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Association between risk of ischemic stroke and liver enzymes levels: a systematic review and meta-analysis

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Abstract

Background Ischemic stroke is a major public health concern, contributing significantly to global morbidity and mortality. Recent studies have suggested that alterations in liver enzymes may be linked to the risk of developing a stroke. However, the relationship between liver enzymes and ischemic stroke remains unclear.

Objective To examine the potential role of liver enzymes as biomarkers for ischemic stroke.

Methods We systematically searched four databases for articles investigating the association between liver enzymes and ischemic stroke up to March 20th, 2024. Newcastle Ottawa Scale judged the quality of included studies. Risk ratio (RR), hazard ratio (HR), or odds ratio (OR) were extracted and statistically analyzed by RevMan and R software. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessed the certainty of evidence.

Results Increased levels of gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) have shown statistically significant association with increased ischemic stroke risk (RR: 1.43, 95% CI: [1.30 to 1.57], $P > 0.00001$) and (RR: 1.60, 95% CI: [1.22 to 2.10], $P = 0.0006$), respectively. Conversely, increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) showed no significant association with ischemic stroke risk (RR: 0.92, 95% CI: [0.68 to 1.24], $P = 0.58$) and (RR: 1.43, 95% CI: [0.83 to 2.49], $P = 0.20$), respectively. The evidence for all outcomes had a low or very low level of certainty.

Conclusion GGT and ALP could be potential biomarkers for increased ischemic stroke risk, which necessitates careful follow-up. However, AST and ALT did not show such association.

Key Points

- The relationship between liver enzymes and ischemic stroke risk is still unclear.
- We systematically reviewed and analyzed previously published cohort and case control studies.
- A significant positive association was found between levels of GGT and ALP enzymes with ischemic stroke risk.
- No significant association was found between ALT and AST enzymes levels with ischemic stroke risk.
- Further studies are still needed to investigate the causal relationship between different levels of liver enzymes and the risk of ischemic stroke.

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Keywords Ischemic stroke, Gamma-glutamyl transferase, GGT, Alkaline phosphatase, ALP, Alanine aminotransferase, ALT, Aspartate aminotransferase, AST, Cerebral infarction, Cerebral ischemia, Liver biomarkers, Liver enzymes

Introduction

Stroke is one of the most common causes of death and disability, with most of the burden in developing and middle-income countries [1, 2]. It causes the deaths of 5.5 million people annually around the world [3]. Stroke is an acute neurological disease due to a disturbance in brain perfusion, leading to impairment in its function [4]. It is further classified into hemorrhagic and ischemic, the most common (84.4%).

Ischemic stroke occurs due to severe stenosis or occlusion of major cerebral arteries. The interruption of blood flow leads to oxygen-glucose deprivation in nervous cells. The irreversible damage process of ischemic stroke includes two consecutive steps, namely acute and delayed neuronal cell death [5]. Acute brain injury is directly caused by severe ischemia. It occurs within minutes after stroke onset, while delayed neuronal cell death is mainly caused by brain edema and occurs several days following stroke onset [6]. Several risk factors for ischemic stroke are known and could be prevented, such as hypertension, hyperlipidemia, increased coagulability, smoking, premature ventricular complex, diabetes mellitus, and atrial fibrillation [3]. Previous research has found that identifying and targeting ischemic stroke-prone individuals plays an important role in ischemic stroke management [3].

As a time-dependent disease, acute stroke management must be coordinated and effective to provide the optimal treatment as early as possible. The treatment of the acute phase of ischemic stroke includes general measures to ensure patient hemodynamic stability, the use of reperfusion therapies, such as intravenous thrombolytics and mechanical thrombectomy, improving cerebral protection by monitoring the homeostasis of certain variables such as blood pressure, glycemia, temperature, or oxygenation, as well as preventing cerebral and systemic complications [7].

Liver enzymes are considered as indicators of hepatobiliary dysfunction [8]. The gamma-glutamyl transpeptidase (GGT) enzyme facilitates intracellular absorption of glutathione extracellularly, which is a result of normal metabolic activities and plays a key role in oxidative stress protection for the cell [9]. GGT may have a role in the oxidative and inflammatory pathways that lead to atherosclerosis, according to recent research. It is believed that oxidative stress predisposes people to cardiovascular disease, which can result in ischemic stroke, and vascular and endothelial damage, which causes atherosclerosis [10, 11]. Additionally, serum alkaline phosphatase (ALP) level might be one of the independent risk factors causing ischemic stroke. Such assertion is underscored by the fact that high levels of serum ALP would enhance vascular calcification by catalyzing the hydrolysis of organic pyrophosphate, leading to atherosclerosis, which is a main risk factor for ischemic stroke [12].

Aspartate transaminase (AST) and alanine transaminase (ALT) are primarily considered biomarkers of liver injury; their peripheral blood levels can also impact blood glutamate concentration and memory function [13]. Higher levels of AST and ALT have been associated with increased blood glutamate levels that have been closely linked to the development of acute lung injury and a poor prognosis after ischemic stroke [14, 15]. Additionally, elevated glutamate can contribute to excitotoxicity and neuronal damage in the context of ischemic brain injury. Furthermore, some studies have shown that an elevated AST/ALT ratio (the De Ritis ratio) is associated with poorer outcomes after ischemic stroke [16]. Further research is necessary to determine the precise pathways linking transaminase enzymes, glutamate, to ischemic stroke. Nonetheless, the information currently available points out the potential involvement of these enzymes in excitotoxicity and neuronal damage associated with stroke [14–16].

Based on previous studies, there are strong implications and suggestions that liver enzyme levels may be independently associated with ischemic stroke risk and clinical outcomes. This systematic review and meta-analysis aim to summarize the current available data and analyze the relationship between liver enzymes and the risk of ischemic stroke.

