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Article

2022

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How to cite

RAABE, Andreas et al. Herniation World Federation of Neurosurgical Societies Scale Improves Prediction of Outcome in Patients With Poor-Grade Aneurysmal Subarachnoid Hemorrhage. In: Stroke, 2022, vol. 53, n° 7, p. 2346–2351. doi: 10.1161/strokeaha.121.036699

This publication URL: <https://archive-ouverte.unige.ch/unige:184051>

Publication DOI: [10.1161/strokeaha.121.036699](https://doi.org/10.1161/strokeaha.121.036699)

CLINICAL AND POPULATION SCIENCES

Herniation World Federation of Neurosurgical Societies Scale Improves Prediction of Outcome in Patients With Poor-Grade Aneurysmal Subarachnoid Hemorrhage

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BACKGROUND: Favorable outcomes are seen in up to 50% of patients with World Federation of Neurosurgical Societies (WFNS) grade V aneurysmal subarachnoid hemorrhage. Therefore, the usefulness of the current WFNS grading system for identifying the worst scenarios for clinical studies and for making treatment decisions is limited. We previously modified the WFNS scale by requiring positive signs of brain stem dysfunction to assign grade V. This study aimed to validate the new herniation WFNS grading system in an independent prospective cohort.

METHODS: We conducted an international prospective multicentre study in poor-grade aneurysmal subarachnoid hemorrhage patients comparing the WFNS classification with a modified version—the herniation WFNS scale (hWFNS). Here, only patients who showed positive signs of brain stem dysfunction (posturing, anisocoric, or bilateral dilated pupils) were assigned hWFNS grade V. Outcome was assessed by modified Rankin Scale score 6 months after hemorrhage. The primary end point was the difference in specificity of the WFNS and hWFNS grading with respect to poor outcomes (modified Rankin Scale score 4–6).

RESULTS: Of the 250 patients included, 237 reached the primary end point. Comparing the WFNS and hWFNS scale after neurological resuscitation, the specificity to predict poor outcome increased from 0.19 (WFNS) to 0.93 (hWFNS) (McNemar, $P<0.001$) whereas the sensitivity decreased from 0.88 to 0.37 ($P<0.001$), and the positive predictive value from 61.9 to 88.3 (weighted generalized score statistic, $P<0.001$). For mortality, the specificity increased from 0.19 to 0.93 (McNemar, $P<0.001$), and the positive predictive value from 52.5 to 86.7 (weighted generalized score statistic, $P<0.001$).

CONCLUSIONS: The identification of objective positive signs of brain stem dysfunction significantly improves the specificity and positive predictive value with respect to poor outcome in grade V patients. Therefore, a simple modification—presence of brain stem signs is required for grade V—should be added to the WFNS classification.

REGISTRATION: URL: <https://clinicaltrials.gov>; Unique identifier: NCT02304328.

GRAPHIC ABSTRACT: A [graphic abstract](#) is available for this article.

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Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.121.036699>.

For Sources of Funding and Disclosures, see page 2351.

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Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

aSAH	aneurysmal subarachnoid hemorrhage
GCS	Glasgow Coma Scale
hWFNS	herniation World Federation of Neurosurgical Societies
mRS	modified Rankin Scale
PPV	positive predictive value
WFNS	World Federation of Neurosurgical Societies

In 1988, the current World Federation of Neurosurgical Societies (WFNS) classification was introduced to grade the severity of aneurysmal subarachnoid hemorrhages and to allow prognostic predictions.¹ It is based on the Glasgow Coma Scale (GCS) score and the presence or absence of major neurological deficits.¹ Despite the wide acceptance of the WFNS scale, it has some inherent limitations.² With progressive brain stem dysfunction, that is, higher WFNS grades (corresponding to lower GCS grades), the classification switches from positive signs, such as withdrawal to pain (GCS 6), flexion (GCS 5), and extension posturing (GCS 4) to a negative sign—no motor response—to assign a GCS score of 3.

