Relationship Between Leukocyte Counts and Large Vessel Occlusion in Acute Ischemic Stroke

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Abstract

**Background:** Neuroinflammation plays an important role in the pathogenesis of acute ischemic stroke (AIS) and peripheral leukocyte counts have proved to be independent predictors of stroke severity and outcomes. Clinical significance of large vessel occlusion (LVO) in AIS is increasing, as these patients are potential candidates for endovascular thrombectomy and likely to have worse outcomes if not treated urgently. The aim of our study was to assess the relationship between on admission leukocyte counts and the presence of LVO in the early phase of AIS.

**Methods:** We have conducted a cross-sectional, observational study based on a registry of consecutive AIS patients admitted up to 4.5 hours after stroke onset. Blood samples were taken at admission and leukocyte counts were measured immediately. The presence of LVO was verified based on the computed tomography angiography scan on admission.

**Results:** Total white blood cell (WBC) and neutrophil counts were significantly higher in patients with LVO than those without LVO (P<0.001 respectively). After adjustment for potential confounders total WBC counts (adjusted OR: 1.405 per 1x10^9/L increase, 95% CI: 1.209 to 1.632) and neutrophil counts (adjusted OR: 1.344 per 1x10^9/L increase, 95% CI: 1.155 to 1.564) were found to have the strongest associations with the presence of LVO. Total WBC and neutrophil counts had moderate ability to discriminate an LVO in AIS (AUC: 0.667 and 0.655 respectively). No differences were recorded in leukocyte counts according to the size of the occluded vessel and the status of collateral circulation in the anterior vascular territory. However, total WBC and neutrophil counts tended to be higher in patients with LVO in the posterior circulation (p= 0.005 and 0.010 respectively).

**Conclusion:** Higher admission total WBC and neutrophil counts are strongly associated with the presence of LVO and has moderate ability to discriminate an LVO in AIS. Detailed evaluation of stroke-evoked inflammatory mechanisms and changes according to the presence of LVO demands further investigation.

Background

Secondary neuroinflammation plays an important role in the pathogenesis of acute ischemic stroke (AIS). Ischemic brain damage elicits systematic inflammatory response and cause a time-dependent activation of peripheral immune cells [1]. Leukocyte counts and ratios (such as neutrophil-to-lymphocyte ratio) in peripheral blood proved to have good prognostic value to predict outcomes and post-stroke complications [2, 3]. Higher leukocyte counts, especially neutrophil elevation is also associated with increasing severity and larger infarct volumes in AIS [4, 5].

Approximately 20–40% of AIS cases are caused by large vessel occlusion (LVO), early detection of which is crucial because these patients are potential candidates for endovascular thrombectomy (EVT) and have worse outcomes if not treated urgently [6, 7]. Large vessel occlusion tends to cause more severe strokes and place large cerebral territories at ischemic risk [8]. Therefore, the magnitude of peripheral inflammatory response may be related to the presence of LVO, however previous studies did not
investigate this context. The aim of our study was to examine the relationship between on admission total and differential leukocyte counts and the presence of LVO in the early phase of AIS.

**Methods**

**Study population**

We have conducted a cross-sectional, observational study based on a prospectively collected registry of consecutive AIS patients admitted up to 4.5 hours after symptom onset to the comprehensive stroke centres (CSC) of two university hospitals between October 2017 and October 2019. Blood samples were collected on admission. Total and differential leukocyte counts were measured immediately with an automated hemocytometer (Sysmex XN-1000; Sysmex, Kobe, Japan). We have recorded demographic data, vascular risk factors, baseline clinical variables, baseline laboratory values, medications at stroke onset and times from onset to sample collection for each patient. On admission stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).

Our outcome of interest was the presence of LVO on the on admission computed tomography angiography (CTA) scan. According to Rennert et al. [9] unilateral, acute occlusion of the internal carotid artery (ICA), M1, M2 and M3 segments of the middle cerebral artery (MCA), A1 and A2 segments of the anterior cerebral artery (ACA), vertebral artery (VA), basilar artery (BA), P1 and P2 segments of the posterior cerebral artery (PCA) and tandem occlusions were considered. Collateral circulation in the anterior vascular territory was evaluated using the multiphase CTA (mCTA) collateral score. Patients were dichotomized into two groups according to good (mCTA 4-5 points) and poor (mCTA 0-3 points) collateral circulation. Evaluation of CTA scan and mCTA collateral score was done by trained neuroradiologist as a standard of care who were blinded to clinical data.

