Missing Data in Ambulatory Blood Pressure Monitoring (ABPM) Studies

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This poster reflects the views of the authors and should not be construed to FDA's views of policies.

Abstract

Ambulatory blood pressure monitoring (ABPM) study is recommended as an important safety study in the 2022 Assessment of Pressor Effects of Drugs Guidance for Industry. To facilitate both regulatory and industry in successfully implement this guidance, we studied missing data issues in ABPM studies and recommended appropriate statistical methods through our 2024 ORISE project. Four statistical methods: multiple imputation (MI), inverse probability weighting (IPW), augmented inverse probability weighting (AIPW), and a combined MI and IPW method (MIIPW) were evaluated in the project through real data and simulated data with missing data proportions ranging from 10% to 50% under two missing mechanisms:1) missing completely at random (MCAR), missing at random(MAR). Performance metrics, including percentage bias, standard error, false negative rate, and coverage rate, were assessed. MI and IPW were more sensitive missing data with increased percentage bias as missing rate increased. AIPW and MIIPW controlled bias more effectively at lower missing data rates but still exhibited increased bias as missing data proportions increased. MI and MIIPW showed less variability compared to IPW and AIPW. While performance of those four methods were similar at lower missing rates (<30%), IPW and AIPW outperformed the others at higher missing rates (>30%). AIPW demonstrated a double-robust property, maintaining performance even when statistical model was mis-specified. The project provides important insights for statistical analysis of missing data in ABPM studies. Statistical methods like AIPW, especially in scenarios with high missing data rates, can be appropriate method for analyzing missing data in ABPM studies.

Introduction

The assessment of blood pressure (BP) effects can be suboptimal in drug development programs, and consequently the long-term effects of small, sustained increases in BP caused by chronically used drugs can go unnoticed.

The US Food and Drug Administration (FDA) issued draft guidance in 2018 for premarketing assessment of the pressor effects of drugs. The ambulatory blood pressure monitoring (ABPM) study is the preferred method to obtain precise estimates of BP measurements in the targeted patient population. Small increases in BP are less of a concern for drugs that are intended to be used short-term; therefore, BP assessment is focused on detecting larger increases using careful assessments of cuff sphygmomanometry measurements at study visits in clinical trials.

The revised Assessment of Pressor Effects of Drugs Guidance released in 2022 have made significant changes. ABPM study is recommended as an important safety study in this guidance. Many sponsors have submitted new study designs following the guidance. There has been empirical research in this area, but almost all of them lack statistical rigors.

This project seeks to investigate 1) missing data patterns in ABPM data collections; and 2) appropriate statistical methods in analyzing missing data in ABPM study.

Acknowledgement

We want to thank Drs. Yi Tsong and Atiar Rahman for their support for this project.

Methods

1. ANCOVA model is the primary analysis in the ABMP studies

The outcome Y is CHG (Change from Baseline in 24 Hour mean) and covariates include BASE (24H Hour of Baseline) and AGEGR1 (Age Group).

Denote Y_i and $\boldsymbol{X}_i$ denote the values of Y and **X** for individual $i = 1,2,\dots,n$. R_i indicates the missing of Y_i. R_i=1 if Y_i observed, R_i=0 if Y_i missing. θ as the model parameters. θ is estimated as the value $\hat{\theta}$ that solves the score equations:

$$\sum_{i=1}^{n} U_i(\theta) = 0, \text{ where } U_i(\theta) = X_i(Y_i - \theta^T X_i).$$

Our **target parameter** $Y = c'\theta$ where c' is the given weights for each covariates.

2. Missing data mechanisms

(1) Missing Completely at Random (**MCAR**)

The probability of missingness is independent of the data.

$$P(R=1|\mathbf{X},Y) = P(R=1)$$

(2) Missing at Random (**MAR**)

The probability of missingness depends on the set of observed responses but are unrelated to the specific missing values.

$$P(R=1|\mathbf{X},Y) = P(R=1|\mathbf{X})$$

3. Statistical methods for missing Data

We compare four statistical methods: (a) Multiple imputation (**MI**);(b) Inverse probability weighting (**IPW**); (c) Augmented inverse probability weighting (**AIPW**); (d) Combined MI and IPW method (**MIIPW**).

Simulation

- The simulated data with n=100 to achieve 85% power.
- Overall treatment effect=3.
- The desired missing proportion $\pi = 10\%, 20\%, 30\%, 40\%, 50\%$.
- Covariate AGEGR1 is sampled from the proportional from the real data.

