Serum inflammatory markers as predictors of neurological status in patients with stroke in the course of hypertension: a two-center study

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Abstract

Introduction. Every year, 60.000 people have stroke incidents in Poland. Despite the fact that it can be prevented, stroke remains the leading cause of morbidity and mortality worldwide. Hypertension is one of the leading risk factors for the stroke incident. The aim was to assess the relationship between inflammatory markers and clinical status of hypertensive patients with the stroke.

Material and methods. 713 patients with stroke in the course of hypertension from the Departments of Neurology in Bytom and Zabrze were enrolled in the retrospective study. They were divided into groups: N1, R1 (with improvement in NIHSS and Rankin results, respectively) and N2, R2 (with deterioration or no changes in NIHSS and Rankin between the day of admission and discharge).

Results. The majority of patients were females [%] (51.5 *vs* 48.5). Women were significantly older than man [years] (78.0 *vs* 69.0, P = 0.001, respectively) and had higher NIHSS results at admission [points] (6.0 *vs* 5.0, P = 0.001, respectively). There were significant differences in the serum CRP [mg/l] (4.75 vs 9.40, P = 0.001) and WBC [10^3/µL] (8.58 vs 9.02, P = 0.006) between N1 and N2, respectively and between R1 and R2: WBC (8.50 *vs* 9.00, P = 0.006) and CRP (4.20 *vs* 8.70, P = 0.001), respectively. A significant correlation between CRP and NIHSS on admission was observed (R = 0.191, P < 0.05). NIHSS and Rankin score on admission were correlated with age (R = 0.212, and R = 0.231, P < 0.05, respectively). CRP was related with the volume [cm^3] of lesions in CT (R = 0.170, P < 0.05).

Conclusions. Inflammation seems to be associated with the worse neurological status of patients with stroke and hypertension. Age and sex affect the clinical course of stroke. CRP may indicate the size of changes in CT.

Key words: stroke, hypertension, NIHSS, Rankin, inflammation, CRP, WBC

Introduction

Stroke, in its classic definition, is interpreted as a neurological deficit caused by an acute focal damage of the central nervous system and is one of the leading causes of disability and mortality worldwide [1].

In 2005, the incidence of stroke was estimated at 16 million worldwide, predicting that in 2030 this figure would increase to 23 million [2]. In 2013 in the United States stroke was the fifth leading cause of death. Despite declining mortality, nearly 800 000 people per year experience a new or recurrent stroke,

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and about 140,000 of stroke victims die [3]. Due to the widespread access to a specialist treatment and improved medical standards in developed countries, the survival rate of stroke victims should increase.

According to researchers, stroke remains the leading preventable cause of morbidity and mortality worldwide, and it can be prevented by e.g. lifestyle modification, pharmacological treatment of hypertension, hypercholesterolemia or atrial fibrillation (AF) [4]. It is worth emphasizing that hypertension substantially increases the risk of stroke, accounting for as much as 52% of cases [5].

In order to determine the degree of neurological deficits after stroke, and to predict the outcome, specific scales were created, such as the National Institute of Health Stroke Scale (NIHSS), the modified Rankin scale (mRS) and Barthel index (BI) [6].

The aim of our study was to assess the association between sex, age and the severity of stroke in patients with hypertension. Specifically, the study aimed to evaluate the inflammatory markers and the CT-assessed lesions volume on the clinical outcome of patients.

Material and methods

Our study is a retrospective analysis of medical records from two referral centers located in Upper Silesia region, Poland. Initially, we analyzed the records of 1000 patients hospitalized between 2013 and 2016 who were diagnosed with cerebrovascular diseases from the Departments of Neurology in Bytom, and Zabrze. All patients were treated for primary hypertension, diagnosed according to the European Societies of Hypertension and Cardiology Guidelines (2013) [7, 8].

The inclusion criteria were as follows: age > 35 years, inhabitancy of the Upper Silesia region, diagnosis of stroke based on the World Health Organization (WHO) definition, primary hypertension prior to stroke or TIA, ongoing antihypertensive therapy. The exclusion criteria were as follows: secondary stroke caused by trauma, brain tumor or brain metastases, persistent migraine aura without infarction, Todd's paresis and signs of infection.

