Sensitivity analysis of unmeasured confounding for adjusted survival curves using inverse probability weights

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Abstract

Objectives. Kaplan–Meier survival curves adjusted for confounders have been presented based on the use of inverse probability weights. However, in observational studies, some confounders may not be measured. In these situations, it is important to evaluate the potential impact of unmeasured confounding quantitatively. Here, we propose a simple method for sensitivity analysis of adjusted survival curves using the inverse probability weights.

Methods. We derived inverse probability weights, in which confounding risk ratios used as sensitivity parameters for unmeasured confounding were included. Using the weights with some plausible values for sensitivity parameters, a sensitivity analysis was performed.

Results. The proposed method of sensitivity analysis was applied to observational study data. The results demonstrate that this new method can be applied to adjusted survival curves without complex computer programming.

Conclusions. The proposed sensitivity analysis has the disadvantage of using sensitivity parameters as measures of risk as opposed to focusing on time to event. Nevertheless, the method is simple to perform and will aid researchers in evaluating the potential impact of unmeasured confounding on the Kaplan–Meier survival curves.

KEY WORDS: *confounding risk ratio, epidemiologic methods, observational studies, potential outcomes.*

Introduction

In observational studies without random assignment of treatment, unadjusted Kaplan–Meier survival curves may be misleading due to confounding. Therefore, some researchers have discussed the need to adjust survival curves for confounding (1–4). To produce adjusted survival curves, Cole and Hernán (3) and Xie and Liu (4) used an inverse probability weight (IPW), defined as the inverse of the probability of an individual subject's receiving a specific treatment or exposure on the measured covariate vector.

In actual observational studies, both unmeasured and measured confounders may be present. In such situations, adjusted Kaplan–Meier survival curves may also be misleading due to unmeasured confounding. Although analyses cannot be conducted to adjust for unmeasured confounding, it is important to quantitatively evaluate its potential impact. Therefore, we propose a sensitivity analysis of unmeasured confounding for application to survival curves.

Methods

Calculations used X as an exposure indicator and assumed the now-standard deterministic potential-outcome model, in which $Y_{X=1}$ and $Y_{X=0}$ are the potential outcome indicators under $X = 1$ and $X = 0$, respectively (5, 6). This model is currently used in several textbooks (7–9). The expectations of potential outcomes $E(Y_{X=1})$ and $E(Y_{X=0})$ are then the expectations of Y, if the entire study population is exposed to or administered a factor ($X = 1$) and if the entire study population is not ex-

posed to or administered a factor ($X = 0$), respectively. Causal effects are contrasts between these two expectations. It should be noted that the observed outcome Y is equal to the potential outcome $Y_{X=x}$ whenever $X = x$. Hence, $E(Y \mid X = x) = E(Y_{X=x} \mid X = x)$.

In the following sections, we first review the IPW method for adjusting binary or continuous outcomes, which has increasingly been used to adjust for confounding. Next, the adjusted Kaplan–Meier survival curves for measured confounding are reviewed. Finally, we propose a new method of sensitivity analysis for the influence of unmeasured confounding on Kaplan–Meier survival curves.

The IPW method

Informally, the IPW method approaches adjustment for confounding by multiplying the IPW by each subject i ($i = 1, \ldots, n$), where the weight is equal to the inverse of the probability of an individual subject's receiving a specific treatment or exposure X on the measured covariate vector Z. The probability is often calculated using a logistic regression model; i.e., the logistic model of Z on X is fitted, and the predicted probabilities $\Pr(X = x_i \mid Z = z_i)$ are estimated from the fitted model. These probabilities are used to calculate the weights $w_i = \Pr(X = x_i \mid Z = z_i)^{-1}$. For example, a weight of 1.2 for an individual is interpreted to indicate that 1.2 describes the number of subjects with the same background as the individual's own. Once this manipulation has been performed for all individuals, a pseudo-population is created. In this pseudo-population, the covariates are unrelated to exposure.

