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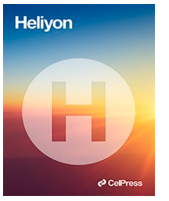

Review article

Effects of cortisol on cognitive and emotional disorders after stroke: A scoping review

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ABSTRACT

Objectives: Stroke-induced cognitive and mood disorders are closely related to glucocorticoids released during hypothalamic-pituitary-adrenal (HPA) axis activation. There are many studies on the relationship between cortisol levels and post-stroke cognitive impairment (PSCI) and post-stroke depression (PSD). This paper provides a scoping review of these studies to clarify the effect of cortisol on PSCI and PSD, thereby providing a theoretical basis for clinical diagnosis and treatment.

Materials and methods: We searched for literature published up to October 2023 on the association of cortisol with post-stroke cognitive and emotional disorders in the PubMed, Web of Science, Cochrane Library, CNKI and Wanfang databases. Relevant papers were identified and the effects of cortisol on cognitive and emotional disorders after stroke were analyzed by literature induction.

Results: Eighteen papers were included, including cross-sectional studies and cohort studies. The subjects suffered ischemic stroke or hemorrhagic stroke. Cortisol levels were measured from samples of blood, saliva or hair. Most patients showed increased basal cortisol levels and changes in cortisol circadian rhythms. Most studies report that patients with high cortisol levels on admission (acute phase of stroke) are more likely to experience cognitive decline and depression later in life.

Conclusions: Admission cortisol level may be a promising biomarker for predicting cognitive and emotional prognosis after stroke.

1. Introduction

Stroke is a common cerebrovascular disease that poses a serious threat to human health and life [1]. Post-stroke depression (PSD) and post-stroke cognitive impairment (PSCI) are common complications after stroke [2]. The Stroke and Cognition Consortium (STROKOG) harmonized data from 13 studies based in 8 countries found that 44 % of stroke participants admitted to hospital were impaired in global cognition [3]. Among stroke survivors, cognitive impairment is a major cause underlying disability/dependence [4]. A large cohort study found that 25.4 % stroke patients developed depression within 2 years after study entry, while only 7.8 % reference population experienced depression [2]. However, in clinical practice more attention is often paid to the physical dysfunction of stroke patients, while their emotional and cognitive deficits are neglected. As a consequence, patients often do not receive timely

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intervention for emotional and cognitive disorders, which ultimately affects the prognosis.

Stroke is strongly associated with stress loading. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation and hyperactivation of the HPA axis have been found in stroke patients. This may be related to uncontrolled activation of proinflammatory processes mediated by focal brain injury. Increased hormone secretion by the HPA axis leads to changes in the expression and properties of corticosteroid receptors in stress-sensitive brain regions, mainly in the limbic system, thereby altering the regulatory mechanisms of the whole system under negative feedback control. Typically, the hippocampal regions with a higher density of glucocorticoid receptors are the first to show pathologic functional and morphological impairments. Damage to the hippocampus, a key structure involved in the formation of memory and mood, can lead to cognitive impairment and depression [5].

Cortisol is the predominant glucocorticoid in the human body. Many studies have been conducted to explore the relationship between cortisol levels and PSCI and PSD. Barugh et al. had conducted a systematic review of the correlation between cortisol levels and prognosis in acute stroke in 2014 [6]. However, PSCI is not included in their review. At present, there is no article that reviews the relationship between cortisol and PSCI. In the past, people usually measured cortisol levels in blood, saliva, urine and cerebrospinal fluid. In recent years, with the progress of measurement technology for hair cortisol concentration (HCC), people have begun to study the relationship between HCC and PSCI and PSD. Since HCC can reflect the comprehensive cortisol level over a period of time, it can better reflect the changing trend of cortisol in stroke patients during the course of the disease. Therefore, we conducted a more detailed and comprehensive scoping review of relevant studies in order to clarify the effect of cortisol levels on cognitive and mood disorders after stroke.

