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Effects of poststroke heart rate variability on the neurological impairment severity and the prognosis among patients with ischaemic stroke: a scoping review

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ABSTRACT

Objectives Changes in poststroke heart rate variability (HRV) might be helpful for early identification of patients with neurological impairment and poor prognosis, which could allow for early intervention to reduce adverse outcomes. The aim of this study is to perform a scoping review to identify the influence of poststroke HRV on the neurological impairment severity and the prognosis among patients with ischaemic stroke (IS).

Design The study design allows us to examine existing research, identify the research gaps and target the important areas for future research. In the search and report process, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines and checklist were used.

Data sources Three databases (PubMed, Web of Science and Ovid MEDLINE (Ovid)) were searched before December 2023.

Eligibility criteria for selecting studies The literature related to the topic of this study was mainly included, and the articles were excluded if they only focused on cerebral haemorrhage or were reviews, guidelines, books, etc.

Data extraction and synthesis Descriptive analysis was used to display the distribution of the included studies and then the summary method was adopted for further analysing.

Results 3251 articles that may be related to the scoping review topic were screened. After title and abstract screening and full-text reading, 21 records were finally included. Whether at discharge (n=6) or after follow-up (n=11), it was found that when the SD of all normal-to-normal intervals (SDNN) or the SD of the averages of normal-to-normal intervals decreased, the neurological impairment severity would be increased, including dysarthria, aphasia and hemiplegia. The root mean square of successive differences, the ratio of low frequency to high frequency and the high frequency were valuable predictors for the occurrence of adverse cardiocerebrovascular events. And the poor prognosis among patients with IS might be influenced by SDNN.

Conclusion This scoping review confirmed that post-IS HRV indicators can predict neurological impairment and prognosis of patients with stroke, highlighting a potential direction for early intervention. Large independent cohorts should be used to evaluate the predictive performance, reliability and potential limitations of these indicators in the future, and it will be important to explore interventions that make HRV change.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This scoping review conducted a comprehensive search for the influence of post-ischaemic stroke (IS) heart rate variability (HRV), including the severity of neurological impairment and the prognosis of IS.
⇒ Thematic analysis was used to analyse and summarise the included literature, and the data came from different populations around the world with good representation.
⇒ This scoping review finds that post-IS HRV indicators can predict neurological impairment and prognosis in patients with stroke, providing a possible direction for early intervention.
⇒ The search was limited to three databases which would result in the exclusion of important studies published in other databases and other languages.
⇒ Due to the nature of the scoping review, the methodological quality of the included studies was not assessed, resulting in equal weight for studies of higher or lower quality.

INTRODUCTION

According to the Global Burden of Disease Study 2021, stroke was the third-leading tertiary cause of death and the fourth-leading tertiary cause of disability in 2021.[1] From 1990 to 2021, absolute increases were seen in the numbers of people who had a new stroke (70.2%, 95% uncertainty intervals (UI): 65.9% to 74.6%) and who died or remained disabled from stroke (as measured by disability-adjusted life-years (DALYs); 32.2%, 95% UI: 21.7% to 42.7%).[1] Stroke accounted for the greatest nervous system DALYs in

2021.[2] It is well known that there are three major types of stroke: ischaemic stroke (IS), cerebral haemorrhage and subarachnoid haemorrhage,[3] with IS having the most constitution of incidence and fatal strokes.[2]

Brain-heart crosstalk assumes significance after IS.[4] It is critical to identify cardiovascular events to effectively control adverse outcomes after IS,[4] so the exploration of the brain's axis is essential. In the brain-heart axis, key mechanisms that cause close brain-heart cross-talk include the hypothalamic-pituitary-adrenal (HPA) axis, immune and inflammatory responses, gut dysbiosis, atherosclerosis and neurohumoral system.[4 5] The activation of the HPA axis leads to a significant increase in catecholamines.[6] The catecholamine storm causes the death of cardiomyocytes, and it also activates the autonomic reflex of the heart, which affects the brain.[5] At the same time, the central autonomic neural network retransmits signals to the heart through the parasympathetic and sympathetic nervous systems.[5 6] According to the brain-heart interaction described in the brain-heart axis, cardiac autonomic function and neuronhormonal pathways involved in regulation are affected after brain injury, while impaired autonomic function of the heart after IS increases the risk of worsening neurological outcomes and secondary complications.[6 7] In addition, if the autonomic neurological regulation function decreased after IS, parasympathetic nerve activity would decrease and the dominance of autonomic nerve innervation would shift to sympathetic nerve, which would lead to the worsening of neurological impairment severity, including dysarthria, aphasia and hemiplegia.[8 9]

