Analysis of diagnostic informative value of the Full Outline of UnResponsiveness Scale in patients with spontaneous supratentorial intracerebral hemorrhage

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The main purpose of the study was to verify the diagnostic informative value of the Full Outline of UnResponsiveness Scale in patients with SSICH based on the comparison with neuroimaging criteria of midline shift severity.

Material and methods. Prospective cohort study of 138 patients in acute period of SSICH was conducted, which included clinical assessment (using the Full Outline of UnResponsiveness (FOUR) Scale and the Glasgow Coma Scale (GCS) scores) and neuroimaging estimation of cerebral injury severity. A comparative analysis of Spearman’s rank correlation coefficients (R) and different areas under the receiver operating characteristic curves (derived from the same cases) was conducted with the help of Z statistic.

Results. The Full Outline of UnResponsiveness Scale was verified as a highly informative tool for the presence and severity of midline shift clinical detection (AUC > 0.80, P < 0.0001) in patients with SSICH, whereas the diagnostic informative value of the FOUR scale within the assessment of severe midline shift clinical signs was higher than that for mild midline shift detection (AUC = 0.97 ± 0.02 versus AUC = 0.84 ± 0.05 for septum pellucidum displacement, P = 0.0158; AUC = 0.99 ± 0.01 versus AUC = 0.92 ± 0.03 for pineal gland displacement, P = 0.0269). The Full Outline of UnResponsiveness Scale had a higher diagnostic informative value than the GCS as for the presence of midline shift clinical signs detection (AUC = 0.81 ± 0.03 versus AUC = 0.67 ± 0.04, P = 0.0002; accuracy 77.5 % versus 63.0 %, P = 0.0085), as well as for the clinical assessment of septum pellucidum displacement severity (AUC = 0.80 ± 0.04 versus AUC = 0.73 ± 0.05, P = 0.0286) and pineal gland displacement (AUC = 0.80 ± 0.05 versus AUC = 0.74 ± 0.05, P = 0.0306) in patients with midline shift <4 mm due to SSICH.

Conclusions. The Full Outline of UnResponsiveness Scale is characterized by the higher diagnostic informative value in clinical detecting midline shift severity in patients with SSICH.
**Materials and methods**

In order to achieve this goal, a comparative study was conducted on 138 patients (79 men and 59 women, mean age 63.6 ± 1.0 years), who underwent a therapy in the Brain Circulation Disorders Department of the Municipal Institution “Zaporizhzhia City Clinical Hospital # 6”.

Inclusion criteria:
1) men and women with SSICH confirmed by the results of clinical and neuroimaging study;
2) admission to the hospital within the first 24 hours of the disease onset;
3) informed consent signed by the patient for study participation.

Exclusion criteria:
1) ≥2 lesions;
2) combined stroke;
3) acute brain circulation disorders in the past medical history;
4) decompensated somatic pathology;
5) oncopathology.

The diagnosis of SSICH was confirmed based on the results of neuroimaging study, which was conducted on admission to hospital using a computed tomography scanner “Siemens Somatom Spirit” (Germany). Lesion size and midline shift severity were considered.

Clinical and neurological study included the assessment of neurological deficit severity on the National Institute of Health Stroke Scale (NIHSS). The Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness Scale (FOUR) were used in order to assess the severity of dislocation syndrome clinical signs.

Statistical analysis of the obtained data was carried out with the help of Statistica for Windows 13 (StatSoft Inc., № JPZ8041382130ARCN10-J) and MedCalc (version 16.4). The distribution normality of the studied traits was assessed by Shapiro-Wilk criterion. Since the majority of indicators distribution did not comply with the laws of normality, descriptive statistics were presented in the form of the median (Me) and interquartile range (Q₁–Q₃). Spearman’s rank correlation coefficient (R) was used for the interrelation between quantitative characteristics assessment. The diagnostic criteria were determined by the ROC analysis. The optimal cut-off values were estimated with the help of Youden index method. A comparative analysis of correlation coefficients and different areas under the receiver operating curves (derived from the same cases) was conducted.
with the help of Z statistic. Chi-squared test was used for the intergroup differences of diagnostic criteria accuracy assessment. P < 0.05 was considered to indicate a statistically significant difference.

**Results**

Baseline NIHSS score in the cohort was 12 (7; 18), FOUR score and GCS score – 16 (14; 16) and 14 (11; 15), respectively.

Midline shift was verified in 78 (56.5 %) cases using neuroimaging studies. The results of the septum pellucidum and pineal gland displacement severity assessment in patients are presented in **Table 1**.

