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Proper Use of Multiple Imputation and Dealing with Missing Covariate Data

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■ BACKGROUND: **Missing data is a typical problem in clinical studies, where the value of variables of interest is not measured or collected for some patients. This article aimed to review imputation approaches for missing values and their application in neurosurgery.**

■ METHODS: **We reviewed current practices on detecting missingness patterns and applications of multiple imputation approaches under different scenarios. Statistical considerations and importance of sensitivity analysis were explained. Various imputation methods were applied to a retrospective cohort.**

■ RESULTS: **For illustration purposes, a retrospective cohort of 609 patients harboring both ruptured and unruptured intracranial aneurysms and undergoing microsurgical clip reconstruction at Erasmus MC University Medical Center, Rotterdam, The Netherlands, between 2000 and 2019 was used. modified Rankin Scale score at 6 months was the clinical outcome, and potential predictors were age, sex, size of aneurysm, hypertension, smoking, World Federation of Neurosurgical Societies grade, and aneurysm location. Associations were investigated using different imputation approaches, and the results were compared and discussed.**

■ CONCLUSIONS: **Missing values should be treated carefully. Advantages and disadvantages of multiple imputation methods along with imputation in small and big data should be considered depending on the research question and specifics of the study.**

INTRODUCTION

Missing data is a common problem in many clinical studies in neurosurgery. In randomized controlled trials and other comparative studies, baseline covariates may be missing, which should be included in the statistical analysis. When developing a prediction model or evaluating a new biomarker or set of single nucleotide polymorphisms, some data may be missing as well.[1-3] This article addressed the question of how we may deal with such missing data.

The problem of missing data occurs when the value of a variable is not measured or collected for some individuals in the sample and that value would be meaningful for analysis if it were available. This problem is often unavoidable and could occur in any type of study, including randomized controlled trials, cohort studies, and case-control studies. Missing data could introduce bias and is often ignored by researchers.[2,4] Both the U.S. Food and Drug Administration and the European Medicines Agency recommend that statistical methods should account for missing data while reporting study results. Most clinical studies contain variables with missing values, which very likely influence the results.[1,5,6]

The risk of bias owing to missing data depends on different factors: 1) patients may refuse to answer specific questions; 2) patients may be lost to follow-up; 3) the investigator may not be

Key words
- Imputed data
- Missingness
- Neurosurgery
- Predictors

Abbreviations and Acronyms
MI: Multiple imputation
mRS: modified Rankin Scale
WFNS: World Federation of Neurosurgical Societies

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able to capture some data because of technical issues; 4) clinicians may not order some specific investigations for some patients. Studies have different proportions of missing values, and the cumulative effect of missingness of several covariates may result in a high missingness proportion. There is no reliable rule of thumb as to what missingness proportion may produce unreliable results.[7,8]

Different patterns for missing values, as addressed by Rubin,[3,9] include the following:

1. Missing completely at random: missing data values are a random subset of the study population—that is, the missingness does not depend on the values of any variables. An example of missing completely at random is where a laboratory result is missing for some individuals because the data were damaged or lost, which is less likely to depend on patients' characteristics.
2. Missing at random: probability of missingness is independent of unobserved data—that is, the missing values do not depend on the value itself but may depend on the observed value of the other variables. For example, missing laboratory results may be due to not ordering laboratory tests for older patients by the clinician (i.e., the missing laboratory values depend on age variable as an observed variable).
3. Missing not at random: data are neither missing completely at random nor missing at random. Hence the probability of missingness depends on unobserved data. For example, data on weight might be missing, as overweight or underweight individuals might be more likely to have their weight measured compared with individuals within normal range.[1,3,5,9-12]

Most researchers include only subjects with full data—that is, subjects without missing values in the analysis (complete case analysis).[4,13] Though this method seems to be very convenient, it often produces underpowered and potentially biased results. This also happens even when researchers do not mean to perform complete case analysis but choose to run regression analyses on statistical software. Without imputation, these techniques automatically assume complete case analysis.

