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Prognostic Biomarkers in Patients with Ischemic Stroke Who Received Thrombolytic Therapy

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Abstract: Background: The aim of the research was to evaluate the association between CRP (C-reactive protein), troponin I, d-dimer, creatinine, glucose, GFR (glomerular filtration rate) and LDL-C (low-density lipoprotein cholesterol) levels at the admission and the results of thrombolytic therapy. Materials and methods: 113 patients who underwent thrombolytic therapy for acute ischemic stroke in Pauls Stradins Clinical University Hospital from 01.01.2015 to 01.01.2016 were studied retrospectively. Blood samples were collected in the emergency department. The neurological status was estimated using the NIHSS (National Institute of Health Stroke Scale). The efficacy of thrombolytic therapy was assessed by comparing NIHSS score at the admission and after treatment. Afterward all patients were divided into three groups—the major improvement (NIHSS > 4), minor improvement (NIHSS ≤ 4) and without any clinical effect. Results: Only the median levels of GFR were significantly (p = 0.015) lower in patients who did not have any clinical improvements after thrombolytic therapy as compared to patients with the major or minor improvements (60.0, IQR (interquartile range) 42.4-72.3 mL/min/1.73m^2; 83.2, IQR 65.3-98.3 mL/min/1.73m^2 and 75.9, IQR 59.2-94.6 mL/min/1.73m^2). Based on the ROC (receiver operating characteristic) curve, the optimal cut-off value of GFR level as an indicator for prediction of worsen clinical outcome after thrombolytic therapy was projected to be 61.65 mL/min/1.73m^2, which yielded a sensitivity of 71.4% and a specificity of 24.5%, the area under the curve was 0.788 (95% CI (confidence interval), 0.648-0.928). According Spearman rank correlation test was founded statistically significant indirect correlation between GFR level and NIHSS score after treatment (r = -0.410, p = 0.020) in patients with severe stroke (NIHSS > 14). Conclusions: GFR level lower than 61.65 mL/min/1.73m^2 at the admission could predict as a worse outcome, especially in patients with severe stroke.

Key words: Ischemic stroke, thrombolytic therapy, effectiveness, clinical outcome, biomarkers.

1. Introduction

The search for ischemic stroke biomarkers should get us an extensive knowledge of pathogenetic mechanisms of disease itself. The aim of the research was to evaluate the association between CRP (C-reactive protein), troponin I, d-dimer, creatinine, glucose, GFR (glomerular filtration rate) and LDL-C (low-density lipoprotein cholesterol) levels at the admission and the results of thrombolytic therapy. It was believed, that routine blood tests carried out in emergency room can be used to identify patients who may benefit from intravenous thrombolytic therapy and predict stroke outcome.

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The current World Health Organization definition of stroke is “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” [1]. There are two types of stroke, hemorrhagic and ischemic. Ischemic stroke occurs far more commonly than the hemorrhagic. According to statistical data for 2014 year of the CDPC (center for disease prevention and control) of Latvia, ischemic stroke was diagnosed in approximately 90% of all stroke patients. Despite effective treatment approaches such as endovascular thrombectomy or intravenous thrombolysis with alteplase, ischemic stroke has remained the leading cause of death and functional disability across the world. The mortality rate in ischemic stroke patients was achieved 87.7 deaths per 100,000 persons

