Evaluation of Skin Sympathetic Nervous Activity for Classification of Intracerebral Hemorrhage and Outcome Prediction

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Research Article

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Abstract

Classification and outcome prediction of intracerebral hemorrhage (ICH) is critical for improving the survival rate of patients. Early or delayed neurological deterioration is common in ICH patients, which may lead to changes in the autonomic nervous system (ANS). Therefore, we proposed a new framework for ICH classification and outcome prediction based on skin sympathetic nervous activity (SKNA) signals. A customized measurement device presented in our previous papers was used to collect data. 117 subjects (50 healthy control subjects and 67 ICH patients) were recruited for this study to obtain their five-minute ECG and SKNA signals. We extracted the signal’s time-domain, frequency-domain, and nonlinear features and analyzed their differences between healthy control subjects and ICH patients. Subsequently, we established the ICH classification and outcome evaluation model based on the eXtreme Gradient Boosting (XGBoost). In addition, HRV as an autonomic nerve assessment method was also included as a comparison method in this study. The results showed significant differences in most features of the SKNA signal between healthy control subjects and ICH patients. The ICH patients with good outcomes have a higher change rate and complexity of SKNA signal than those with bad outcomes. In addition, the accuracy of the model for ICH classification and outcome prediction based on the SKNA signal was more than 91% and 83%, respectively. The ICH classification and outcome prediction based on the SKNA signal proved to be a feasible method in this study. Furthermore, the features of change rate and complexity, such as entropy measures, can be used to characterize the difference in SKNA signals of different groups. The method can potentially provide a new tool for rapid classification and outcome prediction of ICH patients.

I. Introduction

Intracerebral hemorrhage (ICH) is a severe subtype of stroke, also known as hemorrhagic stroke, that accounts for about 30 percent of all stroke patients worldwide [1]. ICH patients have a high mortality and disability rate [2] [3]. However, it is affected by cardiovascular and cerebrovascular diseases such as hypertension rather than external factors and is difficult to detect in the early stage of the disease. Without timely intervention and treatment, there will be a fatal risk [4] [5]. In addition, the hospital treatment of ICH is also a difficult problem [6]–[9]. Choosing the appropriate treatment according to the severity of the disease may be more beneficial in improving the outcome [10] [11]. Therefore, the rapid diagnosis and outcome prediction of ICH is of great significance in choosing appropriate treatment options and improving the survival rate of patients.

The most widely used method for the diagnosis of ICH is non-contrast computed tomography (CT) [12] [13]. Although this method is the gold standard for diagnosis, the diagnostic results are often lagging. The lag of diagnosis brings some troubles to the choice of treatment methods, thus affecting the treatment results. Compared with traumatic ICH, patients with spontaneous ICH may make doctors ignore performing the routine CT examination because the neurological symptoms are not obvious [14].
Some studies have shown that early or delayed deterioration of neurological function is common in ICH patients, leading to a great nervous system disorder [15]-[17]. The damage to the central nervous system after ICH will also affect the autonomic nervous system (ANS), such as the loss of emergency function of the sympathetic nerve. Besides, the autonomic nerve status of ICH patients with different outcomes is also different due to the different degrees of nerve damage. Therefore, some researchers diagnose and evaluate the outcome of the ICH patients based on the changes in the ANS such as the HRV indexes of the patients [17]. However, these changes can be secondary to neurocardiogenic changes [18] or attributed to true myocardial ischemia [19]. And its interpretation and management are also challenging since ECG is prone to multi-source interference.

Skin sympathetic nervous activity (SKNA) [20] is a sympathetic nerve assessment method with the advantages of being real-time and noninvasive, which has achieved good results in clinical scenes such as atrial fibrillation and sleep apnea [21]-[23]. In the previous study, we developed a portable signal acquisition system [24] and applied it for autonomic nerve assessment in various clinical scenarios [23]. However, this technology has not been applied in the clinical scenario of ICH. It is unclear whether this technology can assess the impact of ICH on ANS, and further verification is needed.

In this paper, we try to evaluate changes in features of SKNA signals affected by ICH and provide an ICH classification and outcome evaluation method based on SKNA signals. The main contributions of this paper can be summarized as follows:

1) We used the multi-scale features of the SKNA signal to analyze and evaluate the sympathetic nerve characteristics of healthy control subjects and different outcomes of ICH patients, including time domain, frequency domain, and nonlinear indicators. In this way, the changes in the sympathetic nerve affected by ICH were evaluated from the perspective of signal features.