Heart rate variability (HRV) is the amount of fluctuation in heart rate (HR) around the average HR, which is an assessment tool of cardiac autonomic function, providing the information of the sympathetic–parasympathetic autonomic balance.[6 8] HRV signals essentially originate in the brain, mediating through the sympathetic–parasympathetic nerve innervated by the sinus node.[9] HRV is recorded by ECG, which could be short-term (within 5 min ECG) and long-term (24-hour Holter ECG).[9–11] The measurement methods commonly include: (1) time domain analysis: calculating and representing the time difference between continuous sinus heartbeat; (2) frequency domain analysis: HR signal is decomposed into frequency and quantified its relative strength power; (3) non-linear analysis: It contains correlation dimension, sample entropy (SampEn), approximate entropy (ApEn), etc.[9–11] The indicators of HRV and their roles are presented in table 1.[9–15]

Table 1 The definition and role of the HRV indicators

Indicators, units	Description	Role
Time domain analysis		
SDNN, ms	SD of all NN intervals	Reflects estimates of overall HRV
SDANN, ms	SD of the averages of NN intervals in all 5 min	Reflects estimates of overall HRV
RMSSD, ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals	Reflects parasympathetic function
SDNN Index, ms	Mean of the SD of all NN intervals for all 5 min	Reflects estimates of overall HRV
pNN50, %	pNN50 count divided by the total number of all NN intervals	Reflects parasympathetic function
Frequency domain analysis		
TP, ms^2	Power of total heartbeat interval signal	Reflects estimates of overall HRV
HF, ms^2	Power of the HF band of the heartbeat interval signal	Parasympathetic regulation
LF, ms^2	Power of the LF band of the heartbeat interval signal	Sympathetic and parasympathetic dual regulation
LF/HF	The ratio of LF to HF	A sign of sympathetic–parasympathetic balance
ULF, ms^2	Power in the ultra-low frequency range	Evaluate long-term data, subject to sympathetic influence
VLF, ms^2	Power in the very low frequency range	Sympathetic and parasympathetic dual regulation
Non-linear analysis		
CD2	Correlation dimension	Sympathetic and parasympathetic dual regulation
SampEn	Sample entropy	Suitable for short-term HRV analysis
ApEn	Approximate entropy	Suitable for HRV analysis during exercise

ApEn, approximate entropy; CD2, correlation dimension; HF, high frequency; HRV, heart rate variability; LF, low frequency; NN interval, normal-to-normal interval; pNN50, the percentage of successive beat-to-beat intervals that differ by more than 50 ms; RMSSD, root mean square of successive differences; SampEn, sample entropy; SDANN, SD of the averages of NN intervals; SDNN, SD of all NN intervals; TP, total power; ULF, ultra-low frequency; VLF, very low frequency.

Previous studies have found that autonomic dysfunction can affect stroke prognosis,[7 8] and HRV is proven to be an indicator of autonomic function.[6 16–18] Recently, more and more researchers have focused on the relationship between HRV and the prognosis of IS,[19–22] but there is no unified conclusion on the specific influence relationship. So, the aim of this study is to perform a scoping review to integrate existing research, in order to identify the influence of poststroke HRV on the neurological impairment degrees and the prognosis after IS, which can help in early intervention among patients with IS through the changes in some HRV indicators.