The IPW estimates are yielded from the following forms:

$$E(Y_{X=1}) = \frac{1}{n}\sum_{i=1}^{n} \frac{y_i x_i}{\Pr(X = 1 \mid Z = z_i)}, \qquad [1]$$

$$E(Y_{X=0}) = \frac{1}{n}\sum_{i=1}^{n} \frac{y_i (1 - x_i)}{\Pr(X = 0 \mid Z = z_i)}. \qquad [2]$$

In a simple manner, effect measures are calculated from marginal structural models (10–12); i.e., weighted regression analysis using $w_i = \Pr(X = 1 \mid Z = z_i)^{-1}$ for the exposed subjects and $w_i = \Pr(X = 0 \mid Z = z_i)^{-1}$ for the unexposed subjects as the weights. Note that these weights correspond to the inverses of the denominators of equations [1] and [2], respectively. The causal difference between the exposure groups is produced by a weighted linear regression model, and the causal risk ratio (RR) is produced using a weighted Poisson regression model when the outcome is binary.

Adjusted survival curves with IPW

Using IPW to produce adjusted survival curves is generally based upon using such weights to control for confounding (11). A weighted Cox proportional hazard regression model accounts for confounding variables using the covariate vector, whereby the weights are the estimated IPWs. With this method, the robust variance estimator (13) is used to estimate valid variances under the null hypothesis and to provide conservative confidence intervals (CI). A short SAS (14) program illustrating this method has been reported elsewhere (3).

Sensitivity analysis of unmeasured confounding

Our revised methodology uses two confounding risk ratios (CRRs) (15) within the ith stratum, defined as the ratio of the crude RR to the causal RR, as the sensitivity parameters. The first CRR pertains to the exposed group as the standard population, whereas the second CRR pertains to the unexposed group as the standard population. These CRRs are formalized as α_i and β_i using the following formulas:

$$\alpha_i \equiv \frac{\Pr(Y = 1 \mid X = 1, Z = z_i)}{\Pr(Y = 1 \mid X = 0, Z = z_i)} \Big/ \frac{\Pr(Y_{X=1} = 1 \mid X = 0, Z = z_i)}{\Pr(Y_{X=0} = 1 \mid X = 0, Z = z_i)}$$

$$= \frac{\Pr(Y_{X=1} = 1 \mid X = 1, Z = z_i)}{\Pr(Y_{X=1} = 1 \mid X = 0, Z = z_i)},$$

$$\beta_i \equiv \frac{\Pr(Y = 1 \mid X = 1, Z = z_i)}{\Pr(Y = 1 \mid X = 0, Z = z_i)} \Big/ \frac{\Pr(Y_{X=1} = 1 \mid X = 1, Z = z_i)}{\Pr(Y_{X=0} = 1 \mid X = 1, Z = z_i)}$$

$$= \frac{\Pr(Y_{X=0} = 1 \mid X = 1, Z = z_i)}{\Pr(Y_{X=0} = 1 \mid X = 0, Z = z_i)}.$$

These sensitivity parameters are applied in the context of the sensitivity analysis of unmeasured confounding for causal RR (16, 17).

It is important to note that both α_i and β_i can be regarded as bias factors, defining the sign of bias due to un-

measured confounding (18, 19). Using the RR for the exposed group as the standard population, when $\alpha_i > 1$ for all i, the RR adjusting for only measured confounders is larger than the true RR. This situation occurs when both the unmeasured confounder–outcome relationship and the unmeasured confounder–exposure relationship are either positive or negative. Conversely, $\alpha_i < 1$ for all i implies that the RR adjusting for only measured confounders is smaller than the true RR. This situation occurs when the unmeasured confounder–outcome relationship and the unmeasured confounder–exposure relationship have opposite signs. No bias due to unmeasured confounding exists when $\alpha_i = 1$. β_i is also interpreted for the RR in a similar manner, with the unexposed group as the standard population.