Patients without CTA assessment or whose laboratory results were missing due to sampling or measurement errors were excluded. We have also excluded patients who had infection or surgery within 2 weeks prior to the stroke, those who had relevant neurological events (transient ischemic attack [TIA] before or seizures after stroke onset), those who take immunomodulatory medications and those with haematological malignancies, as these conditions could influence peripheral leukocyte counts.

**Statistical analysis**

Data analysis was performed using SPSS (version 26.0, IBM, New York). Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range (IQR) where appropriate. Categorical variables were presented as counts and percentages. In the univariate analysis the comparison of continuous variables was performed using t test or Mann-Whitney U test. Normality was assessed using the Shapiro-Wilk test and visually, based on Q-Q plots and histograms. Categorical data were compared using the Pearson X^2 test or the Fischer exact test when expected values in any cell was below 5. Univariable and multivariable binary logistic regression analysis was performed to assess the associations between leukocyte counts and the presence of LVO, variables with P value ≤0.1 in the
univariable analysis were included in the multivariable model. Total white blood cell (WBC) count, each leukocyte subtype counts and neutrophil-to-lymphocyte ratio (NLR) were entered in a separate model because of multicollinearity. The ability of leukocyte counts to discriminate the presence of LVO was assessed using the receiver operating characteristic analysis, area under the curve (AUC) was calculated for each variable. Odds ratios (OR) and 95% confidence intervals (CI) were presented where appropriate, P<0.05 was considered as statistical significance.

Results

During the study period 514 patients were screened, after exclusions the data of 419 patients were analysed (Fig. 1). The main age of the study cohort was 67.7 ± 12.2 years (43.9% female), 167 patients had LVO (39.9%). Demography and baseline characteristics of the cohort are presented in Table 1. Univariable associations between baseline variables and the presence of LVO are presented in Table S1 of the Supplementary material.
|                                | LVO present (N = 167) | LVO absent (N = 252) | P value |
|--------------------------------|----------------------|----------------------|---------|
| **Demographic characteristics**|                      |                      |         |
| Age, years, median (IQR)      | 68 (61–79)           | 69 (59–77)           | 0.258   |
| Gender, female, % (n)         | 52.1 (87)            | 38.5 (97)            | **0.006** |
| **Elapsed times**             |                      |                      |         |
| Onset-to-sample time, min, median (IQR) | 83 (55–124) | 88 (59–139) | 0.313   |
| Sample-to-CTA time, min, median (IQR) | 16 (6–25)   | 12 (5–28)            | 0.684   |
| **Parameters on admission**   |                      |                      |         |
| NIHSS score on admission, median (IQR) | 12 (7–17)  | 6 (4–8)              | **<0.001** |
| On admission SBP, mmHg, median (IQR) | 158 (140–177) | 167 (145–180) | **0.004** |
| On admission DBP, mmHg, median (IQR) | 85 (78–96)  | 90 (80–100)          | **0.004** |
| Body temperature, °C, median (IQR) | 36.4 (36.1–36.5) | 36.4 (36.2–36.6) | 0.069   |
| Blood glucose, mmol/L, median (IQR) | 6.89 (5.90–8.10) | 6.43 (5.61–8.35) | 0.120   |
| INR, ratio, median (IQR)       | 1.02 (0.95–1.08)    | 0.99 (0.94–1.04)     | **0.003** |
| **Vascular risk factors**     |                      |                      |         |
| Smoking, % (n), 60 missing    | 39.1 (52)            | 31.4 (71)            | 0.139   |
| Hypertension, % (n), 13 missing | 81.6 (133)        | 77.8 (189)           | 0.352   |
| Diabetes mellitus, % (n), 19 missing | 21.4 (34)     | 30.3 (73)            | **0.049** |
| Hyperlipidaemia, % (n), 36 missing | 50.7 (76)       | 53.6 (125)           | 0.568   |
| Atrial fibrillation, % (n), 23 missing | 32.9 (52)     | 17.2 (41)            | **<0.001** |
| Coronary artery disease, % (n), 33 missing | 27.7 (43)   | 23.4 (54)            | 0.332   |
| Chronic heart failure, % (n), 23 missing | 15.0 (24)    | 7.6 (18)             | **0.019** |
| Previous stroke/TIA, % (n), 22 missing | 17.6 (28)    | 25.2 (60)            | 0.074   |
| Malignancy, % (n), 31 missing | 16.4 (25)          | 9.3 (22)             | 0.036   |

