\lambda(t)$, of the prostheses. The hazard is assumed to be of the form

$$\lambda_i(t) = \lambda_0(t) \exp(\beta X_i)$$

Where $\lambda_0(t)$ is an unspecified function describing the relation between hazard and time t, common for all subjects i contributing one event only, and where X_i is a set of observed explanatory variables. Finally, β represent the weights on the hazard of these explanatory variables. The hazard ratios, $\exp(\beta)$, are commonly interpreted as relative risk estimates.

The proportional hazards model is based on the assumption that events occur independently, which clearly is doubtful when subjects contribute more than one event each.

The proportional hazards model can, however, be extended into a model allowing subjects to contribute multiple events: a frailty model [2]. In short, this is achieved by including a patient-specific random effect factor, γ (the frailty), into the model, and by evaluating hazard rates conditional on this factor.

Table 2: Results of proportional hazards, and shared gamma frailty, models for prosthesis failure risk.

Covariate	Proportional hazards model		Shared gamma frailty model	
	HR	95% CI	HR	95% CI
Model 1				
Type (UKA vs TKA)	1.84	1.71 – 1.97	1.98	1.83 – 2.14
Model 2				
Type (UKA vs TKA)	1.85	1.73 – 1.99	1.94	1.80 – 2.10
Age (years)	0.97	0.96 – 0.97	0.96	0.96 – 0.97
Male sex	1.11	1.02 – 1.19	1.10	1.01 – 1.19

$$\lambda_i\,(t\mid\gamma) = \lambda_0\,(t)\exp(\beta X_i + \gamma Z_i)$$

Here Z_i may be interpreted as a set of explanatory, unobserved, variables. The shared gamma frailty model, which we have used, assume that jointly γ follow a log gamma distribution. In this model the failure rates of a patient is assumed to be mutually independent.

$$\lambda_i\,(t\mid\gamma) = Y_i\,\lambda_0\,(t)\,\exp\,(\beta X_i)$$

The Y_i (assumed gamma distributed) denote the individual frailty effects on prosthesis survival; if $Y_i = 1$ for all i, the frailty model reduces to the usual proportional hazards model for independent observations.

The parameters of the frailty models were estimated using the penalised partial likelihood method. We used the statistical software R V1.5 http://www.r-project.org/ for the calculations on a computer running Linux with a 1 GHz Intel processor.

Results

Comparing the revision risk between TKA and UKA, see Table 2, among all 55298 prostheses and ignoring bilaterality by using a traditional proportional hazards analysis, yields a hazard ratio estimate of 1.84 (95% CI 1.71 – 1.97). Incorporating covariates for age and sex leaves this estimate relatively unchanged.

Accounting for subject dependency among bilateral prostheses, by performing the comparison using a shared gamma frailty model, yields a hazard ratio estimate of 1.98 (95% CI 1.83 – 2.14). Again, incorporating covariates for age and sex does not change the estimate much.

Estimated frailty was statistically significant neither in the first frailty model (Model 1; p = 0.90) nor in the second one (Model 2; p = 0.73).

Discussion

In spite of the problem often being identified in analyses of prosthesis survival, there has hitherto been no generally accepted view on the effects of ignoring bilaterality. For instance, the Norwegian Arthroplasty Register has reported [3] results for hip arthroplasties, which are based on an assumption that the revision risk of unilateral prosthesis does not differ from that of all prostheses combined, while the Finnish Endoprosthesis Register has reported that the second of bilateral hip operations have a significantly lower risk of revision than a unilateral operation [4] and therefore suggests that including bilateral prostheses can bias prosthesis survival estimates.

It seems reasonable to assume that bone-quality, body weight, and activity level are important factors for survival of hip/knee prostheses and thus, that the survival of bilaterally operated patients is correlated. The question we tried to answer was, if the bias of such correlation substantially affects the revision risk estimates if bilaterality is ignored. As we were not primarily focusing on presenting revision risk estimates we did not elaborate on potential confounding factors.

Our finding was that the effect of ignoring subject dependency of bilateral operations is negligible; in this study the ordinary proportional hazards model produced results similar to the results of the shared frailty model with hazard ratio estimates of 1.85 and 1.94 respectively, when accounting for differences in age and sex by including these factors as covariates in the model. Both these results seem to be compatible with the observed crude five-year revision risks of 4.9% and 9.3% for UKA and TKA respectively.

An intuitive explanation for the phenomenon that ignored bilaterality does not invalidate the results, is that the bias generated by ignoring dependency only comes from bilaterally operated patients with both of their prostheses revised, and such patients are very few (148 patients or 0.3%) in the studied population. This might not

be the case in other study populations if bilateral or multiple events are more common. The problem is possibly further complicated by the likely relation between prevalence of bilaterally operated patients and length of follow up.

In two recent studies, Ripatti and Palmgren [3], and Schwarzer et al. [4], with methodologies similar to ours, evaluated the effects of neglecting bilaterality in analyses of hip arthroplasty revision risk; their findings were similar to ours. Both these studies were, however, based on much fewer observations, 826 prostheses among 562 patients, and 505 prostheses among 455 patients, respectively.

Conclusions
We conclude that the revision risk of knee prostheses in general can be analysed without consideration for subject dependency, at least in study populations with a relatively low proportion of subjects having experienced bilateral revisions.

Abbreviations
OA Osteoarthritis

RA Rheumatoid arthritis

SKAR Swedish Knee Arthroplasty Register

TKA Tricompartmental

UKA Unicompartmental

Competing interests
Dr Robertsson plays a leading role in the administration of, and use of information from, the Swedish Knee Arthroplasty Register.

Authors' contributions
JR and OR together designed the study. JR drafted the manuscript and performed the statistical analysis. OR defined the study population and contributed data. Both of the authors read and approved the manuscript.

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