It is difficult to use α_i and β_i in a sensitivity analysis, as the number of sensitivity parameters is equal to the number of subjects. Thus, we assume that the values of sensitivity parameters are equal for all individuals; i.e., $\alpha \equiv \alpha_1 = \ldots = \alpha_n$ and $\beta \equiv \beta_1 = \ldots = \beta_n$. When unmeasured confounding is taken into account, using these sensitivity parameters, the following weights can be employed in place of $w_i = \Pr(X = x_i \mid Z = z_i)^{-1}$:

$$w_i = 1 + \frac{\Pr(X = 0 \mid Z = z_i)}{\alpha \Pr(X = 1 \mid Z = z_i)} \text{ for subjects with } X = 1, \quad [3]$$

$$w_i = 1 + \frac{\beta \Pr(X = 1 \mid Z = z_i)}{\Pr(X = 0 \mid Z = z_i)} \text{ for subjects with } X = 0. \quad [4]$$

The IPW estimators take the following forms in the case of a binary outcome:

$$\Pr(Y_{X=1} = 1) = \frac{1}{n}\sum_{i=1}^{n}\left\{1 + \frac{\Pr(X = 0 \mid Z = z_i)}{\alpha \Pr(X = 1 \mid Z = z_i)}\right\} y_i x_i , \quad [5]$$

$$\Pr(Y_{X=0} = 1) = \frac{1}{n}\sum_{i=1}^{n}\left\{1 + \frac{\beta \Pr(X = 1 \mid Z = z_i)}{\Pr(X = 0 \mid Z = z_i)}\right\} y_i (1 - x_i) \quad [6]$$

When no unmeasured confounder exists, $\alpha = \beta = 1$ and equations [5] and [6] are consistent with equations [1] and [2], respectively. The derivations of equations [5] and [6] are presented in the Appendix.

The sensitivity analysis is conducted using a weighted Cox proportional hazard model incorporating weights [3] and [4] in place of $w_i = \Pr(X = x_i \mid Z = z_i)^{-1}$. In this analysis, the plausible ranges of α and β are determined prior to performing the sensitivity analysis, and some values within the ranges are examined. The next section demonstrates the application of this sensitivity analysis.

Results

The proposed sensitivity analysis is illustrated using data from an observational study comparing disease-free survival (DFS) for 76 patients with Ewing's sarcoma (1). In this study, 47 patients received a novel treatment (S4), while the remaining 29 patients received one of three standard treatments (S1–S3). We use data reported by Cole and Hernán (3). Figure 1 presents the unadjusted

