PhUSE 2018

Paper PP14

Subpopulation Treatment Effect Pattern Plot (STEPP) for categorization of baseline characteristics

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ABSTRACT

Subpopulation Treatment Effect Pattern Plot (STEPP) have been widely used in clinical research, mainly to study how the treatment effect varies across values of a continuously measured covariate.

Often we face the situation where we need to analyze an endpoint by subgroups of a continue covariate, but we do not know how to categorize it. This paper will show how to exploit STEPP method for this purpose. STEPP graphs reporting Hazard Ratios and Rates will be created with a macro implemented by Valos and used as a sort of guide for choosing the meaningful cut-offs for categorizing the covariate to create subgroups.

INTRODUCTION

Interactions between treatment and covariates, such as prognostic factors, in randomized trials are important because they are essential ingredients of individualized treatments rather than assuming that one size fits all. Such factors are often called predictive. When the covariate is continuous, such interactions are often sought by crude statistical methods, typically involving categorizing the continuous covariate. When treatment effects in subgroups are compared; the results may depend on the cut point chosen. Categorization of the variable of interest is often tricky: sometimes guidelines help us, other times previously used cut-offs can be found in literature. To decide what is the right cut-offs for selecting subgroups of subjects we decided to use STEPP method.

We have been asked by the Sponsor to investigate the predictive value of Time from diagnosis (TFD) of the disease to start of treatment, but pre-specified cut-offs could bring to a meaningless result.

Using the STEPP we firstly explored the association between TFD and morbidity/mortality events (MM), then we chosen cut-offs for categorization based on our findings.

STEPP METHOD

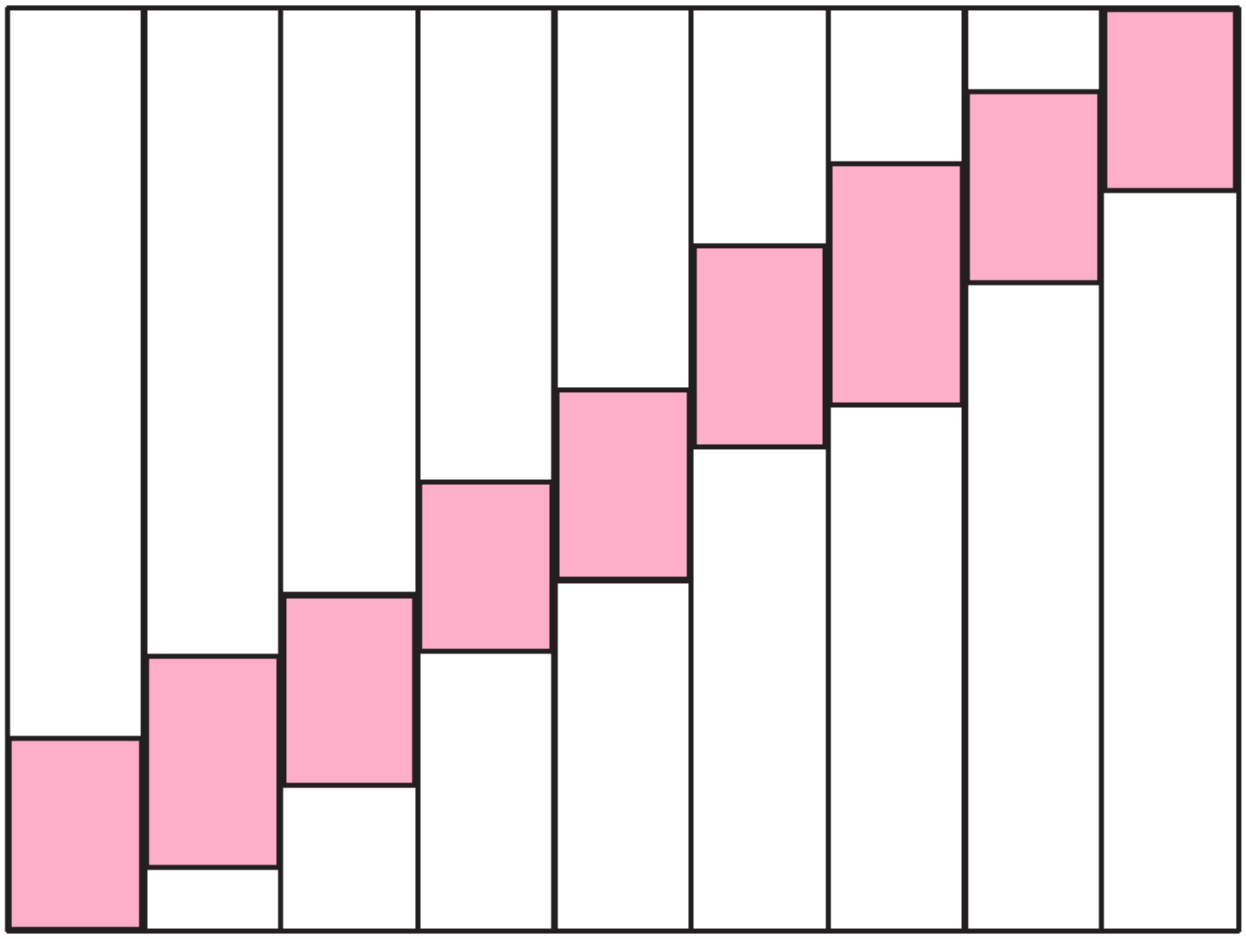
This method is based on constructing overlapping subpopulations of patients with respect to a variable, and in observing the pattern of the treatment effects estimated across the subpopulations.

