Original article

Multivariate approach in analyzing medical data with correlated multiple outcomes: An exploration using ACCORD trial data

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ABSTRACT

Background: In clinical setting, to answer a research question, very often more than one outcome variables are used which are statistically correlated. Univariate analysis approach, which is commonly used in such context, violates the assumption of independence for correlated variables, while multivariate approach could give more robust and precise clinical decision by accounting this correlation. This paper is a demonstration of the change in statistical decision in multivariate approach compared to univariate approach in analysing medical data with multiple correlated outcome variables.

Method: The data used in this paper was the ACCORD trial data and the variables were Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) which are correlated. The condition of bivariate normality was checked after removing the outliers. We compared the differences in means of SBP and DBP separately between the groups at different follow up time points by univariate approach using unpaired 't' test and thereafter together by bivariate approach using Hotelling 'T²'. Further the role of varied levels of correlation between SBP and DBP coupled with the variations in sample size in changing the statistical inference has been investigated. Robustness of these results were demonstrated through 1000 samples of simulated data from Accord trial data.

Results: The statistical decision regarding difference in means of either SBP or DBP between the two groups at baseline, 12th, 36th and 84th month in both univariate and bivariate approaches were similar. At baseline and 84th month the hypotheses were accepted and at 12th and 36th month the hypotheses were rejected with both the approaches. However at 60th and 72nd month the univariate and multivariate approach results contradicted each other which reflect the significance of correlation in modifying the inference. The analysis results further indicated that varied levels of correlation and sample size too modify the inference in bivariate approach and contradict univariate results.

Conclusion: Studies with multiple correlated outcomes, the multivariate approach which accounts this statistical correlation has potential to change statistical decisions and provide more precise results. Hence multivariate approach is recommended in such situations.

1. Introduction

In the analysis of clinical research data, statistical estimation and testing of a hypothesis are the two major components for the decision making process. The commonly practiced hypothesis testing method is the univariate parametric or nonparametric approach that deals with only one outcome variable at a time. Under these approaches, the assumptions of statistical independence between the variables are violated

for correlated outcome variables. The analysis for each outcome variable is carried separately under the assumption that outcomes are independent resulting in multiple conclusions and inflating false discovery rates.¹ In a clinical research setting, to answer any research question, very often researcher use more than one primary outcome measurements from each subject which are correlated. In the context of blood pressure (BP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) are correlated to the extent of more than 0.50 and even more than

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0.70 in certain disease conditions.^{2,3} The lipid parameters associated with blood pressure are also correlated.⁴ The correlation of total cholesterol (TC) with triglyceride (TG), low-density lipoprotein (LDL), and very large density lipoprotein (VLDL) reported to the extent of 0.36, 0.94, and 0.34 respectively; while of TG with VLDL as 0.972.⁵ Similar correlations between lipid parameters were also reported.^{6–8} The univariate analysis under such a situation ignores the extra information contained in the correlation between the outcome variables as well as the number of parameters under comparison. The increasing number of outcomes comparison increases the probability of type-I error (α). Though, in univariate approach α error can be adjusted; but fails to account for the role of correlation and hence is more likely to end up with less precise results and hence biased decisions.

