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# Heart Rate Variability as a Biomarker for Predicting Stroke, Post-stroke Complications and Functionality

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Ty Lees[1,2,3], Fatima Shad-Kaneez[2,3], Ann M Simpson[2,3], Najah T Nassif[2,3], Yiguang Lin[2] and Sara Lal[1,2,3]

[1]Neuroscience Research Unit, School of Life Sciences, University of Technology Sydney, Broadway, NSW, Australia. [2]School of Life Sciences, University of Technology Sydney, Broadway, NSW, Australia. [3]Centre for Health Technologies, University of Technology Sydney, Broadway, NSW, Australia.

**ABSTRACT**

**BACKGROUND:** Heart rate variability (HRV) is a non-invasive measure of the function of the autonomic nervous system, and its dynamic nature may provide a means through which stroke and its associated complications may be predicted, monitored, and managed.

**OBJECTIVE:** The objective of this review is to identify and provide a critique on the most recent uses of HRV in stroke diagnosis/management and highlight areas that warrant further research.

**METHODS:** The MEDLINE, CINAHL, and OVID MEDLINE databases were canvassed using a systematic search strategy, for articles investigating the use of HRV in stroke diagnosis and management. Initial paper selections were based on title alone, and final paper inclusion was informed by a full-text critical appraisal.

**RESULTS:** The systematic search returned 98 records, of which 51 were unique. Following screening, 22 records were included in the final systematic review. The included papers provided some information regarding predicting incident stroke, which largely seems to be best predicted by time- and frequency-domain HRV parameters. Furthermore, post-stroke complications and functionality are similarly predicted by time- and frequency-domain parameters, as well as non-linear parameters in some instances.

**CONCLUSIONS:** Current research provides good evidence that HRV parameters may have utility as a biomarker for stroke and for post-stroke complications and/or functionality. Future research would benefit from the integration of non-linear, and novel parameters, the hybridisation of HRV parameters, and the expansion of the utilisation of predictive regression and hazard modelling.

**KEYWORDS:** Stroke, Heart Rate Variability, HRV, biomarker

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**CORRESPONDING AUTHOR:** Sara Lal, Neuroscience Research Unit, School of Life Sciences, University of Technology Sydney, PO Box 123, Broadway, NSW 2007, Australia. Email: Sara.Lal@uts.edu.au

## Introduction

Stroke, a neurovascular event characterised by the interruption of blood supply within the brain,[1] is a leading cause of disability[2] and currently the second leading cause of death worldwide (behind only ischaemic heart disease).[2] Stroke was attributed as the cause of approximately 6.2 million deaths worldwide in 2015.[2] It is commonly associated with motor deficits,[3] sensory impairments,[4] cognitive impairment,[5] and possibly death. Furthermore, stroke has been commonly associated with autonomic dysfunction[6–8] and cardiovascular responses[9] that may subsequently increase mortality and morbidity rates.[10]

Heart rate variability (HRV) is the measurement and recording (typically via an electrocardiogram [ECG]) of the time interval between successive heartbeats.[11] It has been demonstrated to reflect the activity of the autonomic nervous system (ANS) and its sympathetic and parasympathetic branches,[12] which control almost all visceral, vascular, and metabolic functions.[13] Furthermore, reduced HRV is considered to be a predictor for general mortality[14,15] and the development of cardiovascular risk factors including hypertension and obesity.[16] With respect to HRV analysis, research has traditionally used linear time-domain variables such as SDNN (standard deviation of all normal to normal RR [NN] intervals), RMSSD (the root mean square of the sum of squares of differences between adjacent NN intervals), and pNN50 (the number of pairs of NN intervals that differ by more than 50 ms), as well as frequency-domain parameters such as low-frequency (LF) power, high-frequency (HF) power, and the ratio of the two (LF/HF) to examine physiological conditions, psychological states, and pathologies.[11,17–19] More recently, due to the continuous and variable nature of the ECG data from which HRV is derived, researchers have used non-linear parameters such as approximate entropy (ApEN), multiscale entropy (MSE), and detrended fluctuations (DFA),[20–22] to provide additional or alternative insights into the investigated physiological/psychological states.

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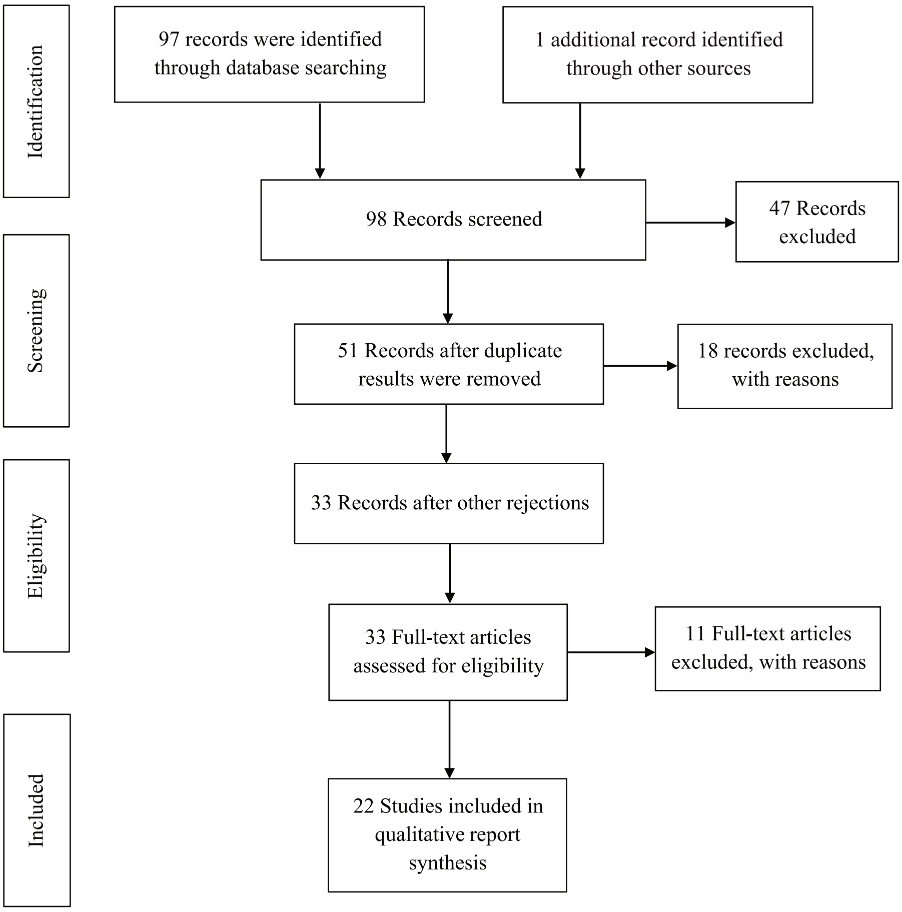


**Figure 1.** Flow diagram for the systematic review method. Modified from PRISMA method[24].

Thus, the present review aimed to examine and discuss literature that has investigated the utility of HRV parameters as biomarkers for stroke and/or post-stroke outcomes, complications, and functionality, as the assessment of cardiac autonomic function might yield important predictive and/or prognostic value regarding stroke and its related mortality and morbidity.[23]

## Methods

### *Selection criteria for the present review*

*Review period.* This systematic review was confined to the relevant articles returned by the systematic literature search, with the aim of reviewing the most recent advances in the utilisation of HRV as a biomarker of stroke and its outcomes and complications.

