RESEARCH ARTICLE

APOA2–265 T>C Polymorphism as A Genetic Marker Associated with Lipid Profiles and Cardiovascular Risk in A Healthy Indonesian Population

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Abstract

BACKGROUND: Apolipoprotein A (APOA)2–265 T>C polymorphism significantly affects lipid metabolism and body composition, as well as plays a key role in cardiovascular diseases (CVD) and metabolic syndrome. In this study, association between the APOA2 polymorphism, lipid profiles, body composition, and cardiovascular disease (CVD) risk in a healthy Indonesian population was investigated. Although similar studies have been conducted in other populations, this study addresses the urgent need to understand genetic factors influencing lipid profiles in Southeast and East Asia, where hypercholesterolemia rate keep rising, particularly in Indonesia.

METHODS: A cross-sectional study involving 84 healthy participants was performed. Genotyping for the APOA2–265 T>C polymorphism was conducted using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Plasma levels of APOA2 and APOB100 were measured with enzyme-linked immunosorbent assay (ELISA), and APOB100/APOA2 ratio was calculated to assess CVD risk. Lipid profiles were evaluated with enzymatic methods, and body fat percentage was measured using calipers.

RESULTS: CT/CC genotypes showed significantly lower plasma APOA2 levels compared to the TT genotype (p=0.0215). APOB100/APOA2 ratio was significantly higher in CT/CC genotypes (p=0.0020) and remained significant after Bonferroni correction. No significant differences were found in lipid profiles and body fat percentages between genotypes after correction, although trends suggested higher cholesterol and low-density lipoprotein (LDL) levels in TT genotypes and higher median body fat percentages in CC/CT genotypes.

CONCLUSION: APOA2–265 T>C polymorphism is linked to changes in lipid profiles and body composition, potentially raising CVD risk in CT/CC genotypes. However, limited sample size and modest effect sizes suggest that the practical use of APOA2 genotyping for risk assessment might require further investigation.

KEYWORDS: APOA2 polymorphism, APOB100, hypercholesterolemia, cardiovascular disease, lipid profile, body fat percentage

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Introduction

Hypercholesterolemia, characterized by elevated blood cholesterol levels, is a significant risk factor for cardiovascular diseases (CVD), including atherosclerosis, coronary artery disease, and stroke. Globally, approximately 39% of adults have elevated total cholesterol (≥5.0 mmol/L), with high non-high-density lipoprotein (HDL) cholesterol contributing to an estimated 4.4 million deaths annually.

(1,2) Elevated low-density lipoprotein (LDL) cholesterol is a leading risk factor for CVD, and recent data highlight its significant role in global mortality trends.(3) The association between non-HDL cholesterol and mortality due to CVD emphasizes the need for effective lipid-lowering strategies, particularly in populations with high LDL cholesterol levels.(4)

While cholesterol-related mortality has decreased in high-income countries, it has more than doubled in Southeast Asia and tripled in East Asia over recent decades, reflecting a growing disease burden in middle-income regions.(5,6) In Indonesia, the prevalence of hypercholesterolemia was reported at 34.4% in 2018, based on the National Basic Health Research (RISKESDAS), underscoring its role as a public health concern.(7)

Genetic factors play a crucial role in determining individual lipid profiles, and among these, variations in the apolipoprotein A *(APOA)2* gene have gained significant attention. The *APOA2* gene, located on chromosome 1q23-q25, encodes Apolipoprotein A-II, the second most abundant protein in HDL.(8) This protein modulates lipid metabolism by influencing the structure and function of HDL particles, reverse cholesterol transport, and the antioxidant capacity of HDL.(8) The APOA2–265 T>C polymorphism (rs5082), a T-to-C substitution in the gene's promoter region, has been linked to variations in APOA2 levels, lipid profiles, and CVD risk. This polymorphism affects the transcription of *APOA2*, thereby altering its expression and potentially influencing lipid metabolism and the risk of hypercholesterolemia.(9,10)

