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Original Article

Combining Multiple Imputation and Inverse-Probability Weighting for Analyzing Response with Missing in the Presence of Covariates

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Introduction: Missing values are frequently seen in data sets of research studiesespecially in medical studies.Therefore, it is essential that the data, especially in medical research should evaluate in terms of the structure of missingness.This study aims to provide new statistical methods for analyzing such data.

Methods: Multiple imputation (MI) and inverse-probability weighting (IPW)aretwo common methods whichused to deal with missing data. MI method is more effectiveand complexthan IPW.MI requires a model for the joint distribution of the missing data given the observed data.While IPW need only a model for the probability that a subject has fulldata .Inefficacy in each of these models may causeto serious bias if missingness in dataset is large .Anothermethod that combines these approaches to give a doubly robust estimator.In addition, using of these methodswill demonstrate in the clinical trial data related to postpartum bleeding.

Results: In this article, we examine the performance of IPW/MI relative to MI and IPW alone in terms of bias and efficiency.According to the results of simulation can be said that that IPW/MI have advantages over alternatives.Also results of real data showed that,results of MI/MI doesnot differ with the results of IPW/MIsignificantly.

Conclusion: Problem of missing data are in many studies that causes bias and decreasing efficacy inmodel.In this study, after comparing the results of these techniques,it was concludedthat IPW/MI method has better performance than other methods.

Introduction:

In most medical studies, any individual or unit may tests under the initial measurement and repeated measures over time. In such studies, incomplete data, or so-called missing data is inevitable.Such data create challenges in analysis and modeling (1). When there is missing in data, so piece of information lost, thus the accuracy of estimates reduce. This decrease in accuracy can directly be related to the missing data or methods that are used to analyze these data, but more fundamental problem that can cause due to missing data is the bias in the estimates. It can lead to inaccurate and unreal conclusions. Assigning appropriate values for missing data is one of the challenges in data preprocessing in many areas (2).In recent years, many methods have been proposed to overcome these problems. However, unfortunately, for reasons such as lack of knowledge, many researchers have used primitive methods. While using these methods in many cases, because of the bias that enter into question may decrease data quality. It could be considered four categories of strategies to deal with missing data. The first and easiest strategy, including the removal of units with incomplete data and performing statistical analysis relied on data that were

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available at all times measurement. Unfortunately, the method of complete-case analysis(CC) is very common among researchers because of its simplicity. In most cases, it may lead to biased results. Other strategies include imputation, weighting methods and methods based on the likelihood function. In general, all of the above methods do imputation of missing values with specific amounts, except that in the first method, imputation of missing values do clearly and directly, but in the other two methods do indirectly. Purpose of imputation is placement reasonable values rather than missing values. Conditional on making different assumptions about the pattern of missing data mechanism, theused method will be different (3-4). The statistical activities conducted in the introducing and studying the advantages and disadvantages of each of the above strategies is very wide.Also It is clear that simple analysis of available data cause bias in the estimation of parameters, but the exact impact of incomplete datadepend on the number of missing values, as well as the correlation between response variables and independent variables and indicators is missing data(5). Several factors can affect accessing on response or covariates or both of themat different times to be missing. Inverse Probability Weighted (IPW) method is an appropriate method to handle this (6). Under completely at random mechanism(MCAR), analysis based on Generalized Estimating Equations(GEE) provide consistent estimates of regression parameters,but if the data missingnessshow mechanism at random (MAR) or not random,so analysis based on GEE give incompatible estimates of regression parameters(7). Rubin and Rotnizki introduced group of inverse probability weighted generalized estimating equations (IPWGEE)that gives consistent estimates when missingness is at random. In this method, weights are derived from missingness models, these models should properly be determined to achieve consistent estimates (8). Two alternatives are inverse-probability weighting (IPW) and multiple imputation (MI). In IPW method, only complete cases are accounted for the analysis, but to rebalance the complete cases, weights are used. This method can also usein a study to adjust for various sampling fractions. In MI method, data drawn from an imputation modelare replaced with missing data. In general, despite the complexity of MI method is more efficient than IPW, so that IPW method is just need a probability model, the imputation model must describe the joint distribution of all missing data, on condition of observed data. The analyst may be nervous about relying on this possibly complex and misspecified imputation model, because, each of these models, if missingness is high, it may cause significant bias. They are sampling weights that rebalance thesample to make it representative of the population. According to the above contents, focus of this paper is to review and compare combination of MI and IPW methods using a simulation study.As well as to demonstrate the use of these methods, analyze the data from a clinical trialabout hemorrhage after vaginal delivery.

