

RESEARCH ARTICLE

Correlates of depressive risk in leukoaraiosis: Sleep dysfunction, female gender, and cardiac history with no contribution from thyroid hormones

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Leukoaraiosis, characterized by white matter hyperintensities on magnetic resonance imaging (MRI), has been associated with an elevated risk of depression. However, the risk factors for depressive tendency in this population have not been systematically investigated. Thyroid dysfunction is involved in the pathogenesis of depression. Free thyroxine (FT4) correlates with severe leukoaraiosis. This study aimed to identify factors associated with the risk of depression in individuals with leukoaraiosis and evaluate the potential role of thyroid hormones in this relationship. 100 patients with leukoaraiosis between April 2024 and March 2025 were enrolled. Clinical data including Fazekas grading scores, thyroid hormone concentrations, and other laboratory test outcomes were gathered. The subjects were divided into two groups according to Hamilton Depression Rating Scale (HAMD-17) with the score of 7 and above as depressive risk group and the score less than 7 as non-risk group. Univariate statistical analysis and multivariate logistic regression modeling were adopted for inter-group data comparison and correlation exploration. 21 subjects (21.0%) were identified as a depressive risk population. FT4 levels demonstrated a progressive elevation with worsening Fazekas grades ($P < 0.05$), but the correlation between FT4 and the severity of leukoaraiosis was weak, albeit statistically significant ($r = 0.218$, $P < 0.05$). Univariate statistical analyses showed that the incidence of sleep disturbance was significantly higher in the depressive risk group ($P < 0.001$). Further multivariate logistic regression modeling validated three independent correlates to depressive tendency as sleep disorders (OR = 23.320, 95% CI: 3.857 – 141.004, $P < 0.01$), female gender (OR = 35.828, 95% CI: 1.895 – 677.529, $P < 0.05$), and prior cardiac disease records (OR = 9.325, 95% CI: 1.310 – 66.380, $P < 0.05$). There was no difference in thyroid function markers between the two-grouped populations. In subjects showing leukoaraiosis on MRI, higher FT4 levels were related to severe leukoaraiosis. Sleep dysfunction, female gender, and previous cardiac medical history emerged as independent associated factors for depressive risk, whereas thyroid hormone concentrations showed no significant association with depressive risk.

Keywords: leukoaraiosis; depressive risk; thyroid hormones; sleep disorders; female; cardiac history.

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Introduction

Leukoaraiosis, also known as brain white matter hyperintensity lesions, is a typical imaging

feature of cerebral small vessel diseases. The typical imaging manifestations are hyperintense on T2-weighted imaging (T2WI) and/or fluid-attenuated inversion recovery (FLAIR) sequences

of brain magnetic resonance imaging (MRI), accompanied by hypointensity on T1-weighted imaging (T1WI) [1]. This radiological phenomenon is widely prevalent in the general population and particularly has higher prevalence in elderly populations. Epidemiological studies have revealed that its prevalence is in the range of 36.5% to 100% in people over 40 years old around the world [2]. Previous clinical research has highlighted the fact that the presence of leukoaraiosis can increase the risk of developing depressive symptoms [1-3]. However, the associated factors and underlying mechanisms of this link remain unclear to date.

The pathological changes of leukoaraiosis include local tissue edema, glial cell proliferation, chronic cerebral ischemia, and inflammatory reactions [4]. The occurrence and progression of leukoaraiosis relate to abnormal cerebral blood flow self-regulation mechanisms, venous vascular collagen deposition, blood-brain barrier functional damage, unbalanced neurovascular coupling effects and genetic susceptibility characteristics [1]. Recognized risk factors for this condition involve aging progression, hypertension and blood pressure volatility, diabetes mellitus, smoking behaviors, dyslipidemia, arteriosclerosis, elevated homocysteine levels, vitamin D nutritional status, obesity, gender differences, low educational levels, racial attributes, genetic predisposition, free thyroxine concentrations, cerebral microbleeds and prior ischemic stroke history with partial influencing factors still requiring further verifications [2, 5]. Prior clinical studies have validated that leukoaraiosis pathological changes can elevate depressive morbidity risk, especially among elderly patient groups [2, 4, 6]. Brain imaging studies have observed wider distributions of white matter lesions in patients with major depressive disorder [7]. However, academic controversies also persist. One elderly population survey discovered higher leukoaraiosis prevalence among black individuals with depression, while such racial disparities were not observed in white populations [8].

