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## THE PROGNOSTIC VALUE OF LEUKOCYTE IN CEREBROVASCULAR DISEASES

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### Abstract

**Introduction.** Among adult neurological diseases, cerebrovascular diseases (CVD) are common and important. Therefore, to fight against the preventable prognostic factors in these patients has an important role in reducing the severity of the disease.

**Methods.** In this study, during the six-month period, 98 patients hospitalized at the neurology services after the first evaluation at the emergency department were examined retrospectively. Their white blood cell (WBC) counts are recorded and the relationship of them with mortality in the hospital was researched. Median of the age was 73 (37-99). M:F ratio was 0.78.

**Results.** 87(88.8%) of the patients diagnosed as ischemic CVD and others were hemorrhagic CVD. In hospital mortality was 19.4%, %66.3 of them were discharged with sequel and %14.3 of them without any complication and sequel. Mean value of WBC was  $9.30 \pm 3.31$  ( $10^3/\mu\text{L}$ ) in ischemic CVD and  $10.05 \pm 5.45$  ( $10^3/\mu\text{L}$ ) in hemorrhagic CVD group, there wasn't any statistical difference. WBC values of dead patient group was higher than the alive patient group.

**Conclusion.** In alive patient group, there wasn't any difference of WBC between patient with and without sequel. There wasn't any relationship between type of CVD and prognosis. Leucocytes contribute the onset and continuation of ischemic CVD and elevations in leukocytes may be independently associated with markers of subclinical atherosclerosis and increased risk of ischemic stroke. The increased level of the WBC of patients diagnosed with CVD was considered to be an important role in the severity of the disease.

**Key words:** ischemic, haemorrhagic, white blood cell, cerebrovascular disease, prognosis.

### Резюме

## ПРОГНОСТИЧЕСКАЯ ЦЕННОСТЬ ЛЕЙКОЦИТАРНОГО ПОКАЗАТЕЛЯ ПРИ ЦЕРЕБРОВАСКУЛЯРНЫХ ЗАБОЛЕВАНИЯХ

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**Введение.** Цереброваскулярные заболевания являются одними из самых распространенных и значимых среди неврологических заболеваний у людей пожилого возраста. В связи с этим борьба с предотвратимыми прогнозическими факторами у этих пациентов играет важную роль в снижении тяжести заболевания.

**Материалы и методы.** В настоящем исследовании представлена ретроспективная оценка 98 пациентов, госпитализированных в отделения неврологии после первой оценки в отделении неотложной медицины, в течение шестимесячного периода. Проведено исследование количества лейкоцитов (WBC) и их связи со смертностью в больнице. Медиана возраста составляла 73 года (37-99 лет), соотношение M:F составляло 0,78.

**Результаты.** У 87 (88,8%) пациентов был диагностирован ишемический инсульт, в остальных случаях наблюдалось нарушение мозгового кровообращения по геморрагическому типу. В стационаре смертность составила 19,4%, из них 66,3% были выписаны с последствиями инсульта, 14,3% из них не имели каких-либо осложнений и последствий. Среднее значение WBC было  $9,30 \pm 3,31$  ( $10^3/\text{мкл}$ ) в группе с ишемическим инсультом и  $10,05 \pm 5,45$  ( $10^3/\text{мкл}$ ) в группе геморрагического инсульта, статистически значимых различий не было установлено.

**Заключение.** Значения WBC в группе умерших пациентов были выше, чем в группе выживших пациентов. В группе выживших пациентов не было различий по шкале WBC между пациентами с последствиями инсульта и без них. Не установлено связи между типом инсульта и прогнозом. Лейкоцитоз способствуют возникновению и усугублению ишемического инсульта, повышение уровня лейкоцитов может быть независимо связано с маркерами

субклинического атеросклероза и повышенным риском ишемического инсульта. Повышенный уровень лейкоцитов у пациентов с диагнозом ССЗ считается важным фактором в прогнозе тяжести заболевания.

**Ключевые слова:** ишемия, геморрагия, лейкоциты, цереброваскулярные заболевания, прогноз.

### Түйіндеме

## ЦЕРЕБРОВАСКУЛЯРЛЫҚ АУРУЛАР КЕЗІНДЕГІ ЛЕЙКОЦИТТЕР ҚОРСЕТКІШІНІҢ БОЛЖАМДЫҚ МӘНІ

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**Кіріспе:** Цереброваскулярлық аурулар егде жастағы адамдарда жиі кездесетін маңызды неврологиялық аурулардың бірі болып табылады. Соңдықтан осы науқастарда алдын-ала болатын болжамдық факторларға қарсы күрес жүргізу аурудың ауырлығын тәммендетуде маңызды рөл атқарады.

