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Original Article

Divergent roles of circulating miR-133 and miR-155 in modulating angiotensin II levels among hypertensive patients in Melanesian and non-Melanesian populations

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Abstract

The therapeutic approach to hypertension often varies across racial and ethnic groups; however, antihypertensive treatments have not yet been tailored to account for these variations in Indonesia, a country with diverse racial and ethnic groups. In addition, microRNA-133 (miR-133) and microRNA-155 (miR-155) play critical roles in cardiac muscle homeostasis and inflammatory responses, but their specific functions in hypertension remain unclear. The aim of this study was to investigate the correlation between circulating miR-133 and miR-155 levels and angiotensin II (ANG-II) levels in hypertensive patients from Melanesian and non-Melanesian populations in Indonesia. A cross-sectional study was conducted in Jayapura, Indonesia among Melanesian and non-Melanesian hypertensive patients. The levels of ANG-II were quantified using sandwich ELISA, while the relative expression of miR-133 and miR-155 levels were measured by real-time PCR. Differences between the two groups were assessed using the Mann-Whitney test, and correlations between miR and ANG-II levels were determined using the Spearman correlation test. The relative expression levels of miR-133 and miR-155 in the Melanesian group were significantly higher than in the non-Melanesian group; 6.94-fold (3.85 vs 0.55) and 2.1-fold higher (0.19 vs 0.09), respectively. MiR-133 had a moderate negative correlation with ANG-II in both Melanesian (r=-0.538; p<0.001) and non-Melanesian (r=-0.649; p<0.001). However, miR-155 had no significant correlation with ANG-II levels in either the Melanesian group (p=0.551) or non-Melanesian group (p=0.159). This study highlights that miR-133 levels are significantly correlated with ANG-II concentrations in both Melanesian and non-Melanesian hypertensive patients, suggesting that miR-133 may play a regulatory role in the ANG-II pathway. These findings provide insights into the potential of miR-133 as a biomarker for hypertension management in diverse populations.

Keywords: Hypertension, angiotensin II, Melanesia, microRNA, small RNA

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Introduction

Hypertension is a primary risk factor contributing to cardiovascular diseases, which remain the leading cause of mortality globally [1]. Data from the world health organization (WHO) in 2021 state that hypertension is responsible for approximately 9.4 million deaths annually worldwide [2,3]. Hypertension-related diseases, such as coronary artery disease and stroke, are the leading causes of hypertension-related deaths [4]. It is estimated that 46% of adults with hypertension

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are unaware of their condition, and only 42% of the total hypertensive population have been diagnosed [5]. This lack of awareness exacerbates the progression of hypertension into cardiovascular complications, including heart disease. Additionally, the utilization of antihypertensive drugs is influenced by multiple factors, including race [6]. Evidence suggests significant disparities in antihypertensive drug use between white and black populations [7]. In addition, the therapeutic approach to hypertension differs across racial groups in regions such as Europe, Africa, the Americas, and Asia, as demonstrated by WHO in its guideline for the pharmacological treatment of hypertension in adults [8]. However, in Indonesia, antihypertensive treatment has not yet been tailored to account for racial or ethnic variations.

Indonesia has a substantial Melanesian population, estimated at 13 million people [9], primarily residing in Papua, East Nusa Tenggara, and the Maluku Islands [10]. The significant presence of the Melanesian population in Indonesia elevates the severity of hypertension to a critical public health issue. A previous study conducted in Jayapura demonstrated that the Melanesian ethnic group exhibited a higher prevalence of metabolic syndrome compared to the non-Melanesian population, with hypertension being particularly prominent [11]. Grade 2 hypertension was predominantly observed in the Melanesian population, with a prevalence of 33.6% in Mamberamo Raya Regency, Papua Province [11]. Another study from West Papua further indicated that the Melanesian group was more susceptible to hypertension-related complications, such as coronary heart disease [12]. Given the high prevalence of hypertension in Indonesia's Melanesian population, it is important to conduct further research into the genetic and epigenetic factors contributing to this condition.