The systematic search for the present review was initially conducted on October 10, 2017, and subsequently updated on December 7, 2017.

*Types of studies and study design.* All research studies published during the specific period in English as full peer-reviewed journal articles were included in the current review.

*Categories of effects.* All studies were included based on the primary search measures stipulated in the Primary Effects (see below). Studies were not excluded based on the field of research or method of investigation used.

*Primary effects.* The identification and/or evaluation of HRV as a biomarker for stroke and its complications were selected as primary effects. These criteria were not confined to any major research area, as a broad evaluation of the knowledge base was intended for the present review. The selection criteria were guided by the collective expertise of the authors.

### *Literature search methods*

Only peer-reviewed journal publications with availability of a complete full text, irrespective of their chosen design and country of origin, were used for this review.

Those studies that were published in a language other than English, or those that were structured as Review articles, Editorials, Letters to the Editor, News releases, Research highlights or letters, commentaries and Technical papers, were excluded.

### *Electronic database search*

The databases selected for the systematic search were MEDLINE, CINAHL, and OVID MEDLINE (Ovid MEDLINE In-Process & Other Non-indexed Citations, Ovid

MEDLINE Daily, Ovid MEDLINE, and Ovid OLDMEDLINE [1946 to present]).

The primary search terms were confined to the title field and included Heart Rate Variability, HRV, and Stroke. The descriptors and synonyms were modified according to the specific requirements of each database.

The search structure for the included databases is described below. The MEDLINE and CINAHL databases were searched together using the same inputs and hence their results were pooled.

The specific search syntax for both the MEDLINE and CINAHL databases was as follows:

| | NO. OF RESULTS |
|---|---|
| TI Heart Rate Variability | 8022 |
| TI HRV | 335 |
| TI Stroke | 114 612 |
| 1 OR 2 | 8296 |
| 3 AND 4 | 55 |

In addition, it is important to note that of the 55 results returned from the MEDLINE and CINAHL databases, 41 were attributed to MEDLINE and the remaining 14 to CINAHL.

Finally, the specific search syntax for the OVID MEDLINE databases was as follows:

| | NO. OF RESULTS |
|---|---|
| Heart Rate Variability.ti. | 7029 |
| HRV.ti. | 300 |
| Stroke.ti. | 86 465 |
| S1 OR S2 | 7275 |
| S3 AND S4 | 42 |

*Selection of studies.* Following the database searches, duplicate records were removed, and 2 authors (T.L. and S.L.) subsequently evaluated the returned article titles. No disagreement was identified between the 2 reviewers. The authors identified one additional record that was added to the initial selection pool.

Following this visual inspection, other rejection criteria, as previously described were applied after which full texts for each of the selected titles were sourced and critically appraised for inclusion in the final review.

## Results and Discussion

A total of 97 results were returned by the systematic search across all databases, and the authors identified one additional record. Of these, 47 were found to be duplicate results, and once removed provided 51 unique papers to be potentially included in the present review. After the application of the aforementioned exclusion processes, 33 papers were identified for initial inclusion and further examination. Of these 33 papers, following a detailed examination, 22 were included in the final review and are subsequently discussed. The remaining 11 papers were excluded as they did not provide any insight regarding the utilisation of HRV for the prediction of stroke and its complications. The systematic review search and selection procedure are presented in Figure 1.

Research regarding the utilisation of HRV as a predictor in stroke can be separated into 2 categories. The first category contains research that has focussed on incident stroke and the HRV variations found in patients with stroke, whereas the second category focuses on HRV variations and their associations with post-stroke outcomes, functionality, and/or complications. Finally, it should be noted that most of the papers included in the present systematic review examined patients who had experienced ischaemic stroke, and those with haemorrhagic stroke were often not included or reported on. It would be worthwhile to determine whether the results of the research covered in this review translate to haemorrhagic stroke or whether they remain true for only ischaemic stroke.

### *Biomarkers for stroke prediction*

Of the 22 papers included in the final review, 12 provided results regarding HRV changes found in patients with stroke, and/or the predictive quality of HRV parameters for incident stroke.

*Short-term HRV analysis.* Of the 12 articles regarding HRV changes in stroke, 5 made use of short-term (less than 24 hours) HRV analysis. The earliest of these papers was from Naver et al[25] who aimed to determine whether cardiac autonomic reflexes in patients with monofocal stroke differed based on the hemispheric location of the lesion. Capturing two 1-minute ECG recordings following a 15-minute rest and 2 more recordings during an orthostatic tilt test at 80° from 23 patients with stroke (aged 59 ± 13 years, 13 right- and 10 left-sided lesions), 11 patients with a history of a single transient ischaemic attack (aged 59 ± 16 years), and 21 healthy controls (aged 61 ± 12 years), Naver et al[25] found that HRV, expressed as the RR index (mean ratio between longest and shortest RR intervals per respiratory cycle) varied between left- and right-sided lesions, with the right side showing a significant reduction in RR index parameters. In terms of identifying stroke, it appears that the RR index may be useful in identifying the hemispheric location of stroke but not the identification of stroke itself, so it may have some utility in the assessment of stroke, but not the prediction of stroke.

Fifteen years later, Chen et al[26] captured 5-minute ECG to reappraise the cardiac autonomic impact (as represented by frequency-domain HRV parameters) of acute ischaemic stroke (126 patients; 69 men, aged 63.2 ± 12.9 years) and compared

HRV parameters in large artery atherosclerosis (32 patients, 21 men, aged 64.3 ± 12.1 years) and small-vessel occlusion aetiologies (56 patients, 28 men, aged 61.7 ± 11.7 years); all patients were compared with 114 control subjects (41 men, aged 54.5 ± 8.8 years). Means comparison revealed that all HRV variables (very LF (VLF), LF, HF, and LF to HF ratio [LF/HF]) significantly differed between patients with stroke and controls, whereby patients reported reductions in VLF, LF, and HF, as well as an increase in LF/HF. Furthermore, LF, HF, and LF/HF remained significantly different, compared with the controls, after controlling for age, sex, hypertension, diabetes, dyslipidaemia, and smoking status. Subsequent receiver operating characteristic (ROC) analysis revealed that the HF parameter had the highest area under the curve (AUC) of 0.71, with the LF parameter a close second with an AUC of 0.66, indicating that both low and HF HRV parameters possess some predictive capacity for acute ischaemic stroke. Similar research focussing on the further development of these predictive models, perhaps via the hybridisation of HRV parameters, be they time domain, frequency domain, or non-linear, may provide additional insight and improve the prediction accuracy for stroke.