Method:

IPWGEE method:

GEEmethod was presented for the first time by Liang and ziger as a way to analyze longitudinal data. Robins et al, did bias adjustment, resulting from unanswered units by weighting the method of Liang and Ziger,in which weight for each unit can be considered as a diagonal matrix(9). Also, Fitzmuris et al, have presented another type of weighting for generalized estimating equations of Liang and Ziger, which the weight for each unit was considered only as a number (10). When missingness is MAR, methods based on full vectors or standard GEE method give bias estimates of mean. In contrast, methods based on likelihood that determines the full joint distribution of responses accurately, give valid estimates. Of course, there is one important condition, that the full joint distribution must be properly specified. In practice, this means that not only mean response model must identify correctly, the model of intrapersonal communication should be select properly. In summary, when missingness is MAR, any wrong inference about mean is very sensitive in determining joint distribution of response vector(10,11).Standard GEE method need a model for the average of observations conditional on predictor variables. In MAR, this model does not hold for the observed data generally, so credibility of analysis is compromised. Using a simple weighted GEE method to modify the analysis is needed in which weights are estimated using a model for missingness probability, therefore, the missingness model must accurately identify and estimate (8,12).

Multiple Imputation

MI has become an important and influential approach for dealing with statistical analysis of incomplete data. During this recently period, the range of application of MI has spread from sample surveys to include many diverse areas such as the analysis of observational data from public health research and clinical trials. Although we are mainly concerned here with the analysis of incomplete longitudinal data, we provide first, an introduction to the method in its generic form.MIis now a well-established technique for analyzing data sets wheresome units have incomplete observations. Provided that the imputation model is correct, the resulting estimates are consistent.

MI is now a well-established technique for analyzing data sets where some units have incomplete observations. Provided that the imputation model is correct, theresulting estimates are consistent.

Suppose that we are faced with a conventional estimation problem for a statistical modelwitha $(p \times 1)$-dimensional parameter vectorβ, if no data were missing (the complete data), a consistent estimator of β is obtained as the solution to the estimating equation. In MI method,missing data are replaced by data obtained from the imputation model. This operation repeats M times. As a result, M complete data set produce. Each of these collections analyze separately and provide an estimate of the model parameters (θ). If $\widehat{\theta}$ is an estimator of the complete data set and$\widehat{V}$ is the estimated variance, then $\widehat{\theta}_{(\mathrm{m})}$ and $\widehat{V}_{(\mathrm{m})}$ are estimated parameters from the mth imputed data sets (m = 1, . . . , M).Rubin introduced estimatedθ with $\widehat{\theta}_{\mathrm{M}}$ and $\mathrm{var}(\widehat{\theta}_{\mathrm{M}})$ with$\widehat{V}_{M}$,in which:

$$\widehat{\theta}_{\mathrm{M}} = \frac{1}{M}\sum_{m=1}^{M}\widehat{\theta}_{\mathrm{M}}$$

$$\widehat{V}_{M} = \frac{1}{M}\sum_{m=1}^{M}\widehat{V}_{(\mathrm{m})} + (1+\mathrm{M}^{-1})(\mathrm{M}-1)^{-1}\times\sum_{m=1}^{M}(\widehat{\theta}_{(\mathrm{m})} - \widehat{\theta}_{\mathrm{M}})(\widehat{\theta}_{(\mathrm{m})} - \widehat{\theta}_{\mathrm{M}})^{T}$$

