Human urinary kallidinogenase decreases the incidence of post-stroke cognitive impairment in acute ischemic stroke patients

Xu Yan\(^1,2\), Huan Chen\(^3\), Xiuli Shang\(^2,\*)

\(^1\)Department of Neurology, The First People’s Hospital of Shenyang, 110041 Shenyang, Liaoning, China
\(^2\)Department of Neurology, The First Affiliated Hospital of China Medical University, 110001 Shenyang, Liaoning, China
\(^3\)Department of Neurology, The Fourth Affiliated Hospital of China Medical University, 110032 Shenyang, Liaoning, China

\(*\)Correspondence: xiulishangcmu@126.com (Xiuli Shang) Academic Editor: Hongmin Wang
Submitted: 22 November 2021 Revised: 27 January 2022 Accepted: 8 February 2022 Published: 8 April 2022

Abstract

Background: Post-stroke cognitive impairment (PSCI) is a common symptom of stroke and affects the quality of life and prognosis of stroke survivors. In our study, we evaluated the efficacy of Human urinary kallidinogenase (HUK) on cognitive function in acute ischemic stroke (AIS) patients, and discussed the role of cystatin C (CysC) in improving PSCI. Methods: We enrolled a retrospective cohort with prospective follow-up. From August 2020 to May 2021, 130 patients completed the final follow-up. Among them, 61 patients received HUK combined with basic treatment, which we defined as the HUK group, and 69 patients received basic treatment, which we defined as the control group. We compared the changes of CysC, urea nitrogen and creatinine levels after one week of treatment between the two groups. Cognitive function was assessed by Montreal Cognitive Assessment (MoCA) at 3-month after AIS. Results: No significant differences in demographic data and Laboratory tests between two groups before treatment. A total of 67 patients (51.5%) were diagnosed as PSCI at 3-month follow-up, among which, 25 patients were in the HUK group and 42 patients were in the control group. Compared with the control group (60.9%), the incidence of PSCI was significantly lower in the HUK group (41.0%). In addition, the serum CysC level after a week of treatment significantly decreased from baseline in HUK group \((p = 0.037)\), in comparison, the serum CysC level in the control group was basically unchanged \((p = 0.951)\). There was a significant negative correlation between MoCA score and the level of CysC after treatment \((p = 0.003, r = -0.373)\). Conclusions: HUK can reduce the risk of PSCI at 3-month in AIS patients. The decrease of serum CysC level may be one of the mechanisms by which HUK reduces the incidence of PSCI.

Keywords: acute ischemic stroke; post-stroke cognitive impairment; human urinary kallidinogenase; CysC

1. Introduction

Acute ischemic stroke (AIS) is one of the diseases with the highest morbidity in the world. Although the incidence rate of stroke has decreased in recent years, the absolute number of stroke is gradually increasing. It has become the main cause of disability in human beings and poses a serious threat to human health [1–3]. Post-stroke cognitive impairment (PSCI) is one of the common symptoms after stroke. The prevalence of PSCI ranges from 20 to 80 percent, varying for the difference of countries, ethnicities and diagnostic criteria [4]. Previous studies have reported that PSCI may be related to many factors, such as infarct location, vascular risk factors, inflammatory mediators [5,6], etc. At the same time, PSCI is also an independent predictor of recurrent ischemic stroke [7], affecting the quality of life and prognosis of stroke survivors.

Human urinary kallidinogenase (HUK), one of the tissue kallikreins, is a glycoprotein extracted from humanurine, which plays a biological role by activating the positive regulation of the kallikrein–kinin system [8]. Previous studies have confirmed the positive effects of HUK in the treatment of AIS, including reducing ischemic cerebral injury, decreasing recurrence risk and promoting good recovery [9,10]. However, the effect of HUK on cognitive function after AIS has not been reported. Therefore, we designed this experiment to study the influence of HUK on PSCI. Additionally, since HUK mainly acts on kidney and blood vessels, and is eliminated through urine [11], we examined the related indicators of renal function before and after HUK treatment to observe the influence of HUK on them.

