`casebase`: **An Alternative Framework For Survival Analysis and Comparison of Event Rates** by Sahir Rai Bhatnagar*, Maxime Turgeon*, Jesse Islam, James A Hanley and Olli Saarela. (*joint co-authors)

Response to the reviewers[1]

We thank the reviewers for their constructive comments, which we believe has significantly improved our manuscript. In this document, we reproduce the reviewers comments, and provide our response to each of them below. For a quick reference, here are the main changes to the manuscript:

- We re-wrote the entire introduction to focus on the motivation and why the package needs to exist.
- We clarified the "Theoretical Details" section by expanding our discussion of person moments, case series, and base series.
- We refocused the first Case Study to highlight what we believe is the strength of the case-base sampling framework, which is flexible hazard modelling (e.g. non-linear time effect, non-proportional hazard) within a single framework.
- We clarified the use of "cumulative incidence" throughout and restricted it to the competing-risk setting.
- We added a discussion of Poisson regression for survival analysis, and how it differs from case-base sampling, to our manuscript.

Reviewer 1

A primary critique is that after reading pages 1 and 2, I still had no idea what this package is doing nor a good feel for why it needs to exist. This is coming from someone who has worked in survival analysis for over 3 decades. This is not meant to be mean: if we assume that the package is worthwhile, and you want people to use it, this needs to be addressed up front. Let me break down the issue into more practical advice.

Reviewer Point P 1.1 — The introduction put me off with things that were incorrect and/or "fluff". Overdone salesman pitches sometimes show up in the innovation and significance sections of grant applications, but even there they tend to decrease rather than increase the reader's enthusiasm.

a. "... stepwise estimates of the survival function that can be difficult to interpret". Since the entire research world seems to handle Kaplan-Meier curves just fine, this is a statment that has no face validity. I've never heard that complaint from an actual user. Actually, the KM may sometimes be preferred to smooth estimates, since the 'bumps' provide a visual estimate of precision; when there are multiple curves explicit confidence bands often make a plot too busy.

[1] October 26, 2021

b. "... opens the door to an extensive array of modeling tools. Indeed, lasso and elastic-net regression can be used..." Both of these apply directly to survival data/ Cox models. Read the help page for glmnet.

Turn down the rhetoric.

Reply: We have substantially re-written the introduction to focus on the reason why our package needs to exist. Overall, the ultimate goal of our package is to make fitting flexible hazards accessible to more end users, with the hopes that they will favor reporting absolute risks over hazard ratios (this is also mentioned in your comment 1.3 below). We try to frame our package as an alternative framework for survival analysis, not a competing one. More specifically, case-base sampling is a parametric approach which directly models the hazard function in continuous time, using the well-understood and familiar logistic regression. It allows one to model flexible functions of time and their interactions with covariates. For example, in our first case study, we fit the interaction between `survival::psplines(time)` and a binary treatment variable. The following code shows how we can fit the hazard function using the formula interface:

```
fit <- fitSmoothHazard(DeadOfPrCa ~ pspline(Follow.Up.Time, df = 2) * ScrArm,
                       data = ERSPC)
```

From the fitted object, we can readily obtain the hazard function by treatment group, the time-dependent hazard ratio, and the absolute risk with standard errors using `plot`, `absoluteRisk`, and `confint` methods:

```
# hazard function for each arm
plot(fit, type = "hazard", hazard.params = list(xvar = "Follow.Up.Time", by = "ScrArm"))

# hazard ratio
new_data <- data.frame(ScrArm = factor("Control group",
                                levels = c("Control group","Screening group")),
                       Follow.Up.Time = seq(1, 12, by  = 0.1))

plot(fit, type = "hr", newdata = new_data, var = "ScrArm", xvar = "Follow.Up.Time")

# absolute risk and confidence intervals
new_data <- data.frame(ScrArm = c("Control group", "Screening group"))
new_time <- seq(0,14,0.1)
risk <- absoluteRisk(fit, time = new_time, newdata = new_data)
conf_ints <- confint(risk, fit)
```

An experienced user can likely do this with existing packages, but even so, it is not so straightforward to obtain these quantities with their standard errors. Related to your comment 1.4 below, we contrast the Whitehead (1980) approach with the casebase approach and show that Poisson regression can lead to some computational issues when the censoring fraction is large are the events are sparse.

