Predicting hemorrhagic transformation in posterior circulation stroke patients not treated with reperfusion therapies

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Research Article

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Abstract

Introduction

Posterior Circulation (PC) stroke represents one-fifth of all ischemic strokes, with peculiar physiological characteristics. Hemorrhagic Transformation (HT) is a dreaded complication among stroke patients. Many predictive scores of this complication have been proposed, but none is designed specifically for PC stroke patients – therefore, patients who are not eligible to reperfusion therapies (RT) represent about 80% of hospitalized cases. We propose a scoring system to assess the HT risk in PC stroke patients not submitted to RT.

Methods

We retrospectively evaluated data of patients diagnosed with PC stroke not treated with RT from 5 Comprehensive Stroke Centers (four in Brazil, 1 in the US) from 2015 to 2018. All patients underwent CT scan or MRI at admission and a follow-up neuroimaging within seven days. Independent variables identified in a logistic regression analysis were used to produce a predictive grading score.

Results

We included 952 patients in the final analysis. The overall incidence of HT was 8.7%. Male gender (1 point), NIH Stroke Scale at admission $\geq$ 5 points (1), blood glucose at admission $\geq$ 160mg/dL (1), and cardioembolism (2) were independently associated with HT. The AUC of the grading score (0 to 5 points) was 0.713 (95% CI 0.65-0.78). Subjects with a score $\geq$ 3 points had an OR of 4.8 (95% CI 2.9-7.9, p<0.001) for HT.

Conclusions

Our score is accurate in identifying patients at higher risk of HT. This score may be useful for evaluating secondary prevention and stratifying patients in the context of even clinical trials.

• Introduction

Hemorrhagic transformation (HT) is one of the most frequent and threatening complications of ischemic stroke, with a clinical spectrum ranging from asymptomatic patients to ominous neurological outcomes$^{1,2,3,4}$. Furthermore, identifying stroke patients at high risk for HT could lead to an individualized approach for this subset. Thus, recognizing HT risk factors may play a key role in setting this stratification$^5$.

Literature regarding scoring systems for predicting HT mainly focuses on stroke patients who have undergone Reperfusion Therapy (RT). Conversely, the PROpHET score predicts HT risk in Anterior Circulation (AC) stroke patients not submitted to RT$^6$. Nevertheless, all previous scoring systems do not...
specifically address HT risk in patients with posterior circulation (PC) ischemic stroke not submitted to RT.

Posterior circulation stroke accounts for one-fifth of all ischemic strokes and is related to increased mortality rates. Spontaneous HT frequency following posterior ischemic strokes ranges from 5.9–7.8%. The significant prevalence and the particularities concerning posterior circulation reinforce the need to create a scoring system to accurately predict the HT risk in this population.

Therefore, we propose a practical scoring system – the PC PROpHET score - to specifically quantify HT risk in PC stroke patients not submitted to RT, based on clinical and laboratory findings readily available in the emergency department.

• Methods

Patients

All patients diagnosed with ischemic stroke not treated with RT admitted from 2015 to 2018 were eligible. We retrospectively evaluated data from 4 Comprehensive Stroke Centers in Brazil and 1 in the US. We assessed the posterior circulation ischemia by a well-defined neuroimaging finding on admission or follow-up evaluation within seven days from the admission. We considered the posterior circulation involvement as a neuroimaging finding (by CT Scan or MRI) suggestive of acute cerebral ischemia in the territories of vertebral, basilar, and posterior cerebral artery and their branches. In patients who did not have well-defined neuroimaging findings, we considered as having a posterior circulation stroke those who had a posterior circulation syndrome (according to the Oxfordshire Community Stroke Project classification) without any acute ischemia in the anterior circulation. Patients with simultaneous anterior and posterior circulation involvement were also included, but the HT was only considered if attested in posterior circulation territories. We excluded patients who did not have a head CT scan or MRI at admission and a follow-up neuroimaging within 2 to 7 days.

We assessed the etiology of the events based on the Trial of Org 10172 in Acute Stroke Treatment - Stop Stroke Study. Two board-certified vascular neurologists completed and supervised this assessment. Patients with incomplete evaluation were classified as having an 'Undetermined Cause.'