2) We first proposed applying SKNA signal analysis in ICH classification and outcome prediction. We found that different features of SKNA seemed to be related to the occurrence and outcome of ICH. We use machine learning tools to establish the ICH classification and outcome prediction model based on SKNA features. The finding of this study has potential value for clinical diagnosis and evaluation of ICH and helps to develop appropriate treatment and rehabilitation strategies. In addition, the noninvasive and rapid implementation capability of the SKNA-based method further promotes its application in the objective examination tool of ICH.

In this manuscript, the detail of the experiment was first described, followed by the data analysis framework. Section details the experimental results. Sections IV and V give the discussion and conclusion.
II. Method And Materials

A. Subjects

Table I summarizes the demographic information of this study. Sixty-seven subjects with ICH (age 55.5 ± 17.7 years, mean ± standard deviation) and 50 healthy control subjects (age 57.2 ± 10.2 years, mean ± standard deviation) from the First Affiliated Hospital of Nanjing Medical University participated in this study. The inclusion criteria of the study include the following:

1) age over 18 years old;
2) medical stability after admission to participate;
3) patients with spontaneous acute cerebral hemorrhage.

Exclusion criteria were patients with ischemic stroke, hemorrhagic conversion, atrial fibrillation, or other arrhythmias and with hemodynamic instability or shock. Clinical symptoms evaluated the outcome of patients two weeks after onset. The electronic medical record system obtained demographic data, medical history, laboratory examination, imaging, and other clinical baseline data. According to the Glasgow Outcome Score, death, severe coma, severe disability, and unable to live independently are evaluated as bad outcomes. Moderate disability, still living independently, and returning to normal life, are assessed as good outcomes. Control participants were recruited from an outpatient department of cardiovascular medicine. They were gender and age-matched participants who had not experienced the...
cardiovascular or neurological event. The participants provided written informed consent to participate in the study. The Ethics Committee of the First Affiliated Hospital of Nanjing Medical University has approved the patient experimental protocols under study number 2015-SRFA-085.

B. Signal acquisition system

A portable signal acquisition device has been developed for signal acquisition. This device consists of an analog front end based on a front-end chip (ADS1299, Texas Instruments) and a low-power microcontroller (STM32L4, STMicroelectronics), and software for monitoring based on LABVIEW 2019 (National Instruments). The sampling frequency of the system is 4 kHz, and the system noise floor is 0.8 µV. We compared the system performance with the commercial system and achieved the same performance in our previous study. Some key parameters are summarized in TABLE II, and more detailed information refers to our previous study [24].

C. Experimental setup and protocol

The experiment was carried out in the intensive care unit. Three electrodes (3M, #2570) were placed in the body, as shown in Fig. 1 [25]. The sampling frequency was 4 kHz, and the signals were recorded continually during measurement. The recording time of data is 5 minutes. All subjects were asked to stay supine and avoid unnecessary movement during the recording. The purpose of the experiment is to record the spontaneous sympathetic nervous activity of the subjects under the static state and further compare the differences between these spontaneous neural activities. All the data are imported into MATLAB (R2021a) for further processing.

D. Data analysis

1) Data preprocessing

Figure 1 shows the flowchart of the signal analysis framework in this study. All recordings go through the same preprocessing step before further analysis. A 50 Hz notch filter was applied to all recordings to reject power line interference. After the notch filter, ECG was separated by a 0.5–150 Hz band-pass filter, and SKNA was separated by a 500 to 1000 Hz band-pass filter.

2) HRV analysis

The HRV analysis was used to interpret the changes in ECG rhythm after ICH, which is also the method for the ANS evaluation [26]. First, we used a QRS detection algorithm to identify the R-peaks on the ECG waveforms [27]. Then, temporal, spectral, and nonlinear features of HRV are calculated with the R-peak to R-peak interval sequence. We calculated Nine HRV features for this study: the mean RR interval (MEAN), the standard deviation of all RR intervals (SDNN), the root mean square of the differences between adjacent RR intervals (RMSSD), the low-frequency power in the frequency band from 0.04 Hz to 0.15 Hz (LF), the high-frequency power in the frequency band from 0.15 Hz to 0.4 Hz (HF), the ratio between LF
and HF (LF/HF), the ratio between LF and total power (LF/(LH + HF)), the sample entropy of the RR intervals (SampEn), the fuzzy measure entropy of the RR intervals (FuzzyMEn) [26].