Based on patients' medical history, 713 patients met primary inclusion criterion; 661 were diagnosed with ischemic stroke, 50 with hemorrhagic stroke and 2 with a transient ischemic attack (TIA).

211 patients were excluded because they were not diagnosed with primary hypertension prior to admission. Another 49 patients admitted that they did not take medications against hypertension, 15 were found

to suffer from upper respiratory infection before admission, 6 had a secondary stroke caused by trauma, 3 were suspected of brain tumor, 2 were diagnosed with persistent migraine aura without infarction and 1 had documented Todd's paresis.

Clinical state of the patients was evaluated upon admission before the treatment was introduced. The patients' data were re-evaluated at discharge using the NIHSS and RANKIN scales. Similarly, the CT-based size of stroke lesion and the change of its volume [cm^3] were analyzed in two corresponding timepoints: at baseline (CT1), and at discharge (CT2).

As the study design was retrospective based on the analyses of available clinical data, no Ethical Committee Board approval was mandatory, as regulated by the rules and regulations of our Center.

Statistical analysis

Continuous variables were presented as the median and an interquartile range (IQR). The categorical variables data were presented as percentages. The groups were compared using the nonparametric Mann-Whitney U test. The analysis of correlations between variables was conducted using the Spearman rank correlation analysis. Statistical significance was defined as P < 0.05. Statistical analyses were performed using the software Statistica 13 (Statsoft, Tulsa, Oklahoma, USA).

Results

The median age in the whole study group was 75.0 years [65.0–81.0]. 358 (50.21%) of the participants were females and 355 (49.79%) were males. Women and men significantly differed in age. The median age was 78.00 [70.00–83.00] and 69.00 [63.00–78.00], P < 0.001 for females and males, respectively. The comparison of the clinical data with respect to sex was presented in Table I. Females and males had significantly different percentage of patients with stenosis of cervical arteries, myocardial infarction and AF. They also differed in NIHSS score, Rankin score but they did not differ in the volume of stroke lesion in CT. In general, patients had from 1 to 4 stroke lesions detected in CT, however, the majority, of them (93.04%) had 1 lesion.

The study group was divided depending on the NIHSS and RANKIN results on the day of admission and discharge into groups: patients with improvement in NIHSS (N1; n = 487), with deterioration or no change in NIHSS or patients who were found dead (N2; n = 225), with improvement

Table I. The comparison of the clinical state in the whole study group divided according to sex

Issue	Female (n = 358)	Male (n = 355)	P
Stenosis of cervical arteries (%)	25.42	38.31	< 0.001
Myocardial infarction (%)	29.61	39.72	0.005
Atrial fibrillation recognized prior to stroke (%)	29.05	18.31	0.001
Atrial fibrillation present during hospitalization (%)	34.64	23.45	0.001
NIHSS on admission	6.00 [3.00–12.00]	5.00 [3.00–8.00]	< 0.001
NIHSS at discharge	3.00 [2.00–10.00] n = 308*	3.00 [1.00–5.00] n = 317*	0.001
Rankin on admission	4.00 [3.00–5.00]	4.00 [3.00–4.00]	< 0.001
Rankin at discharge	3.00 [2.00–5.00] n = 306*	2.00 [1.00–4.00] n = 317*	< 0.001
The sum of the volume of all lesions in CT1 [cm³]	3.50 [1.60–12.56]	4.00 [1.82–12.00]	0.79
The sum of the volume of all lesions in CT2 [cm³]	3.35 [1.70–11.22]	2.80 [1.40–12.00]	0.23

In the rest of cases death was found; the sum of the volume of all lesions in patient in CT1 was 3.85 [1.70–12.00] cm³ and in the CT2 at the end of hospitalization was 3.00 [1.50–11.90] cm³. The greatest lesion in CT1 was 3.50 [1.70–10.08] cm³ and in the CT2 was 3.00 [1.5–11.25] cm³. In 50.70% [72] of patients between CT1 and CT2 the whole volume of all lesions remained unchanged. In 28.17% [40*] it has increased and in 21.13% it has decreased. Patients included in the study were treated with: Loop Diuretics, Aldosterone Antagonists, Thiazides, Thiazide-like Diuretics, ACE Inhibitors, ARBs, Beta-Blockers and Calcium Channel Blockers
CT1 — computed tomography on admission; CT2 — computed tomography at discharge; NIHSS — National Institutes of Health Stroke Scale