In comatose, intubated, and ventilated poor-grade patients, sedation, muscle relaxation, or insufficient pain stimuli may mimic a missing motor response and lead to assignment of a false GCS score of 3, which is a considerable confounder in the GCS and WFNS scales. This is demonstrated by a rate of favorable outcomes of 24% to 50% of aggressively treated grade V patients.^{3–6} Owing to the considerable proportion of WFNS grade V patients with favorable outcomes, this grade does not allow futility to be predicted and cannot be used to limit treatment.⁷

Various studies have reported on the impact on outcome of aneurysmal subarachnoid hemorrhage patients in whom signs of brain stem dysfunction were identified.^{8–12} Using a simple modification of the WFNS scale, we have previously shown an improvement in the prediction of mortality and poor outcomes in a retrospective cohort study.¹³ This modification is based on the pathophysiology of brain stem dysfunction, which is the underlying event in patients with GCS grades 3 to 5. As herniation progresses from flexion (GCS 5) to extension posturing (GCS 4), any further deterioration must inevitably be pathophysiologically associated with positive clinical signs of herniation progression. Thus, instead of using no motor response, we only graded patients as GCS 3 when they also showed additional pupillary signs of herniation, such as mydriasis.

To further evaluate and validate our previous finding of a significantly better poor-grade scoring, we performed the prospective multicentre observational study

Impact of Herniation on WFNS Grading and Outcome in Spontaneous Subarachnoid Hemorrhage—a SWISS SOS Observational Trial. Specifically, we sought to compare the specificity and positive predictive value (PPV) of this new herniation WFNS (hWFNS) scale for predicting poor outcome and mortality with the classic WFNS scale.

METHODS

The data supporting the findings of this study are available from the corresponding author upon request.

Study Design

This international prospective observational study included patients being screened in 7 Swiss and 1 German neurosurgical department between December 2015 and November 2019. Inclusion criteria were (1) spontaneous SAH, (2) age ≥ 18 years, (3) $GCS \leq 12$, and (4) consent of the patient or the patient's next of kin. Exclusion criteria were (1) SAH due to any other cause or structural abnormality (arterio-venous malformation, dural arterio-venous fistula, cavernous malformation, dissection, tumor or trauma) of the brain and (2) foreseeable difficulties during follow-up.

We compared the grading of WFNS grade IV and V patients to a modified grading system—the hWFNS scale. According to the original WFNS scale, a GCS score of 3 to 6 corresponds to WFNS V and a GCS score of 7 to 12 corresponds to WFNS IV.¹ For the new hWFNS grade V, we included only patients with positive signs of brain stem dysfunction.¹³ Patients with a GCS score of 6 to 12 or with no motor response but otherwise intact brain stem function were graded hWFNS Grade IV (Table 1). Thus, a patient graded as GCS 3 (no motor response) but with 3-mm symmetrical pupils and prompt reaction to light was assigned hWFNS Grade IV instead of WFNS grade V.¹³ Patients were examined after neurological resuscitation. All initial assessments (WFNS, hWFNS) were performed by clinicians throughout their daily routine to reflect the current standard of grading. All follow-up investigations were performed by an independent trained investigator or study nurses blinded to the clinical course. Modified Rankin Scale (mRS) was assessed during a structured telephone interview 6 months ± 14 days post ictus.¹⁴ Data were entered into a REDCap database, which was hosted by the Clinical Trial Unit of the University of Bern. The study was approved by each local ethics committee and was registered (NCT02304328). The reporting of this study is according to the TRIPOD guideline.

Clinical Management

SAH was confirmed by either computed tomography, magnetic resonance imaging, or lumbar puncture. Patients were treated according to current guidelines, which included early angiography and transfer to an intensive care unit.^{15,16} First-line treatment included neurological resuscitation (insertion of external cerebrospinal fluid drainage in case of hydrocephalus, treatment of seizure, and general intensive care measures). Aggressive treatment of poor-grade patients was at the discretion of the treating surgeon and was based on parameters like clinical presentation, age, pretreatment morbidities, and the patient's expressed wishes.

Table 1. Grading of Poor-Grade Patients After Subarachnoid Hemorrhage

	WFNS	Herniation-modified WFNS
IV	GCS score 7–12	GCS score 6–12 including false GCS score 3 gradings where patients show no motor response but have otherwise normal pupillary response and no other sign of brain stem dysfunction
V	GCS score 3–6	GCS score 4–5 or signs of brain stem dysfunction other than posturing, confirming deep coma and a true GCS 3 score

GCS indicates Glasgow Coma Scale; and WFNS, World Federation of Neurosurgical Societies.