Many studies had analyzed the data through a univariate approach with correlated outcomes. A clinical trial using a univariate approach concluded that the fixed low-dose triple combination antihypertensive medication had better blood pressure control than usual care; even correlated lipid parameters were compared separately treating them independent and conclusions were made.⁹ Another clinical trial evaluated the effect of nattokinase consumption against placebo over the change in SBP and DBP. The change over time within the groups was compared by paired and between the groups by unpaired *t*-tests.¹⁰ For the comparability of the groups at baseline in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, SBP and DBP were compared by unpaired *t*-test.^{11–13} The study while assessing the relationship between inter-arm systolic BP difference (IASBPD) and cardiovascular disease risk factors reported increased SBP and DBP in the high IASBPD group (≥ 10 mm Hg) than normal IASBPD group (< 10 mm Hg) by using the univariate mode of analysis.¹⁴ The effectiveness of amlodipine against the nifedipine in lowering ambulatory BP in sustained hypertension was investigated and compared between the groups at the base, 4-week, and 8-week using unpaired *t*-test.¹⁵ Similarly Chen et al. in one randomized trial of 8 weeks investigated efficacy and tolerability of initial high (5.0 mg/d) vs. low (2.5 mg/d) doses of S(–)-amlodipine in hypertension. The univariate unpaired *t*-test was applied to compare the mean change of clinic as well as ambulatory BP between the two groups.¹⁶ Another study by Yang et al. compared bisoprolol with metoprolol CR/ZOK to control the dynamic heart rate (HR) and blood pressure (BP) in mild-to-moderate primary hypertensive patients. The difference of average change in HR, SBP & DBP between the two treatment groups was compared by using unpaired *t*-test.¹⁷ Similarly in many trials, improvement in lipid parameters which are correlated were assessed using a univariate approach and concluded on the effectiveness of interventions.^{11–14,18–23} These articles, though not in the context of blood pressure, cited with the objective that the decision are likely to change, if the correlation would have been accounted among the lipids which are ignored in univariate approach.

The multivariate approach is a statistical technique that jointly analyses more than one outcome measures, which may be correlated, based on their joint distribution. This approach simultaneously assembles all the outcome variables in a vector form in such a way that the entire vector is considered as a random variable that follows a multivariate distribution. The conventional univariate approach that ignores the extra information contained in the correlation among the outcomes is accounted in a multivariate approach in its functional distribution. Compared to univariate, multivariate approach reduces the probability of type-I error and increases the power of the test. Historically, multivariate methods do exist and theories have been developed.²⁴ For example, in the univariate approach, the *p* values for testing the difference of means of mass and snout-vent length of two genera of lizards were 0.46 and 0.08 respectively; indicating their statistical similarity. But the same when analyzed accounting correlation between mass and snout-vent length using the bivariate approach, resulted in the rejection of a hypothesis of no difference ($p < 0.001$).²⁴ Despite its importance, the multivariate approach has not been very often applied in clinical data analysis probably due to a lack of awareness, complex

mathematical methods and difficulty in computation. However at present software packages like SPSS,²⁵ R,²⁶ STATA,²⁷ are available those can address these issues.

The present paper compares the results of the multivariate approach with that of univariate using clinical data of the ACCORD lipid trial. This study demonstrates; how statistical inference changes, if a multivariate approach is applied to analyze correlated outcomes compared to univariate. The variables selected for demonstration are SBP and DBP as outcome variables and compared between the placebo and fenofibrate groups measured at various follow-up times. Further, the role of magnitude and direction of correlation between variables as well as of sample size in changing the inference has been demonstrated through simulation in the bivariate approach of analysis. The authors also investigated the corresponding decision emerging in a univariate context for comparison.

2. Methods

2.1. Brief description of data

The ACCORD lipid trial data used in this paper was obtained from National Heart, Lung, and Blood Institute (NHLBI). This was an open-label randomized multi-centric trial organized through clinic sites in the US and Canada. A total of 5518 eligible participants were randomly allocated into two groups (2730 on placebo and 2744 on fenofibrate). The BP of individuals were measured monthly for four months and every fourth months thereafter till 84 months. Trial details with objectives and primary results were published elsewhere.^{11–13}

2.2. Participants under analysis

After removing outliers at each follow-ups, the number of participants left under analysis at baseline were 2704 in placebo and 2716 in fenofibrate groups that reduced successively at different further follow-ups. At 84th months these in respective groups were only 237 and 233. Even though there was a considerable losses to follow up, this would not have affected results of our paper since we compared at each time point results of univariate with that of multivariate. Details of participants subjected to analysis at different time points are indicated in Table-1.