An alternative method dealing with missing values is to replace the missing values with plausible values, called imputation. Mean value imputation is a common approach where the missing values are replaced by the mean value. A better method might be conditional mean imputation, where a regression model is used to replace the missing values of a continuous variable with expected values conditional on the observed values. Single imputation (mean value imputation and conditional mean imputation) methods perform the imputation with certainty, as the missing values are imputed using equal weights of the other observed variables. Multiple imputation (MI), on the other hand, incorporates some uncertainty about the true value of the imputed variables.[3,5,11,14,15]

Imputation methods can address uncertainty owing to missing values, where such missingness could potentially bias study results. This article aimed to provide a brief introduction to imputation approaches for missing values and their application in neurosurgery.

MATERIALS AND METHODS

Complete-Case Analysis and Single Imputation

In complete case (or listwise deletion) analysis, the study includes only individuals with complete data in the statistical analysis. The assumption is that individuals with missing data are a random sample of the study population. Given this assumption is valid, the results of complete case analysis would be accurate on average (point estimation), though the confidence intervals are expected to be wider. Different covariates may have different proportions of missing values, and the statistical power may be significantly reduced using complete case analysis. Hence complete case analysis may be a less efficient method, as observed information can be disregarded.[5,7,16]

Single imputation methods, where missing values are imputed using the mean value of the observed data or the expected value using regression models, are alternative approaches to handle missing data. Single imputation does not provide uncertainty for imputed values, as only one single value is imputed. Performing single imputation would potentially increase the sample size and decrease the variability, resulting in underestimated standard errors, which overstates precision, as they treat imputed values as if they were true.[3,12,17,18]

Multiple Imputation

Rubin[3,9,19] developed an MI framework to account for uncertainty and to preserve important data relationships. MI creates multiple plausible values for missing data. Once the missing values are imputed, multiple imputed data sets will be analyzed separately, and the results of each will be combined into one single set of test statistics, parameter estimates, and standard errors. The aim of MI is to provide unbiased and valid statistical inference for both variables with and variables without missing data. Rubin[3,9,19] termed MI as a proper imputation model. The MI inference involves 3 major stages, as follows:

1. The missing data are imputed m times, and m complete data sets will be generated. At this stage, covariates (including variables for subsequent analysis) that can help to impute missing data are included. Depending on the missingness pattern and the imputed variable type (binary, categorical, continuous), missing data in each m data set are drawn from the distribution of missing data.
2. The m complete data sets are analyzed separately using standard statistical methods (the exact analysis that would be performed in the absence of missing data). Estimated associations will differ in each m data set. The statistics are then extracted from the analysis in each of the m imputed data sets.
3. The results from the m complete data sets are combined using Rubin's rule for inference. The pooled estimate of the statistic is the average of the estimated statistics across all the m data sets. Between-imputation variation and within-imputation uncertainty will be taken into account for the calculation of variance of the estimated statistic.

The different strategies for imputation methods are summarized in **Table 1**. MI is widely used as a standard approach to deal with

Table 1. Summary of Imputation Approaches for Missing Values and Their Assumptions

Method	Description	Assumptions	Advantages	Limitations
Complete case analysis (listwise deletion)	Individuals with complete data on all variables will be included	Individuals with missing data are a random sample of study population	Convenient	Underpowered owing to smaller sample size, lack of precision (wide confidence interval), nonresponse bias
Single imputation	Missing values are replaced by mean value or using expected values via regression models	Missing data are independent of values on all other measured covariates	Convenient	Nonresponse bias, overstate the precision (small standard error)
Multiple imputation	Missing values are imputed m times	MCAR, MAR, MNAR	Unbiased estimates, reliable standard errors, preserving sample size and statistical power	Time-consuming and requires statistical expertise