While previous studies have explored this in different populations, this current research concentrated on a healthy Indonesian cohort, offering important insights into genetic variations specific to this population and their implications for CVD risk. Studies have shown that individuals carrying the C allele of the APOA2–265 T>C polymorphism tend to have higher body mass index (BMI) and are more prone to obesity compared to those with the TT genotype. (4,11,12) This association is thought to be mediated through alterations in dietary intake and lipid absorption, which subsequently affect body fat accumulation and distribution. (5,13) Dyslipidemia, characterized by elevated levels of total cholesterol, LDL, and triglycerides, along with low levels of HDL, is a significant risk factor for CVD.(14-17)

Apolipoproteins, such as APOA2 and APOB100, are critical components of lipoprotein particles and play essential roles in lipid metabolism. APOA2 is the second most protein component of HDL and is involved in reverse cholesterol transport, whereas APOB100 is a primary component of LDL and is responsible for the transport of cholesterol to peripheral tissues.(8) The balance between these apolipoproteins, often expressed as the APOB100/APOA2 ratio, is a strong predictor of CVD risk, with higher ratios indicating a greater risk of atherosclerosis and related cardiovascular events.(9,18)

Understanding the genetic basis of lipid metabolism and body composition can aid in the development of personalized healthcare strategies. However, there is a need to explore how the APOA2–265 T>C polymorphism interacts with lifestyle factors, such as diet and physical activity, to influence lipid profiles and CVD risk in diverse populations. This study was conducted to investigate these interactions in a healthy Indonesian population, contributing to the growing body of research on genetic and environmental determinants of cardiovascular health. We hypothesize that the C allele of the *APOA2* rs5082 polymorphism is associated with lower plasma levels of APOA2 and a higher APOB100/APOA2 ratio, indicating an increased risk of hypercholesterolemia and CVD.

Methods

Study Design and Subject Recruitment

A cross-sectional analytical observational study was conducted in Depok, Indonesia, from January to March 2023. Based on the sample size calculation conducted prior to the study, a total of 84 clinically healthy subjects were recruited based on the following inclusion criteria: adults aged 18–60 years; no history of chronic diseases such as diabetes, CVD, or renal disorders; and not taking any lipid-lowering medication. Exclusion criteria included pregnant or lactating women, individuals with acute illnesses or infections at the time of the study, and participants who had undergone major surgery within the last six months. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Trisakti (Approval No. 36/KER-FK/I/2023). All subjects provided written informed consent before enrolling in the study.

Sample Collection and DNA Extraction

Blood samples were collected from subjects via venipuncture following standard clinical protocols. Plasma was separated by centrifugation at 3,000 rpm for 10 minutes and stored at -80°C until further analysis. DNA was extracted from whole blood using the Quick DNA Miniprep Plus Kit (Catalog No. D4068; Zymo Research, Tustin, CA, USA) following the manufacturer's protocol. The procedure involved cell lysis

to release DNA, which was subsequently bound to a silica column. After multiple wash steps to remove impurities, DNA was eluted in a low-salt buffer. DNA purity and concentration were assessed using a Nanophotometer® N50 (Implenn GmbH, Munich, Germany). Only samples with a concentration of ≥15 ng/µL and an A260/280 ratio of 1.8–2.0 were used for downstream analysis.

Analysis of *APOA2* Polymorphism

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was conducted to amplify the *APOA2* gene segment containing the rs5082 polymorphism. Each 50 µL PCR reaction consisted of 25 µL of MyTaq HS Red Mix (Catalog No. BIO-25047; Meridian Bioscience, Memphis, TN, USA), 10 pmol of each primer, and 2 µL of template DNA. The nucleotide sequences of these primers were shown in Table 1. Thermal cycling was performed using the Sensoquest Lab Cycler 48 (SensoQuest GmbH, Göttingen, Germany), with the following protocol: the process began with an initial denaturation at 95°C for 10 minutes. This was followed by 30 cycles, each consisting of denaturation at 95°C for 30 seconds, annealing at 59.5°C for 30 seconds, and extension at 72°C for 30 seconds. The procedure concluded with a final extension at 72 °C for 5 minutes.(19)

After amplification, 10 µL of the PCR products were digested with FastDigest BsmI enzyme (Thermo Scientific, Waltham, MA, USA) at 37°C for 5 minutes. Digested products were separated on a 3% agarose gel stained with Floro+ Green Nucleic Acid Stain (1st Base, Singapore, Singapore) and visualized under blue light using Accuris SmartBlue Transilluminators (Accuris Instrument, Edison, NJ, USA). In the presence of the T allele, the BsmI enzyme cleaved the 273 bp PCR product into two fragments of 215 bp and 58 bp. The resulting band patterns were used to determine the rs5082 genotypes.(19)