At hospital transfer/discharge, patients had their functionality assessed by our local trained nursing staff using the modified Rankin score.

Hemorrhagic transformation

Our analysis considered HT as any radiology and clinical type of HT in our analysis. HT was diagnosed using international imaging criteria (European Cooperative Acute Stroke Study, ECASS II trial) when evidence of blood or hemoglobin products within the recent ischemic area was present on neuroimaging within seven days of admission in both derivation and validation groups. Radiological subgroup
classification of HT was also assessed based on the ECASS II trial\textsuperscript{15}. Hemorrhagic infarction 1 (HI1) was
defined as small petechiae along the margins of the infarct; hemorrhagic infarction 2 (HI2) as confluent
petechiae within the infarced area but no space-occupying effect; parenchymal hemorrhage (PH1) as
blood clots in 30\% or less of the infarced area with some slight space-occupying effect; and
parenchymal hemorrhage (PH2) as blood clots in more than 30\% of the infarced area with substantial
space-occupying effect.

**Neuroimaging**

All patients underwent CT Scan or MRI at admission and a follow-up neuroimaging within 2 to 7 days as per the institution protocol. Follow-up images were performed using magnetic resonance imaging (MRI) in 81.6\% of patients in our sample. All neuroimages were evaluated by radiologists not involved in patient care and not aware of the patients’ clinical syndrome or functional status. The Posterior Circulation Alberta Stroke Program Early CT score (PC-ASPECTS)\textsuperscript{16} and the presence of leukoaraiosis were a part of the standard radiology report of one participant center. The PC-ASPECTS was performed by trained radiologists. In the validation group, both CT and MRI were also adopted to determine the presence of HT within seven days from hospital admission. Patients with a visible hypodensity on not eligible areas for the PC-ASPECTS at admission were excluded from the final analysis. Patients without any visible hypodensity were classified as having PC-ASPECTS 10.

**Statistical analysis**

Descriptive statistics were used to report patients’ characteristics. Appropriateness of parametric testing was assessed with the Kolmogorov-Smirnov test. The independent samples t-test was used to compare means between patients with and without HT. Nonparametric data were compared using the Mann-Whitney test. Categorical variables were compared with the Chi-square test. Variables that had an association with HT with a p-value < 0.1 were selected for multivariable analysis. A multivariable model was built using the likelihood ratio test for comparison between models. The calibration of the model was assessed with the Hosmer-Lemeshow test. Independent predictive factors identified in logistic regression analyses were then used to produce a predictive grading score for HT. The score of each variable was defined based on coefficients of the multivariable logistic equation by rounding to the nearest integer. Bootstrapping was used to reduce bias in performance estimates. We assessed the discrimination of the score using the area under the receiver operating characteristic (AUROC) curve. The optimal cutpoint of the PROpHET PC was defined using the Youden Index. Statistical analysis was performed with SPSS 26 software (Chicago, Ill., USA) and MedCalc 19.0.4.

**Standard protocol approvals, registrations, patient consents, and data availability**

The hospital IRB approved this study. All the national ethical requirements were observed to support the research. The IRB waived the need for informed consent for the validation group as the data collection was retrospective. All data used in the analyses are presented in the tables and figures. Unidentified data can be publicly shared.
• Results

In the final analysis, we included 952 patients with posterior circulation involvement admitted in the participant’s centers from 2015 to 2018. The data were collected retrospectively. Patients without medical records appropriately fulfilled, follow-up neuroimaging within seven days, or unavailable information from the hospital admission (n = 5131) were excluded. The overall incidence of HT was 8.7% (n = 83/952). The mean age was 64.4 (±15.9) years. Males represented 59% of all patients – also, patients with HT were males predominantly (73.5 versus 57.6%, p = 0.005). The baseline NIH Stroke Scale was 6 [4, 10] – patients with HT had higher scores at admission: 18 [12, 20] versus 6 [4, 10] points. Demographic and baseline characteristics of patients with and without HT are shown in Table 1.
### Table 1
Baseline characteristics of patients with and without hemorrhagic transformation

