Preliminary Report

Case-Only Method to Estimate the Relative Incidence of Adverse Events for Comparison of Two Treatments: Application in Disseminated Intravascular Coagulation Patients

Chris Fook Sheng Ng\textsuperscript{1}, Yutaka Matsuyama\textsuperscript{2} and Yasuo Ohashi\textsuperscript{3}

\textsuperscript{1}Department of Human Ecology, School of International Health, Graduate School of Medicine, The University of Tokyo
\textsuperscript{2}Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo
\textsuperscript{3}Department of Integrated Science and Engineering for Sustainable Society, Faculty of Science and Engineering, Chuo University

\textit{e-mail}: chrisng-tyk@umin.ac.jp

Measuring the relative performance of a new treatment in the post-marketing environment is often challenging due to the lack of suitable control. We explore a case-only method to estimate the relative incidence of adverse events in disseminated intravascular coagulation (DIC) patients for comparison of two treatments. We proposed a heuristic approach that borrows its intuition from the self-controlled case series method with modification to the selection of control period. In DIC patients, the method of taking the post-treatment period for self-control is inappropriate because patients generally begin with a high risk of adverse events, which gradually improve with treatment. Instead, we randomly matched the timelines of DIC patients receiving competing treatments for baseline adjustment. Since only the timelines with at least an adverse event, that is, the “cases,” were required, the required sample sizes were smaller. Estimates were comparable to those obtained from the randomized trial and cohort method, and better than results based on the 1-to-1 matched case-control and binary response cohort design. Although the proposed approach loses the benefit of self-matching, with careful matching of patients and repeated random matching of time periods, the method has a potential to be useful for the post-market monitoring of new treatment for DIC or similar diseases.

\textit{Key words}: case-only, relative incidence, post market surveillance, adverse event, disseminated intravascular coagulation.

1. Introduction

In clinical and public health research investigating adverse reactions to medical products, identifying suitable group for comparison has always been a challenge. The choice of comparison
group often varies depending on study designs. In randomized controlled trial, comparison is between subjects randomly allocated to receive different interventions (Stolberg et al., 2004). When a randomized controlled trial is not feasible, observational study such as the cohort or case-control study is often used (Lu, 2009). Comparison group in a cohort study can come from the source population or an unexposed population otherwise similar. In case-control study, comparison is between two groups of individuals differing in outcome. For investigation of a transient effect of exposure on an acute outcome, case-only designs that compare the incidence rates of adverse outcome between the exposed and unexposed time periods have been proposed (Farrington, 1995; Farrington et al., 1996; Maclure, 1991).

Case-only methods have the appeal of providing consistent estimates using only information on cases (i.e., patients who suffered adverse events), when sample size allows (Andrews, 2001; Glanz et al., 2006; Maclure et al., 2012; McClure et al., 2008). Maclure’s (1991) case-crossover method and Farrington’s (1995) self-controlled case series (SCCS) method are two such designs that have been widely applied. The key feature of the two methods is self-matching within the same subject, which controls for confounding and selection bias by all measured and unmeasured characteristics that do not vary over time (Maclure, 1991; Farrington, 2004). Although both methods have been frequently used in the monitoring of medical products, the type of application differs. For situations that do not conform to the underlying assumptions, modifications are often required (Maclure et al., 2012).

In the post-marketing surveillance of interventional treatment, identification of suitable comparison group can be difficult. An example used in this study is the monitoring of bleeding-related adverse events in patients diagnosed with disseminated intravascular coagulation (DIC) disorder. There is currently no method to estimate relative risk for the evaluation of treatment options for DIC in the post-marketing environment. For monitoring that includes only subjects receiving new treatment, the case-only method comes to mind. Because all patients diagnosed with DIC are treated immediately, the case-crossover method is not suitable due to a stationary assumption that requires the probability of exposure to be the same for all time intervals (Whitaker et al., 2006). The straightforward implementation of the SCCS method does not produce estimate for treatment comparison when each subject has only received one type of treatment. Moreover, the nature of DIC disease sets itself apart from the typical characteristics of a vaccine study where the SCCS method is often applied. In vaccine studies, the disease being prevented is often absent and unrelated to any adverse drug reactions (Farrington, 2004). In the case of DIC, adverse events are often associated with the underlying bleeding condition being treated. These adverse events often occur with greater frequency at the beginning but gradually improve with treatment over time (Saito et al., 2007). In consideration of these features, it is essential to devise a method for comparing the risks of different interventions for DIC disease.

