Analysis of Randomized Clinical Trial in the Presence of Non-Compliance: Comparison of Causal Models

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Non-compliance is a common deviation from randomized clinical trials protocol. Standard approaches for comparing the effects of drugs in randomized clinical trials in the presence of non-compliance are intention-to-treat, as-treated and per-protocol analysis. Each of these approaches has disadvantages when evaluating the effect of medication in present of non-compliance. The current study compared the accuracy of instrumental variable (IV), intention-to-treat, as-treated and per-protocol technique. We assumed that non-compliance occurred for some patients in the new treatment group only, and independent of the patient outcomes. To compare these techniques, various scenarios were simulated. The MSE value for both PP and IV models changes only under the influence of the value of w (non-compliance ratio). That is, at all values of θ (treatment effect), the MSE of these two models increases with increasing non-compliance ratio, and changing the value of θ does not affect the MSE. The MSE value for the AT model if the non-compliance occurs only in the intervention group, this value changes only under the influence of the w value That is, in this case, in all values of θ, the MSE value increases with increasing non-compliance ratio, and changing the value of θ does not affect the MSE. But the MSE value of the ITT model is strongly influenced by the value of θ. At low θ values the MSE value of this model is lower than other methods and better estimates the therapeutic effect, and in this case with increasing the w, the MSE value increases very

little. But as the θ increases, so does the MSE value, and in this case, as the w increases, the MSE value increases sharply.

Keywords: causal model, non-compliance, randomized clinical trials, simulation

1. Introduction

A randomized controlled clinical trial (RCT) is a standard and valid method for evaluating the causal/ therapeutic effects of a drug or medical interventions (Hulley et al. 2013). Intention to treat analysis (ITT) is common standardized method for analyzing RCTs (Hernán & Hernández-Díaz 2012; Gruber et al. 2014), but note that ITT ignores adherence behavior (Heritier et al. 2003; Peugh et al. 2017). In RCTs, all participants must receive the prescribed treatment methodically until the end of the study. In practice, this does not occur. In randomized experiments with human groups, non-compliance frequently occurs on some of participants. In this case, ITT analysis may provide biased estimates from causal effects, which may decrease the power of the test (Boatman et al. 2017; Lyu, 2018). When in clinical trials patients do not receive full doses of the prescribed medication, researchers usually use the intention-to-treat, per-protocol (PP), as-treated (AT) or Instrumental variable (IV) to compare the treatment effects between groups (Blackwell 2017; Mostazir et al. 2019).

Previous studies on the superiority of these analytical methods have not provided general rule, and each is based on data collected (Matilde Sanchez & Chen, 2006). In addition to choosing these methods, many researchers have tried to modify the effects of non-compliance and evaluate the treatment effects as to make them as valid as possible by using statistical models (Bang & Davis, 2007). In this regard, some researchers have tried to modify the sample size estimation formulas to moderate the effect of non-compliance rather than using statistical models (Soltanian & Faghihzadeh, 2012; Whitehead et al. 2016), that increasing sample size may not be cost-effective in RCTs.

There continues to be disagreement amongst statisticians and analysts on which of the methods to use (Ye et al. 2014; Adewuyi et al. 2015). In this study, we attempted to provide a simple rule based on sample size and rate of non-compliance to select analytical methods in the presence of non-compliance in RCTs.

To apply the results of the simulation study, a randomized clinical trial study was used to evaluate effect of medication administration education on nurses' compliance with medication administration care standards.

The validity of treatment effects estimation among the four techniques was assessed by a simulation study and the mean square error (MSE) index in present of patients' non-compliance.

2. Methods

2.1. Notation and estimators

A simple design for RCT was formulated with binary treatment and a continuous outcome. Let Y_{1i} and Y_{0i} be a pair of counterfactual outcomes, where i (i =1, 2, …, n) is a subject allocated to the new treatment or placebo, respectively. Let r_i denote a randomization group indicator that will equal 0 if individual i is randomized to the placebo, and 1 if individual i is randomized to the new treatment. Suppose that each individual has a crossover or switching indicator s_i, which is equal to 0 if individual i remains in the randomization arm, and 1 if individual i emigrates to the opposite arm. Set q_i as the treatment received which equals 0 or 1 for the individual receiving the placebo or the new treatment, respectively. The treatment effect is defined as $\mu_1 - \mu_0 = \theta$, where μ_1 and μ_0 are average outcome for the individual receiving the new treatment and placebo, respectively. We assumed that non-compliance occurred for $n'(n' < n)$patients in the new treatment group only, and independent of the patient outcomes. The standard deviation is considered same in the two groups for simplicity. We denote the response variable with Y_{1i} for those who received the new treatment then they follow a normal distribution with mean and varianse μ_1 and σ^2, and Y_{0i} for those who receive the placebo they follow a normal distribution with mean and varianse μ_0 and σ^2, and Y'_{0i} for those who did not comply new treatment (from intervention to control group) they follow a normal distribution with mean and varianse μ_0 and $\sigma,^2$ and ε_i is error term in the linear model that follow a normal distribution with mean and varianse 0 and $\sigma.^2$ In the study, it was assumed that the data following a distribution would as normal. In each case, the treatment effect was estimated by the likelihood function.