Table II. Baseline characteristics of the study groups divided according to the assessment of the clinical status in National Institutes of Health Stroke Scale

	NIHSS improvement (n = 487)	NIHSS deterioration (n = 225)	P
Age (years)	73.00 [64.00–80.00]	77.00 [68.00–83.00]	< 0.001
Sex (male) (%)	51.54	46–67	0.23
NIHSS on admission	5.00 [3.00–9.00]	5.00 [2.00–23.00]	0.72
NIHSS at discharge	2.00 [1.00–4.00]	3.00 [2.00–8.00] n = 138**	< 0.001
Rankin on admission	4.00 [3.00–4.00]	4.00 [2.00–5.00]	0.56
Rankin at discharge	2.00 [1.00–3.00] n = 485*	3.00 [2.00–4.00] n = 138**	< 0.001
Improvement in Rankin [%]	76.18 n = 486*	6.22	< 0.001

*the data from the rest of patients were not achievable; **in the rest of cases death was found
NIHSS — National Institutes of Health Stroke Scale

in RANKIN (R1; n = 385) and with deterioration or no change in RANKIN or patients who decreased (R2; n = 327).

The study groups N1 and N2 had significantly different age, NIHSS score at discharge and Rankin score at discharge. The baseline characteristics of the study groups were presented in Table II. These study groups significantly differ in percentage of patients with stenosis of cervical arteries. There were also significant differences in the results of C-Reactive Protein (CRP [mg/l]; 4.75 [1.93–13.65] vs. 9.40 [2.08–41.72], P = 0.001) and White Blood Cells (WBC [103/μL]; 8.58 [7.15–10.40] and 9.02 [7.28–12.04], P = 0.006) between N1 and N2 respectively. The comparison of comorbidities between these groups was presented in Table III. The

volume of stroke lesion in CT was significantly greater in N2. The results in CT were shown in Table IV.

The baseline characteristics of the study groups R1 and R2 were presented in Table V. There were significant differences in age, NIHSS score on admission and at discharge and Rankin score at discharge. The comparison in comorbidities between these groups was shown in the Table VI. These groups significantly differed in percentage of patients with stenosis of cervical arteries. There were significant differences in WBC (8.50 [6.99–10.39] vs. 9.00 [7.29–11.46], p = 0.006) and CRP (4.20 [1.80–10.87] vs. 8.70 [2.09–37.70], p = 0.000) between R1 and R2 respectively. The volume of stroke lesion in CT was significantly greater in R2 (Table VII).

Table III. Comorbidities in the study groups divided according to the assessment of the clinical status in National Institutes of Health Stroke Scale

Comorbidities	N1 (n = 487)	N2 (n = 225)	P
Ischemic stroke (%)	94.66	88.89	0.22
Carotid artery stenosis (%)	34.91	25.33	0.01
Thrombolysis (%)	10.72 n = 485*	8.44	0.63
Myocardial infarction (%)	33.47	36.89	0.37
Diabetes type 2 (%)	40.95 n = 486*	41.78	0.86
Obesity (%)	4.72	5.33	0.90
Smoking (%)	5.75	6.67	0.84

*the data from the rest of patients were not available

Table IV. The results in computed tomography in the study groups divided according to the assessment of the results in National Institutes of Health Stroke Scale

	NIHSS improvement (n = 487)	NIHSS deterioration (n = 225)	P
The sum of the volume of all lesions in CT1 [cm^3]	2.80 [1.60–8.00] n = 181*	6.00 [2.65–19.85] n = 88*	0.001
The sum of the volume of all lesions in CT2 [cm^3]	2.60 [1.40–7.00] n = 251*	6.24 [2.08–26.88] n = 103*	< 0.001
The difference of the volume of lesions between CT1 and CT2 [cm^3]	0.00 [0.00–0.00] n = 107*	[0.00–4.50] n = 35*	0.03
The greatest lesion in CT 1 [cm^3]	2.70 [1.60–7.00] n = 181*	5.67 [2.65–17.50] n = 88*	0.001
The greatest lesion in CT 2 [cm^3]	2.50 [1.26–6.00] n = 251*	6.00 [2.08–23.68] n = 103*	< 0.001