2. Methods

2.1 Study population

We retrospectively collected the consecutive patients with AIS who had been hospitalized at the First Affiliated Hospital of China Medical University from August 2020 to May 2021 and the demographic data and clinical information were collected within a month of discharge from the hospital. Inclusion criteria included: (1) age \(\geq 18\) years old; (2) those who were first diagnosed as AIS by magnetic resonance imaging; (3) onset time less than 72 h; and (4) those who had the results of peripheral blood on admission and had the results of CysC, urea nitrogen and creatinine after one week of treatment. Exclusion criteria included: (1) patients with cerebral hemorrhage; (2) patients...
with a history of any central nervous system diseases; and (3) patients who cannot cooperate with clinical examinations due to difficulties in hearing, vision or speaking. We also excluded the patients who were treated with endovascular therapy or intravenous thrombolysis during hospitalization. The survey was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was provided by all participants or their legal representatives.

2.2 Study design and therapeutic methods

We obtained the data of patients from our database system and baseline data of demographic characteristics, clinical features, and medication history of the eligible patients during hospitalization were recorded. We divided the eligible patients into two groups based on the treatment they received. Both of the two groups received basic treatment according to their condition, including neuroprotection, lipid-lowering therapy with statins, antiplatelet therapy, controlling blood pressure and blood glucose. We defined the patients received HUK combined with basic treatment as the HUK group, and the patients received only basic treatment as the control group. In the HUK group, 0.15 PNA unit of HUK injection plus 100 mL saline in intravenous infusion was taken once a day for 7 consecutive days. Peripheral blood of AIS patients in both groups was collected respectively on admission and one week after admission. Biochemical parameters were measured on an automated haematology analyzer. This was a retrospective cohort with prospective follow-up. During the follow-up, we would systematically control the patients’ blood pressure and blood glucose. We compared the differences in cognitive function between the two groups 3 months after stroke. We also discussed the changes of CysC, urea nitrogen and creatinine level after treatment and the correlation with PSCI.

2.3 Assessment of outcomes

The primary outcome was cognitive function at 3-month after AIS. We used the Montreal Cognitive Assessment (MoCA) to assess cognitive function. The total score of MoCA is 30 points, and the lower the score, the more severe the cognitive impairment [12]. On the basis of criteria, cognitive function is classified as follows: no cognitive impairment is defined by scores from 27 to 30, PSCI is defined by scores from 0 to 26, and post-stroke dementia (PSD) is defined by scores from 0 to 22. In this analysis, a score of ≤ 26 on the MoCA indicated cognitive impairment [12,13].

2.4 Statistical analysis

Baseline characteristics were compared among the two groups. Continuous variables were expressed as means with standard deviations (SD). Differences between groups were tested using the independent-samples t-test or analysis of variance (ANOVA). Categorical variables were described by frequencies with percentages, and the χ² test was used to examine differences. Pearson’s correlation coefficients and scatter plots were used to investigate the relationship between CysC and PSCI. For all the analyses, p < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS program (Version 21.0, SPSS Inc., Chicago, IL, USA).

3. Results

During August 2020 to May 2021, a total of 150 patients were enrolled in this study, of which 130 cases were eligible for the study. Twenty patients were lost to follow-up or refused to complete the scale at 3 months. The demographic data and clinical information are shown in Table 1. 61 patients were in the HUK group, and 69 patients were in the control group. No significant differences in age, sex, smoking, drinking, diabetes, hypertension, cardiovascular disease, atrial fibrillation, National Institute of Health Stroke Scale (NIHSS) and modified Rankin scale (MRS) score at admission was found between the two groups. Laboratory indicators at admission, such as uric acid, low-density lipoprotein cholesterol (LDL-cholesterol) and homocysteine (HCY), were also not statistically significant between the two groups.

A total of 67 patients (51.5%) were diagnosed as PSCI at 3 months follow-up, among which, 25 patients were in the HUK group and 42 patients were in the control group. We presented MoCA score of all patients at 3 months in Table 2. Compared with the control group (60.9%), the incidence of PSCI was lower in the HUK group (41.0%), and the difference was statistically significant (p = 0.024). Although the incidence of PSD in the HUK group (8.2%) was lower than that in the control group (10.1%), the difference was not statistically significant (p = 0.147).

We respectively compared the changes of CysC, urea nitrogen, creatinine levels in the HUK and control group before and after treatment in Table 3. The serum CysC level decreased from baseline in HUK group, and the difference was statistically significant (p = 0.037). In comparison, the serum CysC level in the control group was basically unchanged before and after basic treatment (p = 0.951). Creatinine in control group were also decreased from baseline. No significant difference in urea nitrogen levels were found before and after treatment.

