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RESEARCH ARTICLE

The Relationship between Blood Pressure with P-Selectin in Indonesian Hypertension Patients

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Abstract

Objective: The involvement of vascular inflammation is shown in the initiation and development of hypertension. P-selectin plays an important role in the inflammatory response through the initiation of leukocyte adhesion in platelets and endothelial cells. The purpose of this research was to determine the relationship between blood pressure and P-selectin in Indonesian hypertensive patients. Methods: The cross-sectional design study was conducted in 56 patients with hypertension, aged 40 to 60 years, blood pressure and serum P-selectin (sP-selectin) concentration measured. sP-selectin was determined by a colorimetric ELISA sandwich. Interpretation of the relationship between blood pressure components and sP-selectin concentration was carried out by statistical analysis. Results: It was found that sP-selectin level did not correlate significantly with systolic blood pressure ($r = 0.078$; $P = 0.568$), diastolic blood pressure ($r = -0.014$; $P = 0.921$), mean arterial pressure ($r = 0.062$; $P = 0.648$), and pulse pressure ($r = 0.062$; $P = 0.648$). Conclusion: Our results concluded that the increase in blood pressure components was not significantly associated with an increase in circulating sP-selectin concentration in hypertensive patients. Thus, there was no significant correlation between blood pressure and P-selectin in hypertensive patients. The tendency of positive results indicated an inflammatory involvement in hypertension.

Keywords: *Blood pressure, P-selectin, hypertension, Vascular inflammation adhesion, ELISA.*

Introduction

Hypertension or high blood pressure is a medical condition where constricted arteries increase resistance to blood flow and cause an increase in blood pressure against the vessel wall [1, 2]. In industrialized countries, hypertension is one of the main health problems. In Indonesia, hypertension is also a health problem that needs to be considered in primary health services because the incidence rate is high and the long-term consequences are caused [3].

Hypertension is a major risk factor for cardiovascular disease, kidney failure and stroke [4, 5].The relationship between blood pressure and the risk of cardiovascular disease is continuous, consistent and independent of other risk factors. The higher the blood pressure, the greater the likelihood of myocardial infarction, stroke and kidney failure [6, 7]. Various studies have shown evidence of the involvement of vascular inflammation in the initiation and development of hypertension. Hypertension is thought to be the result of arterial pathology similar to atherosclerosis where inflammation in atherosclerosis and hypertension is initiated by the same agent of injury [5, 8, 9].

Platelets prove to play a role in the development of atherosclerosis in humans. In addition to its role in hemostasis and thrombosis, platelets regulate various inflammatory responses and are the key to atherothrombosis. The inflammatory response in the vascular is very dependent on cell adhesion molecules [10, 11, 12].

P-selectin plays an important role in the initiation of leukocyte adhesion in platelets and endothelial cells. After activation of platelets and endothelial cells, P-selectin stored in α-platelet granules and Weibel-Palade bodies endothelial cells are translocated rapidly to the cell surface. P-Selectin regulates tissue factors in monocytes and produces leukocyte accumulation in the area of vascular injury along with thrombosis and inflammation [13].

Materials and Methods

Sample

Serum from 56 patients as samples, with with the following inclusion criteria: Hypertension patients according to JNC VII 2003 criteria who have not received antihypertensive drug therapy or have stopped antihypertensive drug therapy for at least 1 month; Age 40-60 years; Willing to take part in the study by signing informed consent. Subjects who were suffering from acute inflammation (indicated by hs-CRP concentration> 10 mg/L) or were taking anti-inflammatory drugs, people with diabetes mellitus, impaired renal function were excluded from the study.

Reagent

The reagent used to determine P-selectin levels is the Quantikine reagent produced by R & D Systems, Inc. in Minneapolis, Cat No BBE 6 Lot 242437.

Research Methods

The research was carried out as an observational study with a cross-sectional design. Blood pressure was measured by mercury sphygmomanometer. Measurements were made twice on different days or on the same day with an interval of 15 minutes and the value of blood pressure was the average of the two measurements. The criteria for hypertension refer to JNC VII 2003, namely if the systolic blood pressure is 40140 mmHg and/or diastolic blood pressure is ≥90 mmHg [14].

Measurement of P-selectin concentration in serum using quantitative sandwich immunoassay technique with a 530 reader. The results were expressed in units of ng / mL. The data obtained were then analyzed by standard statistical analysis using the SPSS for Windows version 13.0 program. The level of significance (significance) used is 5% [15].

