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Article

Identification of Atherosclerosis Based on The Differences in Cholesterol and Creatinine in Indonesia with Multivariate Analysis of Variance

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Abstract. Atherosclerosis is a chronic inflammatory disease indicated by plaque build-up in the arteries due to increased total cholesterol, low-density lipoproteins (LDL), triglycerides, and decreased high-density lipoproteins (HDL). It is also associated with disruption of renal function high creatinine blood level. This study aims to identify atherosclerosis based on differences in total cholesterol, HDL, LDL, triglycerides, and creatinine levels in 35.509 residents from 33 provinces and rural-urban areas in Indonesia. This study uses two-factor MANOVA where the province and rural-urban are the factors, followed by ANOVA and Tukey's test. Results show differences between total cholesterol, HDL, LDL, triglyceride, and creatinine levels of the residents among provinces and rural-urban areas. The Residents from Bangka Belitung and North Sulawesi provinces have the highest risk of atherosclerosis, and Jambi province has the most balanced condition. Urban residents tend to be at risk for atherosclerosis due to high levels of LDL, while rural residents are at risk by low HDL or high creatinine levels

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1. Introduction

Atherosclerosis is a chronic inflammatory disease marked by plaque formed in the arteries due to fat build-up and causing a blockage [1-3] . One pathogenesis of atherosclerosis is dyslipidemia or lipid metabolism abnormality in the blood. Dyslipidemia and atherosclerosis have been established as the main risk factors for Coronary disease [4-5] . According to [6] along [7-8] states that about 71% or 41 million deaths in the world in 2016 was caused by non-communicable diseases (NCD), and about 43.44% or 17.9 million deaths were caused by cardiovascular disease (heart and blood vessel disease). The disease is also a significant cause of NCD in low to middle-income countries, as described in a study by [9] regarding the incidence of NCD based on its main risk factors to carry out further studies in determining other factors likely to influence similar diseases. Similar to the result of Riskesdas in 2007, 2013, and 2018 which showed the trend of increased NCD prevalence where coronary heart disease (CHD) is about 12.9 % and become the second leading cause of death after stroke in Indonesia [10].

Primary diagnosis of dyslipidemia was established after the increase of total cholesterol, low-density lipoprotein (LDL), triglyceride and the decrease of high-density lipoprotein (HDL) in blood [11-13]. According to [14-19]. stated that high cholesterol levels measured after total cholesterol, LDL, and triglyceride are the main risk factor in the pathogenesis of atherosclerosis. The study by [20-23] stated that HDL plays a role in preventing atherosclerosis. Besides the aforementioned criteria, dyslipidemia is also usually found in chronic renal disease (CKD) patients and associated with atherosclerosis [24-25] . The study by [26] stated that an increase in creatinine blood level is one of the signs of renal failure. In those patients, there will be a sudden decrease in renal function in filtering the blood from the toxic substance, causing heart disease.

The disease pattern in Indonesia is affected greatly by environmental changes, demography, economy, society, and culture. The lack of nutritional fulfillment caused by an unbalanced diet is related to poor health and increases the risk of getting NCD [27]. This condition is associated with the risk of atherosclerosis affected by diet and sociodemography [28-30]. On the same side, the variety of cultures in Indonesia also affects the people's diet. According to [31-32] stated that culture determines the behavior and eating habit of the population, which means that diet pattern will vary because of cultural differences. It is interesting to find out whether the risk pattern of atherosclerosis will be different along with the cultural differences in each region in Indonesia.

The differences in the residential area between rural and urban also affect the eating pattern of the population. According to [33-34], the changing environment from rural to urban is causing a change in eating patterns. Nowadays, the leading difference is the habit of urban residents consuming processed and fast food, which contains high-fat percentages. The data for [35] stated that monthly spending per capita for urban residents on processed food and drink is about 35.55%, while rural residents are 25.47%. Meanwhile, urban residents tend to have a sedentary lifestyle with less physical activities, which is on the opposite side of the effort to balance diet based on the government's policy [36].

This study's objective is to identification of atherosclerosis based on the differences in cholesterol blood levels, which are total cholesterol, HDL, LDL, triglyceride, and creatinine, of the Indonesian population. A similar study [37] discussed cardiovascular disease based on the risk factors for dyslipidemia, hypertension, and dysglycemia in rural-urban residents in South India. Meanwhile, in this study, identification of atherosclerosis was carried out by looking at differences in total cholesterol, HDL, LDL, triglyceride, and creatinine levels in the blood of the Indonesian population seen from the cultural differences in the eating patterns of the residents of each province and rural-urban areas. According to [38], total cholesterol, HDL, LDL, triglyceride, and creatinine have their role but relate to each other in atherosclerosis. The method used is two-factors multivariate analysis of variance (MANOVA) without interaction with different provinces and rural-urban areas as the primary factor. The MANOVA method is chosen because it will show the dependency between the variable measured [39-41].

2. Research Method

2.1. Data

The data used in the study is secondary data on cholesterol and creatinine levels of 35,509 people from 33 Provinces in Indonesia from the National Research and Innovation Agency (BRIN). The data contains information about total cholesterol, HDL, LDL, triglyceride, and creatinine levels of residents in 33 provinces and differentiated based on rural-urban areas in Indonesia. The total respondent adapted to the total population in each province resulted in disproportional data. In this study, total cholesterol, HDL, LDL, triglyceride, and creatinine are the variable response, and the explanatory variable are province and rural-urban.