3) **SKNA analysis**

The feature analysis of the SKNA signal can be divided into three categories: time domain, frequency domain, and nonlinear features. Time domain features and frequency domain features are common in biomedical signal processing [28], but most time-frequency domain features have not been widely used and interpreted for SKNA signal analysis [21] [22]. In this study, we used 39 features for evaluation and comparison, most of which were defined in the time domain, and calculated a small number of frequency-domain features and nonlinear features. The detailed definitions and the related works of these features are listed in TABLE V of the appendix [29]-[46].

Besides, this study introduced the entropy measure to evaluate the SKNA signal. It is necessary to reduce the dimension of the data before calculating the entropy measure, considering the computing memory and time. We reduce the data dimension based on signal integration. The reduced dimension signal can be expressed as

\[
iSKNA(n) = \frac{\sum_{i=1}^{f \times t} abs(x(i))}{f \times t}
\]

where \( f \) is the sampling frequency of the sequence, and \( t \) is the time window. Towards the parameter of all entropy measures, the default value of time scale \( t \) is set to 20 ms, and tolerance \( r \) is set to 0.1.

4) **Statistical analysis**

The normality was performed by the Kolmogorov-Smirnov test. Continuous variables were presented as the average ± standard deviation. An independent Student’s t-test was performed to analyze the difference in the HRV and SKNA parameters between the ICH patients and healthy control subjects, the ICH patients with good and bad outcomes, ICH patients with good outcomes and healthy control subjects, ICH patients with bad outcomes and healthy control subjects, respectively. A p-value less than 0.05 was considered statistically significant for a two-tailed test. Statistical analyses were performed using SPSS (version 24.0, IBM) and MATLAB (R2021a).

5) **Classification of ICH and outcome prediction**

We used the classification tool, the eXtreme Gradient Boosting (XGBoost), as the classifier for ICH classification and outcome prediction. We developed two classifiers to evaluate the performance of the different features for two different classification tasks, respectively, including:

(1) a binary classification task to differentiate between the ICH patients and healthy control subjects;
(2) a binary classification task to differentiate between the ICH patients with good and bad outcomes.

We used a total of 39 features of the SKNA signal for training. 5-fold cross-validation was performed with 80 percent of subjects (40 healthy control subjects and 55 ICH patients) for training, and the remaining 20 percent (10 healthy control subjects, 6 ICH patients with good outcomes, and 6 ICH patients with bad outcomes) were used for testing. During the training process, we set aside 20 percent of subjects (8 healthy control subjects, 5 ICH patients with good outcomes, and 6 ICH patients with bad outcomes) from the training set for model validation and hyperparameter optimization in every iteration of the 5-fold cross-validation. An early stopping strategy was used to avoid overfitting. This is, the training would stop when the performance on the validation set was not improved for ten consecutive rounds. To explore what features contributed most to each classification task, the Shapley Additive Explanation (SHAP) value was used to quantify the importance of each feature on each classification task [47].

The classification accuracy, recall, precision, and F1 were used to evaluate the performance of classification and outcome prediction using the SKNA features. These indexes can be defined as

\[
\text{Precision} = \frac{TP}{TP + FP} \times 100\%
\]

\[
\text{Recall} = \frac{TP}{TP + FN} \times 100\%
\]

\[
F1 = \frac{2 \ast \text{Precision} \ast \text{Recall}}{\text{Precision} + \text{Recall}} \times 100\%
\]

\[
\text{Acc} = \frac{TP + TN}{TP + TN + FP + FN} \times 100\%
\]

where TP is the number of subjects classified as positive by both the label and the model, and TN is the number of subjects classified as negative by both the label and the model. FP is the number of subjects classified as positive by the model and not by the label. FN is the number of subjects classified as negative by the model and not by the label.

iii. Results
In this study, we analyzed the results from three aspects, including the influence of parameters on the robustness of SKNA-based entropy, statistical analysis of signal features between different groups, and performance of the ICH classification and outcome prediction models, as shown below.