We explore a case-only method to estimate the relative incidence of bleeding-related adverse
events in DIC patients for the comparison of two competing treatment options. Our study is motivated by the need to monitor and evaluate the performance of a new treatment for DIC in the post-marketing environment. Briefly, the procedure involves resampling of patients followed by the repeated random matching of timelines between patients receiving the new and conventional treatment. Since adverse events can potentially be related, and therefore violates the Poison assumption of independent outcome, modification to include only the first event is also considered. For each resample, the ordinary SCCS method was applied to estimate the relative incidence of adverse events.

2. Methods

2.1 Data

Our proposed case-only approach is applied within the DIC context in this study. DIC is a disorder of blood clotting caused by various clinical conditions including severe infection, sepsis, major tissue injury or cancer (Toh and Dennis, 2003; Levi and Ten Cate, 1999). Heparin is a common treatment, though newer alternatives have also been introduced (Saito et al., 2007; Warren et al., 2001, Abraham et al., 2003; Aoki et al., 2002; Feinstein, 1982). The case-only method for the comparison of DIC treatments was demonstrated using data from a completed phase III randomized controlled trial of a new antithrombotic treatment. The use of secondary data from a randomized trial allows the comparison of results. The original clinical trial compared the efficacy and safety of a new recombinant human soluble thrombomodulin (RHST) therapy to the conventional treatment of low-dose unfractionated heparin in DIC cases related to hematologic malignancy or infection (Saito et al., 2007). A total of 231 patients diagnosed with DIC associated with hematologic malignancy or infection were randomized to receive either the RHST (116 patients) or heparin (115 patients). RHST was administered 30 minutes a day for 6 consecutive days via drip, while heparin was given all day for 6 consecutive days. Results indicated the new drug significantly improved DIC compared to heparin (Saito et al., 2007). For our study, we examined two types of outcome—bleeding-related and serious adverse events as defined in the original trial by Saito et al. (2007) (Table 1). Bleeding-related adverse events were observed for 14 days from the start of infusion. They included new or exacerbated bleeding and organ symptoms, and abnormal changes in clinical laboratory findings. Serious adverse events such as death, life-threatening events, prolonged hospitalization, and permanent or significant disorder or dysfunction were documented throughout the 28-day observation period. Not all patients who underwent treatment exhibited adverse events. On the other hand, some showed multiple adverse symptoms. Only the cases, patients who documented adverse events, were included in the analysis.
Table 1. Frequency of bleeding-related and serious adverse events from a randomized controlled trial by Saito et al. (2007) for the assessment of safety and efficacy of recombinant human soluble thrombomodulin treatment in disseminated intravascular coagulation patients in comparison to heparin treatment.

<table>
<thead>
<tr>
<th>Adverse Outcome</th>
<th>Treatmenta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombomodulin (n = 116)</td>
</tr>
<tr>
<td>Bleeding related adverse events</td>
<td></td>
</tr>
<tr>
<td>first 7 days from start of infusion</td>
<td>79 (50)</td>
</tr>
<tr>
<td>first 14 days from start of infusion</td>
<td>129 (64)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
</tr>
<tr>
<td>first 7 days from start of infusion</td>
<td>27 (19)</td>
</tr>
<tr>
<td>during 28-day observation period</td>
<td>60 (37)</td>
</tr>
</tbody>
</table>

a number in parenthesis denotes the frequency of patients.