To obtain parameter estimates in this method, Rubin merger ruleswere used. A single estimate for regression parameter estimates obtain by averaging from m obtained estimates. Standard error obtains by combining between variance and within-imputation variance.To calculate covariance of regression coefficients, the related formula is used.The formula for calculating the estimated regression coefficients is:

$$\hat{\beta} = \overline{\beta} = \frac{1}{m}\sum_{k=1}^{m}\hat{\beta}^{(k)}$$

The formula for calculating regression covariance:

$$\frac{1}{m}\sum_{k=1}^{m}\widehat{\mathrm{cov}}(\hat{\mathrm{B}}^{k})+(1+\frac{1}{m})\frac{1}{m-1}\sum_{k=1}^{m}(\hat{\mathrm{B}}^{k}-\bar{B})(\hat{\mathrm{B}}^{k}-\bar{B})'$$

MI is usually more efficient and so it is preferred to IPW. MI should work well, if the imputation model is correctly specified. But, if many data are being imputed, any inadequaciesin the imputation model may lead to substantial bias.If few variables are missing on a case, it may be favoriteto impute them, rather than exclude them.Whereas, if many variables are missing onthe same case, the imputation model should be thejoint distribution of all these variables, and if many individualshave many missing variables, the possibly of misspecified imputation model maybe nervous for analyst. This situation could arise, for example, ina longitudinal study when whole blocks of data are missingonsome of the individuals due to missed visits, or in a surveywhen some individuals have declined to answer whole setsof related questions. In such situations, the analyst may feel more confident using IPW.

Simulation study:

In this section, we explore IPW/MI for linear regression with imputed outcome. The analysis model is fitted only to individuals with complete X and missing Y.

Simulation Model:

Analysis model have been fitted only for full covariates and response variables will be impute in persons. Analysis of the sample must deal with two stages of missingness:

Stage1: missingness in X and Stage2: missingness in Y.

At stage 1, one could either exclude individuals with incomplete X or impute missing X. Similarly, each individual with missing Y not already excluded at stage 1 could either be excluded at stage 2 or have Y imputed. At each stage, if exclusion is used, one can either adjust for the exclusion using IPW or not adjust. Thus, there are three possibilities at each stage, giving 3 × 3 = 9 possible strategies in total. Denote a strategy by ST1/ST2, where ST1 and ST2 are each CC (exclude and do not weight), IPW (exclude and weight) or MI (impute). In IPW/MI, the focus of this article, individuals with missing X are excluded and weights used to adjust for this; individuals with complete X but missing Y have Y imputed.CC/CC uses only individuals with complete X and Y and there is no weighting. IPW/IPW uses the same individuals, but weights them by the inverse of their probability of being a complete case. In MI/MI, all missing values are imputed. We also consider CC/IPW, CC/MI, and IPW/CC, but not MI/CC or MI/IPW, which combine disadvantage of specifyingan imputation model for X with losing out the potential efficiency of imputing Y.

Production of data:

The purpose of the following simulation is three-fold: to verify $\hat{V}$ is approximately unbiased for IPW/MI; to show IPW/MI can be more efficient than IPW/IPW; and to show MI/MI can yield biased parameter estimators when the stage1 (for X) or stage 2 (for Y given X) imputation model is misspecified and that IPW/MI remains approximately unbiased or at least less biased than MI/MI in these situations. The data-generating mechanism has been chosen to illustrate these points. It will now be described and then its features elucidated.

Data $X=(x_1,x_2,x_3,x_4,x_5)$ and Y were generated for N = 1000 individuals. For each individual, X1 was one with probability 0.5 and zero otherwise, X_2, X_3, and X_4 were independent and identically distributed N(0,1) and finally, X5 was sampled $N(x_2\times x_3,1)$. Response Y was generated from:

$$Y = -3 + x_1 x_2 + x_1 x_3 + 0.5\, x_2 x_3 + x_4 + 0.5\, x_5 + \varepsilon \quad \varepsilon \sim N(0,1) \quad (1)$$

X1 was observed for all N individuals.With probability $0/8 - 0/6\, x_1$, (X_2, X_3, X_4, X_5)was observed;otherwise it was missing. If (x_2, x_3, x_4, x_5) was observed, Y was observed with probability $\{1 + \exp(-1.5 + 0.6\, x_2 x_4)\}^{-1}$; otherwise Y was missing. The analysis model was $Y = \theta_0 + \theta_2\, x_2 + \theta_3\, x_3 + \theta_{23}\, x_2 x_3 + e$, where $E(e \mid x_2, x_3) = 0$. Therefore, $Z = (1, x_2, x_3, x_2 x_3)$. By integrating (7) with respect to x_1, x_4, x_5, it can be shown that this analysis model is correctly specified and the trueθ is $(\theta_0, \theta_2, \theta_3, \theta_{23}) = (-3, 0.5, 0.5, 1)$.