Fig. 1 presents linear correlation between MoCA score and the level of CysC after treatment. There was a significant negative correlation between MoCA score and the level of CysC after treatment both in HUK group (p = 0.003, r = −0.373) and control group (p = 0.023, r = −0.274).

4. Discussion

This prospective study showed that patients treated with HUK had a higher MoCA scores at 3-month compared with control group. There was no significant differ-
Table 1. Basic characteristics of all patients between the two groups.

| Variables* | HUK group (n = 61) | Control group (n = 69) | $\chi^2/t$ | $p$ |
|------------|-------------------|------------------------|------------|-----|
| Age (year) | $63.7 \pm 10.93$  | $65.77 \pm 9.62$       | $-1.145$   | 0.254 |
| Sex (male) | 43 (70.5)         | 41 (59.4)              | 1.736      | 0.188 |
| Current smoking (n, %) | 22 (36.1) | 23 (33.3) | 0.107 | 0.744 |
| Current drinking (n, %) | 7 (11.5) | 6 (8.7) | 0.278 | 0.598 |
| Hypertension (n, %) | 43 (70.5) | 47 (68.1) | 0.086 | 0.770 |
| Cardiovascular disease (n, %) | 11 (18) | 13 (18.8) | 0.014 | 0.906 |
| Diabetes (n, %) | 27 (44.3) | 27 (39.1) | 0.351 | 0.553 |
| Atrial fibrillation (n, %) | 4 (6.6) | 6 (8.7) | 0.016 | 0.899 |
| NIHSS at admission | $5.39 \pm 4.88$ | $5.32 \pm 4.12$ | 0.094 | 0.925 |
| MRS score | $2.38 \pm 1.39$ | $2.48 \pm 1.24$ | $-0.438$ | 0.662 |

| Lesion location (n, %) |          |           |          |     |
|------------------------|----------|----------|----------|-----|
| Frontal lobe           | 6 (9.8)  | 11 (15.9)| 1.062    | 0.303|
| Parietal lobe          | 8 (13.1) | 14 (20.3)| 1.186    | 0.276|
| Temporal lobe          | 5 (8.2)  | 6 (8.7)  | 0.01     | 0.919|
| Occipital lobe         | 3 (4.9)  | 2 (2.9)  | 0.02     | 0.888|
| Basal ganglia          | 22 (36.1)| 17 (24.6)| 2.013    | 0.156|
| Brainstem              | 9 (14.8) | 6 (8.7)  | 1.164    | 0.281|
| Cerebellum             | 5 (8.2)  | 8 (11.6) | 0.415    | 0.519|
| Other                  | 3 (4.9)  | 5 (7.3)  | 0.034    | 0.853|

| Stroke etiology (n, %) |          |           |          |     |
|------------------------|----------|----------|----------|-----|
| Atherosclerosis        | 38 (62.3)| 50 (72.5)|          |     |
| Cardio embolism        | 4 (6.6)  | 6 (8.7)  |          |     |
| Small vessel occlusion | 18 (29.5)| 13 (18.8)|          |     |
| Other undetermined etiology | 1 (1.6) | 0 (0.0)  |          |     |