2.2. Intention to treat analysis

This analysis compares patients according to their assigned treatments, regardless of whether they complied with the treatment. This method ignores the compliance status completely. It estimates the treatment effect using the following regression equation and likelihood function ($L_{ITT}(\mu, \theta, \sigma)$), respectively,

$$y_i = \mu + \theta r_i + \varepsilon_i$$

$$L_{ITT}(\mu, \theta, \sigma) = \prod_{i=1}^{n} \varphi(y_i; \mu + \theta r_i, \sigma)$$

where, μ and $\mu + \theta$ are the means of the outcome in control and new treatment groups, respectively, $\varphi(\cdot)$ denote normal distribution and σ is a same standard deviation in both groups. Also, y_i is continues outcome, ε_i is error term in the linear model and θ is the difference between the mean outcomes in the two groups.

$$\theta_{ITT} = E(Y \mid r = 1) - E(Y \mid r = 0) \rightarrow \hat{\theta}_{ITT} = \overline{Y}_{r=1} - \overline{Y}_{r=0}$$

In this study all of patients in placebo group receiving the placebo then the average of them follow a normal distribution with mean and varianse μ_0 and $\frac{\sigma^2}{n}$.

$$\overline{Y}_{r=0} = \frac{\sum_{i=1}^{n} Y_{0i}}{n} \sim N\left(\mu_0, \frac{\sigma^2}{n}\right)$$

But in the new treatment group, patients receiving the placebo then the average of them follow a normal distribution with mean and varianse μ_0 and $\frac{\sigma^2}{n'}$, and $n - n'$ patients receiving the new treatment then the average of them follow a normal distribution with mean and varianse μ_1 and $\frac{\sigma^2}{n-n'}$, then

$$\overline{Y}_{r=1} = \frac{\sum_{i=1}^{n-n'} Y_{1i} + \sum_{i=1}^{n'} Y'_i}{n} \sim N\left(\frac{(n-n')\mu_1 + n'\mu_0}{n}, \frac{\sigma^2}{n}\right)$$

then,

$$\hat{\theta}_{ITT} = \overline{Y}_{r=1} - \overline{Y}_{r=0} = \frac{\sum_{i=1}^{n-n'} Y_{1i} + \sum_{i=1}^{n'} Y'_i}{n} - \frac{\sum_{i=1}^{n} Y_{0i}}{n} \sim N\left(\frac{(n-n')\mu_1 + n'\mu_0}{n} - \mu_0, \frac{2\sigma^2}{n}\right)$$

$$E(\hat{\theta}_{ITT}) = E(\overline{Y}_{r=1} - \overline{Y}_{r=0}) = \frac{(n-n')\mu_1 + n\mu_0}{n} - \mu_0 = (\mu_1 - \mu_0)\left(1 - \frac{n'}{n}\right) = \theta\left(1 - \frac{n'}{n}\right)$$

We define $w = \frac{n'}{n}$ so that w is the rate of non-compliance and in this method the value of bias is, $b(\hat{\theta}_{ITT}) = E(\hat{\theta}_{ITT}) - \theta = \theta(1-w) - \theta = -w\theta$ and standard error of this estimator is $SE(\hat{\theta}_{ITT}) = \frac{\sigma^2}{n}$. The estimation of $SE(\hat{\theta}_{ITT})$ will be $\widehat{SE}(\hat{\theta}_{ITT}) = \sqrt{\frac{2S^2_{pooled}}{n}}$, which $S^2_{pooled} = \frac{(n-1)S^2_{r=1} + (n-1)S^2_{r=o}}{2n-2} = \frac{S^2_{r=1} + S^2_{r=o}}{2}$ and

$$MSE = \left(\hat{\bar{\theta}} - \theta\right)^2 + \left(SE(\hat{\theta})\right)^2 = (-w\theta)^2 + \frac{2S^2_{pooled}}{n}.$$

Therefore, MSE of ITT estimator is a function from w and θ. When non-compliance rate (i.e., w) or θ parameter increased, the MSE of ITT method increases.