2.2 Analysis

The timeline of a DIC patient during the trial is depicted in Figure 1. Direct implementation of the SCCS method as described by Whitaker et al. (2006) would always yield a relative incidence of above one because the unexposed control period following a therapy would tend to have fewer adverse events. Since DIC is a critical diagnosis, all patients diagnosed with the disease are necessarily treated one way or another. In practice, it is reasonable to assume all DIC patients who needed treatment but did not receive the RHST would at least be given the customary heparin treatment. Therefore, the exposure period of patients receiving heparin treatment can be assumed as the baseline control period for patients receiving a different therapy.

We modified the SCCS method by replacing the self-control period with the exposure period
of a patient receiving competing treatment. Specifically, we conjoined the 7-day exposure period (6 days of treatment plus one day of washout) of patients receiving RHST to the exposure period of those treated with heparin (Figure 2), labeled as the “control” period for the RHST patient. Because the control period was borrowed from a different patient, we used resampling to allow more combinations of control per RHST patient so as to minimize potential bias related to a single control selection. We randomly selected a hundred patients from each treatment arm and joined the exposure periods of competing treatments. The newly combined timelines without an adverse event (i.e., non-cases) were dropped and the SCCS analysis was performed (Whitaker, 2010). The procedure was replicated for a thousand times. Simple random samplings with and without replacement were attempted. The median of the bootstrap distribution of relative incidence estimates obtained from resampling was reported as the point estimate. The nonparametric 95% bootstrap percentile confidence intervals were taken from the 2.5 and 97.5 percentile of the bootstrap distribution (Efron and Tibshirani, 1993).

![Fig. 2. New timeline after joining the exposure period of patients receiving the newer recombinant human soluble thrombomodulin to the exposure period of those receiving the conventional heparin treatment. Light shaded region is assumed the control period.](image)

To estimate the relative incidence of bleeding-related adverse events based on the timeline in Figure 2, let \( t_{ij} \) corresponds to interval \( j \) for individual \( i \). The interval \( j = 1 \) corresponds to the exposure period during which RHST was administered, while \( j = 0 \) is the control period taken from the exposure period of another patient receiving heparin. Adverse events are assumed to occur randomly as a non-homogenous Poisson process. The frequency of adverse events for individual \( i \) within each time period is denoted \( n_{ij} \). We have \( e^{\phi_i} \) as the baseline incidence of adverse event for patient \( i \), and \( e^{\beta_1} \) the relative incidence for exposure \( j = 1 \). For patient \( i = 1 \) who is at risk \((j = 1)\), the length of the first interval is \( t_{11} = 7 \) days. Therefore, the Poisson incidence rate for this interval is \( \lambda_1 = 7e^{\phi_1} + \beta_1 \). In the second interval, since there is no RHST exposure, \( \lambda_2 = 7e^{\phi_1} \). The Poisson rate for the entire observation period is therefore \( \Lambda = 7e^{\phi_1}(e^{\beta_1} + 1) \).

Assume an adverse event occurs in the first interval \((j = 1)\). If this were a cohort study, the patient’s contribution to the Poisson likelihood would be \((\lambda_1 e^{-\lambda_1}) \times e^{\lambda_2} = \lambda_1 e^{-\Lambda} \), since an adverse event was documented in the first interval. However, the probability of one or more adverse events occurring during the observation period is \( \Lambda e^{-\Lambda} \). Therefore, the conditional
The likelihood for the above patient is
\[
\frac{\lambda_1 e^{-\Lambda}}{\Lambda e^{-\Lambda}} = \frac{\lambda_1}{\Lambda} = \frac{7e^{\phi_1 + \beta_1}}{e^{\phi_1} (e^{\beta_1} + 1)} = \frac{e^{\beta_1}}{e^{\beta_1} + 1}
\]

Because of the similar baseline effects for the exposed and control patients, \(e^{\phi_1}\) cancels off. The likelihood for this timeline can also be thought of as based on the multinomial probability that an adverse event occurs in the first interval, given that it occurs in one of the intervals 0 and 1. The multinomial likelihood is
\[
l(\beta_1) = \left(\frac{e^{\beta_1}}{e^{\beta_1} + 1}\right)^1 \times \left(\frac{1}{e^{\beta_1} + 1}\right)^0
\]

Taking the logarithm of the summation of likelihood for all patients in the sample and maximizing it, we can obtain an estimate for \(\beta_1\) with their relative incidence for exposure effect \(e^{\beta_1}\).