2.3. Statistical method

For comparison, the participants on placebo were considered as group one and on fenofibrate as group two. The null (H_0) and alternative (H_1) hypotheses to test the differences of means of SBP and DBP in univariate approach were:

$$H_0^{SBP} : \mu_{SBP}^{(1)} = \mu_{SBP}^{(2)} \text{ against } H_1^{SBP} : \mu_{SBP}^{(1)} \neq \mu_{SBP}^{(2)}$$

$$H_0^{DBP} : \mu_{DBP}^{(1)} = \mu_{DBP}^{(2)} \text{ against } H_1^{DBP} : \mu_{DBP}^{(1)} \neq \mu_{DBP}^{(2)}$$

Further, the null (H_0) and alternative (H_1) hypotheses to test the differences of a vector of means of SBP and DBP in bivariate approach were:

$$H_0 : \mu^{(1)} = \begin{bmatrix} \mu_{SBP}^{(1)} \\ \mu_{DBP}^{(1)} \end{bmatrix} = \mu^{(2)} = \begin{bmatrix} \mu_{SBP}^{(2)} \\ \mu_{DBP}^{(2)} \end{bmatrix} \text{ against } H_1 : \mu^{(1)} = \begin{bmatrix} \mu_{SBP}^{(1)} \\ \mu_{DBP}^{(1)} \end{bmatrix} \neq \mu^{(2)} = \begin{bmatrix} \mu_{SBP}^{(2)} \\ \mu_{DBP}^{(2)} \end{bmatrix}$$

In the ACCORD lipid trial, the analysis carried out was at baseline, 12th, 36th, 60th, 72nd, and 84th months. The SBP and DBP were considered as two random correlated outcome variables denoted by X_{SBP} and X_{DBP} with their respective population mean μ_{SBP} and μ_{DBP} . In the vector form, the random variable for the i^{th} ($i = 1, 2$) group at any time

Table 1

Comparison of means of SBP and DBP between the placebo and fibrate groups at different follow-ups using univariate analysis (Independent 't' test).

Time of recording	Trial Group	Number of participants			Mean $\pm$ SD		r
		Recorded for BP	Outliers	Under analysis	SBP mm Hg	DBP mm Hg	
Baseline	Placebo	2730	26	2704	133.57 $\pm$ 17.17	73.96 $\pm$ 10.73	0.574
	Fibrate	2744	28	2716	133.36 $\pm$ 17.02	73.82 $\pm$ 10.49	0.554
Difference of means & (p-value)					0.21 (p = 0.661)	0.14 (p = 0.633)	0.564*
12month	Placebo	2582	40	2542	129.65 $\pm$ 16.19	71.29 $\pm$ 10.15	0.560
	Fibrate	2585	35	2550	128.62 $\pm$ 16.19	70.11 $\pm$ 10.04	0.528
Difference of means & (p-value)					1.03 (p = 0.023)	1.18 (p < 0.001)	0.554*
36month	Placebo	2380	25	2355	129.89 $\pm$ 16.49	69.58 $\pm$ 10.04	0.525
	Fibrate	2409	31	2378	128.42 $\pm$ 16.43	68.49 $\pm$ 9.96	0.500
Difference of means & (p-value)					1.47 (p = 0.002)	1.09 (p < 0.001)	0.514*
60month	Placebo	1025	14	1011	129.68 $\pm$ 16.06	68.45 $\pm$ 10.24	0.555
	Fibrate	1018	10	1008	129.88 $\pm$ 16.01	67.20 $\pm$ 9.75	0.457
Difference of means & (p-value)					-0.20 (p = 0.779)	1.25 (p = 0.005)	0.506*
72month	Placebo	290	4	286	130.40 $\pm$ 15.42	67.59 $\pm$ 9.16	0.454
	Fibrate	301	4	297	131.23 $\pm$ 15.57	66.18 $\pm$ 9.03	0.408
Difference of means & (p-value)					-0.83 (p = 0.518)	1.41 (p = 0.061)	0.427*
84month	Placebo	241	4	237	128.72 $\pm$ 15.55	67.52 $\pm$ 9.99	0.564
	Fibrate	237	4	233	128.94 $\pm$ 17.71	65.79 $\pm$ 9.54	0.476
Difference of means & (p-value)					-0.22 (p = 0.885)	1.73 (p = 0.053)	0.514*