Genetic factors in hypertension involve the *angiotensinogen* (*AGT)* gene, which is critical in the renin-angiotensin-aldosterone system (RAAS). The *AGT* gene encodes angiotensinogen protein, which is converted into angiotensin II (ANG-II), a potent vasoconstrictor [13]. A previous study indicated that *AGT* gene expression leads to elevated levels of ANG-II [14]. ANG-II activates the angiotensin II type 1 receptor (AGTR1), inducing vasoconstriction in smooth muscle cells [15], thereby contributing to elevated blood pressure in hypertensive patients [16]. However, research focusing on ANG-II has primarily addressed its role in blood pressure regulation, without fully elucidating the severity of hypertension progression towards cardiovascular disease. Epigenetic mechanisms offer a promising avenue for identifying biomarkers that can more accurately reflect the severity of hypertension and its progression to cardiovascular pathology. Epigenetic factors such as microRNA-133 (miR-133) and microRNA-155 (miR-155) may play a significant role in the severity of hypertension. Circulating plasma miR-133 levels in patients with arterial hypertension and obesity have been established as biomarkers frequently used to predict the severity of hypertension in the pathogenesis and development of hypertension heart disease [17]. The interaction between miR-133 and ANG-II concentrations could reflect cardiac muscle homeostasis and may help mitigate hypertrophic changes [18]. On the other hand, miR-155 is implicated in the modulation of inflammatory responses associated with hypertension [19]. miR-155 interacts with the ATR1, which is activated by ANG-II to promote vasoconstriction [20]. Variations in the expression levels of miR-133 and miR-155 and their correlation with ANG-II concentrations may provide valuable insights into the degree of hypertension severity and its potential progression.

Therefore, the aim of this study was to investigate the correlation between circulating miR-133 and miR-155 levels and ANG-II concentrations in hypertensive patients from both Melanesian and non-Melanesian populations in Indonesia. By elucidating the roles of these microRNAs (miRs) in the regulation of ANG-II and blood pressure, this research sought to provide novel insights into mechanisms underlying hypertension severity. The findings may contribute to the development of preventive strategies for mitigating hypertension and associated cardiovascular diseases in genetically diverse populations.

Methods

Study design and setting

A cross-sectional study was conducted in Jayapura, Papua Province, Indonesia, involving hypertensive patients from Melanesian and non-Melanesian populations. Hypertensive patients

from healthcare facilities who consented to participate in the study were interviewed, and underwent physical examinations and laboratory tests. Interviews were conducted to gather information on Melanesian or non-Melanesian ancestry, smoking status, alcohol consumption, and physical activity. Physical examinations assessed blood pressure, weight, height, and waist circumference. The laboratory tests included fasting glucose, urine analysis, creatinine levels, and measurements of miR-133 and miR-155 levels.

Patients and criteria

This study included Melanesian and non-Melanesian hypertensive patients with inclusion criteria of ages 30–50 years who have not consumed any antihypertensive medication in the past five weeks. The Melanesian individuals were those with Melanesian ancestry from both the father and mother, while non-Melanesians had ancestry from both parents who were of non-Melanesian descent residing in Jayapura (Javanese, Bugis, and Sundanese ethnicities). All patients on antihypertensive treatment or with a history of acute myocardial infarction, heart failure, valvular abnormalities, congenital heart disease, kidney failure, and diabetes were excluded from the study.

Sample size and sampling

The sample size for this study was calculated based on the minimum sample size required for correlation analysis. The correlation coefficient (r=0.303) was obtained from a relevant previous study (p=0.007) [21]. A one-tailed significance level (α=0.05) was chosen, and the power was set at 80% to minimize the risk of a Type II error. Based on these parameters, the minimum required sample size was determined to be 67 participants. In this study, plasma samples were collected from 79 hypertensive patients, including 39 individuals from the Melanesian population and 41 from the non-Melanesian population. The samples were recruited using a convenience sampling method, following the inclusion and exclusion criteria.

Data collection

The subjects involved were patients from primary healthcare facilities in Jayapura, Indonesia. Data collection was conducted with the subjects' informed consent, ensuring voluntary participation. The confidentiality of the subjects' data was guaranteed through de-identification. The procedure began with obtaining consent, followed by interviews, physical examinations, blood collection, and laboratory tests. The interviews assessed ethnicity, physical activity, smoking status, and alcohol consumption. The ethnicity interview included questions about the father's and mother's ethnic backgrounds for classification into Melanesian or non-Melanesian groups. The physical activity interview aimed to assess the subjects' daily activities and the duration of exercise in minutes. Smoking and alcohol consumption questions were closed-ended, with responses recorded as 'yes' or 'no.' Blood pressure measurements were conducted by medical staff from the Jayapura Health Center using an automatic sphygmomanometer (Omron, Kyoto, Japan). Blood pressure was measured three times, and the average of these measurements was used in the study. Physical examinations were conducted to assess the physical parameters of subjects in both the Melanesian and non-Melanesian populations, including measurements of body weight, height, and waist circumference. A total of 3 mL of venous blood samples were collected for laboratory tests. After a short centrifugation at 3,000 × g for 10 minutes, the isolated plasma was used for fasting blood glucose, urea, and creatinine measurements which were performed at Litbangkes Jayapura, Indonesia. Additional blood samples were transferred to the National Cardiovascular Center Harapan Kita Hospital, Jakarta, Indonesia, where they were stored in a -80°C freezer before further use.