A Cox model for each subpopulation calculates hazard ratios and confidence intervals. Confidence intervals do not take in account the fact a subject is considered in different subgroups, so inference cannot be done with this technique and its goal is just descriptive, for finding the cut-off to be used for categorizing the variable of interest.

The theory of sliding window approach has been taken from the paper "Patterns of treatment effects in subsets of patients in clinical trials" (Bonetti, 2004). Fixing two parameters r1 and r2 where r1 is the largest number of overlapping patients, and r2 is the number of patients in each subpopulation with $r1 < r2 < n$, and then defining the first subpopulation P1 as containing patients having the variable of interest ranging between the smallest observed covariate value (*l1*) and the (*r2/n×100*)th percentile of the observed distribution, taken as *u1*. Should such exact percentile not exist, *u1* is defined so that at least *r2* patients fall in P1. To define the next subpopulation P2 the value *l2* is found so that at most *r1* patients fall between *l2* and *u1*, the next subpopulation is so formed by removing r2 minus r1 patients with the lowest covariate values from the current subpopulation and replacing them with the next r2 minus r1 patients in the ordered list. . Then, *u2* is defined so that P2 contains at least *r2* patients. This process is repeated until the last possible population is defined.

Figure 1 below gives an idea of how subpopulations are created. Each vertical white bar indicates the whole cohort, while each pink bar indicates the subpopulation within the cohort.