The general form of the multinomial log-likelihood conditioning on the number of events \(n_i\) observed for individual \(i\) during the 14-day observation period is
\[
l(\beta) = \sum_{ij} n_{ij} \log \left[ \frac{\exp(\beta_j) t_{ij}}{\sum_r \exp(\beta_r) t_{ir}} \right]
\]

The above multinomial model can be fitted as a Poisson model with a log link function. Response variable is the number of adverse events in each interval, \(n_{ij}\), and the natural log of time period \(\ln(t_{ij})\) is included as an offset. The associated Poisson main effects model is \(n_{ij} \sim \text{Poisson}(\lambda_{ij} t_{ij})\).

Instead of the 7-day exposure period, we also considered joining the entire observation period of patients receiving different treatments. That is, 14 plus 14 days for the bleeding-related adverse events and 28 plus 28 days for the serious adverse events. The rationale for this variation is to fully account for the residual effect of treatment. The subsequent random sampling procedure stays the same as described.

In DIC disorder, adverse events can often be related. The SCCS method which depends on the Poisson assumption of independent outcome may not work in situation when the recurrent outcomes are associated. A possible solution to circumvent this issue is by restricting analysis to the first observed adverse event while ignoring the subsequent ones (Whitaker et al., 2006). With this modification, even when an adverse event is death, since only the first event is considered, the SCCS approach remains valid.

For comparison of results, we also analyzed the data as if it were a (i) 1-to-1 matched case-control study, (ii) cohort design with count response (i.e., the count of adverse events), and (iii) cohort design with binary response (i.e., absence or presence of adverse events). For the matched case-control study, patients who documented adverse events were randomly matched to those without. The matched data was analyzed using conditional logistic regression to obtain the odds ratios for bleeding-related and serious adverse events. The random-matching procedure was repeated for a thousand times. Separate analysis was performed for observation period of
different duration. For the cohort study assumption, the relative risks of adverse events were estimated using Poisson regression model with robust error variances. When adverse outcome was assumed dichotomous, logistic regression was used to estimate the odd ratios. Note that these alternative analyses are solely for comparison.

All analyses were performed in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

Relative measures estimated under different study designs for the comparison of adverse events between the RHST and heparin treatment were summarized in Table 2 and 3 for the bleeding-related and serious adverse events, respectively. The estimated relative risk from the randomized controlled trial based on 7 days of observation for bleeding-related adverse events was significant at 0.763 (95% confidence intervals: 0.586, 0.993). When the length of the observation period was doubled, the estimated relative risk became insignificant at 0.846 (0.685, 1.045). These relative risks were computed from patient frequency (who documented at least an adverse event). The relative incidences of adverse events estimated by the proposed case-only method that included all adverse events without sampling replacement were slightly lower but significant. When only the first adverse event in each patient was considered, the estimated relative incidences based on repeated sampling without replacement were 0.764 (0.689, 0.839) and 0.848 (0.776, 0.921) for the 7- and 14-day observation periods, respectively, which were very comparable to