according to Latvian CDPC statistical data for 2014 year [2]. Clinical outcome of the ischemic stroke may depend on several factors such as advanced age, stroke severity, medical complications or comorbidities [3]. The most frequent serious medical complications include pneumonia, congestive heart failure, cardiac arrest, deep vein thrombosis, pulmonary embolism and urinary tract infection. Hemorrhagic transformation is an important complication of ischemic stroke, especially after thrombolytic therapy. There are several factors, which might be used as predictors of hemorrhagic transformation. Massive cerebral infarction, grey matter infarction, atrial fibrillation, hyperglycemia, lower total cholesterol and LDL-C, lower platelet count, poor collateral vessels, elevated globulin level, radiological predictors (early CT (computed tomography) signs, hyperdense middle cerebral artery sign), micro- and macro-albuminuria might be associated with increased hemorrhagic transformation risk [4]. A host of prestroke comorbid conditions are associated with an increased risk of poor outcome following ischemic stroke. Atrial fibrillation, diabetes mellitus, heart failure, renal dysfunction or cancer might negatively influence the treatment efficacy [5-7]. Moreover, a recently conducted meta-analysis showed strong statistically significant relationship between having an anemia and the worse clinical outcome in patients with ischemic stroke [8]. Apart from common comorbidities, sickle cell trait also was associated with poor prognosis [9]. Olowoyo et al. [9] observed an increase of 30-day mortality rate among the patients with sickle cell trait than the controls.

2. Materials and Methods

2.1 Materials

This study had a retrospective design. Nine hundred and forty-five patients admitted to the Stroke Unit at the department of Neurology of the Pauls Stradins Clinical University Hospital of Riga from 01.01.2015 to 01.01.2016 were enrolled in this study. The inclusion criteria were: (a) diagnosis of ischemic stroke based on history, neurological examination and multimodal CT evaluation (noncontrast CT, CT-angiography and perfusion CT), (b) eligibility for intravenous thrombolytic therapy with alteplase 0.9 mg/kg according to current guidelines. The exclusion criteria were: (a) admission to the hospital later than 4.5 hours of the onset of neurological focal symptoms, (b) suspicion of acute coronary syndrome (history, ECG changes, elevated cardiac troponin levels or creatine kinase isoenzyme MB (CK-MB) levels), (c) suspicion of acute bacterial infection based on clinical examination and history, (d) fatal outcome during hospitalization. There were 832 patients that were excluded due to the mentioned factors. The final study group consisted of 113 patients, 67 women and 46 men.

The following variables were collected for all patients: age, gender, initial stroke severity as assessed using the NIHSS (National Institute of Health Stroke Scale), NIHSS score after thrombolytic therapy, initial CRP, troponin I, d-dimer, creatinine, glucose, GFR and LDL-C levels in blood serum and stroke etiology according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria. Treatment effectiveness was assessed by comparing NIHSS score at the admission and 24 hours after thrombolytic therapy. Afterward all patients were divided into three groups—the major improvement, minor improvement, and without any clinical effect. Early neurological improvement corresponding to an increase of more than 4 points from the baseline NIHSS score was classified as the major improvement, consequently minor improvement was classified as increasing of not more than 4 points. Any patient with neurological deterioration after received thrombolytic therapy was classified into group—without any clinical effect.

2.2 Methods

Statistical analysis was performed using IBM SPSS software. The level of significance was set at $p < 0.05$.

Continuous variables were presented as median with IQR (interquartile range) and results for categorical variables were expressed as percentages. Group comparisons of continuous variables were performed using Kruskal-Wallis H and Mann-Whitney U tests for independent samples. The chi-square test was used for categorical comparisons of data. The relationship between GFR level at the admission and NIHSS score 24 hours after thrombolytic therapy was determined using Spearman rank correlation coefficient. ROC (receiver operating characteristic) curves were utilized to evaluate the accuracy of GFR to predict worse outcome. The area under the curve (AUC) was calculated as measurements of the accuracy of the test.

3. Results

Among the 113 patients with acute ischemic stroke, the major improvement after received thrombolytic therapy was determined in 54 patients, minor improvement in 52 patients, and only 7 patients did not had any clinical effect. The baseline characteristics of 113 patients are described in Table 1.

Advanced age was associated with reduced effectiveness of intravenous thrombolysis ($p < 0.05$). The mean age of patients who had significant neurological improvement was 67.15, simultaneously the mean age of patients who had not any clinical effect was 78.86. The gender and the stroke severity also had influence on thrombolysis ($p < 0.05$). Male gender was associated with poor short-term outcome. A more severe stroke on admission surprisingly was associated with a better effect of the thrombolytic therapy. The median NIHSS score in patients with the major improvement was significantly higher as compared to patients with minor improvement and without any clinical effect (12, IQR 8-16; 8, IQR 6-11; 10, IQR 7-18, $p < 0.05$). Stroke etiology was not associated with any clinical outcome after thrombolytic therapy ($p > 0.05$).