Figure 1



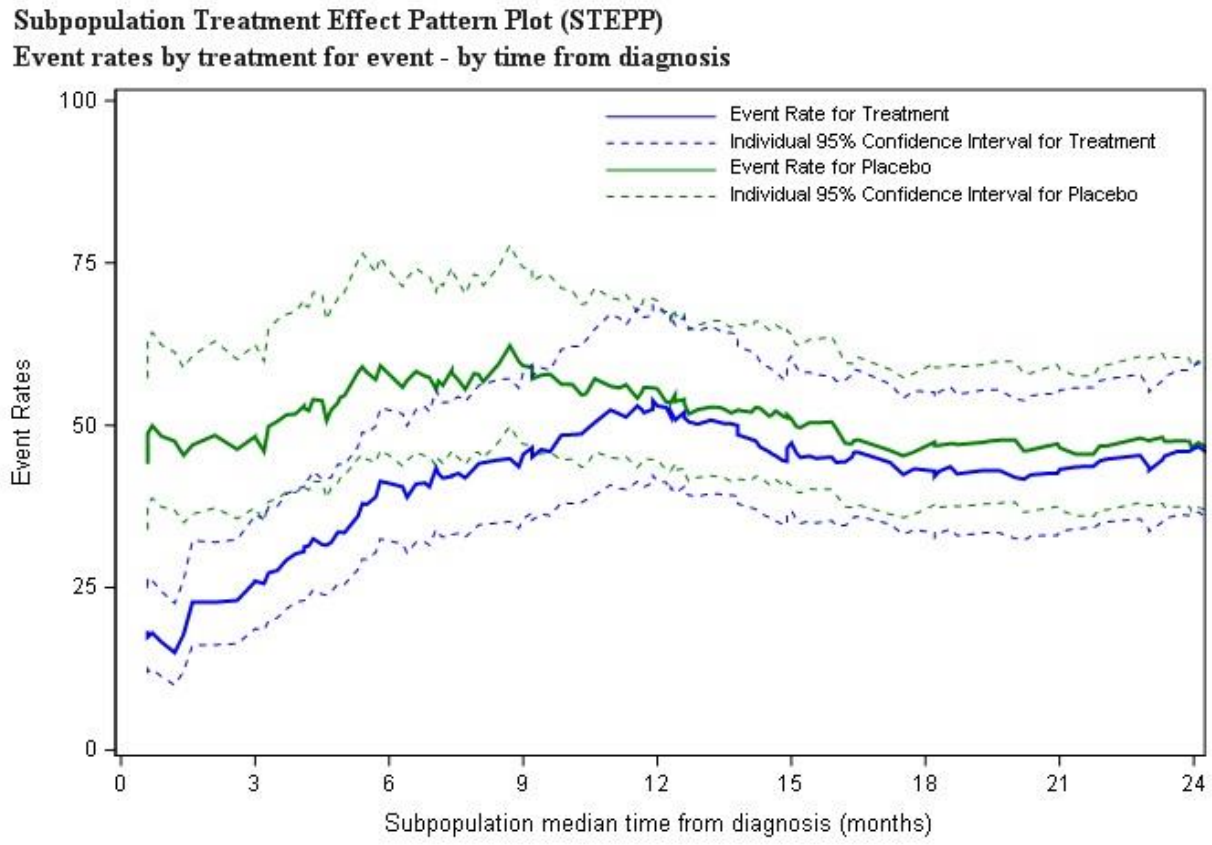
The numbers of subpopulations and of overlapping patients are important parameters, and must be chosen by the investigator. We chose to take 200 patients in each subpopulation and 199 overlapping patients in TFD analysis. This scenario provides relatively precise estimates of treatment effect and a large number of windows. Keeping *n1* close to *n2* produces limited patient turnover from window to window, thus smoothing enough the resulting curve.

STEPP FOR TIME FROM DIAGNOSIS

The MM rate in each subpopulation was plotted against TFD values for each treatment arm. If a covariate has no effect, MM rates should be similar for all subpopulations, with any differences resulting from chance alone.

The Figure 2 plot is one way of exploring prognostic effects of TFD nonparametrically. On x axis there is the median value of each TFD subpopulation, Event Rate is on y axis and blue and green lines correspond to Treatment and Placebo arm respectively. Solid line represents the event rates, the dashed ones reflects 95% Confidence Intervals.