Mild septum pellucidum displacement (1–5 mm) was detected in 50 (36.3 %) patients, moderate (6–10 mm) and severe (>10 mm) – in 18 (13.0) and 10 (7.2 %) patients, respectively. Mild pineal gland displacement (1–5 mm) was detected in 44 (42.4 %) patients, moderate (6–10 mm) and severe (>10 mm) – in 11 (8.0 %) and 7 (5.1 %) cases, respectively.

The analysis results of the informative value of the FOUR Scale within the clinical assessment of septum pellucidum displacement severity in comparison with the GCS are presented in **Table 2**.

As the data shows, the AUC value when using the FOUR Scale as the tool for the verification of clinical signs of severe septum pellucidum displacement (>10 mm) constituted 0.97 ± 0.02 (P < 0.0001), which exceeded the values of FOUR Scale for the clinical detection of mild septum pellucidum displacement (1–5 mm) (AUC = 0.84 ± 0.05, P = 0.0158). AUC values were also high when FOUR Scale was used for the verification of the clinical signs of severe pineal gland displacement as well as those of mild pineal gland displacement. They constituted 0.99 ± 0.01 (P < 0.0001) and 0.92 ± 0.03 (P < 0.0001) respectively (**Table 3**).

It was determined that the FOUR Scale was statistically more significant than the GCS as for the diagnostic informative value when used as a tool for the clinical detection of midline shift (AUC = 0.81 ± 0.03 versus AUC = 0.67 ± 0.04, P = 0.0002), as well as for the severity assessment of the septum pellucidum displacement <4 mm (AUC = 0.80 ± 0.04 versus AUC = 0.73 ± 0.05, P = 0.0286) and pineal gland displacement <4 mm (AUC = 0.80 ± 0.05 versus AUC = 0.74 ± 0.05, P = 0.0306). However, the aforementioned scales were compared on the basis of the discriminate potential of the midline shift >5 mm and >10 mm clinical signs detection.

**Table 1.** The structure of the dislocation syndrome severity in patients

<table>
<thead>
<tr>
<th>Midline shift</th>
<th>Septum pellucidum displacement, n (%)</th>
<th>Pineal gland displacement, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>absent</td>
<td>60 (43.5)</td>
<td>60 (43.5)</td>
</tr>
<tr>
<td>1 mm</td>
<td>7 (5.1)</td>
<td>7 (5.1)</td>
</tr>
<tr>
<td>2 mm</td>
<td>13 (9.4)</td>
<td>18 (13.0)</td>
</tr>
<tr>
<td>3 mm</td>
<td>15 (10.9)</td>
<td>19 (13.8)</td>
</tr>
<tr>
<td>4 mm</td>
<td>8 (5.8)</td>
<td>12 (8.7)</td>
</tr>
<tr>
<td>5 mm</td>
<td>7 (5.1)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>6–10 mm</td>
<td>18 (13.0)</td>
<td>11 (8.0)</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>10 (7.2)</td>
<td>7 (5.1)</td>
</tr>
</tbody>
</table>

**Table 2.** Comparative analysis of the informative value of the Full Outline of UnResponsiveness Scale and Glasgow Coma Scale within the clinical assessment of septum pellucidum displacement severity in patients with SSICH

<table>
<thead>
<tr>
<th>Septum pellucidum displacement</th>
<th>Full Outline of UnResponsiveness Scale</th>
<th>Glasgow Coma Scale</th>
<th>Z statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC ± SE</td>
<td>P</td>
<td>AUC ± SE</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>&gt;0 mm</td>
<td>0.81 ± 0.03</td>
<td>&lt;0.0001</td>
<td>0.67 ± 0.04</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;1 mm</td>
<td>0.80 ± 0.03</td>
<td>&lt;0.0001</td>
<td>0.66 ± 0.04</td>
<td>0.0003</td>
</tr>
<tr>
<td>&gt;2 mm</td>
<td>0.76 ± 0.04</td>
<td>&lt;0.0001</td>
<td>0.67 ± 0.05</td>
<td>0.0003</td>
</tr>
<tr>
<td>&gt;3 mm</td>
<td>0.80 ± 0.04</td>
<td>&lt;0.0001</td>
<td>0.73 ± 0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>0.85 ± 0.04</td>
<td>&lt;0.0001</td>
<td>0.80 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>0.84 ± 0.05</td>
<td>&lt;0.0001</td>
<td>0.82 ± 0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>0.97 ± 0.02</td>
<td>&lt;0.0001</td>
<td>0.96 ± 0.02</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Table 3.** Comparative analysis of the informative value of Full Outline of UnResponsiveness Scale and Glasgow Coma Scale within the assessment of pineal gland displacement severity in patients with SSICH