2. Methods

Searches were conducted in the PubMed, Web of Science, Cochrane library, CNKI and Wanfang databases, including articles included from the establishment of the database to October 2023. The complete search logic (search with title, abstract and key words) are: (“cortisol” OR “Hydrocortisone”) AND (“Stroke” OR “Cerebrovascular Accident*” OR “Cerebral Stroke” OR “Cerebrovascular Stroke”) AND (“Cognitive Impairment” OR “Cognitive Dysfunction” OR “Cognitive Disorder” OR “Cognitive Decline” OR “Mental Deterioration”) OR (“Depression” OR “Depressive Symptom*” OR “Emotional Depression”).

2.1. Inclusion criteria

1. Population: recruited 10 or more participants after stroke (ischemic stroke and hemorrhagic stroke).
2. Research contents: the relationship between cortisol and cognitive or depressive impairment after stroke.
3. Main outcome measures: cortisol levels in blood, saliva or hair and the cognitive or emotional state of the patient.
4. Design: observational study.
5. Language: English or Chinese.

2.2. Exclusion criteria

1. Duplicate publications
2. Animal experimentation
3. Interventional studies
4. Subjects were non-stroke patients.
5. Reviews, conference papers and dissertations

Barugh [6] published a systematic review on the correlation between cortisol and PSD that included relevant literature published before April 2013. Therefore, relevant literature published prior to April 2013 was excluded from the current analysis.

2.3. Study selection

EndNote X9 is used for document management. Duplicate publications were found and removed. Firstly, the articles that do not meet the inclusion criteria are eliminated according to the title and abstract. Two reviewers then independently evaluate the eligible full text. Differences between reviewers are discussed to reach a consensus and resolved by a third reviewer.

2.4. Data extraction

Data were extracted using standardized data collection forms and included details on the study design, participant characteristics, and outcome measures. The effects of cortisol on cognitive dysfunction and depression after stroke were analyzed using a literature summarization approach.

2.5. Quality assessment

The Joanna Briggs Institute, Practical Application of Clinical Evidence System (JBI PACES) was used to evaluate the quality of cross-sectional studies and cohort studies.

3. Results

The search for keywords resulted in a total of 315 articles from the 5 databases. Of these, 60 were removed due to duplication, leaving 255 articles for further screening of the abstract and title. A further 224 articles were removed because they did not meet the afore-mentioned inclusion criteria. Following assessment of the remaining 31 articles for eligibility, 13 were removed, leaving 18 articles for review in the present study. Five studies used a longitudinal methodology, and 13 were cross-sectional studies. The selection process for these articles is outlined in Fig. 1.

3.1. Methodological quality

Confounders were not identified in 4 of the 18 observational studies and no measures were taken to control for confounders [7–10], and the cause of loss of follow-up was not described or analyzed in 1 of the 5 cohort studies [11]. The rest of items result in "Yes". The quality of these studies was generally high (Table S1).

3.2. Measurement of cortisol

Of the 18 included studies, 12 measured cortisol in the blood (Tables 1 and 2). One study used the dexamethasone suppression test (DST) and a short adrenocorticotropic hormone (ACTH) stimulation test, 11 measured blood cortisol in the early morning, and one measured blood cortisol in the morning and afternoon. Five studies measured salivary cortisol: two measured the change in bedtime and post-awaken saliva cortisol levels, 2 measured salivary cortisol after DST, and one measured salivary cortisol in the afternoon. Three studies measured the cortisol concentration in hair (HCC).

