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The Correlation between Hematological Parameters and Transcranial Color Doppler (TCD) with Severity of Acute Ischemic Stroke – A Cross-Sectional Study

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ABSTRACT
To access correlation between both hematological profile and Transcortical Color Doppler (TCD) ultrasonography with stroke severity by using National Institute of Health Stroke Scale (NIHSS) score. This cross-sectional study was conducted from August to December 2016. Hematological profiles (hemoglobin count [Hb], hematocrit [Hct], platelet, and erythrocyte sedimentation rate [ESR]), TCD ultrasound measurements (mean flow velocity [MFV], peak systolic [PS], end-diastolic velocity [EDV], and pulsatility index [PI]) on middle cerebral artery (MCA) and internal carotid artery (ICA), and severity of stroke according to NIHSS score was measured. Both hematological profiles and TCD ultrasound measurements were compared with stroke severity, then test of correlation was conducted. There were 90 patients enrolled in this study. Positive correlation between NIHSS score with Hb (r = 0.519), Hct (r = 0.481), and ESR (r = 0.519). On TCD measurements, negative correlation was found between NIHSS score with MFV and PS on both MCA (r = - 0.615 and r = - 0.336, respectively) and ICA (r = -0.570 and r = -0.596, respectively), and end-diastolic velocity on ICA (r = -0.477). Positive correlation was found between NIHSS score and pulsatility index on MCA (r = 0.568). There is positive correlation between NIHSS score with hematological parameters (Hb, Hct, and ESR) and PI on MCA. Negative correlation was found between NIHSS score with MFV and PS on both MCA and ICA, and EDV on ICA. The strongest correlation was found to be MFV on MCA.
Keywords: Hematological profiles, transcranial color doppler, acute ischemic stroke, NIHSS
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INTRODUCTION
Stroke is one leading cause of death and functional impairement in the world. Since stroke is major healthcare problem in Southeast Asia, burden of stroke is high in Southeast asian countries(1). In Indonesia, as one of Southeast Asian countries, stroke prevalence was 1.21% of all population above 15 years old but numbers are higher in older age (above 55 years old, OR 5.8)(2). World Health Organization stated that 21.2% Indonesian died from stroke at 2012, which accounts for number one cause of death in Indonesia(3). This high mortality could be caused by presence of risk factors and uneven distribution of facility and professionals across Indonesia(4). Analysis of Indonesia Basic Health Research (Riskesdas), showed that stroke occured primarily in older age and patients who suffered from coronary heart disease, diabetes mellitus, hypertention and heart failure(2). Among those with stroke, ischemic stroke occurs more frequently than other types of stroke(1). In Indonesia, around 70% of stroke was ischemic type which has atherosclerotic origins(4).
Despite many major breakthroughs occurred, most clinician believe that this entity still holds many complexities. Multiple factors have been studied to determine prognostic factor of stroke. Hematological profile is one of the most appealing issues due to its easy-to-use and widespread availability. Studies assessing relevant hematological markers and its influences on functional outcome especially in acute ischemic stroke (AIS) was being conducted nowadays on multiple centers(5–8).Another appealing noninvasive diagnostic test which can be used is transcranial doppler (TCD) ultrasonography. Using principle of the Doppler effect, this test could give clinician fast insight of blood flow condition within the intracerebral vessels(9). Internal carotid artery (ICA) was important cerebral vessel since it covers wide cerebral area. Its perforating branches supply basal ganglia, internal and external capsule, and claustrum, while its cortical branches supply insula and also area of frontal, parietal and temporal lobes(10). Internal carotid artery was the most common site of stenotic site, therefore every changes in ICA would affect middle cerebral artery (MCA)(11).
In this study, correlation between both hematological profile, TCD, and functional outcome of stroke was assessed. National Institute of Health Stroke Scale (NIHSS) was used as tool to evaluate functional outcome of patient with ischemic stroke.