A. Robustness of SKNA-based entropy

To evaluate the robustness of different entropy measures under different parameters, we calculated three entropy measures of the ICH patients and healthy control subjects with tolerance $r$ ranging from 0.1 to 0.25, as shown in Fig. 2(a). Experimental results showed that the values of SampEn, ApEn, and FuzzyEn from ICH patients and healthy control subjects become smaller with the increase of the $r$ value. However, these three entropy measures between ICH patients and healthy control subjects showed a significant difference with different $r$ values. The SKNA-based entropy method may be robust for SNA complexity assessment post-ICH in different $r$ values.

We also compared the entropy measures of ICH patients and healthy control subjects with different time scales ranging from 20 to 220 ms, which can be seen in Fig. 2(b). With the increase in scale, the changing trend of SampEn, FuzzyEn, and FuzzyMEn is not obvious, and the difference between ICH patients and healthy control subjects is almost unaffected by the time scale. However, ApEn and PermEn decrease with the increase of time scale, and the difference between ICH patients and healthy control subjects gradually decreases. DistEn shows an upward trend with the increase of the time scale, and effort on the difference between ICH patients and healthy control subjects does not show a consistent law.

B. Features analysis

1) ICH patients and healthy control subjects

Fig. 3 shows the statistical results of the HRV analysis in ICH patients and healthy control subjects. MEAN, SDNN, RMSSD LF, and HF of the ICH patients were higher than those of healthy control subjects, while LF/(LH+HF), LF/HF, SampEn, and FuzzyMEn of the ICH patients were lower than those of healthy control subjects. However, these parameters showed no statistical difference. In other words, it is difficult to distinguish the difference in autonomic nerve changes between the ICH patients and healthy control subjects by HRV analysis.

The comparison results between the ICH patients and healthy control subjects with SKNA features are shown in Fig. 4 and TABLE III. All SKNA features of healthy control subjects showed significant differences compared with the ICH patients except COV, FR, and PermEn. The F-values of 28 features were more than 20. In other words, we can easily distinguish between healthy control subjects and ICH patients by the SKNA feature. In addition, the statistical results showed that the ZC, SSC, SKEW, FMN, and all entropy features of ICH patients were higher than those of healthy control subjects. In contrast, other features were lower than those of healthy control subjects.

2) ICH patients with good and bad outcomes
Fig. 5 shows the statistical results of HRV features of the ICH patients with different outcomes and healthy control subjects. The experimental results showed no significant difference in HRV features between the ICH patients and healthy control subjects. ICH patients were divided into two groups with good and bad outcomes, which were compared with healthy control subjects. The HRV frequency domain features of the ICH patients with good outcomes, LF/HF and LF/(LF+HF), show significant differences from that of healthy control subjects. In addition, HRV features of the ICH patients with good outcomes showed no significant difference from those with bad outcomes.

Similarly, we compare the ICH patients with the good and bad outcomes to healthy control subjects based on the SKNA features, as shown in Fig. 6 and TABLE III. According to the outcome of ICH patients, we divided into two groups: good outcomes and bad outcomes. The experimental results show that there are still significant differences in SKNA features between these two groups and healthy control subjects. Compared with the good and bad outcomes, the mean values of other features with the good outcome are higher than those with the bad outcome except for WA, MYOR, SKEW, FR, PermEn. However, these features did not show significant differences between good and bad outcomes. ZC, SSC, TM, FMN, SampEn, ApEn, Disten, FuzzyEn, and FuzzyMEn of the ICH patients with the good outcome were significantly higher than those with the bad outcome. By comprehensively comparing the results of healthy control subjects, these features can not only distinguish between healthy control subjects and ICH patients but also distinguish the sympathetic nerve activity of the ICH patients with the good and the bad outcome.

D. ICH classification and outcome prediction

The performance of the classification and outcome prediction model is shown in Fig. 7. The precision, recall, F1, and accuracy of the ICH classification model were higher than 83%, while that of the outcome prediction model was higher than 80%. Besides, the precision and F1 of the ICH classification are slightly higher than that of the outcome prediction model. This may be caused by the limited validation set and the more features that significantly differ between healthy control subjects and ICH patients. Significantly, limited by the size of the verification set, the results of the classification tasks were not to prove the performance of the application using SKNA signal in ICH classification and outcome prediction but to prove the feasibility of using SKNA signal combined with machine learning tools in ICH classification and outcome prediction.