More recently, Fyfe-Johnson et al[27] analysed time- and frequency-domain HRV parameters in 2-minute ECG readings from 12 550 middle-aged adults (816 of whom experienced incident stroke at a median follow-up of 22 years) of the Atherosclerosis Risk in Communities (ARIC) study.[28] In the full study cohort demographic-adjusted Cox regression models (controlling for age, sex, and race), individuals in the lowest quintiles of SDNN (hazard ratio [HR] = 1.4; 95% confidence interval [CI] = 1.1-1.7), mean NN (HR = 1.7; 95% CI = 1.3-2.1) and RMSSD (HR = 1.4; 95% CI = 1.2-1.8) were at a higher risk of stroke. However, these associations were attenuated after a more complete covariate adjustment. Interestingly, further analysis controlling for diabetes status showed higher stroke risk to be associated with the lowest HRV quintiles for SDNN (HR = 2.0; 95% CI = 1.1-4.0), RMSSD (HR = 1.7; 95% CI = 0.9-3.2), LF ratio (HR = 1.5; 95% CI = 0.8-3.0), and HF power (HR = 1.7; 95% CI = 0.9-3.0). Irrespective of a number of non-significant regression models, this research largely demonstrated that reductions in time- and frequency-domain HRV parameters were consistently associated with increased risk of incident stroke, particularly among patients with diabetes and as such may prove useful in the prediction of stroke.

Around the same time, Kuzemczak et al[29] performed a longitudinal study examining baseline HRV parameters (time domain, frequency domain, and a number of novel indices) and stroke development in 139 patients with stable ischaemic heart disease (57 men, aged 58.98 ± 9.63 years). At a mean follow-up of 70.06 ± 4.29 months, 6 patients reported positive for stroke and exhibited significantly reduced time-domain variables of SDNN, de Hann long-term irregularity (the interquartile range of the radius location of particular $T_{RR}$ intervals in 2-dimensional space estimated for 128 consecutive R waves), Yeh interval index (a rate of standard deviation to mean value of successive 30-second intervals), Organ BAND (comparison of every temporary heart rate [HR] value corresponding with the RR interval to the averaged HR value), Dalton standard deviation, Zugaib short-term variability (the mean value of absolute differences between successive $D_i$ [time interval difference/sum ratio] values and their median estimated for 128 subsequent $T_{RR}$ intervals), and Zugaib long-term variability (the averaged deviation estimated for 128 subsequent $T_{RR}$ intervals). In addition, in the frequency domain, total power (TP), as well as wavelet indices 2, 3, and 4, were significantly reduced in patients with stroke. From these results, it could be concluded that ischaemic heart disease patients with stroke demonstrate baseline reductions in primarily novel time-domain and time- and frequency-domain baseline HRV parameters and that with further research may exhibit some predictive capacity. However, these were data derived from only 6 patients and would require significant additional research in both healthy and patient cohorts, particularly as a number of these variables are rarely used in HRV research. Finally, these novel parameters are promising and warrant additional future research in broader applications, beyond just stroke research.

Finally, Constantinescu et al[30] broadly examined linear and non-linear HRV in 15 patients with right-sided middle cerebral artery ischaemic stroke (MCA) (8 men, aged 59.7 ± 10.3 years), 15 patients with left-sided MCA (7 men, aged 59.4 ± 8.43 years), and 15 healthy controls (8 men, aged 59.33 ± 7.28 years). In their analysis, patients with left-sided stroke presented significantly elevated RR, normalised LF power (LFnu), LF/HF, SD1 (the standard deviation of the points perpendicular to the line-of-identity of a Poincaré plot), DFA $\alpha 1$, and DFA $\alpha 2$ values ($P \leqslant .03$) when compared with controls, at rest. These patients also exhibited significantly reduced pNN50 and normalised HF power (HFnu) values ($P \leqslant .04$). Similarly, the LFnu, HFnu, LF/HF, SD1, DFA $\alpha 1$, and DFA $\alpha 2$ values of patients with right-sided stroke differed significantly when compared with the control patients ($P \leqslant .05$). Moreover, time-domain (eg, RMSSD), frequency-domain (eg, LFnu), and non-linear HRV parameters (eg, DFA $\alpha 1$) were also able to separate the 2 stroke groups. In an echo of the previous research from Naver et al,[25] the results of this work suggest an asymmetric lateralised ANS response in patients with stroke (patients with left-sided stroke experience parasympathetic dominance, and patients with right-sided experience sympathetic dominance) and that, with further research, this HRV patterning could potentially be used to provide information relevant to the prediction and localisation of stroke.

Summarily, research using short-term HRV for the direct predictive of stroke is limited, as only 2 of the 5 included papers reported predictive analysis. However, as collective these papers do suggest that time-domain HRV parameters, eg, SDNN; frequency-domain HRV parameters, eg, LF; and HF, as well as novel parameters, eg, Zugaib variability differ in patients with stroke when compared with controls, and as such may be targets for the future development of predictive models of stroke.

*Long-term HRV analysis.* The remaining 7 papers relevant to this section made use of long-term (equal to or greater than 24 hours) HRV analysis in their investigations. Korpelainen et al[31] quantitatively assessed the effect of stroke on HRV circadian rhythm, by recording a 2-channel 24 hour ambulatory ECG from 32 patients with stroke (22 men, aged 53.6 ± 12 years) and 32 controls (22 men, aged 51.9 ± 10.5 years) during the acute phase of stroke and at 6 months after infarct. Night-to-day ratios of acute-phase HRV parameters were found to be significantly reduced in patients with stroke, with the RR interval and HRV TP ratio remaining significantly reduced at 6-month follow-up. It is possible that these reductions could provide some insight into stroke and/or functional outcome; however, further research to test the predictive ability of reductions in these parameters is required. Most importantly, it was found that the circadian rhythm of HRV (in particular, the VLF, LF, and HF components) is abolished in acute ischaemic stroke (irrespective of lesion location or hemisphere), and this abolition was reversed as circadian HRV oscillation had returned at 6-month follow-up. Given these longitudinal changes, examining circadian HRV oscillation in at-risk individuals and following up on those individuals who suffer a stroke may provide further insight into the utility of HRV for the prediction of stroke.

Korpelainen et al[32] published a second similar study which also recorded 24-hour ambulatory ECG data in a cohort of 46 patients with incident stroke (33 men, aged 52.1 ± 11.2 years) during the acute phase of stroke and at a 6-month follow-up. Control data from 30 healthy individuals (21 men, aged 51.8 ± 10.8 years) were also recorded at the 6-month time point. In the acute phase, it was found that SDNN, VLF, LF, and SD2 (the standard deviation along the line-of-identity of a Poincaré plot) parameters were significantly reduced in patients with stroke (both hemispheric and brainstem infarctions) when compared with the healthy controls. At 6-month follow-up, the SDNN, VLF, and LF parameters of patients with hemispheric infarction were still reduced in comparison with those of the controls. The results demonstrate that stroke is associated with a suppression of time- and frequency-domain and non-linear Poincaré HRV parameters. These stable HRV parameter variations may provide some predictive information regarding incident stroke; however, appropriate hazard or regression modelling is required.