**Therapy at stroke onset**

Abbreviation: LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; INR, International Normalized Ratio; TIA, transient ischemic attack.
|                      | LVO present (N = 167) | LVO absent (N = 252) | P value |
|----------------------|-----------------------|----------------------|---------|
| Antiplatelet, % (n), 23 missing | 40.3 (62)             | 36.0 (87)            | 0.388   |
| Anticoagulant, % (n), 28 missing    | 17.6 (27)             | 9.7 (23)             | 0.021   |
| Lipid lowering, % (n), 23 missing   | 27.7 (43)             | 22.4 (54)            | 0.228   |
| Antihypertensive, % (n), 24 missing  | 72.9 (113)            | 66.7 (160)           | 0.190   |
| Antidiabetic, % (n), 24 missing     | 16.4 (25)             | 24.0 (58)            | 0.070   |

Higher total WBC counts were recorded in LVO patients than those without LVO (9.27 × 10^9/L vs. 7.61 × 10^9/L; P < 0.001). Regarding major leukocyte subtypes, median neutrophil counts were significantly higher in the LVO group (6.05 × 10^9/L vs. 4.69 × 10^9/L; P < 0.001). In contrast, no significant difference was recorded between the groups for the other subtypes (Fig. 2). Neutrophil-to-lymphocyte ratio values was slightly higher in patients with LVO (2.83 versus 2.56; P = 0.034). Increasing onset to sample times correlated with higher neutrophil counts (Spearman r, 0.175; P < 0.001), lower lymphocyte counts (Spearman r, -0.229; P < 0.001) and increasing NLR values (Spearman r, 0.275; P < 0.001).

On admission total WBC, neutrophil, lymphocyte, monocyte and basophil counts were associated with the presence of LVO in the univariable binary logistic regression analysis. Independent associations were found between total WBC, neutrophil, lymphocyte and basophil counts and the presence of LVO after adjustment for potential confounders (Table 2). There was a trend between increasing NLR values and the presence of LVO in the univariable analysis (OR: 1.079 per 1-point increase, 95% CI: 1.001 to 1.164; P = 0.048), but this trend was not present after adjustment for confounders (OR: 1.022 per 1-point increase, 95% CI: 0.924 to 1.131; P = 0.672).
Table 2
Associations between leukocyte counts and the presence of large vessel occlusion in acute ischemic stroke

|                                    | Crude OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
|------------------------------------|-------------------|---------|----------------------|---------|
| Total WBC (1 x 10^9/L increase)    | 1.292 (1.187 to 1.405) | < 0.001 | 1.405 (1.209 to 1.632) | < 0.001 |
| Neutrophil (1 x 10^9/L increase)   | 1.296 (1.181 to 1.421) | < 0.001 | 1.344 (1.155 to 1.564) | < 0.001 |
| Lymphocyte (1 x 10^9/L increase)   | 1.321 (1.064 to 1.641) | 0.012   | 1.631 (1.106 to 2.407) | 0.014   |
| Monocyte (0.1 x 10^9/L increase)   | 1.112 (1.018 to 1.214) | 0.018   | 1.048 (0.903 to 1.217) | 0.535   |
| Eosinophil (0.1 x 10^9/L increase) | 0.955 (0.807 to 1.131) | 0.596   | 1.043 (0.799 to 1.363) | 0.755   |
| Basophil (0.01 x 10^9/L increase)  | 1.106 (1.024 to 1.194) | 0.010   | 1.296 (1.119 to 1.501) | < 0.001 |

Abbreviation: OR, odds ratio; CI, confidence interval; WBC, white blood cell; L, litre.

Receiver operating characteristic analyses demonstrated moderate ability of total WBC (AUC: 0.667, 95% CI: 0.613 to 0.721; P < 0.001) and neutrophil counts (AUC: 0.655, 95% CI: 0.600 to 0.710; P < 0.001) to discriminate the presence of LVO. Marginally significant ability was detected for NLR values (AUC: 0.563, 95% CI: 0.505 to 0.621; P = 0.030), and the abilities of other leukocyte subtypes to discriminate an LVO were not significant (Figure S1 in the Supplementary material).

