Original Article

Glomerular Filtration Rate is Associated with Hemorrhagic Transformation in Acute Ischemic Stroke Patients without Thrombolytic Therapy

Ming-Su Liu[1,2], Yan Liao[3], Guang-Qin Li[1,2]

[1]Department of Neurology, First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
[2]Chongqing Key Laboratory of Neurobiology, Chongqing 400016, China
[3]Department of Neurology, Chengdu 363 Hospital of Southwest Medical University, Chengdu, Sichuan 610000, China

Abstract

Background: Whether there is a relationship between glomerular filtration rate (GFR) and hemorrhagic transformation (HT) after acute ischemic stroke (AIS) is still under debate. The aim of our study was to determine whether the GFR level is a predictor of HT in AIS patients without thrombolytic therapy (TT).

Methods: Consecutive AIS patients without TT were included in this prospective study from January 2014 to December 2016 in the First Affiliated Hospital of Chongqing Medical University. We divided them into two groups (HT and non-HT group) and meticulously collected baseline characteristics and laboratory and imaging data of interested individuals. Multivariate regression analysis was performed to assess the correlation between GFR and HT in stroke patients without TT.

Results: Among 426 consecutive patients, 74 (17.3%) presented HT (mean age: 65 ± 12 years, number of male patients: 47) on the follow-up scans. In multivariate regression analysis, HT was significantly associated with low GFR (odds ratio [*OR*] = 3.708, confidence interval [*CI*] = 1.326–10.693, *P* = 0.013), atrial fibrillation (AF; *OR* = 2.444, *CI* = 1.087–5.356, *P* = 0.027), large cerebral infarction (*OR* = 2.583, *CI* = 1.236–5.262, *P* = 0.010), and hypoalbuminemia (HA; *OR* = 4.814, *CI* = 1.054–22.153, *P* = 0.037) for AIS patients without TT.

Conclusions: The present study strongly showed that lower GFR is an independently predictor of HT; in addition, large infarct volume, AF, and HA are also important risks of HT for AIS patients without TT, which offered a practical information that risk factors should be paid attention or eliminated to prevent HT for stroke patients though the level of evidence seems to be unstable.

Key words: Glomerular Filtration Rate; Hemorrhagic Transformation; Nonthrombolytic Treatment; Stroke

Introduction

Acute ischemic stroke (AIS) is one of the leading causes of mortality and severe disability worldwide.[1,2] Hemorrhagic transformation (HT), a frequent complication of AIS, may be a natural evolutional consequence in all infarcts to some degree[3,4] and up to 40% or even 43% of patients with ischemic stroke.[5,6] HT is related to higher mortality, early neurological deterioration, and worse long-term functional outcome, not only for patients with symptomatic HT (sHT)[7,8] but also for those with asymptomatic HT (aHT).[9,10] The acquisition of HT is more important social concern when interventional management (intravenous or intra-arterial thrombolysis and endovascular therapy) are increasingly used due to which may increase recanalization rate, but at the same time increased the risk of HT.[11] Therefore, identifying some risk factors predisposing to HT may lead to new preventive strategies. The incidence of kidney dysfunction is higher in stroke patients and, in turn, kidney damage is an important predictor of mortality and all devastating vascular events in patients with AIS.[12,13] Some studies reported that kidney dysfunction is a risk factor for ischemic stroke;[14,15]

Address for correspondence: Dr. Guang-Qin Li, Department of Neurology, First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
E-Mail: liguangqin@tom.com

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.235873

Received: 28-02-2018 **Edited by:** Li-Shao Guo
How to cite this article: Liu MS, Liao Y, Li GQ. Glomerular Filtration Rate is Associated with Hemorrhagic Transformation in Acute Ischemic Stroke Patients without Thrombolytic Therapy. Chin Med J 2018;131:1639-44.

meanwhile, hemorrhage stroke was significantly associated with kidney dysfunction in some other studies.[16,17] Whether there was an association between kidney dysfunction and HT in AIS patients is still under debate. Some studies[18,19] showed a strongly negative association between glomerular filtration rate (GFR) and HT after ischemic stroke, while Micozkadioglu *et al*. demonstrated that no significant relationship existed between GFR and HT after ischemic stroke.[20] The aim of our prospective study was to determine whether the GFR level is associated with HT in consecutive AIS patients without thrombolytic therapy (TT) so as to eliminate the effect of thrombolysis, as a leading confounding factor for HT.

Methods

Ethical approval

The study was conducted in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the *Declaration of Helsinki*. The Ethics Committee of the First Affiliated Hospital of Chongqing Medical University approved the study, and all patients signed informed consent.