After 10 years, D'Addio et al[33] continued the investigation of the utility of long-term HRV analysis for the prediction of stroke. Their study investigated 14 male patients with stroke, and a group of 7 healthy controls, and applied fractal (calculated using Higuchi algorithm) and β-exponent analysis to 24-hour Holter ECG recordings. In their analysis, it was found that the Higuchi fractal dimension (FD) parameter was significantly different in the patients with stroke when compared with the controls,[33] but it did not separate patients who had a single lesion or multiple lesions from each other. These variations suggest that fractal and non-linear HRV approaches, eg, β-exponent analysis could be useful in identifying stroke. However, these results were derived from a small patient cohort, and there is no direct comment on the predictive nature of the investigated variables in the paper. As a final note, future research on the use of HRV to predict stroke would do well to incorporate such variables as they do hold some promise.

Binici et al[34] used 48-hour Holter ECG data from 653 individuals recorded in the Copenhagen Holter study[35] and regression and Cox proportional hazard modelling to develop predictive models of stroke. Using the HRV parameter, SDNN, and a primary end point of first event of stroke, Binici et al[34] found that stroke risk was significantly associated with nighttime SDNN (HR = 0.669; 95% CI = 0.509-0.88; $P$ = .004). This relationship was maintained in a fully adjusted model (HR = 0.675; 95% CI = 0.513-0.888; $P$ = .005), which controlled for age, sex, smoking status, diabetes, blood pressure, cholesterol, high-sensitive C-reactive protein, N-terminal prohormone B-type natriuretic peptide, and triglycerides. With respect to the present review, the association between reduced nighttime HRV and stroke in apparently healthy individuals (beyond conventional risk factors) suggests that nighttime SDNN may hold some value in the prediction of incident stroke; however, additional research is required to further examine the predictive utility of SDNN.

Watanabe et al[36] took a more complete approach and used both time- and frequency-domain HRV parameters, as well as MSE analysis, to predict ischaemic stroke in 173 patients with permanent atrial fibrillation (AF) (123 men, aged 69 ± 11 years). Their analysis determined that only the mean sample entropy of the VLF band ($MeanEn_{VLF}$) was significantly greater in patients who experienced ischaemic stroke (n = 22) than those who did not (n = 151); mean sample entropy in the 2 VLF sub-divisions (VLF1 and VLF2, respectively) was also significantly increased. Follow-up–adjusted Cox hazard regression analyses identified that the $MeanEn_{VLF2}$ was the best independent predictor of ischaemic stroke (HR = 1.80; 95% CI = 1.17-2.07). The sensitivity and specificity of the model were modest at 66.7% and 64.3%, respectively. Furthermore, $MeanEn_{VLF}$ was found to be the second best predictor (HR = 1.74; 95% CI = 1.14-2.62) with an unreported sensitivity and specificity. From this analysis, it could be suggested that the $MeanEn_{VLF}$ parameters may provide a measure of ischaemic stroke risk in permanent AF patients and hence the prediction of stroke. As a point of note, future research would benefit from determining whether these results translate to other at-risk and healthy individuals.

Most recently, Bodapati et al[37] assessed 24-hour time-domain, frequency-domain, and non-linear HRV parameters in the Cardiovascular Health Study (CHS).[38] Using 24-hour Holter monitor ECG data from 884 stroke-free participants (338 men, aged 75.3 ± 4.6 years), they found that the 68 participants with incident stroke reported significantly reduced coefficient of variance (CV%), SDNN index values, natural log–transformed ultra-LF power (lnULF), VLF, TP, and power law slope values (SLOPE); Cox hazard models only retained the CV% and SLOPE parameters. Using optimised risk separation values for CV% SLOPE in the Cox model, it was determined that possessing both low CV% and low SLOPE was associated with an HR = 3.5 (95% CI = 1.8-6.8; $P < .001$) for incident stroke. These results indicate that the HRV parameters CV% and SLOPE improve prediction of incident stroke over a validated clinical risk score alone and as such should be targeted in future research. Furthermore, frequency-domain HRV variables (ULF, VLF, and TP) warrant additional attention as they also differed significantly between patients with stroke and health controls, despite not significantly contributing to the hazard models.

Finally, in their cross-sectional study, Wei et al[39] examined HRV in 232 patients with acute ischaemic stroke (134 men, aged 69 ± 19 years) who also had varying degrees of renal dysfunction. Using a 12-channel 24-hour ambulatory ECG recorded in the acute phase (between 2 and 7 days after hospital admission), they found that the 3 patient groups (with normal, mild dysfunction, and moderate renal dysfunction) differed significantly regarding the SDNN index, VLF, LF, and LF/HF parameters. Therefore, with further predictive research using regression and/or hazard modeling, it is possible that these parameters could distinguish patients with stroke from healthy controls.

In summary, research using long-term HRV analysis in the prediction of stroke provides only a brief insight into the prediction of stroke, with 3 of the 7 reviewed papers using predictive analysis. Nonetheless, the reviewed research suggests that time-domain HRV parameters, eg, SDNN; frequency-domain HRV parameters, eg, HF; as well as non-linear parameters including Poincaré values, and even circadian oscillations in HRV differ between patients with stroke and healthy controls, and as such may have the capacity to predict stroke. A brief summary of the research articles investigating HRV (both short term and long term) in stroke presented in section 'Biomarkers for stroke prediction' can be found in Table 1.

### *Biomarkers for post-stroke outcomes, complications, and function*

With respect to the utility of HRV parameters in the determination of post-stroke outcomes, complications, and/or functionality, 12 papers of those included in the present review each provided some insight.

*Short-term HRV analysis.* Of these 12 articles, 10 used short-term HRV analysis (less than 24 hours) in their examination of post-stroke outcomes, complications, and/or functionality.

*Patient mortality.* First, in addition to examining location specific HRV changes in stroke, Naver et al[25] reported that 6 of their study patients died within 12 to 60 months post-stroke (5 right sided and 1 left sided) and it was determined that these patients had a lower HRV index than the rest of the tested patients (n = 17). Thus, it could be suggested that an observed reduction in RR index could be indicative of patient mortality risk; however, further analysis such as ROC analysis or Cox proportional hazard modelling with larger sample sizes is required.

Gujjar et al[40] similarly examined short-term HRV parameters in acute stroke, using a 5-minute segment of an hour-long ECG recording captured from 25 patients with stroke (13 men, aged 39.76 ± 17.97 years). In their analysis, it was found that LFnu, VLF percentage, and absolute power, as well as TINN (the triangular interpolation of NN interval histogram), were implicated in patient mortality (11 of the 25 patients died at follow-up). However, of these variables, only LFnu parameter was retained by a subsequent multiple logistic regression.[40] Thus, it could be suggested that as these HRV parameters correlate with post-stroke survival, they may be useful in predicting patient mortality. However, the used patient count was low and of varying causes, so further research would be beneficial, particularly work that included a healthy control group.