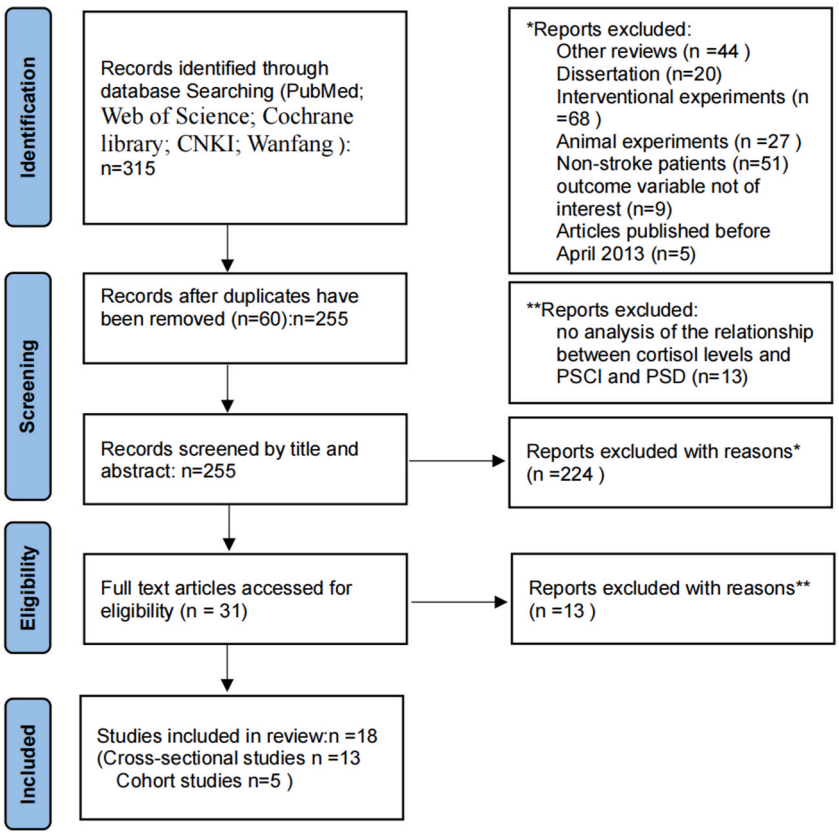

Fig. 1. Flow chart.
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Table 1
Characteristics of the literature related to cognitive disorders.

Author	Country	Design	Number of patients	Mean age	Stroke type	Sample	Baseline mean cortisol concentration(nmol/l)	Diagnostic criteria	Correlation between cortisol and outcome
Olsson et al. (1992) [9]	Sweden	Cross-sectional study	16	71 ± 11	Acute ischemic stroke	Serum	387 ± 195	DSM-III-R	No significant difference in serum cortisol levels between the delirium and non-delirium groups in the mornings.
Marklund et al. (2004) [12]	Sweden	Cross-sectional study	88	71 ± 11	Acute ischemic stroke	Serum	447 ± 367	A 3-point scale	Patients presenting with acute disorientation in the AIS group had significantly higher fasting serum cortisol levels than non-disoriented patients on both day 1 and day 4 of hospitalization in the morning.
Ben et al. (2017) [13]	Israel	Cohort study	65	66.7 ± 8.6	Acute ischemic stroke	Hair	35.9(20.2,70.1)pg/mg	NeuroTrax computerized cognitive testing, MoCA	Higher admission HCC was associated with poorer cognitive function ($p = 0.038$).
Casas et al. (2017) [14]	Argentina	Cross-sectional study	30	Female: 82 ± 9 Male: 70 ± 13	Acute ischemic stroke	Plasma	Female AIS: 557.33 Female control: 194.48 Male AIS: 423.69 Male control:179.53	Test photos, the abbreviated questionnaire of Pfeiffer	Higher levels of cortisol and estradiol were associated with more noticeable neurological, cognitive and functional deficits in women compared to men.
Tene et al. (2018) [10]	Israel	Cohort study	182	66.8 ± 9.6	Acute ischemic stroke	Saliva	Bedtime cortisol: 44.3 ± 4.4 Post-awakening:18.8 ± 11.8	NeuroTrax computerized cognitive testing, MoCA	Higher baseline cortisol levels were significantly correlated with poorer cognitive function 12 and 24 months after the index event.
Wang et al. (2021) [15]	China	Cross-sectional study	200	CIS-MCI:62.25 ± 8.33 CIS:46.32 ± 10.25	Ischemic stroke	Saliva	CIS-MCI:2.48 ± 0.57 CIS:0.85 ± 0.13	Expert consensus on prevention and treatment of cognitive impairment in China (2016)	Salivary cortisol levels were significantly higher in the CIS-MCI group than in the CIS group.
Zhanina et al. (2022) [7]	Russia	Cohort study	45	56 ± 5	Ischemic stroke	Serum, saliva, hair	HCC:48.7 ± 5.7(pg/mg) Serum:NR Saliva: NR	MoCA	Serum cortisol and saliva levels were significantly higher in patients with PSCI than without PSCI in acute period of IS.