This data-generating mechanism was chosen for three reasons. First, the $x_1 x_3$ and $x_1 x_2$ interactions in (1) mean the relation between Y and $(x_2 x_3)$ is different in the two strata defined by X_1. Also, the probability that (X_2, X_3) is observed differs: in one stratum it is 0.2; in the other, 0.8. Thus, the relation between Y and (X_2, X_3) is different in individuals with complete X and incomplete X. Failure to adjust for the missingness at stage 1, by weighting or imputation, will therefore lead to bias in θ_2, θ_3. Therefore, CC/IPW, CC/MI, and CC/CC will be biased.

Second, for individuals with observed (x_2, x_3, x_4, x_5) the probability Y is observed depends on X_4, which is not in the analysis model but is associated with*Y*. This causes the relation between Y and X described by the analysis model to be different in the set of complete cases from in the set with complete X but missing Y. In particular, because the probability of Y being missing depends on X_2,X_4, the relation between Y and X_2 will be different in the two sets. Failure to adjust for the missingness at stage 2 will therefore lead to bias (specifically in θ_2). Therefore, IPW/CC, MI/CC, and CC/CC will be biased.

Third, X_5 is included in the data-generating mechanism for Y to show that using MI at stage 1 can cause bias if the imputation model for X is misspecified (see results for MI*/MI in table1). A total of 1000 datasets were generated and the seven methods applied to each. For each of $(\theta_0, \theta_2, \theta_3, \theta_{23})$ and each method, the mean of the 1000 parameter estimates and 1000 estimated variances was calculated. The empirical SE was calculated as the standard deviation of the parameter estimates where a method involved imputation, 10 imputations were performed.

Data analysis using a combination method of multiple imputations:

For MI/MI, the (correctly specified) imputation model at stage 1 was:

$$(X_2, X_3, X_4) \sim N\{(\gamma_2, \gamma_3, \gamma_4), \Sigma_1\} \text{ and } X_5 \mid X_2, X_3 \sim N(\gamma_5 + \gamma_6 X_2 + \gamma_7 X_3 + \gamma_8\, x_2 x_3, \Sigma_2)$$

Non-informative normal and inverse-Wishart priors were used, yielding normal and inverse-Wishart posteriors. For CC/MI, IPW/MI, and MI/MI, the (correctly specified) imputation model used at stage 2 was:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{123} X_1 X_2 X_3 + \varepsilon$$

Data analysis using a combination method inverse probability weighting:

For IPW.CC, IPW.IPW, and IPW/MI, weights were estimated by fitting the (correctly specified) missingness model for stage 1. Note that, because X_1 is binary,

$W = (\delta_0 + \delta_1 X_1)^{-1} = \delta_0^{-1} - \delta_1 X_1 \{\delta_0(\delta_0 + \delta_1)\}^{-1}$ is a linear function of X_1, hence, as the stage 2 imputation model includes $X_1 Z, Z$, it implicitly includes WZ. For CC/IPW and IPW/IPW, weights were estimated using the (correctly specified) model.

For stage 2:

$$\log itP(\text{Yobserved} \mid \text{Xobserved}) = \delta_2 + \delta_3 X_2 + \delta_4 X_4 + \delta_5 X_2 X_4$$

For IPW/IPW, the probability of being a complete case is the product of these two probabilities. Table1 shows mean parameter estimates, empirical SEsand square roots of the mean estimated variances. It canbeseen that IPW/MI yields approximately unbiased estimatorsof parameters and SEs.