| Laboratory variables |          |           |          |     |
|----------------------|----------|----------|----------|-----|
| Uric acid, $\mu$mol/L | 318.46 ± 151.37 | 322.41 ± 94.66 | $-0.18$ | 0.857|
| HDL-cholesterol, mmol/L | 1.12 ± 0.62  | 1.1 ± 0.3 | 0.234    | 0.815|
| Triglyceride, mmol/L | 1.63 ± 0.75  | 1.76 ± 1.12 | $-0.769$ | 0.443|
| Total cholesterol, mmol/L | 4.8 ± 1.11   | 4.77 ± 1.42 | 0.106    | 0.916|
| LDL-cholesterol, mmol/L | 3.14 ± 0.97  | 2.99 ± 1.22 | 0.772    | 0.442|
| Glycated hemoglobin, % | 6.87 ± 1.63  | 6.73 ± 1.75 | 0.451    | 0.653|
| HCY, $\mu$mol/L | 16.18 ± 9.15 | 14.97 ± 8.86 | 0.767    | 0.445|
| Hemoglobin, g/L | 139.59 ± 19.85 | 131.88 ± 24.73 | 1.942    | 0.054|
| CysC, mg/L | 1.37 ± 0.62  | 1.3 ± 0.6 | 0.673    | 0.502|
| Urea nitrogen, mmol/L | 7.85 ± 4.2  | 6.88 ± 2.85 | 1.556    | 0.122|
| GFR, mL/min per 1.73 m$^2$ | 76.42 ± 24.48 | 78.77 ± 23.27 | $-0.56$ | 0.576|
| Creatinine, $\mu$mol/L | 92.79 ± 45.43 | 91.3 ± 79.46 | 0.128    | 0.898|
| Uric acid, $\mu$mol/L | 318.46 ± 151.37 | 322.41 ± 94.66 | $-0.18$ | 0.857|
| HDL-cholesterol, mmol/L | 1.12 ± 0.62  | 1.1 ± 0.3 | 0.234    | 0.815|
| Triglyceride, mmol/L | 1.63 ± 0.75  | 1.76 ± 1.12 | $-0.769$ | 0.443|
| Total cholesterol, mmol/L | 4.8 ± 1.11   | 4.77 ± 1.42 | 0.106    | 0.916|
| LDL-cholesterol, mmol/L | 3.14 ± 0.97  | 2.99 ± 1.22 | 0.772    | 0.442|
| Glycated hemoglobin, % | 6.87 ± 1.63  | 6.73 ± 1.75 | 0.451    | 0.653|
| HCY, $\mu$mol/L | 16.18 ± 9.15 | 14.97 ± 8.86 | 0.767    | 0.445|
| Hemoglobin, g/L | 139.59 ± 19.85 | 131.88 ± 24.73 | 1.942    | 0.054|
| CysC, mg/L | 1.37 ± 0.62  | 1.3 ± 0.6 | 0.673    | 0.502|
| Urea nitrogen, mmol/L | 7.85 ± 4.2  | 6.88 ± 2.85 | 1.556    | 0.122|
| GFR, mL/min per 1.73 m$^2$ | 76.42 ± 24.48 | 78.77 ± 23.27 | $-0.56$ | 0.576|
| Creatinine, $\mu$mol/L | 92.79 ± 45.43 | 91.3 ± 79.46 | 0.128    | 0.898|

NIHSS, National Institute of Health Stroke Scale; MRS, modified Rankin scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HCY, homocysteine; HUK, human urinary kallidinogenase; CysC, cystatin C; GFR, glomerular filtration rate. *Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as frequency (%).
Table 2. Outcomes of MoCA score of all patients at 3 months.

| Group          | MoCA score | χ²  | p    |
|----------------|------------|-----|------|
| HUK group (n = 61) | ≤22 5 (8.2) | 7 (10.1) | 5.237 | 0.073 |
|                | 22<Y≤26 20 (32.8) | 35 (50.7) | 5.126 | 0.024 |
|                | >26 36 (59.0) | 27 (39.1) | 0.147 | 0.702 |
| Control group (n = 69) | ≤22 5 (8.2) | 7 (10.1) | 0.147 | 0.702 |

HUK, human urinary kallidinogenase; MoCA, Montreal Cognitive Assessment; PSCI, post-stroke cognitive impairment; PSD, post-stroke dementia.

Table 3. Comparison of CysC, urea nitrogen, creatinine levels before and after treatment.

| Group          | Time          | CysC (mg/L) | Urea nitrogen (mmol/L) | Creatinine (µmol/L) |
|----------------|---------------|-------------|------------------------|---------------------|
| HUK group (n = 61) | Before treatment | 1.37 ± 0.62 | 7.85 ± 4.2 | 92.79 ± 45.43 |
|                | After treatment | 1.31 ± 0.6  | 7.19 ± 3.43 | 88.74 ± 59.69 |
|                | t value       | 2.128       | 1.283               | 0.909               |
|                | p value       | 0.037       | 0.204               | 0.367               |
| Control group (n = 69) | Before treatment | 1.3 ± 0.6  | 6.88 ± 2.85 | 91.3 ± 79.46 |
|                | After treatment | 1.3 ± 0.67 | 6.61 ± 5.41 | 84.72 ± 84.15 |
|                | t value       | 0.061       | 0.502               | 4.274               |
|                | p value       | 0.951       | 0.617               | 0.000               |

HUK, human urinary kallidinogenase; CysC, cystatin C.