As for the second point, a similar question was raised by the other reviewer (Reviewer Point 2.5). We have clarified the relationship between `casebase` and `cv.glmnet` within the manuscript. In Example 3,

we are comparing two approaches: case-base sampling, where the hazard is estimated using penalized logistic regression; and Coxnet, which is a regularized version of the Cox model. As in Examples 1 and 2, the function `fitSmoothHazard` starts by sampling the case series and base series and calculating the offset term. With `family = "glmnet"`, the data is then transformed to match the expected matrix input of `cv.glmnet`, before calling `cv.glmnet` with the offset term. In other words, `fitSmoothHazard` abstracts away most of the necessary data processing. If a user fits a model using `cv.glmnet` and the Cox family, then they are fitting a semi-parametric model that is different from the case-base model. On the other hand, if the user tries to fit a model using `cv.glmnet` and their original data (i.e. without `fitSmoothHazard`), then the results will not be valid, assuming the model fit converges at all.

Reviewer Point P 1.2 — The package is based on a 2009 paper by Hanley and Miettinen, and here lies one of the issues. It is difficult to argue with the strong impact OM has had on the epidemiologic literature, for the good, but a significant downside to his work is the use of an alternate and unique vocabulary. For instance, all of us are familiar with the cumlative distribution function $F(t) = Pr(X \leq t)$ and it's compliment the survival curve $S(t) = 1 - F(t)$. In the OM world $F(t)$ is now the "cumulative incidence function" $CI(t)$; a completely unnecessary substitution. (Also a very confusing one, since the CIF is not the integral of the incidence). The words "case", "base", "person-moments" are likewise something quite peculiar. The overall title of casebase will possibly be confused with "case only" study designs in genetics (someone reads it as "case based"). If you want people to know what's up you will need to provide a translation service.

I took the time to read the 2009 paper, and I still don't know what this sentence means (page 2 of submission) "with the person-moments where $dR_i(t) = 1$ constituting the base series." What is R counting? When would dR be zero? Nor is rho or Q clear to me. The author's need to give actual, clear definitions.

Reply: We clarified the use of cumulative incidence, restricting it to the competing risk setting. We also expanded our discussion of person moments, case series, and base series at the beginning of the section Theoretical Details to provide more detail and clarity.

To summarize, there are two main counting processes: the "usual" one $N(t)$, which counts the events of interest and whose hazard we want to model; and $R(t)$, which arises from the case-base sampling process. Then $Q(t)$ is simply their sum. The process $R(t)$ can be thought of as a "nuisance process" whose purpose is to allow us to write down a (partial) likelihood that can be maximized. We are **not** interested in modelling the hazard $\rho(t)$ for the process $R(t)$, and in fact it is completely user-defined (and so there is no point in trying to model it). Currently, our package only allows one sampling mechanism, corresponding to $R(t)$ being homogeneous over the whole study base; however, as pointed out in the discussion, future work will look at providing a user-interface for specifying the case-base sampling mechanism.

Reviewer Point P 1.3 —

The H and M paper includes a valid justification, which is missing here. That is that the users of Cox models rarely provide the necessary information to compute absolute risk. This is a major gap in reporting; absolute risk is as important as relative risk, maybe more so in fact. There are 2 solutions. i. Train users to include that information (it's an extra computing step for a Cox model, but not diffucult) or ii. use an alternative model where the baseline hazard has a simple parametric form (and train authors to report those coefficients).

Aside: Short of the journals making it a requirement, I have low expectations for any "train users" plan. Page limit are often so severe that any sentence which can be omitted is leapt upon like a press gang seizing a drunk. (This particular personal pessimism should not count against the paper.)

Reply: We agree and have addressed this issue up front in our introduction, as well as our response to your first comment 1.1. One step towards this goal would be to give users tools that allow them to easily compute and visualize the hazard function, time-dependent hazard ratios, and absolute risks. Our first case study highlights these features of the casebase framework. We would like to re-iterate however, that we are not saying this is a better approach than other frameworks (e.g. Cox model), but one that is perhaps more familiar and within reach of a junior level data analyst.