Study population

We analyzed consecutive patients admitted to the First Affiliated Hospital of Chongqing Medical University who were diagnosed as AIS[21] without TT between January 2014 and December 2016 in this prospective study. Patients who did not undergo repeated computed tomography (CT) or magnetic resonance imaging (MRI) during hospital period, died, or discharged in 72 h and who had complicated bleeding tendency diseases were excluded.

Clinical and laboratory examinations

The clinical, laboratory, and imaging data were collected at admission. Diabetes mellitus (DM) was defined according to the following criteria: previous use of insulin or oral antihyperglycemic agent, fasting blooding glucose >7.0 mmol/L or postprandial blood glucose after 2 h >11.1 mmol/L, or glycosylated hemoglobin levels >6.5%.[22] Hypertension was defined as previous hypertension and taking antihypertensive medication, systolic blood pressure (BP) >140 mmHg (1 mmHg = 0.133 kPa), or diastolic BP >90 mmHg.[22] Atrial fibrillation (AF) was defined as prior AF history before stroke, long-term use of anticoagulant agent, and AF in admission indicated by electrocardiogram.[23] Large cerebral infarction was defined as infarction area is larger than 3 cm and involved main supply area from two large blood vessels of brain anatomical site main supply area.[24] A value of 30 g/L was used to discriminate patients with hypoalbuminemia (HA) from a normal serum albumin, because this degree of HA is associated with more significant clinical consequences and more optimal benefit from therapy.[25]

GFR was estimated using the Modification of Diet in Renal Disease method equation.[26] Identification of kidney damage was established based on the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation guidelines.[27]

HT was defined as secondary bleeding in infarction area and it was categorized as hemorrhagic infarction and parenchymal hematoma.[28] HI was defined as a petechial infarction without space-occupying effect (subclassified as, HI1: small petechiae along the margins of the infarct; HI2: more confluent petechiae within the infarcted area), while PH was defined as hemorrhage with space-occupying effect (subclassified as, PH 1: hematoma in ≤30 of the infarcted area with some slight space-occupying effect; PH 2: dense hematoma in >30% of the infarct area with substantial space-occupying effect or any hemorrhagic lesion outside the infarct area.[29] In cases of more than one hemorrhagic lesion on imaging, the worst possible HT category was assumed.[30] All patients underwent a follow-up brain CT or MRI images during hospitalization and identification of HT based on the consensus reached by a neurologist and radiologist.

Statistical analysis

Statistical analyses were performed using the SPSS 22.2 software package (SPSS Inc., IBM, New York, USA). Continuous variables were analyzed by the Student's *t*-test, and the Chi-squared or Fisher's exact test was used to analyze categorical variables. Univariate tests were used to compare baseline characteristics between two groups. All variables were subjected to multivariate regression analysis to identify independently predictors for HT. A significant difference was taken at $P < 0.05$ and 95% confidence interval (*CI*) was given.

Results

Among 426 consecutive patients included in the analysis, 74 had HT (mean age: 65 ± 12 years, number of male patients: 47) on follow-up scans while 352 had no HT (mean age: 64 ± 11 years, male: 211). With regard to the HT prevalence, the present study revealed a similar HT rate (17.3%) with the previous studies.[18,20] The baseline characteristics including clinical, laboratory, and radiological variables of patients (e.g., body mass index [BMI], prior stroke history, DM, hypertension, AF, large cerebral infarction, serum urea nitrogen, albumin and creatinine, and estimated GFR) with and without HT are shown in Table 1.

In univariate analysis, HT was apparently associated with the presence of hypertension disease (odds ratio [*OR*] = 0.463, *CI* = 0.276–0.774, $P = 0.003$), AF (*OR* = 3.814, *CI* = 1.870–7.775, $P < 0.001$), large cerebral infarction (*OR* = 2.883, *CI* = 1.506–5.520, $P = 0.001$), serum albumin level (*OR* = 4.971, *CI* = 1.214–20.353, $P < 0.001$), and low GFR (a low calculated GFR with a value <60 ml·min^{-1}·1.73 m^{-2} was defined low GFR) based on the value of estimated GFR (*OR* = 1.993, *CI* = 0.994–3.995, $P = 0.048$); however, no significant difference existed in other variables such as age ($P = 0.502$), gender ($P = 0.431$), BMI ($P = 0.222$), prior stroke history ($P = 0.148$), DM ($P = 0.765$), serum urea nitrogen ($P = 0.475$), and serum creatinine ($P = 0.501$) between HT group and NHT group.

In multivariate regression analysis, low GFR (*OR* = 3.708, *CI* = 1.326–10.693, *P* = 0.013) independently predicted higher risk of HT for AIS patients who did not receive thrombolysis therapy; moreover, HT was also significantly associated with AF (*OR* = 2.444, *CI* = 1.087–5.356, *P* = 0.027), large cerebral infarction (*OR* = 2.583, *CI* = 1.236–5.262, *P* = 0.010), and HA (*OR* = 4.814, *CI* = 1.054–22.153, *P* = 0.037). In addition, HT was inversely associated with hypertension disease (*OR* = 0.472, *CI* = 0.268–0.816, *P* = 0.008). As expected, all of these indicated the robustness of the conclusions. The results of the individuals regarding HT based on the multivariate regression analyses are summarized in Table 2.