AIS: acute ischemic stroke; HCC: hair cortisol concentration; CIS: cerebral ischemic stroke; MCI: mild cognitive impairment; PSCI: post-stroke cognitive impairment; IS: ischemic stroke; NR: not reported.

Table 2
Characteristics of the literature related to depression.

Author	Country	Design	Number of patients	Mean age	Stroke type	Sample	Baseline mean cortisol concentration(nmol/l)	Diagnostic criteria	Correlation between cortisol and outcome
Kwon et al. (2015) [16]	Korea	Cross-sectional study	28	62.5 ± 7.9	Stroke	Saliva	NR	Beck Depression Inventory II or the Hamilton Depression Rating Scale	Post-stroke depression showed a blunted CAR.
Wei et al. (2015) [17]	China	Cross-sectional study	182	Youth PSD group: 35. 38 ± 11. 35 Older PSD group: 58. 26 ± 11. 31 Youth non-PSD group: 34. 38 ± 9. 28	Stroke	Serum	Youth PSD group: 635 ± 226 Older PSD group: 641 ± 208 Youth non-PSD group: 513 ± 217	HAMD-14 Scale	Among youth, there was a significant difference in cortisol levels between the PSD and non-PSD groups.
Terroni et al. (2015) [8]	Brazil	Cross-sectional study	36	Anhedonic: 49 ± 15.6 Non-anhedonic: 52.1 ± 15.4	Ischemic stroke	Saliva	Anhedonic: 44.62 ± 16.67 Non-anhedonic: 30.47 ± 22.69	the Structured Clinical Interview Patient Version axis I	Patients with anhedonia had significantly larger diurnal variation and higher morning levels of salivary cortisol.
Zhang et al. (2016) [18]	China	Cohort study	100	PSD:62.4 ± 6.2 Non-PSD:64.1 ± 5.1	Stroke	Serum	PSD:508. ±119.51 Non-PSD:420.83 ± 70.04	DSM-IV, HAMD-21 Scale	Afternoon cortisol levels in PSD group were significantly higher than those in non-PSD group.
Colledge et al. (2017) [11]	Austria	Cross-sectional study	15	57.2 ± 10.7	aSAH	Hair	3.28 ± 1.8	Beck Depression Inventory	In patients with aSAH, higher HCC was significantly associated with increased depressive symptoms, hypochondriac beliefs, decreased life satisfaction, and increased sleep complaints.
Zhang et al. (2018) [19]	China	Cross-sectional study	113	PSD: 59.7 Non-PSD: 58.3	Stroke	Serum	PSD: 0.276 Non-PSD:0.232	HAMD Scale	Serum cortisol in PSD patients was significantly higher than non-PSD.
Sun et al. (2021) [20]	China	Cross-sectional study	175	NR	Stroke	Serum	PSD: 314.64 ± 69.17 Non-PSD: 196.82 ± 59.12	"ICD-10 Classification of Mental and Behavioral Disorders"	Serum cortisol is an independent risk factor for the development of depression after stroke.
Zheng et al. (2021) [21]	China	Cohort study	239	PSD: 60. 62 ± 13. 72 Non-PSD: 60. 51 ± 13. 64	Acute ischemic stroke	Plasma	PSD:463.40 (317.90,792.42) Non-PSD: 227.04 (146.94,340.55)	HAMD-17 Scale	Plasma cortisol in PSD patients was significantly higher than non-PSD.
Gong et al. (2022) [22]	China	Cohort study	159	PSD: 63.19 ± 14.32 Non-PSD: 61.97 ± 13.69	Acute ischemic stroke	Serum	PSD:371.49 (277.03,455.73) Non-PSD:266.53 (213.23,320.39)	HAMD-24 Scale	Serum cortisol and severity of depression are positively correlated ($r = 0.423$, $p < 0.01$).
Zhanina et al. (2022) [7]	Russia	Cohort study	45	56 ± 5	Ischemic stroke	Serum, saliva, hair	HCC:48.7 ± 5.7 (pg/mg)	Beck Depression Inventory or the Hamilton Depression Rating Scale	Significant differences were found neither in the changes in salivary nor serum and hair cortisol levels between patients with PSD and without PSD.
Gao et al. (2022) [6]	China	Cross-sectional study	100	62.83 ± 6.03	Ischemic stroke	Serum	PSD:0.276 Non-PSD:0.242	HAMD-17 Scale	Serum cortisol and HAMD scores are positively correlated ($r = 0.253$, $p < 0.031$).
Yuan et al. (2023) [23]	China	Cross-sectional study	150	Non-PSD:56.19 ± 10.82 PSD:56.83 ± 11.26	Stroke	Serum	PSD:362.22 ± 116.86 Non-PSD:210.26 ± 58.68	HAMD Scale	Plasma cortisol in PSD patients was significantly higher than non-PSD.