Results and Discussion

The study was conducted by determining the P-selectin concentration in 56 serum samples that met the criteria. Patients consisted of 17 men (30.36%) and 39 women (59.64%). The data obtained were then analyzed statistically using the SPSS for Windows version 13.0 program. Data on the characteristics of the research subjects can be seen in Table 1.

Table 1: Characteristics of research subjects

Parameter	Mean ± SD	Unit
Age	51.75 ± 5.27	years
GOT	23.64 ± 10.35	U/L
GPT	25.46 ± 14.18	U/L
Glucose	88.36 ± 10.33	mg/dL
Cholesterol	218.40 ± 39.82	mg/dL
HDL	52.0 ± 11.46	mg/dL
Triglicerides	156.07 ± 92.93	mg/dL
Creatinine	0.76 ± 0.19	mg/dL
Clearance	96.23 ± 21.65	mL/menit
TDS	146.16 ± 14.65	mmHg
TDD	93.48 ± 7.44	mmHg
LP	91.05 ± 9.07	cm
TB	154.04 ± 7.86	cm
BB	63.24 ± 10.001	kg
P-selektin	107.11 ± 29.14	ng/mL

Description: GOT = Glutamate Oxaloacetate Transaminase; GPT = Glutamate Pyruvat Transaminase; HDL = High Density Lipoprotein; TDS = Systolic Blood Pressure; TDD = Diastolic Blood Pressure; LP = Stomach Circles; TB = Height; BB = Weight

Data from the measurement of P-selectin levels and blood pressure can be seen in descriptive statistics in Table 2. Data processing began with a test of the distribution (normality) of the data using the Kolmogorov-Smirnov test statistic [16].

The results of the data distribution test are shown in Table 3. The results obtained indicated that the P-selectin data was normally distributed because it had a significant probability value> 0.05. Meanwhile, the variable data of TDS and

TDD were not normally distributed with a significance value of <0.05. Because the TDS and TDD variable data were not normally distributed, the data analysis was continued by the non-parametric statistical method to test the relationship using Spearman rank correlation. The results of Spearman's rank correlation analysis between TDS and TDD with P-selectin are summarized in Table 4.

Table 2: Descriptive blood pressure and P-selectin statistics

Variable	N	Minimum value	Maximum value	Mean	Standard deviation
TDS	56	110	180	146.16	14.65
TDD	56	80	120	93.48	7.44
P-selektin	56	53	176	107.11	29.14

Table 3: Kolmogorov-Smirnov TDS, TDD, and P-selectin test results

	TDS	TDD	P-selektin
Kolmogorov-Smirnov Z value	1.364	2.550	0.553
Asymp significance	0.048	0.000	0.920

Table 4: Correlation of TDS and TDD with P-selectin

Parameter	Correlation coefficient	Significance level
TDS - P-selektin	0.078	0.568
TDD - P-selektin	-0.014	0.921

Correlation coefficient results of the analysis were tested with statistical hypotheses and obtained the level of meaningfulness as shown in Table 4. The correlation between TDS and P-selectin was 0.078 and the correlation was 0.61% with a significance level of 0.568. The correlation between TDD and P-selectin was -0.014 and the correlation was 0.02% with a significance level of 0.921. This value was stated to be not significant at α 0.05 in two directions and it was concluded that there was no significant relationship between TDS and P-selectin and between TDD and P-selectin so that the correlation coefficient value was 0.078 and -0.014 was not significant. Data on Mean Arterial Pressure (MAP) and Pulse Pressure (PP) were processed as TDS and TDD to see the relationship with P-selectin in hypertensive patients. MAP was obtained by calculation (TDS + 2TDD) /3 [17]. PP was calculated by subtracting TDS by TDD. Data from the calculation of MAP and PP with P-selectin concentration can be seen in descriptive statistics in Table 5.