Discussion

AIS is a devastating disease with often followed by subsequent HT, which further aggravated the already devastating clinical condition. Many of available therapeutic strategies are limited by an increased risk of HT though regarding to emergent management of AIS tremendous advances has been made. After onset of AIS, the reduction in ATP and Na^+/K^+-ATPase activation could lead to a variety of metabolic derangement and a complex infarct region by oxidative stress, excitotoxicity, necrosis, apoptosis, and matrix proteolysis,[31] which collectively lead to the breakdown of the blood-brain barrier (BBB), and at the same time, a neuroinflammatory response also further perturbs homeostasis and cerebrovascular anatomy.[32,33] The consequent breakdown of BBB predisposes to HT when the ischemic issue obtains reperfusion eventually.[34] Some studies showed that the degree of anatomical and physiological disruption greatly depended on the duration of ischemia,[35] which is also consistent with the mechanisms that HT is associated with increased vascular permeability within 72 h after onset[18] while another one is spontaneous restoration of blood circulation in the capillary bed during

Table 1: Baseline characteristics of stroke patients with and without HT

Variables	HT (*n* = 74)	NHT (*n* = 352)	*OR* (95% *CI*)	*P*
Age (years)	65.69 ± 12.79	64.61 ± 11.58		0.502
Male, *n* (%)	48 (64.9)	211 (59.9)	1.232 (0.731–2.081)	0.431
BMI (kg/m^2)	23.61 ± 3.06	23.07 ± 3.26		0.222
Diabetes mellitus, *n* (%)	14 (18.9)	72 (20.5)	0.907 (0.480–1.715)	0.765
Hypertension, *n* (%)	28 (37.8)	200 (56.8)	0.463 (0.276–0.774)	0.003*
Atrial fibrillation, *n* (%)	15 (20.3)	22 (6.3)	3.814 (1.870–7.775)	<0.001*
Large infarct volume, *n* (%)	17 (23.0)	33 (9.4)	2.883 (1.506–5.520)	0.001*
Prior stroke history, *n* (%)	7 (9.5)	18 (5.1)	1.939 (0.779–4.824)	0.148
GFR, *n* (%)				
<60 ml·min^{-1}·1.73 m^{-2}	13 (17.6)	34 (9.7)	1.993 (0.994–3.995)	0.048*
≥60 ml·min^{-1}·1.73 m^{-2}	61 (82.4)	318 (90.3)		
Serum creatinine, *n* (%)				
≥81 μmol/L	22 (29.7)	120 (34.1)	0.818 (0.474–1.411)	0.501
<81 μmol/L	52 (70.3)	232 (65.9)		
Serum urea nitrogen, *n* (%)				
≥8.8 mmol/L	8 (10.8)	29 (8.2)	1.350 (0.591–3.085)	0.475
<8.8 mmol/L	66 (89.2)	323 (91.8)		
Hypoalbuminemia, *n* (%)	4 (5.4)	4 (1.1)	4.971 (1.214–20.353)	<0.001*

*P<0.05. Date are presented as number of patients or means ± SD. HT: Hemorrhage transformation; NHT: No hemorrhage transformation; *OR*: Odds ratio; GFR: Glomerular filtration rate; BMI: Body mass index; *CI*: Confidence interval; SD: Standard deviation.

Table 2: Multiple logistic regression analysis between factors and HT in AIS patients without TT

Variables	*B*	*OR* (95% *CI*)	*P*
Aged (age ≥80 years)	−1.485	0.841 (0.305–2.031)	0.716
Obesity (BMI ≥28 kg/m^2)	0.370	1.447 (0.564–3.382)	0.414
Diabetes	−0.113	0.893 (0.432–1.742)	0.749
Hypertension	−0.752	0.472 (0.268–0.816)	0.008*
Atrial fibrillation	0.894	2.444 (1.087–5.356)	0.027*
Large infarct volume	0.950	2.583 (1.236–5.262)	0.010*
Prior stroke history	0.931	1.478 (0.513–3.837)	0.441
Low GFR (<60 ml·min^{-1}·1.73 m^{-2})	1.310	3.708 (1.326–10.693)	0.013*
High serum creatinine (≥81 μmol/L)	−0.730	0.482 (0.208–1.009)	0.067
High BUN (≥8.8 mmol/L)	0.090	1.094 (0.409–2.649)	0.849
Hypoalbuminemia	1.571	4.814 (1.054–22.153)	0.037*