Reviewer Point P 1.4 — On a statistical front, there already exist simple methods for substituting in a smooth hazard. See Whitehead (Applied Statisics 1980, 268-275) for instance: A quick look at the KM normally allows one to break it into 3-4 segments over which log(S(t)) is approximately linear. Split the follow-up time into epochs based on those cutpoints (survSplit will do this), and fit simple Poisson regression to the result with one intercept per epoch. One can even use many splits and model time as a spline, but this conflicts with the "simple reporting" goal. In what ways is this approach better? (There may be several, I don't know.)

Reply: We added a discussion of Poisson regression for survival analysis, and how it differs from casebase sampling, to our manuscript. Our approach differs from what the reviewer describes in two ways: it assumes a continuous model of time (unlike Poisson regression), and it does not rely on the user making choices about cut points (unlike using `survSplit`).

In practice, we find that Poisson regression can lead to some computational issues when the censoring fraction is large and events are sparse. For illustration, we provide a comparison of these two approaches here. We follow the online textbook by Carstensen for fitting splines-based Poisson models. The code to reproduce Figure R1 below is available in a public gist (link here). In this Figure, we are plotting the hazard as estimated using case-base sampling with splines (using `pspline`), and a splines-based Poisson regression model. Panel A uses the lung dataset from the survival package, and the hazard is estimated for a 60-year-old male patient; Panel B uses the ERSPC data from our casebase package, and the hazard is estimated for the treatment arm.

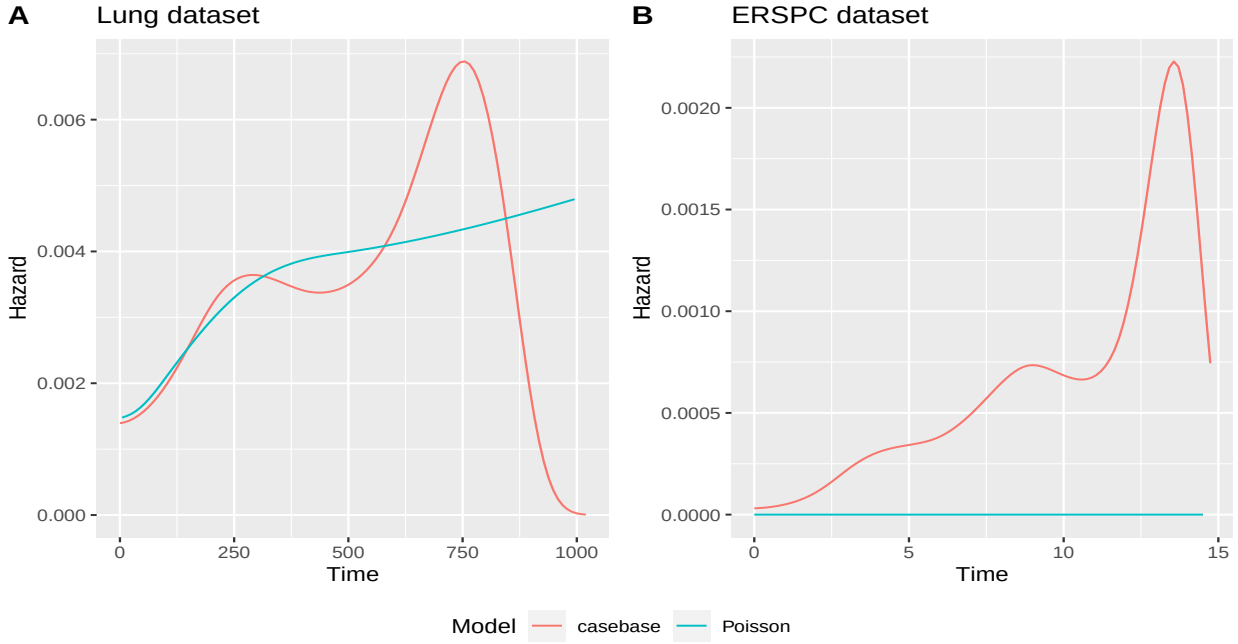
For the lung dataset, we can see good agreement up to time 250. However, for the ERSPC dataset, which has a large censoring fraction, we can see that the splines-based Poisson model fails to converge. This lack of convergence is reported as a warning in R, but it can also be seen from the flat hazard function (Figure R1, B). With the ERSPC dataset, our approach is able to fit a model while the Poisson approach could not converge.