Laboratory measurement

Fasting blood glucose levels, urea, and creatinine were measured using spectrophotometry at Litbangkes, Jayapura, Indonesia. The creatinine examination was conducted using the spectrophotometric method based on the Jaffe method principle [22] using reagents from Merck (Merck, Darmstadt, Germany). Blood glucose testing was performed using the glucose oxidase-peroxidase (GOD-POD) enzymatic method [23] using dedicated reagents from Roche (Roche, Mannheim, Germany). Blood urea levels were measured using the urease-Berthelot enzymatic

reaction [24]. All absorbances were measured using a spectrophotometer (Thermo Fisher Scientific, California, USA).

ANG-II measurement

The levels of ANG-II were measured using the sandwich ELISA technique with the Human Angiotensin II ELISA kit (Elabscience, Texas, USA). Plasma samples (50 µL each) were incubated with antibodies immobilized on the wells of an ELISA plate. Each sample, along with standards and blanks, was tested in duplicate. The ELISA procedure was performed following the manufacturer's protocol. Optical density (OD) readings were measured at 450 nm using a Multiskan GO ELISA reader (Thermo Fisher Scientific, California, USA). The OD values were then converted into plasma ANG-II concentrations using a 4-parameter logistic (4PL) standard curve.

MiR-133 and miR-155 measurements

RNA was isolated from plasma using the miRNeasy Serum/Plasma Kit (Qiagen, California, USA) with a sample volume of 200 µL sample, adhering strictly to the manufacturer's protocol. To quantify the RNA, 2 µL of the total isolated RNA was measured using a Multiskan-Go spectrophotometer (Thermo Fisher Scientific, California, USA) and the RNA concentration was then standardized to 2 ng/µL as templates for cDNA synthesis targeting miR-133 or miR-155. Reverse transcription was conducted using the TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems, California, USA) in conjunction with TaqMan primers specific for miR-133 or miR-155 (Applied Biosystems, California, USA). A reaction mix of 10.5 µL was combined with 4.5 µL of RNA template, yielding a total reaction volume of 15 µL. The reverse transcription reactions were performed on an ABI Veriti 9902 Thermal Cycler (Applied Biosystems, California, USA). The thermal cycling protocol was as follows: initiation at 16°C for 30 minutes, followed by 40 cycles of annealing and elongation at 42°C for 30 minutes, denaturation at 85°C for 5 minutes, and a final hold at 4°C. The cDNA product was subjected to real-time PCR analysis using TaqMan Fast Advanced Master Mix (Applied Biosystems, California, USA), and the TaqMan miR-133 or miR-155 Assay (Applied Biosystems, California, USA). The reaction mix was prepared with a final volume of 15.5 µL per well, to which 4.5 µL of the cDNA template was added. Real-time PCR was performed using the ABI 7500 fast real-time PCR system (Applied Biosystems, California, USA). The thermal cycling protocol was set to the comparative CT method, with the following parameters: an initial incubation at 50°C for 2 minutes, activation at 95°C for 20 seconds, denaturation at 95°C for 3 seconds, and annealing at 60°C for 30 seconds, for a total of 40 cycles. The data were collected as CT values and analyzed using the $2^{-\Delta\Delta CT}$ method.

Statistical analysis

To determine the differences in demographics, clinical, and laboratory data between Melanesian and non-Melanesian groups, Chi-squared test, Mann-Whitney test, or independent student t-test were used as appropriate. Comparison of ANG-II and relative levels of miR-133 and miR-155 between Melanesian and non-Melanesian groups were conducted using independent Student's t-test or Mann-Whitney U test, as appropriate. The correlations and associations between clinical and laboratory variables and relative expression of miRs were conducted using Spearman correlation and Mann-Whitney test, respectively. Statistical analyses were conducted using SPSS software version 29.0.0.0 (IBM, New York, USA).