*P<0.05. *OR*: Odds ratio; GFR: Glomerular filtration rate; BUN: Blood urea nitrogen; BMI: Body mass index; *CI*: Confidence interval; TT: Thrombolytic therapy; AIS: Acute ischemic stroke; HT: Hemorrhage transformation.

the first 2 weeks.[18,35] Therefore, it is necessary to identify risk factors or precipitants for HT aimed to take feasible measures to prevent hemorrhage in setting of AIS when the mechanisms of HT are mainly clear. Importantly, it has appeared that matrix metalloproteinase-9 activity,[36] AF,[18] large infarct volume,[17,37] hypertension,[38] albuminuria,[39] hyperglycemia,[40] and thrombolysis therapy[41,42] were predictors for HT. Unfortunately, little data were existed to confirm whether the renal insufficient may contribute to HT.

The present study demonstrated that low GFR was associated with increased risk of HT for AIS patients who did not receive thrombolysis therapy, which is in line with the result of two previous studies,[18,19] but slightly discriminating with the study of Micozkadioglu *et al*.[20] Nevertheless, it is worth mentioning that previous data possessed some unsolved restriction. In Lee *et al*.'s[18] study, the most disadvantage is the inclusion of some patients with thrombolysis. As in the previous study,[11] TT was revealed as the leading risk of HT in AIS patients. The actual correlation between GFR and HT could be confounded by TT due to TT are more strongly responsible for the increased HT risk rather than impaired renal function.[18] Actually, the correlation between levels of GFR and HT was more evident in patients without TT. In addition, relatively small-scale size and inclusion of individuals with thrombolysis were obviously limitations for Marsh *et al*.'s[19] study, which are also particularly prone to lead to bias. Regarding the different results of Micozkadioglu *et al*.'s study, it was attributed to only conducting the univariate analysis for variable of interest. They did not performed multivariate regression analysis to eliminate the confounding factors for GFR variable (e.g., carotid artery disease,[20] serum calcium,[20] AF,[18] large infarct volume,[17,37] hypertension,[38] and albuminuria[39]), which are powerful impact factors on HT for AIS patients and could cover or even inverse the actually correlation between GFR and HT. In our study, the inclusion of patients without thrombolysis only represents the considerable strengths, and multivariate regression analysis was also performed to ensure the robustness of the conclusions.

It has been well accepted that GFR is the best measure of overall kidney function for disease and the GFR <60 ml·min^{-1}·1.73 m^{-2} means a half or more loss of renal function. What proposed mechanisms could explain the association between renal insufficient and HT? It has been appeared that renal insufficient has a bleeding tendency due to platelet dysfunction and induces abnormal platelet–vessel wall interaction.[43] Renal dysfunction was related to endothelial dysfunction and inflammation, which could accelerate vascular activation and leukocyte infiltration in the process of hemorrhage converting.[18] A few studies showed that renal dysfunction could increase the hemorrhage microangiopathy and lead to brain hemorrhage at last when renal impairment is related to cerebral small-vessel disease. It may contribute to the lack of nitric oxide (NO) when NO has a function in adjusting microcirculation and BBB.[44,45] Renal insufficiency increases the risk of cardioembolic infarction partly through the induction of AF because AF increased with decline in renal function.[46] In addition, AF and large infarct volume induced by cardioembolic infarction were also associated with HT.[17,37] Furthermore, the disturbances in the coagulation system coupled with an altered response to medication may be a predictor of HT in CKD patients.[47] The correlation between serum urea nitrogen and creatinine and HT was not found in the study. This raises the possibility that serum urea nitrogen and creatinine are affected by a lot of extrarenal factors such as the excess production from high-protein diet, gastrointestinal bleeding, trauma, infection, fever, and malnutrition, as a result, leading to an obviously increased serum urea. In addition, the level of serum creatinine will also increase at situations of taking drugs (e.g., methoxamine and cimetidine) or other nonrenal disease (e.g., hyperthyroidism and acromegaly) without the rise of GFR.[48] To our knowledge, a single measurement of serum creatinine is not an ideal measure of renal function, not as sensitive and accurate as the GFR, which could lead to cover the actual correlation between renal function and HT.[8] Thus, little data existed on the relation of HT and serum urea nitrogen and creatinine to now and further investigations are still warranted.

In line with the previous studies,[17,18,37,40,49] our study also disclosed that large cerebral infarction, AF, and HA are associated with increased risk of HT for AIS patients. It will appear massive cerebral edema and severe BBB damage when patients exist large infarction volume, which could accelerate microvascular injury, facilitate HT rate, and expand hemorrhage size after reperfusion.[50] The presence of AF is associated with greater volumes of more severe hypoperfusion, most likely attributable to poorer collateral circulation quality in AIS patients. This results in the increased infarct growth, higher final infarct volume, and more frequent severe HT.[49] The upper of HT in HA patients may attributed to the absence of effect from albumin. Because albumin has been proved to be markedly neuroprotective in AIS and traumatic brain injury based on the theories of directly protecting both parenchymal and vascular elements of the brain, maintaining microvascular integrity, diminishing brain edema, inhibiting endothelial cell apoptosis, transporting fatty acids to the post-stroke brain, and exerting antioxidant effects.[51-53] In addition, our finding is consistent with new discovery by recent study[51] that low level of serum albumin within 24 h was an independent predictor of HT.