Reviewer Point P 1.5 — In the comparisons with other packages, the authors overlooked that the standard survival::survfit function provides Aalen-Johansen estimates; both the KM and competing risks are special cases of the AJ.

More importantly, the competing risks literature defines "cumulative incidence" as something quite different than Hanley and Miettinen's definition (equation 2 of 2009 paper.) If casebase is implementing H&M, then this whole discussion of the CI is very confusing.

Reply: As noted above, we clarified throughout the use of cumulative incidence, restricting it to the competing-risk setting. We also included Cox regression and the Aalen-Johansen estimator to our comparison of cumulative incidence estimates (Case Study #2).

Figure R1: Estimates of the hazard function on two different datasets. The red line corresponds to a case-base approach with splines; the blue line corresponds to a Poisson approach using splines. **A**: Lung dataset from the survival package. **B**: ERSPC dataset from the casebase package.



Reviewer Point P 1.6 — Page 5. "The case based approach described in section 2.2 can be visualized as ..." There is no section 2.2. (Other than figures and tables there are no numbers in this reviewer's copy at all.)

Reply: We removed the mention of a numbered section.

Reviewer Point P 1.7 — Page 6. I am very confused by this plot. In the ERSPC data there is no date of enrollment, and a subject's follow-up times ends at prostate cancer (PCA) death, other death, or last follow-up. How then can a data point for a case be within the gray area. For example, died of PCA at 5 years, but the gray for this person extends out to 10. Labeling a subject as a case before the actual occurence of PCA death is an example of immortal time bias, a source of many false inference schemes.

Reply: We updated Figure 1 in the manuscript to explain the process of constructing a population-time plot. In particular, we discuss why some red points appear within the grey area.

A population-time plot helps to visualize incidence density. The grey area can be thought of as infinitely thin horizontal rectangles ordered by length of followup (Figure 1 A). Then, we label each event using a red point; as the reviewer points out, these events occur at the end of follow-up, so at the end of a grey horizontal line (Figure 1 B). Visually, these labelled points along the edge of the grey space are not visually distinct enough to demonstrate incidence density. To help the visualization, these points are randomly moved along their vertical axis, resulting in these points appearing in the grey space (Figure 1 C). Finally, we plot a sample of the base series, uniformly from the entire grey space (Figure 1 D) creating the complete population time plot. We have updated our manuscript to include this information.

Reviewer 2

This article provides an overview of the `casebase` package and a comparison with other survival packages. The package's main goal is to analyze survival data allowing users to estimate smooth baseline hazards over time. Their claim is that these results are easier to interpret. The methods for this approach have been published previously and are sound. Whether this approach is useful in practice is less clear based on the examples shown in the paper.

Reviewer Point P 2.1 — In several spots the authors claim that a smoothed estimate of absolute risk is easier to interpret, however by smoothing the data, they are also losing information. Specifically, the height of the steps provides a quick way to determine a crude estimate of the variability. Additionally, in Figure 5 the smoothed curve overestimates the relapse risk at the beginning of the time interval (this was not mentioned as a possible problem with their approach).

Reply: The reviewer brings up an important point that we overlooked. As previously mentioned in the Discussion, parametric bootstrap can be used to create confidence bands around the case-base estimates. We took the opportunity to implement this bootstrap approach in the newest version of the package, and we added an illustration of this approach to the first case study. In Figure 4, we can now see a comparison of the (stratified) Kaplan-Meier curves and the bootstrap confidence bands.

Reviewer Point P 2.2 — A small point, but in the paper the code uses categorical values for ScrArm but in the dataset it is coded as 0/1

```
new_data <- data.frame(ScrArm = c("Control group", "Screening group"))
```

Reply: We updated the dataset in the package to use categorical values.

Reviewer Point P 2.3 — In Example 1 the code shows how to estimate the hazard ratio as function of time. If part of the goal of the paper is to provide comparisons with other survival packages, it might be useful to note that it is easy to estimate the HR within periods of time using the coxph function. This also "fixes" the problem that they are trying to solve.