Results

Patients' characteristics of hypertensive patients

The characteristics of hypertensive patients from Melanesian and non-Melanesian populations included in this study are presented in **Table 1**. Our data suggested a significant age difference between the groups, with the Melanesian group being younger than the non-Melanesian group (median 46 vs 50 years) (p=0.002). Additionally, there was a significant difference in abdominal circumference between the two populations, with the Melanesian population exhibiting a larger abdominal circumference than the non-Melanesian population (**Table 1**). No significant differences were observed between the two groups across other demographic variables.

Table 1. Demographic data of hypertension patients of Melanesian and non-Melanesian populations from Jayapura, Indonesia

Characteristic	Melanesian (n=38) n (%)	Non-Melanesian (n=41) n (%)	*p*-value
Sex			
Male	6 (15.8)	11 (26.8)	0.358[a]
Female	32 (84.2)	30 (73.2)	
Age (year), median (range)	46 (34–55)	50 (34–55)	0.027[b*]
Body weight (kg), median (range)	70 (40–95)	65 (51–98)	0.222[b]
Height (cm), median (range)	153.5 (142–184)	155 (145–172)	0.825[b]
Body mass index (kg/m²), mean±SD	28.6±5.0	27.6±4.2	0.341[c]
Body mass index category			
Underweight	2 (5.3)	0 (0)	0.186[a]
Normal	6 (15.8)	11 (26.8)	
Overweight	30 (78.9)	30 (73.2)	
Abdominal circumference (cm), mean±SD	96.3±11.3	90.8±10.5	0.026[c*]
Physic activity (minute/week), median (range)	720 (540–1020)	720 (540–1080)	0.091[b]
Fasting serum glucose (mmol/L), median (range)	87.5 (51–193)	101 (61–355)	0.060[b]
Urea (mg/dL), median (range)	23 (14–43)	22.5 (15–59)	0.328[b]
Creatinine (mg/dL), median (range)	0.9 (0.7–1.5)	0.9 (0.7–2.2)	0.612[b]
Smoking	7 (18.4)	5 (12.2)	0.648[a]
Alcohol consumption	4 (10.5)	3 (7.3)	0.705[a]
Systolic blood pressure (mmHg)			
Hypertension grade 1 (140–159)	21 (55.3)	18 (43.9)	0.571[a]
Hypertension grade 2 (160–179)	11 (28.9)	16 (39)	
Hypertension grade 3 (≥180)	6 (15.8)	7 (17.1)	
Diastolic blood pressure (mmHg)			
Hypertension grade 1 (85–89)	7 (18.4)	13 (31.7)	0.387[a]
Hypertension grade 2 (90–99)	19 (50)	18 (43.9)	
Hypertension grade 3 (100–120)	12 (31.6)	10 (24.4)	

[a]Analyzed using Chi-squared test
[b]Analyzed using Mann-Whitney test
[c]Analyzed using an independent Student t-test
[*]Statistically significant at $p<0.05$

Comparison of ANG-II levels between hypertension patients of Melanesian and non-Melanesian populations

Given the non-normal distribution of the data, ANG-II concentration was analyzed using the Mann-Whitney U test, and the findings demonstrated no statistically significant difference between the Melanesian and non-Melanesian populations (**Figure 1**). Nonetheless, the ANG-II concentration was higher in the non-Melanesian population compared to the Melanesian population (**Figure 1**).

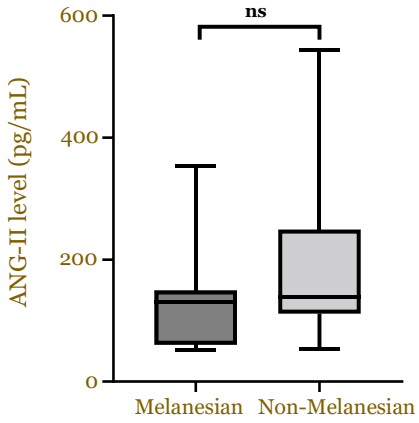

Figure 1. Comparison of angiotensin II (ANG-II) levels between Melanesian and non-Melanesian hypertension patients. Ns: not significant.