PATIENTS AND METHODS
Patients and study design
This cross-sectional study was conducted at Adam Malik General Hospital, Medan from August to December 2016. All patients with ischemic stroke on admission was included. Ischemic stroke diagnosis was confirmed with standardized non-contrast head computed tomography (CT) and patients were receiving antiplatelet therapy. Patients with previous history of stroke or another space occupying lesions, large hemispheric malignant ischemic stroke with obvious potentials source of cardio embolism, essentials heart, liver and/or kidney disorders, pneumonia, sepsis, seizure at the beginning or during hospitalization, massive upper and/or lower gastrointestinal bleeding were excluded.

METHODS
On the first day of admission, hematological profile, TCD ultrasound and functional outcome of stroke was measured. Informed consent was asked from the patients him/herself or in any condition cannot be fulfilled, it was given by their legal responders before all procedures were

conducted. Five milliliters of blood samples to measure the hemoglobin (Hb) count, hematocrit (Hct), platelet, and erythrocyte sedimentation rate (ESR) of the patients. These process was routine procedure of the hospital and results were retrieved from medical record. Measurement of TCD parameters were done using SONARA/tek® Transcranial Doppler System (Natus Neurology, USA) to obtain mean flow velocity (MFV), peak systolic (PS), end-diastolic velocity (EDV) and pulsatility index (PI) value. Measurement of TCD was done from the posterior temporal window on the subjects and matched the same depth of each correlating arteries for MCA (towards flow, depth 30-65 mm) and terminal ICA (towards flow, depth 55-65 mm) while still based on as low as reasonably achievable (ALARA) principle of TCD examination(12,13). Functional outcome of stroke was evaluted using NIHSS. Subjects were divided into 3 groups according to NIHSS: mild stroke (NIHSS<4), moderate stroke (NIHSS 4-15) and severe stroke (NIHSS > 15)(14). This study was approved by Health Research Ethical Committee, Faculty of Medicine, Universitas Sumatera Utara.

Statistical analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Distribution of Hb, Hct, ESR, MFV, PS, EDV, PI were analyzed using Kolmogorov-Smirnov test. Comparison of normally distributed data according to severity of stroke was done by using one-way ANOVA with post-hoc Scheffe test, while Kruskal-Wallis test with post-hoc Dunn test was used otherwise. After comparison test, correlation test (Pearson or Spearman) were conducted according to the distribution of data. P values < 0.05 was considered significant.

RESULTS

Between August 2016 to December 2016, this study enrolled 90 patients, all of which were grouped for the severity of stroke according to NIHSS with characteristics, hematological parameters, and measurement of TCD in MCA and ICA as shown in Table 1.

Hematological parameters (Hb, Hct, platelet, and ESR) of patients were compared according to severity of stroke. There were significant differences in Hb, Hct, and ESR, but not on platelet (Fig 1). Post-hoc analysis using Dunn test showed there were statistically lower Hb, Hct, and ESR in severe stroke compared to mild ($p < 0.0001$, $p < 0.0001$, and $p = 0.0001$, respectively) and moderate stroke ($p < 0.0001$, $p < 0.0001$, and $p < 0.0001$, respectively). There were statistically lower Hct in moderate stroke compared to mild stroke ($p = 0.032$), but the similar result could not be found in Hb and ESR ($p = 0.148$ and $p = 0.113$, respectively). Moderate positive correlation were found between NIHSS score with Hb ($r = 0.519$; $p = 0.001$), Hct ($r = 0.481$; $p = 0.003$) and ESR ($r = 0.519$; $p = 0.001$).