<table>
<thead>
<tr>
<th></th>
<th>All patients (N = 952)</th>
<th>HT (n = 83)</th>
<th>No HT (n = 869)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (± SD)</strong></td>
<td>64.4 (15.9)</td>
<td>64.3 (6.4)</td>
<td>64.3 (16.7)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>59</td>
<td>73.5</td>
<td>57.6</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Weight, kg, mean (± SD)</strong></td>
<td>77 (15.4)</td>
<td>72.8 (17.1)</td>
<td>77 (15.2)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>NIH Stroke Scale at admission, points, median (IIQ)</strong></td>
<td>6 [4, 10]</td>
<td>18 [12, 20]</td>
<td>6 [4, 10]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NIH Stroke Scale at admission, ≥ 5 points, %</strong></td>
<td>39.4</td>
<td>36.5</td>
<td>59.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Blood glucose at admission, mg/dL, mean (± SD)</strong></td>
<td>141.5 (49.4)</td>
<td>143.8 (52.2)</td>
<td>114.3 (18.3)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Blood glucose at admission ≥ 160 mg/dL, %</strong></td>
<td>24.5</td>
<td>36.7</td>
<td>23</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure at admission, mmHg, mean (± SD)</strong></td>
<td>154.6 (29.5)</td>
<td>164 (56)</td>
<td>153.3 (27.8)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure at admission, mmHg, mean (± SD)</strong></td>
<td>85.4 (16.8)</td>
<td>91.7 (26.3)</td>
<td>84.9 (16.5)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/L, mean (± SD)</strong></td>
<td>13.6 (2.1)</td>
<td>15.7 (0.97)</td>
<td>13.3 (2.1)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>White blood cells, /mm³, median (IIQ)</strong></td>
<td>9300 [7700, 10080]</td>
<td>11100 [9667, 11470]</td>
<td>9113 [7643, 12080]</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Platelets, /mm³, median (IIQ)</strong></td>
<td>234000 [192300, 271000]</td>
<td>184100 [176900, 224700]</td>
<td>234700 [199200, 271000]</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Calcium, mg/dL, median (IIQ)</strong></td>
<td>9.8 [9.3, 10.2]</td>
<td>9.4 [9.3, 9.6]</td>
<td>9.8 [9.3, 10.3]</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Creatinine, mg/dL, mean (± SD)</strong></td>
<td>1.18 (1.13)</td>
<td>1.16 (0.32)</td>
<td>1.17 (1.18)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Uric acid, mg/dL, mean (± SD)</strong></td>
<td>4.55 (1.77)</td>
<td>3.4 (1.8)</td>
<td>4.6 (1.7)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>LDL, mg/dL, mean (± SD)</strong></td>
<td>129.8 (60.9)</td>
<td>84.7 (17.4)</td>
<td>132.8 (62.5)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Triglycerides, mg/dL, mean (± SD)</strong></td>
<td>162.4 (128)</td>
<td>93 (39)</td>
<td>169 (133)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate, ml/min/1.73m², mean (± SD)</strong></td>
<td>79.6 (33.1)</td>
<td>69 (22.5)</td>
<td>80.5 (33.8)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**SD** = Standard Deviation; **IIQ** = Interquartile interval; **LDL** = Low density lipoprotein; **MRI** = Magnetic resonance imaging; **PCA** = Posterior cerebral artery; **PC-ASPECTS** =; **ESUS** =; **IV** = Intravenous; **mRS** = Modified Rankin Scale; **PROPhET PC** = Predictive score of hemorrhagic transformation in posterior circulation stroke patients not submitted to reperfusion therapies

