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A Cross Sectional On Leukocytes, Blood Glucose, Cholesterol, Triglyceride, Temperature, Onset, Comorbidities, Sex, And Benson's Relaxation Response

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Abstract. *The increase in physiological response may lengthen ischemic duration, cause recurrent stroke risk and worsen the complication of AIS (Acute Ischemic Stroke) attack which results in impairment and death. The identification of AIS patients with the risk of increasing physiological response is essential during treatments in hospitals. Some of the factors related to the increase of physiological response had been identified, yet the factors that include the intervention remain unknown. The factors are leukocyte, blood glucose, total cholesterol, triglyceride, temperature, onset, coexisting disease, gender, and Benson's relaxation response. This observational analysis research uses cross-sectional design. The total number of subjects are 42 AIS patients that include 21 respondents in control group and 21 respondents in intervention group. The results of the study show that the level of Leukocyte p= 0.790; Blood Glucose p= 0.565; Total Cholesterol p= 0.982; Triglyceride p= 0.782; Temperature p= 0.50; Onset p= 0.028; Coexisting Disease p= 0.345; Sex p= 0.707; Benson's Relaxation Response p= 0.019. Based on the results of the study, it is concluded that Onset and Benson's Relaxation Response are significant factors in physiological response of AIS patients.*

INTRODUCTION

The increase of physiological response in AIS patients may cause various types of complication such as musculoskeletal problems, dysphagia, bladder and bowel dysfunction, inability to perform self-care, damaged skin integrity, and disorder of aspects related to depression and social features.[1,2] The effects of complication in AIS patients include lengthened ischemic duration, recurrent stroke risk, and worsened post-AIS attack complication which may lead to impairment and death. Initial identification of factors related to the increase of physiological response in AIS patients is highly essential during treatments in hospitals in order to prevent complication that may worsen the outcome of stroke. There are many factors related to the physiological response of AIS patients, such as premature neurological deficit, patients' age[3], high blood glucose level, high body temperature, recurrent stroke[4], medical complications[5], leukocyte, lipid profile[6], onset[7],

coexisting diseases such as Chronic Heart Disease (CHD) and Diabetes Mellitus (DM) which relate to outcome function in females.[8]

Some of the contributing factors in the increase of physiological response had been identified, yet the factors that include the intervention remain unknown. Therefore, further research in the factors related to physiological responses of AIS patients which include intervention as one of the variables is needed. Based on this matter, this research is aimed at analysing the factors related to physiological responses of AIS patients in several hospitals in Semarang area. This research hypothesizes that there are connections between those factors and physiological response of AIS patients.

In the United States, stroke is the fourth leading cause of death among all diseases, with an annual incidence of 795.000, resulting in nearly 130.000 deaths a year.[9] Stroke is the main cause of death in Indonesia, with the percentage of 15.4%. The prevalence of stroke increases to 12,1 per 1000 residents in the year of 2013.[10] It is estimated that 500.000 residents have stroke attack per year, around 2,5% or 125.000 people die and the rest have moderate impairment. That statement supports an argument that averagely once every 3 days there is 1 Indonesian resident, old or young, dies due to stroke.[11] The number of ischemic stroke patients in K.R.M.T Wonsonegoro Regional Public Hospital Semarang 156 cases, while in Tugurejo Regional Public Hospital Semarang there were 284 cases found.[12,13]

The factors related to physiological responses of AIS patients in this study are leukocyte, blood glucose, total cholesterol, triglyceride, temperature, onset, coexisting diseases, gender, and Benson's relaxation response. High level of leukocyte in acute cerebral ischemic phase is a significant independent predictor in initial severity level of severe stroke attack after 72 hours and change in disability.[14] Random level of blood glucose with NIHSS input and improvement show a significant connection ($p=0.024$ and $p= 0.047$).[3] The nature of total cholesterol as a risk factor in ischemic stroke somehow is paradoxical but this correlation justifies that cholesterol can act as a supportive agent and neutralize free radicals as well as oxidative stress.[15] Although it is not significant, the result of triglyceride serum increase correlated with the decrease of NIHSS score.[16] The increase of body temperature beyond normal is an independent risk factor that results in bad outcome, and it is connected to higher morbidity and mortality as well as expanded infarction.[17] Patients who show partially decreasing symptoms have more possibility to postpone the pre-hospital phase faster than those who show no sign of improvements.[18] The first ischemic stroke case with coexisting disease, aged older than 60 years, showed a significant connection with bad outcome and mortality.[19]