*the data from the rest of patients were not available
CT1 — computed tomography on admission; CT2 — computed tomography at discharge

Table V. Baseline characteristics of the study groups divided according to the results in Rankin scale

	R1 (n = 385)	R2 (n = 327)	P
Age (years)	73.00 [64.00–80]	77.00 [68.00–83.00]	< 0.001
Sex (male) (%)	52.99	46.48	0.084
NIHSS on admission	5.00 [3.00–8.00]	6.00 [3.00–13.00]	0.02
NIHSS at discharge	2.00 [1.00–3.00]	4.00 [2.00–8.00] n = 240**	< 0.001
Improvement in NIHSS (%)	96.36	35.47	< 0.001
Rankin on admission	4.00 [3.00–4.00]	4.00 [3.00–5.00]	0.83
Rankin at discharge	2.00 [1.00–3.00] n = 384*	3.00 [2.00–5.00] n = 239**	< 0.001

*the data from the rest of patients were not achievable; **in the rest of cases death was found
R1 — patients with improvement in Rankin; R2 — patients with no change in Rankin, with deterioration and patients who was found death; NIHSS — National Institutes of Health Stroke Scale

Table VI. Comorbidities in the study groups divided according to the assessment of the results in Rankin scale

Comorbidities	R1 (n = 385)	R2 (n = 327)	P
Ischemic stroke (%)	94.55	90.83	0.055
Carotid artery stenosis (%)	35.06	28.13	0.05
Thrombolysis (%)	11.49 n = 383*	8.26	0.15
Myocardial infarction (%)	33.77	35.47	0.63
Type 2 diabetes (%)	38.80 n = 384*	44.04	0.16
Obesity (%)	4.16	5.81	0.31
Smoking (%)	4.68	7.65	0.10

*the data from the rest of patients were not achievable
R1 — patients with improvement in Rankin; R2 — patients with no change in Rankin, with deterioration and patients who was found death

Table VII. The results in computed tomography in the study groups divided according to assessment of the results in Rankin scale

	Rankin improved (n = 385)	Rankin deteriorated (n = 327)	P
The sum of the volume of all lesions in CT1 [cm^3]	2.75 [1.60–6.60] n = 134*	5.46 [1.84–16.42] n = 135*	< 0.01
The sum of the volume of all lesions in CT2 [cm^3]	2.45 [1.20–5.48] n = 198*	6.04 [2.00–26.12] n = 156*	< 0.001
The difference of the volume of lesions between CT1 and CT2 [cm^3]	[0.00–0.00] n = 81*	0.00 [0.00–2.40] n = 61*	0.09
The greatest lesion in CT 1 [cm^3]	2.75 [1.60–6.00] n = 134*	5.00 [1.80–16.42] n = 135*	0.01
The greatest lesion in CT 2 [cm^3]	2.30 [1.20–5.00] n = 198*	6.00 [2.00–24.28] n = 156*	< 0.001

*the data from the rest of patients were not available
CT1 — computed tomography on admission; CT2 — computed tomography at discharge; R1 — patients with improvement in Rankin; R2 — patients with no change in Rankin, with deterioration and patients who decreased

The state and clinical course of the patients according to their age was analyzed. The NIHSS score on admission correlated with age (R = 0.212, P < 0.05) (Figure 1).

A significant correlation was observed between RANKIN on admission and age of participants (R = 0.231, P < 0.05).

The results of laboratory tests of the whole group of patients with hypertension treated before stroke were evaluated. 51.97% of patients had CRP above the normal limit and 33.23% of patients had WBC above the normal range. The relation between the results in clinical scales and CT and values in laboratory tests was analyzed. A significant correlation between CRP and NIHSS on admission was observed (R = 0.191, P < 0.05).

The sum of the volume of all lesions in CT2 was related to CRP (R = 0.17, P < 0.05).