Comparison of relative expression miR-133 and miR-155 between hypertension patients of Melanesian and non-Melanesian populations

The relative expression of miR-133 in the Melanesian population was 3.85 (0.81–21.02), and 0.55 (0.08–4.30) in the non-Melanesian population. The relative expression level of miR-133 in the Melanesian population was 6.94-fold higher than in the non-Melanesian population (p<0.001) (**Figure 2A**). A similar difference was observed for miR-155. The relative expression of miR-155 in the Melanesian population was 0.19 (0.02–2.11) and 0.09 (0.02–1.06) in the non-Melanesian population (**Figure 2B**). The relative expression of miR-155 was 2.1-fold higher in the Melanesian population compared to the non-Melanesian population (p=0.001).

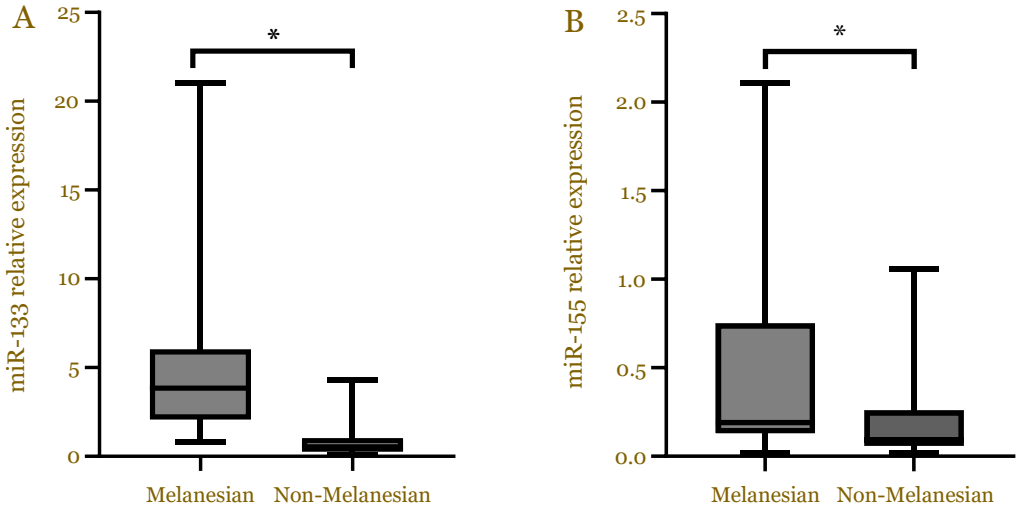

Figure 2. Comparison of microRNA-133 (miR-133) and microRNA-155 (miR-155) relative expression in Melanesian and non-Melanesian populations. Comparison of miR-133 (A), comparison of miR-155 (B).

Correlation of relative expression miR-133 and miR-155 and ANG-II in hypertension patients of Melanesian and non-Melanesian populations

Correlations between the relative expression miR-133 and miR-155 and ANG-II were measured using Spearman correlation analysis, and the results are presented in **Table 2** and **Figure 3**. The results showed that miR-133 was negatively correlated with ANG-II levels in both the Melanesian and non-Melanesian populations. In contrast, miR-155 showed no correlation with ANG-II levels in either the Melanesian or non-Melanesian populations (**Table 2**).

Table 2. Correlation between microRNA-133 (miR-133) and microRNA-155 (miR-155) expression with angiotensin II (ANG-II) levels in hypertension patients of Melanesian and non-Melanesian populations

Population	MicroRNA	ANG-II[a]	
		r	*p*-value
Melanesian	MiR-133[a]	-0.538	<0.001*
	MiR-155	0.100	0.551
Non-Melanesian	MiR-133[a]	-0.649	<0.001*
	MiR-155	-0.224	0.159

[a]Analyzed using Spearman correlation test
*Statistically significant at p<0.05

Factors associated with relative expression of miR-133 and miR-155 in hypertension patients of Melanesian and non-Melanesian populations

The correlation and associations between clinical and laboratory variables with relative expression of mRNAs were conducted, and the results are presented in **Table 3** and **Table 4**. There was a moderate correlation between creatinine levels and relative expression of miR-133a in the Melanesian population (r=0.370; p=0.022) (**Table 3**). Additionally, in the Melanesian population, there was a weak positive correlation between fasting blood glucose levels and miR-

155 expression (r=0.349; p=0.032) (**Table 3**). In the non-Melanesian population, a significant difference in the relative expression of miR-133a was observed based on smoking status (p=0.017) (**Table 4**). In addition, there was a significant difference in miR-133a expression based on sex in the Melanesian group (p=0.013) (**Table 4**). The relative expression of miR-133a and miR-155 did not demonstrate any significant association with systolic or diastolic blood pressure in either the Melanesian or non-Melanesian populations.