'r' is the Pearson's correlation coefficient between SBP & DBP, * Correlation of combined data set of both fibrate and placebo groups.

point is represented as $X^{(i)} = \begin{bmatrix} X_{SBP}^{(i)} \\ X_{DBP}^{(i)} \end{bmatrix}$ with their population mean as

$\mu^{(i)} = \begin{bmatrix} \mu_{SBP}^{(i)} \\ \mu_{DBP}^{(i)} \end{bmatrix}$ and the population covariance matrix $\Sigma^{(i)}$ as $\begin{bmatrix} \sigma_{SBP}^{(i)} & \sigma_{SBP,DBP}^{(i)} \\ \sigma_{DBP,SBP}^{(i)} & \sigma_{DBP}^{(i)} \end{bmatrix}$, where $\sigma_{SBP}^{(i)}$ and $\sigma_{DBP}^{(i)}$ are variances of SBP and DBP and $\sigma_{SBP,DBP}^{(i)} = \sigma_{DBP,SBP}^{(i)}$ covariance between SBP and DBP of the i th group. The observation of SBP and DBP of j^{th} sampled participant in i th group of

sample size n_i is represented as $x_j^{(i)} = \begin{bmatrix} x_{j(SBP)}^{(i)} \\ x_{j(DBP)}^{(i)} \end{bmatrix}$ ($j = 1, 2, \dots, n_i$) with

sample mean vector as $\bar{x}^{(i)} = \begin{bmatrix} \bar{x}_{SBP}^{(i)} \\ \bar{x}_{DBP}^{(i)} \end{bmatrix}$ and sample covariance matrix $S^{(i)}$

as $\begin{bmatrix} s_{SBP}^{(i)} & s_{SBP,DBP}^{(i)} \\ s_{DBP,SBP}^{(i)} & s_{DBP}^{(i)} \end{bmatrix}$ where, $s_{SBP}^{(i)}$ and $s_{DBP}^{(i)}$ are the sample variances of

SBP and DBP and $s_{SBP,DBP}^{(i)} = s_{DBP,SBP}^{(i)}$ is the sample covariance between SBP and DBP for the i th group. The pooled covariance matrix S was obtained as:

$$S_{pooled} = \frac{1}{\sum_{i=1}^2 (n_i - 1)} \sum_{i=1}^2 (n_i - 1) S^{(i)}$$

The data was checked for the outliers separately for each group at each follow up using the condition of Mahalanobis distance square $d_j^2(i) = (x_j^{(i)} - \bar{x}^{(i)})' \frac{1}{S^{(i)}} (x_j^{(i)} - \bar{x}^{(i)}) > \chi_2^2(0.005) = 10.60$ and outliers were removed. Thereafter, bivariate normality assumption was verified for each group and was found to be satisfied.²⁴ Initially, the differences of means of SBP and DBP between the groups at each follow-up were tested separately using an unpaired t -test; the group-specific 95% CIs of means of SBP and DBP as well as of the differences between the groups were also obtained. While in bivariate approach, the statistical significance of the difference of mean vector of (SBP, DBP) between the groups was tested using the Hotelling's T^2 statistic:

$$T^2 = [(\bar{x}^{(1)} - \bar{x}^{(2)}) - (\mu^{(1)} - \mu^{(2)})]' \left[\left(\frac{1}{n_1} + \frac{1}{n_2} \right) S_{pooled} \right]^{-1} [(\bar{x}^{(1)} - \bar{x}^{(2)}) - (\mu^{(1)} - \mu^{(2)})]$$

which is distributed as

$$\frac{(n_1 + n_2 - 2)p}{(n_1 + n_2 - p - 1)} F_{p, n_1 + n_2 - p - 1}(\alpha)$$