METHOD

The method used in this study is observational analysis with cross-sectional design, using the patients' medical record as data source. The subjects are chosen using consecutive sampling method. The subjects are AIS patients and the total number of the subjects is 42.

The research instrument used in this study is assessment format, National Institute of Health Stroke Scale (NIHSS), and Mini Mental State Examination (MMSE). The assessment format includes data on age, gender, leukocyte, blood glucose, lipid profile, temperature, onset, and coexisting disease. NIHSS is used to measure the physiological response AIS patients in the domain of motoric, sensorial, visual, and awareness level. The other instrument, MMSE, is used to measure mental functions of the patients during sampling. The inclusive criteria of the patients chosen as subjects in this study are: 1) Patients who are diagnosed with AIS and hospitalized at Alamanda, Dahlia 2,3 and 4 rooms in Tugurejo Regional Public Hospital Semarang and Yudistira, Nakula 2 and 3 rooms in K.R.M.T Wongsonegoro Regional Public Hospital Semarang; 2) Patients are completely compos mentis; 3) Patients are able to communicate well; 4) Patients are in healthy mental state measured with MMSE 27-30; 5) Patients are able to commit to the research processes. The exclusive criteria are: 1) Patients receive thrombolytic therapy; 2) Patients receive psychotropic therapy; 3) Patients have comorbid malignancy; 4) Patients with severe stroke according to NIHSS criteria > 25; 5) Patients have amputation extremity that hinder the motoric examination of arms and legs using NIHSS scores; 6) Patients with intubation or other physical barriers.

The location of the research is in

Alamanda, Dahlia 2,3, and 4 rooms in Tugurejo Regional Hospital Semarang and Yudistira, Nakula 2 and 3 rooms in K.R.M.T Wongsonegoro Regional Public Hospital Semarang.

The independent variables analysed in this study are factors related to physiological response such as leukocyte, blood glucose level, total cholesterol, triglyceride, temperature, onset, coexisting disease, gender, and Benson's relaxation response. The dependent variable is physiological response change. The statistical test carried out in this study is quantitative with bivariate test using correlation and multivariate test using linear regression.

Research ethics for this study was issued from Ethics Commission of Diponegoro University Medical Faculty or Dr. Kariadi Regional Public Hospital with the issue number 468/EC/ FK-RSDK/ VII/ 2017. This study was carried out using 4 basic ethics principals: respecting human dignity of the subjects, respecting the subjects' privacy and confidentiality, respecting inclusivity justice, and considering the advantages as well as disadvantages of the study.

RESULTS AND DISCUSSION

The characteristics result from 42 respondents in the respondents' age shows a statistically insignificant difference (p= 0.999). The characteristics result in the respondents' gender shows a statistically insignificant difference as well (p= 0.355) (Table 1).

Table 1. Demographic Characteristics (Age and Gender)

Variable	Total Frequency (%) (n = 42)	P*
Age		
30-44	3 (7.1)	0.999
45-59	17 (40.5)	
60-74	21 (50)	
75-90	1 (2.4)	
Gender		
Male	18 (42.9)	0.355
Female	24 (57.1)	
Total	**42 (100)**	

Note: *= Chi-Square Test

There were various coexisting diseases found in the respondents of this study. They are hypertension, Diabetes Mellitus (DM), heart disease, vertigo, kidney disease, and lungs disease. Based on the calculation, there were 2 respondents who had no coexisting disease (4.8%), while the respondents with coexisting diseases are larger in number, 21 respondents or 50%. The result of coexisting disease statistical test is insignificant (p= 0.13) (Table 2).