2.2. Method

For example, there is k independent sample with n size comes from a p-variant population which is followed normality multivariate and homogeneity of covariance matrix then the Analysis Multivariate of Variance (MANOVA) model without interaction with factors A and B are below [42].

$$\boldsymbol{y}_{ij} = \boldsymbol{\mu} + \boldsymbol{\tau}_i + \boldsymbol{\beta}_j + \boldsymbol{\varepsilon}_{ij}$$
$$i = 1,2,\dots,a, \;\; j = 1,2,\dots,b$$

with $\boldsymbol{y}_{ij}$ as the vector response in factor A level-i and factor B level-j, $\boldsymbol{\mu}$ is the main vector, $\boldsymbol{\tau}_i$ is vector effect factor A level-i to vector response, $\boldsymbol{\beta}_j$ is vector effect factor B level-j to vector response, $\boldsymbol{\varepsilon}_{ij}$ is vector residual in factor A level-i and factor B level-j.

2.3 Procedure

This research is a quantitative study where the results are to be achieved in the differences of total cholesterol, HDL, LDL, triglycerides, and creatinine levels of residents between province and rural-urban areas in Indonesia. The implications are expected to provide an overview of the health condition of Indonesian residents, especially regarding the early detection of atherosclerosis. The data analysis technique in this research uses descriptive and inferential analysis using R-Studio and SPSS version 25.0 for windows. Descriptive analysis was used to describe total cholesterol, HDL, LDL, triglyceride, and creatinine residents in proportion percentage, which was grouped based on category, as shown in Table 1.

Table 1. Lipid blood level classification

Cholesterol Levels	Unit	Normal	Moderate	Abnormal
Total Cholesterol	mg/dL	<200	201 – 239	≥240
HDL	mg/dL	≥60	41 – 59	≤40
LDL	mg/dL	≤130	131 – 159	≥160
Triglyceride	mg/dL	<150	150 – 199	≥200

Source: processed from [43]

According to [44] stated that the normal creatinine level in Indonesia is 0.7 – 1.3 mg/dl in men, while in women is 0.6 – 1.1 mg/dl.

Inferential analysis was used to see the differences in total cholesterol, HDL, LDL, triglycerides, and creatinine residents between province and rural-urban in Indonesia using multivariate analysis of variance (MANOVA) with two factors. The complete analysis steps can be explained based on the flowchart in Figure 1.