NR: not reported; PSD: post-stroke depression; a SAH: aneurysmal subarachnoid haemorrhage; HCC: hair cortisol concentration; CAR: cortisol awakening response.

3.3. Cortisol levels and changes over time following stroke

Three studies [8,13,21] reported HCC prior to stroke onset (range: 35.9–48.7 pg/mg). One study [13] found significantly higher HCC in stroke patients compared to healthy controls (20.79 ± 10.96 pg/mg) ($p < 0.05$).

Morning serum cortisol levels during the acute phase of stroke ranged from 227.04 nmol/l [17] to 641 nmol/l [22]. Four studies [14,17,18,22] compared serum cortisol levels in the acute phase of stroke in the PSD group (range: 371.49–508.89 nmol/l) with a non-PSD group (range: 227.04–420.83 nmol/l), with one of these studies finding no significant difference [14]. Three of the studies found significantly higher serum cortisol levels in the PSD group compared to non-PSD group. Four studies reported morning serum cortisol levels in healthy controls (range: 179.53 nmol/l [12] to 446 nmol/l [10]).

Three studies measured cortisol levels at multiple time points and found decreasing levels in hair [8], saliva [11], and serum [24]. However, Zhanina et al. found that salivary cortisol did not decrease after stroke, reporting instead that maximal levels were observed one year after stroke [8].

3.4. Relationship between cortisol and post-stroke cognitive impairment

3.4.1. Blood cortisol levels and PSCI

Post-stroke delirium is a common complication in stroke patients and is characterized by acute impairment of consciousness. This is often accompanied by varying degrees of cognitive dysfunction, affective disorders, attention deficits, and disturbed sleep cycles. Delirium prolongs hospitalization, increases patient mortality, and may lead to poorer functional outcomes [25]. Olsson et al. [10] studied the relationship between serum cortisol levels and delirium in 16 patients with acute ischemic stroke (AIS). They found no significant difference in morning serum cortisol levels between the delirium and non-delirium groups. However, Marklund et al. [24] showed that patients in the AIS group presenting with acute disorientation had significantly higher fasting serum cortisol levels than non-disoriented patients on the morning of day 1 and day 4 of hospitalization ($n = 88$). The reason for this discrepancy may be the small sample size in the study by Olsson et al. However, these authors reported a significantly elevated cortisol response 30 min after ACTH in patients with an acute confusional state (ACS) compared to those without ACS ($p < 0.05$). Moreover, serum cortisol levels after the dexamethasone suppression test (DST) correlated with the presence of ACS ($r = 0.66$, $p < 0.05$) [10]. The results showed increased responsiveness of the adrenal cortex to ACTH during the These findings indicate that multiple sites within the HPA axis are disrupted early after stroke, with the changes being associated with acute cognitive dysfunction.

Previous studies have reported a different prognosis for AIS according to gender [14]. Neuroactive steroids are cholesterol-derived hormones that have the ability to regulate the normal and pathological nervous system [26]. Based on the above, Casas et al. [12] investigated whether AIS affected the plasma concentration of multiple neuroactive steroids. Higher levels of cortisol and estradiol were associated with more noticeable neurological, cognitive and functional deficits in women compared to men. It is generally believed that females may be more resistant to cerebral ischemic injury in adulthood than males. However, Casas et al. found that the decline in sex steroids after menopause, together with increased HPA activation, can alter the role of sex steroids from neuroprotective to neurotoxic [27,28].