Table 2. Coexisting Disease Factor Category

Category	Total (%) (n = 42)	P*
Non-coexisting disease	2 (4.8)	0.13
One coexisting disease	21 (50.0)	
More than one coexisting diseases	19 (45.2)	
Total	42 (100)	

Note: *= Chi-Square Test (CI= 95%)

Factors related to physiological response are leukocyte, blood glucose, total cholesterol, triglyceride, temperature, onset, as well as physiological response 1,2, and 3 interpreted in Mean value and Standard Deviation. Mean±SD leukocyte factor 10.021±3.4470 mg/dL; blood glucose 148.98±96.500 mg/dL; total cholesterol 212.45±42.279 mg/dL; triglyceride 164.79±91.897 mg/dL; temperature 36.781±0.5782°C; and onset 2.21±.2.007 days (Table 3).

Physiological response in 42 respondents from both control and intervention groups showed as Physiological Response 1 is the baseline, Physiological Response 2 is pre-test and Physiological Response 3 is post-test. Mean±SD of Physiological Response 1 and 2 is between 6-8 with moderate stroke interpretation, while Physiological Response 3 is 4.98 with mild stroke interpretation. This result data show that there were differences between Physiological Response 1 (baseline), Physiological Response 2 (pre-test), and Physiological Response 3 (post-test) (Table 3).

Table 3. Factors Related to Physiological Response (N=42)

Variable	Mean	±	SD	P*
Leukocyte	10.021	±	3.4470	1.000
Blood Glucose	148.98	±	96.500	1.000
Total Cholesterol	212.45	±	42.279	1.000
Triglyceride	164.79	±	91.897	1.000
Temperature	36.781	±	0.5782	0.103
Onset	2.21	±	2.007	0.000
Physiological Response 1	7.40	±	4.254	0.176
Physiological Response 2	7.38	±	4.299	0.126
Physiological Response 3	4.98	±	4.331	0.249

Note: *= Chi-Square Test (CI= 95 %)

Bivariate test of the factors related to physiological response can be seen in Table 4. Study on 42 respondents shows that physiological response is not correlated to p value in the following factors: leukocyte 0.939, blood glucose 0.913, total cholesterol 0.482, triglyceride 0.114, temperature 0.704, coexisting disease 0.263, and gender 0.746. This study found that there is a correlation among physiological response, onset, and Benson's relaxation response (p= 0.007 and p= 0.0005) (Table 4).

Table 5 show, it can be seen that multiple regression linear test on leukocytes, blood glucose, total cholesterol, triglyceride, temperature, gender, and coexisting disease shows $p > 0.05$ which means that statistically, those factors have no significant correlation to physiological responses of AIS patients. Onset and Benson's relaxation response factors show $p < 0.05$ which means that those factors have significant correlation to AIS patients' physiological responses.

In other words, the patients' physiological response can be predicted using Benson's relaxation response and onset variables. Coefficient B from every decline in AIS patients' onset by 1 day means that the physiological response will decrease by 0.281 after being controlled using Benson's relaxation response. Coefficient B from Benson's relaxation response done with AIS patients shows that the physiological response of the patients will decrease by 1.195 after being controlled by onset (Table 5).

Table 4. Factors Related to Physiological Response Delta (N=42)

Variable	P
Leukocyte	0.939*
Blood Glucose	0.913*
Total Cholesterol	0.482*
Triglyceride	0.114*
Temperature	0.704*
Onset	0.007*
Coexisting Disease	0.263**
Benson's Relaxation Response	0.005**

Note: * Pearson Correlation Test and ** t-test

Table 5. Factors Related to Physiological Response (N=42)

Model	Unstandardized Coefficients		Standardized Coefficients	t	P*
	B	SE	Beta		
(Constant)	4.963	0.752		6.601	0.000
Leukocyte	-0.021	0.079	-0.042	-0.269	0.790
Blood Glucose	-0.002	0.003	-0.087	-0.581	0.565
Total Cholesterol	0.000	0.007	-0.004	-0.022	0.982
Triglyceride	-0.001	0.004	-0.058	-0.279	0.782
Temperature	0.306	0.450	0.099	0.679	0.501
Onset	-0.281	0.123	-0.321	-2.283	0.028
Coexisting Disease	-0.456	0.477	-0.131	-0.956	0.345
Benson's Relaxation Response	-1.195	0.488	-0.344	-2.449	0.019