In the two classification tasks, the top ten features of importance are shown in Fig. 8. SampEn, TM, WAMP, DistEn, COV, PermEn played important roles in both classification tasks. This result is similar to that of the analysis of feature differences. Moreover, although KURT, FMN, and CARD show strong importance in the classification task, they did not show similar importance in the outcome prediction task. The feature importance based on SHAP is not identical to the feature difference analysis, which
may be caused by the calculation method of similarity between these features. Notably, nonlinear features such as TM and entropy measures show strong importance in both classification tasks.

**Iv. Discussion**

This study evaluated the changes in sympathetic nervous activity affected by ICH based on the multiscale feature of the SKNA signal. We recorded the 5-minute ECG and SKNA signals of 50 healthy control subjects and 67 ICH patients and comprehensively analyzed and compared the signals based on the HRV and SKNA features. This study comprehensively assesses the SKNA signal feature in the ICH classification and outcome prediction.

**A. Comparison with other technology**

At present, the state of patients after ICH can be evaluated by CT, but this method is difficult to obtain results in a short time. The lack of diagnostic information may lead to untimely treatment in some scenarios where medical conditions are scarce. Moreover, the radiation of CT technology should also be considered. The SKNA-based method can make up for this shortcoming to some extent. In addition to its diagnostic ability and the non-invasive, the SKNA-based method can be performed with a convenient experimental setup and protocols. It only needs three electrodes to obtain high-frequency biopotential signals on the body surface, thus avoiding potential and time-consuming protocols in previous studies such as 24-hour HRV analysis. Instead, the SKNA features use a simplified protocol to provide side information for classification and outcome, similar to clinical routine.

**B. Finding of this study**

Feature selection is the key to explaining signal differences and classification tasks. From comparison results of SKNA features between the ICH patients and healthy control subjects, ZC, SSC, SKEW, FMN, and entropy measures of ICH patients were significantly higher than those of healthy control subjects. From the perspective of features, the frequency content [29], slope change [29], or complexity [41]-[45] of the SKNA signal of ICH patients are higher than those of healthy control subjects. In contrast, other features, such as amplitude [29] and energy [30], are lower. Therefore, the sympathetic nervous activity of ICH patients is inhibited, showing smaller and more irregular neural activity. From comparison results of SKNA features between the ICH patients with the good outcome and the bad outcome, ZC, SSC, TM, FMN, and entropy measures of ICH patients with a good outcome were significantly higher than those of ICH patients with a bad outcome, while the other features have no significant difference. From this point of view, it is impossible to distinguish the different outcomes of ICH patients by the overall amplitude or energy of the signal. The frequency content and complexity of the signal are the keys to predicting the outcome of ICH patients. Therefore, from the pathology perspective, some ICH patients have abnormal sympathetic nerve activities under sympathetic nerve inhibition. According to the change rate [29], frequency [39], complexity [41][42], and other feature of SKNA, outcome information of ICH can be provided.
Entropy measures are important methods for bioelectric signal analysis. However, it is still uncertain which entropy measure is the best in all clinical applications [44] [45]. Therefore, in detail, we compare the performance of six entropy measures under different parameters and objects. SampEn, ApEn, and FuzzyEn are hardly affected by tolerance r, according to the experimental results. Therefore, choosing different R values in an appropriate range has little effect on the entropy measure. Towards the different time scales, the difference between the ICH patients and healthy control subjects of SampEn and FuzzyEn has not changed. The difference between ICH patients and healthy subjects from FuzzyMEEn decreases slightly as the time scale t increases but is still acceptable. In addition, we found that the calculation results of ApEn, PermEn, and DistEn changed with the increased time scale and affected the discrimination ability of ICH patients and healthy subjects. Therefore, SampEn, FuzzyEn, and FuzzyMEEn may be more robust than ApEn, PermEn, and DistEn for applying entropy measures to evaluate the difference of SKNA after ICH. In practical application, the three entropy measures ApEn, PermEn, and DistEn may perform better by choosing the appropriate time scale.

