Misinterpretation of time-to-first event curves can lead to inappropriate treatment

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Take home message

Evaluation of treatment effect durability over time cannot be based on analyses that examine the first of many events. Here, we explain how misinterpretation of survival curves led to wrong conclusions in the recent Suissa and Ariel's editorial [1].

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To the Editor:

Great care should be taken when assessing the consistency of treatment effect over time based on a survival curve plot, and even more so when a treatment affects a repeating event endpoint such as exacerbations rather than an event that can occur only once, like death.

In their recent editorial in this journal [1], Suissa and Ariel make the assertation that survival functions plotted from Kaplan-Meier estimates from Figure 1b in the IMPACT study [2] "*clearly show that the difference in the rate of exacerbation between LAMA/LABA/ICS and LAMA/LABA over follow-up is due to the first-month's surge, with practically no differences in the subsequent rates between the two groups*". However, this statement is based on a misunderstanding of the survival analyses presented.

The events plotted on the figure are the *first* moderate or severe COPD exacerbations experienced by a patient in the IMPACT study. Suissa and Ariel's statements about exacerbation rates refer to the rate of <u>first</u> exacerbations only, and not to the rate of all exacerbations during the study.

Their conclusion that the rates of *first* exacerbations, and ratio between those rates changes over time is correct. However, this is entirely in line with statistical theory for repeated events with overall constant rates. It cannot be used to support any conclusion that the difference in the rate of exacerbation is due to a "first month's surge". The "digitised" curve of first events behaves entirely consistently with constant rate events. Drawing any conclusions about the durability of the treatment effect on *all* exacerbations from this digitised plot, which shows only first exacerbations, is methodologically incorrect.

Consider a repeating event endpoint (such as exacerbations) in two treatment groups, A (low constant rate) and B (high constant rate). Initially the gradient of the survival curve for the <u>first</u> event for treatment B (high rate) will be very steep, because all patients are "at risk" of an event. As fewer and fewer patients are left available to have a first event, the gradient will necessarily diminish. The gradient of the survival curve for the <u>first</u> event for treatment A (low rate) will eventually become steeper. Eventually the two survival curves for time to *first* event will converge despite event rates being different in both arms, as illustrated in the Figure which is described by the equations below.

Suppose that in treatment arm A events occur at a constant annual rate of 1.0, and in treatment arm B events occur with a constant annual rate of 1.5. The exponential survival functions (i.e. the functions that describe survival for events with constant hazard rates) are given by:

$$S^{TreatmentA}(t) = 1 - \exp(-\mathrm{t})$$

$$S^{TreatmentB}(t) = 1 - \exp(-1.5\mathrm{t})$$

Where *t* is the time in years [3]. The resulting survival curves can be plotted and it is also possible to differentiate with respect to *t*, to obtain the gradient $G(t) = \mathrm{S}'(\mathrm{t})$ of the survival curves which corresponds to the digitised plot presented by Suissa and Ariel.

$$G^{TreatmentA}(t) = \exp(-\mathrm{t})$$

$$G^{TreatmentB}(t) = 1.5\exp(-1.5\mathrm{t})$$

These survival curves converge, and the gradient of both curves start to diminish, with the gradient functions crossing exactly as shown in the real data (Figure). It is important to understand this phenomenon occurs for constant rate events, and therefore its presence should not be taken as evidence that the rates are not constant.

This can be understood in the following way: the cumulative incidence or survival curve only describes the first event experienced by each patient. If treatment A consistently reduces the rate of events, then these first events will be delayed but they will still occur. While patients on treatment A are experiencing their first events there are simply fewer patients on the treatment B arm who are still "at risk" of a first event, these events having already occurred. By this point patients on treatment B are having second or third events, which are not captured by a time to first event analysis, thus the rate of their first events has diminished.

This illustrates that conclusions about the durability of the treatment effect over time cannot be based on analyses restricted to looking at only the first event of many. To imply that the treatment effect diminishes because one survival curve catches up with another is inappropriate and risks propagating incorrect information, which could lead to harm to patients if treatment is withdrawn or not used.

References

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3. Modelling Survival Data in Medical Research - D. Collett, published by Chapman and Hall, London. First Edition 1994, Chapter 1.