<45 Years	>64 Years	45-64 Years
9.02%	24.6%	66.4%

- Covariate BASE is obtained from the cyclic fluctuation model:

$$SBP(t) = Base\ \{1 + \sum_{j=1}^{n} A_j * \cos\left[\frac{j*\pi*(t-PHS_j)}{12}\right]\} + \mu_i + e_{it}$$

where $\mu_i$is the random effect of the subject i, e_{it} is the random error.

- We consider **4** settings:

1. Setting 1:

Outcome is obtained from CHG=$\frac{3}{mean\ (BASE)}$ *BASE + N(0, 10^2)

Analysis model is CHG~BASE.

2. Setting 2:

Outcome is obtained from CHG= $\frac{1}{mean\ (BASE)}$ BASE+ $\frac{1}{\Pr(AGER1.1)}$ AGEGR1.1 + $\frac{1}{\Pr(AGER1.2)}$ AGEGR1.2 +N(0, 10^2)

Analysis model is CHG~BASE+AGEGR1.

3. Setting 3 (Model misspecification: under fitting):

Outcome is obtained from CHG= $\frac{1}{mean\ (BASE)}$ BASE+ $\frac{1}{\Pr(AGER1.1)}$ AGER1.1 + $\frac{1}{\Pr(AGER1.2)}$ AGER1.2 +N(0, 10^2)

Analysis model is CHG~BASE.

4. Setting 4: (Model misspecification: over fitting):

Outcome is obtained from CHG=$\frac{3}{mean\ (BASE)}$ *BASE + N(0, 10^2)

Analysis model is CHG~BASE+AGEGR1.

- Performance metrics:

(1) Percentage Bias=$\frac{\hat{Y}-Y}{Y}$ *100; (2) SE Ratio=$\frac{SE\ (\hat{Y})}{SE\ (Y)}$;

(3) False Negative Rate (FNR) = $\frac{UCL<3}{N}$*100;

(4) Coverage Probability of 95% Confidence Interval.

Results

For the percentage bias, MI and IPW are more sensitive to higher levels of missingness. AIPW and MIIPW offer better control of bias at lower missing probabilities but are not immune to increases in bias as the missing data proportion rises. MI and MIIPW have smaller variability than IPW and AIPW methods. For FNR and coverage probability, for the smaller missing rate (<30%), all the methods has similar performance. However, for the larger missing rate (>30%), IPW and AIPW methods have better performance. AIPW method shows the double robust property when the regression model is mis-specified.

Table 1. Percentage error and SE ratio under **MCAR** for **setting 1**.

Setting1:MCAR	Percentage Error (%)				SE Ratio(%)			
Missing prob (%)	MI	IPW	MIIPW	AIPW	MI	IPW	MIIPW	AIPW
10	-0.742	-0.591	-0.56	-0.437	1.052	1.050	1.059	1.055
20	-3.140	-3.091	-3.288	-2.783	1.108	1.116	1.117	1.122
30	-5.943	-4.621	-6.344	-3.823	1.185	1.201	1.191	1.202
40	-8.039	-7.518	-8.339	-6.904	1.274	1.298	1.277	1.299
50	-6.182	-4.454	-6.02	-3.667	1.376	1.434	1.38	1.421

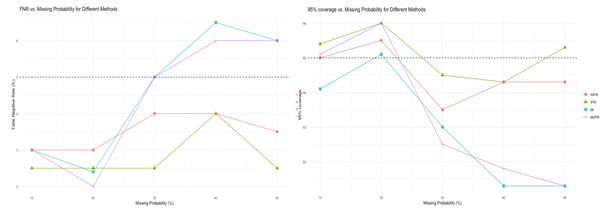

Figure 1. False Negative Rate (FNR) [Left] and coverage probability [right] under **MCAR** for **setting 1**.

Table 2. Percentage error and SE ratio under **MAR** for **setting 1**.

Setting1:MAR	Percentage Error (%)				SE Ratio(%)			
Missing prob (%)	MI	IPW	MIIPW	AIPW	MI	IPW	MIIPW	AIPW
10	3.150	2.965	2.844	2.594	1.068	1.071	1.085	1.072
20	2.187	2.649	1.926	2.02	1.128	1.149	1.156	1.135
30	2.152	4.272	2.707	3.624	1.198	1.259	1.226	1.226
40	2.424	2.971	2.682	2.466	1.307	1.403	1.331	1.347
50	4.666	5.17	4.574	3.99	1.398	1.611	1.418	1.484

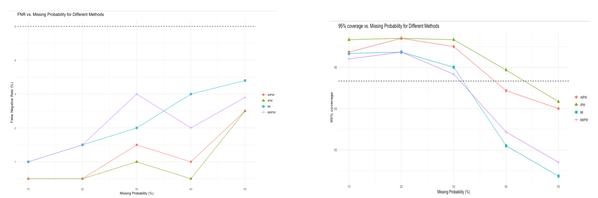

Figure 2. False Negative Rate (FNR) [Left] and coverage probability [right] under **MAR** for **setting 1**.