Although hypertension has been thought to predict subsequent HT after AIS in some studies,[38,54] our data did not support the hypothesis that hypertension is a risk of increasing HT, but a protective factor for HT in nonthrombolysis patients, which seemed to violate the possible mechanism that the increased hydrodynamic pressure would provide an increased driving force as blood extravasates into the brain after a more abrupt reperfusion profile on clot lysis.[28] However, lower recanalization rate and reperfusion often occur in nonthrombolytic patients and

therefore HT occurs rare when blood flow did not restore even in high-blood pressure condition. On the contrary, mild increased blood pressure facilitated collateral circulation and improved functional outcome in the unrecanalyzed patients; furthermore, the lower blood pressure may result in additional cerebral ischemia, especially in unrecanalyzed patients.[55] Unfortunately, the underlying reason of correlation between HT and hypertension in patients without thrombolysis is poorly understood; therefore, more studies are required to elucidate the potential mechanism.

This study systematically determines the correlation between GFR and HT through sufficiently selected patients without TT in order to completely control the largest confounding factor of thrombolysis for the analysis of actual correlation between GFR and HT. However, some limitations should also be mentioned before generalizing the present findings. First, this is a prospective analysis and it is difficult to account for some unmeasured variables that likely influenced HT such as smoking history and serum lipid. Second, the study is single center-based sample size, allowing the possibility of type II errors. Third, we investigated the total HT rather than sHT that associated with worse functional outcome due to small sample size. Nevertheless, HT itself has an influence on worse outcome even aHT was also associated with poor outcome after AIS.[7-10] Thus, our conclusion should also be reached with caution before further large-scale research with addressing the aforementioned limitations confirmed our findings.