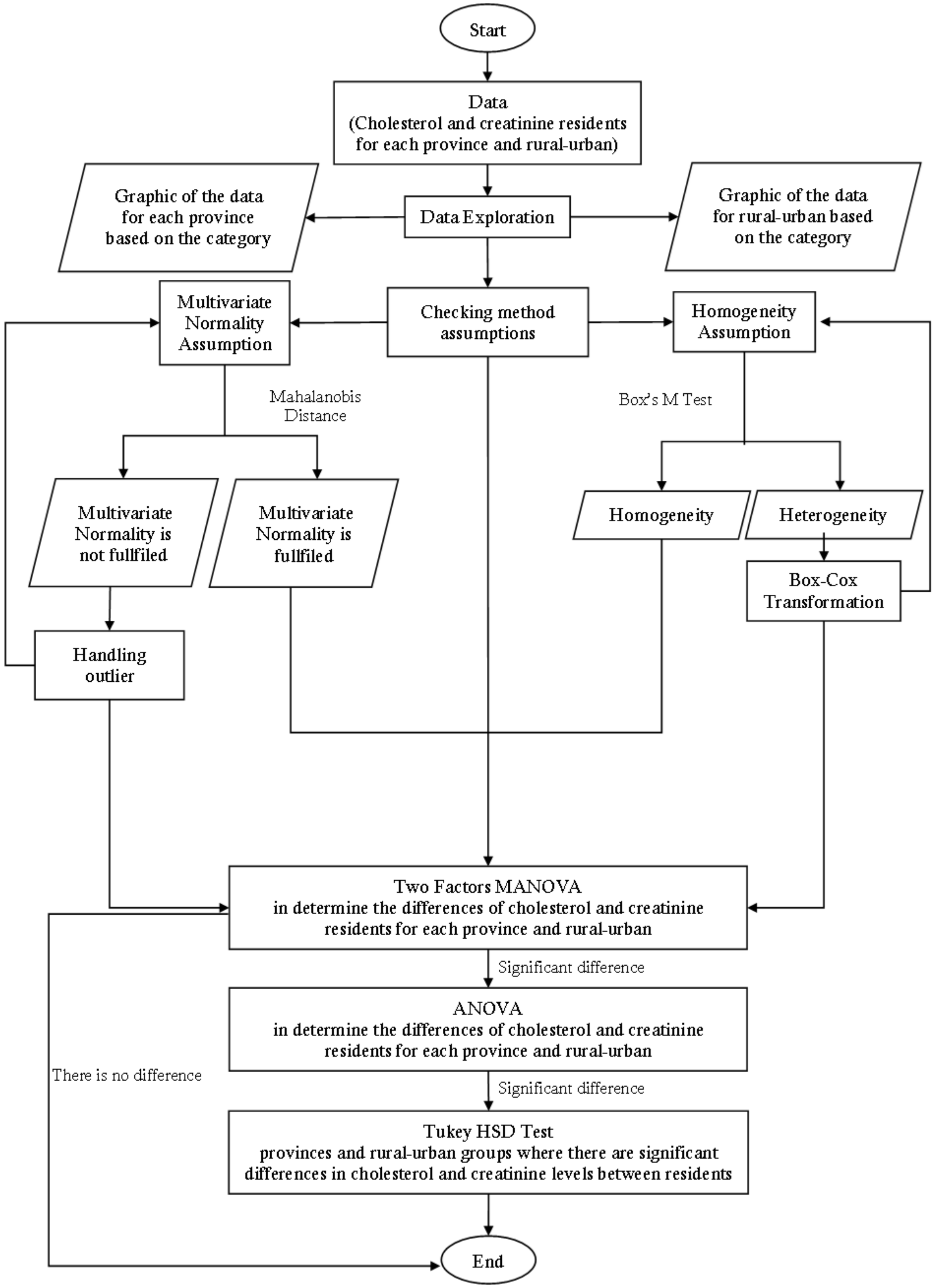

Figure 1. Research flow chart

The results of MANOVA can be accounted for when the data meets the assumptions of multivariate normality, homogeneity of within group factors variance covariance, and independence [45-46]. Fulfillment of multivariate normality assumptions can be carried out using the mahalanobis distance criterion. When plot mahalanobis distance (after sequenced) toward chi-square score for each object forms a straight line, then the data is distributed multivariate normal distribution. The other criteria can be used by correlating mahalanobis distance and chi-square score for each object. When correlation is present, it can be implied that the data has multivariate normal distribution [47-48]. If the criteria are unfulfilled, the outlier data will be deleted. Homogeneity assumptions can be checked using the Box's M test [49].

This test is susceptible to the non-normality of multivariate data, and the total data used is unbalanced in every factor category. If the data is not fulfilled the criteria for homogeneity, transformation Box-Cox will be done to each variable. Meanwhile, in this case, the assumption of independence is considered fulfilled because the data was collected by the related parties and experts in his field. The independent observation has usually been conditioned when the data has been extracted.

The analytical procedure uses the MANOVA method to find out the differences of variables measured together (multivariate) and will be continued with Analysis of Variance (ANOVA) to see the different characteristics in each variable when the result of the MANOVA test is significantly different. If the ANOVA test is significantly different too, then the post hoc Tukey HSD procedures will be done. Tukey HSD test determines the level pair of treatment factors with an evident difference in variable response

3. Results and Discussion

3.1. Data Exploration

The data contains information about the total cholesterol, HDL, LDL, triglyceride, and creatinine blood levels of 35,509 people from 33 Provinces and rural-urban in a city in Indonesia. The risk of atherosclerosis is higher when total cholesterol, HDL, LDL, triglyceride, and creatinine are abnormal. Figure 1 is the percentage of population proportion in every 33 provinces with total cholesterol, HDL, LDL, triglyceride, and creatinine blood levels grouped based on the category in Table 1.

3.1.1. Cholesterol and Creatinin Level Residents in Each Province

The result in Figure 2-5 shows that most people in each province have normal total cholesterol levels. The proportion of residents with the highest result with the biggest risk of atherosclerosis caused by abnormal total cholesterol levels comes from Bangka Belitung Island Province (code = 18), while East Nusa Tenggara Province (code = 53) is the lowest. Most of the people in each province have the poor condition in lowering the atherosclerosis risk, which can be seen from the result proportion where the HDL level in moderate and abnormal are bigger than the normal group. Jambi Province (code = 15) has the highest number for good results, while Papua Barat Province (code = 91) is the opposite.

Based on LDL level, the majority are prone to the risk of atherosclerosis, which can be seen from the proportion of residents in each province. The result of LDL is a moderate level. East Nusa Tenggara has the best result, while Central Sulawesi (code = 72) has the opposite. Based on triglyceride levels, most people tend to have a lower risk of atherosclerosis caused by excessive calories. North Maluku Province (code = 82) has the best result, while South Sulawesi Province (code = 73) has the worst. Meanwhile, the renal function of the residents is mostly normal, and the risk of atherosclerosis caused by renal disorder is low. Bengkulu Province (code = 17) has the best result, while North Sulawesi Province (code = 71) has the worst.