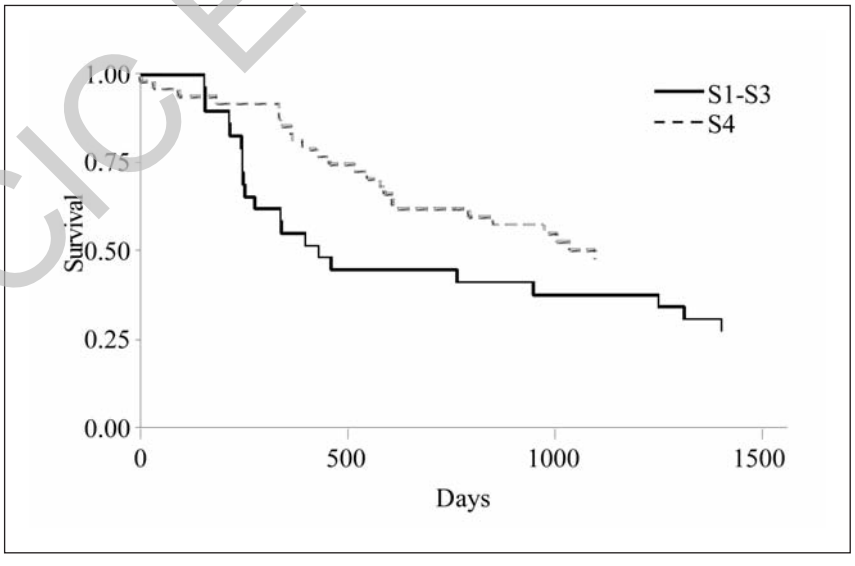

Figure 1. Unadjusted survival curves for 76 patients with Ewing's sarcoma

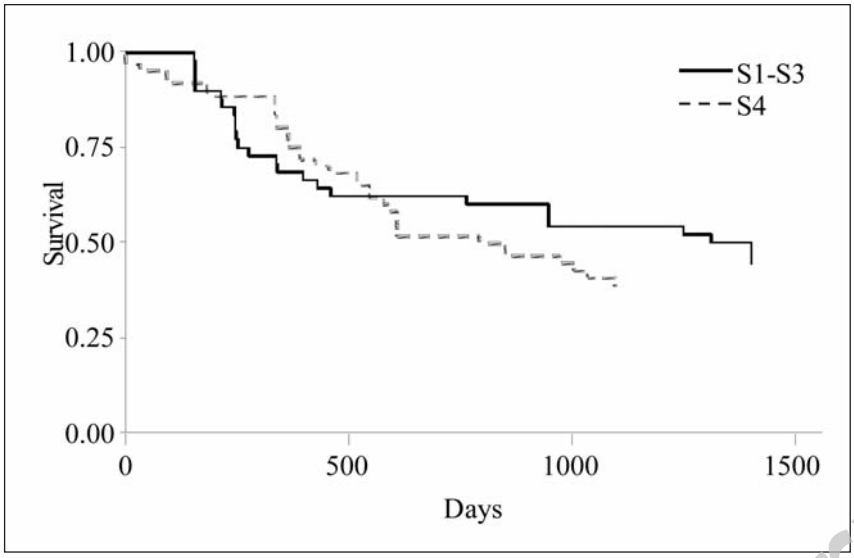

Figure 2. Survival curves for 76 patients with Ewing's sarcoma adjusting using IPW

survival curves for treatment S4 versus S1–S3. The unadjusted Cox proportional hazard model yields a hazard ratio (HR) of 0.534 (95% CI: 0.299, 0.955). This unadjusted analysis suggests that the S4 treatment was beneficial for reducing the risk of Ewing's sarcoma recurrence in comparison with the S1–S3 treatment.

In addition to the data on time to recurrence and the presence of censoring, we can use serum lactic acid dehydrogenase (LDH) data that have been dichotomized into < 200 and ≥ 200 international units. LDH is an enzyme that is thought to be related to tumor burden and that is regarded as a strong predictor of tumor recurrence. Therefore, LDH is considered a confounder. Figure 2 displays the survival curves with IPW adjusted for LDH. The adjusted Cox proportional hazard model with IPW yields a HR of 1.110 (robust 95% CI: 0.739, 1.668). The adjusted analysis with IPW suggests that investigators should not conclude that a difference exists between the S4 and S1–S3 treatments in the risk of recurrence of Ewing's sarcoma.

In general, age and performance status are also strong risk factors of DFS for patients with sarcoma and should be considered confounders in this study. However, these factors must be regard as unmeasured confounders, as there are no data pertaining to these factors. Thus, it is important to quantitatively evaluate the potential impact of unmeasured confounding on DFS. Therefore, the proposed sensitivity analysis was applied to these data. The ranges of sensitivity parameters α and β were established as $1/3 \le \alpha \le 3$ and $1/3 \le \beta \le 3$. These ranges were not based on any particular rationale, but CRRs (sensitivity parameters) are generally regarded as possibly not being very large compared with the ratio of the adjusted HR to the crude HR (1.110/0.534 = 2.079). Thus, the upper limit of sensitivity parameters was set as 3, and the lower limit was set as the inverse. The HRs were calculated by applying some values of α and β within these ranges. The results of these analyses are presented in Table 1. The HR had the largest value when $(\alpha, \beta) = (1/3, 3)$ and the smallest value when $(\alpha, \beta) = (3, 1/3)$.

Figure 3 displays the Kaplan–Meier survival curves when $(\alpha, \beta) = (1/3, 3)$ and $(3, 1/3)$. Figure 3(a) shows the most harmful outcome of treatment S4 under $(\alpha, \beta) = (1/3, 3)$, where the HR is 1.584 (robust 95% CI: 1.184, 2.120). Conversely, Figure 3(b) displays the most beneficial outcome under $(\alpha, \beta) = (3, 1/3)$, where the HR is 0.782 (robust 95% CI: 0.475, 1.287). The results of sensitivity analysis demonstrate, at minimum, that

Table 1. Hazard ratios generated using some values of α and β within $1/3 \le \alpha \le 3$ and $1/3 \le \beta \le 3$.