Methods

Protocol and registration

This systematic review and meta-analysis followed the criteria of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [17]. We registered this study protocol on the PROSPERO database for systematic reviews (registration number CRD42024526973).

Study inclusion and exclusion criteria

The inclusion and exclusion criteria for the meta-analysis were as follows: the target population included patients diagnosed with ischemic stroke. The indicators included blood levels of gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Only observational studies (cohort and case-control studies) were included. The outcome included the statistical estimates of the hazard ratio (HR), odds ratio (OR), and

risk ratio (RR) for ischemic stroke with liver enzymes. If studies lacked available data or were in non-English languages, they were excluded. If studies included patients with hemorrhagic stroke, subarachnoid hemorrhage, or other space-occupying lesions, they were also excluded. Studies of cross-sectional design, case reports, case series, and reviews were excluded as well.

Literature search and data extraction

We conducted systematically rigorous and comprehensive research from inception until March 2024 on PubMed, Scopus, Web of Science, and the Cochrane Library.

Appropriate Medical Subject Headings (Mesh) were used to find the keywords in the search strategy with no limitations on time, country, language, or study design. References of the included studies were checked thoroughly for relevant articles. The detailed search strategy is shown in Supplementary File, Appendix 2.

Study selection

The literature screening process involved four independent reviewers who assessed the titles, abstracts, and full texts to judge whether they met the eligibility criteria. Titles, abstracts, and full-text screenings were done using Rayyan and Google spreadsheets, respectively [18, 19]. In cases of disagreements between the investigators, they used a consensus-based approach to make decisions. If needed, a fifth investigator was consulted to help resolve any disputes that arose.

Data extraction

Four independent researchers utilized an online spreadsheet to retrieve the necessary data from the included studies and used standardized forms for consistency [19]. The extracted data included study characteristics (including first author, year of publication, title of the paper, study design, and the country), population characteristics (including the percentage of males, mean age, study population, sample size, study follow-up time, duration of the study, stroke ascertainment, and the cutoff values or quartile of AST, ALT, GGT, and ALP levels), and outcomes data (including odds, risk, and hazard ratios of ischemic stroke). The graphical data from the original studies was extracted using Web Plot Digitizer, a semi-automated software tool that allows for the retrieval of the underlying numerical data by reverse engineering the visual representation of the image [20]. Any disagreements during the data extraction process were settled by discussion with a fifth researcher.

Assessment of included studies' quality

The Newcastle Ottawa Scale (NOS) was adopted for the quality assessment of cohort and case-control studies, with values ranging from 0 to 9 [21]. The NOS awards a maximum of four points for selection, two for comparability, and three for outcomes. The scale judges the quality of studies based on selection, comparability, and outcome or exposure. Studies with a score of 7 to 9 were rated as excellent quality, 4 to 6 as intermediate quality, and < 3 as low quality.

Statistical analysis

Review Manager version 5.4 (RevMan) was used for the statistical analysis and to synthesize forest plots [22]. The DerSimonian and Laird random-effect model was adopted in all outcomes to consider both within- and between-study variability [23]. The analysis was based on a risk ratio (RR) and a confidence interval (CI) of 95% using the generic inverse variance method. Given the rarity of the outcome, the hazard ratios were considered to approximate the equivalent measure of RR [24]. A statistically significant P-value was considered if it was < 0.05. Using the Higgins score (I^2), the heterogeneity of the included studies was evaluated; I-square values $\geq 50\%$ were indicative of high heterogeneity [25]. A chi-square P value less than 0.1 was considered significant heterogeneity. Regarding sensitivity analysis, we used R software to conduct leave-one-out plots [26]. Sensitivity analysis was conducted by omitting one study at a time to assess the heterogeneity and test the robustness of the results. Furthermore, we conducted a visual inspection of the funnel plots [27] and Egger's test [28] to assess potential publication bias once the available number of studies is equal to or more than ten studies.

Assessment of the quality of evidence

The Grading of Recommendations, Assessment, Development, and Evaluation criteria (GRADE) [29] was used to assess the level of certainty of the generated evidence via the GRADE pro-Guideline Development online Tool (GDT) [30]. The rating process referred to the GRADE Handbook and guidelines [31, 32]. This tool assesses and classifies the evidence into four levels of certainty: very low, low, moderate, and high, considering the following domains of evaluation: risk of bias, inconsistency, indirect evidence, imprecision, publication bias, and other domains like dose-response effect and plausible confounding.

Results

Study selection

Searching the literature systematically yielded 5541 potentially relevant records from various databases, including PubMed, Cochrane Central, Scopus, and Web of Science. Rayyan online software [18] was utilized for removing duplicates, which appeared to be 1116 records. Titles and abstracts screening was conducted on 4425

records, yielding 94 articles that met the eligibility criteria for our research question. The final step was the full-text assessment, and 74 records were excluded for reasons. Therefore, 20 studies were included in this review [33–52]. Additionally, reference lists of these included studies were manually checked to identify any potentially relevant studies missed during the initial search process. The process of searching as well as the number of included and excluded studies are shown in Fig. 1.