*These results can represent an accumulative incidence of involved arteries.
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<th>No HT (n = 869)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performed MRI, %</td>
<td>81.6</td>
<td>82.9</td>
<td>77.4</td>
<td>0.34</td>
</tr>
<tr>
<td>PC-ASPECTS, mean (± SD)</td>
<td>8.9 (1)</td>
<td>8.8 (0.3)</td>
<td>8.8 (1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Artery (or branches) involvement*, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>35.1</td>
<td>57.1</td>
<td>28.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Basilar</td>
<td>70.8</td>
<td>46.4</td>
<td>74.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Vertebral</td>
<td>3</td>
<td>3.5</td>
<td>2.04</td>
<td>0.004</td>
</tr>
<tr>
<td>Presence of leukoaraiosis, %</td>
<td>48.8</td>
<td>53</td>
<td>48.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Occipital, %</td>
<td>31.8</td>
<td>41.3</td>
<td>31</td>
<td>0.18</td>
</tr>
<tr>
<td>Cerebellar, %</td>
<td>34.3</td>
<td>39</td>
<td>33.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Pons, %</td>
<td>13.7</td>
<td>6.5</td>
<td>14</td>
<td>0.18</td>
</tr>
<tr>
<td>Medulla, %</td>
<td>6.3</td>
<td>0</td>
<td>6.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Midbrain, %</td>
<td>6.1</td>
<td>4.3</td>
<td>6.2</td>
<td>0.99</td>
</tr>
<tr>
<td>Thalamus, %</td>
<td>20.1</td>
<td>17.4</td>
<td>20.4</td>
<td>0.70</td>
</tr>
<tr>
<td>Multiple foci, %</td>
<td>15.6</td>
<td>13</td>
<td>15.7</td>
<td>0.83</td>
</tr>
<tr>
<td>Hemorrhagic transformation, %</td>
<td>8.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>History of Arterial Hypertension, %</td>
<td>70.8</td>
<td>70.3</td>
<td>74.5</td>
<td>0.63</td>
</tr>
<tr>
<td>Diabetes Mellitus, %</td>
<td>33.3</td>
<td>32.7</td>
<td>33.4</td>
<td>0.99</td>
</tr>
<tr>
<td>History of Dyslipidemia, %</td>
<td>44.9</td>
<td>50</td>
<td>44.4</td>
<td>0.65</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>21.8</td>
<td>21.5</td>
<td>23.8</td>
<td>0.78</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>9.2</td>
<td>4.5</td>
<td>9.6</td>
<td>0.70</td>
</tr>
<tr>
<td>Prior Stroke, %</td>
<td>21</td>
<td>20.4</td>
<td>25.4</td>
<td>0.38</td>
</tr>
<tr>
<td>Prior use of anti-platelets, %</td>
<td>30.1</td>
<td>31</td>
<td>24.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Left atrial diameter, mm, mean (± SD)</td>
<td>37.2 (6.9)</td>
<td>35.5 (5)</td>
<td>37.4 (7)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

SD = Standard Deviation; IIQ = Interquartile interval; LDL = Low density lipoprotein; MRI = Magnetic resonance imaging; PCA = Posterior cerebral artery; PC-ASPECTS=; ESUS=; IV = Intravenous; mRS = Modified Rankin Scale; PROPHET PC = Predictive score of hemorrhagic transformation in posterior circulation stroke patients not submitted to reperfusion therapies

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<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Cardio-aortic embolism, %</td>
<td>23.3</td>
<td>44.6</td>
<td>21.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESUS, %</td>
<td>24.6</td>
<td>18.8</td>
<td>25.2</td>
<td>0.6</td>
</tr>
<tr>
<td>NIH Stroke Scale at discharge or hospital transfer, points, median [IIQ]</td>
<td>4 [2, 10]</td>
<td>23 [13, 27]</td>
<td>4 [2, 8]</td>
<td>0.006</td>
</tr>
<tr>
<td>mRS at discharge or hospital transfer, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27.9</td>
<td>9.1</td>
<td>29.6</td>
<td>0.04</td>
</tr>
<tr>
<td>1</td>
<td>31.2</td>
<td>31</td>
<td>36.4</td>
<td>0.63</td>
</tr>
<tr>
<td>2</td>
<td>19.1</td>
<td>18.8</td>
<td>22.7</td>
<td>0.58</td>
</tr>
<tr>
<td>3</td>
<td>10.7</td>
<td>10</td>
<td>18.8</td>
<td>0.27</td>
</tr>
<tr>
<td>4</td>
<td>8.1</td>
<td>8</td>
<td>9.5</td>
<td>0.68</td>
</tr>
<tr>
<td>5</td>
<td>2.2</td>
<td>0</td>
<td>2.4</td>
<td>0.99</td>
</tr>
<tr>
<td>In-hospital death, %</td>
<td>1.7</td>
<td>6.4</td>
<td>1.18</td>
<td>0.03</td>
</tr>
<tr>
<td>PROpHET PC Score, points, median [IIQ]</td>
<td>2 [2, 4]</td>
<td>6 [2, 8]</td>
<td>2 [2, 4]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PROpHET PC Score ≥ 3 points, %</td>
<td>22.7</td>
<td>52.8</td>
<td>18.9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SD = Standard Deviation; IIQ = Interquartile interval; LDL = Low density lipoprotein; MRI = Magnetic resonance imaging; PCA = Posterior cerebral artery; PC-ASPECTS =; ESUS =; IV = Intravenous; mRS = Modified Rankin Scale; PROpHET PC = Predictive score of hemorrhagic transformation in posterior circulation stroke patients not submitted to reperfusion therapies

*These results can represent an accumulative incidence of involved arteries.

