Gamma-glutamyl Transferase Levels are Associated with the Occurrence of Post-stroke Cognitive Impairment: A Multicenter Cohort Study

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Abstract

**Background:** Gamma-glutamyl transferase (GGT) can maintain the physiological concentration of glutathione in cells, and protect them from oxidative stress-induced damage. However, its role in post-stroke cognitive impairment (PSCI) remains unknown. Here, we explored the impact of serum biomarker-GGT on PSCI.

**Methods:** We conducted a prospective, multicenter cohort study. 1, 957 participants who suffered a stroke and measured baseline GGT were enrolled from the Impairment of Cognition and Sleep (ICONS) study of the China National Stroke Registry-3 (CNSR-3). They were categorized into four groups according to the quartiles of baseline GGT levels. Cognitive function was assessed by using the Montreal Cognitive Assessment (MoCA) approach. The multiple logistic regression models were performed to evaluate the relationship between GGT and PSCI at 3 months follow-up.

**Results:** Among 1,957 participants, 671 (34.29%) patients suffered PSCI at 3 months follow-up. The highest GGT level quartile group exhibited a lower risk of PSCI in the fully adjusted model [OR (95% CI): 0.69 (0.50-0.96)], relative to the lowest group. Moreover, incorporation of GGT to the conventional model resulted in a slight improvement in PSCI outcomes after 3 months (NRI: 12.00%; IDI: 0.30%).

**Conclusions:** Our findings demonstrated that serum GGT level was inversely associated with the risk of PSCI, with extremely low levels acting as a risk factor for PSCI.

Background

Stroke is a leading cause of disabilities and mortalities, affecting one in every four people worldwide\(^\text{[1-3]}\). Cognitive impairment, which is a common stroke complication, has attracted numerous research attention. Approximately 50% of stroke survivors reportedly manifested cognitive dysfunction, 6 months after stroke, and were more likely to develop dementia within the following 3 years, which significantly affected their quality of life\(^\text{[4-5]}\). Moreover, a community-based epidemiological survey in China reported that incidences of post-stroke cognitive impairment (PSCI) and dementia were 56.6% and 23.2%, respectively, 3 months after stroke\(^\text{[6]}\). However, diagnosis and prognosis of PSCI remain a challenge\(^\text{[7-8]}\).

Gamma-glutamyl transferase (GGT) is a serum metabolic biomarker that was mainly used to assess liver function\(^\text{[9-10]}\). Recent studies demonstrated GGT can maintain the physiological concentration of glutathione in cells and reflect the balance state of oxidation-antioxidant in the body\(^\text{[11-12]}\). A study found GGT was related to decreased cognitive function in diabetics\(^\text{[13-14]}\). In addition, a retrospective study in Korea found that GGT variability was also associated with Alzheimer's disease, suggesting that concentration of serum GGT may predict cognitive decline\(^\text{[15]}\). Similarly, studies observed serum metabolites including GGT were differentially expressed in patients with PSCI and post-stroke non-cognitive impairment\(^\text{[16-17]}\), suggesting GGT may affect PSCI occurrence.

However, limited data observed the role of GGT in PSCI, and to date, only a handful of models have been constructed for predicting PSCI. Notably, these models are mainly constructed based on cerebrovascular risk factors, and the effect of non-cerebrovascular risk factors on PSCI remains unclear. Thus, the relationship between GGT and PSCI needs further study. In addition, expert consensus states that the diagnosis of PSCI usually refers to cognitive dysfunction after a stroke event in 6 months, and most patients suffered cognitive impairment in 3 months after stroke\(^\text{[4-6]}\). Therefore, we aimed to explore the association of serum biomarker-GGT with PSCI during 3 months follow-up. We present this study in accordance with the STROBE reporting checklist.