Study characteristics

After literature screening, our meta-analysis included 20 publications that aligned with the eligibility criteria, comprising 10 prospective cohorts, four case-cohort

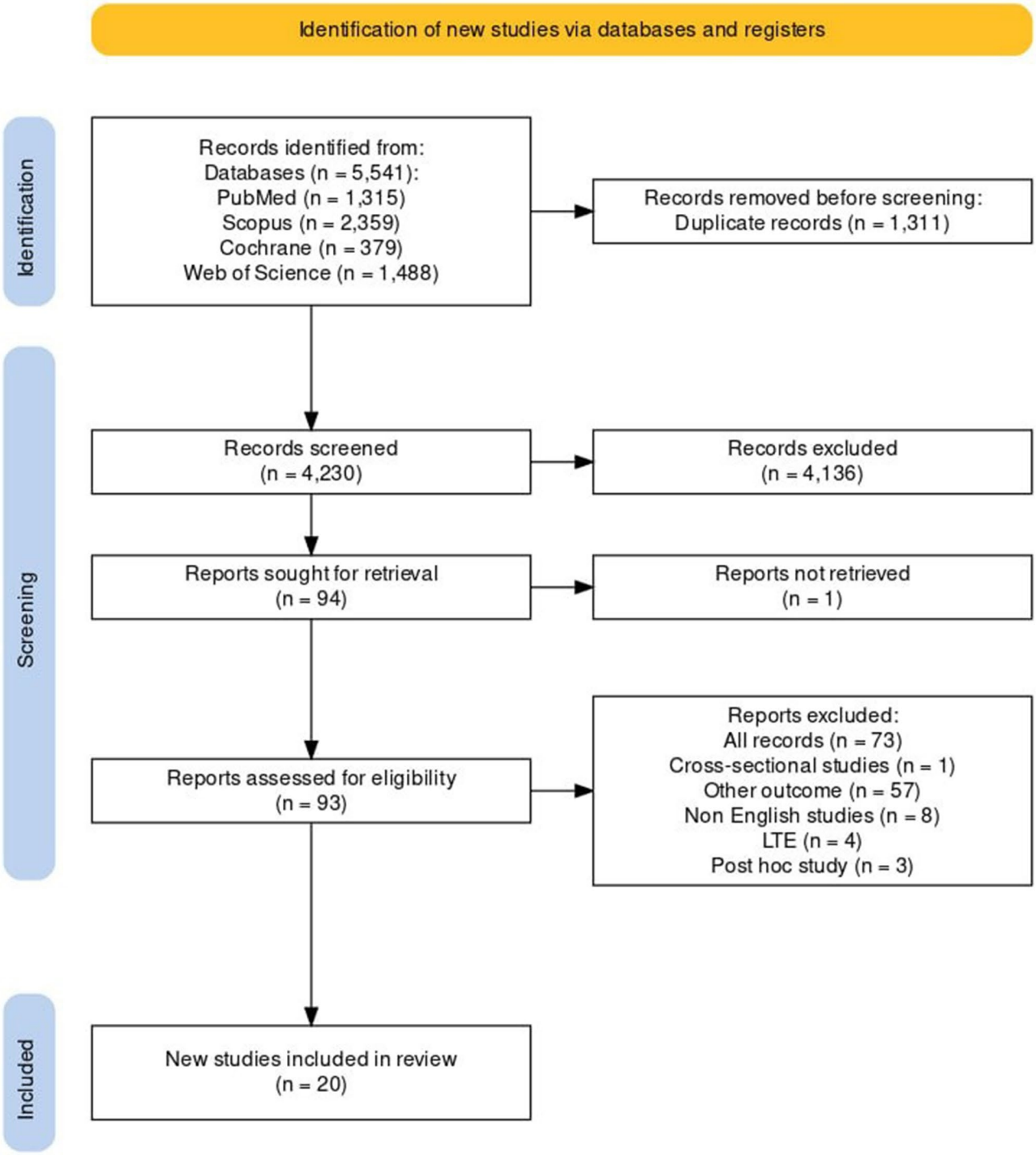

Fig. 1 PRISMA diagram of study selection process

studies, three retrospective cohorts, and three case-control studies. All 20 articles were published from 2000 to 2023, including 880,108 patients. Six of the studies were conducted in Korea, four in Japan, four in China, and two in the United States, with single studies in Finland, Germany, Pakistan, and Greece. Follow-up periods and participant baseline characteristics varied between studies. Information on the demographics and features of the included studies is provided in detail in Table 1.

Quality assessment

The quality of the included studies was assessed using NOS for cohort and case-control studies. Eighteen of the included studies were judged as excellent quality, scoring 7 or higher out of 9, while two studies [38, 41] were of intermediate quality, scoring 5,6 points respectively, mostly due to limitations in population selection and outcome measures. Detailed information about the studies' quality assessment is shown in the Supplementary file, Appendix 3.

Association between liver enzymes and ischemic stroke

A total of 14 studies investigated the association between increased levels of GGT and the incidence of ischemic stroke. High levels of GGT demonstrated a statistically significant increased risk for ischemic stroke incidence (RR: 1.43, 95% CI: [1.30 to 1.57], $P > 0.00001$) (Fig. 2).

In another analysis, six studies were examined to assess the risk of IS associated with high ALP levels. Higher levels of ALP were significantly associated with increased risk for the development of ischemic stroke (RR: 1.60, 95% CI: [1.22 to 2.10], $P = 0.0006$) (Fig. 3). However, there was notable heterogeneity among individual studies ($P = 0.01$; I2 = 65%).Conversely, a pooled analysis of six studies investigating ALT levels found no significant link between elevated ALT and ischemic stroke incidence (RR: 0.92, 95% CI: [0.68 to 1.24], $P = 0.58$) (Fig. 4). This analysis also revealed significant heterogeneity among the studies ($P = 0.0007$; I2 = 76%).

Lastly, five studies explored the association between AST levels and stroke. The combined analysis indicated no statistically significant correlation between increased AST levels and the risk of ischemic stroke (RR: 1.43, 95% CI: [0.83 to 2.49], $P = 0.20$) Fig. 5. Furthermore, there was significant heterogeneity among studies ($P > 0.00001$; I2 = 91%).

