Leukocyte subtypes in acute stroke are predictive of outcome independently of infections

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BACKGROUND and AIM

Complex interactions between the CNS and the immune peripheral system in cerebrovascular diseases are increasingly recognized and appear to be bidirectional[1]. Brain ischemia directly triggers, mainly through the autonomic nervous system, a strong systemic inflammation involving the direct stimulation of the bone marrow, the spleen, the lung and the liver. In turn, after acute ischemic stroke, leukocyte subtypes play both detrimental and protective roles, both in the brain and in the periphery, by mediating microvascular reperfusion impairment, blood brain barrier disruption, development of post-stroke infections as well as neuroprotection and neurorepair processes[2]. We aimed to determine whether leukocyte subtype counts after ischemic stroke are associated with functional outcome and hemorrhagic complication independently from the occurrence of pre-existing and post-stroke infections.

METHODS

We retrospectively examined 633 patients with acute ischemic stroke or transient ischemic attack (TIA), admitted to our hospital within 4.5 h from symptom onset between 2009- 2015. One hundred twenty-three patients with history of previous recent infections, haematological malignancies or pre-stroke functional dependence (modified Rankin Scale, mRS>2) were excluded. Blood samples for complete blood cell counts, CRP, glucose and fibrinogen were collected within 48h from symptom onset.

RESULTS

Neutrophil counts were positively associated with stroke severity ($p<0.001$), larger stroke extent (TACI in OXFORD classification, $p<0.001$; Figure 1) and worse 3-month functional outcome ($p<0.001$); lymphocyte and eosinophil counts were inversely correlated with stroke severity ($p<0.001$) and stroke extent ($p<0.01$ and <0.001 respectively) and lower levels were found in patients with 3-month poor outcome ($p<0.001$).

N. of included patients	n=510
Demographic characteristics	
Age – mean (SD)	71.8 (12.1)
Male sex – n (%)	297 (58.2%)
Vascular Risk Factors	
Hypertension – n (%)	352 (69.0%)
Diabetes – n (%)	95 (18.6%)
Smoking – n (%)	135 (26.5%)
Dyslipidemia – n (%)	109 (21.4%)
CAD – n (%)	95 (18.6%)
Atrial fibrillation – n (%)	154 (30.1%)
Thrombolysis – n (%)	196 (38.4%)
Baseline NIHSS – mean (SD)	8.8 (7.2)
Early Post-Stroke Infections – n (%)	93 (18.2%)

Table 1. General Features of the study population.

		Discharge NIHSS		**3-month Functional Outcome**			**3-month Mortality**			**Parenchymal hematoma**		
	Mean *n=510*	***Coeff***	**p**	**mRS<3** *n=300*	**mRS≥3** *n=210*	**p**	**Alive** *n=480*	**Death** *n=30*	**p**	**No** *n=493*	**Yes** *n=17*	**p**
WBC	8.39 ± 2.80	*[c]0.337*	0.000	7.82 ±2.32	9.21 ±3.22	0.000	8.22 ±2.57	11.11 ±4.56	0.000	8.28 ±2.65	11.58 ±4.78	0.000
Neutrophil	5.78 ± 2.75	*[c]0.471*	0.000	5.02 ±2.11	6.85 ±3.17	0.000	5.57 ±2.46	9.08 ±4.55	0.000	5.65 ±2.53	9.51 ±5.29	0.000
Lymphocyte	1.76 ± 0.68	*[c]-0.411*	0.000	1.93 ±0.68	1.51 ±0.60	0.000	1.79 ±0.68	1.15 ±0.40	0.000	1.77 ±0.67	1.34 ±0.81	0.011
NL-R	4.17 ± 4.37	*[c]0.564*	0.000	3.01 ±2.07	5.84 ±5.97	0.000	3.79 ±3.22	10.26 ±11.10	0.000	3.86 ±2.96	13.31 ±15.69	0.001
Monocyte	0.70 ± 0.27	*[c]0.137*	0.002	0.67±0.22	0.74±0.33	0.007	0.69±0.26	0.84±0.42	0.031	0.70±0.27	0.67±0.23	0.628
Eosinophil	0.14 ± 0.16	*[c]-0.506*	0.000	0.18 ±0.18	0.08 ±0.12	0.000	0.15 ±0.17	0.02 ±0.05	0.000	0.14 ±0.16	0.06 ±0.14	0.001
EoLeu-R	0.019 ± 0.022	*[c]-0.514*	0.000	0.025 ±0.023	0.011 ±0.016	0.000	0.020 ±0.022	0.003 ±0.008	0.000	0.020 ±0.022	0.007 ±0.016	0.002

Table 2. Unadjusted association of the leukocyte subtype counts/ratios with study outcomes. *Statistics*: Spearman correlation for discharge NIHSS, [C] Spear. coefficient; Mann-Whitney U test for functional outcome, mortality and parenchymal hematoma.