3.4.2. Salivary cortisol levels and PSCI

Over time, erratic cortisol fluctuations may affect the integrity of the hippocampus, which is a glucocorticoid receptor-rich region [15]. To study cortisol fluctuation after stroke and its effect on cognition, Tene et al. [11] evaluated the salivary cortisol level (at bedtime on the day of hospital admission and 30 min post-awakening the next morning) and cognitive function in 182 patients with acute stroke over a period of two years. On average, patients' salivary cortisol levels showed a downward trend since onset, but patients with high admission bedtime cortisol levels (baseline levels) still maintained higher salivary cortisol levels than those with low baseline levels. The cognitive results of follow-up showed that Higher baseline cortisol levels were significantly correlated with poorer cognitive function 12 and 24 months after the index event.

A cross-sectional study [29] of patients with cerebral ischemic stroke (CIS) revealed that the salivary cortisol level was significantly higher (0.85–3.65 nmol/L) in patients with mild cognitive impairment (MCI). Moreover, receiver operating characteristics analysis showed that the area under the curve of salivary cortisol as a diagnostic indicator of MCI after CIS was 0.982, and the sensitivity and specificity were 0.973 and 0.980, respectively. Therefore, the salivary cortisol level in stroke patients, both in the acute and the recovery phase, is prognostic for the patients' cognitive function.

3.4.3. Hair cortisol levels and PSCI

Long-term exposure to glucocorticoids has been linked to impaired cognitive ability [30]. Hair cortisol concentrations (HCC) is considered to be an effective indicator to reflect the comprehensive cortisol level in the past period of time [19]. Ben et al. [21] investigated the correlation between pre-stroke cortisol levels and PSCI by studying HCC. They collected hair samples from 65 acute stroke patients within three days of onset, and followed the cognitive function of these patients for 2 years. The results showed that higher baseline level HCC was associated with poorer cognitive function, after adjustment for age, gender, body mass index and APOE e4 carrier status ($HR = 6.553$, $p = 0.038$). Besides,Ben et al. also found larger ischemic lesion volume was significantly associated with higher HCC on admission. As a result, the authors deduced that the HPA axis of the brain was poorly regulated in patients with prolonged stress prior to the onset of stroke, and therefore HCC were higher. Meanwhile, high HCC made brain tissue susceptible to greater damage from cerebral ischemia, which ultimately led to the onset of cognitive decline [21].

3.5. Relationship between cortisol and post-stroke depression

PSD mainly occurs 2 months to 1 year after stroke and is characterized by apathy, loss of interest, sleep disturbance, and depressed mood. In addition to affecting stroke recovery, PSD also has negative effects on patient quality of life and neurological functioning [20]. Therefore, early recognition and diagnosis of PSD are needed to improve the effectiveness of stroke treatment and promote clinical recovery.

Barugh [6] systematically reviewed studies on the correlation between cortisol and PSD published prior to April 2013. The current investigation systematically reviewed studies on the correlation between cortisol and PSD that were published after April 2013.

3.5.1. Blood cortisol levels and PSD

The predictive value of high cortisol levels in blood for PSD was supported by the results of three studies (with a total of 573 patients) [17,18,31]. One study (n = 239) found that early morning plasma cortisol levels in patients with AIS predicted PSD at 6 months [17]. Circadian-related changes in the circulating cortisol level in humans affects the timing of blood collection [32]. One study (n = 100) found that afternoon serum cortisol levels were higher in the PSD group than in the non-PSD group, while morning cortisol levels were similar in both groups and significantly higher than in healthy controls [14].

Additionally, serum cortisol is also strongly associated with the time to onset of PSD. A cross-sectional (n = 113) study found that serum cortisol levels were significantly higher in patients with a PSD onset of less than 5 months than in patients with an onset of more than 5 months [20].