2.3. As-treated analysis

The as-treated analysis compares patients by the treatment they actually received (Soltanian et al. 2010). It then estimates the treatment effect using the following regression equation and likelihood function ($L_{AS}(\mu, \theta, \sigma)$), respectively,

$$y_i = \mu + \theta q_i + \varepsilon_i$$

$$L_{AS}(\mu, \theta, \sigma) = \prod_{i=1}^{n} \varphi(y_i; \mu + \theta q_i, \sigma)$$

where, μ and $\mu + \theta$ are the means of the outcome in actually-received and not-received treatment groups, respectively; $\varphi(\cdot)$ denote normal distribution; σ is a same standard deviation in both groups; y_i is continues outcome, ε_i is error term in the linear model and $\boldsymbol{\theta}$ is the difference between the mean outcomes in the two groups.

In this method $\theta_{AT} = E(Y|q=1) - E(Y|q=0)$ then $\hat{\theta}_{AT} = \overline{Y}_{q=1} - \overline{Y}_{q=0}$.

All of patients in placebo group and n' patients from the new treatment group are receiving the placebo then

$$\overline{Y}_{q=0} = \frac{\sum_{i=1}^{n} Y_{0i} + \sum_{i=1}^{n'} Y_i'}{n+n'} \sim N\left(\frac{n\mu_0 + n'\mu_0}{n+n'}, \frac{\sigma^2}{n}\right) = N\left(\mu_0, \frac{\sigma^2}{n+n'}\right)$$

And $n + n'$ patients from the new treatment group are receiving the new treatment then

$$\overline{Y}_{q=1} = \frac{\sum_{i=1}^{n-n'} Y_{1i}}{n-n'} \sim N\left(\mu_1, \frac{\sigma^2}{n-n'}\right)$$

Then

$$\hat{\theta}_{AT} = \overline{Y}_{q=1} - \overline{Y}_{q=0} = \frac{\sum_{i=1}^{n-n'} Y_{1i}}{n-n'} - \frac{\sum_{i=1}^{n} Y_{0i} + \sum_{i=1}^{n'} Y_i'}{n+n'} \sim N\left(\mu_1 - \mu_0, \frac{\sigma^2}{n+n'} + \frac{\sigma^2}{n-n'}\right)$$

$$E(\hat{\theta}_{AT}) = E(Y \mid q=1) - E(Y \mid q=1) = \mu_1 - \mu_0 = \theta.$$

We define $w = \frac{n'}{n}$, w is rate of non-compliance and in this method the value of bias is $b(\hat{\theta}_{AT}) = E(\hat{\theta}_{AT}) - \theta = \theta - \theta = 0$.

And standard error of this estimator is, $SE(\hat{\theta}_{ITT}) = \sqrt{\frac{\sigma^2}{n+n'} + \frac{\sigma^2}{n-n'}}$ and was estimated by

$$\widehat{SE}(\hat{\theta}_{ITT}) = \sqrt{\frac{s_p^2}{n+n'} + \frac{s_p^2}{n-n'}} = \sqrt{\frac{2s_p^2}{n}\frac{1}{(n-n')}} = \sqrt{\frac{2s_p^2}{n}}\sqrt{\frac{1}{1-w^2}},$$

where

$$S_{pooled}^2 = \frac{(n-n'-1)S_{q=1}^2 + (n+n'-1)S_{q=0}^2}{2n-2} \text{ and}$$

$$MSE = \left(\bar{\hat{\theta}} - \theta\right)^2 + \left(SE(\hat{\theta})\right)^2 = \frac{2S_{pooled}^2}{n}\frac{1}{1-w^2}.$$

Therefore, MSE of AT estimator is a function from *w*. When non-compliance rate (*w*) increased, the MSE of AT method increases.

2.4. Per-protocol analysis

In this analysis, the patients who did not fully comply with treatment protocol were excluded from the analysis (Schochet & Chiang 2011). The treatment effect then was estimated using the following regression equation, $\boldsymbol{y_i = \mu + \theta r_i' + \varepsilon_i}$.

Let $\boldsymbol{r_i'}$ denote a randomization group indicator for patients who fully comply with treatment protocol that will equal 0 if individual *i* is randomized to the placebo and 1 if individual *i* is randomized to the new treatment.

Therefore, the likelihood function of per-protocol approach is $L_{PP}(\mu,\theta,\sigma) = \prod_{i=1}^{n}\varphi(y_i;\mu+\theta r_i',\sigma)$, where μ and $\mu + \theta$ are the mean outcomes for patients who fully complied with the treatment protocol in the placebo and active groups, respectively; $\varphi(.)$ denote normal distribution; σ is a same standard deviation in both groups. Measures of $\boldsymbol{y_i}$, $\boldsymbol{\varepsilon_i}$ and θ are the same as before and $\varphi(\cdot)$ denote normal distribution.

In this method, $\theta_{PP} = E(Y|r'=1) - E(Y|r'=0)$ then $\hat{\theta}_{PP} = \overline{Y}_{r'=1} - \overline{Y}_{r'=0}$.