Sensitivity analysis

The sensitivity analysis approach was pursued to explore different sources of heterogeneity among studies and test the stability of the results. All the pooled outcomes were found to be robust, and omitting any study did not influence the pooled RR and p-value. The heterogeneity in ALP and AST outcomes was resolved by omitting Uehara et al. (2018) (Supplementary file, Appendix 1 A, Fig. 6), and Tan et al. (2016) (Supplementary file, Appendix 1B, Fig. 7), respectively. Remarkably, the heterogeneity in ALT was not resolved merely by omitting one study but by omitting two studies (34, 50). The forest plot of AST after omitting the mentioned studies is shown in the Supplementary file, Appendix 1 C, Fig. 8.

Publication bias

According to Cochrane recommendations, examining funnel plot asymmetry is meaningful only when there are at least ten studies in the meta-analysis [53]. Therefore, only the GGT outcome was assessed for publication bias. Neither the funnel plot nor Egger's test indicated the presence of publication bias ($P = 0.12$) (Supplementary file, Appendix 1D, Fig. 9).

Certainty of evidence

The quality of evidence regarding the liver enzymes' associations with ischemic stroke was assessed using GRADE. Given the nature of the involved studies, which were only observational, the quality of evidence was low initially. GGT enzyme level association with ischemic stroke outcome yielded low-quality evidence without downgrading the evidence at any domain. However, ALP, ALT, and AST associations with ischemic stroke outcomes were downgraded because of serious limitations in imprecision and/or inconsistency domains. A summary of the findings and the GRADE evaluation of the outcomes are represented in the Supplementary file, Appendix 4.

Discussion

The current meta-analysis provides class-one evidence regarding the capability of liver enzymes to be considered as potential biomarkers for the development of ischemic stroke, encompassing 20 studies with 880,108 patients of variable age ranges. Our pooled analysis exhibited an increased risk of ischemic stroke incidence associated with higher levels of GGT and ALP enzymes. However, the pooled results failed to prove any significant association between ALT or AST enzymes and the development of ischemic stroke. Most studies were judged to be of excellent quality by the Newcastle Ottawa scale. However, the heterogeneity was explicit and obvious in most of the outcomes, mostly because of the variation in the baseline characteristics of the involved population and the study's methodology as well. Nevertheless, sensitivity analysis showed the stability and robustness of the results. Additionally, the evidence for these outcomes had a low or very low level of certainty because the original study design was only observational studies.

Out of 14 included studies reporting the association between GGT level and ischemic stroke, seven studies followed a prospective cohort design, three followed

Table 1 Summary and baseline characteristics of included studies

First author (year of publication)	Country	Male *n* (%)	Age range	Duration (years)	Stroke ascertainment	Cutoff values or quartile (IU/L)	Adjusted covariates
Jousilahti et al. (2000)	Finland	7176 (48.5)	25–64	13	T national hospital discharge register (ICD-8 & ICD-9)	**M**: 10.8, 16.4, 24.6, 64.2 **W**: 7, 9.9, 13.6, 33.9	Age, study year, smoking, TC, SBP, DBP, BMI
Kim et al. (2005)	Korea	108 464 (100)	35–59	10	The Korea Medical Insurance Corporation (KMIC)	< 35, (35–69) and ≥ 70	Age, BMI, blood pressure, FBG, TC, smoking, and alcohol consumption
Korantzopoulos et al. (2009)	Greece	175 (53.2)	77.6 *	5	History, physical examination, imaging study (non-contrast brain CT scan), full cardiac evaluation and carotid Doppler ultrasound	< 16, 16–21, 21–27, > 27	Sex, age, smoking habits, BMI, HTN, DM, metabolic syndrome and serum levels of lipid parameters, glucose, insulin, creatinine, uric acid, AST, ALT, ALP, and total bilirubin
Shimizu et al. (2010)	Japan	3471 (36.7)	40–69	18.1 [a]	Physicians examination, CT/MRI, clinical criteria	**M**: < 15, (15–24), (24–45), > 45 **W**: < 8, (9–11), (11–16), > 16	Age and community, BMI, smoking, alcohol intake, TC, serum triglycerides, serum albumin, AST, ALT, SBP, antihypertensive medication use, and DM
Weikert et al. (2013)	Germany	940 (38.9)	35–65	8.2 [b]	Medical records and death certificates, brain imaging (MRI or CT), and ICD-10	**GGT: M**: (3.3–15.4), (16.5–25.3), (26.4–42.9), (44.0-2401) **W**: (1.1–7.7), (8.8–12.1), (13.2–19.8), (20.9–485) **ALT: M**: (5.5–17.6), (18.7–24.2), (25.3–35.2), (36.3–265) **W**: (2.2–12.1), (13.2–15.4), (16.5–20.9), (22.0-209)	Age, sex, BMI, waist circumference, smoking, alcohol intake, education, sports, HTN, DM, total and HDL-cholesterol, and hsCRP
Shimizu et al. (2013)	Japan	4098 (38.1)	40–69	16	National insurance claims, physicians, death certificates, and cardiovascular risk surveys	**M**: 63, (63–72), (73–83), (84–96),96 **W**: 59, (59–70), (71–82), (83–98), 98	Age and community, BMI, smoking, alcohol consumption, TC, serum albumin, AST, ALT, g-GTP, GFR, SBP, antihypertensive medication use, DM, thyroid disease, and for women menopausal status
Ryu et al. (2014)	South Korea	558 (51.6%)	20–82	1	MRI brain, assessment of FLIAR and T1-weighted sequences	<53, (54–63), (64–76), ≥ 77	Age, sex, HTN, DM, smoking, CHD, serum phosphate, calcium, ALT, LDL-cholesterol, C-reactive protein (log-transformed), and GFR
Tan et al. (2016)	China	760 (57.0)	18–39	5.5	WHO criteria and CT or MRI scan	**AST**: (5–18), (19–22), (23–29), (30–531) **GGT: (**7–16), (17–25), (26–42), (43–898)	Age, gender, HTN, DM, dyslipidemia, atrial fibrillation, history of stroke, alcohol consumption and smoking, NIHSS score, and SBP
Dar et al. (2016)	Pakistan	288 (73.8)	40–80	0.5	CT scan of brain was performed, and diagnosis was confirmed	> 27 IU/L	N/A
Liang et al. (2017)	China	312 (64.2)	65.59 *	2.5	According to the WHO criteria	N/A	Age, sex, SBP, DBP, cigarette smoking
Uehara et al. (2018)	Japan	55 (67)	69.3 *	7.5	DWI to evaluate whether acute ischemic lesions were present	**ALP**: ≥292 U/L	N/A