![Fig. 1. Linear correlation between MoCA score and the level of CysC after treatment.](image)

There was a significant negative correlation between MoCA score and the level of CysC after treatment. (a) HUK group. (b) Control group. HUK, human urinary kallidinogenase; CysC, cystatin C.

ence in PSD at 3-month between the two groups, but PSCI did, so early scale assessment and related examination is necessary. At the same time, we found the level of serum CysC decreased significantly after treatment, while the control group did not. And there was a significant negative correlation between the decreased CysC level and PSCI in HUK group. These results suggest that treatment with HUK decreased the risk of PSCI, and the serum CysC level during treatment may play a role in reducing the morbidity of PSCI.

HUK has been listed as a state category I new drug approved by China’s State Food and Drug Administration, widely used in the treatment of AIS. Previous studies have demonstrated that HUK can promote good recovery and reduce disability rates [9,10]. Recently, a multicenter, phase IV study which enrolled 1206 eligible patients showed that HUK not only had an acceptable safety and tolerability profile in patients with AIS, it can also effectively improve neurological function, further confirming its clinical efficacy in a real-world large population [14]. However, whether HUK can improve cognitive function in patients after AIS has not been studied. PSCI has always been a hot research topic, and PSCI is closely related to poor stroke outcomes [15]. Previous studies have reported some factors associ-
ated with PSCI, such as, alkaline phosphatase, vitamin D and endostatin, but few studies have reported how to reduce the incidence of PSCI [16–18]. In our study, we reported that HUK can reduce the incidence of PSCI compared with the control group, providing treatment for the prevention of high-risk PSCI patients.

HUK is positively regulated by the kallikrein-kinin system, and catalyzes the hydrolysis of low molecular weight kininogens to vasoactive kinins, which activates the bradykinin B1 and B2 receptors and induces a series of biological effects [19]. Activation of the kallikrein-kinin system can protect neural function, and reduce neuro inflammation and oxidative stress [20]. One animal study showed that HUK treatment reduced neurodegeneration, necrosis and apoptosis, and the PI3K/AKT/FoxO1 signaling pathway may be involved in this process [21]. In addition, it has been reported that HUK can decrease both Aβ1-40 and Aβ1-42 serum levels, thus preventing the development and progression of AD [22]. Therefore, HUK may affect the cognitive function of patients through different mechanisms. In our study, we examined the related indicators of renal function before and after HUK treatment, and found that the level of CysC decreased significantly after treatment, while no change was observed in the control group, suggesting that one of the mechanisms of HUK reducing the incidence of PSCI may be its effect on the level of serum CysC.

CysC is a new biomarker, which is closely related to cardiovascular and cerebrovascular diseases, has been paid more and more attention in recent years [23,24]. Previous studies found that the increase of CysC was strongly associated with dementia and cognitive impairment [25–27]. Compared with patients without AIS, the serum CysC levels in patients with AIS is significantly higher, and it can be used as a predictor of the risk of AIS [28].

Furthermore, one study suggested that high serum CysC level can increase the risk of vascular dementia after AIS and detection of CysC and CST3 gene polymorphism may contribute to the early diagnosis of vascular dementia [29]. Therefore, reducing CysC levels may reduce the incidence of PSCI. Our study has confirmed that there was a significant negative correlation between MoCAs score and the level of CysC after treatment in two groups, which may explain the mechanism of preventing the occurrence of PSCI under the effect of HUK.

CysC is closely related to kallikrein–kinin system. CysC and kininogens are all belong to the cystatin superfamily, both of which were inactivated by cathepsin D [30]. HUK can activate kallikrein–kinin system and transfer kininogens hydrolysis into kinin, then exert biological effects. How does HUK act on CysC is not clear so far. The mechanism may be that activated kinin accelerates CysC degradation, but further researches are needed.

5. Conclusions

In conclusion, HUK can reduce the risk of PSCI at 3-month in AIS patients. Although the incidence of PSD between the two groups was not statistically significant, there was also a decrease in HUK group. Early attention to the cognitive status of stroke patients is necessary. The decrease of CysC may be one of the mechanisms by which HUK reduces the incidence of PSCI, which may provide a new mechanism for PSCI prevention.