Another cross-sectional research targeting participants under 65 years old detected no measurable differences in leukoaraiosis severity between depressive patients and healthy control subjects [7].

Thyroid hormones can promote glial cell growth and proliferation activities [9]. Beyond the roles of thyroid hormones in development, they are critical in adulthood for regulating cerebral neuroplasticity, angiogenesis, neuronal regeneration, cytoskeletal dynamics balance, and intracellular material transport within both neurons and glial cells. Thyroid endocrine abnormalities participate in the pathological processes of multiple neurological diseases, covering depressive disorders, epilepsy, Alzheimer's disease, and Parkinson's disease [10]. Thyroid hormones are also implicated in the pathophysiology of depressive disorders. The limbic system, serving as the core emotional regulatory area of the brain, distributes abundant thyroid hormone receptors, which participate in the pathological evolution of emotional affective disorders [11]. Dysfunction of the hypothalamic-pituitary-thyroid regulatory axis has long been associated with depressive symptom occurrence [12], while inflammatory reactions and genetic susceptibility can also mediate the interactive relationship between thyroid disorders and depression development [13]. Those experiencing depression and anxiety show elevated risks for thyroid system complications with correlation magnitude strengthening as depression and anxiety intensify [14]. Clinical observations revealed that most patients with depression did not present with overt thyroid dysfunction, but subtle quantitative variance in thyroid function indexes was observed in some cases [15]. Both hyperthyroidism and hypothyroidism conditions along with excessively high or low TSH concentrations can promote depressive episode onset [13, 16-19], although the statistical association between hypothyroidism and depression is relatively low [16]. Hyperthyroid patients are prone to developing various depressive emotional manifestations [13]. Even in the normal range,

higher FT4 concentrations and lower TSH correlate with higher risks of depression [20]. Pharmaceutical intervention shows that single medication with levotriiodothyronine (LT3) and levothyroxine (LT4) cannot directly alleviate core depressive symptoms [12, 17], yet these thyroid hormone preparations can generate auxiliary therapeutic effects when combined with conventional antidepressant drugs [22]. Individual research outcomes also support LT4 medication benefits for improving depressive manifestations in subclinical hypothyroidism patients [12]. LT3 adjuvant treatment can accelerate therapeutic responses to antidepressants and enhance drug efficacy for refractory depression cases, while LT4 exhibits auxiliary curative effects in clinical intervention for drug-resistant depressive disorders [23]. Long-term antidepressant medication may trigger adaptive fluctuations in human thyroid hormone profiles [22]. However, some studies confirmed stronger depressive correlations with clinical hypothyroidism than subclinical thyroid dysfunction [16], while other reports suggested higher depressive rates in subclinical hypothyroidism patients [17]. Age stratification analysis revealed inverse correlations between depressive severity and FT4, FT3, as well as TT3 indicators across different age groups [11]. In adult depressive patients, TT4 exhibits negative correlations with depression severity in the elderly, but positive correlations in the younger depressed patients [11]. Some studies detected neither significant correlations between normal-range changes in TSH/FT4 concentrations and depressive risk [24], nor the correlations with clinical or subclinical hyper- or hypothyroidism [18]. Free thyroxine (FT4) has been proven to serve as an independent hazard factor for both the occurrence and severity of leukoaraiosis [5, 25]. Mild abnormal fluctuations in thyroid hormone levels such as slight increases in serum FT4 content are observed in patients with depression [15]. Hypothyroidism [16, 17], hyperthyroidism [13], elevated thyroxine (T4) [20], or low thyroid-stimulating hormone (TSH) within normal reference ranges may facilitate the emergence of depressive disorders [18, 19].

Additionally, patients suffering from depression face higher probability of developing thyroid system dysfunction in the course of illness progression [14]. However, thyroid hormones have not been systematically evaluated in the population with leukoaraiosis who are at risk of depression.

This study investigated the clinical correlates associated with depressive tendency in subjects with leukoaraiosis and determined whether thyroid hormones were involved. In this cross-sectional study, univariate analysis and multivariable binary logistic regression were performed after clinical data collection. The results of this study could help elucidating the underlying mechanisms and lay the foundation for developing intervention programs for leukoaraiosis patients at potential risk of depression.