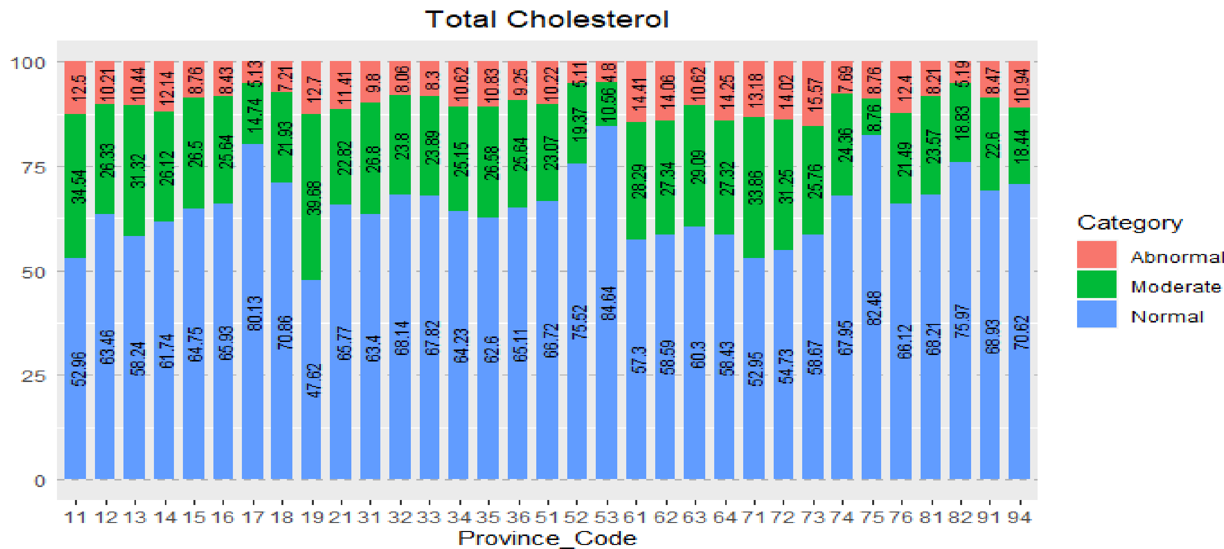

Figure 2. Percentage residents in each province according to category cholesterol

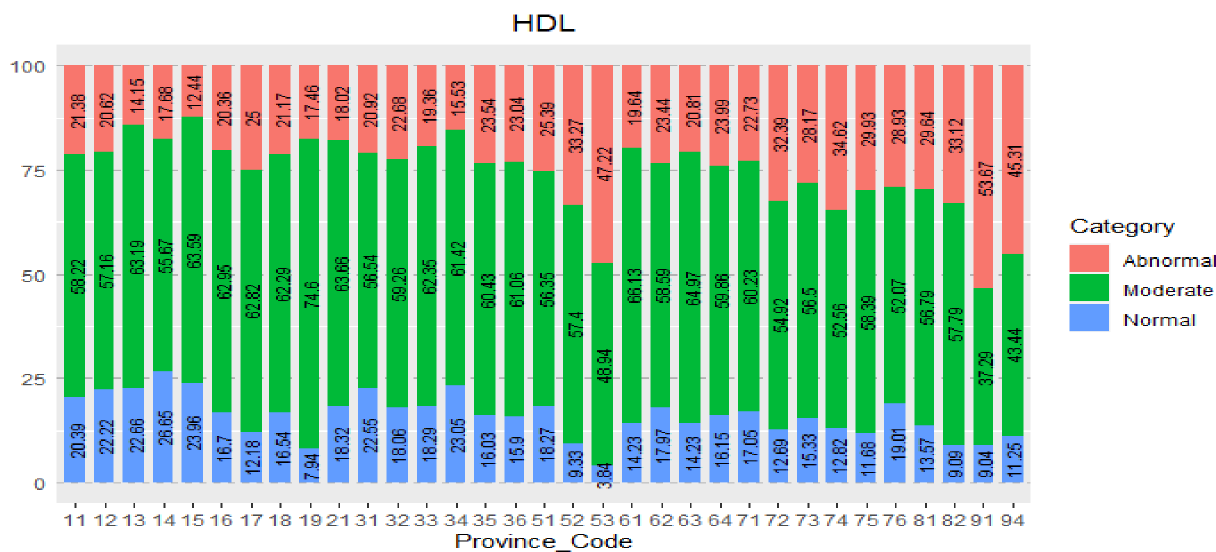

Figure 3. Percentage residents in each province according to category HDL

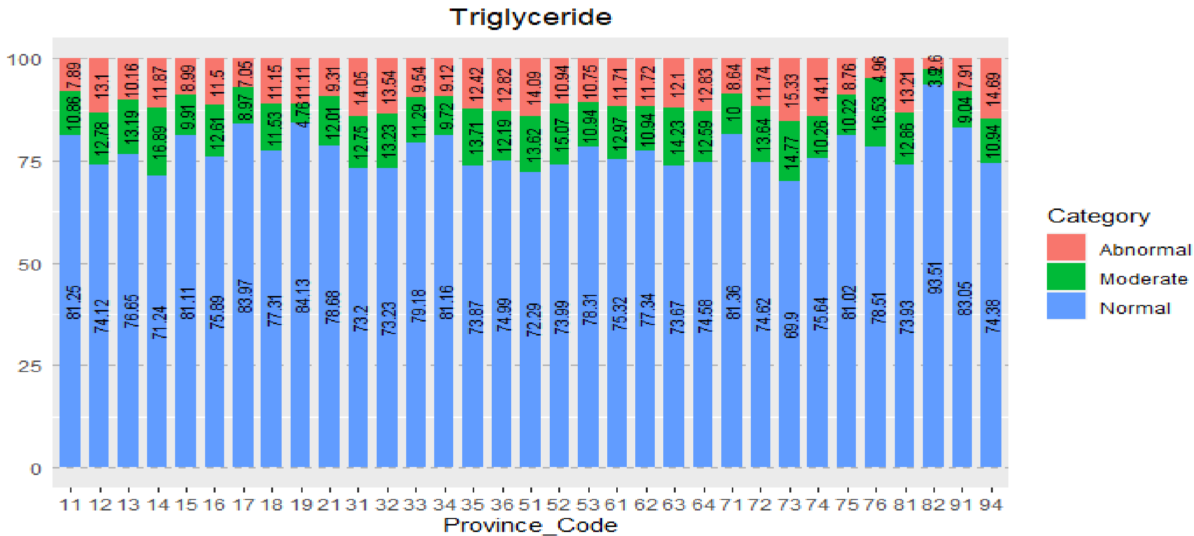

Figure 4. Percentage residents in each province according to category Triglyseride