After 6 years, He et al[41] used logistic regression analysis to comment on the clinical prognostic significance of the FD of HRV in patients with stroke (n = 327; 158 men, aged 61.12 ± 9.74 years). Using ROC analysis, they found that the critical point for mortality prediction was an FD lesser than or equal to 1.05, and that mortality risk was higher in patients who met this criteria (odds ratio [OR] = 0.276; 95% CI = 0.135-0.567; $\chi 2 = 12.32$; $P = .000$); of the 42 patients who were deceased at follow-up, 20 met these criteria. This analysis provides some insight into the prediction of patient mortality post-stroke; however, it does need further development. Indeed, the authors conclude that the integration of HRV markers, eg, FD, with traditional stroke risk stratifiers may provide a more effective assessment of stroke patient mortality, and this could prove a fruitful future research endeavour.

*Patient function.* In a broad functional examination, Arad et al[42] recorded ECG data from 16 patients (10 men, aged 73 ± 10 years) who had experienced ischaemic stroke and correlated HRV parameters (SDNN, LF, and HF) to the functional independence measure (FIM) score.[43] Their analysis identified significant positive relationships between all HRV parameters and FIM on admission ($r \geqslant .57$; $P \leqslant .02$) and discharge ($r \geqslant .60$; $P \leqslant .02$), and so it can be suggested that HRV analysis may prove useful in examining functional outcome of patients with stroke. However, it should be noted that the ECG data analysed were recorded in a large temporal window, 1 to 6 weeks post-stroke onset, and, as such, it is unknown whether the relationships reported will persist in a longitudinal context.

Graff et al[44] similarly used acute-phase time-domain, frequency-domain, and other non-linear and complexity-based HRV parameters to predict functional outcome (as measured

**Table 1.** Summary table of included research articles examining heart rate variability and its relationship to stroke.

| STUDY | STUDY POPULATION | OBJECTIVE | PRIMARY RESULTS |
|---|---|---|---|
| Naver et al[25] | 23 patients with stroke (aged 59 ± 13 years); 11 patients with TIA (aged 59 ± 16 years); 21 healthy controls (aged 61 ± 12 years) | To study autonomic influence on heart rate in patients with monofocal stroke to determine whether the lesion location moderates this influence | RR index varied between left- and right-sided lesions, with the right side showing a significant reduction in RR index parameters |
| Chen et al[26] | 126 patients with stroke (69 men, aged 63.2 ± 12.9 years); 32 patients with LAA (aged 64.3 ± 12.1 years); 56 patients with SVO (aged 61.7 ± 11.7 years); 114 healthy controls (41 men, aged 54.5 ± 8.8 years) | To reappraise the impact of cardiac autonomic function in patients with acute ischaemic stroke by measuring HRV and compare the differences of HRV in patients between LAA and SVO subtypes | ROC analysis revealed that the HF parameter (derived from 5 minute ECG recordings) had the highest AUC of 0.71, with the LF parameter a close second with an AUC of 0.66, indicating that both low- and high-frequency HRV parameters possess some predictive capacity for acute ischaemic stroke |
| Fyfe-Johnson et al[27] | 12 550 middle-aged adults, of which 816 were patients with incident stroke | To estimate the association between HRV and primary incident stroke | Adjusted Cox regression models demonstrated that individuals in the lowest quintiles of SDNN (HR = 1.4; 95%; CI = 1.1-1.7), mean NN (HR = 1.7; 95% CI = 1.3-2.1), and RMSSD (HR = 1.4; 95% CI = 1.2-1.8) were at a higher risk of stroke. Controlling for diabetes status showed higher stroke risk to be associated with the lowest HRV quintiles for SDNN (HR = 2.0; 95% CI = 1.1-4.0), RMSSD (HR = 1.7; 95% CI = 0.9-3.2), LF ratio (HR = 1.5; 95% CI = 0.8-3.0), and HF power (HR, 1.7; 95% CI = 0.9-3.0) |
| Kuzemczak et al[29] | 139 patients with stable ischaemic heart disease (57 men; 58.98 ± 9.63 years), of which 6 converted to stroke | To compare baseline HRV (traditional and novel indices) in stable patients with ischaemic heart disease with and without stroke in long-term observation | At a mean follow-up of 70.06 ± 4.29 months, 6 patients reported positive for stroke and exhibited significantly reduced time-domain variables of SDNN, de Hann long-term irregularity, Yeh interval index, Organ BAND, Dalton standard deviation, Zugaib short-term variability, and Zugaib long-term variability. In addition, in the frequency domain, TP, as well as wavelet indices 2, 3, and 4, were significantly reduced in patients with stroke |
| Constantinescu et al[30] | 15 patients with right-sided MCA (8 men, aged 59.7 ± 10.3 years); 15 patients with left-sided MCA (7 men, aged 59.4 ± 8.43 years); 15 healthy controls (8 men, aged 59.33 ± 7.28 years) | To investigate cardiac autonomic activity in patients with ischaemic stroke and to assess HRV non-linear parameters besides linear ones | Patients with left-sided stroke presented significantly elevated RR, LFnu, LF/HF, SD1, DFA $\alpha 1$, and DFA $\alpha 2$ values ($P \leqslant .03$) when compared with controls, at rest. These patients also exhibited significantly reduced pNN50 and normalised high-frequency power (HFnu) values ($P \leqslant .04$). Similarly, the LFnu, HFnu, LF/HF, SD1, DFA $\alpha 1$, and DFA $\alpha 2$ values of patients with right-sided stroke differed significantly when compared with the control patients ($P \leqslant .05$) |
| Korpelainen et al[31] | 32 patients with stroke (22 men, aged 53.6 ± 12 years); 32 healthy controls (22 men, aged 51.9 ± 10.5 years) | To quantitatively assess the effects of brain infarction on circadian rhythms of heart rate and heart rate variability | Night-to-day ratios of acute-phase HRV parameters (SDNN, RMSSD, VLF, LF, HF, TP, LF/HF derived from 24-hour ambulatory ECG) were found to be significantly reduced in patients with stroke, with the RR interval and HRV total power ratio remaining significantly reduced at 6-month follow-up. Most importantly, circadian rhythm of HRV (in particular, the VLF, LF, and HF components) was abolished in acute ischaemic stroke and reversed at 6-month follow-up |

