Research Progress on the Application of Serum Cystatin C in Patients with Ischemic Stroke

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Abstract: Ischemic stroke, as a chronic noncommunicable disease with high incidence and disability rates, has become a significant global public health issue. Cystatin C, an endogenous biomarker that sensitively reflects glomerular filtration function, has been widely used in recent years for the clinical assessment of cerebrovascular diseases. This study reviews the latest research findings on the correlation between ischemic stroke and serum cystatin C levels from domestic and international sources. It provides an overview of the relationship between the two and their current clinical applications, aiming to offer a reference for disease management and condition monitoring in ischemic stroke patients.

***Keywords*:** ischemic stroke, serum cystatin C, clinical application, research progress

1. Introduction

Stroke is a major chronic noncommunicable disease that seriously threatens public health, ranking as the second leading cause of death and the third leading cause of disability among adults worldwide [1, 2]. Ischemic stroke (IS) is the most common type, accounting for approximately 83% of all stroke cases [3], with a trend toward younger onset ages [4]. The number of cases is projected to reach 40.7682 million by 2040 [5]. Serum cystatin C (CysC), an objective indicator of renal function, has been demonstrated in recent studies to hold significant value in assessing IS severity, monitoring disease progression, and predicting prognosis [6]. Given this, identifying biomarkers with both high sensitivity and specificity is crucial for guiding early, precise interventions in IS patients and improving clinical outcomes. Therefore, this study reviews the current research on the relationship between IS and CysC, aiming to comprehensively examine their underlying mechanisms and clinical value. This review provides a reference for healthcare professionals to facilitate early identification, risk assessment, and targeted interventions for IS.

2. Overview of CysC

Cystatin C is a naturally occurring cysteinopeptidase inhibitor in the body, primarily produced by nucleated cells. It is a low molecular weight, basic, non-glycosylated protein involved in regulating proteolytic processes both inside and outside cells, and can induce atherosclerosis formation [7, 8]. In healthy adults, serum CysC concentrations range approximately from 0.6 to 1.2 mg/L, with a half-life of about 2 hours [8, 9]. Under physiological conditions, cystatin C levels remain stable, present in various body fluids with relatively constant secretion. It is largely unaffected by factors such as diet, gender, or age, with the highest concentration found in cerebrospinal fluid [7, 10, 11]. CysC is implicated in multiple biological processes, including vascular remodeling, coagulation, inflammatory responses, and the pathophysiology of atherosclerosis [12, 13]. Furthermore, CysC undergoes nearly complete glomerular filtration and is enzymatically degraded after reabsorption in the proximal tubules. This characteristic demonstrates its close correlation with glomerular filtration rate (GFR), making it valuable for early diagnosis of renal insufficiency and long-term monitoring of renal function changes. It is considered an important indicator for assessing renal impairment [11, 14, 15]. With advances in medical technology, diverse methods exist for detecting CysC. Commonly used clinical techniques include immunodiffusion, radioimmunoassay, and enzyme immunoassay [11, 16, 17]. Currently, CysC level changes serve not only as a vital indicator for assessing renal function and predicting prognosis in patients with urogenital malignancies, but also find extensive application in the diagnosis, condition assessment, and treatment monitoring of cerebrovascular diseases. It has established itself as a reliable and highly credible biological marker in clinical practice.

3. Correlation Analysis Between CysC and IS

CysC, as a sensitive indicator for evaluating renal function, is closely associated with the pathological process of IS, but its underlying mechanisms remain incompletely understood. The physiological and pathological foundations of the kidney and brain exhibit striking similarities, providing crucial evidence for their interconnectedness in disease progression. This

correlation manifests in two key aspects: From a structural perspective, both organs share consistent vascular characteristics as high-flow, low-resistance terminal organs, rendering them highly sensitive to blood pressure fluctuations and hemodynamic changes; Pathologically, both the early stages of renal injury and the initial phase of IS onset are closely associated with core pathological factors such as vascular endothelial cell damage and atherosclerosis[18]. Given these shared physiological and pathological foundations, CysC—as a key indicator of renal function—naturally exhibits a strong correlation with the pathogenesis and progression of IS.