MCAR, missing completely at random; MAR, missing at random; MNAR, missing not at random.

missing data and has become more popular with software packages available including IBM SPSS (IBM Corporation, Armonk, New York, USA), Stata (StataCorp LLC, College Station, Texas, USA), SAS (SAS Institute Inc., Cary, North Carolina, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity Analysis

Sensitivity analysis is used to check the assumptions made for missing data mechanisms and to show how such assumptions influence the results. This is useful for verification of whether the missing at random assumption is valid in a specific case. The National Research Council of the National Academy of Sciences recommends that sensitivity analysis for such assumptions should be part of the primary statistical analysis in clinical trials. Sensitivity analysis should be prespecified in the statistical analysis plan; however, post hoc sensitivity analysis might be valid. Sensitivity analysis could involve the replacement of missing data with the worst or best values in the observed data (worst-case and best-case scenarios), and the aim is to check the robustness of results under a reasonable case scenario. These 2 scenarios could

Table 2. Descriptive Analysis of the Case Study

Variable	Complete Cases, Number (%)	Missing Cases, Number (%)	Mean ± SD/Frequency (%)
Outcome			
mRS score at 6 months	354 (68.5)	163 (31.5)	2.6 ± 2.1
0–2			214 (60.45)
3–6			140 (39.55)
Predictors			
Age, years	517 (100)	0 (0)	53.2 ± 12.6
Male sex	517 (100)	0 (0)	153 (29.6)
Aneurysm size, mm	499 (96.5)	18 (3.5)	7.3 ± 4.6
Hypertension	502 (97.1)	15 (2.9)	377 (75.1)
Smoking	366 (70.8)	151 (29.2)	224 (61.2)
WFNS grade (pre-op)	435 (84.1)	82 (15.9)	2.4 ± 1.7
Location	517 (100)	0 (0)	
ACA			40 (7.7)
ACOM			160 (31)
Paraclinoid ICA			35 (6.8)
MCA			214 (41.4)
PC			68 (13.2)

mRS, modified Rankin Scale; WFNS, World Federation of Neurosurgical Societies; pre-op, preoperative; ACA, anterior cerebral artery; ACOM, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; PC, posterior circulation.

Table 3. Association Analysis Using Different Imputation Methods: Case Study

Variable	Complete Case	Single Imputation 1*	Single Imputation 2†	Single Imputation 3‡	Multiple Imputation 1*	Multiple Imputation 2†	Multiple Imputation 3‡
Age, years	0.98 (0.95—1.01)	0.98 (0.96—1.00)	0.98 (0.96—1.00)	0.98 (0.97—0.998)§	0.98 (0.96—1.00)	0.98 (0.96—1.00)	0.98 (0.96—1.00)
Male sex	0.72 (0.34—1.56)	1.22 (0.69—2.18)	1.22 (0.68—2.18)	0.96 (0.64—1.44)	1.16 (0.64—2.14)	1.24 (0.67—2.29)	1.23 (0.57—2.65)
Aneurysm size, mm	1.03 (0.95—1.13)	1.01 (0.95—1.07)	1.01 (0.95—1.07)	1.01 (0.96—1.05)	1.02 (0.96—1.08)	1.03 (0.97—1.09)	1.02 (0.96—1.09)
Hypertension	0.38 (0.16—0.90)§	0.61 (0.32—1.15)	0.60 (0.31—1.14)	0.85 (0.55—1.32)	0.57 (0.29—1.12)	0.57 (0.29—1.13)	0.65 (0.31—1.36)
Smoking	0.71 (0.34—1.48)	0.50 (0.27—0.91)§	0.50 (0.27—0.91)§	0.66 (0.44—0.997)§	0.67 (0.33—1.37)	0.63 (0.32—1.22)	0.63 (0.36—1.08)
WFNS grade (pre-op)	0.57 (0.45—0.74)§	0.50 (0.41—0.60)§	0.49 (0.41—0.60)§	0.72 (0.62—0.83)§	0.49 (0.39—0.60)§	0.48 (0.39—0.58)§	0.48 (0.39—0.58)§
Location‖							
ACA	1.10 (0.27—4.39)	1.02 (0.36—2.93)	1.01 (0.35—2.90)	1.45 (0.64—3.28)	1.04 (0.34—3.24)	1.00 (0.32—3.08)	1.10 (0.31—3.87)
ACOM	1.97 (0.62—6.22)	0.95 (0.41—2.20)	0.97 (0.42—2.23)	0.88 (0.48—1.60)	0.97 (0.40—2.31)	0.92 (0.38—2.21)	0.96 (0.35—2.63)
Paraclinoid ICA	0.57 (0.12—2.76)	0.46 (0.14—1.50)	0.45 (0.14—1.50)	0.70 (0.29—1.71)	0.52 (0.15—1.75)	0.48 (0.14—1.67)	0.48 (0.13—1.79)
MCA	1.99 (0.68—5.78)	1.23 (0.56—2.68)	1.25 (0.57—2.75)	1.05 (0.59—1.87)	1.34 (0.58—3.11)	1.29 (0.55—3.06)	1.30 (0.53—3.21)