In this study, all patients in the placebo group receiving the placebo then

$$\overline{Y}_{r'=0} = \frac{\sum_{i=1}^{n} Y_{0i}}{n} \sim N\left(\mu_0, \frac{\sigma^2}{n}\right)$$

But in the new treatment group, n' patients who receiving the placebo were excluded from the analysis and $n - n'$ patients receiving the new treatment then

$$\bar{Y}_{r'=1} = \frac{\sum_{i=1}^{n-n'} Y_{1i}}{n-n'} \sim N\left(\mu_1, \frac{\sigma^2}{n-n'}\right)$$

Then

$$\widehat{\theta_{PP}} = \bar{Y}_{r'=1} - \bar{Y}_{r'=0} = \frac{\sum_{i=1}^{n-n'} Y_{1i}}{n-n'} - \frac{\sum_{i=1}^{n-n'} Y_{0i}}{n} \sim N\left(\mu_1 - \mu_0, \frac{\sigma^2}{n} + \frac{\sigma^2}{n-n'}\right)$$

and

$$E(\widehat{\theta_{PP}}) = E(\bar{Y}_{r'=1} - \bar{Y}_{r'=0}) = \mu_1 - \mu_0 = \theta$$

$$b(\hat{\theta}) = E(\hat{\theta}) - \theta = \theta - \theta = 0$$

We defined $w = \frac{n'}{n}$, w is rate of non-compliance and in this method the value of bias is,

$$b(\hat{\theta}_{PP}) = E(\widehat{\theta_{PP}}) - \theta = \theta - \theta = 0$$

and standard error of this estimator as follows,

$$SE(\theta_{PP}) = \sqrt{\frac{S_p^2}{n} + \frac{S_p^2}{n-n'}} = \sqrt{\frac{S_p^2}{n}\frac{2n-n'}{(n-n')}} = \sqrt{\frac{2S_p^2}{n}}\sqrt{\frac{2-w}{2(1-w)}}$$

where, $S_p^2 = S_{pooled}^2 = \frac{(n-n'-1)S_{r'=1}^2 + (n-1)S_{r'=1}^2}{2n-n'-2}$

and $MSE = \left(\bar{\hat{\theta}} - \theta\right)^2 + \left(SE(\hat{\theta})\right)^2 = \frac{2S_{pooled}^2}{n}\frac{2-w}{2(1-w)}$.

Therefore, MSE of PP estimator is a function from w. When non-compliance rate (w) increased, the MSE of PP method increases.

2.5. Instrumental variable model

The instrumental variables (IVs) are used to control for confounding and measurement error in studies. In this study, random allocation r is referred to the instrumental variable because it satisfies two conditions. It causes variation in the treatment received variable (q) and it does not have a direct effect on the outcome variable (Y), only indirectly through the treatment received variable. The treatment effect then was estimated using the following two-stage regression technique

(Baker et al., 2016; DiazOrdaz et al. 2016; Wang et al. 2017). In first stage we estimate $\widehat{q_l}$ from $E(q \mid r)$, i.e., $\widehat{q_l} = \alpha_0 + \alpha_1 r_i$, and in second stage it was considered, $y_i = \mu + \theta\widehat{q_l} + \varepsilon_i$. Therefore, the likelihood function of two-stage regression technique is $L_{IV}(\mu, \theta, \sigma) = \prod_{i=1}^{n} \varphi(y_i; \mu + \theta\widehat{q_l}, \sigma)$.

For a binary instrument, the simplest method of estimation of equation (2) in the IV framework is the Wald estimator (Angrist et al. 1996):

$$\theta_{IV} = \frac{Co\upsilon(Y, r)}{Co\upsilon(Y, q)} = \frac{E(Y \mid r = 1) - E(Y \mid r = 0)}{E(q \mid r = 1) - E(q \mid r = 0)}$$

In this study $E(q \mid r = 0) = 0$ because all of patients in placebo group receiving the placebo and $E(q \mid r = 1) = \frac{n - n'}{n}$. Then

$$\hat{\theta}_{IV} = (\overline{Y}_{r=1} - \overline{Y}_{r=0}) \Big/ \frac{n - n'}{n}$$

$$\widehat{\theta_{IV}} = \frac{\overline{Y}_{r=1} - \overline{Y}_{r=0}}{\frac{n - n'}{n}} = \left(\frac{\sum_{i=1}^{n-n'} Y_{1i} + \sum_{i=1}^{n'} Y_i' - \sum_{i=1}^{n'} Y_{0i}}{n} \right) \Bigg/ \left(\frac{n - n'}{n} \right) \sim N\left(\mu_1 - \mu_0, \frac{2n\sigma^2}{(n - n')^2} \right)$$

$$E(\widehat{\theta_{IV}}) = E(\overline{Y}_{r=1} - \overline{Y}_{r=0}) \Big/ \left(n - n' \Big/ n \right) = \theta.$$