<table>
<thead>
<tr>
<th>Method</th>
<th>7 days of observation</th>
<th>14 days of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>0.763</td>
<td>(0.586, 0.993)</td>
</tr>
<tr>
<td>Case-only (all adverse events)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no replacement</td>
<td>0.638</td>
<td>(0.555, 0.733)</td>
</tr>
<tr>
<td>with replacement</td>
<td>0.580</td>
<td>(0.411, 0.863)</td>
</tr>
<tr>
<td>Case-only (first adverse event)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no replacement</td>
<td>0.764</td>
<td>(0.689, 0.839)</td>
</tr>
<tr>
<td>with replacement</td>
<td>0.683</td>
<td>(0.522, 0.895)</td>
</tr>
<tr>
<td>Matched case-control design (1 : 1)</td>
<td>0.583</td>
<td>(0.515, 0.636)</td>
</tr>
<tr>
<td>Cohort design (count response)</td>
<td>0.637</td>
<td>(0.448, 0.905)</td>
</tr>
<tr>
<td>Cohort design (binary response)</td>
<td>0.583</td>
<td>(0.346, 0.981)</td>
</tr>
</tbody>
</table>

CI: confidence intervals.

- The relative incidence estimates and the corresponding percentile confidence intervals for the case-only method were obtained from the bootstrap distribution based on 1,000 replications.
- The odds ratios and the corresponding percentile confidence intervals for the matched case-control design were obtained through similar bootstrapping procedure.
Table 3. Estimated relative measures for serious adverse events in patients with disseminated intravascular coagulation disorder.

<table>
<thead>
<tr>
<th>Method</th>
<th>7 days of observation</th>
<th>28 days of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>0.725</td>
<td>(0.425, 1.234)</td>
</tr>
<tr>
<td>Case-only (all adverse events)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no replacement</td>
<td>0.767</td>
<td>(0.581, 0.963)</td>
</tr>
<tr>
<td>with replacement</td>
<td>0.592</td>
<td>(0.317, 1.053)</td>
</tr>
<tr>
<td>Case-only (first adverse event)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no replacement</td>
<td>0.727</td>
<td>(0.583, 0.900)</td>
</tr>
<tr>
<td>with replacement</td>
<td>0.563</td>
<td>(0.316, 0.929)</td>
</tr>
<tr>
<td>Matched case-control design (1 : 1)</td>
<td>0.667</td>
<td>(0.357, 1.111)</td>
</tr>
<tr>
<td>Cohort design (count response)</td>
<td>0.765</td>
<td>(0.418, 1.401)</td>
</tr>
<tr>
<td>Cohort design (binary response)</td>
<td>0.671</td>
<td>(0.347, 1.294)</td>
</tr>
</tbody>
</table>

CI: confidence intervals.

*a,b* Refer to the caption of Table 2.

The above pattern was also observed in the results for serious adverse events (Table 3). Likewise, the case-only first-event relative incidence estimates without sampling replacement were fairly comparable to the estimates from the randomized trial. The case-only all-event estimates without sampling replacement were very close to the cohort-based approach for count response. Percentile confidence intervals by the case-only design were likewise narrower. Almost all the case-only estimates for the 7-day observation period were significant compared to the estimates by other designs.

4. Discussion

Unlike clinical trial, the post-marketing monitoring of treatment in DIC patients is challenging due to the lack of suitable control group. The technique of self-control using the unexposed post-treatment period of a patient does not work because treatment is interventional in nature which coincides with the diagnosis of DIC disease. Adverse events of interest are often highly as-
associated with the underlying DIC condition, which often improves over time with treatment. This implies the likelihood of adverse events after exposure period generally reduces with time. To compare the relative incidence of adverse events between two treatments in the post-marketing environment, a control group receiving the conventional treatment is required. The proposed case-only method works by modifying the baseline period of patients receiving new treatment through repeated random matching of exposure periods from patients receiving the alternative treatment. For each resample, relative incidence was computed using the SCCS method and the bootstrap estimates were obtained after a certain number of replications. We demonstrated this method using secondary data from a completed randomized controlled trial.