METHODS

Protocol and registration

No systematic or scoping review has been conducted about the effects of poststroke HRV on the neurological impairment degrees and the prognosis among patients with IS. Based on the framework of Arksey and O'Malley for scoping review,[23] this study followed their five steps: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarising and reporting the results. The study design allows us to examine existing research, identify the research gaps and target the important areas for future research.[23] In the search and report process, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines and checklist (online supplemental appendix 1) were used.[24 25]

Search strategy

Our research team consisted of three neurology professors, one intensive care medical professor, one medical postgraduate in neurology and one medical postgraduate in cardiology. In November 2023, two medical postgraduates searched three medical databases: PubMed, Web of Science and Ovid. Terms related to 'ischemic stroke' and 'heart rate variability' were identified for each database using a variety of keywords, Medical Subject Headings and subject headings, which are described in detail in online supplemental appendix 2. The searches were conducted before December 2023 without restrictions on the publication data of articles. We used EndNote X9 to organise all the identified researches, and the author (RZ) removed the duplicates automatically and manually. After removing the duplication, 2997 records remained for filtering based on the eligibility criteria.

Eligibility criteria

All authors of this study were involved in adapting the eligibility criteria to demographic, conceptual and contextual tools,[26] with extensive experience and knowledge related to the research topic. The author (RZ) identified 15 studies from a random sample of 150 studies for discussion with the research group to formulate the eligibility criteria. All authors made an agreement on the final eligibility criteria: (1) the topic was about the effect of poststroke HRV and the neurological impairment degree or the prognosis among patients with IS; (2) the sample contained adult patients with IS, who were above 18 years old of any gender or race, and all patients were diagnosed based on imaging and clinical symptoms within HRV examination; (3) all types of studies were considered for inclusion; (4) the language was English or Chinese. We excluded the article which only observed haemorrhagic stroke. The article types including review, meta-analysis, conference proceedings, research protocol, guidelines, books and news were also excluded.

Data selection

Our research team consisted of three neurology professors, one intensive care medical professor, one graduate student in neurology, and one graduate student in cardiology. After deleting duplicate articles, one researcher (RZ) read the title and abstract of the included literature for preliminary screening, after which the full text would be read for secondary screening. All the selections were compatible with the eligibility and exclusion criteria. The second researcher (JH) also evaluated the eligibility of the literature in the same way. When these two researchers had disagreements, our research team would have a discussion until a consensus was reached on the evaluation results of each paper. After two rounds of screening and group discussions, all researchers searched the reference lists of the included articles and of the previous reviews, which did not generate new records.

Charting the data

Standardised data extraction tables were used to extract the data to be analysed (online supplemental appendix 3), including author(s), publication data and country, study type, study population and their characteristics, sample size, follow-up time, indicators of HRV and key findings relevant for the scoping review questions. Descriptive analysis and data summary were used to show the distribution of the included studies. Topic summary was used to describe the studies and main findings related to the research questions and objectives. The two main topics are: (1) effects of poststroke HRV on the neurological impairment degrees and (2) effects of poststroke HRV on the prognosis. In addition, the integration is also based on HRV time domain index and HRV frequency domain index. The research group solved all conflicts internally.

Patient and public involvement

No patient was involved.

RESULTS

A total of 3251 articles possibly related to the review topic were identified. EndNote X9 software was used to sort out the literature, and a total of 254 duplicated articles were identified and removed by comparing the title, author, publisher and year of publication with the bibliographic

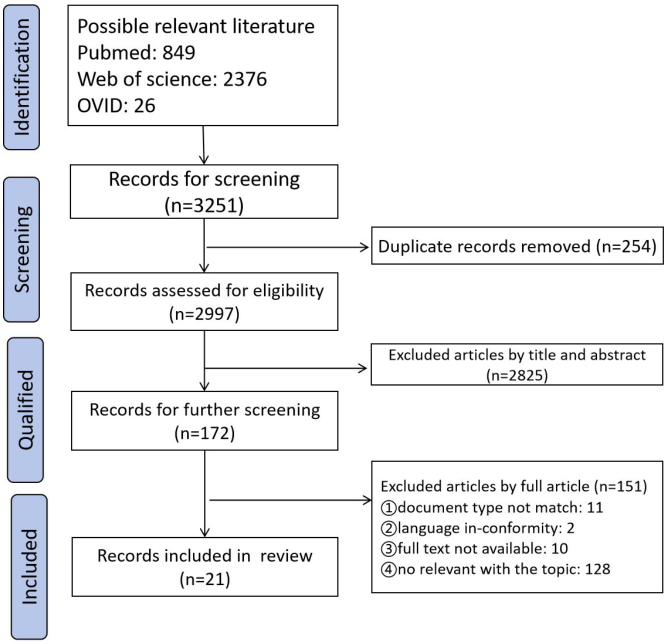

Figure 1 Flow chart of study selection process.