We define $w = \frac{n'}{n}$, w is rate of non-compliance and in this method the value of bias is

$$b(\hat{\theta}_{PP}) = E(\widehat{\theta_{PP}}) - \theta = \theta - \theta = 0.$$

And standard error of this estimator equal by

$$SE(\theta_{IV}) = \frac{1}{1 - w} \sqrt{\frac{2S^2_{pooled}}{n}}$$

that $S^2_{pooled} = \frac{(n-1)S^2_{r=1} + (n-1)S^2_{r=0}}{2n - 2} = \frac{S^2_{r=1} + S^2_{r=0}}{2}$

and $MSE = (\bar{\hat{\theta}} - \theta)^2 + (SE(\hat{\theta}))^2 = \frac{2S^2_{pooled}}{n} \frac{1}{1-w^2}$.

Therefore, MSE of IV estimator is a function from w. When non-compliance rate (w) increased, the MSE of IV method increases.

2.6. Simulation study

Several scenarios were simulated to compare models with different non-compliance rates and treatment effects. Treatment effect (θ) varies from zero to eight, and non-compliance rates (w) varies from zero to 0.97 for any θ, and Then, Y_{0i} and Y_{1i} were generated from normal distributions having means of μ_0 and μ_1, respectively; at equal standard deviation (SD) five for two groups. In the alternative situation, Y_{0i} and Y_{1i} are generated from normal distributions having means $\mu_0 = 60$ and $\mu_1 = 60 + 0$, respectively, with respect to standard deviation 5 for two groups. The observed outcome for each patient was calculated by $y_i = q_i\, Y_{1i} + (1 - q_i)\, Y_{0i}$, where q_i is either 0 or 1 for the patient receiving the placebo or the new treatment, respectively. It was assumed that the pattern of non-compliance was all-or-none, where compliers received 100% of the allocated treatment and non-compliers received none of it. The probability of non-compliance was the proportion of units that did not receive anything according to the protocol or the proportion of units that crossed to the other arm (w). For the placebo group, $w = 0$, while, for the new treatment group, varies from zero to 0.97 for different scenarios. In addition, switching indicator s_i for each individual in new treatment group was generated from a Bernoulli distribution with a probability of w. This indicator for the placebo group was 0. Indicator that shows new or control group, was generated for each individual from a Bernoulli distribution with a probability of 0.5 of being assigned to either group. Data sets were generated for both groups by equal size ($n_1 = n_2 = 100$) in 882 (9×98) scenarios. In each scenario, 1000 samples were generated with different Treatment effects (9 θs) and non-compliances rates (98 ws).

2.7. Comparison indices

We calculated the mean of θ for 1000 samples $(\bar{\hat{\theta}})$ and 95% CI for $\bar{\hat{\theta}}$. Also MSE index was used to compare the four methods, i.e. ITT, per-protocol, as-treated and instrumental variable methods. The MSE is calculated as $MSE = (\bar{\hat{\theta}} - \theta)^2 + (SE(\hat{\theta}))^2$, where $SE(\hat{\theta})$ is the standard deviation of the empirical distribution of the estimates from all iterations (Burton et al. 2006).

3. Results

3.1. Simulated analysis

The data was generated 1000 times based on the assumptions and scenarios mentioned in section 2.6. Y_{1i} and Y_{0i} are generated from normal distributions having means $\mu_0=60$ and $\mu_1=60+\theta$, respectively, with respect to standard deviation 5 for two groups. Then the treatment effect were estimated by the ITT, AT, PP and IV methods. The $\bar{\hat{\theta}}$ of difference between treatments effects were calculated under non-compliance rates and sample sizes of 100 for any group.