Lipid Profile and Body Composition Analysis

Lipid profiles, including total cholesterol, LDL, HDL, and triglycerides, were measured. LDL cholesterol was measured directly using homogeneous assays, while HDL cholesterol was measured using precipitation techniques. Triglycerides and total cholesterol levels were measured using standard enzymatic assays. Body composition was assessed using BMI calculated by the weight in kilograms (kg) divided by height in meters (m) squared formula, while the body fat percentage was measured using caliper measurements.(20)

Table 1. Primer sequences for *APOA2* polymorphism site.

Primer	Sequence
APOA2 F	5’ CAT GGG TTG ATA TGT CAG AGC-3’
APOA2 R	5’ TCA GGT GAC AGG GAC TAT GG 3’

Measurement of APOA2 and APOB100 Levels

Plasma levels of APOA2 and APOB100 were measured using enzyme-linked immunosorbent assay (ELISA) kits (Catalog No. E-EL-H0096 for APOA and E-EL-H0010 for APOB1000; Elabscience, Houston, TX, USA) according to the manufacturer's protocol. Briefly, plasma samples were diluted appropriately and added to 96-well plates coated with antibodies specific to APOA2 and APOB100. After incubation at 37°C and washing to remove unbound material, the enzyme-conjugated secondary antibodies were added, followed by a substrate solution to produce a colorimetric reaction. The reaction was terminated by adding a stop solution, and the absorbance was then measured at 450 nm with a MP96 microplate reader (Safas, Monaco, Monaco). Concentrations of APOA2 and APOB100 were calculated based on standard curves generated from recombinant proteins provided in the kits.

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA). The Kolmogorov-Smirnov test was used to determine the normality of data distribution. The Mann-Whitney U test and unpaired t-test were applied to compare plasma levels of APOA2, APOB100, lipid profiles, and body fat percentage between the TT genotype group and the CC/CT genotype group. To correct multiple comparisons and reduce the risk of false positives, a Bonferroni correction was applied. Additionally, regression models were considered to adjust for confounding variables such as age, gender, and BMI. Statistical significance was set at $p<0.05$.

Results

Demographic Data of Subjects

The demographic characteristics of the study subjects were summarized in Table 2. A total of 84 individuals subjects in the study, representing a diverse sample of clinically healthy adults. The age distribution showed that 39.29% of the participants were aged 51-60 years, and 36.90% were aged 41-50 years. The gender distribution was skewed towards females, who comprised 60.71% of the sample, while

Table 2. Characteristic subjects (n=84).

Parameter	n (%)
Age	
31-41 years	6 (7.14)
41-50 years	31 (36.90)
51-60 years	33 (39.29)
>60 years	14 (16.67)
Gender	
Male	33 (39.29)
Female	51 (60.71)
Educational Level	
Elementary	7 (8.33)
Junior High	14 (16.67)
Senior High	45 (53.57)
Bachelor	18 (21.43)
Occupational	
Interpreneur	9 (10.71)
Private Employee	18 (21.43)
Housewife	42 (50.00)
Teacher	3 (3.57)
Others	12 (14.29)

males made up 39.29%. Education levels varied, with the majority having completed Senior High School (53.57%) and a significant portion holding a Bachelor's degree (21.43%). Occupationally, the largest group of subjects were housewives (50.00%), followed by private employees (21.43%).

Distribution of *APOA2* Genotypes

PCR-RFLP analysis was performed to genotype the *APOA2* rs5082 polymorphism. The digestion of PCR products with BsmI enzyme revealed distinct band patterns corresponding to the TT, CT, and CC genotypes. The TT genotype exhibited two fragments of 215 bp and 58 bp, while the CT genotype showed three fragments of 273 bp, 215 bp, and 58 bp (Figure 1). The CC genotype displayed a single fragment of 273 bp. The distribution of genotypes among the subjects was presented in Table 3. The TT genotype was the most prevalent, accounting for 77.38% of the subjects, while the CT and CC genotypes comprised 17.86% and 4.76%, respectively.