review function of EndNote X9 software. In the title and abstract screening stage, 2825 papers were excluded. Through reading the full text, 151 articles were excluded. The study group had a discussion and reached a consensus on the evaluation results of each paper. Finally, 21 core papers were included in the scoping review. Figure 1 depicts the process of article identification and selection following the PRISMA-ScR reporting guidelines.[24 25]

Description of included studies

General characteristics of the literature included in this scope review are shown in online supplemental table 1. A total of 21 articles were included, published from 1996 to 2023, two of which were based on database analysis. Except for three articles without following up the included patients, the remaining articles were followed up from 7 days to 5 years. Based on the two main topics of the scope review ((1) Neurological Impairment Degrees and (2) Prognosis), 15 articles[19–21 27–37] were about the neurological impairment degrees, 3 articles[38–40] dealt with the prognosis and 3 articles[41–43] had both topics. A thematic summary was conducted according to the two themes, and table 2 shows the results of the thematic summary of the included literature.

Effects of poststroke HRV on the neurological impairment degrees

In the included literature, the evaluation of the degree of neurological impairment was based on the modified Rankin score, the National Institutes of Health Stroke Scale (NIHSS), the Scandinavian Stroke Scale, the Barthel index or the Rivermead motor assessment. Early neurological outcome was almost based on NIHSS of the admission or the discharge. Included records (n=6) had found that as HRV decreased, the neurological impairment degrees increased.[20 27 31 33–35] Three studies[28–30] were conducted in the rehabilitation centre, which found that patients with decreased HRV indicators (SD of all normal-to-normal intervals (SDNN), SD of the averages of normal-to-normal intervals (SDANN), triangular index) had poorer recovery of limb function after standardised rehabilitation exercise. In these studies,[19 21 22 27 31 32 34 36 37 42 43] patients with IS were followed up for a period of time after discharge, and it was found that changes in multiple HRV indicators could predict neurological impairment after IS. SDNN was the most widely reported in the included articles and was proven to be a valuable predictor of neurological deficits after stroke.[27 28 36 42 43] When SDNN decreased, the severity of neurological impairments after stroke increased.[27 28 36 42 43] HF was the second most mentioned index, but its predictive performance reached disagreement. Some researchers found the decrease of HF predicted better neurological function after stroke,[21 34 35] but some studies thought the decrease of HF predicted poor neurological impairments after stroke.[31 33]

Effects of poststroke HRV on the prognosis

These studies focused on the occurrence of adverse cardiocerebrovascular events among patients with IS.[22 38 40–43] When the decrease of SDNN, root mean square of successive differences (RMSSD), NN intervals and ratio of low frequency to high frequency (LF/HF)[22 39–43] or the increase of HF occurs,[40] the incidence rate of adverse cardiocerebrovascular events after IS would increase. As for the death rate of patients with IS, it would increase if SDNN[39] and NN intervals[22] decreased.

DISCUSSION

Overall, we identified 21 articles related to the association between poststroke HRV and the neurological impairment or the prognosis among patients with IS. The included articles were published from 1996 to 2023, two of which were based on database analysis. The total population of included articles was 19 625, covering the population from many countries, and the results of our scoping review are certainly representative and have a certain extrapolation. Except for three articles without following up the included patients, all the remaining articles were cohort studies having a follow-up with high level of evidence. However, due to the nature of the scoping review, we only used a thematic analysis to analyse the data and lacked an assessment of heterogeneity in the included literature.