Abbreviations

PSCI, Post-stroke cognitive impairment; HUK, Human urinary kallidinogenase; AIS, acute ischemic stroke; CysC, cystatin C; MoCA, Montreal Cognitive Assessment; PSD, post-stroke dementia; ANOVA, analysis of variance; SFDA, Food and Drug Administration; B1R and B2R, bradykinin B1 and B2 receptors.

Author contributions

XS and XY designed the research study. HC performed the research. XS provided help and advice on the experiments. XY analyzed the data. XY and HC wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study involving human participants were reviewed and approved by the Regional Medical Scientific Research Ethics Committee of the First Affiliated Hospital of China Medical University (IRB no. 2021457). The patients/participants provided their written informed consent to participate.

Acknowledgment

We would like to thank the reviewers for their careful reading and useful comments that helped us to improve the final version of this paper.

Funding

This study was supported by grants from Shenyang Science and Technology Plan Projects (20-205-4-047) and Natural Science Foundation of China (81871104).

Conflict of interest

The authors declare no conflict of interest.

References

[1] Lindsay MP, Norrving B, Sacco RL, Brainin M, Hacke W, Martins S, et al. World Stroke Organization (WSO); Global Stroke Fact Sheet 2019. International Journal of Stroke. 2019; 14: 806–817.

[2] Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of Stroke in Europe. Stroke. 2020; 51: 2418–2427.
[3] Kim J, Thayabaranathan T, Donnan GA, Howard G, Howard VJ, Rothwell PM, et al. Global Stroke Statistics 2019. International Journal of Stroke. 2020; 15: 819–838.

[4] Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. Annals of Translational Medicine. 2014; 2: 80.

[5] Tu J, Wang L, Wen H, Xu Y, Wang P. The association of different types of cerebral infarction with post-stroke depression and cognitive impairment. Medicine. 2018; 97: e10919.

[6] Ding M, Xu Y, Wang Y, Li P, Mao Y, Yu J, et al. Predictors of Cognitive Impairment after Stroke: a Prospective Stroke Cohort Study. Journal of Alzheimer’s Disease. 2019; 71: 1139–1151.

[7] Kwon HS, Lee D, Lee MH, Yu S, Lim J, Yu K, et al. Post-stroke cognitive impairment as an independent predictor of ischemic stroke recurrence: PICASSO sub-study. Journal of Neurology. 2020; 267: 688–693.

[8] Huang Y, Wang B, Zhang Y, Wang P, Zhang X. Efficacy and safety of human urinary kallidinogenase for acute ischemic stroke: a meta-analysis. Journal of International Medical Research. 2020; 48: 300060520943452.

[9] Han D, Chen X, Li D, Liu S, Lyu Y, Feng J. Human Urinary Kallidinogenase decreases recurrence risk and promotes good recovery. Brain and Behavior. 2018; 8: e01033.

[10] Wu D, Lyu Y, Zhong P, Liu F, Liu X. Human Urinary kallidinogenase promotes good recovery in ischemic stroke patients with level 3 hypertension. Brain and Behavior. 2017; 7: e00752.

[11] Wei Z, Lyu Y, Yang X, Chen X, Zhong P, Wu D. Therapeutic Values of Human Urinary Kallidinogenase on Cerebrovascular Diseases. Frontiers in Neurology. 2019; 9: 403.

[12] Mijailović MD, Pavlović A, Brainin M, Heiss W, Quinn TJ, Ihle-Hansen HB, et al. Post-stroke cognitive impairment - a comprehensive review. BMC Medicine. 2017; 15: 11.

[13] Pendlebury ST, Cuthbertson FC, Welch SJV, Mehta Z, Rothwell PM. Underestimation of Cognitive Impairment by Mini-Mental State Examination Versus the Montreal Cognitive Assessment in Patients with Transient Ischemic Attack and Stroke. Stroke. 2010; 41: 1290–1293.

[14] Ni J, Yao M, Wang LH, Yu M, Li RH, Zhao LH, et al. Human urinary kallidinogenase in acute ischemic stroke: A single-arm, multicenter, phase IV study (RESK study). CNS Neuroscience & Therapeutics. 2021; 27: 1493–1503.