²⁶Clinically, it is proven that SBP and DBP are positively correlated.^{2,3} However for the demonstration purpose we assumed different levels of positive and negative correlations between SBP and DBP. The bivariate normally distributed 1000 samples for the measurement of SBP and DBP at 72nd month for varying levels of correlation and sample sizes were generated using simulation. The simulation was initiated with a sample size of 100 and continued to increase till 95% of samples were consistently started getting rejected in the bivariate approach at varying levels of correlation. Further, the corresponding decision of univariate was also seen. The analysis was carried out using SPSS Version 19 and R Studio version 3.6.1.^{25,26}

3. Results

3.1. Univariate and bivariate decisions

The correlation coefficients between SBP and DBP in placebo and fenofibrate groups at different follow-ups varied between 0.40 and 0.60. The univariate approach did not show a significant difference of means for either SBP or DBP between placebo and fibrate groups at the baseline, 72nd and 84th months ($p > 0.05$); while at 12th and 36th months, both SBP and DBP means differed significantly ($p < 0.05$). At the 60th month, the difference of means of SBP between the groups was insignificant ($p = 0.779$) while DBP differed significantly ($p = 0.005$). Similar was the decision indicated by 95% univariate CIs of the difference of means between the groups (Table- 1 & 2).

The statistical decisions regarding difference in mean between groups based on univariate and bivariate approaches were similar at four time points and differed at two-time points (Table- 3). At baseline, 12th, 36th, and 84th months of follow-ups, both univariate and bivariate approaches resulted in similar decisions either accepting or rejecting the hypothesis of no difference. At the 60th month, the univariate approach indicated no significant difference in mean SBP ($p = 0.779$) between groups but a significant difference for mean DBP ($p = 0.002$). However in the bivariate approach, analysing SBP and DBP jointly indicated an overall significant difference ($p = 0.002$) at this time point. Further, at 72nd months in the univariate approach, no significant difference of means between the groups was observed for both SBP ($p = 0.518$) and DBP ($p = 0.061$), on the other hand, the bivariate approach indicated a significant difference ($p < 0.05$) resulting in the rejection of equality of

Table 2

Univariate 95% CIs of means of SBP and DBP of placebo and fibrate groups as well as of the difference between the groups at different follow up.

Time of recording	Trial Group	95% CI (Univariate)	
		SBP mm Hg	DBP mm HG
Baseline	Placebo	(132.92, 134.22)	(73.56, 74.36)
	Fibrate	(132.72, 134.00)	(73.43, 74.21)
Difference		(-0.70, 1.12)	(-0.43, 0.71)
12month	Placebo	(129.02, 130.28)	(70.90, 71.68)
	Fibrate	(127.99, 129.25)	(69.72, 70.50)
Difference		(0.14, 1.92)	(0.63, 1.73)
36month	Placebo	(129.22, 130.56)	(69.17, 69.99)
	Fibrate	(127.76, 129.08)	(68.09, 68.89)
Difference		(0.53, 2.41)	(0.52, 1.66)
60month	Placebo	(128.69, 130.67)	(67.82, 69.08)
	Fibrate	(128.89, 130.87)	(66.60, 67.80)
Difference		(-1.59, 1.19)	(0.38, 2.12)
72month	Placebo	(128.61, 132.19)	(66.52, 68.66)
	Fibrate	(129.45, 133.01)	(65.15, 67.21)
Difference		(-3.35, 1.69)	(-0.07, 2.89)
84month	Placebo	(126.73, 130.71)	(66.24, 68.80)
	Fibrate	(126.65, 131.23)	(64.56, 67.02)
Difference		(-3.22, 2.77)	(-0.03, 3.49)

Table 3

The decision about the difference of means of SBP and DBP emerging in univariate and bivariate approaches at different follow up.