Table 1 (continued)

First author (year of publication)	Country	Male *n* (%)	Age range	Duration (years)	Stroke ascertainment	Cutoff values or quartile (IU/L)	Adjusted covariates
Alexander et al. (2018)	United States of America	13,607 (45%)	64.7 *	4	Medical records and death certificates	**AST: M**: (15.4, 18.5, 21.3, 25.5), **W**: AST (14.1, 16.4, 19.4, 23.1) **ALT: M**: (12.1, 15.1, 18.9, 24.2), **W**: (9.3, 12.5, 14.9, 19.2) **GGT: M**: (17.0 21.6, 28.1, 41.8), **W**: (12.8, 16.9, 22.6, 31.2)	Age, race, and Framingham stroke risk factors
Yang et al. (2018)	South Korea	236,889 (51.9%)	20–84	10	General health clinical examination and ICD-10, code: I63	(10–17), (13–25), (18–39), (32–90)	Age, sex, alcohol consumption, BMI, SBP, FBG, TC, hemoglobin, AST, ALT, DM, previous stroke, HTN, atrial fibrillation, ischemic heart disease, heart failure, liver disease, cancer, CKD, osteoporotic fracture, smoking status, antiepileptic drug or rifampicin use, pregnancy within 1 year, and social economic status
Yang et al. (2020)	South Korea	525 (59.6)	68.93 *	15	The National Institutes of Health Stroke Scale score, and TOAST classification	**M**: ≤20, (21–29), (30–53), and ≥ 54 **W**: ≤14, (15–21), (22–34), and ≥ 35	Sex, age, BMI, SBP, FBG, TC, AST, ALT, previous stroke, HTN, DM, hyperlipidemia, liver disease, and smoking
Ruban et al. (2020)	United States of America	5,504 (43.7)	45–46	24.2 [a]	Stroke hospitalizations records, ICD-9 or ICD-10 and physician review	**AST: M**: <12, 12–15, 16–21, ≥ 25; **W**: <16, 16–18, 19–21, ≥ 22 **ALT: M**: <18, 18–21, 21–25, ≥ 22; **W**: <12, 10–12, 13–16, ≥ 17 **GGT: M**: <18, 18–24, 25–37, ≥ 38; **W**: <13, 13–17, 18–28, ≥ 29	Age, sex, race-center; BMI, smoking status, drinking status, education level, SBP, HTN medication, DM, HDL, TC, lipids medication, and CHD
Lee et al. (2021)	Korea	118,375 (56.5%)	57.8 *	5	Medical records and ICD, code: I63	<16, (≥ 16, < 24) (≥ 24, < 41), ≥ 41	Age, gender, BMI, systolic BP, FBG, TC, eGFR, smoking amount (pack-year), alcohol intake and physical activity
Li et al. (2022)	China	8,506 (68.03)	62.33 *	4	WHO criteria, and neuroimaging (MRI or brain CT)	**M**: <19, 19–27, 27–43, ≥ 43 **W**: <14, 14–20, 20–29, ≥ 29)	Age and sex, BMI, smoking, alcohol consumption, medical histories, SBP, DBP, NIHSS score at admission, pre-stroke mRS score, TOAST types (including large-artery atherosclerosis, cardioembolic, small-vessel occlusion, other determined etiology, and undetermined cause), medications during hospitalization (including antiplatelet therapy, anticoagulation treatment, antihypertensive treatment, lipid-lowering drugs), and laboratory tests (FBG, TC, triglycerides, ALT, AST levels)
Kim et al. (2023)	Korea	1,968 (63.6)	48–87	8.9 [a]	Hospitalization records with stroke code ICD-10, code: I63	**M: ≤**20, 21–30, 31–52, ≥ 54 **W**: ≤11, 12–15, 16–22, ≥ 23	Age, sex, residential area, health insurance type, insurance premium, BMI, fasting serum glucose, TC, AST, ALT, cigarette smoking, alcohol consumption, physical activity, family history of stroke, Charlson comorbidity index, and aspirin use, presence of atrial fibrillation/flutter

Table 1 (continued)

First author (year of publication)	Country	Male *n* (%)	Age range	Duration (years)	Stroke ascertainment	Cutoff values or quartile (IU/L)	Adjusted covariates
Liu et al. (2023)	China	11,408 (43.2)	M: 65.2 * W:58.9 *	7.3 [c]	Hospital records, and medical insurance documents	**M**: < 69, 69–84, 84–100, > 100 **W**: < 71, 71–87, 87–105, > 105	Age, admission batch, BMI, smoking status, drinking status, physical activity, HTN, hyperlipidemia, DM, aspirin usage, anticoagulants usage, menopausal status (women only), family history of CVD, and eGFR, WBC
Arafa et al. (2023)	Japan	3,379 (45.7)	< 50, 50–59, 60–69, or ≥ 70 **	16.7 [a]	The US National Survey of Stroke criteria based on CT or MRI images	**ALT**: ≤ 30, 31–50, > 50 **AST**: ≤ 30, 31–50, > 50 **GGT**: ≤ 50, 51–100, > 100	Age, BMI, smoking, alcohol consumption, HTN, DM, HDL-C, TC, CKD, and cardiac murmur

