Robustness of individual and marginal model-based estimates: A sensitivity analysis of flexible parametric models

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https://doi.org/10.1016/j.canep.2018.10.017
Received 5 July 2018; Received in revised form 29 October 2018; Accepted 30 October 2018
Available online 12 November 2018
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1. Introduction

Flexible parametric survival models (FPMs), which were first introduced by Royston and Parmar, have been used in a range of settings [1,2]. The models have been used to estimate survival in epidemiological studies with applications involving international comparisons [3] and they have also been adapted to clinical trials settings [4]. The methodology has been extended to the relative survival framework in population-based data [5]. It has also been used to assess statistical cure methodology has been extended to the relative survival framework in population-based data [5]. It has also been used to assess statistical cure and they have also been adapted to clinical trials settings [4]. The models have been used to estimate survival in epidemiological studies with applications involving international comparisons [3] and they have also been adapted to clinical trials settings [4].

Population-based studies that include all patients in a geographically-defined population provide a measure of the effectiveness of the healthcare system in diagnosing and treating the cancers that arise. A commonly reported measure of cancer survival is relative survival, which compares the all-cause survival for a group of cancer patients to the expected survival of a comparable group in the general population that is free of the cancer of interest [8].

An increasing number of population-based studies perform analysis of cancer survival, which compares the all-cause survival for a group of cancer patients to the expected survival of a comparable group in the general population that is free of the cancer of interest [8].

A small debate exists on the number of knots used for the splines. Sensitivity analyses are often conducted to ensure that the df does not influence the estimates. A simulation study, showed that the estimated relative effects are insensitive to the correct specification of the baseline hazard and that, provided enough knots are selected, complex hazard functions can be captured [13]. They also showed that absolute effects are well captured. Another simulation study showed that time-

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2. Methods

2.1. Data resources

Data consist of National Cancer Registry Data, provided by Public Health England, on all individuals in England diagnosed with one of the cancers of interest between the start of 2007 and the end of 2013. We included cancer types with both high and low survival after diagnosis and varying characteristics such as age at diagnosis. The 10 cancer types considered are bladder, lung, colon, rectum, stomach, melanoma, prostate, breast, ovarian cancer and Hodgkin lymphoma. Individuals were identified using International Classification of Diseases 10 (Table 1). For patients with multiple tumours only the first tumour for each type of cancer is considered.

2.2. Flexible parametric survival models

In this application, we only consider FPMs that are fitted on the log-cumulative hazard scale rather than the log hazard scale. An advantage of this way of modelling is that the corresponding function is more stable and the process of capturing the shape of the function is easier. FPMs explicitly estimate the log cumulative hazard by using restricted cubic splines for \(n\) knots \[n(t)\mid \beta, k_0\] for the log baseline cumulative hazard is

\[
\ln[H(t|x)] = s(ln(t)|\beta, k_0) + x^T \beta + \sum_{j=1}^{D} s(ln(t)|\delta_j, k_j)x_j
\]

where \(D\) is the number of time-dependent effects and \(s(ln(t)|\delta_j, k_j)\) is the spline function for the \(j\) th time-dependent effect with \(\delta_j\) values for the parameters.

Modelling time-dependent effects usually requires fewer knots than the baseline effects because we actually model departures from the baseline hazard.

FPMs have been extended to estimate excess mortality and relative survival which are commonly reported measures in cancer epidemiology.

2.3. Excess mortality and relative survival

Excess mortality is equal with the difference between the observed (all-cause) mortality in a population of cancer patients and the expected mortality in a comparable group.

Relative survival is the survival analogue of excess mortality and is given as the all-cause survival among the cancer patients divided by the expected survival in a comparable group in the general population with similar characteristics, who are assumed to be free of the cancer of interest [8,16]. The expected survival is considered to be known and is obtained from available life tables.

Relative survival aims to estimate survival in a hypothetical scenario where the cancer of interest is the only possible cause of death and with some assumptions is equivalent to what is known in the statistical literature as net survival, a useful measure for comparing survival between populations, such as countries, or for studying temporal trends [17–19].