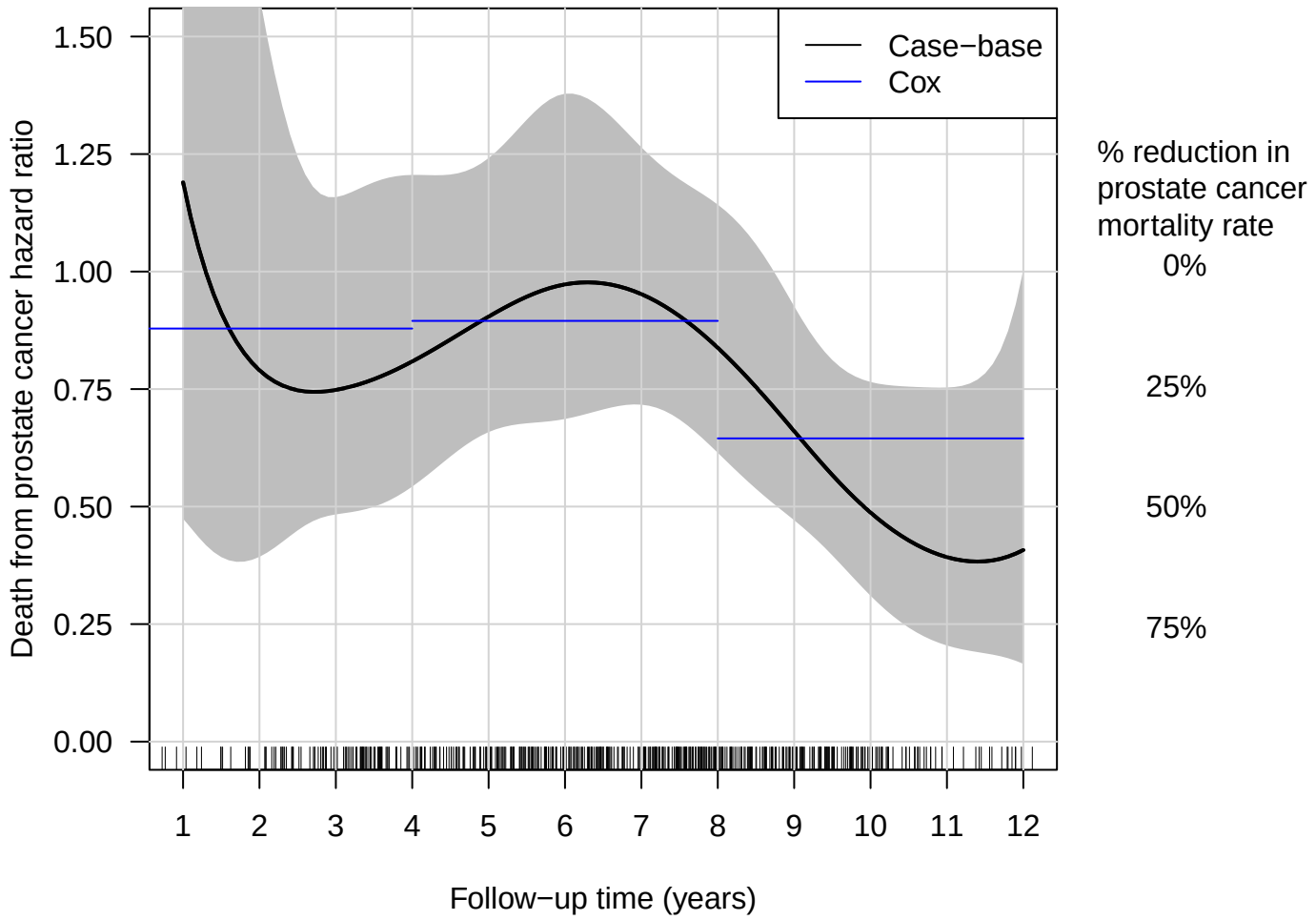
```
ERSPC2 <- survSplit(Surv(Follow.Up.Time, DeadOfPrCa) ~ ScrArm, data= ERSPC,
              cut=c(4,8), episode='period')

coxph(Surv(tstart,Follow.Up.Time,DeadOfPrCa)~strata(period)/ScrArm, data=ERSPC2)
```

Reply: Although a user can estimate piece-wise constant hazard ratios using the function `coxph`, doing so requires the user to select the cut points. On the other hand, with case-base can model the hazard ratio as a smooth function of time. Figure R2 below shows a comparison of the case-base approach and the piece-wise approach based on Cox regression.