Note: *ANOVA (Analysis of Variance)

Stroke might happen to every individual in every age range; however, the occurrence and prevalence of stroke tend to increase significantly in older people. In the whole world, stroke occurrence exponentially increases after 30 years of age with around 95% of stroke happen to people aged 45 years or older, and more than 65% of them are older than 65 years.[20] The majority of respondents' age in intervention group ranges from 45-59 years vold (10 respondents or 47,6%). The majority of respondents' age in control group ranges from 60-74 years (12 respondents or 57,1%). The result of this study is similar to that of the previous one, which shows that the respondents aged 45-54 years old (50%) and 51-65 years old (41,6%).[7,21] According to the theory, cholesterol deposit in atherosclerosis needs to be watched as someone ages, with the most serious consequence on coronary artery. The level of certain arteriosclerosis needs to be considered and the resting blood pressure might increase which can damage arterial wall. The consequences of the damage include stroke and heart failure. Vena might as well worsen by age. The thinning wall might get weaker and stretchy which makes the valve less competent.[22] The majority of AIS respondents' gender in this study is female, with a total number of 24 respondents (57,1%). The previous study showed a similar result, the majority of the respondents' gender was also female. This was proven by data analysis test which showed the percentage of female AIS patient was 57,9% while male AIS patient took 42,1% out of all respondents.[23] The occurrence of stroke in female tends to increase during post-menopause period because before

menopause period, a woman is protected by estrogen hormone. Estrogen helps prevent atherosclerosis process. However, estrogen level decreases after menopause period. Estrogen also helps in increasing HDL. HDL is essential in preventing atherosclerosis process.[24]

Leukocyte factor in this research shows insignificant correlation to physiological response of AIS patients (p= 0.790). It is not in accordance with previous researches which stated that high leukocyte level in acute ischemic cerebral phase was a significant independent predictor in initial severity level of severe stroke attack after 72 hours and change in disability. The occurrence of leukocytosis is associated with thrombolysis resistance, increase in thrombus burden, and microvascular perfusion disorder.[14] The difference of the results in this study occurs because the increase of leukocyte level in AIS patients is still considered as normal (about 3,8-10.6/uL).

Blood glucose level factor in this study shows insignificant correlation to AIS patients' physiological response (p= 0.565). This number corresponds to the result of the previous study which also showed insignificant correlation between random blood glucose level and NIHSS outcome (p= 0.548); however, the correlation between random blood glucose level and NIHSS input was significant (p= 0.011). The result of Chi-Square test between random blood glucose level and NIHSS outcome shows insignificant correlation (p= 1). On the contrary, the correlation between random blood glucose level and NIHSS input and improvement is significant (p = 0.024 and p= 0.047). There is no significant correlation between random blood glucose upon admission to Emergency Room and clinical outcome of AIS patients. However, normal random blood glucose level shows improvements and tends to have a better outcome.[3]

Total cholesterol factor in this study shows insignificant correlation to AIS patients' physiological response (p= 0.982). This number corresponds to the results of the previous study which showed that the level of total cholesterol was 204,29 ± 49,55 mg/ dL. The Spearman correlation shows insignificant correlation between total cholesterol serum level and score function (r = 0,16, P = 0,057). High level of total cholesterol in AIS patients is linked to a better prognosis and higher status of general functional level according to Barthel index. Although the reversal correlation between post-AIS prognosis and total cholesterol level is comparable with the nature of total cholesterol as a risk factor in AIS, somehow this correlation is paradoxical but justifies that cholesterol can act as a supportive agent and neutralize free radicals as well as oxidative stress.[15]

Triglyceride factor in this study shows insignificant correlation to AIS patients' physiological response (p= 0.782). This number corresponds to the results of the previous study that stated the increase of triglyceride serum level correlated to the decrease of NIHSS score, although in an insignificant way. The statistical analysis using Spearman correlation shows that there is no significant correlation between triglyceride level and NIHSS score (p>0.05).[16]