Table 5: Descriptive statistics of MAP, PP, and P-selectin

Variable	N	Minimum value	Maximum value	Mean	Standard deviation
MAP	56	96.67	138.33	111.04	8.0
PP	56	20	90	52.68	12.13
P-selektin	56	53	176	107.11	29.14

Using the same statistics as in TDS and TDP, it was obtained that the correlation between MAP and P-selectin and between TDD and P-selectin was 0.062 and the correlation of 0.38% had a significance level of 0.648. This value was stated to be insignificant at α 0.05 in two directions and it was concluded that there was no significant relationship between MAP and P-selectin and between PP and P-selectin so that the correlation coefficient value of 0.062 was not significant. Based on the large data of systolic and diastolic blood pressure measured, the average P-selectin concentration data classified in level I and II hypertension groups according to criteria in JNC VII 2003 were presented in Tables 6 and 7.

Table 6: Average P-selectin concentration at the level of hypertension based on TDS size

	Level I hypertension (TDS 140-159 mmHg)	Level II hypertension (TDS ≥ 160 mmHg)
P-selectin mean (ng/mL)	108.36±27.61	105.00±29.08

Table 7: Average P-selectin concentration at the level of hypertension based on the amount of TDD

	Level I hypertension (TDD 90-99 mmHg)	Level II hypertension (TDD ≥ 100 mmHg)
P-selectin mean (ng/mL)	105.67±27.44	108.94±33.41

To find out whether there were significant differences in the average P-selectin concentration between level I and II hypertension, two similarities were tested (Mann-Whitney test). The Mann-Whitney test results can be seen in Table 8.

Table 8: Results of the Mann-Whitney test

	P-selectin in hypertension of TDS levels I and II	P-selectin in hypertension TDD levels I and II
Z values	-0.273	-0.256
Asim tot significance	0.785	0.798

The results of the Mann-Whitney statistical test showed that there were no significant differences between the average P-selectin concentrations in level I and II hypertensive subjects both based on TDS and TDD

The following discussion will be very helpful to clearer above results. The sample used was serum 56 patients with hypertension who had previously ascertained its feasibility in attending this study through blood pressure measurements, interviews, and laboratory examinations. Blood pressure was measured by mercury sphygmomanometer. Measurements were made on the patient in a sitting position with the arms placed at the position of the heart. Korotkoff 1 and 5 sounds were used for determination, sequentially, systolic blood pressure (TDS) and diastolic blood pressure (TDD). Measurements were made twice on different days or on the same day with an interval of 15 minutes and the value of blood pressure was the average of the two measurements.

TDS measurement results of sebesar140 mmHg and/or TDD of sebesar90 mmHg were expressed as hypertension, according to JNC VII 2003 criteria. Interviews were conducted to obtain data that supported the study, such as age, sex, height and weight, disease history, drug consumption, smoking habits and alcohol consumption, and so on. Patients aged 40-60 years, not undergoing antihypertensive therapy and willing to sign informed consent were considered to meet the inclusion criteria. Patients who are interviewed were known to be taking anti-inflammatory drugs and suffer/have suffered from diabetes mellitus, kidney failure or acute inflammation excluded from the study.

The patient's blood was then taken and stored in serum to undergo a laboratory examination. Laboratory tests were carried out to determine the condition of the patient's clinical parameters which included fasting blood glucose, creatinine clearance, HDL cholesterol, and triglycerides, GOT / GPT and hs-CRP. Through these parameters, patients suspected of suffering from diabetes mellitus (GDP), impaired kidney function (Creatinine clearance), liver function disorders (GOT, GPT), dyslipidemia (TG, HDL) and acute inflammation (hs-CRP ≥10 mg / dL) excluded from the study. This exclusion criterion was enforced because it could interfere with the interpretation of the relationship of P-selectin concentration in hypertension. According to JNC VII 2003, major cardiovascular risk factors were hypertension, smoking, obesity, lack of physical activity, dyslipidemia, microalbuminuria or estimated glomerular filtration rate <60mL / minute, age (> 55 years in men and> 65 years in women) and disease history cardiovascular. Obesity factors could be identified through abdominal circumference and body mass index (BMI), dyslipidemia through total cholesterol, HDL cholesterol, and triglycerides, while microalbuminuria or glomerular filtration rate (LFG) through creatinine clearance.

Smoking risk factors, alcohol intake, physical activity and family history were known through interviews with patients. The age range used in this study was 40-60 years because according to Cotran the incidence of hypertension increases with age [18]. Age limitation at 60 years is done because older age was a cardiovascular risk factor, namely> 55 years in men and> 65 years in women. Research by Woollard *et al.* in 2006, however, stated that there was no significant correlation between age and concentration of sP-selectin (soluble P-selectin) so that the age factor had no effect on the measurement of P-selectin concentration [19].

