Marginal Structural Model for studying the causal effect between vaso-occlusive crises and occurrence of death or complications in sickle-cell disease patients

Context

Sickle-cell disease (SCD) is one of the most prevalent inherited diseases. Previous research suggests a relationship between Vaso-Occlusive Crises (VOC) (also known as sickle cell pain crisis) death and complications. However, the time-varying effect of VOC on these outcomes prevents the establishment of a causal relationship using classically adjusted models. The number of VOC in the previous year could instead only imply the occurrence of acute complications and death.

Objective

This study aimed to assess the effect of the number of VOCs experienced in the previous year on occurrence of death and common disease-related complications using an Inverse Probability Weighted Marginal Structural Model (MSM-IPW).

Method

IPW OR TRADITIONAL ADJUSTMENT METHODS?

The association between the number of VOC in the previous year and the acute/chronic complication or death is a typical example of a study of a dynamic treatment regimen on a survival outcome (Hernan 2006). The traditional survival model was created to compare non-dynamic regimens i.e. treated versus non treated without any change during the follow up. In the case of a dynamic regimen, the model must include the time-varying treatment (the number of VOC each year) but also all time-varying covariates that could influence the treatment assignment (the presence of each complication in the previous year).

As we intended to estimate the causal effect of VOC on death, the following directed acyclic graph (DAG) was assumed (similar DAG could be drawn for each complications).

Sporious association in traditional model

In case the objective of the study is to quantify the effect of VOC on death, the traditional survival model consists of a Cox model adjusted on VOC and complications. If we adjusted on the effect of a complication in the last year, we would have adjusted on a collider. Indeed, the complication in the last year is the common consequence of VOC two years before and the same complication two years before. This would have created a spurious correlation between the VOC and the complication two years before and imply a modification on the estimation of effect of VOC on death.

Thus the method that adjusts on time-varying VOC and complication is not appropriate for the purpose of this study.

Case of unmeasured confounder

Moreover, in case of an unmeasured variable that could cause some complications and death, there is a risk that a backdoor path is opened.

As the purpose of electronic health records was not to record clinical diagnosis but to record the reimbursement of health consumption, it is plausible to have some unmeasured confounders.

Thus, another method was sought that aimed to reduce these risks.

THE MSM-IPW METHOD

The probability of being in each VOC category was estimated by multinomial logistic models, the probability of being censored each year was approximated by weighted pooled logistic regressions.

Results

The IPW analysis is an interesting tool in case of dynamic time-varying exposure. In this illustration having more than one VOC in the previous 12 months was associated with a higher risk of death and complications. Preventing or reducing the number of VOCs experienced each year may significantly reduce the occurrence of death and some common complications.

Conclusion

Supported by the limitation described above, the estimated causal effect of number of VOC on each complication and death was instead estimated using MSM-IPW Cox models approximated by weighted pooled logistic regressions. The stabilized weights were estimated using a combination of the probability of being in each VOC category and the probability of being censored each year. In each year, these models were adjusted for age, gender, ethnicity, complications and comorbidities as reported the year before.