The relationships between serum biomarkers and effect of thrombolysis were shown in Table 2.

Serum GFR levels on admission were lower in patients who did not have any clinical improvements after thrombolytic therapy as compared to patients with the major or minor improvements (60.0, IQR 42.4-72.3 mL/min/1.73m^2; 83.2, IQR 65.3-98.3 mL/min/1.73m^2 and 75.9, IQR 59.2-94.6 mL/min/1.73m^2). Low serum GFR level was related with reduced effectiveness of intravenous thrombolytic therapy. A significant difference in the median GFR values on admission was observed between groups with different clinical effect of thrombolysis ($p < 0.05$) (see Fig. 1).

Based on the ROC curve, the optimal cut-off value of GFR level as an indicator for prediction of worsen clinical outcome after thrombolytic therapy was projected to be 61.65 mL/min/1.73m^2, which yielded a sensitivity of 71.4% and a specificity of 24.5%, the area

Table 1 Baseline characteristics of acute ischemic stroke patients according to clinical outcome.

Patients data	Effectiveness of treatment			p[a]
	Major improvement NIHSS > 4 (n = 54)	Minor improvement NIHSS ≤ 4 (n = 52)	Without any clinical effect (n = 7)	
Age, mean (min., max.)	67.15 (32, 88)	73.23 (43, 92)	78.86 (71, 94)	0.007
Gender, No. (%):				
Female (n = 67)	33 (49.3%)	27 (40.3%)	7 (10.4%)	0.049
Male (n = 46)	21 (45.7%)	25 (54.3%)	0 (0%)	
Stroke severity, median NIHSS score (IQR)	12 (8-16)	8 (6-11)	10 (7-18)	0.001
Stroke etiology, No. (%)				
Atherothrombotic stroke (n = 28)	13 (46.4%)	14 (50.0%)	1 (3.6%)	0.942
Cardioembolic stroke (n = 75)	36 (48.0%)	34 (45.3%)	5 (6.7%)	
Undetermined etiology (n = 10)	5 (50.0%)	4 (40.0%)	1 (10.0%)	

[a]p for gender and stroke etiology was assessed using Kruskal-Wallis test, but for stroke severity and age using χ^2 test.

Table 2 Serum biomarkers levels on admission according to clinical outcome.

Laboratory findings (median, IQR)	Effectiveness of treatment			p^a
	Major improvement NIHSS > 4 (n = 54)	Minor improvement NIHSS ≤ 4 (n = 52)	Without any clinical effect (n = 7)	
CRP (mg/L)	3.0 (1.5-8.8)	2.5 (0.9-7.0)	3.4 (2.7-9.4)	0.296
LDL-C (mmol/L)	2.68 (2.15-3.27)	2.43 (1.83-2.93)	2.19 (1.75-2.98)	0.128
D-dimer (mg/L)	900 (360-1678)	1,000 (650 -1950)	1,240 (710-2650)	0.300
Troponin I (ng/L)	11 (6-33)	14 (10-30)	17 (10-40)	0.349
GFR (ml/min/1.73m^2)	83.2 (65.3-98.3)	75.9 (59.2-94.6)	60.0 (42.4-72.3)	0.015
Creatinine (μmol/L)	76 (61-88)	77 (68-99)	85 (73-111)	0.100
Glucose (mmol/L)	6.35 (5.70-7.40)	6.15 (5.25-7.28)	7.30 (6.30-8.30)	0.078

[a]p value was assessed using Kruskal-Wallis test.