It is known that brain damage would impair the autonomic regulation function, while the decrease of the autonomic regulation function would aggravate neurological deficits.[8 44 45] HRV was proven to represent autonomic nervous function, which could be obtained in a non-invasive way.[46 47] As for the HRV time domain indicator, SDNN reflects the overall level of HRV.[46] RMSSD and pNN50 reflect parasympathetic nerve activity, which have a positive correlation with parasympathetic nerve function.[46–48] Previous studies had found that SDANN and

Table 2 Summary of the main findings of the included literature relevant to the research topic

Topic	Findings	Reference
Effects of poststroke HRV on the neurological impairment degrees	HRV time domain indicator 1. Most studies have found that the decrease of post-IS HRV would increase the incidence of neurological impairment. 2. SDNN, RMSSD, pNN50, TRIII Index and NN intervals were proven to be statistically significant. It was widely believed that the lower these indicators were, the greater the degree of neurological impairments was. 3. SDNN was the most frequently mentioned indicator. SDNN < 100 ms could be an independent predictor for neurological impairment.	20–22 27–29 32 35 36 41–43
	The HRV frequency domain indicator 1. It was found that frequency domain indicators could predict the neurological impairment, but it did not reach an agreement. 2. Most studies believed that the degree of neurological impairment increased because of the decrease in VLF, LF, LF/HF, TP and the increase in HF. But some studies had found that the lower HF was, the NIHSS score was higher at the early rehabilitation.	19 21 31 33–35 42
	HRV non-linear analysis 1. Non-linear indicators contained ApEn, SampEn, MSE, etc. 2. It was found that the decrease of ApEn, SampEn and MSE would cause the increase of neurological impairment (based on NIHSS and mRS).	31 32 38
	Other SA is based on the transformation of time series into a sequence of symbols, containing 0V%, 1V%, 2LV% and 2UV%. And the greater 2UV% was, the worse the neurological outcome was.	37
Effects of poststroke HRV on the prognosis	HRV time domain indicator As SDNN, RMSSD and NN intervals decreased, the rate of adverse cardiocerebrovascular events and death among IS patients increased.	22 38 39 41–43
	The HRV frequency domain indicator The increase of HF and the decrease of LF/HF would increase adverse cardiocerebrovascular events.	40 42

ApEn, approximate entropy; HF, high frequency; HRV, heart rate variability; IS, ischaemic stroke; LF, low frequency; LF/HF, the ratio of LF/HF; mRS, modified Rankin score; MSE, multiscale entropy; NIHSS, the National Institutes of Health Stroke Scale; NN interval, normal-to-normal interval; pNN50, the percentage of successive beat-to-beat intervals that differ by more than 50 ms; RMSSD, root mean square of successive differences; SA, symbolic analysis; SampEn, sample entropy; SDNN, SD of all NN intervals; TP, total power; TRIII Index, triangular index; VLF, very low frequency.

SDNN index could represent sympathetic nerve activity, and their decrease would cause sympathetic nerve activity to increase.[48 49] But recent studies found that SDANN and SDNN index also reflect overall HRV and are influenced by both sympathetic and parasympathetic activity.[47] According to our scoping review, declines in the above indicators after IS may increase the rate of neurological impairment and poor prognosis, and SDNN is probably the most predictive indicator.[20–22 27–30 32 35 36 42 43] Using HRV to measure cardiac autonomic function has been established and widely used in a non-invasive way.[50] Autonomic dysfunction in stroke is caused by the damage to the central autonomic neurology network.[51] The central autonomic neurology system, described as functional outcomes of stroke, is made up of brain regions in charge of the emotional function, cognition, and behavioural outcomes.[51] Autonomic dysfunction would impair functional outcomes and increase mortality,[52] and HRV has been reported to be a useful predictor of functional outcomes of stroke.[53] SDNN, representing the overall HRV, is probably the most predictive indicator of the severity of neurological impairment and poor prognosis after stroke.