Materials and methods

Study setting and participants

A total of 100 leukoaraiosis patients including 37 males and 63 females, aged from 45 – 90 years old, admitted to the Department of Neurology, Shengzhou People's Hospital (Shaoxing, Zhejiang, China) from April 2024 to March 2025 were recruited for this study. The inclusion criteria were age 18 years and older; meeting the standardized imaging diagnostic criteria for leukoaraiosis diagnosed by brain MRI with lesions showing isointense or hypointense signal on T1WI, and punctate, confluent or diffuse hyperintense signal on T2WI and FLAIR sequences, located in the periventricular or subcortical white matter; no cavitation being observed in the lesions and clearly distinguishable from cerebrospinal fluid signals [1]; signed informed consent forms; fully cooperated with all clinical examinations and scale assessments throughout the study. The exclusion criteria were participants with organic brain lesions capable of triggering white matter signal abnormalities including cerebral infarction, intracranial infection, craniocerebral trauma,

immune system diseases, metabolic disorders, intracranial tumors, hereditary neurological diseases, and toxic damage conditions; individuals with confirmed primary thyroid diseases such as hyperthyroidism, subacute thyroiditis, Hashimoto's thyroiditis, and benign or malignant thyroid tumors; complicated with other mental illnesses including schizophrenia, bipolar affective disorder, and manic episodes; depressive symptoms induced by secondary factors such as major life emergencies, long-term and short-term medication effects, hospital environmental discomfort, menstrual cycle fluctuations, and socioeconomic pressure; with severe multi-organ systemic diseases involving cardiac, pulmonary, hepatic, renal, and hematopoietic systems, as well as terminal critical illness patients; dementia patients unable to complete standardized depressive scale assessments independently. The participants were divided into two groups with 21 patients showing depressive risk and 79 without. The procedures of this study were approved by the Institutional Review Board of Shengzhou People's Hospital, Shaoxing, Zhejiang, China with approval number of 2020-K-Y-023-01. The basic demographic information was recorded upon admission covered age, gender, educational background, and common cerebrovascular risk indicators including hypertension, diabetes mellitus, prior cardiac disease history, stroke records, smoking habits, and alcohol consumption status. Education level was categorized as 0 for no formal education, 1 for primary school, 2 for middle school, 3 for technical secondary school, 4 for high school, 5 for junior college, and 6 for university. Fasting venous blood samples were collected in the morning following admission for laboratory biochemical detection. Thyroid functional indicators of triiodothyronine (TT3), free triiodothyronine (FT3), total thyroxine (TT4), FT4, TSH, and blood lipid profiles and serum homocysteine concentrations were measured. All participants completed the Hamilton Depression Rating Scale (HAMD-17) to evaluate depressive severity through 17 dimensional indicators including depressed mood, guilt

feelings, suicidal ideation, three types of insomnia symptoms, work interest decline, psychomotor retardation, emotional agitation, mental anxiety, physical anxiety reactions, gastrointestinal discomforts, general somatic symptoms, genital system abnormalities, hypochondriac tendencies, weight loss, and disease cognitive awareness. The greater the total score, the more serious the depressive symptoms. Based on the total scores, participants were subdivided into two cohorts including depressive risk group (scores ≥ 7) and non-risk control group (scores < 7). All MRI were obtained using a 1.5-Tesla Apsaras superconducting brain MRI scanner (Kangda Intercontinental Medical Devices Co., Ltd., Ningbo, Zhejiang, China) without the contrast. The severity of leukoaraiosis pathologies were scored using the Fazekas rating system with a range of 0 - 6 points [26]. The grading of periventricular hyperintensity was assessed independently with 0 for no abnormal appearance, 1 for a cap or thin marginal linear lesion, 2 for smooth halo-like lesions, and 3 for irregular periventricular lesions with deep white matter extension. The same scoring system applied to deep white matter hyperintensity with 0 for normal brain, 1 for punctate lesions, 2 for an early confluence of lesions, and 3 for confluent lesions. The sum of periventricular and deep white matter grading scores constituted the total Fazekas score.