Lipid Profile of Subjects with TT and CC/CT Genotypes

The unpaired t-test and Mann-Whitney test, with Bonferroni correction applied for multiple comparisons, revealed no significant difference in lipid profiles between the TT and CC/CT genotype groups (Table 4). The mean cholesterol

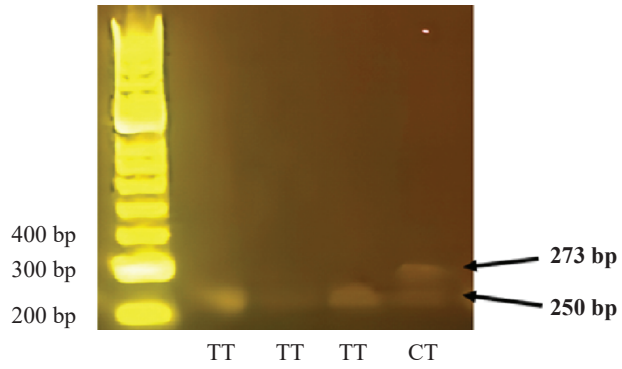

Figure 1. Gel electroforesis analysis showing TT and CT genotypes of *APOA2* gene. The DNA bands are located at 273 bp and 251 bp.

and triglyceride levels in the TT genotype group were higher (203.60±34.81 ng/mL and 83.00 (79.00-88.00) ng/mL) compared to the CC/CT genotype group (198.80±32.58 ng/mL and 78.00 (69.00-106.00) ng/mL). Similarly, the mean LDL levels were higher in the TT genotype group (155.50±29.95 ng/mL) compared to the CC/CT genotype group (150.20±30.02 ng/mL). The median body fat percentage was higher in the CC/CT genotype group (42.34%) compared to the TT genotype group (38.90%). However, this difference was not statistically significant (p=0.5407).

Different Levels of APOA2, APOB100 and APOA2/APOB100 Ratio between APOA2 Genotypes

Plasma levels of APOA2 and APOB100 were measured using ELISA. The results indicated significant differences in APOA2 levels and the APOB100/APOA2 ratio between different genotypes of the *APOA2* rs5082 polymorphism (Figure 2). APOA2 levels were significantly lower in individuals with CT/CC genotypes (737.00 (561.50-789.20) ng/mL) compared to those with the TT genotype (855.80 (827.10-882.30) ng/mL), with p=0.0215. However, after applying the Bonferroni correction for multiple comparisons, this difference was not statistically significant.

Table 3. Distribution of *APOA2* genotypes in participants.

Genotype	n (%)
TT	65 (77.38)
CT	15 (17.86)
CC	4 (4.76)
Total	84 (100.00)

Table 4. Correlation between *APOA2* gene polymorphism and lipid profile and body fat.

Parameter	TT Genotype (n=78)	CC/CT Genotype (n=5)	*p*- value
Cholesterol (ng/mL)	203.60±34.81	198.80±32.58	0.7653[a]
Trigylceride (ng/mL)	83.00 (70.00-88.00)	78.00 (69.00-106.00)	0.6120[b]
HDL (ng/mL)	31.20 (30.60-32.60)	30.40 (28.40-36.30)	0.8709[b]
LDL (ng/mL)*	155.50±29.95*	150.20±30.02*	0.7050[a]
Body fat (%)	38.90 (35.64-41.58)	42.34 (29.20-43.90)	0.5407[b]

[a]Calculated with unpaired T-test, results expressed as mean±standard deviation (SD). [b]Calculated with Mann-Whitney U test, results expressed as median (95% CI).

Similarly, no significant differences were observed between the median APOB100 levels and the *APOA2* genotype groups of TT (52.59 (24.81-114.20) ng/mL) and CC/CT (104.30 (24.81-278.00) ng/mL), with p=0.6362. We then measured the ratio of APOB100/APOA2 to analyze the risk of having CVD. Results showed that the APOB100/APOA2 ratio was significantly higher for individuals with the CT/CC genotypes (0.14 (0.03-0.55)) compared to those with the TT genotype (1.34 (0.71-2.41)) (p=0.0020), and this finding remained significant after Bonferroni correction (α-corrected=0.0062). This suggests that the *APOA2* rs5082 polymorphism significantly affected APOA2 levels, indicating that individuals carrying the CT/CC genotypes may be at a higher risk of CVD due to an unfavorable lipid profile.