<table>
<thead>
<tr>
<th>Pineal gland displacement</th>
<th>Full Outline of UnResponsiveness Scale</th>
<th>Glasgow Coma Scale</th>
<th>z statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC ± SE</td>
<td>P</td>
<td>AUC ± SE</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>&gt;0 mm</td>
<td>0.81 ± 0.03</td>
<td>&lt;0.0001</td>
<td>0.67 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;1 mm</td>
<td>0.80 ± 0.04</td>
<td>&lt;0.0001</td>
<td>0.71 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;2 mm</td>
<td>0.78 ± 0.04</td>
<td>&lt;0.0001</td>
<td>0.74 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;3 mm</td>
<td>0.80 ± 0.05</td>
<td>&lt;0.0001</td>
<td>0.74 ± 0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>0.90 ± 0.04</td>
<td>&lt;0.0001</td>
<td>0.88 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>0.92 ± 0.03</td>
<td>&lt;0.0001</td>
<td>0.91 ± 0.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>0.99 ± 0.01</td>
<td>&lt;0.0001</td>
<td>0.97 ± 0.01</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Optimal cut-off values of the FOUR score and GCS score were determined based on a ROC analysis. They serve as clinical criteria of the midline shift presence, as well as criteria for the clinical assessment of septum pellucidum and pineal gland displacement severity (Tables 4 and 5).

Thus, FOUR score >14 is a clinical diagnostic criterion for mild septum pellucidum displacement (<6 mm) or the absence of displacement (Se = 80.9 %; Sp = 78.6 %); FOUR score >13 is associated with mild pineal gland displacement (<6 mm) or the absence of displacement (Se = 91.7 %; Sp = 72.2 %); FOUR score <12 is a clinical diagnostic criterion for severe septum pellucidum displacement (>10 mm) (Se = 90.0 %; Sp = 90.2 %); FOUR score <10 is associated with severe pineal gland displacement (>10 mm) (Se = 100.0 %; Sp = 96.2 %).

The analysis results of the diagnostic accuracy of the FOUR Scale score when used as the criteria for the clinical assessment of midline shift severity are presented in Tables 6 and 7.

As the presented data show, the FOUR Scale has a high accuracy when used as the assessment tool for the severity of septum pellucidum (86.7–95.7 %) and pineal gland displacement (94.2–96.4 %) clinical signs. The FOUR Scale was as accurate as the GCS when used for the clinical signs of moderate and severe midline shift assessment. However, the FOUR Scale was more accurate than the Glasgow Coma Scale as for the clinical signs of midline shift detection.
(77.5 % versus 63.0 %, Chi-squared = 6.92, P = 0.0085), as well as for the accurate clinical assessment of the severity of septum pellicudum displacement up to 3 mm (70.3 % versus 58.0 %, Chi-squared = 4.54, P = 0.0332) and pineal gland displacement up to 2 mm (76.8 % versus 64.5 %, Chi-squared = 5.03, P = 0.0249).

Based on a correlation analysis along with the calculation of Spearman’s rank correlation coefficients (R) it was determined that the FOUR score was statistically more associated with septum pellicudum displacement (R 95 % CI = -0.65 (-0.54; -0.74), P < 0.0001 versus -0.42 (-0.27; -0.54), P < 0.0001 for GCS score, Z statistic = -2.69, P = 0.0071) and pineal gland displacement (R 95 % CI = -0.65 (-0.54; -0.71), P < 0.0001 versus -0.45 (-0.31; -0.57), P < 0.0001 for the GCS score, Z statistic = -2.39, P = 0.017).

**Discussion**

It was determined that AUC values for the FOUR Scale corresponded to “very high” and “excellent” gradations in accordance with the International Expert Scale of binary classification quality assessment M. H. Zweig, G. Campbell (1993) [17]. The obtained results showed a high diagnostic informative value of the FOUR Scale for the clinical signs of midline shift detection in patients with SSICH in the acute period, furthermore the AUC value was the highest when the FOUR Scale was used as a tool for the verification of clinical signs of severe septum pellicudum displacement (0.97 ± 0.02 versus 0.84 ± 0.05, P = 0.0158) and severe pineal gland displacement (0.99 ± 0.01 versus 0.92 ± 0.03, P = 0.0269). Based on the ROC analysis optimal cut-off values of the FOUR Scale score were determined for the clinical assessment of midline shift severity.