Table 3. Percentage error and SE ratio under **MAR** for **setting 2**.

Setting1:MAR	Percentage Error (%)				SE Ratio(%)			
Missing prob (%)	MI	IPW	MIIPW	AIPW	MI	IPW	MIIPW	AIPW
10	3.151	2.828	2.73	2.658	1.067	1.073	1.083	1.071
20	2.186	2.631	1.749	2.055	1.125	1.139	1.15	1.145
30	2.153	3.595	2.404	3.51	1.197	1.234	1.218	1.256
40	2.424	2.272	2.267	2.04	1.306	1.362	1.321	1.394
50	4.666	5.627	4.22	4.275	1.397	1.52	1.41	1.586

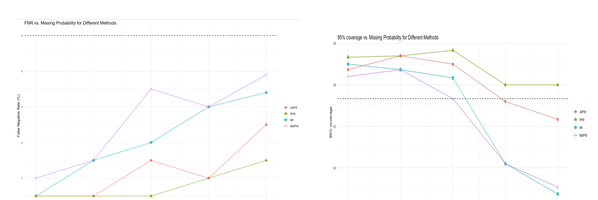

Figure 3. False Negative Rate (FNR) [Left] and coverage probability [right] under **MAR** for **setting 2**.

Table 4. Percentage error and SE ratio for under **MAR** for **setting 3**.

Setting2:MCAR	Percentage Error (%)				SE Ratio(%)			
Missing prob (%)	MI	IPW	MIIPW	AIPW	MI	IPW	MIIPW	AIPW
10	-1.069	2.432	-2.079	-0.402	1.065	1.072	1.084	1.068
20	6.22	5.809	7.917	2.1	1.122	1.131	1.159	1.135
30	-1.992	6.089	-1.81	5.57	1.197	1.223	1.23	1.25
40	**23.962**	9.406	**20.189**	7.954	1.282	1.344	1.315	1.41
50	-8.324	9.582	-5.52	-3.345	1.4	1.504	1.424	1.639

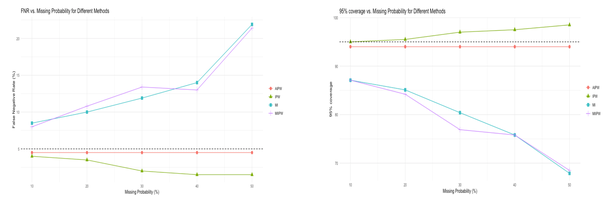

Figure 4. False Negative Rate (FNR) [Left] and coverage probability [right] under **MAR** for **setting 3**.

Table 5. Percentage error and SE ratio under **MAR** for **setting 4**.

Setting3:MAR	Percentage Error (%)				SE Ratio(%)			
Missing prob (%)	MI	IPW	MIIPW	AIPW	MI	IPW	MIIPW	AIPW
10	3.151	2.828	2.73	2.658	1.067	1.073	1.083	1.071
20	2.186	2.631	1.749	2.055	1.125	1.139	1.15	1.145
30	2.153	3.595	2.404	3.51	1.197	1.234	1.218	1.256
40	2.424	2.272	2.267	2.04	1.306	1.362	1.321	1.394
50	4.666	5.627	4.22	4.275	1.397	1.52	1.41	1.586

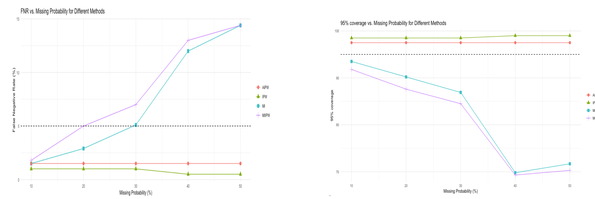

Figure 5. False Negative Rate (FNR) [Left] and coverage probability [right] under **MAR** for **setting 4**.

Conclusion and Future work

The project provides important insights for statistical analysis of missing data in ABPM studies. Statistical methods like AIPW, especially in scenarios with high missing data rates, can be appropriate method for analyzing missing data in ABPM studies.

In the future work, we will need to conduct the simulation when the missing model is mis-specified and check the double-robust property. Furthermore, this project only conducts simulation with one arm, we can also consider simulation with more arms. Additionally, we need to find a way to generate the postbaseline with time t and using the MMRM model along with MI, IPW, AIPW and combined MI and IPW.

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