Early Prognostication of 1-Year Outcome After Subarachnoid Hemorrhage: The FRESH Score Validation

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Background and Aim: The FRESH score is a tool to prognosticate long-term outcomes after spontaneous subarachnoid hemorrhage (SAH). Here, for the first time, we aimed to externally validate the disability part of FRESH using its original four score variables. *Methods:* A total of 107 patients with SAH were prospectively enrolled in the Yale Acute Brain Injury Biorepository between September 2014 and January 2018. 12-month functional outcome was recorded prospectively by trained study investigators using the modified Rankin Scale (mRS). FRESH-scores were calculated retrospectively using the original score variables. We used R^2 statistics to assess goodness of fit, and the area under the receiver operating characteristic curve (AUC) to assess ability of the score to discriminate between favorable and unfavorable (defined as mRS 4-6) outcome. *Results:* We identified 86 patients with SAH with complete 1-year follow-up data. Mean age was 60 years, 60% were women. An aneurysmal bleeding source was found in 71% of patients. 80% underwent aneurysm coiling, and 5% clipping. Sixteen percent of patients were considered high grade on admission (Hunt&Hess score 4 or 5). Discrimination of the FRESH score between favorable and unfavorable outcome was high (AUC 90.8%, confidence interval 81.9%-96.5%). Nagelkerke's (.54) and Cox&Snell's R^2 (.35) indicated satisfactory fit. Exclusion of patients without aneurysmal etiology of SAH did not significantly alter model performance. *Conclusions:* FRESH, a prognostication score of long-term outcomes in patients with SAH showed excellent score performance in this external validation. FRESH may guide the efficient use of hospital resources, family discussions, and stratification of patients in future randomized controlled trials.

Key Words: Subarachnoid hemorrhage—intracranial hemorrhages—prognosis—cohort studies—patient outcome assessment

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INTRODUCTION

Clinical outcome after spontaneous subarachnoid hemorrhage (SAH) can take many forms.[1] Pooled analyses have shown that one quarter of affected persons die within 30 days of disease onset, a number that rises to about one-third of patients at 90 days after the index bleed. At 90 days another quarter is severely disabled (modified Rankin scores 4 or 5), and about 40% have no, mild or moderate disability (mRS 0-3).[2,3] Despite the diversity of outcomes, there is no established prognostication system, as it is used in other types of hemorrhagic stroke.[4,5] The World Federation of Neurosurgeons and the Hunt&Hess scores (WFNS, H&H) are often used, but were not designed to predict long-term outcomes, and they fail to do so.[6] Both scores are based on neurologic deficits and level of consciousness, and do not take into account physiologic parameters which are known to reflect much of the morbidity burden in patients with SAH.[7]

The SAH long-term prognostication score FRESH, published in 2016, incorporates both neurologic and physiologic information obtained within 48 hours of hospital admission.[6] Thus early during the hospital course the score may support intelligent use of hospital resources, provide information that facilitates ethically difficult decision-making, or may be used for stratification in randomized trials. The four score variables – admission H&H, APACHE II-physiologic score, patient age, and aneurysmal rebleed within 48 hours – were the result of an extensive search involving the screening of several 100 data points from patient history, clinical, and imaging variables. Variable selection was partially data-driven and partially the result of a systematic literature search identifying previously described SAH outcome predictors. Selection and weighting of the final score variables was unbiased and accurately reflects the magnitude of the model residuals. FRESH performed exceptionally well in the derivation cohort (n = 1526) with an area under the curve (AUC) of 90%.[6] While a surrogate FRESH score, that used WFNS instead of H&H as one of the four score parameters, was validated in an external patient cohort, the original FRESH score has not been externally validated to date. Here, we aimed to validate FRESH in an independent cohort.

METHODS

Patient Selection and Data Collection

We retrospectively analyzed patient data from the Yale Acute Brain Injury Biorepository, a prospective cohort of patients with ischemic and hemorrhagic stroke, and traumatic brain injury. All patients at Yale New Haven Hospital who were admitted to the neuroscience intensive care unit or inpatient stroke service with an acute brain injury who presented within 96 hours of injury were considered for enrollment. Subjects were enrolled between September 2014 and January 2018 with a primary diagnosis of spontaneous SAH. Upon admission every patient routinely underwent vessel imaging (either CT or MR angiography). Patients who were younger than 18 years of age, and patients in whom the SAH was caused by vascular malformations other than an aneurysm or was a byproduct of a different type of intracranial bleed, were excluded. The entire patient cohort was treated following the same current guidelines.[8] Trained study investigators collected demographic and clinical data prospectively. However, some of the data points necessary to generate the FRESH scores had to be obtained retrospectively. For H&H scores we had 2 investigators review all neurological and neurosurgical notes from the emergency department independently and determine the appropriate score based on Glasgow coma scale and clinical exam documentation. In cases of discrepancies consensus was obtained after review and discussion of the case with a third investigator. For APACHE II scores, mirroring the methods of the original FRESH score paper, we obtained the worst available APACHE score within 24 hours of admission by reviewing clinical and laboratory data in *Epic*, our electronic medical record software. We then calculated the FRESH score for each patient.