Discussion

The epidemiological records show that in 2005––2008 almost one-third of adults in the US suffered from hypertension, and less than a half of them had it sufficiently controlled. This may be associated with an increased mortality and complications rates including myocardial ischemia, strokes, heart failure or chronic kidney disease: all of which escalates public health system costs, up to $131 billion annually [9].

The long period, prior to the hypertension complications development facilitates unfavourable structural and functional cerebral changes i.e.: vessels remodelling, blood-brain barrier integration, diffuse white matter damage, and also changes in the cerebral circulation, including vasodilatation, development of inflammation and oxidative stress or a dysfunction of the baroreceptor reflex [10]. Persistent elevated blood pressure has a considerable impact on the structure of brain arteries, triggering adaptive changes such as hypertrophy and remodeling [11]. Altogether, these mechanisms may contribute to the incident stroke.

Given the fact, that ischemic stroke affects also treated hypertensive patients (with more than 1 blood-lowering drug) [12], suggesting that effective treatment only reduces the risk.
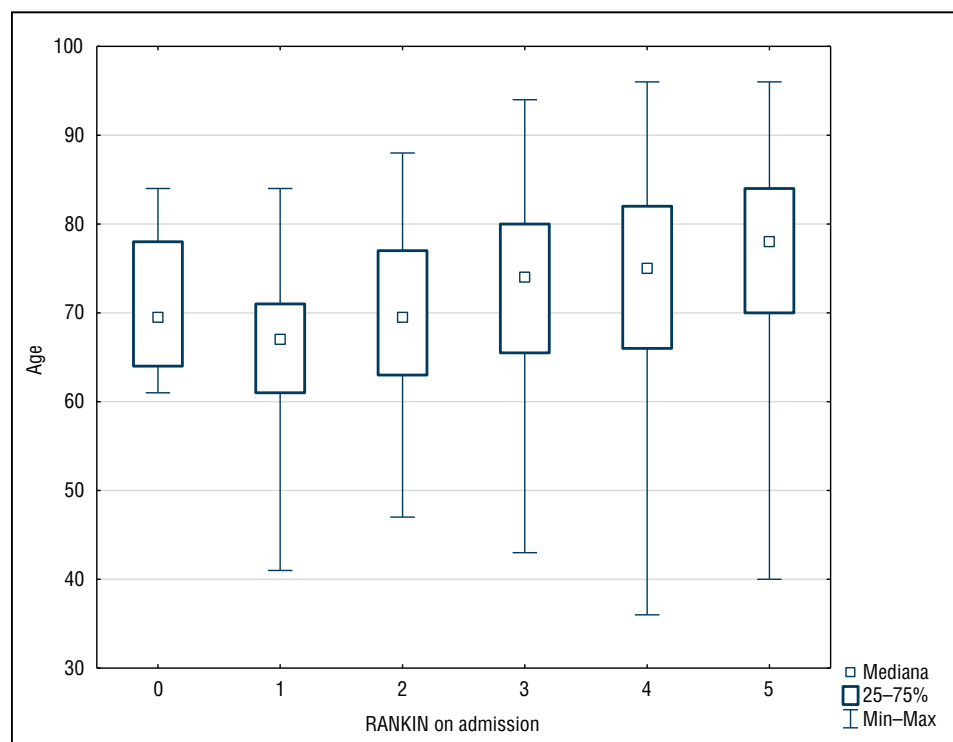
Figure 1. Presentation of the median and interquartile range for the age of patients

In our analysis, we found that women, experience stroke at the older age than men. The study of Holroyd-Leduc et al. conducted in a group of 44,832 patients with an acute stroke also indicated that men were younger than women [13]. This is in line with the results of other reports [14–16].

Interestingly, we have also found that the cardiovascular comorbidities incl. stenosis of the carotid arteries, myocardial infarction and AF are more common in women than in men. Niewada et al. findings indicating that in women AF more often coexists and the stroke is mainly caused by the embolic events (twice as often as in men) [15].

Part of these differences may be ascribed to sexual diversity and the influence of sex hormones may not be disregarded. The estradiol dilates vessels and increases the blood flow, while testosterone has the opposite effect, estrogens also have a positive influence on cerebrovascular reactivity and has anti-inflammatory properties [17]. Therefore, women after menopause, are actually deprived of this protective factor due to the lowering of the estrogens level.