In conclusion, the present study strongly showed that lower GFR is an independent predictor of HT, and in addition, large infarct volume, AF, and HA are also important risks of HT for AIS patients without TT, which offered a practical information that risk factors should be paid attention (e.g., large infarct volume and AF), improved (e.g., GFR), or eliminated (e.g., HA) to prevent HT for stroke patients though the level of evidence seems to be unstable. However, further large-scale researches are urgently needed to confirm our conclusions and determined their actual potential.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: A review. J Stroke 2017;19:286-94. doi: 10.5853/jos.2017.00234.
2. Hong JM, Lee JS, Song HJ, Jeong HS, Choi HA, Lee K, *et al.* Therapeutic hypothermia after recanalization in patients with acute ischemic stroke. Stroke 2014;45:134-40. doi: 10.1161/STROKEAHA.113.003143.
3. Nour M, Scalzo F, Liebeskind DS. Ischemia-reperfusion injury in stroke. Interv Neurol 2013;1:185-99. doi: 10.1159/000353125.
4. Jickling GC, Liu D, Stamova B, Ander BP, Zhan X, Lu A, *et al.* Hemorrhagic transformation after ischemic stroke in animals and humans. J Cereb Blood Flow Metab 2014;34:185-99. doi: 10.1038/jcbfm.2013.203.
5. Lei C, Wu B, Liu M, Chen Y. Asymptomatic hemorrhagic transformation after acute ischemic stroke: Is it clinically innocuous? J Stroke Cerebrovasc Dis 2014;23:2767-72. doi: 10.1016/j.jstrokecerebrovasdis.
6. Guo Y, Yan S, Zhang S, Zhang X, Chen Q, Liu K, *et al.* Lower serum calcium level is associated with hemorrhagic transformation after thrombolysis. Stroke 2015;46:1359-61. doi: 10.1161/STROKEAHA.
7. Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, *et al.* Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2017;48:e343-61. doi: 10.1161/STR.0000000000000152.
8. Tu HT, Campbell BC, Christensen S, Desmond PM, De Silva DA, Parsons MW, *et al.* Worse stroke outcome in atrial fibrillation is explained by more severe hypoperfusion, infarct growth, and hemorrhagic transformation. Int J Stroke 2015;10:534-40. doi: 10.1111/ijs.12007.
9. Dzialowski I, Pexman JH, Barber PA, Demchuk AM, Buchan AM, Hill MD, *et al.* Asymptomatic hemorrhage after thrombolysis may not be benign: Prognosis by hemorrhage type in the Canadian Alteplase for Stroke Effectiveness Study Registry. Stroke 2007;38:75-9. doi: 10.1161/01.STR.0000251644.76546.62.
10. Park JH, Ko Y, Kim WJ, Jang MS, Yang MH, Han MK, *et al.* Is asymptomatic hemorrhagic transformation really innocuous? Neurology 2012;78:421-6. doi: 10.1212/WNL.0b013e318245d22c.
11. Tsivgoulis G, Katsanos AH, Kadlecová P, Czlonkowska A, Kobayashi A, Brozman M, *et al.* Intravenous thrombolysis for patients with in-hospital stroke onset: Propensity-matched analysis from the safe implementation of treatments in stroke-east registry. Eur J Neurol 2017;24:1493-8. doi: 10.1111/ene.13450.
12. Yahalom G, Schwartz R, Schwammenthal Y, Merzeliak O, Toashi M, Orion D, *et al.* Chronic kidney disease and clinical outcome in patients with acute stroke. Stroke 2009;40:1296-303. doi: 10.1161/STROKEAHA.108.520882.
13. Hayden D, McCarthy C, Akijian L, Callaly E, Ní Chróinín D, Horgan G, *et al.* Renal dysfunction and chronic kidney disease in ischemic stroke and transient ischemic attack: A population-based study. Int J Stroke 2017;12:761-9. doi: 10.1177/1747493017701148.
14. Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, *et al.* Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: The Suita study. Stroke 2009;40:2674-9. doi: 10.1161/STROKEAHA.109.550707.
15. Laible M, Horstmann S, Rizos T, Rauch G, Zorn M, Veltkamp R, *et al.* Prevalence of renal dysfunction in ischaemic stroke and transient ischaemic attack patients with or without atrial fibrillation. Eur J Neurol 2015;22:64-9, e4-5. doi: 10.1111/ene.12528.
16. Molshatzki N, Orion D, Tsabari R, Schwammenthal Y, Merzeliak O, Toashi M, *et al.* Chronic kidney disease in patients with acute intracerebral hemorrhage: Association with large hematoma volume and poor outcome. Cerebrovasc Dis 2011;31:271-7. doi: 10.1159/000322155.
17. Holzmann MJ, Aastveit A, Hammar N, Jungner I, Walldius G, Holme I, *et al.* Renal dysfunction increases the risk of ischemic and hemorrhagic stroke in the general population. Ann Med 2012;44:607-15. doi: 10.3109/07853890.2011.582136.
18. Lee JG, Lee KB, Jang IM, Roh H, Ahn MY, Woo HY, *et al.* Low glomerular filtration rate increases hemorrhagic transformation in acute ischemic stroke. Cerebrovasc Dis 2013;35:53-9. doi: 10.1159/000345087.
19. Marsh EB, Llinas RH, Hillis AE, Gottesman RF. Hemorrhagic transformation in patients with acute ischaemic stroke and an indication for anticoagulation. Eur J Neurol 2013;20:962-7. doi: 10.1111/ene.12126.
20. Micozkadioglu H, Ozelsancak R, Giray S, Arlier Z. CKD is associated with recurrent ischemia but not with hemorrhagic transformation in acute ischemic stroke patients. Ren Fail 2014;36:217-21. doi: 10.3109/0886022X.2013.846794.
21. Ahmed N, Lees KR, Ringleb PA, Bladin C, Collas D, Toni D, *et al.*