Values are reported as odds ratio (95% confidence interval).
WFNS, World Federation of Neurosurgical Societies; pre-op, preoperative; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; ICA, internal carotid artery.
*Missing values of the outcome variable are excluded at the imputation stage; outcome variable is used in the imputation stage.
†Missing values of the outcome variable are excluded at the analysis stage; outcome variable is used in the imputation stage.
‡Missing values of the outcome variable are imputed and included at the analysis stage.
§Significant at $P < 0.05$.
‖Reference is posterior circulation.

Table 4. Relative Efficiency of Using Different Number of Imputations for Various Proportion of Missing Values

	Proportion of Missing Values				
Number of Imputations	**10%**	**20%**	**30%**	**50%**	**70%**
3	0.9677	0.9375	0.9091	0.8571	0.8108
5	0.9804	0.9615	0.9434	0.9091	0.8772
10	0.9901	0.9804	0.9709	0.9524	0.9346
20	0.9950	0.9901	0.9852	0.9756	0.9662

show the full theoretical range of uncertainty, and it is recommended that such sensitivity analysis via best-case and worst-case scenarios should be performed separately. The results of the regression models could be compared, and the inference about the missing data influence should be discussed with caution.[5,7,10,15]

As there are several appropriate methods to handle missing data, sensitivity analysis should be performed comparing results of the analysis based on the methods of handling missing data. This is even more important when the missingness proportion is large.[8,20]

RESULTS

For illustration purposes, we used a recently published data set of 609 patients harboring both ruptured and unruptured intracranial aneurysms and undergoing microsurgical clip reconstruction at the Erasmus MC University Medical Center, Rotterdam, The Netherlands, between 2000 and 2019. The full baseline characteristics of the data set are available in our previous publication.[21]

All patients presenting with either a subarachnoid hemorrhage or an unruptured aneurysm that was deemed eligible for treatment in a neurovascular multidisciplinary meeting were included in the study. The outcome, the modified Rankin Scale (mRS) score, was assessed at 6 months. Because of the partially prospective, partially retrospective nature of the data, mRS score at last follow-up was available for a majority of patients, but mRS score at 6 months was available only for 411 patients, which were included in this analysis. We used predefined covariates known to be associated with outcomes in the analysis: age, sex, size of the aneurysm, hypertension, smoking, World Federation of Neurosurgical Societies (WFNS) grade, and aneurysm location. Because of the underpowered group of patients with an unruptured aneurysm, we chose to focus on the patients presenting with a subarachnoid hemorrhage.