There was no gender limitation in this study because differences based on larger sex were limited to older age and it was found that there was no difference in sP-selectin concentration between men and women [19, 20]. However, according to FJ Schoen, gender was the main factor that determinesdblood pressure variation and, according to AD Blann, P-selectin concentration was higher in men. Gender differences in research subjects could cause deviations in the interpretation of results. Therefore, gender restrictions could be done in future research to reduce mixed results [21].

Various studies summarized by Blann reported an increase in sP-selectin concentration in people with diabetes mellitus, smokers, hypertension and hypercholesterolemia [22]. A study of 266 healthy subjects reported an increase in concentration in smokers compared with nonsmokers, but there was no increase in male smokers compared with nonsmokers, higher concentrations in men, no effect of age, and positively correlated with cholesterol concentration. Tailor A *et.al* stated that the state of hypercholesterolemia causes P-selectin-dependent platelet-endothelial adhesion [23]. Hypertension was known as a complex disease with multifactorial character.

Factors related to essential hypertension were a family history of hypertension, increase in age, sex, black race, high sodium intake, glucose intolerance (diabetes mellitus), smoking, obesity, alcohol intake, and lack of potassium, calcium, and magnesium intake [24]. Harrison *et.al* published provided evidence from various studies on the relationship between inflammation and hypertension, although the contribution of the inflammatory process to the etiology of hypertension remains unclear [25]. Pedrinelli *et al*. confirmed this through an increase in the concentration of C-reactive Protein, a marker of low-level inflammation, in hypertension. CRP levels <1, 1-3, and 3-10 mg / L were used as reliable evidence in the interpretation of the risk of cardiovascular disease in a low, average, and high order.

However, if the CRP level was> 10 mg / L, CRP coul not be used to estimate cardiovascular risk and other active inflammatory processes (such as trauma, infection, etc.) ought to be excluded [26]. CRP measurements in estimating cardiovascular risk for primary prevention use the hs-CRP test (high sensitivity) and patients ought to be free of acute inflammation for at least two weeks [27, 29]. Inflammation of hypertension occured through increased expression of several mediators, including leukocyte adhesion molecules [5]. P-selectin facilitates the adhesion of platelets and neutrophils to the endothelium, had procoagulant activity and also increased monocyte phagocytosis. The soluble form of P-selectin could be used as a predictor of cardiovascular events because its concentration in the blood was parallel to the amount expressed on the cell surface. Increased plasma P-selectin concentration was evident in various cardiovascular disorders, including hypertension [21, 29]. If hypertension was the result of an inflammatory response and hypertension also caused proinflammatory conditions, whereas inflammation occured through leukocyte adhesion initiated by P-selectin, hypertension would have a positive correlation with P-selectin. Based on this thinking, this study was conducted to determine the relationship between hypertension represented by systolic blood pressure and diastolic with P-selectin in hypertensive patients.

The results of the correlation test statistical analysis showed that TDS was not significantly correlated with P-selectin ($r = 0.078$; $P = 0.568$) and TDD also did not show a significant correlation with P-selectin ($r = -0.014$; $P = 0.921$). These results indicated that there was no significant relationship between blood pressure and P-selectin in hypertensive patients. The correlation between TDS and P-selectin 0.61% was positive indicating that the higher the TDS the higher the concentration of P-selectin. Increased TDS meant increased pressure on the walls of blood vessels when the heart contracts. High internal pressure would damage the blood vessels and cause a proinflammatory state that triggers the P-selectin expression. McCance *et.al*, however, in his book stated that inflammation contributes to increased blood volume which would increase cardiac output.

The insignificant negative correlation between TDD and P-selectin might be due to the involvement of other adhesion molecules (for example, vascular cell adhesion molecule) and chemokines (for example, monocyte chemoattractant protein) in the recruitment of leukocytes and platelets [30]. The effect of P-selectin on neutrophil to platelet adhesion was shear-dependent, where maximum neutrophil adhesion occured at low shear rates [19, 31]. Blood flow abnormalities were common in hypertension [32].Statistical analysis was also performed on other blood pressure components, namely MAP (mean arterial pressure) and PP (pulse pressure), to determine the correlation with P-selectin. Both gave results ($r = 0.062$; $P = 0.648$) which showed that MAP and PP did not have a significant relationship with P-selectin in hypertensive patients.