Outcome Measures

The primary end point was the difference in specificity of the WFNS and hWFNS grading with respect to poor outcome at 6 months after initial hemorrhage. Poor outcome was defined as mRS score 4 to 6, where 0 indicates no symptoms and 6 signifies death. The secondary end point was the effect of the new scale on prediction of mortality.

Statistical Analysis

The statistical analysis was performed using R, version 3.6.1, through the R studio interface. The descriptive statistics for baseline characteristics, procedural information (therapy and radiology), and follow-up details are shown using frequencies and percentages for categorical variables and mean (\pm SD) or median (interquartile range) for continuous variables. No group comparison was performed for this different information.

To analyze the primary outcome of this study, we based the hypotheses on our earlier retrospective study in which we calculated a specificity and sensitivity for poor outcome for the existing WFNS scale of 0.63 and 0.70, respectively.¹³ For the hWFNS scale, the values were 0.85 and 0.58, respectively. This gives ratios of truly negative and truly positive rates of 1.35 and 0.82. Probabilities for a positive and negative score in the same patient with the 2 scales were estimated to be 0.53 and 0.43, respectively. The prevalence of a poor outcome was 0.61 in this study. With a 2-sided alpha of 0.025 (0.05 divided by 2 for multiple testing, because specificity and sensitivity are both tested), we calculated a minimum sample size of 233. To increase the probability of enrolling enough patients with a poor outcome, we increased the sample size to 250 (probability (ϕ): 0.90; assuming a binomial distribution).

This study tested the null hypothesis that the ratio of the true negative rates (specificity) of the hWFNS and WFNS scales is 1.35; that is, the new scale will identify 35% more patients as truly negative (favorable outcome) than the old scale. In addition, and because of the negative correlation between specificity and sensitivity, we also tested to make certain that the ratio of the true positive rate (sensitivity) is not below 0.82; that is, the new scale will not identify > 18% less patients as truly positive (poor outcome).

To analyze the results of the primary outcome, sensitivity, specificity, and PPVs for the postneurological resuscitation status were obtained to compare the 2 different grading systems—WFNS and hWFNS. The results of the 2 grading systems were compared using McNemar test (specificity and/or sensitivity), while the PPVs were compared using (weighted) generalized score statistics. The same approach was applied to analyze the mortality prediction of the 2 different grading systems, with sensitivity, specificity, and PPV.

RESULTS

Between December 2015 and November 2019, we included 250 patients (mean age 61.2 years, 64% female) in the study. Patients were enrolled at the departments of neurosurgery in 8 hospitals in Switzerland and Germany: Aarau, Basel, Bern, Freiburg im Breisgau, Geneva, Lausanne, St. Gallen, and Zürich. Recruitment rate per department is displayed in the [Supplemental Material](#). Thirteen patients had to be excluded (9 withdrew consent, 3 were lost to follow-up, and 1 had angio-negative SAH), leaving 237 patients to reach the primary end point. One hundred ninety patients (86%) were intubated and ventilated at the time of initial clinical assessment (see Flow Diagram of Patients in the [Supplemental Material](#)). After neurological resuscitation, 40 patients (16%) were classified as WFNS grade IV and 210 (84%) WFNS grade V compared with 190 (76%) hWFNS grade IV and 60 (24%) hWFNS grade V. The hWFNS grading reduced the grade V group to 28% of its original (WFNS) size ($P<0.001$), inverting the proportions of grade IV and V patients in the respective groups.

Primary and Secondary End Points

Two hundred thirty-seven patients reached the primary end point, that is, mRS score after 6 months. The mRS score after 6 months with respect to WFNS and hWFNS grading is displayed in Table 2 and the Figure. Comparing the postresuscitation WFNS with hWFNS, the specificity to predict poor outcome increased from 0.19 to 0.93 ($P<0.001$), whereas the sensitivity decreased from 0.88 to 0.37 ($P<0.001$). The PPV for poor outcome increased from 61.9 to 88.3 ($P<0.001$) (Table 2). Additional evaluations can be found in the [Supplemental Material](#) (Different Dichotomized Outcome, Reclassification Tables, Likelihood Ratio Graphs).