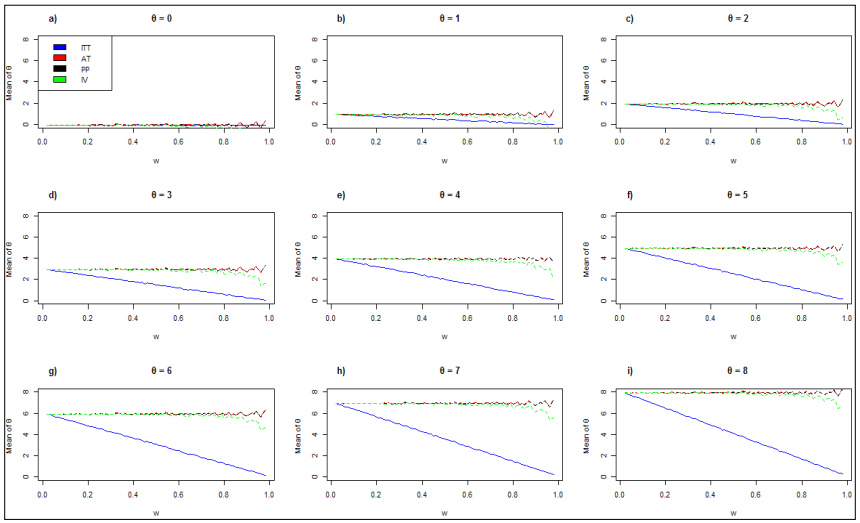
Each graph in figure 1 shows the average estimated treatment effect in 1000 times replicate, for the four methods in a particular treatments effect.These graphs show that the estimates of the three methods AT, PP, and IV are unbiased, but the estimates of the ITT method are biased, and the bias values are a function of two parameters, treatment effect and non-compliance rate, and increase sharply with increase these two values.

Each graph in figure 2 shows the values of MSE for the four methods in a particular treatments effect.When treatments effect is low (i.e., 0 to 2), the ITT estimator had the lowest MSE at various non-compliance rates, followed by the AT, PP and IV methods, while treatments effect increases, MSE for most of situations using the AT provided more reliable estimates than PP, ITT and IV (i.e., 3 to 5). When treatments effect is high (i.e., 6 to 8) the ITT estimator had the highest MSE at various non-compliance rates.

3.2. Example

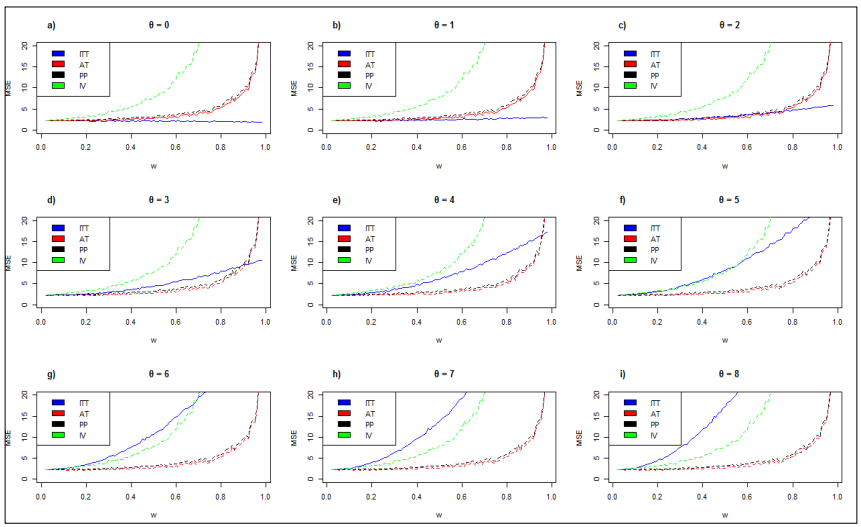
An interventional study was conducted on 76 qualified nurses in Be'sat and Shahid Beheshti hospitals in 2017, in Hamadan City, west of Iran. The hospitals were randomly assigned as intervention and control groups, respectively. Thirty eight nurses were selected from each center. The purpose of that study was done in order to investigate the effect of medication administration education on nurses' compliance with medication administration care standards. In the intervention group the training of the medication administration was conducted by the researcher and by the classroom in small groups and two sessions of two hours (by group discussion) and the control group did not receive any training. In the intervention group, 4 nurses did not follow the protocol of the study because they did not complete the training sessions. But in the control group there is no any non-compliance because they did not receive any training.

The medication administration care standards was considered by nurses as the response variable. This is a practical example upon which the simulation and results were focused. The results show that there were no significant differences between two groups in terms of demographic information. Average age of the nurses for intervention and control group was 31.5 ± 5.69 and 34.26 ± 7.06 years,



W = rate of non-compliance in active group (Varies from 0 to 0.97)
θ = mean of treatment effect estimates
ITT=Intention to treat, AT=As-treated, PP=Per-protocol, IV=Instrumental variable
MSE = mean squared error. All values for any w and θ were obtained from 1000 simulations.

Figure 1. The Average of Estimated Treatment Effect in 1000 Times Replicate



W = rate of non-compliance in active group (Varies from 0 to 0.97)
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ITT=Intention to treat, AT=As-treated, PP=Per-protocol, IV=Instrumental variable
MSE = mean squared error. All values for any w and θ were obtained from 1000 simulations.

Figure 2. Estimated MSE for Different Scenarios

respectively. 31 (81.6%) of the intervention group and 34 (89.5%) of the control group were female. 37 (97.4%) of intervention group and all of the control group had bachelor's degree and above, and 21 (55.3%) of both group were married. Experience working in the ICU was 70.5 ± 6.6 and 65.39 ± 5.8 months for intervention and control groups, respectively.