Methods

**Study population**
All participants were selected from the Impairment of Cognition and Sleep (ICONS) study of the China National Stroke Registry-3 (CNSR-3) from 2015 to 2018 [18]. ICONS is a large national, multi-center, and prospective cohort about 40 hospitals in China[19], which continuously recruits patients with acute ischemic stroke (AIS) and transient ischemic attack (TIA), with no history of cognitive disorder before stroke. Generally, stroke is diagnosed by symptoms, physical signs, scale evaluations, and neuroimages (magnetic resonance or brain computed tomography), according to the World Health Organization criteria [20–21].

Participants were recruited in this study if they: (i) were diagnosed with AIS or TIA and hospitalized from symptoms onset within 7 days; (ii) had their baseline GGT measured and completed standard cognitive function evaluation at 3 months follow-up; (iii) had no history of cognitive dysfunction; and (iv) had a Glasgow Coma Scale 15 points, and the muscle strength of handedness ≥ level 4 after Manual Muscle Testing. Eventually, a total of 1,957 participants were enrolled in our study.

The present study was performed in accordance with the guidelines described by the Helsinki Declaration and was approved by the Ethics Committees of Beijing Tiantan Hospital (No. KY2015-001-01). All participants signed a written informed consent prior to their inclusion in the study.

**Data Collection**

The protocol and the statistical analysis plan have been mentioned in previous studies [20–21]. All participants received a comprehensive and precise assessment on admission, including a collection of their demographic information (age, sex, body mass index, smoking, educational level, among others), and medical history (stroke, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, atrial fibrillation, heart failure, and fatty liver disease). In addition, they were subjected to a detailed physical examination, and several parameters including modified Rankin Scale, NIHSS score, ABCD² score, Glasgow Coma Scale, and Manual Muscle Testing. We also determined exposure to medications during hospitalization, and collected fast blood samples, for laboratory analysis of serum GGT, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol (TC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, effective glomerular filtration rate (eGFR), and serum uric acid (UA). These samples were collected in EDTA anticoagulation blood collection and serum-separation tubes within 24 hours of admission.

**Outcome Evaluation**

Clinical outcome is PSCI occurrence after 3 months follow-up. We applied the Montreal Cognitive Assessment (MoCA) approach to assess cognitive function and adopted a MoCA cut-off point of ≥23/30, which has previously been shown to have the best sensitivity and specificity for detecting PSCI in Chinese patients [6,22–25]. Baseline MOCA evaluation was performed by a certified neuropsychologist, while follow-up MoCA evaluation was performed by a neurologist who was blinded to the baseline assessment.

**Statistical Analysis**

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Participants who lost to follow-up were excluded from this study. Continuous variables were presented as median (interquartile range) and compared using the Kruskal–Wallis test. Categorical variables were expressed as numbers (proportions), then compared using the χ² or Fisher exact tests. Firstly, we categorized all recruited participants into four groups according to baseline GGT quartiles, then collected their characteristics at admission. Thereafter, we analyzed the association between GGT levels and PSCI by using multivariable logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) after adjusting for confounding factors. In addition, since GGT is a metabolic index, many factors independent of cognitive status may affect it, notably liver problems. Thus, potential confounders related to liver function are also taken into account. After that, restricted cubic spline analyses were used to address the association. Then we applied the C statistic, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) to evaluate the degree to which the
model predicted PSCI after the addition of GGT. We conducted the conventional model including age, sex, educational level, BMI, smoking, drinking, NIHSS score at admission, history of stroke, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, atrial fibrillation, and heart failure, and laboratory test of TC, TG, WBC, UA\[^{6,26-29}\]. Finally, we performed subgroup analysis, considering age, sex, body mass index, and alcohol drinking as interaction factors.

All analyses were two-sided, with data followed by P≤0.05 considered statistically significant.