Temperature factor in this study shows insignificant correlation to AIS patients' physiological response (p= 0.501). This result corresponds to the previous study's result that showed the body temperature of patients upon admission was not correlated to infarct measurement or bad results of the analysis. The peak body temperature which are higher during the first days of post-AIS, not during initial admission, is correlated to the bigger size of infarct and bad functional measure.[25] Other studies stated that the correlation between hyperthermia and bad prognosis in AIS patients could be explained because the occurrence of infarct influenced hypothalamus anterior, so the hyperthermia transformed the ischemic penumbra area to bigger infarct and accelerated the occurrence of cerebral necrosis. Ischemic that occurs in acute stroke shows that hyperthermia is one of the independent risk factors that contributes badly to higher rate of morbidity and mortality as well as bigger volume of infarct.[26]

Coexisting disease factor in this study shows insignificant correlation to AIS patients' physiological response (p= 0.345). It corresponds to the results of the previous study that showed coexisting disease had negative correlation to functional result.[27] It is different with the other previous study that showed the first ischemic stroke in a patient aged 60 years old with coexisting disease was significantly correlated to bad outcome and mortality.[19]

Onset factor in this study shows a

significant correlation to AIS patients (p= 0.028). This statement corresponds to the previous study's result which stated that only patients who showed partially decreasing symptoms have more possibility to postpone the pre-hospital phase faster compared to those who showed no sign of improvements. Patients who experience the onset during the night tend to have a better possibility in pre-hospital postponement than those who experience the onset during the day.[18] The average of onset in this study was a few days because of some factors, like most of the respondents had to wait for other family members to make decisions because they were the ones responsible for their treatment fee, knowledge, perception, economy, and transportation.[18,28,39] Onset of AIS that exceeds golden period results in the increase of physiological response value which is shown by the increase of NIHSS values, therefore outcome of stroke patients becomes less promising. The further impact of the lengthened of onset in AIS patients is the widening of ischemic in cerebral tissues which leads to the inevitable worsened complication.

Gender factor in this research shows insignificant correlation to physiological response of AIS patients (p= 0.707). In the previous study, the highest average number of NIHSS was 6,2 (5.5) for male respondents and 5 (3.7) for female respondents. The highest frequency of NIHSS average number in the previous study was moderate with a total number of 58 respondents (48,3%). This explained that the values in NIHSS of females are better than that of males and almost half of the subjects' population had moderate NIHSS value. [30] A different result was shown in another study which stated that the clinical outcome of male ischemic stroke patients is better with the value of $p < 0.005$.[31]

Benson's relaxation response factor in this study shows a significant correlation to AIS patients' physiological response (p= 0.019). This result corresponds to the previous study which stated that the physiological response of AIS patients in intervention group after Benson's relaxation response treatment had improved compared to the physiological response of AIS patients in control group with the value of p= 0.0001.[6] The changes of physiological response occur due to Benson's relaxation response that alters the activity pathway of Hypothalamus Hypophysis Adrenal (HPA) and Sympatho Adreno Medullary (SAM). Both of the main pathways are activated by hypothalamus which secrete Corticotrophin Releasing Hormone (CRH) and causes the pituitary to release Adreno Corticotropic Hormone (ACTH). The quick reaction of SAM pathway causes ACTH to drop and lead to the decrease of the sympathetic nerve's activities. This causes the adrenal medullary to decrease catecholamines epinephrine and norepinephrine which results on the decrease of blood pressure, heart rhythm, breathing, and oxygen consumption. The rather slow HPA pathway's reaction causes ACTH to stimulate adrenal cortex to drop cortisol. The level of cortisol serum is significantly lower following the meditation period.[32]

Nitric Oxide pathway (NO) is also useful in controlling the process of norepinephrine in many different levels including synthetic, secretion, and activity. NO pathway is essential because constitutive NO has lots of amelioration and/or protection capacity, so that it is possible to start a beneficial function to fight the diseases related to stress and re-balance the autoregulatory signalling process.[33]

The limitation of this study lies on the nursing intervention to AIS patients' physiological response that has not been studied further. The limitation of other previous studies lie on the limited number of subjects which affects the result of the multivariate analysis.