The correlation between MAP and PP with P-selectin was 0.38%. The correlations were positive, although this value was not significant, indicating that the mean arterial pressure (MAP) and pulse pressure (PP) increased together with the increased in P-selectin concentration. MAP and PP were characteristic conditions of arteries. The increase in mean pressure and pulse pressure experienced by the arteries would cause vascular damage followed by the expression of P-selectin as an inflammatory response. The insignificant relationship between blood pressure and P-selectin might be caused by P-selectin itself and its function in the body. The p-selectin expression on the surface was short, reaches a peak after 10 minutes and decreases to baseline after 3 hours [21].

This situation caused the interpretation of results to only be carried out accurately if hypertension was a manifestation of low-grade chronic vascular inflammation. As was known, inflammation could not be separated from the occurrence of thrombosis. Inflammation caused atherosclerosis and this condition would worsen the inflammatory state. Thrombosis was also involved and caused atherothrombosis. Similarly, inflammation causes hypertension which will support the pro-inflammatory state to worsen hypertension. Atherosclerosis itself could cause hypertension and vice versa. These events were interconnected and form an endless circle. Therefore, it was difficult to know which event initiated the next event, as well as the role of P-selectin in each event.

Hypertension was classified into two levels by JNC VII based on systolic and or diastolic blood pressure levels. Statistical analysis showed that there were no significant sP-selectin differences between level I and level II hypertension in both TDS (P = 0.785) and TDD (P = 0.798). Research by Spencer *et al.* stated that there was no significant sP-selectin difference between hypertension and target organ damage (TOD) and without TOD [21]. Various studies had reported an increase in sP-selectin concentration in hypertension compared with normotensive control and were thought to occur in a stable period without further improvement which aggravates the state of hypertension. Research on circulating concentration of dissolved cell adhesion molecules, in this case, sP-selectin, in various studies was inconsistent because the increase in molecular circulation concentration is caused by a variety of cellular and molecular factors, including increased gene transcription, changes in mRNA stability, translation changes, shape production other pieces and increased proteolytic breakdown of the cell surface [29]. This acquisition was not entirely independent because it could be influenced by several factors. Blood pressure levels were complex and were determined by genetic, environmental and demographic factors that affected cardiac output and peripheral resistance. The main hemodynamic abnormality in essential hypertension was peripheral resistance. Major factors that determined variations in blood pressure within and between populations include age, sex, body mass index and diet [33].

Body mass index (BMI) could be known through height and weight measurement data. BMI was obtained by dividing body weight (kg) by the square of height (m). The 56 research subjects gave an average BMI of 26.6 ± 3.24, which was a fairly large index number. The sample diet factor was a factor that could not be controlled in the selection process. Acquisition in this study might also be influenced by the level of inflammation that was not enough to cause endothelial damage where P-selectin acts as an inflammatory marker and caused hypertension. Not knowing the onset of hypertension in the sample and the limited number of samples were thought to contribute to the interpretation of results.

In addition, the physiological conditions of each individual that was not the same could also affect data. Poly *et al.* stated that cross-sectional studies were always limited by the presence of unknown confounding variables [34]. Our overall results concluded that there was no significant relationship between blood pressure and P-selectin in Indonesian hypertensive patients. Other researchers mentioned the following. Turkoz *et.al* stated that serum soluble P-selectin levels are increased in BS (Behçet's syndrome) patients when compared with control subjects, suggesting a modulatory role for soluble P-selectin during the course of platelet activation and therefore, atherothrombogenesis formation in BS, especially in active disease [35]. Shalia *et.al* mentioned that a significant negative correlation was observed of sP-selectin

(Spearman rank correlation coefficient (rs) =-0.345, p=0.027) and sPECAM-1 (rs =-0.446, p=0.003) with age in hypertension group. Hypertension may increase expression of certain CAMs while younger hypertensives, in addition, are also at increased risk of atherothrombosis [36]. Laskowska *et.al* studied on elevated maternal serum sP-selectin levels in preeclamptic pregnancies with and without intrauterine fetal growth restriction, but not in normotensive pregnancies complicated by isolated IUGR [37].

Nadar *et.al*, however, claimed that Patients with hypertension had evidence of changes in platelet physiology, as reflected by a higher level of pP-see. Patients with TOD also had larger platelets, with greater mass, and the use of aspirin lowered pP-sel and sP-sel levels. They mentioned that these changes might have implications for the pathophysiology of cardiovascular and cerebrovascular disease in hypertension [38].