All included patients underwent a follow-up neuroimaging. CT scan and MRI (81.6%, n = 777/952) were both used as follow-up neuroimaging. There was no difference in the frequency of evaluation with MRI in patients with or without HT (p = 0.34). The PC ASPECTS was assessed by CT scan or MRI in 202 patients from one center – the mean was 8.9 (± 1) points. This score was not associated with HT in our sample in both bi and multivariate analyses.

The PROpHET PC grading score was derived from the adjusted logistic regression model (Tables 2 and 3) and is presented in Table 4. The accuracy of the derivation model based on 1,000 bootstrap replicates was 90.3%. For the model shown in Table 2, the calibration was estimated by the Brier score (0.122) and the Hosmer-Lemeshow goodness-of-fit test (chi-square 8.76, df 8, p = 0.36). Cox-Snell and Nagelkerke were R² 0.07 and 0.15 respectively. This first model adopted continuous variables after a backward
stepwise. The second model (Table 3) was obtained after the same backward stepwise using dichotomized variables (NIH Stroke Scale at admission and Blood Glucose at admission). This dichotomization was based on the most accurate cutpoint for predicting hemorrhagic transformation from these variables by the Youden's test. This model had an accuracy of 89.2%, Hosmer-Lemeshow goodness-of-fit test (chi-square 11.47, df 8, p = 0.17) - Cox-Snell and Nagelkerke were R² 0.072 and 0.145 respectively. The overall accuracy of these models was assessed by a ROC-AUC. Compared to the model with continuous variables, the model with dichotomized variables had an AUC of 0.72 (SE 0.034, 95% CI 0.66–0.79) versus an AUC of 0.71 (SE 0.036, 95% CI 0.65–0.79), Fig. 1. There was no difference between these areas under the curve (p = 0.8).

### Table 2
Adjusted regression model with continuous variables for predicting hemorrhagic transformation

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-coefficient</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.600</td>
<td>1.822</td>
<td>1.06–3.11</td>
<td>0.02</td>
</tr>
<tr>
<td>NIH Scale at admission</td>
<td>0.077</td>
<td>1.08</td>
<td>1.05–1.11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood glucose (mg/dL) at admission</td>
<td>0.004</td>
<td>1.004</td>
<td>1.002–1.007</td>
<td>0.002</td>
</tr>
<tr>
<td>TOAST – Cardioembolism</td>
<td>1.28</td>
<td>3.605</td>
<td>2.17–5.97</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

OR = Odds ratio; CI = Confidence Interval.; TOAST = Trial of ORG 10172 in Acute Stroke Treatment

### Table 3
Adjusted regression model with dichotomized variables for predicting hemorrhagic transformation

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-coefficient</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.654</td>
<td>1.922</td>
<td>1.10–3.35</td>
<td>0.02</td>
</tr>
<tr>
<td>NIH Scale ≥ 5 at admission</td>
<td>0.870</td>
<td>2.386</td>
<td>1.43–3.97</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood glucose ≥ 160mg/dL at admission</td>
<td>0.673</td>
<td>1.959</td>
<td>1.15–3.33</td>
<td>0.01</td>
</tr>
<tr>
<td>TOAST – Cardioembolism</td>
<td>1.306</td>
<td>3.69</td>
<td>2.19–6.21</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

OR = Odd ratio; CI = Confidence Interval.; TOAST = Trial of ORG 10172 in Acute Stroke Treatment
Table 4
The PROpHET PC (0 to 5 points) score for predicting hemorrhagic transformation in posterior circulation ischemic stroke patients not submitted to reperfusion therapies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1</td>
</tr>
<tr>
<td>NIH Scale ≥ 5 at admission</td>
<td>1</td>
</tr>
<tr>
<td>Blood glucose ≥ 160mg/dL at admission</td>
<td>1</td>
</tr>
<tr>
<td>TOAST – Cardioembolism</td>
<td>2</td>
</tr>
</tbody>
</table>