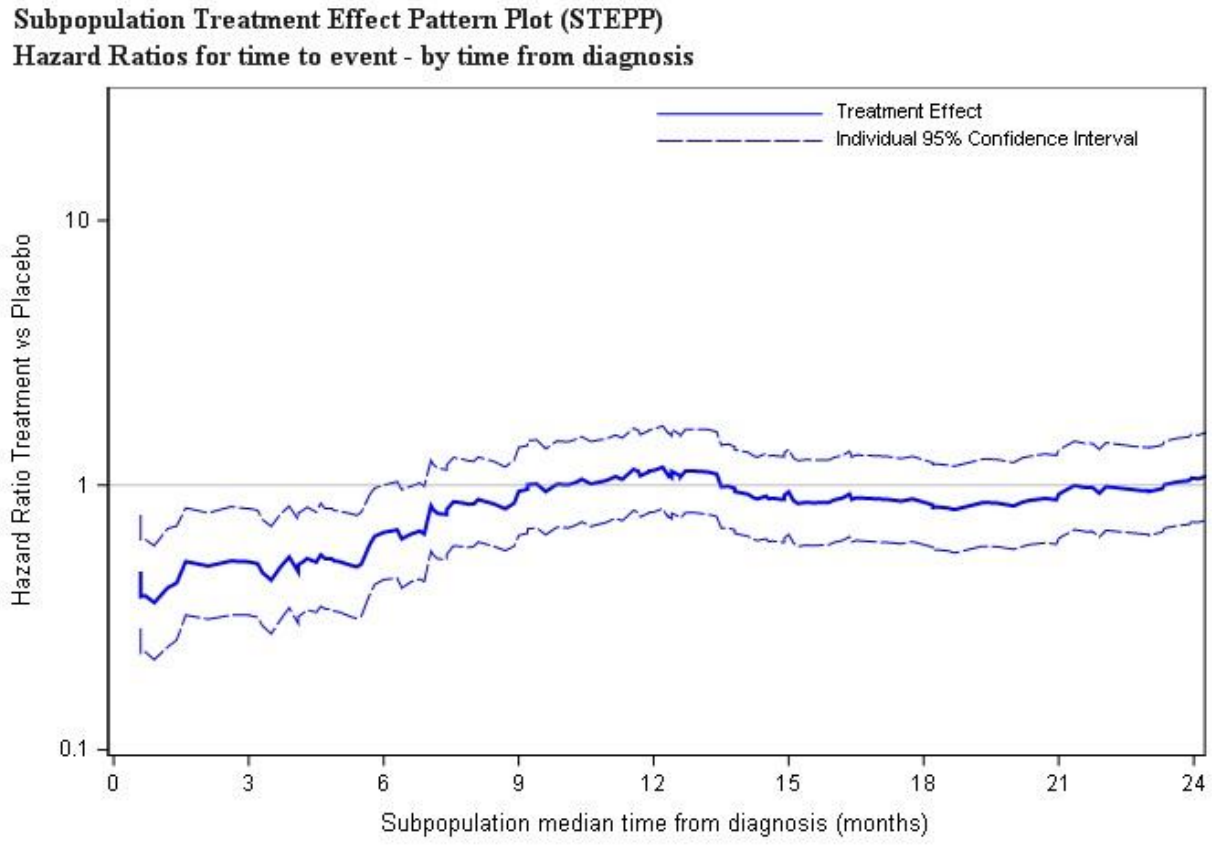
Figure 2



Overlapping subpopulations are derived from a STEPP analysis.
Event Rates and corresponding 95% confidence intervals for each subpopulation are derived from a Poisson model.
Sliding windows set to 200 patients.

In this situation, the difference in MM rates between treatments varies according to the value of TFD. The MM rate for treatment shows a growth from zero up to 9 months and reach the Placebo's Event Rate around 12 months. The Placebo's Event Rate is always worse than the Treatment's one. Both Event Rates seem to increase through TFD before month 12 and then they show to have the same trend. The treatment seems to be effective only if taken within 12 months from diagnosis, with a bigger effect if taken as soon as possible. The magnitude of the treatment effect is better observable in the STEPP where hazard ratios and confidence intervals are shown. Solid line represents the treatment effect expressed as Hazard Ratio and the dashed ones reflect 95% Confidence Intervals. Horizontal grey line set to value 1 indicates when treatment doesn't have effect.