Measurements of TCD (MFV, PS, EDV, and PI) on MCA and ICA were compared according to severity of stroke. There were significant differences in all measurements of TCD on MCA and ICA, except in PI on ICA (Fig 2). Post-hoc analysis showed there were statistically higher median of MFV on MCA and ICA in patients with severe stroke compared to moderate stroke ($p = 0.0003$ and $p = 0.0002$, respectively) and in patients with moderate stroke compared to mild stroke ($p = 0.0080$ and 0.0080, respectively). Statistically higher PS mean were found on MCA and ICA in patients with severe stroke compared to moderate stroke ($p = 0.003$ and $p = 0.023$, respectively), and statistically higher PS mean was found on ICA ($p = 0.0030$), but PS was not significantly different on MCA ($p = 0.718$) in patients with moderate stroke compared to mild stroke. There were significantly differences of EDV on MCA and ICA in patients with severe stroke compared to moderate stroke ($p = 0.0005$ and $p = 0.043$, respectively) and in patients with moderate stroke compared to mild stroke ($p = 0.014$ and $p = 0.0006$, respectively). Post-hoc analysis of PI on MCA showed there was no difference found between severe and moderate stroke ($p = 0.125$), but there was lower PI in patients with moderate stroke compared to mild stroke ($p = 0.0001$). There were strong negative correlation on MCA ($r = -0.615$; $p < 0.001$), and moderate negative correlation on ICA ($r = -0.570$; $p < 0.001$) between NIHSS score and MFV measurement. Weak negative correlation on MCA ($r = -0.336$; $p = 0.045$) and moderate negative correlation on ICA ($r = -0.596$; $p < 0.001$) were found between NIHSS score and PS. Moderate negative correlation were found between NIHSS score and EDV on ICA ($r = -0.477$; $p = 0.003$), but not on MCA ($r = -0.130$; $p = 0.448$). Relationship between NIHSS score and PI was found to be moderate positive correlation on MCA ($r = 0.568$; $p < 0.001$), but not on ICA ($r = 0.228$; $p = 0.182$).

DISCUSSION

This study finds that there are moderate positive monotonic correlation between NIHSS score with Hb, Hct, and ESR. This result is consistent with a study by Kimberly et al(6) that shows for each drop in Hb level of 1 g/dL at the onset of acute ischemic stroke, there is 5.5 ± 2.4 cm^3 increase in the growth of infarct. The larger infarct volumes were associated with lower NIHSS score, especially neglect, language, and visual deficits components(15). Conversely, study by Furukawa et al(16) showed that increased blood viscosity was associated with acute ischemic stroke type small artery occlusion, but not on other types, and study by Song et al(17) strengthen the hypothesis by showing that elevated diastolic blood viscosity have a role in development of small artery occlusion. However, although hematocrit is the most important factor, protein fractions and fibrinogen also has a great contribution affecting blood viscosity(18), and dehydration that leads to elevation of blood viscosity is the major factors responsible for triggering acute ischemic stroke(19,20), not hematocrit itself. As Bhatia et al(5) has stated, increment of ESR has been known as prognostic factor of poor prognosis and more severe deficits, as higher ESR indicates greater increase in fibrinogen therefore causes reduction in cerebral blood flow by increasing blood viscosity. Platelet count between groups are very much alike between mild, moderate and severe stroke and showed no significant associations with severity of stroke. This is in accordance with Bill et al(7) results which showed no significant differences on platelet counts, however study by Yang et al(21) found that both higher ($213 – 450 \times 10^9$/L) and lower ($100 – 155 \times 10^9$/L) platelet count were associated with increased risk of poor functional outcome. Study by Nayak et al(22) showed that hematological parameter (ESR, white blood cell count, polymorph count, lymphocyte count, and total protein) can predict the severity of acute ischemic stroke patients.

This study found negative correlation between most of TCD measurements with severity of stroke, except for PI. The strongest negative correlation with severity of stroke on this study is MFV on MCA, which means lower MFV will cause higher NIHSS score (worsening of functional outcome. Considering Aaslid hypothesis(23) that MFV is one of the TCD value that can be used to assess pressure, flow and velocity of the arterial system and have the highest physiological significances parallel to cerebral blood perfusion and hypoperfusion would be detrimental for stroke functional outcome. Moderate positive correlation between severity of stroke and PI shows an increment in PI is associated with more severe stroke (higher NIHSS score) especially on MCA, this is caused by high remodeling activity which forms stenoses plaque proved by MRA that usually happened on MCA branching(12,24).

Some limitation of this study was to be noted. Due to good clinical practice and intention to treat principles, some of the results (such as platelet counts decrement from loss of dynamic reactivity and acceleration of platelet turnover) inevitably affected by use of antiplatelets therapy and might show some irrelevant results on hematology profile(25,26). On the other hand, this study did not take consideration of some drug used such nootropics on its nature to increase and confound the cerebral blood flow, therefore compromising the TCD value(27,28). Minimal sample size was also one of our limitation, therefore we encourage other future research on this field with larger population to be observed.