**Results**

**Baseline characteristics**

Among 2,625 participants in the ICONS study, 1,957 participants who completed baseline GGT measurements and the 3-months follow-up were enrolled (Fig. 1). They were divided into four groups according to the quartile of GGT level, namely <17, 17~24, 24~37, and ≥37 U/L. A summary of baseline characteristics of the recruited participants are presented in Table 1, Supplementary Table 1. Analysis of these characteristics revealed a significant correlation with GGT levels: age, sex, educational level, smoking, alcohol drinking, body mass index (BMI), diabetes mellitus, hypoglycemic therapy, HDL, TG, TC, AST, ALT, UA, eGFR, albumin.

**Table 1**

| Baseline Characteristics for the enrolled participants based on their GGT quartile |
| Characteristic                        | Total | GGT level | P-value |
|--------------------------------------|-------|-----------|---------|
|                                      |       | Q1(<17.00) | Q2(17.00-24.00) | Q3(24.00-37.00) | Q4(≥37.00) |
| N, (%)                               | 1957  | 480       | 455     | 518     | 504     |
| Age, year, median (IQR)              | 62.00(53.00-69.00) | 64.00(58.00-72.00) | 63.00(55.00-70.00) | 61.00(53.00-68.00) | 57.50(52.00-65.00) |
| Male, n (%)                          | 1419(72.51) | 269(56.04) | 322(70.77) | 393(75.87) | 435(86.31) |
| Education level, n (%)               |       | <0.001    |         |         |         |
| College or above                     | 198(10.12) | 34(7.08)   | 40(8.79) | 63(12.16) | 61(12.10) |
| High school                          | 453(23.15) | 82(17.08)  | 111(24.40) | 139(26.83) | 121(24.01) |
| Middle school                        | 715(36.54) | 179(37.29) | 172(37.80) | 169(32.63) | 195(38.69) |
| Elementary or below                  | 509(26.01) | 166(34.58) | 115(25.27) | 128(24.71) | 100(19.84) |
| Not known                            | 82(4.19)  | 19(3.96)   | 17(3.74)  | 19(3.67)  | 27(5.36)  |
| BMI, kg/m², median (IQR)             | 24.82(23.03-26.85) | 24.50(22.29-26.40) | 24.57(22.86-26.67) | 24.91(23.44-27.06) | 25.25(23.53-27.33) |
| Current smoking, n (%)               | 691(35.31) | 132(27.50) | 137(30.11) | 195(37.64) | 227(45.04) |
| Current drinking, n (%)              | 357(18.24) | 37(7.71)   | 71(15.60) | 95(18.34) | 154(30.56) |
| Medical history, n (%)               |       | <0.001    |         |         |         |
| Stroke or TIA                        | 426(21.77) | 99(20.63)  | 110(24.18) | 119(22.97) | 98(19.44) |
| Hypertension                         | 1240(63.36) | 291(60.63) | 280(61.54) | 349(67.37) | 320(63.49) |
| Diabetes mellitus                    | 447(22.84) | 86(17.92)  | 116(25.49) | 135(26.06) | 110(21.83) |
| Dyslipidemia                         | 202(10.32) | 41(8.54)   | 38(8.35)  | 61(11.78) | 62(12.30) |
| Cardiovascular disease               | 254(12.98) | 70(14.58)  | 58(12.75) | 67(12.93) | 59(11.71) |
| Fatty liver disease                  | 11(0.56)  | 3(0.63)    | 1(0.22)   | 2(0.39)   | 5(0.99)   |
| NIHSS on admission, median (IQR)     | 3.00(1.00-4.00) | 3.00(1.00-5.00) | 3.00(1.00-4.00) | 2.00(1.00-4.00) | 2.00(1.00-5.00) |
| mRS at admission, median (IQR)       | 1.00(1.00-2.00) | 1.00(1.00-2.00) | 1.00(1.00-2.00) | 1.00(1.00-2.00) | 1.00(1.00-2.00) |
| Medication use, n (%)                |       |           |         |         |         |
| Antiplatelet aggregation therapy     | 1913(97.75) | 471(98.13) | 445(97.80) | 508(98.07) | 489(97.02) |
Variables were expressed as median (s) or percentages. Q1, quartile 1 (n - 480): 17 U/L; Q2, quartile 2 (n - 455): 17-24 U/L; Q3, quartile 3 (n - 518): 24-37 U/L; Q4, quartile 4 (n - 504): ≥ 37 U/L. Cardiovascular disease included atrial brillation, coronary heart disease, heart failure. Medication use included drug use history and treatment during hospitalization. BMI, body mass index; NIHSS, the National Institutes of Health Stroke Scale; mRS, the modified Rankin Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; TC, total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, effective glomerular filtration rate; UA, uric acid; IQR, interquartile range.