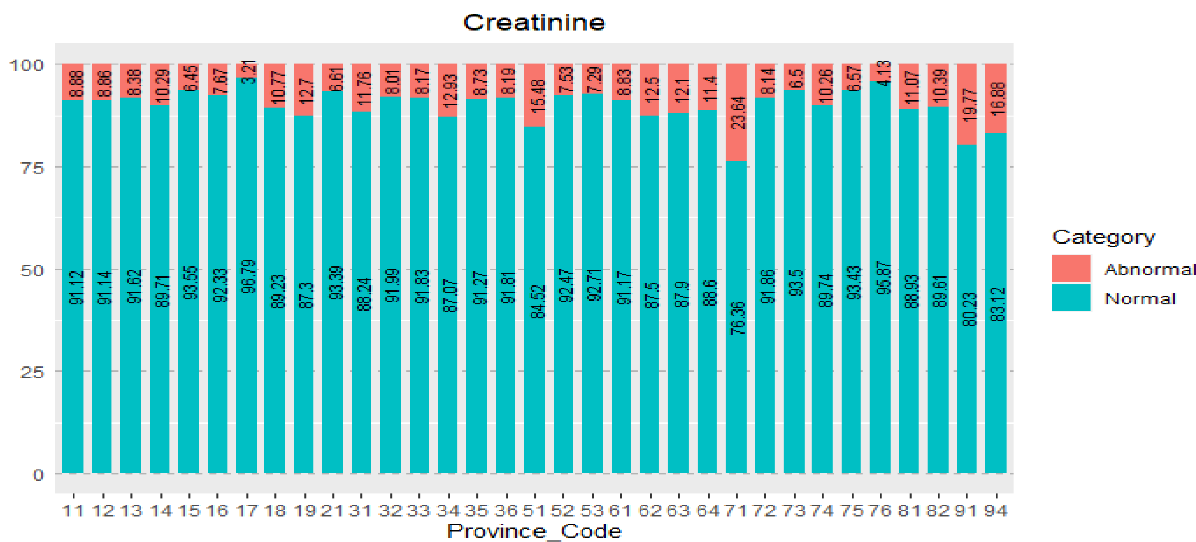

Figure 5. Percentage residents in each province according to category creatinine levels

3.1.2. Cholesterol and Creatinine Level of Residents Rural-Urban

Cholesterol and creatinine levels of residents in the rural-urban are presented by making the mean range plot, as seen in Figure 6. Rural residents' mean range of total cholesterol, LDL, and triglyceride is lower than urban residents. Meanwhile, the mean range of HDL of urban residents is slightly higher. Implying better cholesterol level of people in rural areas, which lower the risk of atherosclerosis. On the other hand, this does not necessarily eliminate the risk factor since rural residents have conditions that are still not optimal in preventing a similar disease. The renal function conditions of most rural and urban residents are good, which can be seen from the normal creatinine range. The mean range of creatinine-level urban residents is wider, indicating a more diverse renal function than rural residents.