Results:

Comparative analysis of the above combination methods:

As explained above, CC/IPW, CC/MI, CC/CC, and IPW/CC are biased for one or more parameters. IPW/IPW and MI/MI are both approximately unbiased. The former is less efficient than IPW/MI because the imputation model at stage 2 uses auxiliary information, i.e. covariates (notably (X_4, X_5))not included in the analysis model. The most efficient unbiased method is MI/MI, confirming that imputation is the best method when the imputation models are correct. However, when the imputation model at stage 1 or stage2 is misspecified, MI/MI may be biased, as half the individuals have incomplete X, fitting the analysis model to the whole sample results in an estimate of θ_{23} is about 0.75 in the row MI*/MI(Table 1).The row IPW/MI* shows the result of IPW/MI with the same misspecified imputation model at stage 2. This method is considerably less biased than MI/MI*, because fewer Y values are being imputed. Therefore, the IPW element of IPW/MI provides some protection against misspecification of the imputation model. Many statistical software have packages and procedures for analyzing missing data. In this paper we have used software R version 3.1.0 and SAS.

Table1 . Mean parameter estimate ("mean"), square root of mean estimated variance ("aSE"), and empirical SE("eSE") for fourparameters and 10 analysis methods. The true value of θ is (θ_0, θ_2, θ_3, θ_{23}) = (−3, 0.5, 0.5, 1).

Method	θ_0			θ_2			θ_3			θ_{23}		
	Mean	aSE	eSE	Mean	aSE	eSE	Mean	aSE	eSE	Mean	aSE	eSE
True	-3.00			0.5			0.5			1.00		
CC/CC	-2.895	0.08	0.079	0.089	0.078	0.087	0.2	0.08	0.087	1.005	0.082	0.091
CC/IPW	-2.893	0.082	0.079	0.196	0.089	0.091	0.20	0.086	0.196	1.004	0.096	0.107
CC/MI	-2.894	0.075	0.075	0.201	0.081	0.083	0.203	0.079	0.083	1.004	0.084	0.086
IPW/CC	-2.893	0.102	0.104	0.387	0.011	0.111	0.495	0.109	0.114	1.007	0.113	0.119
IPW/IPW	-2.891	0.106	0.108	.487	0.118	0.122	0.493	0.112	0.116	1.006	0.121	0.132
IPW/MI	-2.892	0.097	0.094	0.493	0.103	0.103	0.498	0.108	0.107	1.008	0.109	0.112
MI/MI	-2.996	0.089	0.079	0.499	0.092	0.087	0.497	0.090	0.088	1.006	0.098	0.082
MI*/MI	-2.991	0.92	0.083	0.487	0.095	0.093	0.496	0.094	0.096	0.749	0.102	0.084
MI/MI*	-2.994	0.107	0.102	0.1	0.088	0.052	0.098	0.088	0.057	0.396	0.091	0.055
IPW/MI*	-2.993	0.106	0.101	0.487	0.119	0.121	0.495	0.117	0.115	0.776	0.132	0.127

MI*: misspecified imputation model

Real data analysis:

In this section, methods presented in the previous section was performed on real data and compared the obtained results. Mean of parameter estimates for imputed and full data under different conditions for simulated data is shown in table1. The actual data was related to a one blind clinical trial that carried out on 120 qualified mothers that had natural delivery in the birjandVali-Asr hospital. These individuals are selected randomly and were divided into 4 groups of 30(3 groups receiving grape seed powder (50, 100 and 150 mg) and control group (receiving placebo capsule inside it was filled with starch powder). Mother's bleeding calculated by weighting them and their pads, so that one gram increase in weight was taken equivalent to a cc blood. Persons in terms of cutting the volume of bleeding 500ml,were divided into two categories. Here we have used three method (CC / MI, IPW / MI, MI /MI) for data analysis so that missingness modeling IPW/MI at stage 1was considered as the probability that at least one of the predictor variables duration of delivery, units of oxytocin, maternal weight, perineal laceration, episiotomy is missing. For all individuals in different drug doses, complete data were not available and they had missingness. For second stage, the same model used for imputation. 25 imputation steps were done. MI model used only for variables in analyzed model. Table 2 shows the estimated log odds ratios (LOR) and SEs of the variables associated with bleeding after vaginal delivery. As can be seen, using IPW method in first stage (IPW/MI) does not change the results significantly. The biggest difference was in the OR of the units of oxytocin, maternal weight and perineal laceration. The first two methods had roughly smaller SEs. Finally, MI/MI method was used so that all missing values imputed; variables of analysis model and predictors entered in the missingness model of IPW/MI. 100 imputation datasets were generated,the results are shown in Table2. As can be seen, results of this method do not differ with the results of IPW/MI substantially. Only SE values were slightly smaller and a slight increase in LOR valuesofmaternal weight and units of oxytocin was seenin the IPW/MI compared to CC/MI. In fact, LOR of maternal weight in MI/MI is less compared to CC / MI.