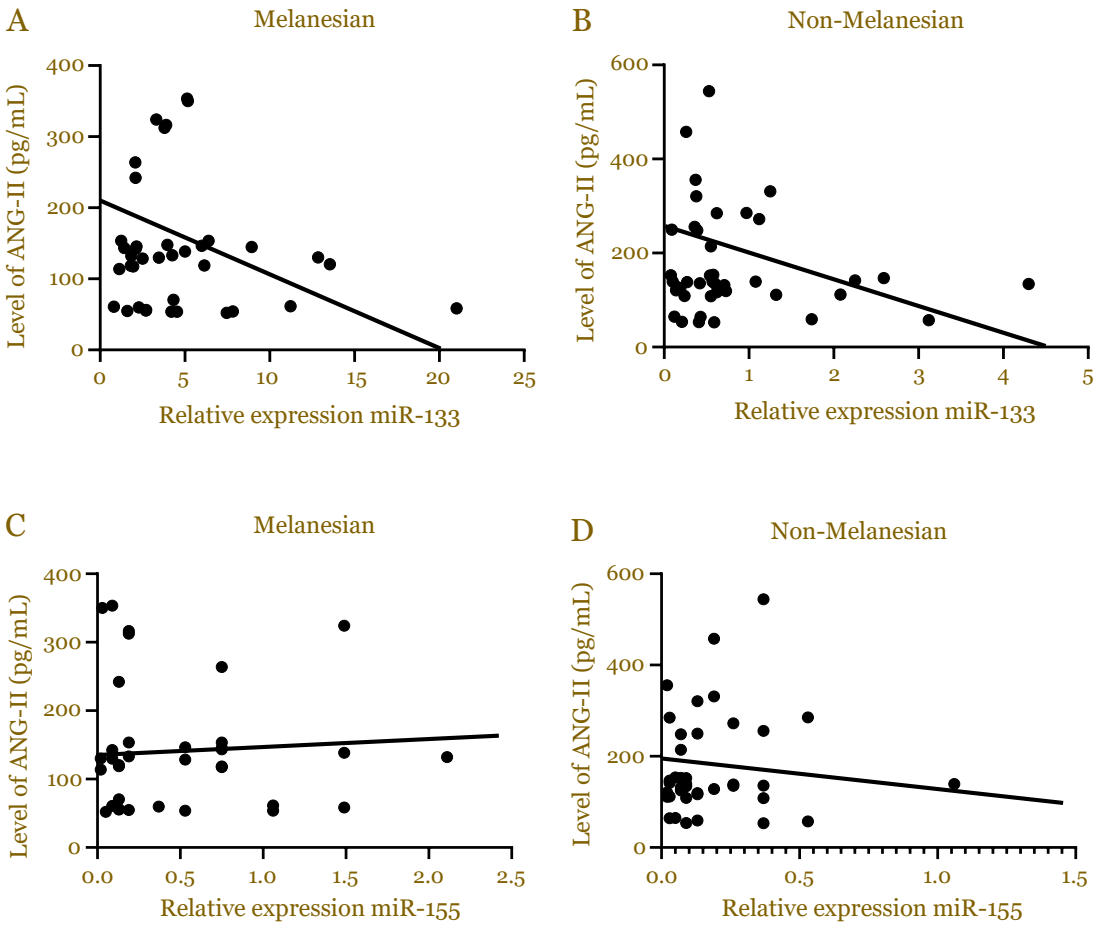

Figure 3. Correlation between relative expression of microRNA-133 (miR-133) (A and B) and microRNA-155 (miR-155) (C and D) with angiotensin II (ANG-II) levels in hypertension patients of Melanesian and non-Melanesian populations.