Table 1 shows the mean of nurses' scores and the effect of the intervention in the presence of non-compliance applying the our methods. As observed, the mean of nurses' scores in both groups, based on all methods, was statistically significant.

Although the treatment effects and the standard errors (SEs) in ITT and PP methods are approximately equal, the simulated results show that when non-compliance rate is low the treatment effects have the equal MSEs based on ITT, PP and AT methods.

Table 1. Estimated Treatment Effect of Five Causal Effects Methods

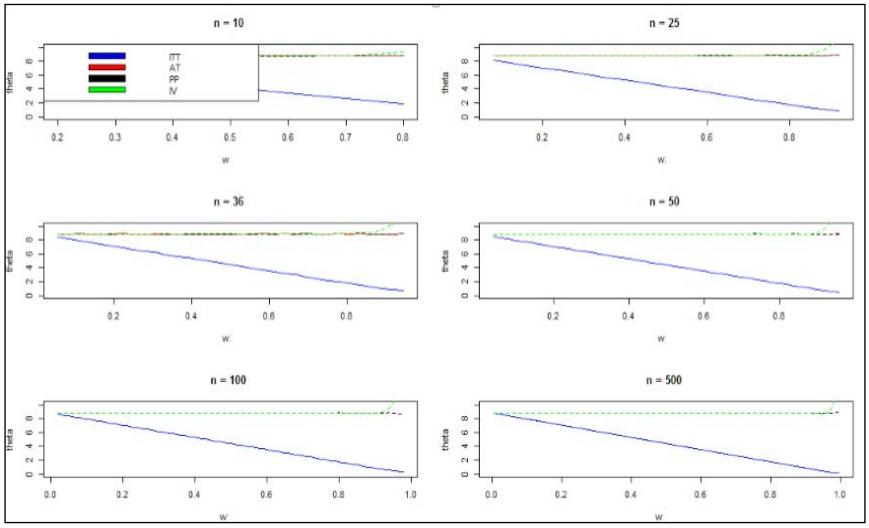
	Method			
	IV	**PP**	**AT**	**ITT**
Placebo effect (μ_0)	57.78	57.78	58.72	57.78
New treatment effect (μ_1)	67.63	66.48	66.49	66.60
(n_1,n_0)	(38, 38)	(34, 38)	(34, 42)	(38, 38)
$\mu_1 - \mu_0 = \theta$	9.85	8.70	7.77	8.82
SE($\hat{\theta}$)*	0.72	0.645	0.82	0.65
CI ($\hat{\theta}$)	(8.41, 11.30)	(7.42, 9.99)	(6.14 , 9.4)	(7.53,10.11)
P-value	<0.001	<0.001	<0.001	<0.001

SE = Standard Error , CI = Confidence Interval

3.3. Simulation Analysis Using Real Data

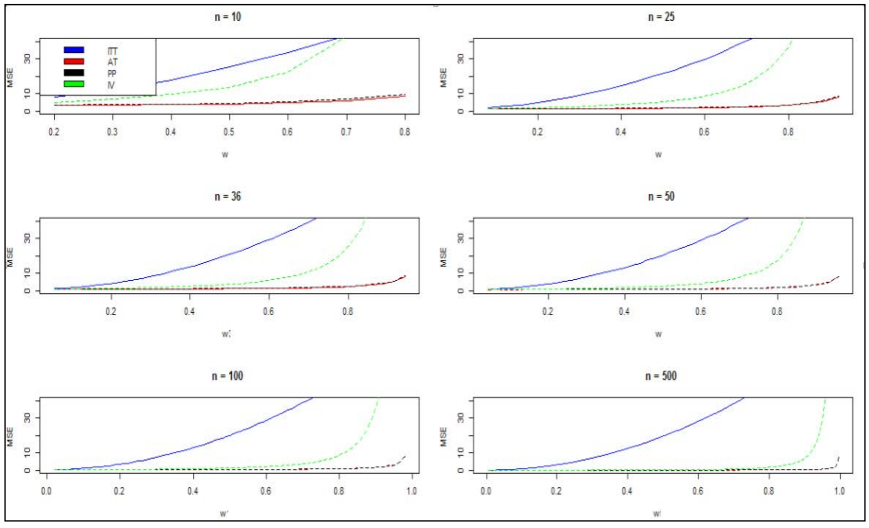
For the comparison of the casual models' performances, the data was selected 1000 times from the interventional study of 76 qualified nurses. The data from this study serve as a pseudo-population. Bootstrap resampling technique used in the simulation study with 1000 bootstrap samples and using increasing sample sizes. the sample sizes was 10, 25, 36, 50, 100 and 500 for any group. These sample sizes have resampled from the pseudo-population 1000 times. Then the treatment effect were estimated by the ITT, AT, PP and IV methods. The $\bar{\hat{\theta}}$ of difference between treatments effects were calculated under non-compliance rates and different sample sizes.