Out of 167 LVO patients 147 (88.0%) had occlusion in the anterior circulation (ICA, M1, M2 and M3 segments of MCA, A1 and A2 segments of ACA). Proximal occlusions (defined as occlusion of ICA or M1 segment of MCA) were found at 105 patients (71.4%). These patients had more severe strokes (median NIHSS score 15 vs. 8; P < 0.001) compared to those with more distal occlusions (M2 and M3 segment of MCA, A1 and A2 segments of ACA), but no significant differences were recorded in leukocyte counts (Table S2 in the Supplementary material). Data on collateral status was available for 145 patients (98.6%). Good collateral circulation was found in 86 patients (59.3%). Patients with poor collateral circulation had higher NIHSS median scores on admission than those with good collaterals (16 vs. 11; P < 0.001), but no significant differences in leukocyte counts were found between the two groups (Table S3 in the Supplementary material).

Twenty patients (12.0%) had LVO in the posterior circulation (VA, BA, P1 and P2 segments of PCA). These patients tended to be younger and had milder strokes than patients with LVO in the anterior circulation. Median admission total WBC and neutrophil counts were significantly higher in patients with posterior
LVO. Lymphocyte and monocyte counts were slightly higher in posterior LVO patients; however, differences did not reach the significance level (Table S4 in the Supplementary material).

**Discussion**

The main finding of our study is that leukocyte counts (especially total WBC and neutrophil) are associated with the presence of LVO in the acute phase of ischemic stroke. Higher total WBC and neutrophil counts could be detected in LVO patients compared to those without LVO, already in the first hours after stroke onset. This highlights the rapid response of systematic inflammatory mechanisms after ischemic brain injury, the extent of which may differ among leukocyte subtypes according to the presence of LVO.

Proinflammatory factors and pathways are activated within minutes after ischemic onset [10]. Neutrophils are the first leukocyte subtype to be upregulated and subsequently infiltrate the ischemic brain tissue [11]. A previous study has reported that neutrophilia is associated with the volume of ischemic tissue in AIS [5]. The presence of LVO can cause blood supply disturbances in large vascular territories and places substantial cerebral areas under ischemic risk, thereby probably increase the magnitude of proinflammatory response. This may explain why higher total WBC counts (mainly due to the increase in neutrophil counts) can be detected in LVO patients compared to those without LVO in AIS.

Our results are consistent with previous studies highlighting the longitudinal changes in leukocyte activation: elevation of neutrophil and decrease in lymphocyte counts over time [12, 13]. It should be noted that lymphocytes are recruited in the later stages of ischemic brain injury [14]. In our study no differences were found in baseline lymphocyte counts between LVO and non LVO patients, which may be because lymphocytes have not yet been extensively activated at this early stage of AIS. This may also be the reason why NLR, which is well established in stroke prognosis prediction [3, 12, 13], hardly differed between the two groups.

Independent associations between increasing counts of neutrophils, lymphocytes and basophils and higher odds of LVO may represent a broad, bi-directional crosstalk between the ischemic brain and the peripheral immune system, which likely affects almost all participants of the immune response quite early after stroke onset. Interestingly in addition to the strong association between neutrophil counts and LVO, the association was also quite strong for basophil counts. Basophil leukocytes have unique role in allergic reactions, parasite infections and autoimmune diseases, however, their role in brain injury is currently unclear [15].

Raising the suspicion of LVO in AIS early on is crucial to ensure appropriate imaging methods and early transportation of patients to an EVT capable CSC. Hence reliable blood-based biomarkers would be valuable to detect patients with LVO early on. Our results demonstrated that the ability of leukocyte counts to discriminate the presence of LVO are limited on their own. This may be because changes in peripheral leukocyte counts are not specific for brain damage and can be influenced by many other confounding factors.
Interestingly leukocytes did not associate with the size of the occluded vessel and with the status of collateral circulation in the anterior vascular territory. These findings are partly consistent with the result of a previous study by Semerano et al., reporting no significant differences in admission leukocyte counts according to the status of collateral circulation [12]. The interplay between the size of occluded vascular territory and the quality of collateral circulation supplemented by other metabolic and genetic factors are highly related to the size and the core and the penumbra within ischemic brain lesions [16, 17]. A study by Buck et al. suggests that early changes in peripheral counts are related to the size of bioenergetically compromised brain tissue [5]. Based on our results the magnitude of early peripheral inflammatory response after LVO may not related to the collateral circulation or the size of occluded artery separately. However, the interaction between these factors may affect the size of ischemic core and penumbra, and thus probably the extent of neuroinflammation as well.