Association Analysis for *APOA2* Genotypes with Lipid Profiles

Logistic regression models were employed to assess the association between the *APOA2* polymorphism and the levels of APOA2, APOB100, and the APOB100/APOA2 ratio, adjusting for age, gender, and BMI (Table 5). The analysis revealed no significant association between the polymorphism and APOA2 or APOB100 levels after adjustment, indicating that these initial differences may be influenced by other factors. However, the APOB100/APOA2 ratio remained significantly associated with the CT/CC genotypes, with an odds ratio (OR) of 1.52 (1.12 - 2.05), p=0.0080, Bonferroni-corrected p=0.0480). Additionally, regression analysis was conducted for lipid profiles, including total cholesterol, LDL, HDL, and triglycerides, as well as body fat percentage (Table 5). However, the analysis did not find any significant associations between the *APOA2* polymorphism and these lipid profiles or body fat percentage after adjusting for confounders and applying the Bonferroni correction.

Discussion

This study provides valuable insights into the influence of the APOA2–265 T>C polymorphism on lipid profiles and body composition in a healthy Indonesian adult population. The findings suggest that *APOA2* polymorphism may impact CVD risk through its effects on lipid metabolism, despite not all results reaching statistical significance due to the study's small sample size.

The results of this study revealed that subjects with the CT/CC genotypes exhibited significantly lower plasma APOA2 levels and a higher APOB100/APOA2 ratio

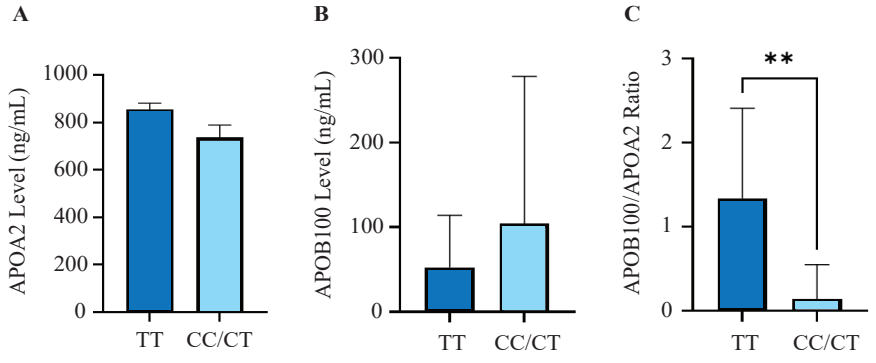

Figure 2. Different levels of APOA2 (A), APOB100 (B), and APOB100/APOA2 ratio (C) in TT & CC/CT genotype groups. Calculated with Mann-Whitney test, the data was presented in median (95% CI). **represents significant difference with p<0.01.

Table 5. Regression results for the APOA2–265 T>C polymorphism and its association with lipid profiles.

Parameter	Genotype	Odds Ratio (OR)	95% CI	*p* -value	p_{corr}
APOA2 Level	TT	Reference	-	-	-
	CT/CC	0.68	0.45 – 1.02	0.0650	0.3900
APOB100/APOA2 Ratio	TT	Reference	-	-	-
	CT/CC	1.52	1.12 – 2.05	0.0080	0.0480*
Total Cholesterol	TT	Reference	-	-	-
	CT/CC	0.92	0.67 – 1.26	0.5800	3.4800
LDL	TT	Reference	-	-	-
	CT/CC	0.89	0.64 – 1.24	0.4700	2.8200
HDL	TT	Reference	-	-	-
	CT/CC	1.05	0.75 – 1.47	0.7800	4.6800
Triglycerides	TT	Reference	-	-	-
	CT/CC	1.10	0.83 – 1.47	0.5000	3.0000
Body Fat Percentage	TT	Reference	-	-	-
	CT/CC	1.15	0.85 – 1.55	0.3600	2.1600

ORs are calculated for the CT/CC genotypes relative to the TT genotype. 95% CI provides a range within which the true OR is likely to fall. *p*-value indicates the statistical significance of the association before correction. p_{corr} represents the *p*-value after Bonferroni correction for multiple comparisons. *Significant if $p<0.05$.