TOAST = Trial of ORG 10172 in Acute Stroke Treatment

The PROpHET PC is represented in Table 4. Each group point represents an odds ratio 1.41 (95% CI 1.2–1.5, p < 0.001) for HT. The AUC of the PROpHET PC (0 to 5 points) was 0.713 (SE 0.03, 95% CI 0.65–0.78). Comparing the accuracy of the regression model (Table 3) and the grading score (Table 4), we did not find a difference (p = 0.9), Fig. 2. The absolute incidence of HT in patients increased per group point (Fig. 2).

The cutpoint was 3 points – with a sensibility of 53% and specificity of 81%. The median of PROpHET score was 6 [2, 8] in those with any HT and 2 [2, 4] in those without HT, p < 0.001. Subjects with PROpHET PC ≥ 3 points had an odds ratio of 4.8 (95% CI 2.9–7.9, p < 0.001) for HT.

A computerized tool was built based on a logistic regression model with continuous variables (Table 3). This tool allows estimating the probability of HT within seven days from the hospital admission, and it is free available at http://www.prophetpc-score.com (Fig. 3).

• Discussion

We present the PROpHET PC score, a practical multicenter derived scoring system for predicting Hemorrhagic Transformation (HT) in patients with Posterior Circulation (PC) stroke not submitted to Reperfusion Therapy (RT). Based on readily available clinical variables, the PROpHET PC score helps quantify the HT risk on this subset of patients accurately.

Literature on HT risk factors for PC stroke in patients not submitted to RT is scarce, for most studies focus on anterior circulation (AC) stroke patients. Lower incidences and higher mortality rates within this population could account for this lack of information.

HT frequency in PC stroke overall ranges from 5.1–43%. Our study reported a frequency rate of 8.7%. The wide range of reported values could represent a previous lack of statistical power given the diminished sample size from previous reports. Moreover, our study only included patients who had not undergone RT, accounting for higher frequency rates in prior studies.
Cardioembolism was the strongest risk for HT in our study. Accordingly, an Italian cohort also reported a powerful correlation among these conditions. Previous studies analyzing PC stroke patients have not found this association statistically significant\textsuperscript{10,17}. Again, the sample size may play a significant role in this apparent contradiction since the limited number of cohort studies on this subject included a maximum of forty-two PC stroke patients who developed HT\textsuperscript{17}. Our study included eighty-three PC stroke patients who presented HT, the largest sample size we encountered in literature. It is worth noting also to stress the stronger and well-established correlation between HT and cardioembolism in AC stroke patients\textsuperscript{6,11,19,20}.

Male gender, NIHSS score at admission and blood glucose levels at admission were also predictors of HT in this population. Results from other researchers are often conflicting regarding HT risk factors on PC stroke patients not submitted to RT\textsuperscript{7,10,17}. Large multicenter cohort studies are required to better understand their role on HT.

Our study found no relationship between the patient PC ASPECTs score and HT risk. In contrast, a Turkish cohort study pointed out a correlation between HT risk and stroke volume greater than or equal to 3.60 +/- 3.29 cm\textsuperscript{3}\textsuperscript{10}. Additionally, a Japanese cohort reported that using a cutoff value of > 2.7 cm, infarct diameter was strongly associated with HT\textsuperscript{17}. This divergence may be due to our single-center analysis concerning this variable, which could underestimate the importance of stroke infarction volume and HT in PC stroke patients.