Discussion

Hypertension in specific populations may exhibit distinct characteristics. This study sought to identify any differences between Melanesian and non-Melanesian populations in Indonesia in terms of the levels of circulating miR-133, miR-155 and ANG-II. The involvement of ANG-II in the RAAS pathway plays a critical role in the elevation of blood pressure in hypertensive patients [25,26]. ANG-II is an active protein that can activate the ATR1 receptor, leading to vasoconstriction [27]. ANG-II is a critical component of the renin-angiotensin system, which plays a pivotal role in the regulation of blood pressure, electrolyte balance, and body fluid volume [21,26,28]. ANG-II is produced through the expression of *AGT* gene, which generates AGT-I that is subsequently converted into AGT-II by ACE-I [29,30]. ANG-II is a potent vasoconstrictor, inducing vasoconstriction and thereby elevating blood pressure [31,32]. Beyond its role as a vasoactive peptide, ANG-II also functions as a cytokine, influencing cell growth, inflammation, and fibrosis [33]. A study indicated that circulating ANG-II levels can range from 90 to 110 pg/mL [26]. In this study, the mean ANG-II levels were 156 pg/mL in the Melanesian population and 165 pg/mL in the non-Melanesian population. Our data indicated that the levels of ANG-II of Melanesian and non-Melanesian populations had no significant differences.

Table 3. Correlation between clinical factors and relative expression of microRNA-133 (miR-133) and microRNA-155 (miR-155) in Melanesian and non-Melanesian populations

Characteristic	Melanesian				Non-Melanesian			
	MiR-133a		MiR-155		MiR-133a		MiR-155	
	r	*p*-value[a]	*r*	*p*-value	*r*	*p*-value	*r*	*p*-value[a]
Blood pressure (systolic) (mmHg)	0.169	0.309	-0.109	0.515	0.139	0.386	0.026	0.871
Blood pressure (diastolic) (mmHg)	0.202	0.223	0.123	0.463	0.239	0.132	-0.138	0.388
Body mass index (kg/m²)	0.100	0.551	0.134	0.421	0.247	0.120	0.156	0.329
Abdominal circumference (cm)	-0.086	0.609	0.192	0.247	0.209	0.190	0.027	0.867
Physic activity (minute/week)	-0.133	0.425	-0.183	0.271	-0.184	0.250	-0.171	0.284
Fasting serum glucose (mmol/L)	-0.061	0.717	0.349	0.032*	0.152	0.344	-0.079	0.623
Urea (mg/dL)	0.252	0.127	0.030	0.857	-0.081	0.616	-0.077	0.632
Creatinine (mg/dL)	0.370	0.022*	-0.106	0.525	-0.146	0.361	-0.018	0.909
Age (years)	0.028	0.866	-0.213	0.199	-0.212	0.183	0.068	0.674

[a]Analyzed using Spearman correlation test
*Statistically significant at $p<0.05$

Table 4. Factors associated with relative expression of microRNA-133 (miR-133) and microRNA-155 (miR-155) expression in Melanesian and non-Melanesian populations

Characteristic	Melanesian				Non-Melanesian			
	MiR-133[a]		MiR-155[a]		MiR-133[a]		MiR-155[a]	
	Median (min-max)	*p*-value	Median (min-max)	*p*-value	Median (min-max)	*p*-value	Median (min-max)	*p*-value
Smoking								
Yes	4.33 (2.11–21.02)	0.080	0.13 (0.02–1.49)	0.582	0.21 (0.10–0.55)	0.017*	0.09 (0.05–0.09)	0.279
No	3.47 (0.81–11.23)		0.37 (0.02–2.11)		0.58 (0.08–4.30)		0.13 (0.02–1.06)	
Alcohol consumption								
Yes	8.38 (2.11–13.55)	0.216	0.11 (0.02–0.19)	0.055	0.12 (0.10–0.55)	0.080	0.07 (0.05–0.09)	0.268
No	3.63 (0.81–21.02)		0.45 (0.02–2.11)		0.56 (0.08–4.30)		0.13 (0.02–1.06)	
Sex								
Male	9.63 (3.31–21.02)	0.013*	0.47 (0.02–1.49)	0.531	0.38 (0.12–0.97)	0.217	0.09 (0.02–0.53)	0.496
Female	3.09 (0.81–11.23)		0.19 (0.02–2.11)		0.56 (0.08–4.30)		0.13 (0.02–1.06)	