*: mean age, **: age divided into categories, a: median follow up years, b: mean follow up years, c: average follow up years, ICD: International Classification of Diseases, Injuries, and Causes of Death, DWI: diffusion-weighted imaging, CT: computed tomography, MRI: magnetic resonance imaging, WHO: world health organization, DM: diabetes mellitus, HTN: hypertension, CKD: chronic kidney disease, WBC: white blood cells, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, TC: total cholesterol, FBG: fasting blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure, GFR: glomerular filtration rate, CHD: coronary heart disease, CVD: cardiovascular disease, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase

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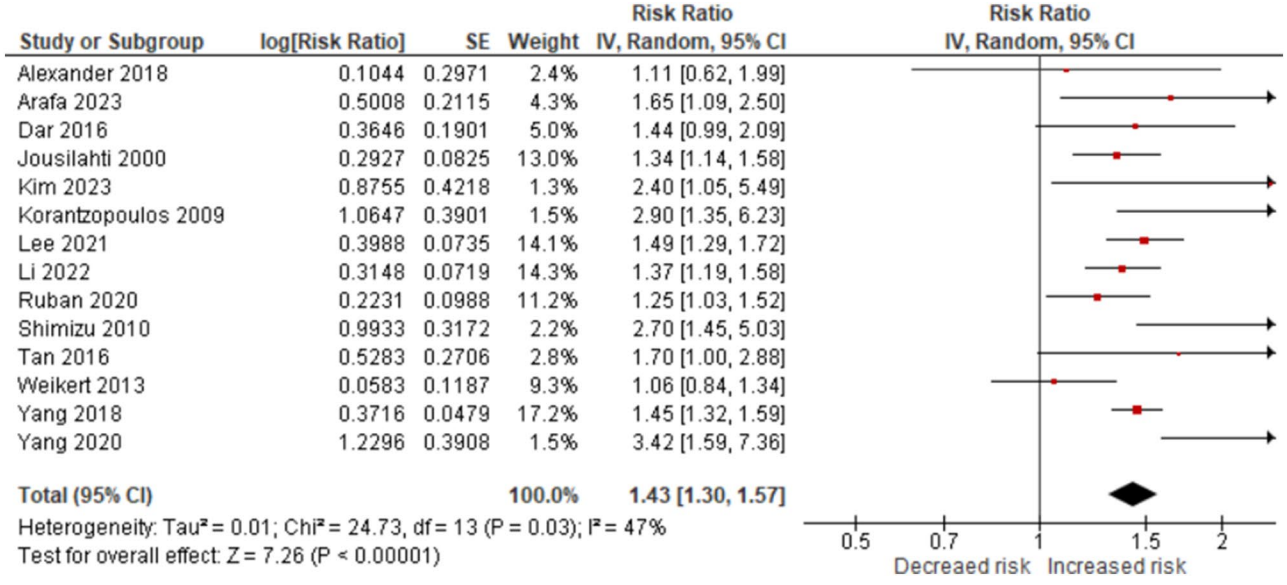

Fig. 2 Forest plot showing the Association between GGT and the risk of Ischemic Stroke

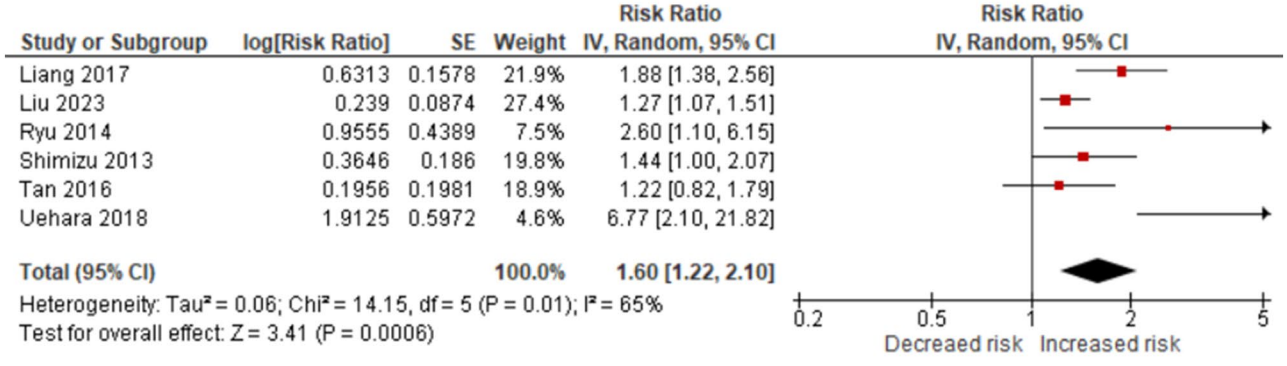

Fig. 3 Forest plot showing the Association between ALP and the risk of Ischemic Stroke