The HRV frequency indicator generally contained LF, very low frequency, HF, ultra-low frequency and LF/HF.[46 47] LF, HF and LF/HF are the most commonly used frequency indicators. LF and HF indicate the power of the heartbeat interval in a specific frequency band.[15] Since the sympathetic nervous system usually influences in low-band power and the parasympathetic nervous system usually influences in high-band power, previous studies have thought that LF represents sympathetic nervous system regulation and HF represents parasympathetic nervous system regulation.[54] Recently, LF is now understood to represent the balance between parasympathetic activity and sympathetic activity, and LF/HF, the ratio of LF to HF, is also proven to represent sympathetic and parasympathetic dual regulation.[46 48 49 55] Our studies had found that the decrease of LF and LF/HF would cause bad outcomes among patients with IS.[21 29 31 33–36 42]

LF and LF/HF represent the balance of autonomic regulation.[46 48 49 55] The destruction of autonomic regulatory pathways may determine the clinical complications of acute and chronic stroke, leading to poor prognosis.[8 56] Moreover, the imbalance of the autonomic neurology system would lead to the development of a prepathological environment of compound risk factors, including hypertension, diabetes and atrial fibrillation, which would aggravate neurological deficits and cause adverse cardiocerebral events after stroke.[8] Hence, LF and LF/HF are the important predictors of the severity of neurological impairment and the adverse cardiocerebral events after stroke.

HF mostly reflects parasympathetic activity.[46 47 54] Studies included in our scoping review have been divided on the effects of HF on patients with IS.[21 31 33–35] The disagreement may arise because HF may easily be distorted when the same frequency of interference is added to the signal.[15] HF is also modulated by the baroreflex, cyclic blood pressure oscillations, environment, age and so on.[57] Therefore, large cohort studies are needed to assess the predictive performance of HF on the prognosis of IS. In addition to time and frequency domain analysis, more and more studies are exploring new ways to evaluate HRV, like ApEn, SampEn and Poincaré plot.[31 32 37] The HRV index may be a valuable predictor of neurological impairment, including dysarthria, aphasia and hemiplegia, and adverse heart and brain events after stroke.

Early detection of HRV changes and intervention may reduce the rate of neurological impairment and adverse events among patients with IS. Katz-Leurer and Shochina[58] had recruited patients with IS and treated them with a personalised aerobic exercise prescription, and it was found that early aerobic training had a positive effect on peak workload and walking parameters in patients with stroke. Impaired autonomic nervous function after IS may lead to the decrease of aerobic activity ability.[58] Increasing aerobic exercise training after stroke can improve the recovery of nerve function and the autonomic nervous function.[58] Wang *et al*[59] gave patients with IS drugs that may affect the cardiovascular autonomic regulation, such as β-blockers, α1-blockers, angiotensin-converting enzyme inhibitors, and it was found that the HRV (RMSSD, LF, HF and total power) of these patients who received the intervention recovered after 72 hours and the neurological function improved more significantly. These cardiovascular drugs may help to normalise HR, blood pressure and autonomic regulation parameters, because these drugs not only can reduce sympathetic outflow and lower HR and blood pressure, but also enhance parasympathetic regulation to varying degrees.[60–62] Siepmann *et al*[63] performed HRV biofeedback training on patients with stroke by instructing them to breathe rhythmically at a given breathing rate and found that patients with acute IS who received HRV biofeedback had improved autonomic neurology function and were able to relieve autonomic symptoms. HRV biofeedback may alleviate autonomic dysfunction and improve clinical outcomes in cardiovascular disease containing IS, which may be because HRV biofeedback could promote respiratory sinus arrhythmia.[64 65] And the promotion of respiratory sinus arrhythmia could improve cardiac autonomic regulation function after IS and provide sustained relief of autonomic symptoms.[64 65] Future studies may explore early intervention measures based on changes in HRV indicators to improve the functional prognosis and outcome of patients with stroke.

Limitations of this review

This scoping review has some limitations to consider. The search was limited to three important databases, and the language limits were Chinese and English, which could result in the exclusion of important studies published in other databases and other languages. In addition, due to the nature of the scoping review, the methodological quality of the included studies was not assessed, resulting in equal weight for studies of higher or lower quality.

Conclusions and future work

This study found that post-IS HRV indicators can predict neurological impairment and prognosis of patients with stroke, providing a new direction for early intervention. However, different studies have different measuring instruments, measuring methods and normal values ranges. Based on different measurement and assessment of HRV, some studies had produced different predictive values. Therefore, future research should explore uniform standards for HRV measurement and evaluation, starting with measuring methods and normal values range. Furthermore, large independent cohorts should be used to evaluate the predictive performance, reliability and potential limitations of these indicators. In addition, it will be important to explore interventions that make HRV change in future studies.

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