Time of recording	Univariate approach		Bivariate approach
	SBP	DBP	
	P value	P value	P-value
Base line	0.661	0.633	0.868
12 month	0.023	<0.001	<0.001
36 month	0.002	<0.001	<0.001
60 month	0.780	0.005	0.002
72 month	0.515	0.061	0.049
84 month	0.883	0.055	0.064

BP which is also in contradiction to the univariate decision. This indicate the appropriateness of multivariate approach.

3.2. Role of sample size and magnitude of correlation in statistical decision through bivariate approach-demonstration through simulation

The role of magnitude of correlation coefficient and sample size for statistical decision in bivariate context was worked out through the simulation (Fig.-1). When variables are positively correlated the minimum required sample size to reject the hypothesis of no difference decreases with increasing correlation. A correlation coefficient of 0.10 between SBP and DBP, the sample size of 1010 or beyond in each group started detecting the group difference consistently; but when the correlation was increased to 0.90, a sample of 140 was enough detect the same difference. When the variables are negatively correlated, the minimum required sample size to reject the group difference increases up to a level and decreases thereafter as moving from correlation -0.10 to -0.90. The required sample size to reject the hypothesis of no difference at correlation -0.10 was 1170 and continued to rise to 1320 at correlation -0.50. But as moved from correlation -0.50 to -0.90, the minimum required sample size successively decreased and was 470 at correlation -0.90. More importantly, the minimum required sample sizes were always higher for the same level of negative correlation than the positive one. The decisions of the univariate approach were in contrast when compared by the decision of bivariate (Fig. 1). At each correlation, not more than 30% of simulated samples rejected the hypothesis of no difference in means of SBP. While more than 95% of samples were rejected the difference of DBP means at correlations between -0.10 and -0.70 and on all other correlations negative or positive; less than 95% samples were rejected. With the minimum required sample size of 140 at correlation 0.90; only 1.9% and 5.5% samples for the differences of means of SBP and DBP were rejected in univariate. This further implicate the role of magnitude of correlation between variables in the inference.

Corresponding percentage (%) of samples rejected in Univariate

SBP:	14.8	26.4	29.4	28.7	27.6	25.2	23.0	17.6	12.1	1.9
DBP:	82.7	97.6	98.4	98.4	96.2	92.6	88.3	75.3	45.2	5.5

Fig. 1. The minimum sample size required to reject the null hypothesis in bivariate approach at varying levels of correlations and the corresponding decision of univariate –A demonstration through 1000 samples of simulated data for 72nd month of blood pressure recording in ACCORD lipid trial.