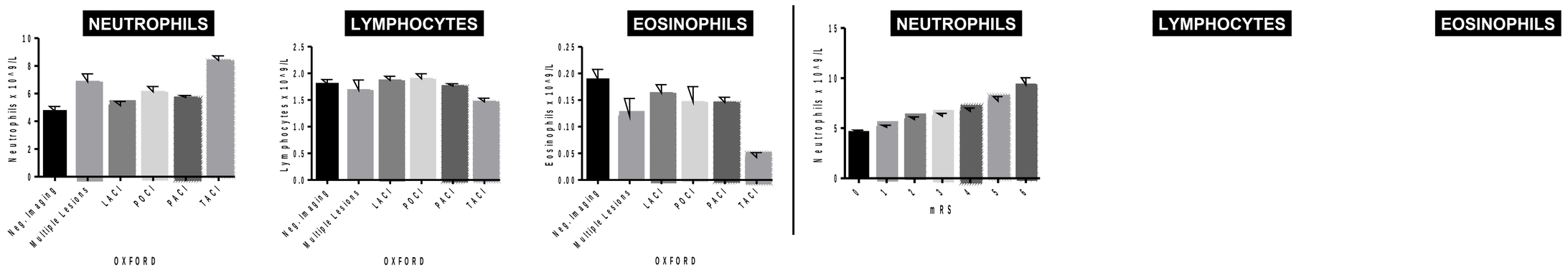

Figure 1. Relationship between OXFORD classification, 3-month mRS score and leukocyte subtypes. Mean and standard error of the mean represented. Abbreviations: TACI: total anterior, PACI: partial anterior, LACI: lacunar, POCI: posterior circulation infarcts.

After adjustment for age, thrombolysis administration, baseline stroke severity score (NIH Stroke Scale, NIHSS), stroke risk factors and early post-stroke infections, independently of infections, lymphocyte and eosinophil counts as well as eosinophil to leukocyte ratio (EoLeu-R) were positively associated, while the neutrophil to lymphocyte ratio (NL-R) was negatively associated with 3-month good functional outcome. High neutrophil counts and NL-R but low lymphocyte, eosinophil counts and EoLeu-R were independently associated to death within 3 months and also to NIHSS at discharge. Patients developing parenchymal hemorrhagic transformation (PH) had higher neutrophil counts.

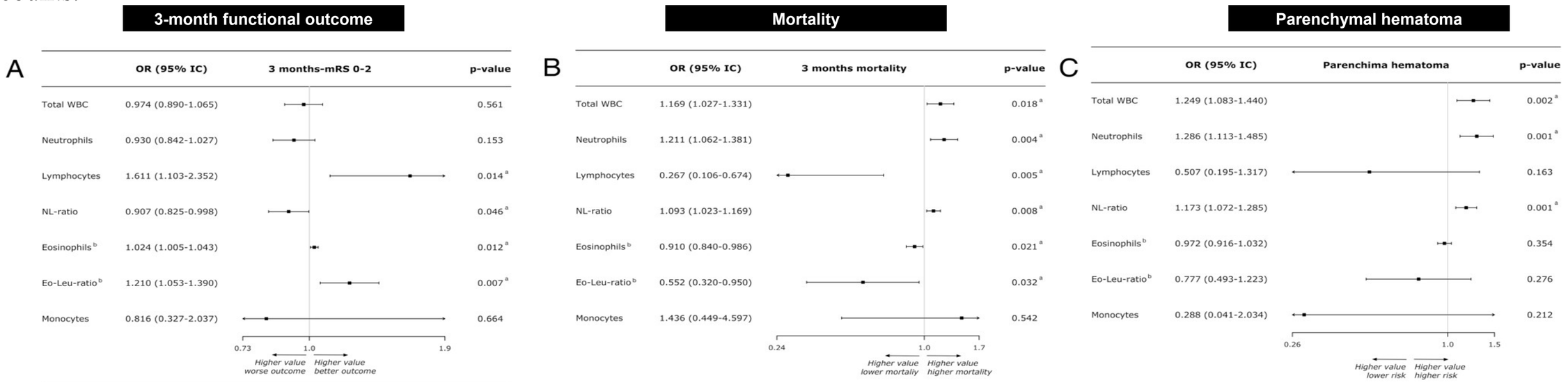

Figure 2. Adjusted association of leukocyte subtype counts/ratios with outcome measures. [a] OD for 0.01-point increase of Eosinophil count and EoLeuR.

CONCLUSIONS

Leukocyte subtype counts and ratios (NLR and EoLeuR) constitute independent predictors of outcome and result associated with haemorrhagic complications, indipendently of infections. The investigation of the mechanisms that might underlie these effects could provide new therapeutical targets.

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