compared to those with the TT genotype. The APOB100/APOA2 ratio remained significantly associated with the CT/CC genotypes even after Bonferroni correction, highlighting its potential as a robust marker for CVD risk. This aligns with previous studies indicating that the APOB100/APOA2 ratio is a superior predictor of coronary heart disease compared to individual lipid parameters such as total cholesterol, LDL, and HDL.(9,17) This apolipoprotein ratios, like the APOB100/APOA2 ratio, reflects the balance between pro-atherogenic and anti-atherogenic lipoproteins, providing a comprehensive assessment of lipid-related CVD risk that often outperforms traditional lipid markers in predicting cardiovascular events.(18) However, it is important to note that this result could be influenced by the small sample size, which may limit the generalizability of the findings.

Interestingly, the *APOA2* polymorphism did not show significant associations with other lipid profiles, such as total cholesterol, LDL, HDL, triglycerides, or body fat percentage, after adjusting for confounders. This indicates that genetic variation may not independently affect these parameters. However, the higher median body fat percentage observed in the CC/CT genotype group suggests a potential impact of the *APOA2* polymorphism on body fat distribution, although no significant differences were detected after applying the Bonferroni correction. This trend implies that more precise body composition measurement tools, such as dual-energy X-ray absorptiometry (DXA) or magnetic resonance imaging (MRI), might reveal subtle differences. Increased body fat percentage is associated with various metabolic disorders, including insulin resistance and metabolic syndrome.(19,20) The higher body fat percentage in the CC/CT genotype group may indicate a greater susceptibility to obesity-related complications, which are closely linked to cardiovascular health.(21)

The observed inverse relationship between APOA2 and APOB100 levels aligns with existing literature suggesting that these apolipoproteins have opposite roles in lipid metabolism. APOA2, a component of HDL, influences reverse cholesterol transport, whereas APOB100 is primarily involved in the transport of cholesterol to peripheral tissues.(8,22) The higher APOB100/APOA2 ratio in the CC/CT genotype group further underscores the potential risk of CVD in these individuals. Elevated levels of APOB100 relative to APOA2 suggest an imbalance favoring atherogenesis, a critical factor in the development of coronary artery disease.(23,24)

While the logistic regression analysis did not identify significant predictors of genotype status when adjusting for confounders, the trend towards significance for APOA2 suggests its potential role in CVD risk stratification. Understanding the genetic basis of lipid metabolism and body

composition can aid in developing personalized healthcare strategies. While the APOA2–265 T>C polymorphism did not show statistically significant differences in all lipid parameters, the trends observed suggest potential clinical relevance. Individuals with the TT genotype, despite having lower body fat percentages, may be at higher risk for dyslipidemia and related cardiovascular conditions. (25,26) Conversely, those with the CC/CT genotype may need to monitor body fat levels and associated metabolic risks closely.(27,28)

The current study has small sample size, particularly the limited number of individuals with the CC genotype, and the lack of control for confounding factors such as dietary pattern, physical activity, and lifestyle. This constraint may have reduced the statistical power to detect significant differences and increased the risk of type II errors (false negatives). Future studies should incorporate larger and more diverse populations to confirm these findings. Additionally, longitudinal studies examining the long-term impact of the *APOA2* polymorphism on lipid profiles and body composition would provide more comprehensive insights. Further research should also explore the interaction of *APOA2* with other genetic and environmental factors to understand the complex mechanisms underlying lipid metabolism and body composition. Further investigation of the combined effects of multiple genetic polymorphisms may help to identify individuals at higher risk for metabolic and CVD, enabling targeted interventions.

Conclusion

The APOA2–265 T>C polymorphism is linked to variations in lipid profiles and body composition, potentially increasing cardiovascular risk in individuals with the CT/CC genotypes. However, due to small sample size, the clinical utility of *APOA2* genotyping for risk stratification is uncertain. Further research with large, diverse populations is needed to validate these findings and explore their clinical implications.

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Authors Contribution

MDH and IH were responsible for the conceptualization and planning of the research, carried out the data acquisition and collection. MDH, IH, JPS and RLV calculated experimental data, and conducted the analysis. MDH, IH, JPS and AJ wrote the manuscript and created the figures. MDH, NP, KSA, MA, and GA provided critical revisions to the manuscript.

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