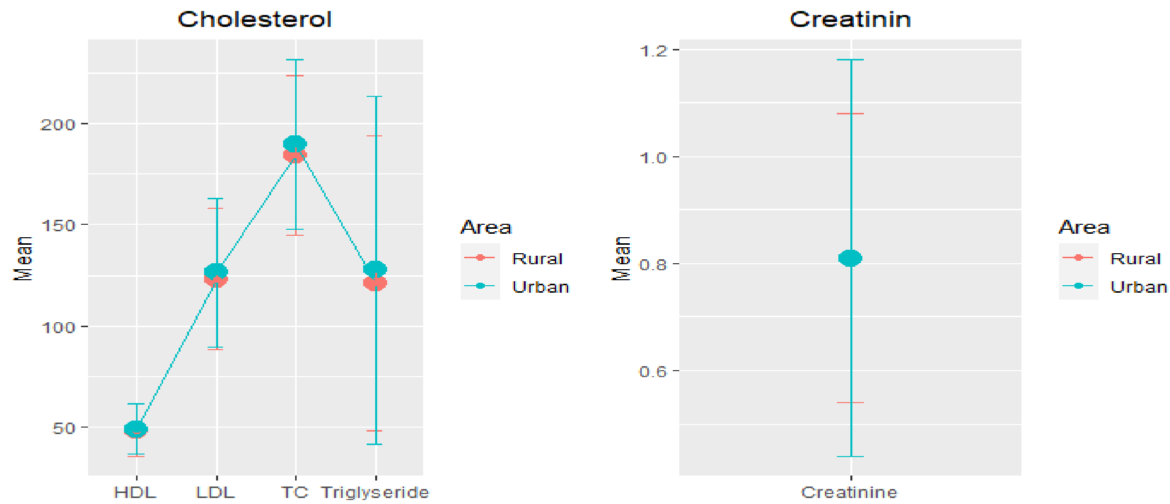

Figure 6. Mean of cholesterol and creatinin level of residents rural-urban

3.2. Checking Assumption

3.2.1. Multivariate Normality Assumption

Plot (a) in Figure 7 forms a non-linear relation pattern, meaning some indication of variable cholesterol creatinine levels are not following multivariate normality distribution. So, the data will be deleted, resulting in 30.685 from 35.509 data and transformation of the data for each variable. Plot (b) in Figure 4 is a quantile-quantile plot between mahalanobis distance and chi–square variable response after the data was processed. The plot forms a linear relation pattern, implying cholesterol and creatinine level variables after the data was processed following the multivariate normality distribution.

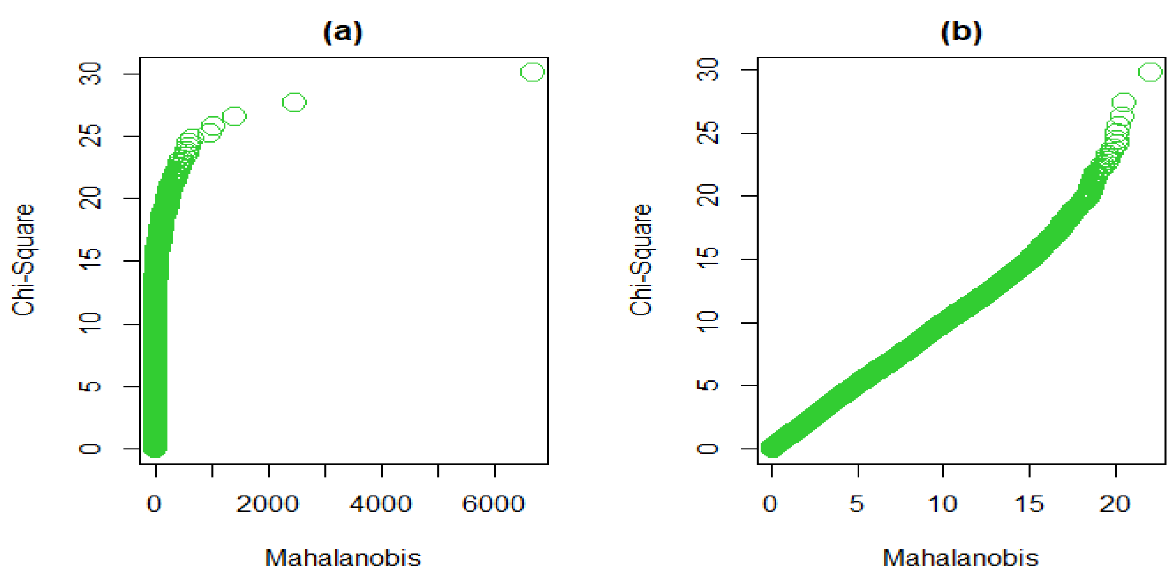

Figure 7. Quantile-quantile plot of cholesterol and creatinine levels (a) actual, (b) without outliers

The correlation of mahalanobis and chi-square strengthens the above result after processing the data. Table 2 shows the correlation result is 0.997 with p-value of 0.000, which is smaller than the significant level of 0.05. The result indicates that variables cholesterol and creatinine levels after the data was processed follows a multivariate normality distribution.

Table 2. Correlation Pearson of Mahalanobis Distance and Chi-Square

Category	*Pearson Corroelation*	*Sig. (p-value)*	Information
Mahalanobis and Chi-Square	0.997**	0.000	Strong Correlation

Note: sign ** indicates a significant correlation value up to 0.01

3.2.2. Homogeneity of Covariance Matrix Assumption

Box's M test result is the heterogeneity of the covariance matrix, so the assumption is not fulfilled. According to [50-51], recommends Pillai's Trace test as a benchmark in determining the result of the MANOVA test because it is able to detect the differences well and result in substance for the MANOVA test even when the normality and homogeneity assumption are not fulfilled.

3.3. Analysis of The Differences of Cholesterol and Creatinine Levels Between the Residents in Each Province and Rural-Urban with 2 Factors MANOVA

The differences in cholesterol and creatinine levels of residents in each province and rural-urban were analyzed simultaneously with two-factors MANOVA test without interaction. The analysis is continued with the two-factors ANOVA test to find the characteristics of residents' total cholesterol, HDL, LDL, triglyceride, and creatinine levels between province and urban-rural. Table 3 is the statistic of the analysis result.