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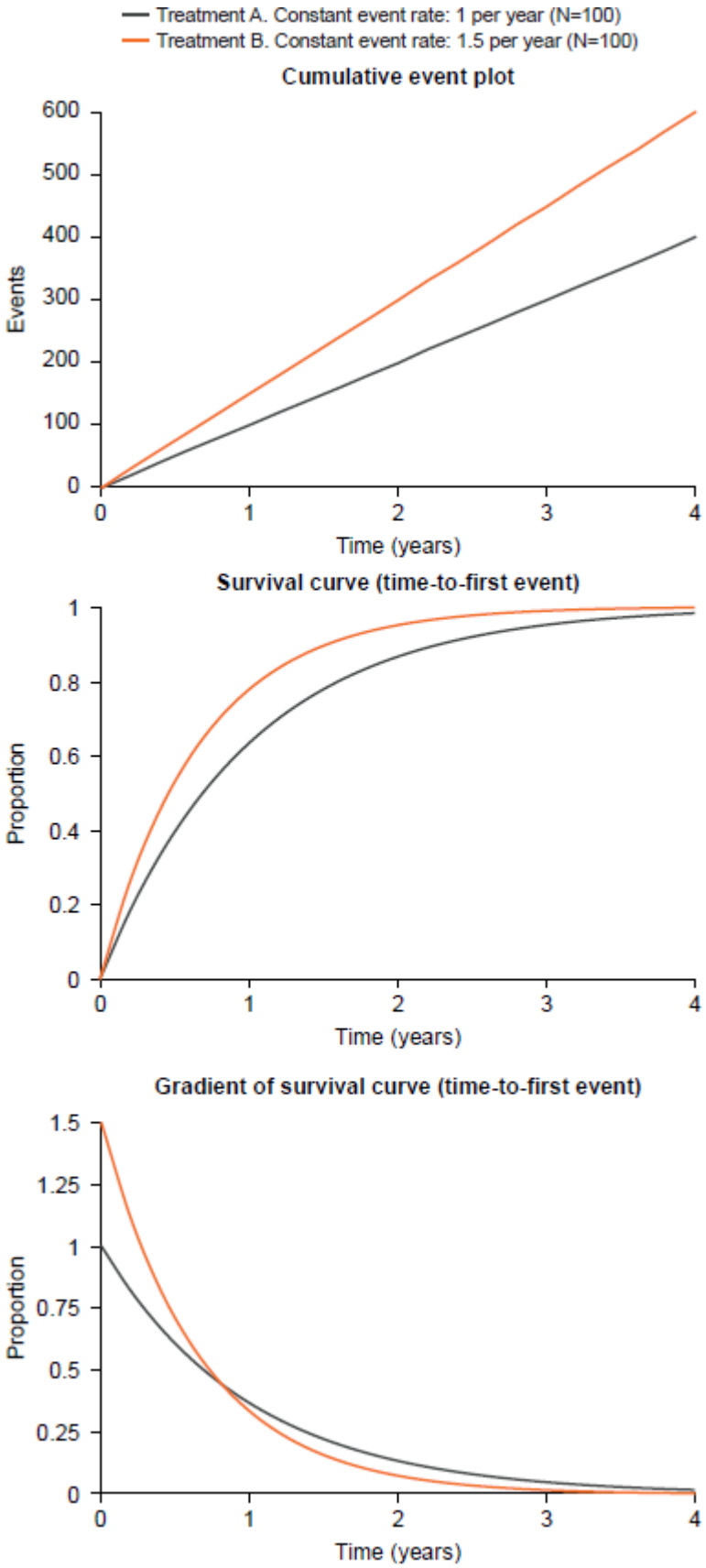
Figure legend

Figure. Hypothetical example of a cumulative event plot, survival curve and gradient of survival curve presented on the same data.


Treatment A. Constant event rate: 1 per year (N=100)
Treatment B. Constant event rate: 1.5 per year (N=100)
Cumulative event plot
Events
Time (years)
Survival curve (time-to-first event)
Proportion
Time (years)
Gradient of survival curve (time-to-first event)
Proportion
Time (years)