Multiple studies suggest that monitoring CysC levels holds significant clinical value for IS patients. Yu Zhijia [19] and Bian Yi[20] et al. found that CysC levels in IS patients increased with worsening neurological deficits, concluding that CysC serves as an important indicator for assessing IS patient prognosis. Shi Yuxi[21] analyzed clinical data from 97 patients with acute ischemic stroke (AIS) and found that CysC levels hold significant predictive value for carotid plaque formation in AIS patients. Wang Jinhua [22] and Liu [23] further suggested that serum CysC also predicts the risk of IS recurrence. Chen Gaiping[24] compared CysC levels at admission and after 14 days of treatment across different severity grades in IS patients, revealing a significant correlation between CysC levels and disease severity. A systematic review [25] encompassing 9 studies involving 3,773 IS patients demonstrated significantly elevated CysC concentrations in IS patients compared to non-IS patients. Thus, CysC levels may be significantly associated with the progression of IS disease. This marker could serve as an important biological indicator for assessing IS patient prognosis, recurrence risk, and disease severity.

4. Current Clinical Application of CysC in IS Patients

4.1 CysC and Post-Stroke Depression

Post-stroke depression (PSD) is a common complication among stroke patients, with an incidence rate exceeding one-third. It typically manifests as symptoms such as low mood, diminished interest, fatigue, and decreased energy, significantly impacting rehabilitation progress, disease prognosis, and quality of life [26, 27]. Cysteinyl cysteinase , an inhibitor of cathepsins, exhibits abnormally elevated levels during cerebral vascular lesions, subsequently inducing emotional changes in patients [28]. Xu Qianqian[29] demonstrated through logistic regression analysis that elevated CysC levels constitute a risk factor for depressive comorbidity in AIS patients. Fang Zhou[30] identified increased CysC levels as an independent risk factor for post-stroke depression (PSD) occurring three months post-discharge in patients with lacunar infarction, suggesting this marker could serve as a novel biomarker for predicting PSD risk. Lian Haojun[31] collected clinical data from 102 AIS patients, revealing a significantly increased incidence of depression in those with CysC $\geq$ 1.09 mg/L. Although elevated CysC levels are closely associated with PSD, its underlying mechanisms remain incompletely elucidated. Proposed mechanisms include CysC-induced microvascular lesions and cerebral microvascular injury leading to neuronal death, thereby impairing serotonergic system function. Concurrently, elevated CysC exacerbates systemic inflammation. The combined effects of these pathophysiological processes ultimately contribute to depressive symptom development [32, 33]. Currently, studies on the psychological status of IS patients both domestically and internationally are largely confined to the post-onset intervention phase, with particularly scarce biological indicators related to this condition. Therefore, future research could adopt CysC as an observational marker for IS patients, aiding in the early screening of PSD onset and enabling the development of targeted early intervention measures to prevent PSD occurrence.

4.2 CysC and Post-Stroke Cognitive Impairment

Post-stroke cognitive impairment (PSCI) exacerbates the physical and psychological damage in stroke patients, serving as a major cause of disability and mortality. In China, the incidence of PSCI reaches 80.97% [34], while 24.0% to 53.4% of acute ischemic stroke (AIS) patients may develop cognitive impairment [35]. Therefore, prioritizing the cognitive status of stroke patients and actively exploring serum biomarkers and predictive indicators associated with PSCI are crucial for achieving early clinical management. Previous studies have demonstrated significant alterations in cystatin C (CysC) levels among patients with cognitive impairment [36]. Chen Hongmei [37] conducted a 3-month cognitive function assessment and follow-up study involving 108 AIS patients within 24 hours of onset as the case group and 50 patients undergoing concurrent physical examinations as the control group. Results indicated a 51.85% incidence of PSCI post-stroke, with higher serum CysC levels correlating to more severe cognitive impairment in stroke patients. A meta-analysis [38] included 10 studies with 728 cases and 898 controls. The results showed that serum CysC levels were significantly higher in the PSCI group than in the control group. Subgroup analysis revealed that serum CysC levels were higher in both the PSCI subgroup with a disease duration <14 days and the subgroup with a disease duration $\geq$14 days compared to the control group. The conclusion was that serum CysC levels in PSCI patients were higher than in patients with normal cognitive function after stroke. The analysis suggested that this may be related to neurodegenerative lesions. Cheng Zhiqing [39] identified serum CysC as a