Outcome after stroke thrombolysis in patients >80 years treated within 3 hours vs. >3-4.5 hours. Neurology 2017;89:1561-8. doi: 10.1212/WNL.0000000000004499.
22. Hao Z, Wu B, Lin S, Kong FY, Tao WD, Wang DR, *et al.* Association between renal function and clinical outcome in patients with acute stroke. Eur Neurol 2010;63:237-42. doi: 10.1159/000285165.
23. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, *et al.* Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Europace 2010;12:1360-420. doi: 10.1093/europace/euq350.
24. Nitta N, Nozaki K. Treatment for large cerebral infarction: Past, present, and future. World Neurosurg 2015;83:483-5. doi: 10.1016/j.wneu.2014.08.054.
25. Porrett PM, Baranov E, ter Horst M. Serum hypoalbuminemia predicts late mortality on the liver transplant waiting list. Transplantation 2015;99:158-63. doi: 10.1097/TP.0000000000000299.
26. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, *et al.* Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006;17:2937-44. doi: 10.1681/ASN.2006040368.
27. Uhlig K, Eckardt KU. A decade after the KDOQI CKD guidelines: Impact on CKD guidelines. Am J Kidney Dis 2012;60:705-6. doi: 10.1053/j.ajkd.2012.08.021.
28. Liu K, Yan S, Zhang S, Guo Y, Lou M. Systolic blood pressure variability is associated with severe hemorrhagic transformation in the early stage after thrombolysis. Transl Stroke Res 2016;7:186-91. doi: 10.1007/s12975-016-0458-6.
29. Yu S, Liebeskind DS, Dua S, Wilhalme H, Elashoff D, Qiao XJ, *et al.* Postischemic hyperperfusion on arterial spin labeled perfusion MRI is linked to hemorrhagic transformation in stroke. J Cereb Blood Flow Metab 2015;35:630-7. doi: 10.1038/jcbfm.2014.238.
30. Kanazawa M, Takahashi T, Nishizawa M, Shimohata T. Therapeutic strategies to attenuate hemorrhagic transformation after tissue plasminogen activator treatment for acute ischemic stroke. J Atheroscler Thromb 2017;24:240-53. doi: 10.5551/jat.RV16006.
31. Fann DY, Ng GY, Poh L, Arumugam TV. Positive effects of intermittent fasting in ischemic stroke. Exp Gerontol 2017;89:93-102. doi: 10.1016/j.exger.2017.01.014.
32. Wang W, Li M, Chen Q, Wang J. Hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke: Mechanisms, models, and biomarkers. Mol Neurobiol 2015;52:1572-9. doi: 10.1007/s12035-014-8952-x.
33. Sifat AE, Vaidya B, Abbruscato TJ. Blood-brain barrier protection as a therapeutic strategy for acute ischemic stroke. AAPS J 2017;19:957-72. doi: 10.1208/s12248-017-0091-7.
34. Horsch AD, Dankbaar JW, van der Graaf Y, Niesten JM, van Seeters T, van der Schaaf IC, *et al.* Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke. Neuroradiology 2015;57:1219-25. doi: 10.1007/s00234-015-1577-6.
35. Li W, Qu Z, Prakash R, Chung C, Ma H, Hoda MN, *et al.* Comparative analysis of the neurovascular injury and functional outcomes in experimental stroke models in diabetic Goto-Kakizaki rats. Brain Res 2013;1541:106-14. doi: 10.1016/j.brainres.2013.10.021.
36. Ramos-Fernandez M, Bellolio MF, Stead LG. Matrix metalloproteinase-9 as a marker for acute ischemic stroke: A systematic review. J Stroke Cerebrovasc Dis 2011;20:47-54. doi: 10.1016/j.jstrokecerebrovasdis.2009.10.008.
37. Kerenyi L, Kardos L, Szász J, Szatmári S, Bereczki D, Hegedüs K, *et al.* Factors influencing hemorrhagic transformation in ischemic stroke: A clinicopathological comparison. Eur J Neurol 2006;13:1251-5. doi: 10.1111/j.1468-1331.2006.01489.x.
38. Ko Y, Park JH, Yang MH, Ko SB, Han MK, Oh CW, *et al.* The significance of blood pressure variability for the development of hemorrhagic transformation in acute ischemic stroke. Stroke 2010;41:2512-8. doi: 10.1161/STROKEAHA.110.595561.
39. Rodríguez-Yáñez M, Castellanos M, Blanco M, Millán M, Nombela F, Sobrino T, *et al.* Micro – And macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke. Neurology 2006;67:1172-7. doi: 10.1212/01.wnl.0000238353.89194.08.
40. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, *et al.* Early hemorrhagic transformation of brain infarction: Rate, predictive factors, and influence on clinical outcome: Results of a prospective multicenter study. Stroke 2008;39:2249-56. doi: 10.1161/STROKEAHA.107.510321.
41. Acampa M, Camarri S, Lazzerini PE, Guideri F, Tassi R, Valenti R, *et al.* Increased arterial stiffness is an independent risk factor for hemorrhagic transformation in ischemic stroke undergoing thrombolysis. Int J Cardiol 2017;243:466-70. doi: 10.1016/j.ijcard.2017.03.129.
42. Gill D, Baheerathan A, Aravind A, Veltkamp R, Kar A. Severe hemorrhagic transformation after thrombolysis for acute ischemic stroke prevents early neurological improvement. J Stroke Cerebrovasc Dis 2016;25:2232-6. doi: 10.1016/j.jstrokecerebrovasdis.2016.04.020.
43. Sohal AS, Gangji AS, Crowther MA, Treleaven D. Uremic bleeding: Pathophysiology and clinical risk factors. Thromb Res 2006;118:417-22. doi: 10.1016/j.thromres.2005.03.032.
44. Cho AH, Lee SB, Han SJ, Shon YM, Yang DW, Kim BS, *et al.* Impaired kidney function and cerebral microbleeds in patients with acute ischemic stroke. Neurology 2009;73:1645-8. doi: 10.1212/WNL.0b013e3181c1defa.
45. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci 2004;5:347-60. doi: 10.1038/nrn1387.
46. Lau YC, Xiong Q, Blann AD, Lip GY. Relationship between renal function and circulating microparticles, soluble P-selectin and E-selectin levels in atrial fibrillation. J Thromb Thrombolysis 2017;43:18-23. doi: 10.1007/s11239-016-1427-3.
47. Berger PB, Best PJ, Topol EJ, White J, DiBattiste PM, Chan AW, *et al.* The relation of renal function to ischemic and bleeding outcomes with 2 different glycoprotein IIb/IIIa inhibitors: The do Tirofiban and ReoPro give similar efficacy outcome (TARGET) trial. Am Heart J 2005;149:869-75. doi: 10.1016/j.ahj.2004.12.002.
48. Tütüncü S, Ziegler AM, Scheitz JF, Slowinski T, Rocco A, Endres M, *et al.* Severe renal impairment is associated with symptomatic intracerebral hemorrhage after thrombolysis for ischemic stroke. Stroke 2013;44:3217-9. doi: 10.1161/STROKEAHA.113.002859.
49. Marsh EB, Gottesman RF, Hillis AE, Maygers J, Lawrence E, Llinas RH, *et al.* Predicting symptomatic intracerebral hemorrhage versus lacunar disease in patients with longstanding hypertension. Stroke 2014;45:1679-83. doi: 10.1161/STROKEAHA.114.005331.
50. Lee M, Saver JL, Alger JR, Hao Q, Starkman S, Ali LK, *et al.* Blood-brain barrier permeability derangements in posterior circulation ischemic stroke: Frequency and relation to hemorrhagic transformation. J Neurol Sci 2012;313:142-6. doi: 10.1016/j.jns.2011.08.048.
51. Che R, Huang X, Zhao W, Jiang F, Wu L, Zhang Z, *et al.* Low serum albumin level as a predictor of hemorrhage transformation after intravenous thrombolysis in ischemic stroke patients. Sci Rep 2017;7:7776. doi: 10.1038/s41598-017-06802-y.
52. Belayev L, Pinard E, Nallet H, Seylaz J, Liu Y, Riyamongkol P, *et al.* Albumin therapy of transient focal cerebral ischemia: *In vivo* analysis of dynamic microvascular responses. Stroke 2002;33:1077-84. doi: 10.1161/hs0402.105555.
53. Belayev L, Saul I, Busto R, Danielyan K, Vigdorchik A, Khoutorova L, *et al.* Albumin treatment reduces neurological deficit and protects blood-brain barrier integrity after acute intracortical hematoma in the rat. Stroke 2005;36:326-31. doi: 10.1161/01.STR.0000152949.31366.3d.
54. Lyden PD. Hemorrhagic transformation during thrombolytic therapy and reperfusion: Effects of age, blood pressure, and matrix metalloproteinases. J Stroke Cerebrovasc Dis 2013;22:532-8. doi: 10.1016/j.jstrokecerebrovasdis.2013.02.001.
55. Martins AI, Sargento-Freitas J, Silva F, Jesus-Ribeiro J, Correia I, Gomes JP, *et al.* Recanalization modulates association between blood pressure and functional outcome in acute ischemic stroke. Stroke 2016;47:1571-6. doi: 10.1161/STROKEAHA.115.012544.