The etiology of LVO in the posterior circulation and the composition of such thrombi (including the proportion of leukocytes) are different from those of the anterior circulation LVO [18, 19]. In our study higher median neutrophil and slightly higher lymphocyte and monocyte counts in the posterior LVO group may be related to these conditions. It should also be noted, that the structure of the brain is slightly different in the posterior territory, with a higher proportion of white matter and with different distribution of glia and neuronal cells [20], which may also influence the extent of inflammation.

Our result may be useful for primary stroke-centres without CTA imaging facilities to consider LVO in AIS patients with very high total WBC or neutrophil counts. However, peripheral leukocyte counts in AIS should be interpreted cautiously, considering that a variety of factors can influence their elevation.

The rapidly evolving, new options in the treatment of AIS due to LVO facilitate the need for better understanding the nature of this type of stroke. Our result may warrant further investigation to explore the relationship between LVO and neuroinflammation in details. The scope of further studies could be the interplay between LVO and well-established inflammatory markers such as acute phase proteins, cytokines, cell adhesion molecules, matrix metalloproteinases, damage-associated molecular patterns, markers of oxidative stress, markers of the complement pathway and annexins [1, 21–24]. Inflammatory markers may also be good candidates to find suitable blood-based biomarkers for early LVO detection [25]. Further, larger scale studies are also needed to examine alterations in neuroinflammation according to the location and the volume of cerebral infarction and ischemic penumbra. As previously discussed, the changes in peripheral leukocyte counts may be epiphenomenal to brain damage. However, previous studies have revealed that higher leukocyte counts in healthy patients are also associated with the increased risk of ischemic stroke events [2, 26]. Further investigation may clarify how peripheral leukocyte counts are related to the risk of suffering an LVO is AIS, or how it may affect the composition of the thrombi.

The main strength of our study is the thorough investigation of multiple leukocyte subtypes in a reasonable number of patients from two university centres. However, our study also has some limitations. The observational, cross-sectional design did not allow to assess cause-effect relationship. No
assessment of ischemic lesion volume or of the size of ischemic core and penumbra was made on admission. Although we attempted to exclude patients whose leukocyte counts may be affected by other conditions, we cannot be sure that all such patients have been excluded. There is a chance of other, unknown confounding factors that were not considered in this study. No CTA was performed in almost 8% of screened cases (mainly due to minor symptoms or contraindications), which might lead to selection bias. The small number of patients with posterior LVO resulted a probably underpowered subanalysis. Finally, automated analysis of leukocyte subtypes with very low number of cells (eosinophil and basophil counts) might be slightly inaccurate.

**Conclusion**

Our study demonstrates that higher on admission total WBC and neutrophil counts are strongly associated with the presence of LVO and has moderate ability to discriminate an LVO in AIS. Further studies are needed to ensure these findings in larger cohorts and to explore the detailed mechanisms of changes in inflammatory pathways after AIS according to the presence of LVO.

**List Of Abbreviations**

AIS acute ischemic stroke  
LVO large vessel occlusion  
EVT endovascular thrombectomy  
CSC comprehensive stroke centre  
NIHSS National Institutes of Health Stroke Scale  
CTA computed tomography angiography  
ICA internal carotid artery  
MCA middle cerebral artery  
ACA anterior cerebral artery  
VA vertebral artery  
BA basilar artery  
PCA posterior cerebral artery  
mCTA multiphase computed tomography angiography  
TIA transient ischemic attack
Declarations

Ethical approval and consent to participate

The study protocol was approved by the Hungarian Medical Research Council (35403-2/2017/EKU). Written informed consent was obtained from each patient according to the Good Clinical Practice (GCP) guidelines.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare no conflict of interest.

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Authors’ contribution

GT designed the study, performed literature search, data acquisition and analysis, statistical analysis and wrote the manuscript. ZNK performed data acquisition, data analysis and reviewed the manuscript. ZS performed data acquisition, data analysis and reviewed the manuscript. IS performed literature search,
data acquisition and reviewed the manuscript. LC designed the concepts of the study, interpreted the data, reviewed and approved the manuscript. LS is the guarantor and designed the concepts of the study, interpreted the data, reviewed and approved the manuscript.

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**Figures**

**Figure 1**

Patient exclusion flowchart.

**Figure 2**

Comparison of admission total white blood cell (WBC) counts, leukocyte subtype counts and neutrophil-to-lymphocyte ratio (NLR) values in acute ischemic stroke according to the presence of large vessel occlusion (LVO). Boxes, 25% to 75% interquartile range; central horizontal bars, median; outer horizontal bars, minimum and maximum values. Statistics: Mann-Whitney U test.

**Supplementary Files**

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