Descriptive statistics and the proportion of missing values are reported in Table 2. Of 517 patients with a subarachnoid hemorrhage, mRS score at 6 months was reported in 354 patients resulting in 31.5% missing values in the outcome variable. Among the predictor variables, smoking status (29.2%) and WFNS grade (15.9%) had the highest proportion of missing values, followed by aneurysm size (3.5%) and hypertension (2.9%). Age, sex, and location variables were reported for all patients.

The complete case method was performed as the baseline model. Mean imputation and MI methods were conducted under the following different scenarios:

1. Patients with missing outcome were excluded in the imputation stage.
2. Patients with missing outcome were included in the imputation stage but excluded in the analysis stage (this is also known as imputation, then deletion).
3. Patients with missing outcome were included in both imputation and analysis stages.

Outcome variable was always used in the imputation stage. The number of imputations necessary is usually 10. We performed the exact analysis using 20 imputations, and the results were comparable with the results of 10 imputations.

Multivariable logistic regression analysis was performed to investigate the association of baseline characteristics and the mRS score at 6 months (0–2 vs. 3–6) using the different imputation methods described above (Table 3). Under the complete case method, the sample size in the analysis was substantially reduced ($n = 197$); effect sizes were different from other models, and hypertension was significant. Such biased estimates can potentially confirm the weak performance of the complete case method in this example, which confirmed that the missingness pattern is not missing completely at random.

In the single imputation approach, missing values were replaced with the mean and mode values for the continuous and categorical variables, respectively. Age, smoking status, and WFNS grade were found to be significantly associated with mRS score at 6 months. The parameter estimates of single imputation scenarios 1 and 2 were comparable (where the analysis was based on $n = 354$); however, they were slightly different from single imputation 3 (where the analysis was based on $n = 517$). Mean imputation would reduce the variability in the data and could potentially change the effect sizes (this is the case when comparing the parameter estimates of the single imputation method with MI results).

Under MI, a fully conditional method was used, as different specifications are required for the variables with missing values. Significant and nonsignificant variables were slightly different compared with the single imputation method. WFNS grade was significantly associated with the outcome in all 3 MI methods, and age was a significant variable under the first MI and second MI methods. Although MI is always superior to any single imputation method, different specifications should be checked while performing MI. If different specifications produce similar estimates, the conclusion about missing data is straightforward. Otherwise, the results might be difficult to interpret, and performing sensitivity analysis (worst-case and best-case scenario) could help with interpretations.[3,22,23]

DISCUSSION

Advantages and Disadvantages

Using MI, complete data can be used for statistical analysis, which results in preserving sample size and statistical power. As MI includes random error, there is random variation in imputed data sets, which helps researchers create unbiased estimates. MI can produce more reasonable standard errors compared with single imputation approaches because repeated estimates are used. Owing to minimized standard errors, MI increases efficacy of the estimates. MI approaches can account for uncertainty owing to missing data, preserve important data relationships, and be applied on different models.[3,9,11,17,19,24]

Three main disadvantages of MI are 1) more effort needed to perform MI and create multiple imputed data sets, 2) more time to conduct the analysis on each imputed data set and combine them, and 3) more computer storage needed for imputed data files. MI is more tedious to perform compared with single imputation, both at imputation stage and when pooling the results. However, the other 2 disadvantages might not be an issue anymore owing to the large capacity of hard disks and available software packages.[3,6,9,11,19,25]

Imputation in Small versus Big Data

Over the last 2 decades, the big data era has led to increased data availability. Missing values in big data is a challenge, as the large sample size may be dramatically reduced if complete case analysis is applied. The other issue with big data is the complex dependency structure among a large number of variables, which makes it difficult to investigate the missingness mechanism. For example, in a multiple-site big data study, if some sites do not collect some variables, imputing such missing data using the observed data from other sites may lead to biased results. Multicollinearity among all the variables is another issue in the imputation stage. There have been arguments about MI performance on big data, and one should note these points before using MI methods.[26]