*(Continued)*

**Table 1.** (Continued)

| STUDY | STUDY POPULATION | OBJECTIVE | PRIMARY RESULTS |
|---|---|---|---|
| Korpelainen et al[32] | 46 patients with incident stroke (33 men, aged 52.1 ± 11.2 years); 30 healthy controls (21 men, aged 51.8 ± 10.8 years) | To quantitatively assess quantitatively the effects of brain infarction on the dynamics of HRV using new complexity and fractal measures and to study correlations between various traditional and new complexity and fractal measures of HR variability in ischaemic stroke | In the acute phase, it was found that SDNN, VLF, LF, and SD2 (derived from ambulatory ECG) parameters were significantly reduced in patients with stroke (both hemispheric and brainstem infarctions) when compared with the healthy controls. At 6-month follow-up, the SDNN, VLF, and LF parameters of patients with hemispheric infarction were still reduced in comparison with those of the controls |
| D'Addio et al[33] | 14 patients with stroke (14 men, aged 65 ± 7 years); 7 healthy controls (aged 45 ± 5 years) | To assess whether the Higuchi FD is capable of discriminating stroke patients from normal subjects and, within patients with stroke, those with a single lesion from those with a multiple lesion | FD was significantly different in the patients with stroke when compared with the controls but it did not separate patients who had a single lesion or multiple lesions from each other |
| Binici et al[34] | 653 healthy middle-aged/elderly individuals (377 men, aged 64.1 ± 6.8 years) | To examine whether reduced HRV is predictive of stroke in apparently healthy middle-aged and elderly subjects and to assess whether nighttime HRV is a better predictive tool than 24-hour HRV | Stroke risk was significantly associated with nighttime SDNN (HR = 0.669; 95% CI = 0.509-0.88; $P = .004$) derived from 48-hour Holter ECG recordings. This relationship was maintained in a fully adjusted model (HR = 0.675; 95% CI = 0.513-0.888; $P = .005$). |
| Watanabe et al[36] | 173 patients with permanent AF (123 men, aged 69 ± 11 years) | To examine whether a novel complexity measurement of the heart rate variability (MSE) was a useful risk stratification measure of ischaemic stroke in patients with permanent AF | Adjusted Cox hazard regression analyses identified that the MeanEnVLF2 as an independent predictor of ischaemic stroke (HR = 1.80; 95% CI = 1.17-2.07). Furthermore, MeanEnVLF was also a predictor of ischaemic stroke (HR = 1.74; 95% CI = 1.14-2.62) |
| Bodapati et al[37] | 884 stroke-free participants (338 men, aged 75.3 ± 4.6 years); 68 converted to incident stroke | To examine whether 24-hour HRV adds predictive value to the Cardiovascular Health Study clinical stroke risk score | Participants with incident stroke reported significantly reduced CV%, SDNN index values, natural log–transformed ultra-low frequency power (lnULF), VLF, TP, and power law slope values (SLOPE). Optimised Cox models determined that possessing both low CV% and low SLOPE was associated with an HR = 3.5 (95% CI = 1.8-6.8; $P < .001$) for incident stroke |
| Wei et al[39] | 232 patients with acute ischaemic stroke with varying degrees of renal function (134 men, aged 69 ± 19 years) | To evaluate the association between autonomic function and stroke in patients with renal dysfunction | SDNN, VLF, LF, and LF/HF derived from a 12-channel 24-hour ambulatory ECG differed significant between the 3 patient groups (with normal, mild dysfunction, and moderate renal dysfunction) and healthy controls |

AF, atrial fibrillation; CI, confidence interval; CMI, complexity index; CV, coefficient of variance; DFA, detrended fluctuations; ECG, electrocardiogram; FD, fractal dimension; FIM, functional independence measurement; HF, high frequency; HR, hazard ratio; HRV, heart rate variability; LF, low frequency; ln, natural log; MSE, multiscale entropy; nu, normalised units; OR, odds ratio; RMSSD, the root mean square of the sum of squares of differences between adjacent NN intervals; ROC, receiver operating characteristic; RR, R to R interval; SD1, the standard deviation of the points perpendicular to the line-of-identity of a Poincaré plot; SDNN, standard deviation of all normal to normal RR intervals; SIE, stroke in evolution; TIA, transient ischaemic attack; TINN, the triangular interpolation of NN interval histogram; ULF, ultralow frequency; VLF, very low frequency.
Table 1 presents a brief summary of the presently reviewed research articles that examined heart rate variability and its relationship to stroke. For each reviewed article, it describes the sample group examined, the study objective, as well as the primary results and HRV measures implicated by the analysis.

by the National Institute of Health Stroke Scale [NIHSS] and modified Rankin scale [mRS]) in 63 patients with acute ischaemic stroke (44 men, aged 62 years). Their results reported that patients with good (n = 47) and poor (n = 16) early outcome were successfully differentiated by the non-linear entropy-based measures: ApEN, SampEn, and FuzzyEn. However, at a 90-day follow-up, the frequency-domain variables of absolute VLF power, absolute LF power, HF%, LFnu, HFnu, and LF/HF differentiated patients based on outcome. In addition, LF/HF was also correlated to functional outcome measures. These results suggest that traditional frequency-domain HRV parameters possess long-term prognostic value, but that the acute phase of stroke was better represented by complexity measures of HRV. As such, it is possible that HRV-based evaluation of functional outcome of ischaemic stroke may rely on differently derived parameters depending on temporal proximity to the initial infarct, and that multiple models may need to be developed.

More recently, Tang et al[45] similarly examined HRV complexity parameters and patient outcome post-stroke. The HRV data were acquired from 150 patients with stroke (70 men, aged 62.0 ± 15.3 years), 77 patients with stroke with AF (43 men, aged 74.3 ± 11.6 years), and 60 healthy controls (38 men, aged 60.9 ± 10.4 years). The analysis found that RMSSD (OR = 0.99; 95% CI = 0.97-1.00) and the complexity index (CMI; OR = 1.18; 95% CI = 1.08-1.28) significantly predicted functional status at the 3-month follow-up (as determined by the mRS) in patients with non-AF stroke. Furthermore, the AUC for predicting a favourable outcome for patients with non-AF stroke for a combined measure of clinical parameters and CMI was 0.903 (95% CI = 0.853-0.954), which was a significant improvement over each component alone ($P = .02$). These results demonstrate that MSE can successfully differentiate between functional outcome of non-AF stroke, AF stroke, and non-stroke controls. Furthermore, higher CMI values were associated with favourable outcome in patients with non-AF stroke and thus may prove to be an early indicator of patient outcome.

*Other outcomes or complications*. In a more specific functional examination, Katz-Leurer and Shochina[46] quantitatively assessed the prognostic value of both time-domain and frequency-domain HRV parameters (derived from 10- to 12-minute supine-free breathing Holter ECG recordings) for the motor and aerobic capacity of patients with ischaemic stroke (n = 39; 19 men, aged 63 ± 10 years). Their analysis found HRV parameters (primarily RMSSD, LF, HF) to be significantly correlated to patient motor performance (as assessed by the Motor Assessment Scale[47]) and aerobic capacity post first stroke. Importantly, this relationship was found to exist in the acute phase (within 2 weeks post-stroke) and persisted up to 3 months later, indicating that it is possible that HRV could be used as an ongoing monitoring method to assess motor and aerobic recovery. In addition, although not a main outcome, Katz-Leurer and Shochina[46] also reported a significant linear relationship between SDNN and the FIM score ($r = .29$; $P < .05$), furthering the previous suggestion that time-domain HRV measures could provide insight into general patient functionality.