**Материалдар мен әдістер.** Бұл зерттеуде алты ай ішінде аурухананың неврология бөліміне жатқызылған 98 науқастың ретроспективті бағалауы ұсынылған, науқастардың алғашқы бағалауы шұғыл медициналық көмек бөлімінде жүргізіліп, олар неврология бөліміне жатқызылған. Лейкоциттердің (WBC) саны мен олардың ауруханалық өліммен байланысы зерттелді. Орташа жас мөлшері 73 жаста (37-99 жас), M:F коеффициенті 0,78 құрады.

**Нәтижелер:** 87 (88,8%) науқаста ишемиялық инсульт диагнозы қойылды, басқа жағдайларда ми қан айналымының геморрагиялық түрі байқалды. Ауруханада өлім-жітім 19,4% -ды құрады, оның 66,3% -ы инсульт салдарынан шығарылды, олардың 14,3% -ында асқынулар мен басқа зардаптар болған жоқ. Орташа WBC ишемиялық инсульт тобында  $9.30 \pm 3.31$  ( $10^3 / \text{мкл}$ ) және геморрагиялық инсульт тобында  $10.05 \pm 5.45$  ( $10^3 / \text{мкл}$ ) болды, статистикалық маңызды айырмашылықтар табылған жоқ.

**Корытынды:** Қайтыс болған науқастар тобындағы WBC мәні тірі қалған науқастар тобына қарағанда жоғары болды. Тірі қалған науқастар тобында инсульттің зардаптары бар науқастар мен зардаптары жоқ науқастар арасында WBC шкаласында айырмашылықтар болған жоқ. Инсульт түрі мен болжамы арасында ешқандай байланыс табылмады. Лейкоцитоз ишемиялық инсульттің дамуына және нашарлауына ықпал етеді, лейкоциттер денгейінің жоғарылауы субклиникалық атеросклероздың белгілерімен және ишемиялық инсульт қаупінің жоғарылауымен тәуелсіз байланысты болуы мүмкін. ЖКЖ ауруы диагнозы қойылған науқастарда лейкоциттердің мөлшерінің жоғарылауы аурудың ауырлығын болжаудың маңызды факторы болып табылады.

**Түйінді сөздер:** ишемия, қан кету, лейкоциттер, цереброваскулярлық аурулар, болжам.

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### Introduction

Cerebrovascular diseases among neurologic problems of adults seen frequently. CVD is the third most common cause of death in the world following cardiovascular diseases and cancer; and also the most common cause of disability. Epidemiologic data reveals that two of every thousand people have a stroke in every year in the world; one third of them die, one third become disabled, one third partially recover [23]. The 80% of CVD are ischemic, 15% are intracerebral hemorrhage, 5% are subarachnoid hemorrhage [13,23].

Age, sex and genetic are the invariable risk factors and hypertension, diabetes, hypercholesterolemia, cardiac diseases, obesity, smoking and alcohol are the variable risk factors for the ischemic stroke resulting from great vessel diseases, but it is controversial their effect on small vessels [18].

It is known that inflammatory response plays role in many CVD, especially ischemic cases [20]. There are various studies that show the importance of inflammatory profile in prognostic value [2,10]. Especially in coronary artery diseases the relationship between

neutrophil/lymphocyte ratio (NLR) and mortality was researched in some studies and significant results are obtained [5].

In our study we investigated the relationship between early phase prognosis and the initial glucose, white blood cell, NLR among the patients admitted to the emergency department and hospitalized with the diagnosis of CVD.

#### Material and method

98 patients admitted to emergency department and hospitalized in a six month period with ischemic or hemorrhagic CVD were included the study. Transient ischemic attacks, epileptic seizures, central nervous system infections were excluded. Patients were examined and reported vital signs, lung X-Ray and urine test. Accompanying infection diseases were excluded. It was included all application clocks. The age, sex, diagnosis, comorbid diseases, CT and MRI reports were recorded. The relationship between initial glucose, WBC, NLR values and the prognosis were evaluated.

The statistical analyses were evaluated by SPSS (Statistical Package for Social Science) 17.0 for windows package program. Continuous variables were expressed as mean, median and standard deviation; ordinal variables as median and mode; nominal variables as number and percentages. The relationship among nominal values was determined by Pearson Chi-Square Test and Fisher's Exact Test. The normal distribution of continuous variables were evaluated by histogram and One-Sample Kolmogorov-Smirnov Test;  $p>0.05$  was accepted as normal distribution. Normally distributed independent variables were evaluated by Independent Samples t-Test; Mann-Whitney U Test was used if the distribution wasn't normal. Normally distributed dependent variables were evaluated by Paired Samples t-Test; Wilcoxon Test was used if the distribution wasn't normal.  $p<0.05$  was accepted as significant.