**Clinical outcomes**

Among the eligible participants, 671 (34.29%) patients suffered PSCI at 3 months follow-up. The correlation between GGT and PSCI is presented in Table 2 and Fig. 2. Summarily, patients in the highest quartile group recorded a 31% decrease in PSCI risk at 3 months follow-up, after adjusting for confounding factors [OR: 0.69 (95%CI: 0.50-0.96)], relative to the lower quartile group.

**Table 2**

Association between GGT levels and PSCI incidence at 3 months follow-up
| Outcomes | GGT No. | Events, N (%) | Unadjusted OR (95% CI) | P value | Model 1 OR (95% CI) | P value | Model 2 OR (95% CI) | P value | Model 3 OR (95% CI) | P value |
|----------|---------|---------------|-------------------------|---------|---------------------|---------|---------------------|---------|---------------------|---------|
| PSCI     |         |               |                         |         |                     |         |                     |         |                     |         |
| Q1       | 207     | 43.13         | 1.00                    |         | 1.00                |         | 1.00                |         | 1.00                |         |
| Q2       | 162     | 35.60         | 0.73(0.56-0.95)         | 0.02    | 0.86(0.65-1.13)     | 0.27    | 0.84(0.64-1.12)     | 0.24    | 0.82(0.61-1.10)     | 0.18    |
| Q3       | 156     | 30.12         | 0.57(0.44-0.74)         | <0.001  | 0.73(0.56-0.97)     | 0.03    | 0.71(0.53-0.94)     | 0.02    | 0.71(0.53-0.96)     | 0.02    |
| Q4       | 146     | 28.97         | 0.54(0.41-0.70)         | <0.001  | 0.80(0.60-1.07)     | 0.14    | 0.77(0.57-1.03)     | 0.08    | 0.69(0.50-0.96)     | 0.03    |

Data were represented as OR (95% CI). Set OR of quartile 1 as the reference. Model 1: adjusted by age, sex, educational level; Model 2: adjusted by model 1 plus BMI, medical history, current smoking, current drinking, and medication use; Model 3: adjusted by model 2 plus laboratory test (LDL, HDL, TC, TG, ALT, AST, eGFR, UA, Albumin); PSCI, post-stroke cognitive impairment; GGT, gamma-glutamyl transferase; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; TC, total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, effective glomerular filtration rate; UA, uric acid; OR, odds ratio; CI, confidence interval.

The ORs for incidence of PSCI according to GGT quartile level were adjusted for variables of model 3 in table 2. PSCI, post-stroke cognitive impairment; Ref, reference.

Notably, results from restricted cubic spline analysis revealed that GGT levels were inversely associated with PSCI at 3 months (Fig. 3). However, once GGT increased over 60U/L, the incidence of PSCI would no longer decrease.

The association between GGT level and PSCI occurrence at 3 months. The ORs from the logistic regression model were adjusted for variables of model 3 in table 2. The red lines indicate adjusted OR, and the blue lines indicate 95%CI. GGT, gamma-glutamyl transferase; PSCI, post-stroke cognitive impairment; OR, odds ratio; CI, confidence interval.

After incorporating GGT into the conventional model to predict PSCI occurrence, we could see a slight improvement in discriminatory power and reclassification over at 3 months follow-up[NRI: 12.00% (P=0.01); IDI: 0.30% (P=0.02)]. We set OR of the highest quartile as the reference, owing to the inverse correlation between GGT and PSCI (Table 3).