A major advantage of relative survival is that it circumvents problems caused by the inaccuracy or non-availability of death certificates as it does not rely on the cause of death information [16].

2.4. Sensitivity analysis

We assessed the reliability of relative survival estimates by using data for a range of cancer types. Age was included in the models as a continuous variable but non-linearity was allowed by using splines. Models on population-based studies usually have non-proportional hazards. For example, the effect of age is bigger in the beginning of the follow-up right. Thus, the time-dependent effect of age was included in the models. We chose varying df to model the baseline excess hazard (i.e. 3,4,5,6,7 df) and the main (i.e. 3,4,5 df) and time-dependent effects (i.e. 2,3,4,5 df) resulting in 60 FPMs for each cancer type. The knots for the baseline excess hazard and the time-dependent effect of age were placed at equally distributed quantiles of the log of the event times. Additional boundary knots were also placed in the minimum and maximum of the distribution of the log of the event times. Similarly, the knots for the main effect of age were placed in equally distributed quantiles of the age distribution. The model estimates are usually not sensitive to the location of the knots [20]. Expected mortality rates were obtained from population mortality files stratified by sex, age and calendar year [21].

Hodgkin lymphoma affects a smaller portion of the population and is particularly common at younger ages. The small number of events and the different profile of the youngest and the oldest patients caused convergence issues for some models. To enable the models to fit and compare different scenarios, even though we allowed time-dependent effects for the effect of age, these were limited to the linear term of the
spline.

For each model we obtained both 1-year and 5-year, age-specific, age-group and internally age-standardised relative survival estimates that are common measures for population-based studies. The age-specific estimates are given for ages 55, 65, 75 and 85. The groups used for the age-group estimates were 18–44, 45–54, 55–64, 65–74 and 75+. For prostate cancer were however obtained for groups 18–54, 55–64, 65–74, 75–84 and 85+, as prostate cancer is frequent in elderly men. Internally age-standardised estimates were estimated as the weighted average of relative survival in each age group, based on the age distribution within our study population. External age standardisation is also possible using weights from standard cancer populations [22].

With continuous data is common to have less stable results in the extremes due to the small number of observations. An issue with relative survival might be that some patients have better survival than expected and this may occur by chance when there are few numbers, such as in the young or elderly. This might lead to negative excess mortality and further issues with the models’ convergence. To make estimates on the extremes more stable and help with convergence problems, we forced patients who were younger than the age corresponding to the 2nd percentile of the age distribution of each cancer type to have the same relative survival as patients of this cut-off age. The same was applied for patients who were older than the age corresponding to the 98th percentile of the age distribution. Thus, 96% of the age distribution was modelled continuously.

The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated for each model [23,24]. Furthermore, we obtained estimates using the Ederer II and Pohar Perme non-parametric methods that require no modelling assumptions, for comparison [8,17,25]. The model with 5, 3 and 3 df for the baseline excess hazard, the main and the time-dependent effects of the covariates were compared against the reference model. This is not considered to be the correct model and it is used only for comparison purposes.

Appendix C for Stata code.

### 2.5. Interactive graphs

We also developed web-based interactive graphs that help users understand the effect of different df on the estimates by comparing the estimations derived by different models. Survival and hazard functions are given over years since diagnosis and the users can choose the models they are interested in. Both age-standardised and age-specific estimates are provided. A major advantage of interactive graphs is being able to control what information is displayed. Further exploration of findings is enabled and therefore users develop a better understanding of the results.

### 3. Results

Data includes a population of more than 1.2 million cancer patients. Patients with Hodgkin lymphoma are the youngest with the average age to be approximately 47 years (Table 1). The oldest are bladder cancer patients, at the mean age of 76 and 74 years for females and males respectively.