On the other hand, small data (small number of observations) may have some computational issues, as MI needs to be run repeatedly, and more runs are needed with high proportion of missing data. Similar computational issues may also arise with a very large number of variables in a small sample size study with high proportion of missingness. In such situations, it would be helpful to perform complete case analysis and compare the results with MI results to see how conclusions differ.[19,24,27]

Statistical Considerations and Pitfalls

The number of required imputations is discussed in the literature. While some authors recommended 3–5 or 5–10 imputed data sets, others suggested the number should equal the percent of the variable with most missingness. As a rule of thumb to increase the reproducibility of research findings, the number of imputation sets should be as large as the missingness proportion. In our example, smoking status indicated the highest percent missingness (approximately ≥20%), which implied that 20 imputations might be advised. However, standard errors along with the parameter estimates should also be estimated accurately. Von Hippel[24] discussed a more advanced method for the number of imputations. As computation may not be an issue with statistical software nowadays, it is not uncommon to come across studies with 20–100 imputation data sets. Rubin and other authors[3,14,19,27] discussed the relative efficiency of different numbers of required imputations by different proportions of missingness (Table 4).

Another common question is: which variables should be included in the imputation? It should be noted that all variables included in the statistical analysis should be included in the imputation stage (congeniality). This also applies to interaction terms among the covariates used in the data analysis, variables correlated with missingness and variables correlated with missing values and the outcome variable. However, the aim is not to impute missing outcomes, but to use the outcome information to impute missing data in the covariates. In the MI, then deletion method recommended by Von Hippel,[24] the strategy is as follows: first, all observations are included in the imputation stage; then, all the subjects with imputed outcome values will be excluded when the analysis is fit at each of the imputed data sets. MI, then deletion tends to be more efficient compared with the scenario where the models are fit on all subjects.[5,11,17,19,24,28,29]

Including nonnormally distributed covariates (e.g., skewed distributions) into the MI method may introduce bias. Most MI algorithms assume that the data are normally distributed, and some ignore this underlying assumption. The recommendation for this issue is to transform such variables to approximate normality before the imputation stage and back-transform them to the original scale after they are imputed.[15]

Optimize the Study Design to Prevent Missing Data

The ideal solution to deal with missing values is to prevent them at the planning stage of the study. Multiple strategies can be added to the design to minimize the occurrence of missing data. Strengthening data collection, data retrieval after patient dropouts, collecting outcome data after patients' withdrawal (if possible), and telephone follow-up to collect additional information (if applicable) are some examples of strategies to avoid the presence of missing data. When designing a study, the researcher should have some ideas about the expected proportion of missing values (using exploratory trials or clinical experience) and the type of missingness. This will help the researcher to prespecify methods for handling missing data along with a reasonable range of sensitivity analysis, which could help verify results of the imputation approach. For example, the mean imputation approach could be preplanned in the design of randomized clinical trials, while MI methods are the most beneficial for observational studies.[5,12,15,20,28,30-32]

CONCLUSIONS

This article reviewed imputation approaches for missing values and discussed their application in neurosurgery. The importance of sensitivity analysis and statistical considerations were explained. For illustration purposes, different imputation approaches were performed to investigate the association of baseline characteristics and the mRS score at 6 months, and the results were compared and discussed. Depending on the research question and study settings, pros and cons of MI methods in small and big data were explained.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Seyed Ehsan Saffari: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Victor Volovici:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Marcus Eng Hock Ong:** Investigation, Methodology, Validation, Writing – review & editing. **Benjamin Alan Goldstein:** Investigation, Methodology, Validation, Writing – review & editing. **Roger Vaughan:** Investigation, Methodology, Validation, Writing – review & editing. **Ruben Dammers:** Data curation, Investigation, Methodology, Validation, Writing – review & editing. **Ewout W. Steyerberg:** Investigation, Methodology, Validation, Writing – review & editing. **Nan Liu:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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