Mortality after 6 months with respect to WFNS and hWFNS grading is presented in Table 2 and the Figure. Comparing postresuscitation WFNS and hWFNS grading, the specificity for prediction of mortality increased from 0.19 to 0.93 ($P<0.001$), whereas the sensitivity decreased from 0.89 to 0.44 ($P<0.001$). The PPV for mortality increased from 52.5 to 86.7 ($P<0.001$).

Withdrawal of Care

In the WFNS V group, 106 patients (87.8%) died and in the hWFNS V group 52 patients (90.4%) died. The percentage of patients from whom the care was withdrawn was equal in both groups, 87.8% for the WFNS and 90.4% for the hWFNS group.

DISCUSSION

The results of this prospective multicentre observational trial confirm that the incorporation of simple signs of

Table 2. Outcome 6 Months After Initial Hemorrhage

	mRS					Mortality				
	0-3	4-6	PPV	Sensitivity (95% CI)	Specificity (95% CI)	Alive	Dead	PPV	Sensitivity (95% CI)	Specificity (95% CI)
WFNS										
Grade IV	18	17 (49%)		0.88 (0.82-0.93)	0.19 (0.12-0.28)	22	13 (37%)		0.89 (0.82-0.94)	0.19 (0.12-0.27)
Grade V	77	125 (62%)	61.9			96	106 (52%)	52.5		
hWFNS										
Grade IV	88	89 (50%)		0.37 (0.29-0.46)	0.93 (0.85-0.97)	110	67 (38%)		0.44 (0.35-0.53)	0.93 (0.87-0.97)
Grade V	7	53 (88%)	88.3			8	52 (87%)	86.7		

mRS indicates modified Rankin Scale; PPV, positive predictive value; and WFNS, World Federation of Neurosurgical Societies.

brain stem dysfunction into the current WFNS scale significantly improves the prediction of poor outcomes at 6 months after aneurysmal subarachnoid hemorrhage. This holds true for outcome dichotomized into favorable (mRS score 0-3) and poor (mRS score 4-6) as well as mortality. Applying the hWFNS scale significantly decreases the overall number of patients being assigned to grade V to only 28% of the size of the grade V groups when using the original WFNS classification. Thus, by making the presence of positive brain stem signs mandatory, it is likely that it would capture the truly severely affected patients and reduce the probability of patients being falsely assigned to grade V.

Given that up to 50% of WFNS grade V patients show a favorable outcome, various authors have proposed variations of the WFNS grading to improve outcome prediction.^{8-12,17} According to the initial report of the World Federation of Neurological Surgeons Committee, the

most important predictor of death and disability was the level of consciousness.¹ Therefore, the more precisely the level of consciousness can be described, the more precise should be the outcome prediction based on the WFNS scale. Since the WFNS scale is based on the GCS score, shortcomings of the GCS score translate into WFNS grading. The major shortcomings of the GCS score are (1) the difficulty in assessing verbal response in intubated patients, (2) a missing sign—no motor response—to allocate the worst grade, and (3) the lack of attention paid to abnormal brain stem reflexes and signs of herniation.^{13,18,19} Consequently, positive signs of progressive brain stem dysfunction including flexor and extensor posturing (motor score) and pupil status are the key features of the hWFNS scale. In fact, Teasdale and Jennett²⁰ stated that they had never recommended using the GCS alone, either as a means of monitoring coma, to assess the severity of brain damage, or to