The FOUR Scale has a statistically higher diagnostic informative value than the GCS when used as a tool for the clinical detection of midline shift (AUC = 0.81 ± 0.03 versus AUC = 0.67 ± 0.04, P = 0.0002; accuracy 77.5 % versus 63.0 %, Chi-squared = 6.92, P = 0.0085), as well as for the severity assessment of the septum pellicudum displacement <4 mm (AUC = 0.80 ± 0.04 versus AUC = 0.73 ± 0.05, P = 0.0286) and pineal gland displacement <4 mm (AUC = 0.80 ± 0.05 versus AUC = 0.74 ± 0.05, P = 0.0306).

The obtained data correspond with the results of other studies, which showed that the FOUR Scale was superior to the GCS in detecting risk of lethal outcome in critically ill patients [14] with acute ischemic stroke [9] and traumatic brain injury [8, 11].

The FOUR Scale showed a higher diagnostic informative value than the GCS within the results of the comparative analysis of the correlation coefficient between the values of these scales and the midline shift severity (R 95 % CI = -0.65 (-0.54; -0.74) versus -0.42 (-0.27; -0.54) for the pairs of indexes of the “FOUR Scale score – septum pellicudum displacement” and the “GCS score – septum pellicudum displacement”, respectively, P = 0.0071) and pineal gland displacement (R 95 % CI = -0.65 (-0.54; -0.71) versus -0.45 (-0.31; -0.57) for the pairs of indexes of the “FOUR Scale score – pineal gland displacement” and the “GCS score – pineal gland displacement”, respectively, P = 0.017).

In our opinion, a higher diagnostic informative value of the FOUR Scale in comparison with the GCS was due, on the one hand, to the fact that the verbal reaction assessment in the structure of the FOUR Scale was absent, and the latter was influenced by the lateralization of the lesion in patients with supratentorial intracerebral hemorrhage. On the other hand, the spectrum of the assessed indexes had some additional criteria for the clinical assessment of the supratentorial structures functional state (respiratory pattern, brainstem reflexes). The study of Y. Hu et al. (2017) showed, that motor response and brainstem responses were verified as independent predictors of conscious awareness recovery in patients with acute ischemic stroke [7]. By the results of M. A. Gorji et al. (2015), the FOUR score was more accurate and practical in intubated patients regarding a lack of verbal response factor in early prediction of mortality in the GCS [6].

All of the above together with numerous studies convincingly proving a high inter-rater agreement of the FOUR Scale using [4,5,10,13,16] makes this scale more useful and preferable than the GCS for the assessment of midline shift clinical signs severity in patients in the acute period of SSICH.

**Conclusions**

1. The FOUR Scale is a highly informative tool for the clinical detection of midline shift presence and severity (AUC > 0.80, P < 0.0001) in patients with SSICH, whereas the diagnostic informative value of this scale within the assessment of severe midline shift clinical signs is higher than for the detection of mild midline shift (AUC = 0.97 ± 0.02 versus AUC = 0.84 ± 0.05 for septum pellicudum displacement, P = 0.0158; AUC = 0.99 ± 0.01 versus AUC = 0.92 ± 0.03 for pineal gland displacement, P = 0.0269).

2. The FOUR Scale has a higher diagnostic informative value than the GCS as for the detection of midline shift clinical signs presence (AUC = 0.81 ± 0.03 versus AUC = 0.67 ± 0.04, P = 0.0002; accuracy 77.5 % versus 63.0 %, Chi-squared test P = 0.0085), as well as for the clinical assessment of septum pellicudum displacement (AUC = 0.80 ± 0.04 versus AUC = 0.73 ± 0.05, P = 0.0286) and pineal gland displacement severity (AUC = 0.80 ± 0.05 versus AUC = 0.74 ± 0.05, P = 0.0306) in patients with midline shift <4 mm due to SSICH.

3. The FOUR score is statistically more associated with septum pellicudum displacement (R 95 % CI = -0.65 (-0.54; -0.74), P < 0.0001 versus -0.42 (-0.27; -0.54), P < 0.0001 for the GCS score, P = 0.0071) and pineal gland displacement (R 95 % CI = -0.65 (-0.54; -0.71), P < 0.0001 versus -0.45 (-0.31; -0.57), P < 0.0001 for the GCS score, P = 0.017).

The perspective for the further scientific research is the assessment of the FOUR score prognostic value in patients with SSICH.

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**Conflicts of interest:** author has no conflict of interest to declare.
References