This study concludes that there is positive correlation between NIHSS score with hematological parameters (Hb, Hct, and ESR) and PI on MCA. Negative correlation was found between NIHSS score with MFV and PS on both MCA and ICA, and EDV on ICA. The strongest correlation was found to be MFV on MCA.

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CONFLICTS OF INTEREST

Nothing to declare

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TABLE AND FIGURES

Table 1. Patient characteristics

	Patients (n= 90)
Age (years old), mean ± SD	60.86 ± 13.41
Sex	
Male	73 (81.1 %)
Female	17 (18.9 %)
History of Hypertension	
Yes	84 (93.3%)
No	6 (6.6%)
History of Hypercholesterolemia	
Yes	58 (64.4%)
No	32 (35.5%)
Stroke severity	
Mild	62 (68.9%)
Moderate	19 (21.1%)
Severe	9 (10%)
Hematological parameters	
Hb (g/dL), median (range)	13.2 (10.4 – 18.4)
Hct (%), median (range)	40.7 (32.2 – 54.7)
Platelet ($10^3/\mu L$), median (range)	247 (164 – 458)
ESR (mm/hour), median (range)	30 (2 – 90)
Transcranial doppler measurement (MCA)	
Mean flow velocity (MFW)(cm/s), median (range)	37.1 (22.6 – 83.7)
Peak systolic flow velocity (PS)(cm/s), mean ± SD	70.36 ± 22.70
End diastolic flow velocity (EDV)(cm/s), median (range)	26 (0.88 – 67.2)
Pulsatility index (PI), median (range)	1.15 (0.69 – 3.96)
Transcranial doppler measurement (ICA)	
Mean flow velocity (MFW)(cm/s), median (range)	27.4 (12.7 – 74.3)
Peak systolic flow velocity (PS)(cm/s), mean ± SD	54.55 ± 16.98
End diastolic flow velocity (EDV)(cm/s), median (range)	13.7 (0.86 – 35.8)
Pulsatility index (PI), median (range)	1.25 (0.84 – 8.64)