Table 3. Statistic for two-factors MANOVA and ANOVA in differences of cholesterol and creatinine levels of residents in each province and rural-urban

	MANOVA				ANOVA		
	Effect	Value	F	p-value	response	F	p-value
Province	Pillai's Trace	0.102	20.009	0.000	Total Cholesterol	17.426	0.000
	Wilks' Lambda	0.901	20.079	0.000	HDL	22.236	0.000
	Lawley - Hotelling Trace	0.105	20.146	0.000	LDL	14.952	0.000
					Triglyceride	9.182	0.000
	Roy's	0.042	40.676	0.000	Creatinine	13.260	0.000
Rural-Urban	Pillai's Trace	0.008	49.299	0.000	Total Cholesterol	130.717	0.000
	Wilks' Lambda	0.992	49.299	0.000	HDL	32.124	0.000
	Lawley - Hotelling Trace	0.008	49.299	0.000	LDL	80.694	0.000
					Triglyceride	0.618	0.432
	Roy's	0.008	49.299	0.000	Creatinine	5.991	0.014

Pillai's Trace Statistical test in Table 3 resulted in a p-value of 0.000 for the province and rural-urban variable with a significant level of 5%. It means there is a difference in cholesterol and creatinine levels between residents in each province and rural-urban. The analysis is carried further with two-factors ANOVA test to find out the characteristics of residents' total cholesterol, HDL, LDL, triglyceride, and creatinine levels between province and rural-urban.

Statistic 2 factors ANOVA test in Table 3 resulted in a p-value of 0.000 for the factor province to every response variable in level 5%. This indicates a difference in total cholesterol, HDL, LDL, triglyceride, and creatinine levels, at least in residents between two provinces in Indonesia. Meanwhile, p-value < 0,05 is for the factor rural-urban to total cholesterol, HDL, LDL, and creatinine variables. It means there is a difference in total cholesterol, HDL, LDL, and creatinine levels in people in the rural and urban areas in Indonesia.

3.4. Tukey Test for The Differences of Cholesterol and Creatinine Levels of The Residents Between Provinces

Tukey HSD test resulted in 9, 9, 10, 3, 6 groups province with different mean for total cholesterol, HDL, LDL, triglyceride, and creatinine levels of residents. It is generally hard to describe the characteristic of differences because each response variabel mean score is overlapping. Based on this result, the re-grouping has been done to province groups where total cholesterol, HDL, LDL, triglyceride, and creatinine of the residents are low, transition, and high.

The transition group is divided into low to moderate, moderate, and moderate to high. Re-grouping is done subjectively by referring to specific criteria. The low and high groups are directly obtained from the Tukey HSD test. The high group was re-described based on the criteria for cholesterol and creatinine levels in Table 1 and other literature, such as the provincial group with high total cholesterol in their residents determined when the mean of total cholesterol greater than 190 mg/dl, according to [52]. Table 4 is the result of the re-grouping that was carried out.

Table 4. Regrouping provinces with differences in cholesterol and creatinine levels among residents

Group		Total Cholesterol
Low		NTT, Bengkulu, Gorontalo, Papua Barat, Maluku Utara
Transition	Low to Moderate	NTB, Papua, Lampung, Jawa Barat, Sumatera Selatan, Maluku, Jawa Tengah, Bali
	Moderate	DKI Jakarta, DI Yogyakarta, Banten, Sulawesi Tenggara, Sulawesi Barat, Kepulauan Riau, Jambi
	Moderate to High	Sulawesi Selatan, Jawa Timur, Riau, Kalimantan Selatan, Kalimantan Tengah, Kalimantan Timur, Sulawesi tengah, Sumatera Barat
High		Kalimantan Barat, Sulawesi Utara, Aceh, Kepulauan Bangka Belitung
Group		**HDL**
Low		Papua Barat, NTT, Papua
Transition	Low to Moderate	NTB, Maluku Utara, Sulawesi Tengah, Gorontalo, Sulawesi Tenggara, Maluku, Kalimantan Tengah, Sulawesi Selatan, Jawa Timur
	Moderate	Bengkulu, Banten, Kalimantan Timur, Kepulauan Bangka Belitung, Sulawesi Barat
	Moderate to High	Jawa Barat, Sulawesi Utara, Bali Kalimantan Selatan, Kalimantan Barat, Sumatera Selatan, Lampung, Aceh, Sumatera Utara, Jawa Tengah, Kepulauan Riau
High		DKI Jakarta, Riau, Sumatera Barat, DI Yogyakarta, Jambi
Group		**LDL**
Low		NTT, Bengkulu, Maluku Utara, Gorontalo
Transition	Low to Moderate	NTB, Lampung, Papua Barat, Papua, Jawa Barat, Bali, Jawa Tengah, Jambi, Sumatera Selatan

	Moderate	DKI Jakarta Banten, DI Yogyakarta, Maluku, Kepulauan Riau, Jawa Timur, Sulawesi Tenggara, Sulawesi Selatan,
	Moderate to High	Sumatera Utara, Riau, Sumatera Barat Kalimantan Selatan, Kalimantan Tengah, Kalimantan Timur, Sulawesi Barat, Kalimantan Barat, Aceh
High		Kepulauan Bangka Belitung, Sulawesi Tengah, Sulawesi Utara
Group		**Triglyseride**
Low		Maluku Utara, Papua Barat, Bengkulu, Aceh, Sulawesi Utara
Transition	Low to Moderate	Gorontalo, DI Yogyakarta, Kepulauan Riau, Jambi, Jawa Tengah, Sumatera Selatan
	Moderate	Maluku, Kalimantan Barat, Sulawesi Barat, Papua, Sulawesi Tenggara, Lampung, Kalimantan Tengah, Sumatera Barat, Kepulauan Bangka Belitung, Kalimantan Selatan, Kalimantan Timur, Banten, NTT, Sulawesi Tengah, Bali
	Moderate to High	Sumatera Utara, Riau, NTB, Jawa Barat
High		Jawa Timur, DKI Jakarta, Sulawesi Selatan
Group		**Kreatinin**
Low		Sulawesi Barat, NTB, Sulawesi Selatan, Banten
Transition	Low to Moderate	Kalimantan Barat, Sumatera Selatan, Aceh, Sumatera Utara
	Moderate	Kepulauan Bangka Belitung, Jawa Barat, Maluku, Kepuluan Riau, Sumatera Barat, Jambi, Jawa Timur, Bengkulu, NTT, Jawa Tengah, Sulawesi Tengah, Sulawesi Tenggara, DKI Jakarta, Gorontalo, Kalimantan Selatan, Maluku Utara
	Moderate to High	Lampung, Kalimantan Timur, Kalimantan Tengah, Riau, Papua
High		DI Yogyakarta, Bali, Papua Barat, Sulawesi Utara