[a] Analyzed using Mann-Whitney test
*Statistically significant at $p<0.05$

The level of ANG-II could be modulated by epigenetic mechanisms involving miR-133a and miR-155. MiR-133 is known to play a critical role in regulating gene expression associated with cardiac hypertrophy and muscle formation [34]. The contribution of miR-133 to hypertension leads to structural changes in the heart due to high blood pressure, such as left ventricular hypertrophy. MiR-133 could influence signaling pathways related to ANG-II, thereby reducing the vasoconstrictive effects induced by ANG-II [35]. MiR-133 affects ANG-II concentration in the RAAS pathway by inhibiting mRNA levels of ANG-II [35]. In addition, miR-155 has been identified as a key regulator in inflammatory and immune responses [36,37]. The involvement of miR-155 in hypertension is linked to pro-inflammatory signaling pathways induced by ANG-II [38]. The role of miR-155 in promoting vascular inflammation may contribute to vascular damage and the development of hypertension [19,39].

In this study, we found that the relative expression of miR-133 and miR-155 was higher in the Melanesian population compared to the non-Melanesian population. This suggests that there is greater inhibition of vasoconstriction and pro-inflammatory signaling in the Melanesian population. The elevated expression of miR-133 suggests the presence of a blood pressure-regulating mechanism in the Melanesian population. In addition, we found that miR-133 was negatively correlated with ANG-II concentration. Specifically, the higher the relative expression of miR-133, the lower the ANG-II concentration in both the Melanesian and non-Melanesian populations. MiR-133 plays a crucial role in maintaining endothelial function by regulating the PI3K/Akt pathway, which influences nitric oxide production [40]. A reduction in miR-133 results in endothelial dysfunction, contributing to chronic vasoconstriction and hypertension [40]. Furthermore, decreased miR-133 expression enhances the expression of the prorenin receptor, thereby activating the RAAS signaling pathway and promoting apoptosis [41].

We found no correlation between the relative expression of miR-155 and ANG-II, suggesting that other mechanisms and interactions may be involved. MiR-155 interacts with ATR1, which is activated by ANG-II [42,43]. MiR-155 is a known regulator of both endothelial nitric oxide synthase (eNOS) and AGTR1, which regulate blood vessel relaxation and constriction [44]. The increased expression of miR-155 suggests the induction of pro-inflammatory factors that may contribute to the severity of hypertension and its progression toward heart disease [45]. Another study reported that miR-155 was positively correlated with inflammatory markers such as C-reactive protein, interleukin-6, and blood pressure [46]. Nevertheless, we did not find a correlation between the relative expression of miR-155 and blood pressure in either the Melanesian or non-Melanesian populations.

Blood pressure differences may be influenced by dietary variations. Indigenous Papuans (Melanesian) typically consume a diet characterized by high fat content, low potassium levels, and elevated alcohol intake, whereas the non-Melanesian population tends to have excessive consumption of fat and sodium [47,48]. Furthermore, environmental factors, including living conditions, contribute to these disparities. Urban populations, with higher intake of processed and fast foods, exhibit an increased prevalence of diabetes and hypertension compared to rural Melanesian populations, such as those residing in the Solomon Islands [49].

The limitations of this study include the relatively small sample size, which may impact the generalizability of the findings. Additionally, genetic variability among individuals within the Melanesian and non-Melanesian populations could have influenced the results, underscoring the need for further research with larger cohorts and more comprehensive genetic analyses. Future studies employing longitudinal designs are necessary to elucidate the causal relationships between alterations in circulating miRs, ANG-II concentrations, and the progression of hypertension over time. Moreover, to accurately assess the genetic and epigenetic influences, the use of more advanced platforms is required. These platforms should be capable of exploring the interplay between genetic factors and the response to antihypertensive therapies through pharmacogenomics.

Conclusion

The relative expression of miR-133 and miR-155 differs significantly between Melanesian and non-Melanesian populations. MiR-133 expression exhibits a negative correlation with ANG-II concentration, whereas miR-155 does not demonstrate this correlation in both populations. The

inverse relationship between miR-133 and ANG-II concentration highlights the potential of miR-133 as a biomarker for hypertension protection and suggests its viability as a target for RNA-based therapeutic interventions via microRNA modulation.

Ethics approval

This study was approved by the Ethics Committee of the National Cardiovascular Center Harapan Kita Hospital, Jakarta, Indonesia, under approval number LB.02.01/VII/370/KEP.024/2023. Informed written consent was obtained from all participants before their inclusion in the study. The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants provided informed consent.

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Competing interests

The authors declared no potential conflicts of interest concerning this article's research, authorship, and publication.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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