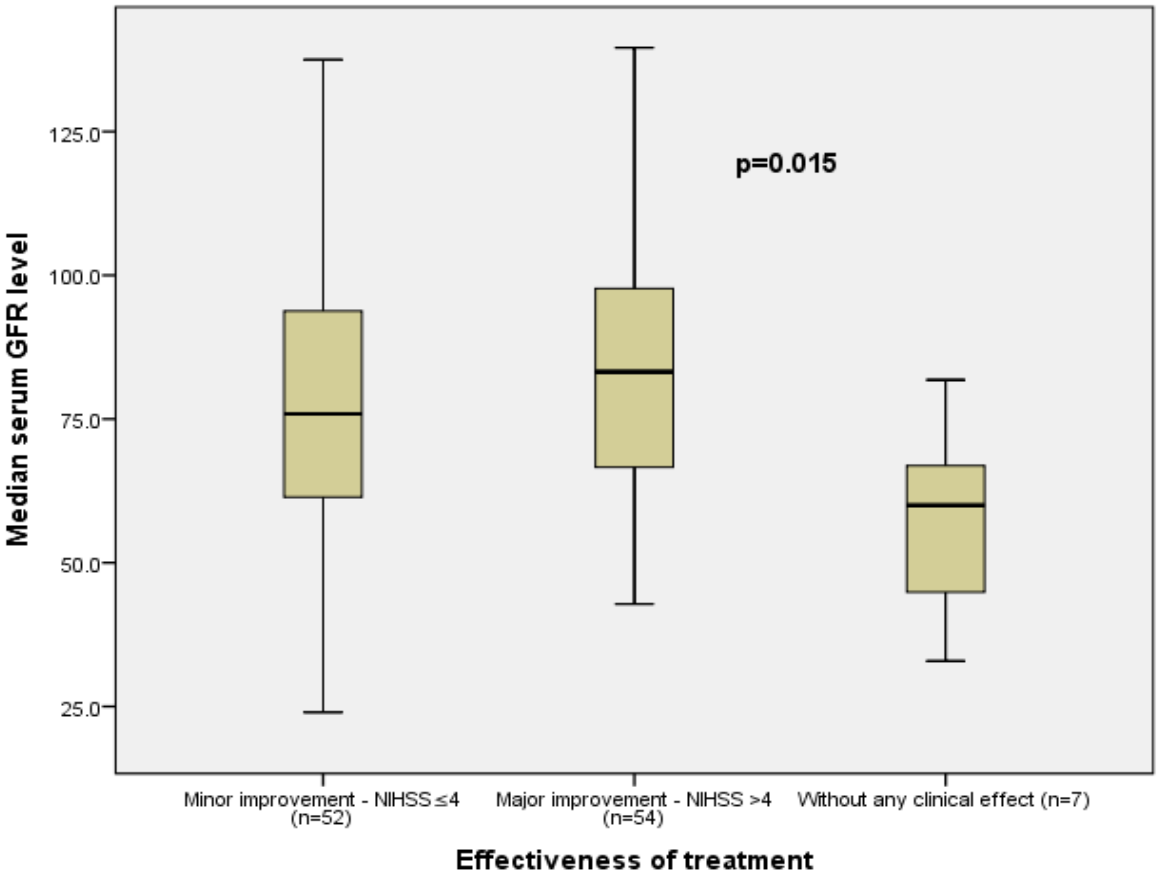

Fig. 1 Serum GFR level on admission in different clinical outcome after thrombolytic therapy.

under the curve was 0.788 (95% CI (confidence interval), 0.648-0.928) (see Fig. 2).

No significant correlations between GFR levels and NIHSS score after thrombolytic therapy were found. Nevertheless in patients with severe ischemic stroke, which defined on admission as 14 and more points according to NIHSS scale, statistically significant indirect correlation was found between GFR level and NIHSS score after treatment (r = -0.410, p = 0.020) (see Fig. 3).