### Table 3

| Clinical outcomes | Model                      | C-statistic               | NRI | IDI            |
|-------------------|---------------------------|---------------------------|-----|----------------|
|                   |                           | Estimate (95% CI)         | P value | Estimate (95% CI) | P value | Estimate (95% CI) | P value |
| PSCI              | Conventional model        | 0.71(0.68-0.73)           | 0.27 | Ref.           | 0.01    | Ref.              | 0.02    |
|                   | Conventional model + GGT  | 0.72(0.69-0.74)           | 0.12 | 0.03-0.21      | 0.003(0.001-0.01) |

Conventional model: added to factor-adjusted models, including age, sex, educational level, BMI, smoking, drinking, NIHSS score at admission, history of stroke, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, atrial fibrillation, and heart failure, laboratory test of TC, TG, WBC, UA. TG, triglycerides; TC, total cholesterol; WBC, white blood cell count; UA,
Subgroup analysis

Odds ratios for GGT and PSCI were stratified by age, sex, BMI, and alcohol drinking. Notably, low- and high-GGT levels refer to the lowest (25%) and highest (75%) quartiles, respectively. P values for the interaction test between GGT and age, sex, BMI, alcohol drinking were 0.91, 0.68, 0.09, and 0.96 at 3 months follow-up (Table 4, Fig. 4). Subgroup analysis revealed no significant interaction between GGT and PSCI.

| Table 4 | Subgroup analysis indicating the correlation between GGT level and PSCI |
|---------|---------------------------------------------------------------|
|         | Low-GGT No. (%) | High-GGT No. (%) | OR (95%) | P value | P interaction |
| Age, years |                |                   |          |         |               |
| <60      | 46(22.22)      | 161(77.78)        | 0.75 (0.48–1.17) | 0.20    | 0.91          |
| ≥ 60     | 161(34.70)     | 303(65.30)        | 0.76 (0.56–1.02) | 0.07    |               |
| Sex      |                |                   |          |         |               |
| male     | 104(23.58)     | 337(76.42)        | 0.81 (0.59–1.10) | 0.18    | 0.68          |
| female   | 103(44.78)     | 127(55.22)        | 0.66 (0.44–1.01) | 0.06    |               |
| BMI, kg/m² |                |                   |          |         |               |
| <25      | 127(35.47)     | 231(64.53)        | 0.61 (0.44–0.86) | 0.004   | 0.09          |
| ≥ 25     | 80(25.56)      | 233(74.44)        | 0.94 (0.64–1.39) | 0.77    |               |
| Drinking |                |                   |          |         |               |
| None     | 192(34.47)     | 365(65.53)        | 0.72 (0.55–0.93) | 0.01    | 0.96          |
| Yes      | 15(13.16)      | 99(86.84)         | 1.02 (0.45–2.31) | 0.97    |               |

Odds ratios for GGT and PSCI were stratified by age, sex, BMI, alcohol drinking. Low-GGT refers to the lowest quartile of 25%, and High-GGT refers to the remaining 75% quartiles. The ORs for incidence of PSCI were adjusted for variables of model 3 in Table 2. GGT, gamma-glutamyl transferase; PSCI, post-stroke cognitive impairment; BMI, body mass index; OR, odds ratio; CI, confidence interval.

Discussion

Results of this large prospective cohort study demonstrated that baseline GGT level was inversely associated with PSCI occurrence. Specifically, extremely low GGT level was a risk factor for PSCI, even after adjusting for confounding factors including age, sex, educational level, smoking, drinking, BMI, some laboratory indicators, and medical history. Interestingly, incorporating GGT into the conventional model resulted in an 11.87% increase incorrect classification in predicting PSCI. Furthermore, correlation analysis of the association between GGT and PSCI across different subgroups revealed no significant change after testing for interactions. This finding indicated that GGT had a consistent effect on PSCI regardless of the patients’ age, sex, BMI, and habit of alcohol drinking.