Conclusion

The results of this study showed a correlation between sP-selectin concentration in the serum of hypertensive patients with blood pressure components, namely systolic blood pressure (r = 0.078; P = 0.568), diastolic blood pressure (r = -0.014; P = 0.921), mean arterial pressure average (r = 0.062; P = 0.648) and pulse pressure (r = 0.062; P = 0.648), not significant. Thus, it could be concluded that there was no significant relationship between blood pressure and P-selectin in Indonesian hypertensive patients. The tendency of positive results indicated an inflammatory involvement in hypertension.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. MacGill M (2018) Everything you need to know about hypertension, [Cited 2019 April 2]. Available from: https://www.medicalnewstoday.com/articles/150109.php.
2. Alexander MR, Yang EH (2019) [Cited 2019 April 15]. Available from: https://emedicine.medscape.com/article/241381-overview.
3. Hussain MA, Huxley RR, Al Mamun A (2015) Multimorbidity prevalence and pattern in Indonesian adults: an exploratory study using national survey data, BMJ Open, 5(12): e0098-10.
4. Drozdzcorresponding D, Kawecka-Jaszcz K (2014) Cardiovascular changes during chronic hypertensive states, Pediatr. Nephrol., 29(9): 1507-16.
5. Li JJ (2006) Medical Progress Inflammation in Hypertension: primary evidence. Chinese Medical Journal, 119(14): 1215-21.
6. Nayak-Rao S, Shenoy MP (2017) Stroke in Patients with Chronic Kidney Disease. How do we Approach and Manage it?, Indian J. Nephrol., 27(3): 167-71.
7. Verdecchia P, Reboldi G, Angeli F, Trimarco B, Mancia G, Pogue J, et.al (2015) Systolic and Diastolic Blood Pressure Changes in Relation With Myocardial Infarction and Stroke in Patients With Coronary Artery Disease, Hypertension, 65: 108-14.
8. Lawson JS (2016) Multiple Infectious Agents and the Origins of Atherosclerotic Coronary Artery Disease, Front. Cardiovasc. Med., 12 | https://doi.org/10.3389/fcvm.2016.00030
9. Delewi R, Yang H, Kastelein J (2013) Atherosclerosis in Textbook of Cardiology (https://www.textbookofcardiology.org/wiki/Atherosclerosis).
10. Gawaz M, Langer H, May AE (2005) Platelets in Inflammation and Atherogenesis. J. Clin. Invest, 115: 3378-84.
11. Wu MD, Atkinson TM, Lindner JR (2017) Platelets and von Willebrand factor in atherogenesis, Blood, 129: 1415-19; doi: https://doi.org/10.1182/blood-2016-07-692673.
12. Carter RA, Wicks IP (2001) Vascular cell adhesion molecule 1 (CD106): A multifaceted regulator of joint inflammation, Arthritis & Rheumatism, 44(5): 985-1230.
13. Wang K, Zhou X, Zhou Z, Mal N, Fan L, Zhang M, et.al (2005) Platelet, Not

Endothelial, P-Selectin Is Required for Neointimal Formation After Vascular Injury, Arteriosclerosis, Thrombosis, and Vascular Biology, 25: 1584-9.