肾小球滤过率与非溶栓性急性缺血性卒中患者出血转化的发生有关

摘要

背景：肾小球滤过率是否与急性缺血性卒中患者出血转化的发生存在关联至今尚不清楚，本研究的目的是探究肾小球滤过率水平是否是非溶栓性急性缺血性卒中患者出血转化发生的预测因素。

方法：本研究回顾性分析2014年1月至2016年12月重庆医科大学第一附属医院收治的非溶栓性缺血性卒中患者。我们将纳入人群分为两组（出血转化组与非出血转化组），并详细的收集其基本信息、实验室指标及影像学资料。采用多元回归模型分析肾小球滤过率与非溶栓性缺血性卒中患者出血性转化发生的关系。

结果：426例纳入的患者中共74例（17.3%）在影像学随访中出现出血转化（平均年龄65±12岁，男性47例）。在多元回归分析中非溶栓性缺血性卒中患者出血转化与低肾小球滤过率（OR=3.708, CI=1.326~10.693，*P*=0.013），房颤（OR=2.444, CI=1.087~5.356，*P* =0.027），大面积脑梗死（OR=2.583, CI=1.236~5.262，*P* =0.010）及低蛋白血症（OR=4.814, CI=1.054~22.153，*P* =0.037）存在显著相关性。

结论：本研究显示低肾小球滤过率是出血转化的独立预测因素，另外大面积脑梗死、房颤及低蛋白血症也均是非溶栓性缺血性卒中患者出血转化的重要危险因素。尽管本研究证据水平略显不高，但提出的一些有关于出血转化应当注意和消除的危险因素为预防卒中患者血转化的发生提供了实用的临床依据。