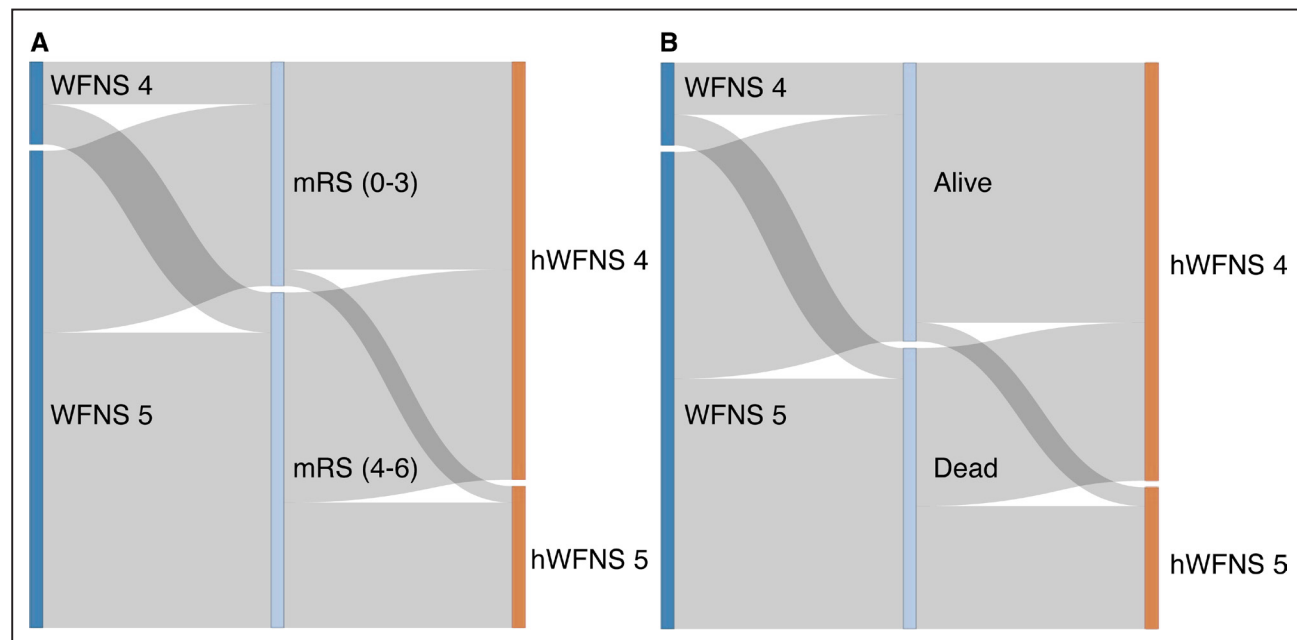


Figure. Sankey diagrams displaying outcome dichotomized in modified Rankin Scale (mRS) score 0 to 3 vs mRS score 4 to 6 and for mortality.

Sankey diagrams of the current World Federation of Neurosurgical Societies (WFNS) scale and the herniation WFNS scale with respect to poor outcome (mRS score 0-3 vs 4-6) and mortality. Note the reduction of patients being assigned to hWFNS grade 5 and the few patients being assigned hWFNS grade 5 and present a good outcome and are still alive at follow-up, respectively.

predict outcome. In an early investigation, these authors had already emphasized that pupil reactions correlate with responsiveness and herniation status.²¹ Thus, clinical assessment in these patients is challenging even for experienced examiners. By limiting grade V to positive signs, we have shown that the hWFNS scale is more robust than the original WFNS grade V.

To achieve wide acceptance, a prognostic scale should be (1) simple and easy to use while avoiding too many variables and complex arithmetic,¹² (2) it should define appropriate breakpoints if the prognostic scale is based on compression of another system,²² and (3) the prognostic scale should have a significant correlation with outcome and significant differences in outcome between grades.²³ Signs of brain stem dysfunction can be easily incorporated into the current WFNS grading system to create a clearer distinction between the 2 poorest WFNS grades and to predict outcome of the worst-affected patients better than is possible with the current WFNS grading.

The results of this prospective study may have major implications for clinical decision-making as well as for clinical studies; in particular, the differentiation between the worst grades may have an impact on whether treatment is initiated or halted.

Limitations of the Study

Our study was performed in Switzerland (98% of patients) and Germany with a rather homogeneous care and a more international center selection would have provided a more robust information about the value of the hWFNS modifications. Also, unlike others, we have not included comorbidities or therapeutic maneuvers into the hWFNS scale. Omitting additional information might limit the prognostic information of the hWFNS scale.

Conclusions

The hWFNS scale improves outcome prediction for poor-grade aneurysmal subarachnoid hemorrhage patients by incorporating signs of brain stem dysfunction into the current WFNS grading. The authors therefore recommend that this simple modification should be added to the current WFNS scale.

ARTICLE INFORMATION

Received July 18, 2021; final revision received December 17, 2021; accepted January 28, 2022.

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Sources of Funding

Dr Fung received financial support of the Swiss Heart Foundation to perform this study.

Disclosures

Dr Regli received travel support from Aesculap AG and grants from Stryker. The other authors report no conflicts.

Supplemental Material

Supplemental Results
Checklist

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