Statistical analysis

SPSS 25.0 (IBM, Armonk, NY, USA) was employed for statistical analysis. Quantitative data were all presented in the form of median and interquartile range regardless of the underlying distribution for consistency in data presentation. Independent sample t-tests and one-way ANOVA analyses were applied for inter-group comparisons of normally distributed quantitative indicators across two or multiple cohorts, respectively. Variational analyses of non-normally distributed data were conducted *via* the Mann-Whitney U test for 2-group comparison and the Kruskal-Wallis H test for multiple-group comparisons. Characteristic counting data were

Table 1. Single factor comparison of clinical data of leukoaraiosis subjects with and without depressive risk.

Variables	Total (n = 100)	Non-depressive risk (n = 79)	Depressive risk (n = 21)	P value
Age (years)	69 (63.0, 75.5)	69 (62.0, 76.0)	69 (67.5, 73.0)	0.508
Female (%)	63 (63%)	47 (59.5%)	16 (76.2%)	0.159
Education level	1 (1, 2)	1 (1, 2)	1 (1, 1)	0.561
Smoking (%)	17 (17%)	14 (17.7%)	3 (14.3%)	0.964
Drinking (%)	19 (19%)	15 (19.0%)	4 (19.0%)	1.000
Hypertension (%)	73 (73%)	59 (74.7%)	14 (66.7%)	0.462
Cardiac disease (%)	21 (21%)	13 (16.5%)	8 (38.1%)	0.063
Ischemic stroke (%)	18 (18%)	14 (17.7%)	4 (19.0%)	1.000
Hemorrhagic stroke (%)	3 (3%)	2 (2.5%)	1 (4.8%)	0.511
Transient ischemic attack (%)	3 (3%)	1 (1.3%)	2 (9.5%)	0.111
Diabetes (%)	25 (25%)	21 (26.6%)	4 (19.9%)	0.478
Hyperlipidemia (%)	51 (51%)	40 (50.6%)	11 (52.4%)	0.887
Sleep disturbance (%)	36 (36%)	20 (25.3%)	16 (76.2%)	< 0.001**
Homocysteine(μmol/l)	9.45 (7.98, 11.15)	9.4 (7.95, 11.20)	9.6 (7.75, 11.75)	0.983
TT3 (nmol/L)	1.32 (1.06, 1.47)	1.32 (1.10, 1.48)	1.29 (1.10, 1.44)	0.178
TT4 (nmol/L)	90.83 (74.41, 107.11)	91.27 (74.95, 108.36)	90.25 (69.56, 101.25)	0.474
FT3 (pmol/L)	3.79 (3.40, 4.21)	3.82 (3.41, 4.22)	3.63 (3.33, 4.03)	0.213
FT4 (pmol/L)	12.23 (11.35, 13.13)	12.2 (11.33, 13.13)	12.26 (11.28, 13.11)	0.514
TSH (mIU/L)	1.41 (0.91, 2.17)	1.41 (0.88, 2.17)	1.41 (1.06, 2.31)	0.531
Total Fazekas score	3 (2, 4)	2 (2, 4)	3 (2, 4)	0.639

Note: ** indicated $P < 0.01$.

presented with case number and proportion, while chi-square test was used for comparison. Spearman rank correlation analysis measured linear association trends between non-normally distributed variables. Multivariate logistic regression analysis was conducted to identify potential independent correlates of depressive risk in individuals with leukoaraiosis, and the results were expressed in terms of odds ratios (OR) and 95% confidence intervals (CI). P values less than 0.05 were defined as statistically significant clinical differences.

Results

21 cases (21%) were identified as having depressive tendency risk, whereas the remaining 79 participants (79%) showed no relevant risk characteristics. The median HAMD-17 score was 10 points in individuals assessed as being at depressive risk with a lower quartile of 7.5 points

and an upper quartile of 12.5 points. The range of HAMD-17 scoring was 7 points (minimum critical value) to 27 points (maximum). Comparisons of baseline characteristics between two groups demonstrated that the incidence rate of sleep disturbance symptoms showed extremely prominent statistical differences, being far higher in the depressive risk population ($P < 0.001$). No remarkable statistical differences emerged in various thyroid hormone concentrations between subjects with leukoaraiosis and depressive risk and those without such tendencies. Spearman correlation analysis further verified that HAMD scoring results had no significant linear correlations with TT3, TT4, FT3, FT4, and TSH levels (Table 1). The different radiological severity grades of leukoaraiosis displayed no direct connection with the occurrence and severity of depressive symptoms. Additional analyses of thyroid hormone markers revealed that FT4 levels were significantly different among different leukoaraiosis severities

Table 2. Correlations of leukoaraiosis grades with depressive risk and thyroid function levels.