Although multi-scale features based on the SKNA signal can provide some diagnostic and outcome prediction information, it seems difficult to define an exact threshold for features to distinguish different states. Therefore, we use the machine learning tool processing the features SKNA signal to diagnose and evaluate the outcome of ICH in this study. The preliminary results show that the classification and outcome prediction model based on SKNA and XGBoost has high accuracy. However, we did not further optimize this model due to the sample size. Therefore, the significance of this work is to explore the possibility of using the SKNA signal for ICH classification and outcome prediction. In future work, a larger sample size and algorithm optimization may further improve the accuracy of the models. Furthermore, we also found that the results of feature importance based on SHAP are not completely consistent with that of feature difference analysis, which may be due to the differences between the model training method and statistical analysis method, as well as the redundancy of features.

C. Limitations

Several limitations might affect the findings of this study. From the perspective of data acquisition, the data were collected from patients after the acute phase for ethical and data stability reasons. Therefore, the onset period of ICH patients is relatively vague, which may also lead to the smaller difference between a good and bad outcome and the mixed analysis results of some data. In addition, since we did not analyze the drug used in these patients, the effect of drugs may also affect the analysis of autonomic nerve system function. From the perspective of signal analysis, this study only focuses on developing SKNA-signal-based biomarkers for sympathetic changes after ICH. Although the SKNA-based method provides some thinking from the perspective of nerve changes in ICH patients, it is necessary to provide additional information with more analysis methods, such as CT images or other invasive nerve signals [12] [13]. By fusing more information from different methods and techniques, the pathological changes caused by ICH can be explained more precisely. In future work, we will observe the recovery track of ICH patients through the SKNA-based method to evaluate whether the change in individual progress over time is constant and quantifiable.
TABLE III
The Detailed Statistical Results of the SKNA-based Features Among the Healthy Control Subjects, the ICH Patients with Good Outcomes, and the ICH Patients with Bad Outcomes.

<table>
<thead>
<tr>
<th>NO.</th>
<th>Feature</th>
<th>Control</th>
<th>ICH-GO</th>
<th>ICH-BO</th>
<th>All</th>
<th>p-value</th>
<th>ICH-GO</th>
<th>ICH-BO</th>
<th>All</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MAV</td>
<td>1.23±0.43</td>
<td>0.74±0.23</td>
<td>0.72±0.16</td>
<td>0.73±0.19</td>
<td>***</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RMS</td>
<td>0.8±0.86</td>
<td>0.99±0.34</td>
<td>0.95±0.21</td>
<td>0.97±0.28</td>
<td>***</td>
<td>0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>VAR</td>
<td>3.1±1.53</td>
<td>1.1±0.84</td>
<td>0.96±0.49</td>
<td>1.01±0.67</td>
<td>***</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>WLI(10°)</td>
<td>14.29±49.14</td>
<td>91.69±25.30</td>
<td>89.69±17.45</td>
<td>89.69±21.34</td>
<td>***</td>
<td>0.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>EWL(10°)</td>
<td>121.6±25.42</td>
<td>92.74±15.81</td>
<td>89.78±11.24</td>
<td>91.18±13.48</td>
<td>***</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>ZCC(10°)</td>
<td>392.6±10.93</td>
<td>418.4±16.58</td>
<td>400.4±12.45</td>
<td>408.8±16.89</td>
<td>***</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SSC(10°)</td>
<td>424.6±12.50</td>
<td>451.3±16.42</td>
<td>427.1±16.50</td>
<td>438.5±20.33</td>
<td>***</td>
<td>**</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>WAMP(10°)</td>
<td>119.1±2.11</td>
<td>119.2±1.36</td>
<td>118.40±0.63</td>
<td>118.35±1.03</td>
<td>***</td>
<td>0.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>SSII(10°)</td>
<td>457.6±43.78</td>
<td>132.5±101.60</td>
<td>115.2±59.54</td>
<td>123.3±81.36</td>
<td>***</td>
<td>0.29</td>
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<td></td>
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<tr>
<td>10</td>
<td>SD</td>
<td>1.8±0.76</td>
<td>0.99±0.34</td>
<td>0.95±0.21</td>
<td>0.97±0.28</td>
<td>***</td>
<td>0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>ASM</td>
<td>0.5±0.10</td>
<td>0.4±0.07</td>
<td>0.4±0.04</td>
<td>0.4±0.05</td>
<td>***</td>
<td>0.86</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td>ASS(10°)</td>
<td>828.6±131.52</td>
<td>638.0±96.58</td>
<td>654.30±66.24</td>
<td>656.04±80.77</td>
<td>***</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>CAR</td>
<td>485.7±304.25</td>
<td>154.0±113.17</td>
<td>122.2±49.46</td>
<td>137.7±85.86</td>
<td>***</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>COV(10°)</td>
<td>158.4±81.87</td>
<td>146.4±38.73</td>
<td>17.45±14.41</td>
<td>78.3±289.40</td>
<td>0.79</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>DAM</td>
<td>1.1±0.41</td>
<td>0.7±0.20</td>
<td>0.7±0.14</td>
<td>0.7±0.17</td>
<td>***</td>
<td>0.48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>DASD</td>
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TABLE IV
Comparison between this study and the other related technology.