In this study, the estimated relative incidences by the case-only method using only the first adverse events with no sampling replacement were very comparable to the relative risk estimates of the randomized controlled trial which were computed based on patient count. Given the adverse events in a DIC patient were likely associated, they could be regarded as a single episode by including only the first adverse event for each patient in the SCCS analysis. This first-event approach is analogous to looking at the frequency of patients who experienced at least an adverse outcome. The results are comparable due to the similarity in terms of the unit of analysis based on patient count. Nonetheless, the case-only method utilized only information from cases, that is, the combined timelines from the exposure periods of RHST and heparin patients with at least an adverse event, whereas the relative risks from the randomized trial were computed based on the full sample size.

When all adverse events were considered, estimates from the case-only method were very close to the results based on cohort method for count data. This is because the SCCS method is based on the cohort logic, which relies on the same underlying Poisson model for count events (Farrington, 2004). The proposed case-only method requires only the cases (i.e., at least an event in the combined timelines), as opposed to the cohort method that requires information on all treated patients.

The percentile confidence intervals obtained through the resampling procedure were consistently narrower than the relative risk estimates achieved by the randomized controlled trial. As an inference based on subsamples is generally less efficient than that based on the entire samples, theoretical justification of the proposed method is the subject for future research. This tendency did not appear to be influenced by the number of cases in terms of the number of patients with at least an adverse event. Despite fewer patients with serious adverse events, the estimated confidence intervals remained narrow in comparison to the results of randomized controlled trial. This tendency also did not seem to be influenced by the length of observation period, though estimates obtained using longer observation period appeared to have a more comparable statistical significance relative to the estimates from the randomized controlled trial. Notwithstanding, likewise observed in the estimates of the 1 : 1 matched case-control design with similar bootstrap-
ping procedure, we noted the observed small variance could potentially be attributed to the small sample size from the randomized data used for bootstrapping (Scheiner and Gurevitch, 1998). Further investigation is required to understand the influence of sample size and the length of observation period on the bootstrap estimates of confidence intervals using actual or simulated post-marketing data.

This study did not adjust for the age of the patients by virtue of the use of randomized data. A previous subpopulation analysis has showed no confounding bias in this dataset (Saito et al., 2007). Nevertheless, age effect in the baseline incidence can be easily adjusted for using the same SCCS approach (Farrington et al., 1996). In addition, the method can be adapted to handle repeated exposure, different types of exposure, or varying degree of exposure within a single patient (Whitaker et al., 2006).

Estimation using the case-only method is susceptible to bias associated with the selection of control as in a case-control study. Although the case-only method relies on the SCCS method for the estimation of relative incidence, there is no self-control since the proposed method requires a different group of patients as a control pool for repeated random matching of time period. When applying the method to non-randomized data, this concern can be minimized by (i) the prior matching of patients on all known confounders to ensure homogeneity between treatment groups prior to implementing the proposed case-only method; and (ii) increasing the number of replications used to obtain the bootstrap estimates. This idea of matching in the proposed case-only method is different from the matching mechanism in a matched case-control study. Matching in the case-only method is between groups with different treatment exposures, whereas in the matched case-control study, it is by patients’ outcome.

Given the lack of surveillance data at the point of study, we explored a modified case-only method using randomized trial data to estimate the relative risk of adverse events that were common in DIC patients. The sampling of 100 patients from each treatment group is arbitrary, given the clinical trial data. Together, the number of sampling required for each treatment arm and the consistency of the estimator based on the modified approach, which can affect the identifiability of the bootstrap estimator, should be further investigated theoretically using actual or simulated post-market monitoring data.

5. Conclusions

In conclusion, the proposed case-only method with repeated random matching of time periods in patients receiving different treatments can produce reasonable estimates of relative incidence that are comparable to the relative risks obtained in a cohort design and experimental trial, and thus, has potential use for assessing the risk of adverse events related to a new treatment for diseases such as DIC through the borrowing of “control” information from existing patients who received the conventional treatment. Nevertheless, because the proposed method is explored using randomized trial data in this study, further study is required to validate the method using actual or simulated post-market monitoring data.
actual post-marketing data for the monitoring of treatment risk in patients with DIC or similar diseases.

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The authors declare no conflict of interest.

REFERENCES