Total Fazekas score	1 (n = 15)	2 (n = 34)	3 (n = 14)	4 (n = 18)	5 (n = 7)	6 (n = 12)	P value
Depressive risk (%)	1 (6.7%)	8 (23.5%)	5 (35.7%)	4 (22.2%)	1 (14.3%)	2 (16.7%)	0.561
HAMD score	3 (2, 4)	3 (1, 6.3)	1.5 (1, 7.5)	2.5 (1, 6.3)	1 (0, 3)	3 (1.3, 5.0)	0.871
TT3 (nmol/L)	1.15 (1.02, 1.38)	1.36 (1.09, 1.51)	1.33 (1.13, 1.55)	1.33 (1.00, 1.46)	1.38 (1.22, 1.48)	1.38 (1.22, 1.56)	0.503
TT4 (nmol/L)	78.33 (70.88, 95.33)	89.16 (74.39, 108.92)	91.08 (78.79, 106.26)	101.12 (83.01, 112.60)	86.60 (78.09, 105.33)	93.80 (77.74, 111.36)	0.464
FT3 (pmol/L)	3.55 (3.25, 3.82)	3.79 (3.36, 4.42)	3.87 (3.64, 3.97)	3.83 (3.40, 4.18)	3.95 (3.78, 4.57)	3.74 (3.45, 4.52)	0.290
FT4 (pmol/L)	11.59 (11.00, 12.33)	11.83 (11.25, 12.71)	12.19 (11.53, 13.28)	13.51 (12.40, 14.52)	12.48 (11.63, 13.07)	12.06 (11.09, 12.99)	0.020*
TSH (mIU/L)	1.71 (0.82, 2.41)	1.22 (0.86, 2.00)	1.48 (0.86, 1.98)	1.23 (1.00, 2.29)	1.41 (0.99, 2.03)	2.23 (1.06, 2.66)	0.550

Note: * indicated $P < 0.05$.

Table 3. Logistic regression analysis of factors related to depressive risk in leukoaraiosis.

Factors	OR (95% CI)	P value
Age (years)	0.988 (0.910, 1.074)	0.785
Female (%)	35.828 (1.895, 677.529)	0.017*
Education level	1.565 (0.825, 2.967)	0.170
Smoking (%)	1.743 (0.132, 23.069)	0.673
Drinking (%)	2.828 (0.348, 22.959)	0.331
Hypertension (%)	1.007 (0.210, 4.826)	0.993
Cardiac disease (%)	9.325 (1.310, 66.380)	0.026*
Ischemic stroke (%)	1.542 (0.232, 10.259)	0.654
Hemorrhagic stroke (%)	5.294 (0.158, 177.864)	0.353
Diabetes (%)	0.098 (0.009, 1.073)	0.057
Hyperlipidemia (%)	1.025 (0.228, 4.607)	0.974
Sleep disturbance (%)	23.320 (3.857, 141.004)	0.001**
Homocysteine (μmol/L)	1.208 (0.931, 1.567)	0.155
TT3 (nmol/L)	0.027 (0.000, 12.323)	0.248
TT4 (nmol/L)	1.008 (0.947, 1.072)	0.814
FT3 (pmol/L)	1.682 (0.162, 17.441)	0.663
FT4 (pmol/L)	0.633 (0.321, 1.247)	0.186
TSH (mIU/L)	1.048 (0.594, 1.848)	0.872
Total Fazekas score	0.914 (0.562, 1.488)	0.718

Note: * indicated $P < 0.05$. ** indicated $P < 0.01$.