3.5.2. Salivary cortisol levels and PSD

Salivary cortisol is not affected by serum corticosteroid-binding globulin, salivary flow rate, patient age, sex, body mass index and smoking status [33,16], Moreover, it has the advantages of being non-invasive and easy to sample. Therefore, saliva is also often chosen to be applied for the cortisol measurement. Two studies [9,34] reported altered salivary cortisol rhythms in patients with PSD. In most people, a strong peak in cortisol is seen in the period immediately after awakening and is referred to as the cortisol awakening response (CAR) [35]. The CAR is recognized as a reliable indicator of HPA axis function and has been extensively studied in many diseases [36]. Kwon et al. [34] found that PSD patients exhibited sluggish CAR, with no difference in cortisol levels between PSD patients and healthy controls upon awakening. Salivary cortisol levels in the control group rose significantly at 15 and 30 min after awakening compared to just after awakening, but then declined at 45 min. In contrast, cortisol levels in PSD patients did not increase significantly at any sampling time, showing a relatively flat curve. Another study found that patients with anhedonia had significantly larger diurnal variation and higher morning levels of salivary cortisol [9]. Not surprisingly, PSD patients seem to lose the ability to finely regulate the HPA axis.

3.5.3. Hair cortisol concentration and PSD

A cross-sectional study [13] of patients with aneurysmal subarachnoid haemorrhage (aSAH) found that, higher HCC at admission was significantly associated with depressive symptoms, hypochondriasis, decreased life satisfaction, and increased sleep complaints. These findings suggest that long-term mood and sleep disturbances in patients with aSAH are associated with dysregulation of HPA axis. However, in the study by Zhanina et al. [8] significant differences were found neither in the changes in salivary nor serum and hair cortisol levels when comparing the groups of patients with and without PSD.

Although cortisol was measured at different times and in different samples, we can still obtain a relatively clear and complete picture of the effects of cortisol on cognitive and mood disorders after stroke from the results of the above studies (Fig. 2). First of all, before the onset of a stroke, the patient is likely to be in a state of chronic stress, which will gradually lead to an increase in cortisol in

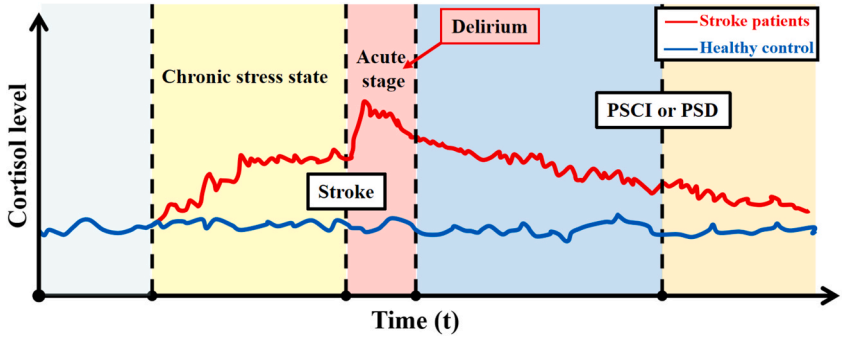

Fig. 2. Cortisol fluctuation in stroke patients.
First of all, before the onset of a stroke, the patient is likely to be in a state of chronic stress, which will gradually lead to an increase in cortisol in the patient's body. When a stroke occurs, this chronically high circulating cortisol level in turn makes the patient's brain tissue more susceptible to damage in the event of a stroke. In acute stress situations like stroke the patient's HPA axis will be further activated to release more cortisol, which will cause the patient to be prone to delirium in the acute phase. Although cortisol levels fall after the acute phase of stroke, they remain high, which ultimately leads to delayed cognitive dysfunction and depression.

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4. Discussion

This is a scoping review of the effects of cortisol on cognitive and mood disorders after stroke. It reviews the relationship between cortisol levels in three different human samples, including blood, saliva, and hair, and PSCI and PSD. Eighteen observational studies met our inclusion criteria. These observational studies use both cross-sectional and longitudinal research methods to observe their relationships. Most studies reported that patients with high admission cortisol levels are more likely to experience cognitive decline and depression later in life. In addition to this, by measuring hair cortisol concentrations, we obtained pre-stroke onset cortisol data in patients. The results showed that patients exposed to high circulating cortisol levels prior to onset were more likely to have delayed cognitive dysfunction and depression. These results suggest that measuring cortisol levels in the acute phase of stroke is of great clinical importance.