	β				
α	1/3	1/2	1	2	3
1/3	1.065	1.147	1.314	1.491	1.584
1/2	1.003	1.081	1.238	1.403	1.491
1	0.900	0.969	1.110	1.256	1.333
2	0.817	0.880	1.007	1.139	1.207
3	0.782	0.842	0.963	1.088	1.153

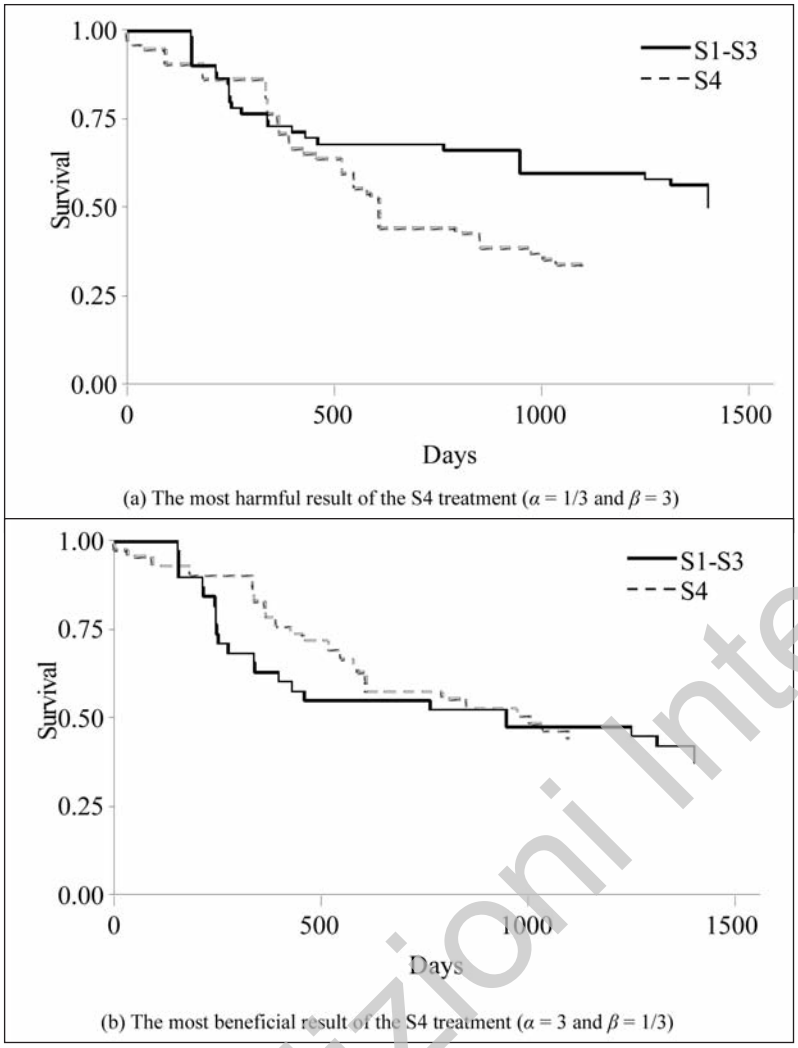

Figure 3. Sensitivity analysis of the survival curves for patients with Ewing's sarcoma. (a) The most harmful result of the S4 treatment ($\alpha = 1/3$ and $\beta = 3$), and (b) the most beneficial result of the S4 treatment ($\alpha = 3$ and $\beta = 1/3$).

treatment S4 is not beneficial in comparison with treatments S1–S3, even when unmeasured confounding variables are taken into account.