Reviewer Point P 2.4 — Table 4 states that it is difficult to estimate absolute risk from a Cox model if there are competing risks, and perhaps that was true at one point, but the survival

Figure R2: Figure 2 from the manuscript, with piece-wise HRs estimated using `coxph` (in blue)



package has been updated for several years now and the statement is no longer correct. This approach should be shown in Example 2 and the statement in Table 4 should be modified. In Example 2 it is unclear what "newdata" values were used for the curves, but the following code illustrates the necessary steps.

```
newdat <- expand.grid(D=c('ALL','AML'), Sex='F', Phase='Relapse',Age=30, Source='PB')

## Cox model for competing risk
cfit <- coxph(Surv(ftime, factor(Status)) ~ Sex + D + Phase +
                Source + Age, data=bmtcrr, id=id)
```

```
## Aalen-Johansen estimate of absolute risk
plot(survfit(cfit, newdata=newdat)[,2], ylim=c(0,1), col=1:2, xmax=60)

## Fine-Grey estimate
fgdata <- finegray(Surv(ftime, factor(Status)) ~ Sex + D + Phase +
                     Source + Age, data=bmtcrr, id=id)

fgfit <- coxph(Surv(fgstart,fgstop,fgstatus) ~ Sex + D + Phase +
                 Source + Age, data=fgdata, weight=fgwt)

plot(survfit(fgfit, newdata=newdat), ylim=c(0,1), col=1:2, fun='event', xmax=60)

## casebase approach
model_cb <- fitSmoothHazard(Status ~ ftime + Sex + D + Phase + Source + Age,
                            data=bmtcrr, time='ftime')
cbfit <- absoluteRisk(object = model_cb,newdata = newdat,
                      time=0:60)
matplot(cbfit[,1], cbfit[,2:3], col=1:2)
```

Reply: We removed any mention of this limitation, and we added the Cox model and the Aalen-Johansen estimate to our comparison of cumulative incidence function estimates (Figure 6).

Reviewer Point P 2.5 — In Example 3, it isn't clear that the casebase approach calls cv.glmnet behind the scenes - that would be easy to mention. Based on this example, the results are virtual identical to just directly calling cv.glmnet so it is unclear what the benefit is to using casebase here, except to show that the code runs.

Reply: We have clarified the relationship between `casebase` and `cv.glmnet` within the manuscript.

In Example 3, we are comparing two approaches: case-base sampling, where the hazard is estimated using penalized logistic regression; and Coxnet, which is a regularized version of the Cox model. As in Examples 1 and 2, the function `fitSmoothHazard` starts by sampling the case series and base series and calculating the offset term. With `family = "glmnet"`, the data is then transformed to match the expected matrix input of `cv.glmnet`, before calling `cv.glmnet` with the offset term. In other words, `fitSmoothHazard` abstracts away most of the necessary data processing.

If a user fits a model using `cv.glmnet` and the Cox family, then they are fitting a semi-parametric model that is different from the case-base model. On the other hand, if the user tries to fit a model using `cv.glmnet` and their original data (i.e. without `fitSmoothHazard`), then the results will not be valid, assuming the model fit converges at all.

Reviewer Point P 2.6 — Notes about the software code:

I think inclusion of gbm is extremely dangerous given all the hyperparameters that need to be evaluated. A better approach, if possible, would be to create the appropriate dataset that can then be analyzed with gbm.

Reply: The inclusion of `gbm` to the casebase package was done at an early stage but never properly evaluated. Moreover, the `gbm` package, on which this implementation relies, is no longer actively

maintained. Therefore, we have removed mentions of `gbm` from the manuscript and from the package documentation. Proper testing and implementation of this approach is now considered future work.