major influencing factor for PSCI through logistic regression analysis, noting its predictive and evaluative role in assessing PSCI risk. Zuo[40] measured serum CysC levels in 1025 IS patients to investigate its correlation with cognitive impairment one year post-onset in mild IS patients. Findings revealed a U-shaped relationship between serum CysC and overall cognitive function, suggesting that measuring serum CysC levels may aid in the early diagnosis of cognitive impairment. Hao's[41] systematic review revealed that AIS patients with cognitive impairment had significantly higher serum CysC levels than controls during follow-ups of less than one month, indicating that elevated CysC levels correlate with poor outcomes in AIS patients. The mechanism by which elevated serum CysC levels may contribute to PSCI involves high CysC levels inducing central nervous system degenerative lesions, exacerbating vascular wall damage, and ultimately leading to PSCI. Currently, the mechanism linking CysC and PSCI requires further investigation, and systematic reviews summarizing the research on their correlation remain incomplete.

4.3 CysC and Cerebral Microbleeds

Cerebral microbleeds (CMBs) frequently coexist in patients with ischemic stroke,closely correlating with the risk of stroke onset and mortality. They also increase the risk of intracerebral hemorrhage, leading to declines in cognitive and motor function among IS patients and adversely affecting rehabilitation progress and prognosis [42, 43]. Gao Qian [44] identified CysC as an independent risk factor for CMBs in IS patients, with a CysC level ≥0.895 mg/L serving as the predictive threshold for CMB occurrence. Li Yinzhen [45] retrospectively analyzed clinical data from 114 IS patients, categorizing them into a group without CMBs (n=73) and a group with IS complicated by CMBs (n=41) based on magnetic susceptibility imaging results. The study found that CysC levels were higher in the CMBs group than in the non-CMBs group, confirming CysC as an independent risk factor for CMBs in IS patients. A domestic meta-analysis incorporating 11 cross-sectional studies and 1 case-control study with 2,622 samples demonstrated significantly higher serum CysC concentrations in the CMBs group compared to controls. The pooled weighted mean difference indicated a positive correlation between elevated serum CysC levels and CMBs risk in IS patients (OR=2.16, 95% CI: 1.32–3.56) [46]. Zhang [47] conducted a cross-sectional study involving 485 AIS patients, finding that CMBs most frequently occurred in deep or infratentorial regions, followed by lobar areas. Additionally, CysC levels in IS patients with CMBs increased with the number of CMBs. Thus, in-depth exploration of risk factors for CMBs in IS patients is crucial for preventing CMBs and improving patient outcomes. Dynamic monitoring of CysC levels can assist clinicians in developing early intervention strategies for IS patients, thereby providing valuable guidance for clinical care.

5. Conclusion

In summary, as a major chronic noncommunicable disease, the incidence, disability rate, and mortality of IS have all shown a year-on-year upward trend in recent years, significantly increasing the disease burden in China. Currently, scholars both domestically and internationally are actively exploring biological markers that can be used to predict and assess the onset and progression of IS, aiming to reduce the risk of IS and its related complications and improve patient clinical outcomes. Given the high similarity between the brain and kidneys in pathophysiological foundations and hemodynamics, research on the correlation between CysC and IS has become a hot topic in this field. However, existing studies still have significant shortcomings: First, the exploration of biological indicators related to their correlation remains incomplete, lacking sufficient validation from large-sample research data. Second, the specific mechanisms of their interaction and the cross-effects of various influencing factors have not been fully elucidated. Therefore, subsequent research should focus on conducting more high-quality basic and clinical studies to identify and validate biological markers with high specificity and sensitivity for both IS and serum CysC. This will clarify the causal relationship and potential mechanisms between the two, providing a reference basis for early warning, disease assessment, and targeted intervention for IS.

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