#### Results

55 of the patients were female (56.1%), M:F ratio was 0.78. Median age was 73 (range 37-99). 87 (88.8%) of the patients were diagnosed as ischemic CVD, other 11 (11.2%) were hemorrhagic CVD. 27 (27.6%) of the patients had previous DM history.

CT was performed for 94 of the patients (63.8%), 60 (63.8%) of them were reported as normal, 23 (24.4%) were ischemic infarct, 11 (11.7%) were intracerebral hematoma. MRI was performed 53 (54.0%) of the patients, 52 (98.1%)

of them was reported as ischemic infarct. Only one patient was diagnosed by only physical examination, both of his CT and MRI was reported as normal.

Mean leukocyte value of the ischemic CVD was 9.30 ( $\pm 3.31$ ) and hemorrhagic CVD was 10.05 ( $\pm 5.45$ ) (figure 1). There wasn't significant difference between leukocyte levels of these groups ( $p=0.514$ ). Leukocyte levels of dead patient group was significantly greater than the alive patient group ( $p=0.003$ ). There wasn't any significant difference between leukocyte levels of squealed patient group and complete recovery group ( $p=0.157$ ).

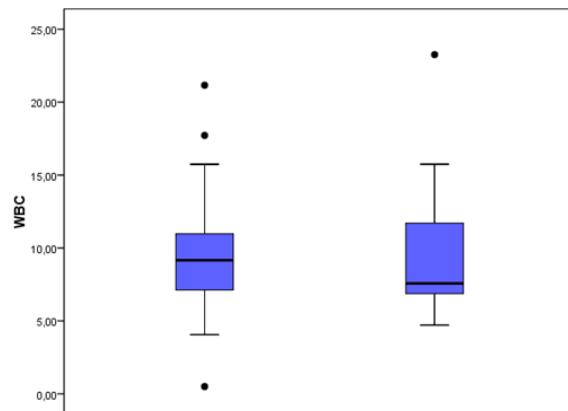


Figure 1. The distribution of the WBC patient.

Mean glucose value of the ischemic CVD was 144.34 ( $\pm 56.78$ ) and hemorrhagic CVD was 131.27 ( $\pm 59.15$ ). There wasn't significant difference between glucose levels of these groups ( $p=0.272$ ). Also there wasn't significant difference between glucose levels of dead and alive patient group ( $p=0.327$ ). There wasn't any significant difference between glucose levels of squealed patient group and complete recovery group ( $p=0.583$ ).

Mean NLR value of the alive patient group was 0.75 ( $\pm 0.13$ ) and the NLR of dead group was 0.74 ( $\pm 0.14$ ). There wasn't significant difference between glucose values of these groups ( $p=0.803$ ). Mean NLR value of the ischemic CVD was 0.74 ( $\pm 0.13$ ) and hemorrhagic CVD was 0.79 ( $\pm 0.10$ ). Also there wasn't significant difference between NLR values of these groups ( $p=0.342$ ).

The mortality rate was 19.4% (19 patients). 65 (66.3%) of the patients were discharged with sequelae and 14 (14.3%) was discharged with complete recovery (figure 2).

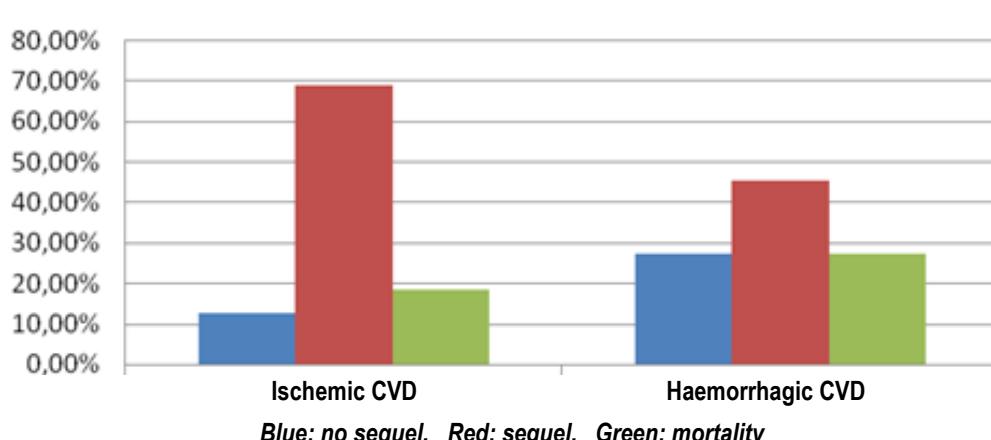


Figure 2. The relationship between diagnosis and prognosis of patients.