Few scoring systems are currently available for predicting the risk of HT, most of them focusing on HT risk after thrombolytic therapy\textsuperscript{19,21,22,23}. Concerning AC stroke patients not submitted to RT, the PROpHET score establishes a scoring system using seven risk factors (male sex, ASPECTS score, presence of leukoaraiosis, hyperdense cerebral middle artery sign, glycemia at admission 180mg/dL, cardioembolism, and lacunar syndrome as a protective factor) for predicting HT. A score $\geq 3$ had 78.2% sensitivity, 75% specificity, and AUROC of 0.82 for all cases of HT. The PROpHET PC score is the first scoring system to address PC stroke patients not submitted to RT specifically. At this moment, no guidelines are instructing to avoid or choose therapies based on predictive scores of HT\textsuperscript{24}. However, the knowledge about risk factors for HT in non-treated patients might help in the decision-making process of therapies for secondary prevention such as initiation of anticoagulation. The PROpHET PC helps identify patients at high or low risk of HT, providing an individualized prediction of HT. In addition, our score may help researchers evaluating acute stage therapies in stratifying patients as a lower or higher risk group in the context of epidemiological and population-based studies or even clinical trials.

This research had several limitations, including those inherent in a retrospective study. CT imaging is frequently insensitive for detecting posterior fossa ischemic stroke and its complications\textsuperscript{25}. Our follow-up imaging method of choice (CT vs. MRI) was not standardized, which could account for a selection bias, even though there was no statistically significant difference between the chosen neuroimaging method on both groups. Also, HT diagnosis was made by a single non-blinded radiologist and was not classified
between symptomatic and asymptomatic HT. Although the PC PROpHET score was not externally validated, data collected from five different worldwide comprehensive stroke centers partially mitigates this concern.

• Conclusions

The PROpHET PC is an accurate and first-ever published predictive score designed explicitly for posterior circulation stroke patients not submitted to reperfusion therapies. This is a quick, easy-to-use, and free available score for identifying patients at higher risk of hemorrhagic transformation.

Declarations

Authors' statement

All the authors take full responsibility for all data included in this paper, the analyses and interpretation, and the conduct of the research as well. Full access to all the data can be requested at any time. All the authors allow the right to publish all data from this research.

General statement

All the authors have read and approved the submitted manuscript. The manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

Full access to all the data can be requested at any time. All the authors allow the right to publish any data from this research.

Ethical Approval and Consent to participate

This project has been approved by our local IRB (Hospital Geral de Fortaleza, Brazil, CAAE 24500719.7.0000.5040)

Human and Animal Ethics

All the national ethical requirements were observed to support the research. The IRB waived the need for informed consent for the validation group as the data collection was retrospective. All data used in the analyses are presented in the tables and figures. Unidentified data can be publicly shared.

The participants or familiars were informed about the objectives of this work and a confidentiality statement. The participants/familiars signed informed consent. Retrospective data was collected after the IRB approval – for these participants, and informed consent was waived.

Consent for publication

The authors state full consent for publishing these data.
Conflicting interests

The authors have no relevant financial or non-financial interests to disclose.

The authors have no competing interests to declare that are relevant to the content of this article.

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The authors have no financial or proprietary interests in any material discussed in this article.

Availability of supporting data

All the authors take full responsibility for all data included in this paper, the analyses and interpretation, and the conduct of the research as well. Full access to all of the data can be requested at any time. All the authors allow the right to publish any and all data from this research.

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Contributorship

Andrade, JBC - Planned the study, interpreted the data, and wrote the final version. Mohr, JP – Supervised the study and reviewed the report. Martins, FF – Collected data and created the digital application. Malheiros, JEF - Collected data, interpreted the data, and wrote the final version. Ikeda, RK - Collected data, interpreted the data, and wrote the final version. Barros, LCM- Collected data, interpreted the data, and wrote the final version. Lima, FO - Supervised the study and reviewed the report. Pontes-Neto, OM - Collected data and interpreted the data. Merida, KLB - Collected data and interpreted the data. Franciscato, L - Collected data and interpreted the data. Marques, MS - Collected data and interpreted the data. Miranda, RCAN- Collected data and reviewed the report. Silva, GS - Supervised the study, interpreted the data, and reviewed the report.

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**References**


Figures
A. The Area Under the Curve (AUC 0.72, 95% CI 0.66-0.79) of a logistic regression model with continuous variables.
B. The AUC (0.72, 95% CI 0.65-0.79) of a logistic regression model with dichotomized variables (NIH Stroke Scale and Blood Glucose at admission).
C. The AUC (0.71, 95% 0.65-0.78) of PROPhET PC grading score. There is no difference between the areas (p=0.9)

Figure 1

Areas Under the Curve of logistic regression models and PROPhET PC grading score