As a common complication after stroke, PSCI could cause serious disabilities, but there is a lack of studies explored the role of GGT in PSCI. Moreover, previous studies got different results when observed the relationship between GGT and cognitive
impairment. The strength is this prospective, multicenter cohort study demonstrated the association between GGT and PSCI, which was rarely described in previous studies, and found GGT level was inversely associated with risk of PSCI.

This result may be explained by the following mechanism. A previous study demonstrated that the expression of GGT is critical for antioxidant defense. GGT contributes to maintaining the physiological concentrations of glutathione and plays a relevant role in protecting cells from oxidative stress damage. GGT induction can be used as a protective adaptation in physiological and pathological processes. Once stroke strikes, levels of inflammatory cytokines increased in the body, and GGT could compensatory increases when catabolism of inflammatory cytokines containing glutathione. In this process, the strong reducing agent - dipeptide cysteiny glycine was produced, as well as more cysteine, which was regarded as the raw material for glutathione synthesis. Both of these two catabolites have antioxidant effects, protecting cells from oxidative stress, and reducing the oxidative damage caused by Aβ deposition. Thus, GGT could play an important role in defending cells against oxidation-induced damage. Moreover, increased GGT in the normal range could also indicate that the liver was better at dealing with oxidative stress. When the degree of oxidative stress in the body decreased, the incidence of PSCI decreased accordingly. Notably, very low GGT levels are indicators of poor liver function and systemic state, as well as the inability to complete the glutamate cycle which is essential for generating enough glutathione to resist oxidative stress.

However, it still had some limitations. Firstly, we adopted a relatively short follow-up period which may have influenced the observed outcomes. Previous studies mainly focused on the relationship between GGT with AD and cognitive decline in later stages of life over 10 years. However, there is no sufficient evidence on the relationship between GGT and PSCI. Since PSCI is closely associated with stroke and is characterized by its fluctuation, the outcome of the association between GGT and PSCI depends on the length of follow-up. Secondly, we found that in the population with higher GGT levels, the biochemical indicators of liver function such as ALT and AST were also higher. It is possible that this part of the population may pay more attention to their health conditions, and could be adopting certain measures on their own to protect their liver function during the follow-up. This may have possibly weakened the potentially dangerous relationship between GGT and PSCI. Thirdly, as an index of biological metabolism, GGT is affected by many factors and presents the characteristics of dynamic change. Nevertheless, this study only observed the relationship between GGT at baseline and PSCI. Since baseline GGT levels may be temporarily altered by stroke events, we cannot be ruled out that the possibility of changes in physical health after a period of certain treatments may cause GGT levels in the group with a higher baseline state to return to normal or even drop to a lower level, thus reducing the possibility of PSCI occurrence.

**Conclusions**

In summary, our results revealed that baseline GGT level was inversely associated with PSCI, with extremely low GGT level considered a risk factor for PSCI. However, the GGT level dynamically changes and its function plays a two-sided role in vivo. Therefore, relying solely on GGT to predict PSCI should be considered carefully. Further longitudinal studies are needed to validate the role of GGT in PSCI.

**Abbreviations**
Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committees of Beijing Tiantan Hospital (No.KY2015-001-01). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.
Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SL and YZ made contributions to the conception and design of the study and substantively revised the manuscript; SL, YP, and XX developed the statistical analyzing procedure and helped in the interpretation of the data; XL and YP were involved in the acquisition of the data. SL and XX have drafted the manuscript.

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Figures

Figure 1

Flowchart in this study.
Figure 2

Forest plots of ORs for incident PSCI according to GGT quartile level.

Figure 3

Spline models about the association between GGT levels and clinical outcomes.
Figure 4
Forest maps of ORs for incident PSCI stratified by different characteristics.

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