There wasn't any difference between prognosis of ischemic and hemorrhagic CVD patient groups ( $p=0.263$ ) (figure 2).

### Discussion

Some hematologic parameters become increasingly important in regulation of cerebral microcirculation and perfusion [19]. In the conditions of the ischemic changes in the heart and brain with the central inflammatory response, peripheral inflammatory response was seen. So leukocyte, neutrophil, C-reactive protein (CRP) and NLR levels can increase [6, 22].

Akopov et al. reported that after 6-12 hours of ischemic stroke high amount of signed PMNL had been seen in slightly perfused brain [1]. Until now it was assumed that inflammatory reaction had been occurred late secondary to tissue necrosis and it had cleared the tissue residues from infarct area. Garcia et al. showed that leukocytes (especially PMNL) had been seen in microvascular vessels from the thirtieth hour of occlusion on rats that had one-sided permanent middle cerebral artery (MCA) occlusion [8]. They also identified that necrosis had developed 72-96 hours after occlusion. This and the other studies show us the leukocyte immigration early to brain parenchyma is independent of the presence of the necrosis and it plays role in the development of brain infarct [9]. In our study the leukocyte levels were normally distributed in ischemic and hemorrhagic CVD group. There wasn't any difference between these two groups. Even though leukocyte count of dead patients was greater than the live ones.

Some studies suggest that harmful effects of leukocytes depend on superoxide anions, tromboxane A2, endothelin-1, prostaglandin H2, cytotoxic enzymes, free oxygen radicals and nitric oxide release [11]. While the acute cerebral ischemia, the neutropenic animals has smaller infarct areas than the control group and the opinion is discussed that leukocytes damage potentially viable cells [17].

The access of the leukocytes to the ischemic region is multi-step process. Respectively, they margin at venules strict on endothelial cells and immigrate to brain parenchyma. During the three phases, leukocyte functions are regulated by inflammation related molecules during cerebral ischemia [7].

It is described that NLR could be used as prognostic indicator at ischemic cardiac diseases, inflammatory response that is triggered by various diseases and some cancer types [12, 21]. In our study, the NLR of the patients that are dead or alive wasn't different and also there wasn't significant difference between NLR of the patients with ischemic and hemorrhagic stroke.

Although new onset or previously diagnosed diabetes mellitus (DM) is seen in 1/3 of the patients with acute ischemic stroke; stress hyperglycemia is present substantially due to cortisone and norepinephrine release in stroke patients. Furthermore relative insulin deficiency consists of increased lypolysis. Stress hyperglycemia disrupt the glucose regulation by development of DM even in patients without having DM [15].

Hyperglycemia causes membrane lipid peroxidation and cell lysis by increasing anabolic metabolism, lactic acidosis and free radical production. Increased blood glucose

disrupts mitochondrial function and metabolic condition at ischemic penumbra area [3]. The bad effect of hyperglycemia on tissue nutrition has been shown before. Despite in some stroke studies, the rapid reduction of glucose is declined, most of the guidelines suggest to reduce the blood glucose by rapid-acting insulin whether or not the patient is diabetic [14]. In the most diabetic patients cerebral ischemia occur faster. Relative insulin deficiency also increases free fatty acids. It causes vascular reactivity together with hyperglycemia [23].

Mankovski et al. described that the glucose level above 130 mg/dL in acute stroke patients is an independent risk factor for stroke severity and mortality. By the contribution of the hyperglycemia, ischemic penumbra turns into infarct, ischemic area expands so infarct severity increases [16].

DM is an important risk factor in ischemic stroke development. It increases the formation of stroke to 1.5 to 3 times and it also doubles the recurrence of stroke. It is important especially in the stroke attack under the age of 55 years. Ischemic stroke is seen more common than the hemorrhagic stroke in diabetic patients and in these patients lacunar infarct, wide infarct, the infarct area at brain stem and posterior circulation area are seen more common [4]. In our study, there wasn't any relationship between glucose levels and the mortality. This condition could be because of the number of the patients with a previous history of DM was low and the sample of the study was small.

In conclusion, in the emergency department, leukocyte count gives us an opinion about prognosis of CVD. It will be useful to evaluate the stroke patients by leukocyte count, in addition to CT, MRI. This study is retrospective. So we didn't achieve patients of scoring tests. This situation was limited our study. Nevertheless we evaluated prognosis as first neurological examination and discharge. We need wider and randomized controlled prospective studies about this issue.

### Conflict Interest

The authors declarated that no conflict interest.

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