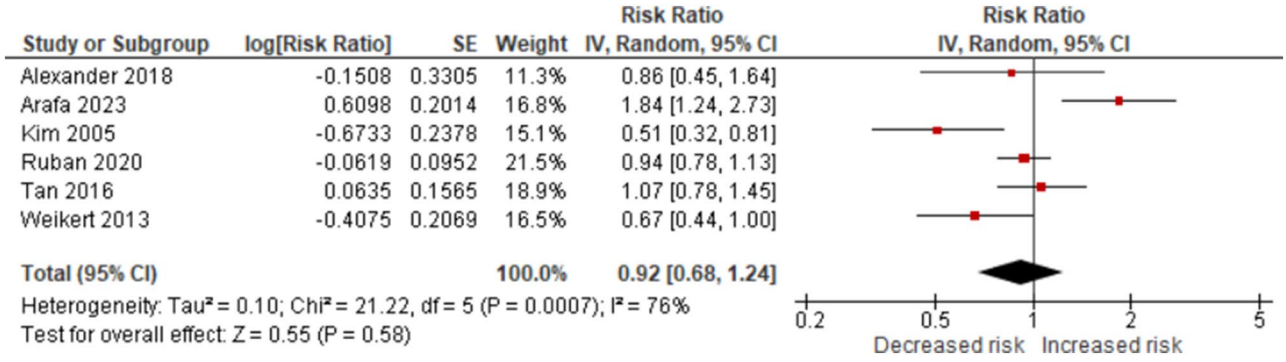

Fig. 4 Forest plot showing the Association between ALT and the risk of Ischemic Stroke

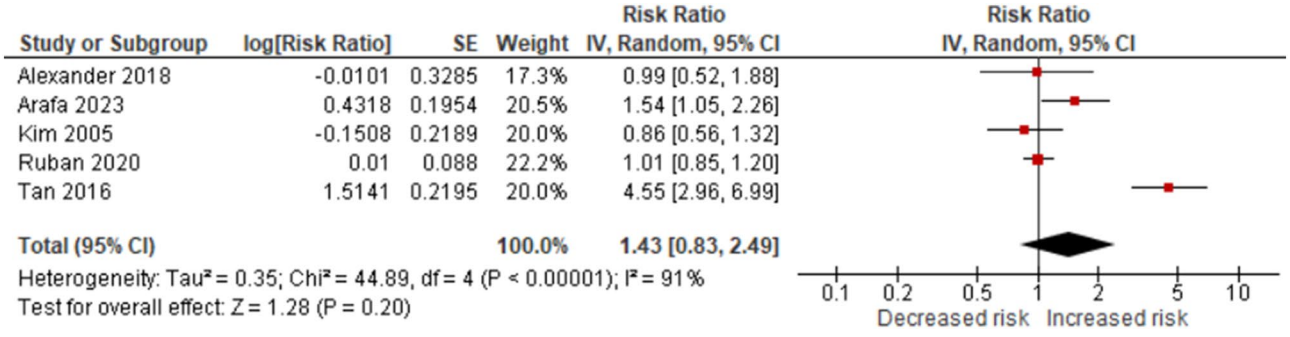

Fig. 5 Forest plot showing the Association between AST and the risk of Ischemic Stroke

a case-cohort design, three followed a case-control, and only one study was of retrospective cohort design. Ten of the studies recruited healthy populations, while four studies included ischemic stroke patients at baseline [34, 42, 43, 47]. All 14 studies enrolled patients free of liver diseases at baseline except for Alexander et al. (2018), which included patients with non- alcoholic fatty liver disease (NAFLD), and Tan et al. (2016), which included patients with hepatitis, fatty liver, liver cirrhosis, and liver dysfunction. Similarly, six studies analyzed the relationship between ALP level and ischemic stroke. Of which, four studies were prospective cohorts, one study was retrospective cohort, and one study was case cohort. All of them enrolled healthy participants at baseline who were free from previous ischemic and liver diseases except for Uehara et al. (2018), which included transient ischemic attack (TIA) patients.

Of the 20 included studies, six revealed the relationship between ALT and ischemic stroke. Three of which were of prospective cohort design, while the other three were of case cohort design. All six studies enrolled healthy populations at baseline except for Alexander et al. (2018), which included ischemic stroke patients and patients with NAFLD. The Association between AST and ischemic stroke was reported in five studies, most of which recruited healthy participants free of any previous ischemic or liver disease at baseline. Nevertheless, Alexander et al. (2018) and Tan et al. (2016) included ischemic stroke patients as well as patients with different liver diseases at baseline.

The high cut-off value of baseline ALP (292 IU/L) as well as including patients with previous TIA may contribute to heterogeneity in ALP outcomes, caused by Uehara et al. (2018). On the contrary, the other five included studies reporting the relationship between ALP level and ischemic stroke enrolled patients with no previously known ischemic disease at baseline along with a lower cutoff value (< 106). While in AST outcomes, unexplained heterogeneity was resolved by omitting Tan et al. (2016), which was the only study that included patients with very high AST levels (up to 531). On the other hand, the rest of the studies' populations had lower levels of AST (< 72). Dramatically, the heterogeneity in ALT results was resolved after omitting two studies. The first is Kim et al. (2005), which included only male patients, and most of them were alcoholics (75.2%). The second is Arafa et al. (2023), which also included only men in the analysis and had no data on liver enzymes at baseline, thus could be a confounding variable. In contrast, the other studies included in the ALT analysis recruited both men and women, with a lower percentage of alcoholic patients at baseline (< 58%).

A previous systematic review and meta-analysis investigating the relationship between GGT and stroke risk found that populations with higher GGT levels experienced an increased risk of developing a stroke [54].

However, it could not define the association between GGT and stroke subtypes. The current available evidence illustrates varying findings regarding the association between liver enzymes and the risk of ischemic stroke. Eleven studies found that a higher risk of ischemic stroke was associated with higher GGT levels, which is consistent with our findings [33, 35, 38, 40, 45–51]. However, one study showed that GGT levels have no association with ischemic stroke risk [41]. Additionally, one study [36] concluded that high GGT levels were associated with a higher risk of total stroke and with ischemic stroke in never-drinking women specifically. Similarly, Alexander et al. (2018) found that higher levels of GGT are associated with increased ischemic stroke risk in women but decreased risk in men. Regarding ALP, similar to our results, five studies found that higher levels of serum ALP were significantly associated with an increased risk of ischemic stroke [39, 40, 42, 44, 52]. However, one study [37] showed that higher ALP levels were associated with a higher risk of ischemic stroke in men but not women. In addition, the study also illustrated that lower levels of ALP were also associated with elevated ischemic stroke risk in both men and women.