CONCLUSION

This study concludes that Onset and Benson's relaxation response factors are significantly correlated to the physiological response of AIS patients. Based on the results of the study, it is advised that nursing interventions need to be done to control the factors related to the physiological response of AIS patients as a preventive act against complication. The upcoming study will identify the factors of AIS patients' physiological response that involve more nursing intervention with a larger number of subjects.

REFFERENCES

1 Smeltzer, S. & Bare, B. 2016. Text Book Medical Surgical Nursing. St. Louis Missouri Elsevier Saunders

2 Feng, C., Fang,M., and Liu, .X,Y., 2014. The neurobiological pathogenesis of poststroke depression. Hindawi Publishing Corporation The Scientific World Journal. http://dx.doi.org/10.1155/2014/521349 Volume 2014 Article ID 521349, 8 pages.

3 Glen Y. C. R. Kabi, R. T., Mieke A. H. N. K. 2013. Gambaran faktor risiko pada penderita stroke iskemik yang dirawat inap neurologi RSUP Prof. Dr. R. D. Kandou Manado.

4 Weimar, C., A. Ziegler, et al. (2002). "Predicting functional outcome and survival after acute ischemic stroke." J Neurol 249(7): 888-95.

5 Saxena, S. K., G. C. Koh, et al. (2007). Determinants of length of stay during poststroke rehabilitation in community hospitals." Singapore Med J 48(5): 400-7.

6 Poonatajaya1, Y. K, Pudjonarko, D. 2015. Hubungan jumlah leukosit saat masuk dengan keluaran pasien stroke non hemoragik. Media medika muda Volume 4, Nomor 4, Oktober 2015 Online : http://ejournal-s1.undip.ac.id/index.php/medico

7 Jiméneza C. L., Sandovalb, J.L. R. C., Arroyob, E. C., M., et al. 2013. Hospital arrival time and functional outcome after acuteischaemic stroke: Results from the PREMIER study. Investigadores PREMIER. 2173-5808/ – see front matter.2013. Sociedad Española de Neurología. Published by Elsevier España, S.L. All rights reserved

8 Bushnell, C. D., Lee, J., Duncan, P. W. L, et al. 2008. Impact of Comorbidities on Ischemic Stroke Outcomes in Women. Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.107.50928. 2008 American Heart Association, Inc.

9 Centers for Disease Control and Prevention. 2016. Stroke facts. Available at: http://www.cdc.gov/stroke/facts.htm. Accessed March 1710 .(Riset Kesehatan Dasar, 2013).

10 Riset Kesehatan Dasar. 2013 Laporan nasional rikesdas. Badan Penelitian dan Pengembangan Kesehatan Kementrian Kesehatan republik Indonesia.

11 PDPERSI. 2010. Stroke, penyebab utama kecacatan fisik. http://pdpersi.co.id. Diakses tanggal 4 Januari 2010.

12 Hospital KRMTWongsonegoro. Prevalensi acute Ischemic Stroke.2017

13 Hospital Tugurejo. Prevalensi acute Ischemic Stroke. 2017

14 Nardi, K., Milia, P., Eusebi, P., Paciaroni, M., et al. 2012. Admission Leukocytosis in Acute Cerebral Ischemia: Influence on Early Outcome.

15 Fathi, Davood., Nomali, Mahin., Hamed. 2015. Total Serum Cholesterol Level and Prognosis of Acute Cerebral Ischemic Stroke. - Volume 9 / Number 2 / 2015. Journal of Society for development in

16 Mariduk,Benny. 2009. Hubungan Kadar Adiponektin Dan Trigliserida Serum Dengan Volume Infark Dan Outcome Pada Pasien Stroke Iskemik Akut.