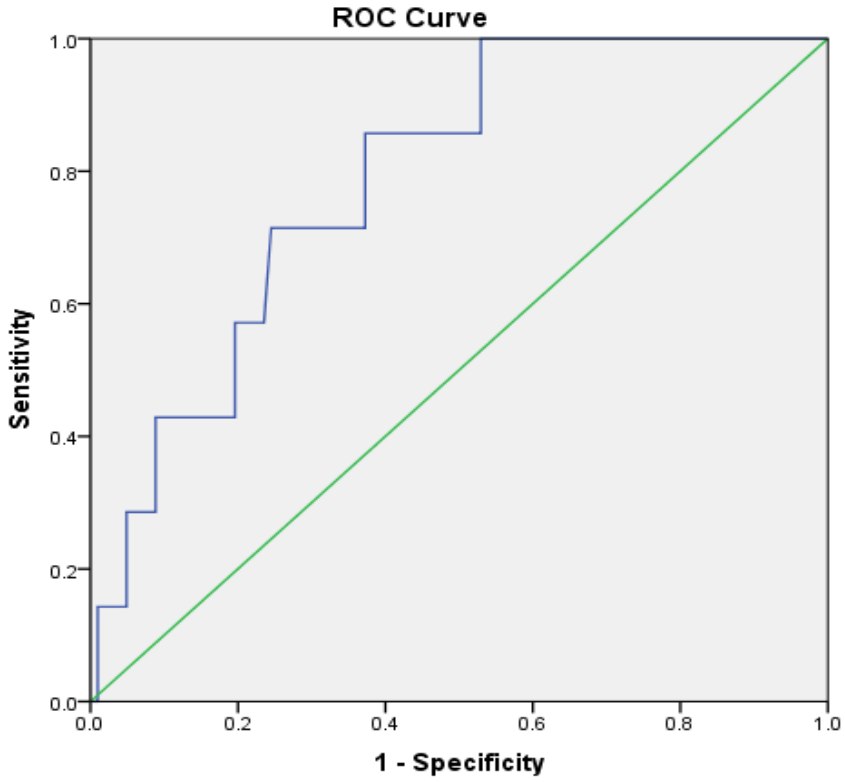

Fig. 2 ROC curves were utilized to evaluate the accuracy of GFR levels to predict worse outcome in patients who underwent thrombolysis.