Table 2A and 2B show the differences in the 1-year and 5-year relative survival estimates between the reference model and the model selected by the AIC or BIC criterion. For the age-standardised estimates, absolute differences remain lower than 0.5 percentage point. In specific, absolute differences between the reference model and the model

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**Table 2A**

| Cancer Type | Group 1 75+ | Group 2 75 | Group 3 65–75 | Group 4 64–54 | Group 5 64–54 |
|-------------|-------------|------------|---------------|---------------|---------------|
| Bladder     | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Lung        | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Colorectal  | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Stomach     | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Breast      | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Prostate    | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Rectum      | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Melanoma    | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Ovarian     | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |
| Hodgkin     | 0.01        | 0.01       | 0.01          | 0.01          | 0.01          |

*The five groups used for the age-group estimates were 18–44, 45–54, 55–64, 65–74 and 75+.*
Table 2B

Differences between the estimates of survival of the reference model with the one with the minimum AIC and BIC respectively, for males as a whole population (standardised), males in age-groups or males aged 55, 65, 75 and 85 by type of cancer.

| Standardised Group | Time (years) | AIC | BIC | pp | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC |
|---------------------|--------------|-----|-----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Bladder 1           | 1            | −0.14 | 0.02 | 0.29 | 0.13 | 0.26 | 0.12 | 0.18 | 0.13 | 0.21 | 0.12 | 0.18 | 0.12 | 0.18 | 0.12 | 0.18 | 0.12 | 0.18 |
| Lung                | 1            | 0.15 | −2.30 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 | −1.08 |
| Rectum              | 1            | 0.05 | −0.11 | 0.05 | −0.11 | 0.05 | −0.11 | 0.05 | −0.11 | 0.05 | −0.11 | 0.05 | −0.11 | 0.05 | −0.11 | 0.05 | −0.11 | 0.05 | −0.11 |
| Stomach             | 1            | 0.05 | −0.16 | 0.05 | −0.16 | 0.05 | −0.16 | 0.05 | −0.16 | 0.05 | −0.16 | 0.05 | −0.16 | 0.05 | −0.16 | 0.05 | −0.16 | 0.05 | −0.16 |
| Bladder 5           | 1            | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Lung                | 5            | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Stomach             | 5            | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |

* The five groups used for the age-group estimates were 18–54, 55–64, 65–74, 75–84 and 85+. Differences between the estimates of survival for the baseline excess hazard, the main and the time-dependent effect of age respectively and BIC (i.e. model with 4,3,2 df for the baseline excess hazard, the main and the time-dependent effect of age respectively) are small (Table 2A).

A bigger variation is observed in 5-year age-specific estimates for prostate cancer (Fig. 3). The largest differences are seen among different df for the main effect of age and for 75 and 85 years old estimates. The selection criteria suggest that a more complicated model will be more appropriate. The AIC chooses the model with 7,4 and df for the baseline excess hazard, the main and the time-dependent effect of age respectively. The equivalent df for the BIC are 7,3 and 3 respectively. However, the differences between the reference model and the models chosen by the selection criteria remains lower than 1 percentage point for all ages (Table 2B).

4. Discussion

We performed sensitivity analyses to assess the sensitivity of estimates obtained from FPPMs on the number of knots chosen for the splines by using relative survival as an example. Even though we used relative survival to conduct the sensitivity analysis, our conclusions can...
also be applied to other settings such as FPMs that do not incorporate the expected mortality. We have also developed web-based interactive graphs that allow the comparison of estimates from different models. We advocate the use of interactive graphs for reporting findings as they allow for additional exploration and improve understanding of results [29–31].

The results of the sensitivity analysis indicate differences between the reference model and the models chosen by the selection criteria for the age-standardised estimates are negligible. Age-group relative survival is less stable, among models, with slightly larger differences for the youngest group, of whom there are fewer patients. For most of the cancers the df for the main and time-dependent effect of age vary the least whereas 4 df seem adequate to capture the underlying baseline excess hazard.

Age-specific estimates are more sensitive to the number of knots chosen but perform well. For most of the cancer types, higher differentiation is observed among models with different df for the splines of the main effect of age. However, the differences between the reference model and the models chosen by the selection criteria remain low. Slightly larger differences were observed for the age of 55 years old at diagnosis for male patients with colon and rectum cancers but this can partly be explained by the smaller number of patients at that age. For such cancer types choosing 3 df seems insufficient for capturing the shape of the main effect of age and more are required. More caution is needed when interest is in age-specific estimates and the choice for the df for the splines should be given further thought, with the hazard and survival function of the cancer considered.