Table 2: LOR and SEs for predictors related to the amount of bleeding after vaginal delivery

variables		MI.MI		IPW.MI		CC.MI	
		SE	LOR	SE	LOR	SE	LOR
maternal weight	Normal weight	0.12	0.18	0.16	0.36	0.15	0.29
	More than normal weight*						
Units of oxytocin		0.25	0.47	0.27	0.55	0.26	0.46
perineal laceration	have	0.17	0.39	0.18	0.44	0.17	0.37
	does not have*						
Duration of delivery		0.21	0.46	0.22	0.47	0.22	0.44
Episiotomy	done	0.02	0.03	0.02	0.02	0.02	0.04
	undone*						

*: Reference level

Discussion:

Particularly the problem of missing data in medical studies in recent years has been highly regarded,so that much literature has been published in this regard.This study compared the results of different approaches to find the best approach in dealing with missing data.Our goal in this study was conducted in order to compare the combination of multiple imputationandinverse weighted estimating equationmethod.On the other hand, this research combines approaches from complete data, multiple imputation and inverse probability weighting and compare these methods in data analysis.Table 1 showed the obtained results from given regression model to the data generated using these approaches; as can be seen, combination of approaches, showed different results in terms of the bias of parameter estimates. In general, the approach of complete data is not an appropriate way to solve the problem of missingdata,because it cause a substantial decrease in sample size and thus, efficiency of estimator.On the other hand, it may cause bias in the data(17-18).Robins and Wang derive a general formula for the asymptotic variance of MI estimator based on complete data estimator solving a set of estimating equations(9).Thisformula applies when improper imputation and a parametricimputation model are used. IPW/MI could be carried outin this way and Robins and Wang's variance formulaused. We used this to show that. In the case of linear regression with MI of a missing outcome, the Rubin's rules variance estimator forIPW/MI is consistent when M = ∞.However, both the asymptotic andfinite-sample biases were found to be small in this study.Schafer comments that"although we may find it difficult to prove good performancefor [MI using a nonmaximum likelihood estimator], that doesnot imply that good performance will not be seen in practice(19).Some researchers may prefer to use straightforward MI(what we called MI/MI). Provided that the imputation modelsare correctly specified, this will be more efficient thanIPW/MI. However, our simulations and real data example have shown that thosewho prefer IPW/MI have some justification for their caution.If the results of IPW/MI and MI/MI are very different,further exploration would be warranted, possibly leadingto refinement of the imputation model(20). IPW/MI will be most appealing when the model for theweights is relatively simple compared with the imputation model. This will not always be so. Also, a limitation of all IPWmethods is their difficulty in handling non monotone missingness in predictors of missingness model. Robins and Gill proposed a procedure for handling such missingness, but this is complicated to use and limited in practice for a small number of missing predictors(21,22).On the other hand, IPW/MI would allow a single set of weights to be used,as imputation could ensure that the set of complete cases werethe same for each analysis.

Conclusion:

The results of this study showed that IPW/MI will be most appealing when the model for the weights is relatively simple compared with the imputation model.On the other hand, given that missing values always will remain unobserved. All existing methods for analysis of missing data includes unidentifiable and non-provable assumptions,so it is better when deal with this data, does not rely on the results of one method solely and an appropriate sensitivity analyzes will need to do in this regard.

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