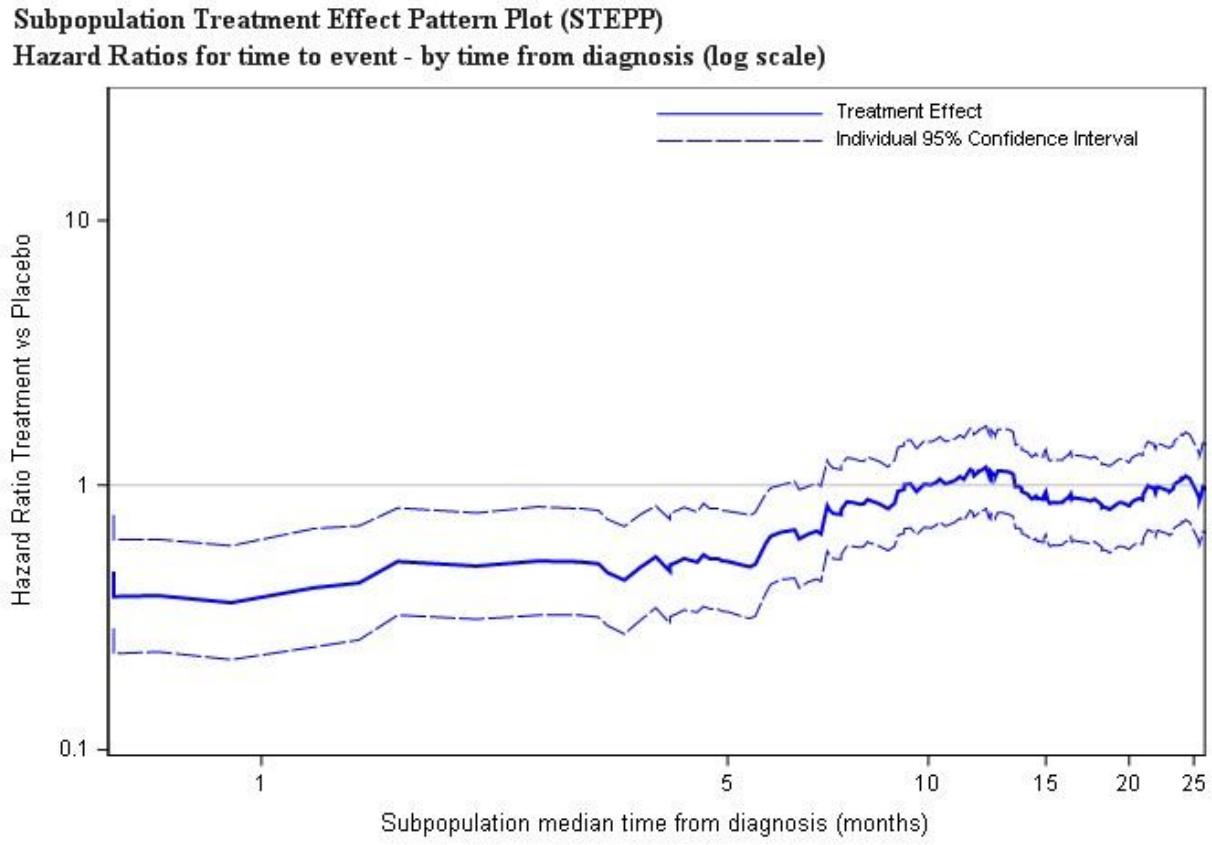
Figure 3



Overlapping subpopulations are derived from a STEPP analysis.
Hazard ratios and corresponding 95% confidence intervals for each subpopulation are derived from a Cox model for time to the event.
Sliding windows set to 200 patients.

The effect of treatment seems to be quite stable for subjects taking treatment within Month 6 from diagnosis, where HR is around 0.5 on average, then slightly decreases for subjects taking treatment between Months 6 and 9 and finally becomes null (HR around 1) for all other subjects with a longer TFD The overall message we can get from the STEPP is that lower TFD is associated with treatment effect, indicating an as soon as better way for treating subjects. Thus STEPP analysis provides evidence of heterogeneous treatment effects related to TFD.
For a better understanding of the effect pattern behind STEPP, a graph with log scale of TFD is shown (Figure 4), because the distribution of subpopulations in y-axis is not linear: the great majority of subjects assumes treatment within 1 year from diagnosis and log scale let us expand the points in the first months.

Figure 4



Overlapping subpopulations are derived from a STEPP analysis.
Hazard ratios and corresponding 95% confidence intervals for each subpopulation are derived from a Cox model for time to the event.
Sliding windows set to 200 patients.

The logarithmic graph supports what noticed before: TFD is influential on the treatment effect and this can be observed in the marked stable trend up to about month 6 and in the decreasing effect highlighted by the growth of the curve up to month 9. The effect reaches null values in subjects treated after more than 9 months from diagnosis, meaning that treatment doesn't have any effect after a certain TFD.

CATEGORIZATION OF TIME FROM DIAGNOSIS

From the above STEPP we observed that TFD is an important prognostic factor and three categories of subjects can be a good solution for categorization.

- Subjects treated within 6 months from diagnosis: they are those with more benefit from treatment
- Subjects treated within 6 and 9 months from diagnosis: a benefit from treatment is still visible but not as strong as in the first category

Subjects treated after 9 months from diagnosis: no beneficial effect for treated subjects.

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