[15] Obaid M, Flach C, Marshall I, D AWC, Douiri A. Long-Term Outcomes in Stroke Patients with Cognitive Impairment: A Population-Based Study. Geriatrics (Basel). 2020; 5: 32.

[16] Jia H, Li H, Liu Y, Liu C, Xue M. Elevated serum alkaline phosphatase as a predictor of cognitive impairment in patients with acute ischemic stroke: a retrospective cohort study. Archives of Gerontology and Geriatrics. 2020; 89: 101404.

[17] Chen H, Liu Y, Huang G, Zhu J, Feng W, He J. Association between vitamin D status and cognitive impairment in acute ischemic stroke patients: a prospective cohort study. Clinical Interventions in Aging. 2019; 13: 2503–2509.

[18] Qian S, Li R, Zhang C, Zhang R, Guo D, Bu X, et al. Plasma Endostatin Levels at Acute Phase of Ischemic Stroke are Associated with Post-Stroke Cognitive Impairment. Neurotoxicology Research. 2020; 37: 956–964.

[19] Chen L, Geng L, Chen J, Yan Y, Yang L, Zhao J, et al. Effects of Urinary Kallidinogenase on NIHSS score, mRS score, and fasting glucose levels in acute ischemic stroke patients with abnormal glucose metabolism: a prospective cohort study. Medicine. 2019; 98: e17008.

[20] Zhao Z, Xu Z, Liu T, Huang S, Huang H, Huang X. Human Urinary Kallidinogenase Reduces Lipopolysaccharide-Induced Neuroinflammation and Oxidative Stress in BV-2 Cells. Pain Research and Management. 2019; 2019: 1–6.

[21] Ma N, Zhao Z, Zhang N, Chen H. Intra-arterial human urinary kallidinogenase alleviates brain injury in rats with permanent middle cerebral artery occlusion through PI3K/AKT/FoxO1 signaling pathway. Brain Research. 2018; 1687: 129–136.

[22] Zhao L, Zhao Y, Wan Q, Zhang H. Urinary kallidinogenase for the treatment of cerebral arterial stenosis. Drug Design, Development and Therapy. 2016; 9: 5595–5600.

[23] Salgado JV, Souza FL, Salgado BJ. How to understand the association between cystatin C levels and cardiovascular disease: Imbalance, counterbalance, or consequence? Journal of Cardiology. 2014; 62: 331–335.

[24] Hojs Fabjan T, Penko M, Hojs R. Cystatin C, creatinine, estimated glomerular filtration, and long-term mortality in stroke patients. Renal Failure. 2014; 36: 81–86.

[25] Sundelof J, Sundström J, Hansson O, Eriksdotter-Jönhagen M, Giedraitis V, Larsson A, et al. Cystatin C levels are positively correlated with both Abeta42 and tau levels in cerebrospinal fluid in persons with Alzheimer’s disease, mild cognitive impairment, and healthy controls. Journal of Alzheimer’s Disease. 2010; 21: 471–478.

[26] Yaffe K, Lindquist K, Shlipak MG, Simonsick E, Fried L, Rosano C, et al. Cystatin C as a marker of cognitive function in elders: findings from the health ABC study. Annals of Neurology. 2008; 63: 798–802.

[27] Kono S, Adachi H, Enomoto M, Fukami A, Kumagai E, Nakamura S, et al. Impact of cystatin C and microalbuminuria on cognitive impairment in the population of community-dwelling Japanese. Atherosclerosis. 2018; 265: 71–77.

[28] Wang Y, Li W, Yang J, Zhang M, Tian C, Ma M, et al. Association between Cystatin C and the Risk of Ischemic Stroke: a Systematic Review and Meta-analysis. Journal of Molecular Neuroscience. 2019; 69: 444–449.

[29] Zeng Q, Huang Z, Wei L, Fang J, Lin K. Correlations of serum cystatin C level and gene polymorphism with vascular cognitive impairment after acute cerebral infarction. Neurological Sciences. 2019; 40: 1049–1054.

[30] Turk V, Stoka V, Turk D. Cystatins: Biochemical and structural properties, and medical relevance. Frontiers in Bioscience. 2008; 13: 5406–5420.