4. Discussion

The multivariate approach is the standard required analysis procedure for analysing the correlated multiple outcome variables. However, in clinical research, most often each outcome variable analyzed separately, named it as univariate analysis, with an assumption that these variables are uncorrelated. Thus, the univariate approach may end up with biased decision and the possibility of imprecise estimates. The aim of this paper is to demonstrate the change in the statistical decision regarding the acceptance or rejection of the hypothesis during multivariate analysis in comparison to univariate approach when correlated multiple outcome variables are involved. We used the ACCORD trial data for this demonstration purpose. The levels of SBP and DBP were positively correlated and associated with CVD related outcomes.^{2,3} Webster et al. compared the change of blood pressure with fixed low-dose triple combination antihypertensive medication against usual care analysing differences of mean reductions in SBP and DBP separately following a univariate approach. The decision favoured the use of fixed low-dose triple combination antihypertensive medication for better control on BP.⁹ But the conclusion might not be robust as the effect of correlation between SBP and DBP was not accounted. In fact, due to larger differences in a mean reduction of SBP (−8.8 mm Hg) and DBP (−4.6 mm Hg) between the groups, the decisions of univariate and multivariate approaches may be similar as seen in the present analysis at 12th and 36th months of follow up. But the result of the multivariate approach might differ from the univariate approach especially for smaller differences between groups as evidenced in the present demonstration at the 60th and 72nd months of follow up. Such situations, the decisions through multivariate approach could contradict with the univariate approach. Further in univariate analysis of our data, at 60th month we observed no difference in mean SBP ($p = 0.779$) but significant difference in mean DBP ($p = 0.005$) between groups which confuses the clinical decision of the utility of intervention. However multivariate approach helped us to arrive unique decision of rejecting the null hypothesis. Similarly at 72nd month the univariate comparison favoured the hypothesis of no difference in both SBP and DBP between the groups ($p = 0.518$ for SBP and $p = 0.061$ for DBP) where in multivariate analysis rejected the null hypothesis ($p < 0.049$). Thus, in situations of multiple correlated and equally important outcomes, the research decision could be inconclusive by adopting a univariate approach where as a unique conclusive decision would be possible by adopting multivariate approach. Jensen et al. compared the nattokinase consumption in reducing the blood pressure in North American hypertensive's by analyzing SBP and DBP separately. The nattokinase group showed a decrease in SBP which was similar to the decrease in the placebo group. But mean DBP was significantly less in the nattokinase group compared to the placebo group ($P < 0.04$) and the beneficial effect of nattokinase consumption to control the BP was concluded.¹⁰ The comparison of the effect of nattokinase consumption through bivariate approach accounting correlation could have provided more precise conclusion. In ACCORD lipid and glycemia trials^{12,13} the group comparability of blood pressure at baseline was shown following a univariate approach. The means of both SBP and DBP of the groups were so close that similar decisions of no difference would emerge either adopt a univariate or multivariate approach, but a little wider difference which may be insignificant in univariate can be significant in bivariate approach due to correlation effect as evidenced in the present analysis at 72nd month. Ma et al. compared the differences of SBP and DBP means between high and normal IASBP groups by univariate approach and reported significant difference, but the bivariate approach could have been more robust.¹⁴ Huang et al. assessed the efficacy of amlodipine and nifedipine-GITS by comparing the reduction of SBP and DBP means with the univariate approach and found similar reduction which might be different if correlation accounted.¹⁵ The correlation among the variables plays a major role in decision making; in this analysis at 84th month of follow-up, both SBP and DBP means were statistically similar in

univariate and bivariate approaches with observed correlation among them ($r = 0.514$). But a little shift of correlation from 0.514 to 0.571, the decision of bivariate approach changed in contrast to univariate, suggesting decisions are sensitive towards correlation. In several trials, the correlated lipid parameters were compared following the univariate approach violating the correlation effect, and accordingly decisions were made separately for each which may not be true.^{11–14,18–23} Therefore, to arrive at a more valid decision, the multivariate technique could have been used in these studies.

Through the simulated data, it has been demonstrated that the inference could be altered with varying levels of correlation between variables and sample size. Higher the level of positive correlation, smaller the minimum required sample size needed to reject the hypothesis of no difference in the bivariate approach. While, in case of negative correlation, as moving from lower to higher levels, the required sample size is likely to increase up to a certain level and to decrease thereafter; but will always be higher than the same level of positive correlation. The corresponding univariate decisions at those minimum sample sizes were in contrast to the bivariate and the rejection of the hypothesis of no difference for SBP was unlikely. Whereas, the hypothesis of no difference for DBP had likelihood of gets rejected at some levels of negative correlations. So, the decisions made are much influenced by sample size as well as the correlation if analyzed using multivariate approach which may be in consonant to the decision of univariate.

5. Conclusion

The present analysis suggests that studies with the multiple correlated outcomes, multivariate approach which accounts for the statistical correlation has potential to change the statistical decisions and provide more precise results. Variations in the correlations and size of the sample do play a vital role in statistical inference. Hence multivariate approach is recommended in such situations.

Declaration of conflicting interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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