In general, when too few df are specified, the estimation may become problematic and is better to specify more knots. In the models with the highest df used for the splines, the estimates are very close.

Fig. 1. Age standardised estimates for 1-year and 5-year relative survival for A) female patients with colon cancer and B) males with prostate cancer. The dots represent the point estimates and the lines either side the 95% confidence intervals. The vertical line, in each plot, represent the estimate obtained by the reference model. Solid, dash and dotted horizontal lines represent 3, 4 and 5 degrees of freedom, respectively, for the main effect of age. (BL: degrees of freedom for the baseline excess hazard, TVC: degrees of freedom for the time-dependent effect of age, A: model chosen by AIC, B: model chosen by BIC, PP: Pohar Perme estimate).

| 1-year | 5-year |
|--------|--------|
| BL    | TVC    |
| 7     | 5      |
| 4      | 3      |
| 2      |        |
| 6     | 5      |
| 4      | 3      |
| 2      |        |
| 5     | 5      |
| 4      | 3      |
| 2      |        |
| 4     | 5      |
| 4      | 3      |
| 2      |        |
| 3     | 5      |
| 4      | 3      |
| 2      |        |

Relative Survival (%)
with the estimates of the reference model and the models selected by the AIC and BIC criteria. Of course too many df should be avoided as they can result in overfitting, especially for datasets with a small number of observations.

Our results are consistent with results from simulation studies that pointed out that estimates are not influenced noticeably by the number of knots, as long as a sensible number of knots is selected [13,14]. In large datasets, the AIC and BIC will select models with high df when a lower value for the df provide a similar fit. In our analysis, the selection criteria chose more complicated models but the differences in the estimates between the models selected by the selection criteria and the reference model were negligible.

A major strength of our analysis is the large number of patients involved in each cancer type that enable reliable conclusions. The cancer types chosen, allow the assessment of FPMs for cancers with varying prognosis and other characteristics. Furthermore, the wide range of df selected for the splines and the 60 FPMs for each type of cancer provided a thorough evaluation of obtained estimates.

Although this study has noteworthy strengths, we should acknowledge potential limitations. The population in our data includes only patients enrolled in one of the cancer registries in England. Populations from other countries may have different characteristics that affect their survival. Moreover, patients above the 98th percentile and below the 2nd percentile of the age distribution were forced to take the same relative survival as those patients at these respective cut-off points. Using these constraints leads to more stable estimates in the extremes where there is less data and helps with some model convergence issues.

5. Conclusions

FPMs overcome some of the limitations that traditional methods encounter and they have the ability to capture the shape of complex hazard functions by using restricted cubic splines. Time-dependent effects can easily be incorporated in FPMs. We showed that age-specific, age-group and age-standardised estimates are not over-sensitive to the specified number of knots and that the use of restricted cubic splines is a valid approach for time-to-event data. We also highly recommend the use of the webtool as an easy way to visualise the differences across different scenarios.

Declarations of interest

None.

Funding

This work was supported by Cancer Research UK [Grant number C1483/A18262].

Authorship contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data and participated in drafting the article. All authors interpreted the data, critically revised the manuscript and gave final approval of the version.
Fig. 3. Estimates for 5-year relative survival for male patients with prostate diagnosed at 55, 65, 75 and 85 years. The dots represent the point estimates and the lines either side the 95% confidence intervals. The vertical line, in each plot, represent the estimate obtained by the reference model. Solid, dash and dotted horizontal lines represent 3, 4 and 5 degrees of freedom, respectively, for the main effect of age. (BL: degrees of freedom for the baseline excess hazard, TVC: degrees of freedom for the time-dependent effect of age, A: model chosen by AIC, B: model chosen by BIC).

Fig. 4. Snapshot from the web-based interactive graphs.
to be published.

Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doi:https://doi.org/10.1016/j.canep.2018.10.017.

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