Taking a new direction, Günther et al[48] analysed time-domain and frequency-domain HRV parameters from 43 patients with acute ischaemic stroke (28 men, aged 62.60 ± 12.19 years) with the goal of examining its predictive capacity for post-stroke infection. Logistic regression models and ROC analysis determined significant AUCs for daytime LF/HF (0.74), LFnorm (calculated as LF/(HF + LF); 0.79) and HFnorm (calculated as HF/(HF+LF); 0.72), as well as nighttime lnLF (0.76) and lnVLF (0.81). Further controlling for diabetes status, β-blocker usage and breathing rate improved most the AUC value of most models. From these results, it could be suggested that frequency-domain HRV variables proved to be reliable predictors of post-stroke infection and were also capable of predicting the development of infections. However, the small sample size renders these predictive models difficult to generalise. Furthermore, it would be interesting to see whether the results varied depending on the type or timing of infection. Finally, it is important to note that the authors do indicate that they have designed a larger subsequent clinical trial.

In a short case study paper, Al-Qudah et al[49] reported on serial HRV testing for the evaluation of autonomic dysfunction in stroke. Their results found that both cases reported an acute approximate 5% reduction in mean RR interval length and an average of 15% recovery at a 45-day follow-up, with the recovery reported to parallel an improvement in clinical status. They go on to suggest that stroke is a dynamic process with recovery phases, and as such, serial HRV testing may function as a non-invasive tool to evaluate the dynamics of stroke. However, although serial HRV testing could prove useful in stroke, this conclusion was determined using data from 2 cases and significantly larger controlled studies are needed to validate serial HRV testing in the prognosis of stroke.

Finally, Chen et al[50] combined traditional time- and frequency-domain HRV parameters with MSE to predict stroke in evolution (SIE; an early worsening of neurological symptoms) as it is associated with a poor clinical outcome[51,52]). Analysing HRV data captured from 90 acute patients with ischaemic stroke (19 of whom met the criteria for SIE) revealed that the RMSSD, LF/HF, CMI, and $Area_{6\text{-}20}$ (the summations of quantitative entropy values of scale 6-20) parameters varied significantly between patients with and without SIE ($P \leq .030$). Furthermore, adjusted multivariable logistic regression analysis (controlling for age, sex, history of hypertension, history of smoking, NIHSS score, and glucose level at admission) determined that only the CMI (OR = 0.897; $P = .020$) and $Area_{6\text{-}20}$ parameters (OR = 0.868; $P = .020$) were significant predictors for SIE. Examination of these results suggests that an acute phase assessment of non-linear MSE HRV may be useful in the prediction of SIE and in some instance appears to be superior (in predictive capability) to conventional linear HRV parameters; however, a larger confirmatory study is required.

Summarily, research investigating short-term HRV analysis and its relationship to post-stroke complications and/or functionality has demonstrated that patient mortality and functionality, post-stroke motor function and infection, as well as SIE are each related to specific HRV changes (primarily in the time and frequency domains), and in some instances can be successfully predicted by HRV parameters such as SDNN, LF, and CMI; however, further predictive analysis and development are required.

**Table 2.** Summary table of included research articles examining heart rate variability and its relationship to post-stroke complications and functionality.

| STUDY | STUDY POPULATION | OBJECTIVE | PRIMARY RESULTS |
|---|---|---|---|
| Naver et al[25] | 23 patients with stroke (aged 59 ± 13 years); 11 patients with TIA (aged 59 ± 16 years); 21 healthy controls (aged 61 ± 12 years) | To study autonomic influence on heart rate and blood pressure in patients with monofocal stroke to determine whether the side of the lesion moderates this influence | RR index varied between left- and right-sided lesions, with the right side showing a significant reduction in RR index parameters |
| Gujjar et al[40] | 25 patients with stroke (13 men, aged 39.76 ± 17.97 years) | To explore the efficacy of HRV measures in predicting outcome among patients with acute severe stroke | LFnu, VLF percentage, and absolute power, as well as TINN derived from 5-minute HRV analysis were implicated in patient mortality. In addition, multiple logistic regression analysis retained only LFnu as a significant predictor of patient mortality |
| He et al[41] | 327 patients with stroke (158 men, aged 61.12 ± 9.74 years) | To investigate the difference of HRV between right-sided stroke and left-sided stroke and to investigate the relative impact of cardiac autonomic imbalance and heart damage on FD of HRV in patients with stroke | ROC analysis determined that the critical point for mortality prediction was an FD (derived from HRV analysis on 512 continuous RR intervals) less than or equal to 1.05, and that mortality risk was higher in patients who met this criteria (OR = 0.276; 95% CI = 0.135-0.567; $\chi^2 = 12.32$; $P = .000$) |
| Arad et al[42] | 16 patients with ischaemic stroke (10 men, aged 73 ± 10 years) | To determine whether HRV spectral parameters correlate with the functional performance in patients hospitalised in a rehabilitation setting following ischaemic stroke | Significant positive relationships between SDNN, LF, HF (derived from 5-minute ECG recordings), and FIM on admission ($r \geq .57$; $P \leq .02$) and discharge ($r \geq .60$; $P \leq .02$) |
| Graff et al[44] | 63 patients with acute ischaemic stroke (44 men, aged 62 years) | To determine simultaneous analysis of multiple HRV parameters might provide results which help to understand better autonomic nervous system changes and their association with functional outcome in patients with the acute ischaemic stroke | ApEN, SampEn, and FuzzyEn (derived from HRV analysis on 512 consecutive RR intervals) successfully differentiated patients with good and poor early outcome. However, at a 90-day follow-up the frequency-domain variables of absolute VLF power, absolute LF power, HF%, LFnu, HFnu, and LF/HF differentiated patients based on outcome |
| Tang et al[45] | 150 patients with stroke (70 men, aged 62.0 ± 15.3 years), 77 stroke patients with AF (43 men, aged 74.3 ± 11.6 years), and 60 healthy controls (38 men, aged 60.9 ± 10.4 years) | To investigate HRV complexity and its association with 3-month functional outcome in patients with acute stroke admitted to the intensive care unit as compared with non-stroke controls | RMSSD (OR = 0.99; 95% CI = 0.97-1.00) and the complexity index (CMI; OR = 1.18; 95% CI = 1.08-1.28) significantly predicted functional status at the 3-month follow-up in patients with non-AF stroke |
| Katz-Leurer and Shochina[46] | 39 patients with ischaemic stroke (19 men, aged 63 ± 10 years) | To assess the connection and the prognostic value of HRV parameters on motor and aerobic capacity in patients after ischaemic stroke 2 weeks and 3 months post event | RMSSD, LF, and HF (derived from 5-minute supine-free breathing Holter ECG recordings) were significantly correlated to patient motor performance and aerobic capacity post first stroke up to 3 months later. SDNN was also significantly correlated to FIM score ($r = .29$; $P < .05$) |
| Günther et al[48] | 43 patients with acute ischaemic stroke (28 men, aged 62.60 ± 12.19 years) | To assess the hypothesis that HRV indices predict the development of early stroke-induced infection | Modelling analysis determined daytime LF/HF, LFnu, and HFnu as well as nighttime lnLF and lnVLF derived from 3-hour HRV analysis to be significant predictors of post-stroke infection |
| Al-Qudah et al[49] | 1 patient with haemorrhagic stroke, 1 patient with ischaemic stroke | To examine serial heart rate variability testing for the evaluation of autonomic dysfunction in stroke | Both cases reported an acute approximate 5% reduction in mean RR interval length and an average of 15% recovery at a 45 day follow-up, with the recovery reported to parallel an improvement in clinical status |