Women with a stroke incident were more often admitted with a higher NIHSS score than men and at discharge in the Rankin assessment woman were worse than man. A study by Santalucia et al. conducted in 1272 stroke patients also showed, that the NIHSS result on admission was significantly worse in women, at discharge they were more often seriously neurologically impaired and the functional results in the mRS at discharge were also worse in comparison with man [16]. This is not completely understood, although one my hypothesize that older women are more often widows, socially isolated and lonely living and it's also suggested that women with an acute stroke more often than men show diffuse and non-specific symptoms, such as confusion, weakness, fatigue or consciousness changes. At admission women, more often present symptoms of aphasia, dysphagia and visual impairment [14–17].

The analyses indicate that both the NIHSS and Rankin results at admission are correlated with age. It is estimated that increase by, both in age and baseline NIHSS increase the chances for poor outcome in stroke survivors by 1.113 and 1.557 times, respectively [18].

Our study also has revealed that patients who showed improvement in NIHSS had significantly lower CRP levels, and WBC counts than patients who had no improvement in NIHSS upon discharge. The study of den Hertog et al. which evaluated the value of CRP in the very early stages of stroke — in the group of patients with ≥ 7 mg/L the NIHSS score upon admission was greater and they more often had AF which translated to cardioembolic strokes [19]. Similar results were observed by other groups [20].

VanGilder et al. demonstrated a positive correlation between an acute CRP increase with a long-term unfavourable outcome, assessed using NIHSS and mRS [21]. It is emphasized that an acute ischemic stroke may cause an increase in CRP levels depicting inflammatory response. This phenomenon, when present may be a poor predictor suggesting extensive tissue damage or co-existing infection additionally, it may correlate with the severity of stroke [19, 20]. Similar results are also characteristic for the number of WBC, the level of which also increases in the course of acute stroke [19].

It is also important to emphasize that in a group of patients with no improvement or with deterioration in NIHSS and Rankin the volume of stroke lesion was greater than in patients with better results. The study of Yaghi et al. on 510 DWI positive patients revealed a graded relationship between the NIHSS result and median DWI lesion volume, what proves that people with minor stroke symptoms have relatively small brain infarcts documented in imaging studies [22]. It is worth to emphasize that despite no improvement in the size of stroke lesions during hospitalization the improvement in NIHSS scale was observed.

In our study, we also assessed the laboratory results of patients before the stroke incident, what indicated, that more than a half of them had elevated level of CRP, and almost 1/3 of them — WBC above the normal range and there was a significant correlation between CRP and NIHSS on admission. The researchers indicate that the level of CRP taken within 12–24h of the onset of stroke is an independent predictor of unfavourable functional outcome of patients in the assessment after one year [21]. Researchers underline that CRP is both a risk and a prognostic factor for ischemic stroke and coronary events — mean CRP was significantly higher in stroke patients especially if stroke was caused by cardioembolism (3-fold increase in risk) and atherosclerosis of large arteries (2-fold increase in risk) [23]. It could be concluded that CRP may be a marker that could initiate basic preventive strategies in the future.

Lastly, it is worth mentioning that the level of CRP was significantly higher in the group of patients who did not improve the clinical condition, but our study also showed that their post-stroke changes in the brain were greater. Other researchers also indicate that the infarct volume is significantly positively correlated with serum CRP level [24]. We have noticed that inflammation was correlated with the magnitude of stroke lesion in CT at discharge, what may suggest that the severity of inflammation at admission indicates the number of cells that have already been damaged. Recent evidence suggests that blood biomarkers may be equally effective in predicting functional outcome as image biomarkers [21].

Conclusions

In conclusion we would like to underscore that hypertensive women experience first-ever stroke at older age as compared to men, however, the volume of brain ischemia at admission is greater in women than in men.

The clinical state of the patients assessed in NIHSS scale shows association with serum inflammatory markers which are coupled with.

The evident association between the volume of stroke lesion in CT and severity of inflammatory process.

Despite no changes in the volume of ischemic brain areas the improvement in NIHSS scale was observed. The easily available serum inflammatory marker seems to predict prognosis prior to brain CT-changes.

Conflict of interest

There are no conflicts of interest.

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