($P < 0.05$). Spearman rank correlation results retained a weak positive correlation between the total Fazekas grading scores and FT4 concentrations with r of 0.218 ($P < 0.05$). Other thyroid functional indicators including TT3, TT4, FT3, and TSH showed no significant numerical fluctuations corresponding to leukoaraiosis lesion severity (Table 2). Multiple confounding factors were incorporated into the multivariate

logistic regression model as covariables including age, gender, educational attainment, hypertension, diabetes, cardiac medical history, cerebral infarction and hemorrhage records, sleep disorder status, smoking and alcohol habits, all thyroid hormone indicators, blood lipid abnormalities, homocysteine content, and total Fazekas grading scores. The comprehensive regression analytical outcomes showed that the

initial univariate statistical analyses did not demonstrate obvious differences in gender proportions and heart disease incidence between the two groups. After adjusting for confounding factors *via* binary logistic regression modeling, female gender with OR of 35.828 and 95% CI of 1.895 – 677.529 ($P < 0.05$) and previous cardiac disease history with OR of 9.325 and 95% CI of 1.310 - 66.380 ($P < 0.05$) emerged as independent correlates for depressive vulnerability. Sleep dysfunction consistently remained statistically significant during univariate screening and final multivariate regression verification, serving as a pivotal independent associated factor for depressive tendency with OR of 23.320 and 95% CI of 3.857 - 141.004 ($P < 0.01$) (Table 3). This phenomenon indicated that gender and cardiac medical history factors were masked by other interfering variables in simple inter-group comparisons with their independent influencing effects only appearing after multi-dimensional data correction. Throughout all statistical procedures, neither univariate nor multivariate analytical methods confirmed any effective correlation between thyroid hormone levels and depressive risk among subjects with leukoaraiosis.

Discussion

The underlying pathological mechanisms by which leukoaraiosis lesions elevate the risk of depressive disorders are not fully understood, and the related risk correlations are underexplored. One popular theory suggests that leukoaraiosis lesions destroy frontosubcortical white matter nerve fiber pathways that are responsible for emotional processing and cognitive information transmission, thus rendering susceptibility to late-onset depressive illnesses [4]. The present research found that sleep disturbance problems, female, and prior cardiac disease history constituted prominent associated factors for depressive symptoms in leukoaraiosis populations. According to general population studies worldwide, sleep disorders are established to be a core feature and

independent predictor of depression onset [27]. Epidemiological data shows that women have 1.6 - 1.7 times the risk of severe depressive morbidity comparing to men [28]. A significant positive correlation has been reported between cardiovascular diseases and depression [21]. While previous investigations into the correlations of depression have largely been conducted in general depressed populations, this study narrowed this focus to a specific subpopulation that subjects with leukoaraiosis who presented with depressive symptoms. The results of this study consistent with previous reports in depressed populations not only validated the generalizability of these established risk factors but also confirmed that they remained clinically relevant in the specific context of leukoaraiosis. This research verified that FT4 content changed synchronously with leukoaraiosis severity, showing higher concentrations in subjects with advanced pathological lesions, which aligned with previous studies [5, 25]. The finding solidified the inherent connection between thyroid hormone metabolism and leukoaraiosis onset, as well as progressive deterioration. This study sought to determine whether thyroid hormone levels were associated with depressive risk in subjects with leukoaraiosis, but no significant association was observed. This result suggested that the thyroid endocrine system might not be directly involved in the development of depressive risk in these subjects, and the mechanisms underlying depressive symptoms in leukoaraiosis might be distinct from those in general depressed populations. However, the relatively small sample size of this study might have limited the ability to detect weak but potentially meaningful associations. Several inherent limitations existed in this research. Single-center enrollment design restricted sample quantity, and cross-sectional observational research nature prevented causal relationship verification. Future multi-center prospective large-sample studies are required to further supplement and validate relevant research conclusions, while exploration of other mechanistic pathways is also worthy of consideration. The results of this study showed

that sleep dysfunction, female, and historical cardiac disease records served as key associated factors that elevated depressive risk for individuals with leukoaraiosis. Free thyroxine levels gradually rose alongside aggravated leukoaraiosis severity, presenting mild positive correlations with lesion progression degrees. No measurable correlation could be proven between thyroid hormone concentration variations and depressive susceptibility among leukoaraiosis subjects. This research raised clinical attention toward depressive risk screening for leukoaraiosis subjects, provided valuable reference evidence for subsequent in-depth mechanistic research, and helped to build targeted preventive strategies against depression complications in leukoaraiosis clinical management.

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