**Table 2.** (Continued)

| STUDY | STUDY POPULATION | OBJECTIVE | PRIMARY RESULTS |
|---|---|---|---|
| Chen et al[50] | 71 patients with stroke without SIE (39 men, aged 64.0 ± 15.3); 19 patients with stroke with SIE (9 men, aged 67.2 ± 18.2) | To investigate whether MSE is a predictor of SIE in patients with non-AF ischaemic stroke | Analysis revealed that the RMSSD, LF/HF, CMI, and $Area_{6\text{-}20}$ (the summations of quantitative entropy values of scale 6-20) parameters varied significantly between patients with and without SIE ($P \leqslant .030$), and adjusted regression models determined that only the CMI (OR = 0.897; $P = .020$) and $Area_{6\text{-}20}$ parameters (OR = 0.868; $P = .020$) were significant predictors for SIE |
| Wei et al[39] | 232 patients with acute ischaemic stroke with varying degrees of renal function (134 men, aged 69 ± 19 years) | To evaluate the association between autonomic function and stroke in patients with renal dysfunction | Found that SDNN, VLF, LF, and LF/HF derived from a 12-channel 24-hour ambulatory ECG differed significant between the 3 patient groups (with normal, mild dysfunction, and moderate renal dysfunction) and healthy controls |
| Sethi et al[53] | 13 patients with acute stroke and unilateral motor weakness (7 men, aged 61 ± 12 years) | To determine whether HRV is associated with motor outcome 3 months after stroke | Acute-phase SDNN derived from a 24-hour Holter Monitor ECG was significantly associated with upper ($r = .70$; $P = .01$) and lower ($r = .60$; $P = .03$) extremity impairment at a 3-month follow-up |

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CMI, complexity index; ECG, electrocardiogram; FD, fractal dimension; FIM, functional independence measurement; HF, high frequency; HR, hazard ratio; HRV, heart rate variability; LF, low frequency; ln, natural log; MSE, multiscale entropy; nu, normalised units; OR, odds ratio; RMSSD, the root mean square of the sum of squares of differences between adjacent NN intervals; ROC, receiver operating characteristic; RR, R to R interval; SDNN, standard deviation of all normal to normal RR intervals; SIE, stroke in evolution; TIA, transient ischaemic attack; TINN, the triangular interpolation of NN interval histogram; VLF, very low frequency.
Table 2 presents a brief summary of the presently reviewed research articles that examined heart rate variability and its relationship to post-stroke complications and functionality. For each reviewed article, it describes the sample group examined, the study objective, as well as the primary results and HRV measures implicated by the analysis.

*Long-term HRV analysis.* Only 2 of the presently reviewed articles used long-term HRV analysis (greater than or equal to 24 hours) in their examination of post-stroke complications or functionality. Most recently, Wei et al[39] commented on post-stroke renal functionality and found that LF/HF was significantly associated with renal function, suggesting that HRV could be used as a proxy measure of renal capacity. In addition, although not commenting on it, Wei et al[39] presented a multinomial linear regression analysis that found the SDNN index ($t = -3.83$; $P < .001$), as well as the VLF ($t = -3.07$; $P = .002$) and LF ($t = -2.79$; $P = .006$) parameters, to be related to stroke severity as measured by the NIHSS score. These results combined with the broad nature of the examination conducted in the NIHSS, ie, examining limb ataxia, language, visual fields, etc; it could be suggested that these HRV variables could be further developed so as to provide insight into patient post-stroke functionality. Furthermore, it would be interesting to examine the relationship between these HRV variables (and others) to 11 individual sections of the NIHSS, to see whether more specific functional information could be derived from HRV changes.

In an examination of post-stroke motor outcome, Sethi et al[53] analysed time-domain HRV data from 13 patients with acute stroke (7 men, aged 61 ± 12 years) who presented with unilateral motor weakness. Acute-phase HRV (SDNN) was significantly associated with upper ($r = .70$; $P = .01$) and lower ($r = .60$; $P = .03$) extremity impairment at a 3-month follow-up and, interestingly, in patients who initially exhibited severe motor impairment; HRV at admission was more strongly associated with motor impairment at follow-up than initial motor impairment. Although no predictive analysis (eg, ROC curves) was conducted, it could be suggested that acute-phase time-domain HRV may function as a biomarker for post-stroke motor outcome; however, additional development and predictive analysis is required to confirm.

Overall, research using long-term HRV analysis to examine post-stroke complications and/or functionality has demonstrated that post-stroke renal function, stroke severity, and post-stroke motor outcome are related to changes in linear frequency- and time-domain parameters such as SDNN, LF, and LF/HF ratio, and that with further work these changes may be used as biomarkers for the prediction or management of these outcomes. A brief summary of each of the aforementioned research articles that investigated HRV (both short term and long term) in relation to post-stroke complications and functionality can be found in Table 2.

## Conclusions

Current literature provides good evidence that various HRV parameters can function as biomarkers for incident stroke, a number of post-stroke outcomes, including motor impairment and mortality, as well as functional measures. Indeed, changes in frequency-domain HRV parameters, primarily LF and HF, predicted stroke or were correlated with functional outcome, post-stroke infection, and patient mortality. Similarly, time-domain HRV parameters, including SDNN and RMSSD, and non-linear entropy parameters, including MSE and FD, predicted stroke and also provided insight into stroke severity, stroke-related motor impairment, functional outcome, and mortality.

Looking ahead, the most obvious research path is the expansion of predictive modelling of stroke using HRV parameters. Although all of the reviewed research provides some insight regarding HRV changes observed in stroke, only 10 of the 22 included papers provided direct predictive analysis. Furthermore, future research would do well to integrate non-linear and novel HRV parameters, such as MSE and FD, into their analysis, particularly of post-stroke outcomes and functionality, as their utilisation is currently limited but has shown promise. In addition, the analysis and utilisation of hybridised parameters (ie, an algorithmic combination of HRV variables, be they time-domain, frequency-domain, or non-linear parameters) in the development of predictive models for stroke may prove to be a fruitful research endeavour in predicting incident stroke, post-stroke outcomes, functionality, and complications, as there has been success using such parameters in other areas.

Overall, HRV analysis appears to provide valuable non-invasive clinical and prognostic information regarding stroke and its outcomes, and with future develop may better enable prediction and detection of stroke, as well as the subsequent treatment and management of patients with stroke.

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## Author Contributions

TL and SL collaboratively designed the systematic search strategy, and conducted the initial article selection. TL conducted the literature search, compiled and developed the initial review and manuscript. SL, FSK, AS, NN, and YL provided expert critique and discussion of the reviewed articles and the initial manuscript.

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