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<th>Technology</th>
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<td>CT[7]</td>
<td>Gold standard for diagnosis</td>
<td>About one hour</td>
<td>1.08±0.18</td>
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<tr>
<td>24-hours HRV[61]</td>
<td>Associated with outcome and diagnosis of ICH</td>
<td>24 hours</td>
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<tr>
<td>5-minutes HRV</td>
<td>Low correlation</td>
<td>5 minutes</td>
<td>No</td>
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<tr>
<td>This work</td>
<td>More than 90% for classification of ICH and outcome prediction</td>
<td>5 minutes</td>
<td>No</td>
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</table>
Conclusion

This study explored the application of SKNA signals in the classification and outcome evaluation of ICH and comprehensively evaluated and compared the differences and importance of multi-scale features of SKNA signals. The results showed significant differences in the features of the SKNA signal between healthy control subjects and ICH patients, specifically in amplitude, frequency content, and complexity. Besides, the ICH patients with a good outcome have a higher change rate and complexity of SKNA signal than those with a bad outcome. Compared with the short-term HRV features, the finding in differences in the SKNA feature may be more helpful for the classification and outcome evaluation of ICH patients using noninvasive electrophysiological signals in the future. Our study supports the hypothesis that changes in sympathetic nerve signals may be related to ICH.

In addition, the model combined with machine learning and the multi-scale SKNA features has achieved high accuracy, which further shows the great potential of the SKNA signal in ICH classification and outcome evaluation. This is the first study to evaluate the impact of SKNA signals on ICH based on
feature engineering and machine learning tools intensively. We expect to provide a new tool for rapid screening of ICH patients.

**Declarations**

**Competing Interests.**

The authors declare no Competing Financial or Non-Financial Interests.

**References**


**Figures**

**Figure 1**

Flowchart of the signal analysis framework in this study. The left side shows the electrodes placed position.

![Flowchart](image)

**Figure 2**

Graphs showing changes in heart rate variability with time scale (ms).
(a) The average and standard deviation of the SampEn, ApEn, and FuzzyEn from ICH patients and healthy control subjects with different tolerance r. (b) The average and standard deviation of the entropy measures from ICH patients and healthy control subjects with different time scale t. Red lines indicated the ICH patients, while blue lines indicated healthy control subjects. *p<0.05, **p<0.01, ***p<0.001, NS no significant difference

**Figure 3**

The statistical results of the HRV features between the healthy control subjects and the ICH patients.
Figure 4

The statistical results of normalized SKNA features between the healthy control subjects and the ICH patients. *p<0.05, **p<0.01, ***p<0.001, NS no significant difference.
Figure 5

The statistical results of the HRV features among the healthy control subjects, the ICH patients with good outcome, and the ICH patients with bad outcome. *p<0.05, **p<0.01, ***p<0.001, NS no significant difference

Figure 6

The statistical results of the normalized SKNA-based features among the healthy control subjects, the ICH patients with the good outcome, and the ICH patients with the bad outcome. *p<0.05, **p<0.01, ***p<0.001, NS no significant difference
Figure 7

Performance of the Two Classification Tasks using XGBoost Models Based on SKNA Features
Figure 8

Importance of input features on diagnosis and outcome prediction. (a) The binary classification task to differentiate between the ICH patients and healthy control subjects (b) A binary classification task to differentiate between the ICH patients with good outcome and bad outcome. The abscissa value corresponding to each feature is the weight that the feature plays in the classification.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- APPENDIX.docx