17 Geurts, Marjolein., Scheijmans, Féline E. V., Seeters, Tom Van,. et al. 2016. Temporal profile of body temperature in acute ischemic stroke: relation to infarct size and outcome. BMC Neurology. 2016. 16:233 DOI 10.1186/s12883-016-0760-7

18 Jiang, Bin., Ru, Xiaojuan., Sun, Haixin., et al. 2016. Pre-hospital delay and its associated factors in first-ever stroke registered in communities from three cities in China.

19 Arabadzhieva, Daniela., Kaprelyan, Ara., Tzoukeva, Alexandra., Branimir Kanazirev. 2015. Cardiovascular comorbidity in acute ischemic stroke.

20 World Health Organization.2015. WHO Disease and Injury Country Estimates for 2008 and 2004. Geneva. Available at: http://www.who.int/healthinfo/ global _ burden _disease/estimates_country/en/index.html (retrieved November 2015)

21 Vitta.R. 2015. Studi penggunaan neuroprotektan pada pengobatan stroke iskemik di RSUD Sidoarjo. repository.wima.ac.id.

22 Scanlon,Valerie C. 2007.Essentials of anatomy and physiology/Valerie C. 5th ed. F. A. Davis Company. Philadelphia.

23 Munir,Badrul., Rasyid, Harun Al., Rosita, Rizky. 2015. Hubungan antara kadar glukosa darah acak pada saat masuk instalasi gawat darurat dengan hasil keluaran klinis penderita stroke iskemik fase akut relationship between the random blood glucose levels during admission at emergency room with clinical output in acute ischemic stroke patients.

24 Price dan Wilson. Pathopysiology. Jakarta. EGC. 2016.

25 William N. Whiteley, Ralph Thomas, Gordon Lowe, et al. 2012. Acute phase markers explain body temperature and brain temperature after ischemic stroke?

26 Dehkharghani, X S., Fleischer, X C.C., Qiu, X D., X M. Yepes, and X F. Tong. 2017. Cerebral Temperature Dysregulation: MR Thermographic Monitoring in a Nonhuman Primate Study of Acute Ischemic Stroke.

27Altinay Goksel Karatepe, Rezzan Gunaydin, Taciser Kaya, and Gul Turkmen. COMORBIDITY IN PATIENTS AFTER STROKE: IMPACT ON FUNCTIONAL OUTCOME. 2008 Foundation of Rehabilitation Information. ISSN 1650-1977 *J Rehabil Med 40*doi: 10.2340/16501977-0269

28 Pinzon, R., Asanti, Lakasmi, Sugianto, Widyo, et al. 2010. Awas stroke: pengertian, gejala, tindakan, perawatan & pencegahan. Yogyakarta: Penerbit ANDI.

29 Kim, Y. S., Sang-Soon, P, Hee-Joon, B, et al. 2011.Stroke awareness decreases prehospital delay after acute ischemic stroke in Korea. BMC Neurology 2011. 11.2

30 Gofi,Abdul., Indera. 2014. Hitung angka lekosit sebagai salah satu prediktor prognosis functional outcomedan lama perawatan rumah sakit pada stroke iskemik akut.

31 Wicaksana, Ignatius Eka Perwira., Wati,Arinta Puspita., Muhartomo, Hexanto. 2017. Perbedaan Jenis Kelamin Sebagai Faktor Risiko terhadap Keluaran Klinis Pasien Stroke Iskemik. JURNAL KEDOKTERAN DIPONEGORO Volume 6, Nomor 2, April 2017 Online : http://ejournal-s1.undip.ac.id/index.php/medico ISSN Online : 2540-8844.

32 Dusek, Jeffery A., and Benson, Herbert. 2009. Mind body medicine: a model of the comparative clinical impact of the acute stress and relaxation responses. Minnesota Medicine. May 2009

33 Stefanoa, George B., Fricchionea, Gregory L., Slingsby,Brian T., Benson, Herbert. 2003. The placebo effect and relaxation response: neural processes and their coupling to constitutive nitric oxide. http://www.MedSciMonit.com/pub/vol_9/no_2/3454.pdf. Med Sci Monit, 2003; 9(2): RA23-34 PMID: 12601303