Each graph in figure 3 shows the average estimated treatment effect in 1000 times replicate, for the four methods in a particular sample size. These graphs



W = rate of non-compliance in active group (Varies from 0 to 0.97)
theta = mean of treatment effect estimates in 1000 times replicate
ITT=Intention to treat, AT=As-treated, PP=Per-protocol, IV=Instrumental variable

Figure 3. The Average of Estimated Treatment Effect in 1000 Times



W = rate of non-compliance in active group (Varies from 0 to 0.97)
theta = mean of treatment effect estimates
ITT=Intention to treat, AT=As-treated, PP=Per-protocol, IV=Instrumental variable
MSE = mean squared error. All values for any w and n were obtained from 1000 simulations.

Figure 4. Estimated MSE for Different Scenarios (Bootstrap Resampling)

show that the estimation of the therapeutic effect using the ITT method depends on the non-compliance rate, so that with increasing the non-compliance rate, the bias of this method increases, but, the estimates of the three methods AT, PP, and IV are unbiased.

Each graph in figure 4 shows the MSE values for the four methods in a particular sample sizes.The MSE value for the AT and PP models is not affected by the w parameter, and as the w parameter increases, the MSE value of these two models will increase slightly.

But, the MSE value of the ITT model is strongly influenced by the value of w, and since the value of θ in this example was large and equal to 8.82, with increasing the value of w, the MSE value also increases sharply. In relation to model IV, the MSE value is affected by both parameters w and n, so that with increasing value of w, the MSE value also increases, but the larger the sample size, the lower the slope of increasing the MSE value will be.

4. Discussion

Our simulation study compared four techniques ITT, AT, PP and IV in presence of non-compliance. We assumed that non-compliance occurred in the new treatment group only, and independent of the patient outcomes. The standard deviation is considered same in the two groups for simplicity. And the sample size in all situations was set to 100 for each group. We proved that the estimates of the three methods AT, PP, and IV are unbiased, but the estimates of the ITT method are biased, and the bias values are a function of two parameters, treatment effect and non-compliance rate, and increase sharply with increase these two values. But the standard error value in the ITT method, unlike the other three methods, is not at all dependent on the value of non-compliance ratio. That is, the standard error value of the ITT method does not change much with increasing the non-compliance ratio. But in the other three methods the standard error rate increases with increasing non-compliance ratio. We used the MSE index to compare the efficacy of the four methods, as can be seen in figure 2 In all the situations, the MSE of the four methods increased with increasing non-compliance ratio. When the non-compliance ratio is negligible, the difference between the four methodes is negligible in terms of MSE, but if the ratio is high, both the AT and PP methodes out perform the IV methode. And for the ITT methode, when the treatment effect is low, the MSE value of this methode is better than the other three methodes. When the treatment effect is high, the ITT methode is weaker than the other three models in estimating the parameters.

As can be seen in Table 1, the IV estimator is larger than that of the estimator ITT. According to sections 2.2 and 2.5, the estimate obtained from the IV method will always be larger than the estimate of the ITT method. Exactly the same relationship exists between the SE values of these two models, meaning that the SE

value of IV Method is always greater than the SE value of the ITT method. Unlike the ITT method, the estimates of IV method are unbiased, but the amount of SE of IV method depend on the non-compliance rate, and as the non-compliance rate increases, the SE value also increases. But, the estimates of the ITT method are biased and its the SE value dont depends on two parameters: the non-compliance rate and the actual treatment effect. These two factors are not present and with the increase of these two parameters are almost constant.

In general in this example, the estimators of the four methods and their SE values are almost close to each other because the non-compliance rate is low (4/38= 0.1), as in Figure 2, It is shown that for low non-compliance rates, the MSE value of the four methods are almost close to each other. Estimators of both AT and PP methods, although are unbiased, but their SE value is dependent on the non-compliance rate and may increase with increasing non-compliance rate.

5. Conclusion

When the non-compliance is independently of the patient's outcome and it occurs only in the new treatment group, if the non-compliance ratio is low we suggested ITT method to comparison between treatment effects, but if it is high the ITT method will be very error free and methods such as AT and PP should be used.

Acknowledgements

This article was supported by funding from Hamadan University of Medical Sciences (Contract No. 9606284157). This work is a part of the results of the PhD thesis of Mr. Ahmadinia, the corresponding author of this paper, supervised by Professor Soltanian, the paper's first author. We would like to thank the Health Sciences Research Center, Faculty of Health, Hamadan University of Medical Sciences.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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