Discussion

We have proposed a sensitivity analysis of unmeasured confounding for Kaplan–Meier survival curves with adjustment for measured confounding. One limitation of this sensitivity analysis is that sensitivity parameters are measures of "risk" even though they are applied to survival analysis; i.e., there is a focus on "time-to-event" analysis. This situation may pose a challenge to the interpretation of sensitivity parameters. As observed for equations [5] and [6], $\Pr(Y_{X=1} = 1)$ becomes smaller as α becomes larger, and $\Pr(Y_{X=0} = 1)$ becomes larger as β becomes larger. Therefore, the causal RR becomes smaller as both α and β become larger. However, these relationships may not hold for survival curves and HRs. For example, as can be seen in Table 1, the present analyses showed that the HR became smaller as α became larger and β became smaller. Conversely, the HR became larger as α became smaller and β became larger. These observations imply that it may be more appropriate to use sensitivity parameters related to time-to-event data rather than the sensitivity parameters presented here, which are related to risk. Nevertheless, the proposed sensitivity analysis has the advantage that it is extremely simple to perform. Specifically, investigators using the SAS program can perform such an analysis following only trivial revision to the SAS program presented as adjusted survival curves for measured confounders (3). Performing a sensitivity analysis using the methods proposed here can assist researchers in explorations of the potential impact of unmeasured confounding. A sen-

sitivity analysis should be performed to evaluate the influence of unmeasured confounders on study results.

Appendix

In this appendix, we derive equations [5] and [6]. $\Pr(Y_{X=1} = 1)$ is transformed as follows:

$$\Pr(Y_{X=1}=1)$$

$$=\sum_{i=1}^{n}\Pr(Y_{X=1}=1\mid Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\sum_{x=0}^{1}\Pr(Y_{X=1}=1\mid X=x,Z=z_i)\Pr(X=x\mid Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\left\{\Pr(X=1\mid Z=z_i)+\frac{\Pr(X=0\mid Z=z_i)}{\alpha_i}\right\}\Pr(Y_{X=1}=1\mid X=1,Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\left\{1+\frac{\Pr(X=0\mid Z=z_i)}{\alpha_i\Pr(X=1\mid Z=z_i)}\right\}\Pr(Y=1\mid X=1,Z=z_i)\Pr(X=1\mid Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\left\{1+\frac{\Pr(X=0\mid Z=z_i)}{\alpha_i\Pr(X=1\mid Z=z_i)}\right\}\Pr(Y=1,X=1,Z=z_i).$$

Therefore, once $1 + \Pr(X = 0 \mid Z = z_i)/\{\alpha_i \Pr(X = 1 \mid Z = z_i)\}$ is calculated and α_i is replaced by α, then $\Pr(Y_{X=1} = 1)$ becomes equation [5]:

$$\Pr(Y_{X=1}=1)=\frac{1}{n}\sum_{i=1}^{n}\left\{1+\frac{\Pr(X=0\mid Z=z_i)}{\alpha\Pr(X=1\mid Z=z_i)}\right\}y_i x_i.$$

Likewise, $\Pr(Y_{X=0} = 1)$ is transformed as

$$\Pr(Y_{X=0}=1)$$

$$=\sum_{i=1}^{n}\Pr(Y_{X=0}=1\mid Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\sum_{x=0}^{1}\Pr(Y_{X=0}=1\mid X=x,Z=z_i)\Pr(X=x\mid Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\{\Pr(X=0\mid Z=z_i)+\beta_i\Pr(X=1\mid Z=z_i)\}\Pr(Y_{X=0}=1\mid X=0,Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\left\{1+\frac{\beta_i\Pr(X=1\mid Z=z_i)}{\Pr(X=0\mid Z=z_i)}\right\}\Pr(Y=1\mid X=0,Z=z_i)\Pr(X=0\mid Z=z_i)\Pr(Z=z_i)$$

$$=\sum_{i=1}^{n}\left\{1+\frac{\beta_i\Pr(X=1\mid Z=z_i)}{\Pr(X=0\mid Z=z_i)}\right\}\Pr(Y=1,X=0,Z=z_i).$$

Therefore, once $1 + \beta_i \Pr(X = 1 \mid Z = z_i)/\Pr(X = 0 \mid Z = z_i)$ is calculated and β_i is replaced by β, then $\Pr(Y_{X=0} = 1)$ becomes equation [6]:

$$\Pr(Y_{X=0}=1)=\frac{1}{n}\sum_{i=1}^{n}\left\{1+\frac{\beta\Pr(X=1\mid Z=z_i)}{\Pr(X=0\mid Z=z_i)}\right\}y_i(1-x_i).$$

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