Based on the result from Table 4, we can conclude that the residents of Bangka Belitung Islands and North Sulawesi have the highest risk of atherosclerosis due to increased mean of total cholesterol, LDL, triglyceride, and creatinine blood levels with low HDL levels. Meanwhile, Jambi has the most balanced.

3.5. The Differences of Cholesterol and Creatinine Levels of The Residents Between Village and City in Indonesia

The statistic test in Table 3 stated differences in total cholesterol, HDL, LDL, and creatinine level among residents in the rural-urban. Based on Table 5, the mean value of total cholesterol, HDL, and LDL of urban residents is higher than rural residents. This result aligns with [53], which states that the prevalence of high total cholesterol, HDL, LDL and creatinine levels for urban residents is higher than for rural. However, these results contradict with the mean creatinine levels of the rural residents in Table 5, which is higher than urban residents. This was expected since some actual data is not included in the testing phase to prevent interference with the necessary assumptions.

According to [54], abnormal cholesterol levels or dyslipidemia are also influenced by other factors such as lifestyle, demographics, geography, ethnicity, and economic status. So, there is no guarantee to state that abnormal cholesterol levels or dyslipidemia in an area are precisely the same or have their own unique characteristics between different regions. For example, the incidence of dyslipidemia in Ghana presented by [55], states a higher prevalence in urban areas for high total cholesterol and LDL levels, while low HDL and high triglyceride levels occur in rural areas. The conditions are slightly different when compared to those that occur in Indonesia. Triglyceride levels of urban residents are higher than rural. Furthermore, a similar incident occurred in China. Total cholesterol, LDL, and triglyceride levels were higher in urban areas, while HDL levels tended to be lower than in rural areas, according to research results [56]. Based on these results and the statistics in Table 5, it can be inferred that the tendency for urban residents in Indonesia to be at risk of atherosclerosis is caused by high LDL levels. While at the same time, it tends to be caused by low HDL levels or abnormal renal function for rural residents.

Table 5. Mean score of cholesterol and creatinine residents in rural-urban

Category	Rural	Urban
Total Cholesterol	180.77a ± 33.06	185.13b ± 33.91
HDL	48.19a ± 10.23	48.94b ± 10.18
LDL	120.14a ± 29.44	123.71b ± 30.41
Triglyceride	110.53a ± 49.22	112.61a ± 51.57
Creatinine	0.794b ± 0.186	0.791a ± 0.196

Note: Different letters indicate there is a significant difference.

4. Conclusion

There are differences in cholesterol levels, which are total cholesterol, HDL, LDL, triglyceride, and creatinine residents in each province in Indonesia, meanwhile between the residents in rural-urban, there are differences in total cholesterol, HDL, LDL, and creatinine levels. Jambi has the most balanced result compared to the other 32 provinces. On the other hand, Bangka Belitung Islands and North Sulawesi have the highest risk for atherosclerosis. Urban residents have higher total cholesterol, HDL, and LDL levels than in rural, which means they are prone to atherosclerosis due to high LDL levels. Meanwhile, rural residents have a higher risk because of low HDL and renal disease.

In particular, it is difficult for the author to provide a statement regarding the reasons for the risk of atherosclerosis between provinces and rural-urban residents in Indonesia. The reason being the limitations of the field of knowledge that the author has. However, based on some of the literature that the authors refer to in this study, we can convey that the risk of atherosclerosis for residents of provinces and rural-urban areas in Indonesia are strongly related to diet and lifestyle.

The vast diversity tribes and cultures in Indonesia determine the differences in eating patterns, lifestyles, and population activities between provinces. At the same time, rural-urban residents have their differences in eating habits that are potentially at risk of atherosclerosis, such as rural residents tend to smoke more cigarettes and urban residents consumes more fast food, according to BPS data. These conditions are also related to differences in economic status among residents, so differences can occur. Nevertheless, the study of atherosclerosis in this research was limited to the cholesterol and creatinine levels of the population. At the same time, other factors such as hypertension, diabetes, and other congenital diseases were also closely related to this disease. The Indonesian government is implementing several programs to control this disease, such as regulating diet, exercise, and herbal alternatives. Another program that needs to be considered for implementation is an effort to improve good nutrition for the population by increasing the residents's awareness of having a healthy diet and balanced nutrition, as well as awareness to be active in carrying out regular health controls.

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