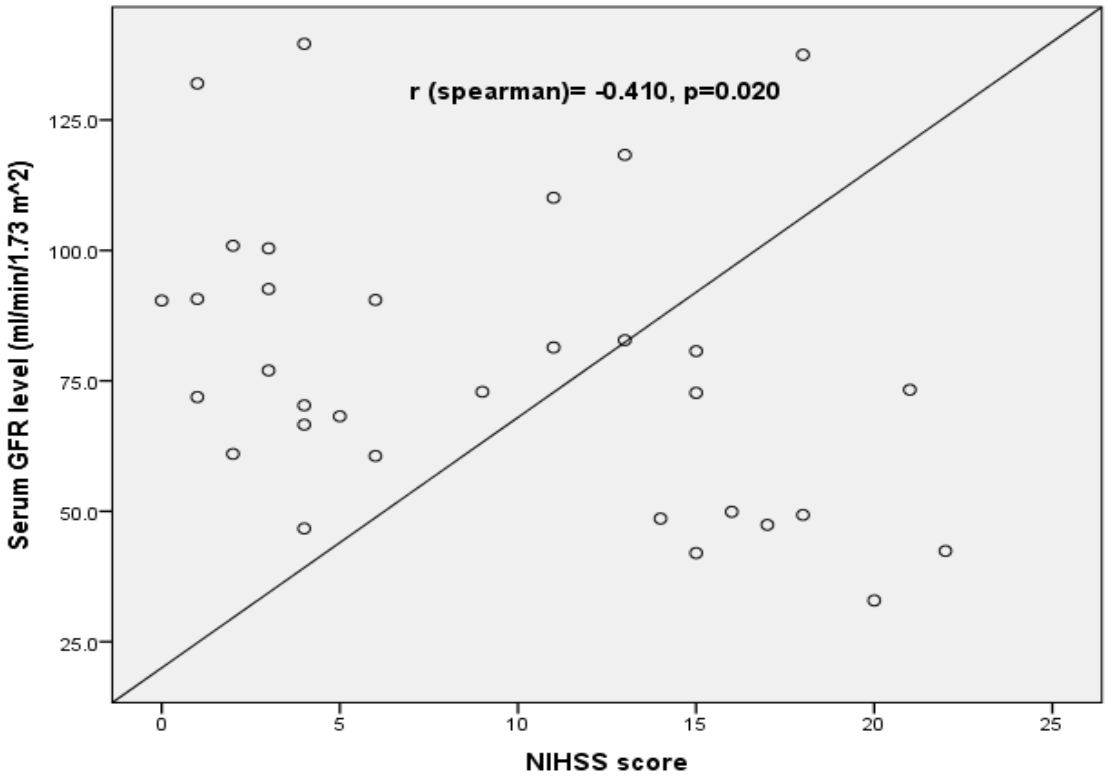

Fig. 3 Correlation between serum GFR level on admission and the NIHSS score after thrombolytic therapy in patients with severe stroke (NIHSS > 14).

4. Discussion

In this study we found that renal impairment may impact the thrombolytic therapy efficacy. Moreover, GFR value, which measures level of kidney function and determines stage of kidney disease, could be used as predictor for thrombolytic therapy effectiveness. In this study GFR level lower than 61.65 mL/min/1.73m^2 before treatment was determined as a poor prognostic biomarker especially in patients with severe stroke (NIHSS > 14). Previous reports on the relationship between renal dysfunction and the risk of a poor outcome were conflicting [10-20]. Among these studies, a GFR level lower than 60 mL/min mostly was used as the definition of renal dysfunction. Furthermore GFR < 30 mL/min was strongly associated with a poor outcome. In several studies increased risk of hemorrhagic complications was observed after received thrombolytic therapy in patients with renal dysfunction [10, 12, 16, 20]. However Power A. et al. did not found any significant association between renal impairment and higher rate of sICH (symptomatic intracerebral hemorrhage). Nevertheless, in the same study renal impairment was associated with reduced efficacy of thrombolysis. However recently a meta-analysis done by Hao Z. et al. showed that renal dysfunction did not increase the risk of poor outcome and sICH in patients who underwent intravenous thrombolysis.

The pathological mechanism whereby renal impairment could impact on thrombolytic therapy effectiveness remains unclear. There are several suggested mechanisms, which could explain association between renal dysfunction and poor clinical outcome in patients with ischemic stroke. The safety of intravenous thrombolysis could be diminished by an increased risk of hemorrhagic complications. Meanwhile patients with renal impairment are indeed at an increased risk of sICH. The underlying mechanisms might be endothelial and platelet dysfunction. Furthermore, patients with renal impairment have more severe white matter disease, which may facilitate sICH after thrombolytic treatment as well [21, 22]. Another mechanism, which could explain reduced intravenous thrombolysis efficacy, is associated with altered fibrin clot properties and structure in patients with renal impairment. In patients who have end-stage renal disease fibrin clot becomes more stiffness and therefore susceptibility to lysis is reduced [23].

This study has some limitations. Firstly, patients did not have CT control examination after receiving thrombolytic therapy for identifying any hemorrhagic complication. Therefore, association between renal dysfunction and increased risk of sICH could not be determined. Secondly, this was a retrospective study and neurological examination of the same patient on admission and 24 hours after thrombolytic therapy was performed by different neurologists. Thirdly, the sample size was relatively small.

5. Conclusions

In this study it was observed that low GFR level on admission could impact on intravenous thrombolytic therapy. GFR level lower than 61.65 mL/min/1.73m^2 at the admission could be predicted as a worse outcome, especially in patients with severe stroke. Thereby in patients with history of kidney disease or abnormal creatinine or GFR levels on admission the risks and benefits of thrombolytic therapy should be assessed particularly.

In future studies, patients with renal impairment and low GFR level need to identify other factors that can reduce thrombolytic therapy effectiveness such as high blood pressure on admission or long time interval between stroke onset and hospital arrival. Electrolyte imbalance and high hematocrit levels which may indicate dehydration also could be studied as ischemic stroke outcome predictors.

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