How does cortisol affect cognition and mood? A growing body of research data suggests that post-stroke damage is not confined to the infarcted area, but also extends to non-ischemic regions of the brain, resulting in secondary, distal, and delayed damage. For example, secondary changes are observed in hippocampal regions distant from the responsible lesion following focal ischemic injury to the cerebral cortex and/or striatum [5]. The hippocampus, a region of the human brain rich in corticosteroid receptors that controls cognitive function and mood, is selectively vulnerable to stress. Stress-induced glucocorticoid release can lead to hippocampal damage through abnormal signaling of these receptors [37]. At present, in addition to the endocrine axis, neurotransmitter, immune and neurotrophic mechanisms are also involved in the pathogenesis of PSCI and PSD. Neurotransmitter mechanisms include monoaminergic mechanisms and excitotoxic effects mediated by glutamate. The monoaminergic mechanism suggests that depression is associated with low levels of monoamine transmitters, particularly 5-HT, norepinephrine and dopamine [38]. Glutamate is an excitatory neurotransmitter, and after acute stroke, glutamate levels in both cerebrospinal fluid and plasma are elevated. Brain-derived neurotrophic factor (BDNF) protects the brain from ischemic damage by regulating levels of cytokines and transcription factors that regulate local inflammation, and stroke-induced hypoxia down-regulates BDNF expression in the brain [39]. Immune and inflammatory mechanisms play a critical role in ischemic injury, and imbalances between pro-inflammatory and anti-inflammatory factors can lead to worsening neurological outcomes [40]. By acting on the abundant cytokine network and its receptors in HPA axis tissues, elevated inflammatory cytokines may lead to further dysregulation of the HPA axis [41].

In fact, the pattern of cortisol fluctuation in patients after stroke was not completely consistent in the included studies. Three studies measured cortisol levels at multiple time points, which found decreasing trends in cortisol levels in hair [8], in saliva [11], and in serum [24], respectively. However, Zhanina et al. [8] did not find a tendency for salivary cortisol to decrease following stroke. On the contrary, cortisol levels reached their maximal levels one year after stroke. The possible reason is that on the one hand, different stroke types and lesion sites have different activation degrees on the HPA axis; on the other hand, different measurement time and methods may also cause differences in the results.

The present scoping review still has limitations. Because of the lack of homogeneity of the data, especially in terms of the time and method of measurement, we chose to analyze the data by literature induction. However this made it difficult to draw a concrete conclusion. Additionally, some studies compared changes in cortisol in PSD patients before and after interventions, but these interventional studies were not included in this review to reduce the effect of interventions on cortisol in stroke patients.

Most of the included studies did not categorize the type of stroke. In fact, different stroke types, such as large vessel stroke and small vessel stroke [42], have different cognitive and emotional outcomes after stroke. Analysis of cortisol levels in patients with different types of stroke will help further reveal the effects of the neuroendocrine axis on cognition and mood. Stroke patients with delayed injury were in a chronic stress state before the onset of stroke, and the causes of this chronic stress state need to be further studied. Old age [23], diabetes, and life events may all be factors leading to chronic stress state.

5. Conclusion

In summary, cortisol is a promising biomarker for prognostic judgment. Early assessment of cortisol concentration in stroke patients is recommended in order to improve the accuracy of cognitive and emotional prognostic evaluations and to guide the development of rehabilitation strategies.

CRediT authorship contribution statement

Tiantian Wang: Writing – review & editing, Writing – original draft, Methodology, Data curation. **Xuan Li:** Writing – original draft, Project administration, Data curation. **Yuanyuan Jia:** Writing – original draft, Data curation. **Yuyao Zhang:** Writing – original draft, Data curation. **Dianhuai Meng:** Writing – review & editing, Resources, Methodology, Conceptualization.

Data availability

Not applicable.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dianhuai Meng reports financial support was provided by Science and Technology Department of Jiangsu Province, China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40278.

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