ALT, on the other hand, had a high diversity of results between studies. In alignment with our observations, two studies [34, 46] implied that ALT has no association at all with the risk of ischemic stroke. Conversely, two studies [40, 50] found that higher levels of ALT were positively associated with increasing the risk of ischemic stroke. Moreover, another study [38] found that higher ALT levels were associated with decreased ischemic stroke risk. Likely, the sixth study [43] showed that higher levels of ALT were associated with decreased ischemic stroke risk in men but not in women. Analogous to what we have reported, three studies [34, 43, 46] found no association between the levels of AST in blood and the risk of ischemic stroke. However, two studies [40, 50] found that high AST levels are positively associated with a higher incidence of cardioembolic stroke and increased risk of cerebral infarction, respectively.

While the exact mechanism linking liver enzymes such as GGT, ALP, ALT, and AST to the development of ischemic stroke is not fully elucidated, previous research has provided some insights into potential underlying mechanisms. Elevated levels of GGT were found to cause oxidative stress and inflammation, which are implicated in the development of atherosclerosis. Moreover, high levels of GGT have also been associated with endothelial dysfunction and arterial stiffness, which are involved in the pathogenesis of ischemic stroke [55, 56]. GGT is also involved in glutamate metabolism; a substance that is significantly crucial for neuronal function as well as excitotoxicity, which leads to cell death during ischemic events [16, 46]. Similarly, elevated ALP levels have been associated with vascular calcification, a process linked to atherosclerosis, an increased risk of cardiovascular events, and ischemic stroke. Additionally, ALP may play a role in inflammation and endothelial dysfunction, further contributing to increasing ischemic stroke risk [57, 58]. Nonetheless, the precise mechanisms of these enzymes in ischemic stroke development still require further and deep investigation.

ALT and AST, although primarily known as markers of liver function, have been implicated in various systemic processes beyond the liver. While their exact role in the pathogenesis of ischemic stroke is less clear, they have been proposed to reflect systemic inflammation, metabolic dysfunction, or subclinical liver disease, all of which could indirectly influence ischemic stroke risk. Some previously published studies correlate AST and ALT enzymes with better stroke outcomes due to their ability to decrease the negative load of the excitotoxicity process [16, 59]. In addition, a study published in 2020 suggests that the balance between AST and ALT levels could have a protective effect against glutamate toxicity [16]. Moreover, low levels of ALT and AST may reflect reduced liver function or poor overall health, which could indirectly increase the risk of ischemic stroke [60].

Strengths and limitations

By systematically searching and synthesizing available cohort and case-control studies, this systematic review and meta-analysis provides a comprehensive overview of the existing evidence on the association between liver enzymes and ischemic stroke risk. Sensitivity analysis showed stability of the results across all outcomes, and there was no publication bias detected in the GGT outcome. Most studies included were of excellent quality, as assessed by the NOS. However, as limitations are inevitable for any study, it is noteworthy to mention the significant heterogeneity observed among studies for ALP, ALT, and AST. Moreover, the number of studies included in the meta-analysis varied for each liver enzyme, with fewer studies for AST compared to other enzymes. Also, two studies were judged to be of intermediate quality according to NOS criteria.

Variations in the population baseline characteristics, study design, sample size, follow-up duration, and adjusted confounding variables could impact the validity of the results. In addition, the assessment of publication bias was limited to GGT due to the insufficient number of studies for other liver enzymes. As a result, the potential for publication bias in the findings related to ALP, ALT, and AST remains uncertain. We also could not investigate the relationship between different levels of liver enzymes and ischemic stroke due to the high variability in the category boundaries of the enzymes among studies. While the meta-analysis demonstrates an

association between elevated levels of GGT and ALP and an increased risk of ischemic stroke, it does not establish causality. Other unmeasured or residual confounding factors may contribute to this observed association.

Conclusion and recommendations

We found that GGT and ALP were significantly associated with an increased risk of ischemic stroke, unlike AST and ALT. However, the certainty of this evidence was judged to be low or very low by GRADE evaluation. From a clinical perspective, GGT and ALP could serve as potential biomarkers for identifying individuals at higher risk of ischemic stroke, applying preventive measures, and controlling modifiable risk factors to decrease the risk of ischemic stroke.

Individuals with elevated GGT and ALP levels may require closer clinical monitoring and follow-up to assess their overall cardiovascular health and ischemic stroke risk. However, further studies are needed to investigate the association between different levels of liver enzymes and whether they can predict ischemic stroke. The different association of GGT and ALP compared to AST and ALT with ischemic stroke risk highlights the need for further research to investigate the specific roles of these liver enzymes in ischemic stroke pathogenesis. Finally, future studies are warranted to explore the underlying biological mechanisms and potential causal relationships, as well as to investigate whether interventions targeting GGT and ALP levels can effectively reduce the risk of ischemic stroke.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Author contributions

O.S.E. and M.A.T. did the conceptualization and methodology, while A.A., S.I., D.E.T. and M.A.A. did the investigation and data curation. H.E.M. and A.M.E. did the formal analysis. O.S.E., A.Z.E., A.A., S.I., and H.E.M. did the Writing - Original Draft. O.S.E. and M.A.T. did the Supervision. O.S.E. did the Project administration. O.S.E., A.M.E., and A.Z.E. did the Writing - Review & Editing. All authors read and approved the final content.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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