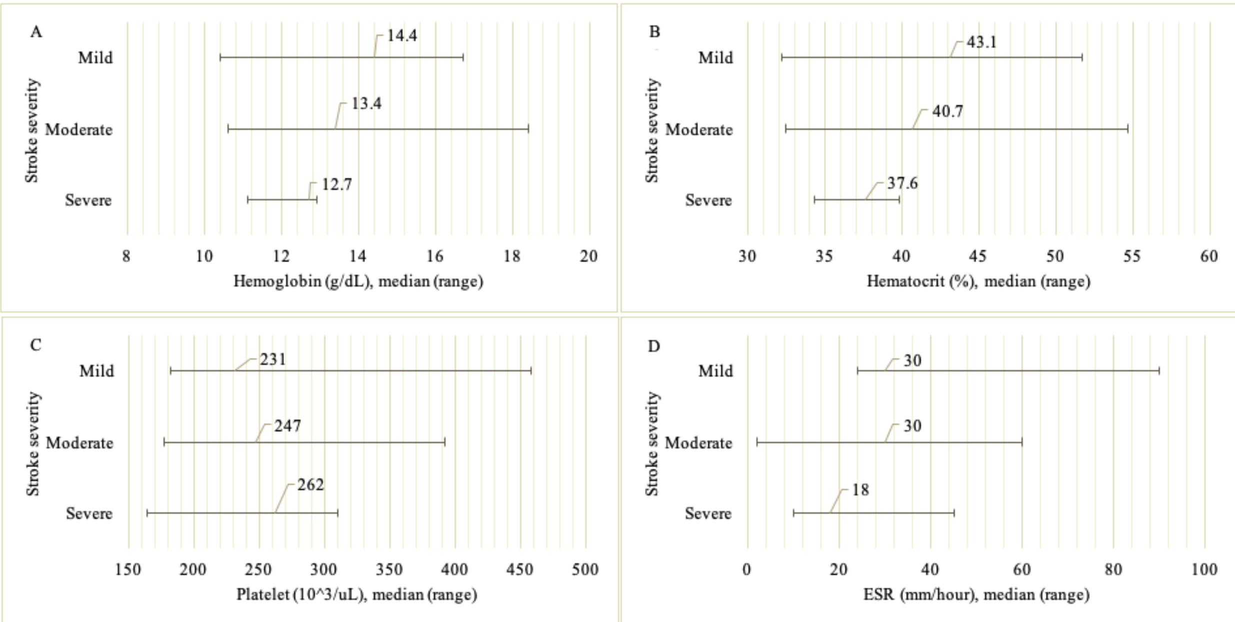

Figure 1: *Hematology parameters, comparison between stroke severity groups. A. Hb (p = 0.0001). B. Hct (p = 0.0001). C. Platelet (p = 0.2400). D. ESR (p = 0.0001)*

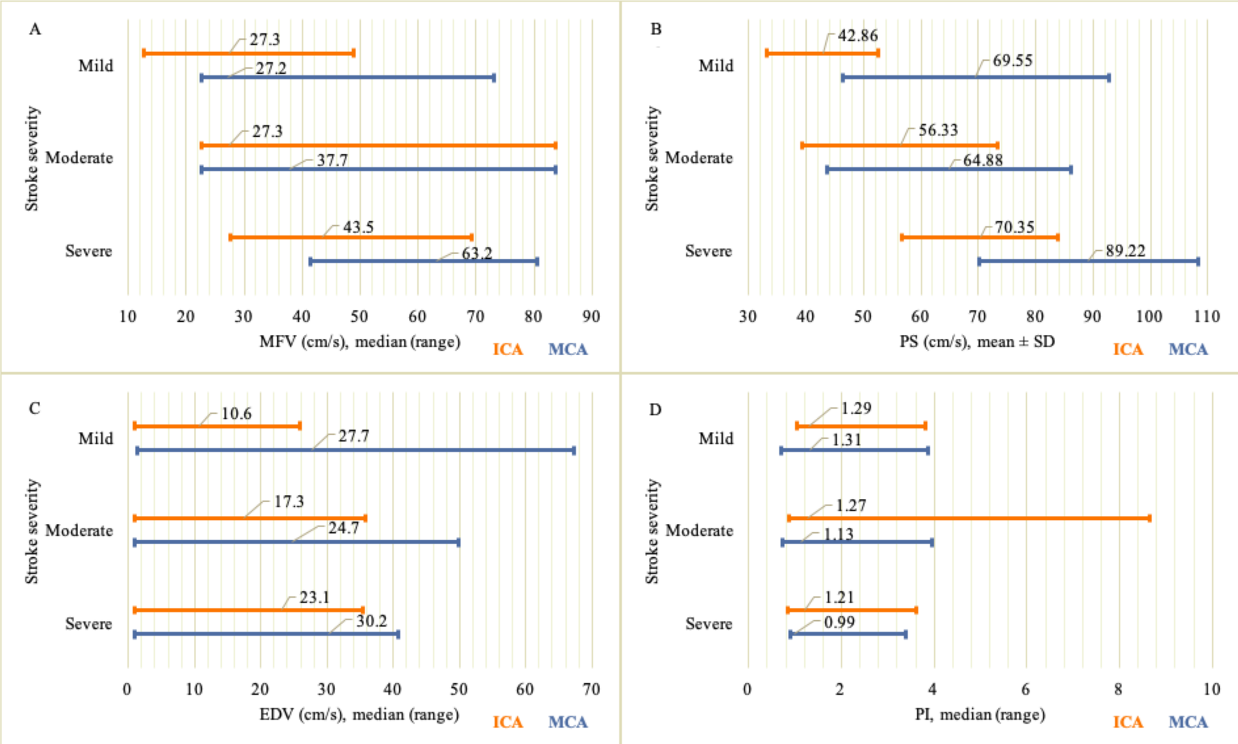

Figure 2: *TCD measurements, comparison between stroke severity groups. A. MFV in MCA (p = 0.0001) and ICA (p = 0.0001). B. PS in MCA (p = 0.0030) and ICA (p < 0.0001). C. EDV in MCA (p = 0.0020) and ICA (p = 0.0001). D. PI in MCA (p = 0.0001) and ICA (p = 0.3130).*