14. JNC (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA, 289: 2560-72.
15. Brahmana V (2013) Introduction to the SPSS Program Application 13.0 For Windows. 2013. [Cited 2019 April 5]. Available from: https://www.academia.edu/34404818/PENGENALAN_APLIKASI_PROGRAM_SPSS_13.0_FOR_WINDOWS
16. Purwanto PA Kolmogorov-Smirnov test statistic.2016/ [Cited 2019 April 5]. Available from: https://www.scribd.com/document/327408006/Kolmogorov-Smirnov-Test-for-Normality.
17. Napoli DM, Papa F (2003) Association Between Blood Pressure and C-Reactive Protein Levels in Acute Ischemic Stroke. Hypertension 42; 1117-23.
18. Andriastuti M, Sastroasmoro S, Firmansyah A. Risk factors of coronary heart disease in children and young adults with parental history of premature coronary heart disease, Paediatrica Indonesiana 2003; 43(3-4): 51-8.
19. Woollard KJ, Kling D, Kulkarni S, Dart AM, Jackson S, Chin-Dusting J et.al (2006) Raised Plasma Soluble P-Selectin in Peripheral Arterial Occlusive Disease Enhances Leukocyte Adhesion. Circ. Res., 98(1):149-56.
20. Deneva-Koycheva TI, Vladimirova-Kitova LG, Angelova EA, Tsvetkova TZ (2011) Serum levels of siCAM-1, sVCAM-1, sE-selectin, sP-selectin in healthy Bulgarian people, Folia Med (Plovdiv). 53(2): 22-8.
21. Blann AD, Nadar SK, Lip GY (2003) The Adhesion Molecule P-selectin and Cardiovascular Disease, Eur. Heart J., 24(24): 2166-79.
22. Blann AD How a Damaged Blood Vessel Wall Contributes to Thrombosis and Hypertension, Pathophysiol Haemost Thromb 2003/2004; 33: 445-8.
23. Tailor A, Granger DN (2003) Hypercholesterolemia Promotes P-Selectin-Dependent Platelet-Endothelial Cell Adhesion in Postcapillary Venules. Arterioscler Thromb Vasc. Biol., 23(4): 675-80.
24. McCance KL, Huether SE (2006) Pathophysiology: The Biologic Basis for Disease in Adults and Children. Vol II. 5th edition. USA: Elsevier Mosby.
25. Harrison DG, Guzik TJ, Lob H, Madhur M, Marvar PJ, Thabet S, et.al (2011) Inflammation, Immunity and Hypertension, Hypertension, 57(2): 132-40.
26. Pedrinelli R, Dell'Omo G, Di Bello V, Pellegrini G, Pucci L, Del Prato S, et.al (2004) Low-Grade Inflammation and Microalbuminuria in Hypertension. Arterioscler. Thromb. Vasc. Biol., 24: 2414-19.
27. Jialal I, Devaraj S, SK Venugopal SK (2004) C-Reactive Protein: Risk Marker or Mediator in Atherothrombosis. Hypertension, 44(1); 6-11.
28. Willerson JT, Ridker PM (2004) Inflammation as a Cardiovascular Risk Factor. Circulation 109(21: 1): II2-10.
29. Brevetti G, Schiano V, Chiariello M (2006) Cellular Adhesion Molecules and Peripheral Arterial Disease. Vascular Medicine, 11(1): 39-47.
30. Wagner DD (2005) New Links Between Inflammation and Thrombosis. Arterioscler Thromb Vasc. Biol., 25: 1321-24.
31. Spencer CG, Gurney D, Blann AD, Beevers DG, Lip GY (2002) Von Willebrand Factor, Soluble P-Selectin, and Target Organ Damage in Hypertension. Hypertension, 40(1):61-6.
32. Lip GH, Blann AD (2000) Does Hypertension Confer a Prothrombotic State? Circulation, 101: 218- 20.
33. Schoen FJ (2005) Blood Vessels. In Kumar V, Abbas AK, Fausto N. Robbins, and Cotran: Pathologic Basis of Disease. 7th ed. Philadelphia: Elsevier Saunders, Inc.
34. Poli KA, Tofler GH, Larson MG, Evans JC, Sutherland PA, Lipinska I, et.al (2000) Association of Blood Pressure With Fibrinolytic Potential in the Framingham Offspring Population. Circulation, 101(3): 264-9.

35. Turkoz Y, Evereklioglu C, Özkiriş A, Mistik S, Borlu M, Özerol IH, et.al (2005) Serum Levels of Soluble P-Selectin Are Increased and Associated With Disease Activity in Patients With Behçet's Syndrome, Mediators Inflamm., 2005(4): 237-41.

36. Shalia K, Vasvani JB, Mashru M, Mokal RA (2009) Circulating levels of cell adhesion molecules in hypertension, Indian Journal of Clinical Biochemistry, 24(4): 388-97.

37. Laskowska M, Laskowska K, Oleszczuk J (2013) Elevated maternal serum sP-selectin levels in preeclamptic pregnancies with and without intrauterine fetal growth restriction, but not in normotensive pregnancies complicated by isolated IUGR, Med Sci Monit., 19: 118-124.

38. Nadar SK, Blann AD, Kamath S, Beevers DG, Lip GYH (2004) Platelet indexes in relation to target organ damage in high-risk hypertensive patients, JACC, 44(2): 2004.