Protocol Approvals and Patient Consents

The study was approved by the Yale University Institutional Review Board. Informed consent for participation in the study was obtained from all subjects, or their legally authorized representatives enrolled between September 2014 and June 2017. After IRB-approved amendment in July 2017, in addition to explicitly consented patients, clinical information was also collected on all patients in the neuroscience intensive care and inpatient stroke units who fit study criteria, a procedural change that minimized selection bias.

Outcomes

Patient outcomes were assessed at 12 months after the index bleed. Trained study investigators contacted patients via telephone at each timepoint to collect the mRS, and multiple other scores to assess quality of life, cognition, and disability. Investigators were episodically observed by study leadership while completing assessments and retrained biennially to ensure the quality of outcome data. The primary outcome in this study was mRS at 12 months.

Statistical Analysis

Statistical analyses were performed using SPSS (version 24) and R (version 1.1.456). Data are presented as median and interquartile range. We dichotomized the mRS to differentiate between favorable (mRS 0-3) and unfavorable outcome (mRS 4-6). Sensitivity and specificity for prognostication of unfavorable outcome were measured by

calculating the AUC of the receiver operating characteristic curve. Confidence intervals of the AUC were produced through bootstrapping. We then quantified goodness-of-fit of the FRESH score using Nagelkerke R^2 and Cox/Snell R^2, commonly used measures for this purpose. A second analysis included only patients with an aneurysmal SAH (excluded patients in this analysis had aneurysm-negative spontaneous SAH). The same statistical analyses described above were used in this group.

RESULTS

The study inclusion process is illustrated in the figure (Fig 1). Baseline characteristics of the score validation cohort are shown in Table 1. There was a female predominance, the average age was 60. The majority of this cohort was white (80%). Sixteen percent of patients had high H&H scores (4 or 5) on admission. In 71% a ruptured aneurysm was considered the cause of the SAH. Eighty percent of aneurysms were treated by coiling. The full range of FRESH grades is 1-9. In our cohort FRESH scores ranged from 1 to 6. Ten patients (11.6%) had a score value of 1, and 28 (32.6%), 20 (23.3%), 15 (17.4%), 6 (7.0%), and 7 (8.1%) patients had score values from 2 to 6, respectively. Overall 16% of patients died within the first year, 21% of all patients had unfavorable outcome at 1-year follow-up (mRS 4-6). Poor outcome at 1 year by FRESH grade is shown in Figure 2.

Score Performance

Table 2 shows discrimination of the FRESH score between favorable and unfavorable outcome as well as goodness of fit.

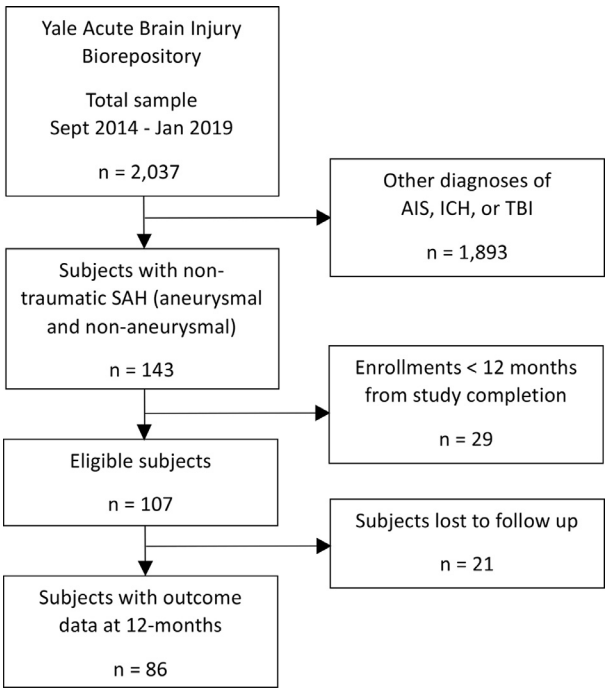

Figure 1. *Inclusion and exclusion of cohort subjects.*

Table 1. *Baseline characteristics*

Characteristic	
n	86
Age, year, mean (SD)	59.5 (13.7)
Female, no. (%)	52 (61)
Ethnicity, no. (%)	
White	69 (80.2)
Black	8 (9.4)
Hispanic	5 (5.8)
Asian	2 (2.3)
Other	2 (2.3)
Hunt&Hess grade (%)	
1	15 (17.4)
2	33 (38.4)
3	22 (25.6)
4	12 (14.0)
5	4 (4.7)
GCS (%)	
3-8	19 (22.1)
9-12	6 (7.0)
13-15	61 (70.9)
Aneurysmal SAH, no. (%)	61 (70.9)
Aneurysm treatment, no. (%)	
Clipping	3 (5.0)
Coiling	48 (80.0)
No treatment	9 (15.0)
APACHE-II *phys*, median (IQR)	6 (4-8)
Fresh score, median (IQR)	3 (2-4)

Abbreviations: GCS, Glasgow coma scale; SAH, subarachnoid hemorrhage; SD, standard deviation.

Exclusion of Patients Without Aneurysm

Similar to the derivation cohort, in part of our patients vessel imaging did not show an aneurysm (29%). Since aneurysmal rebleed is one of the 4 factors in the FRESH model, we hypothesized that model performance would improve when including only patients with aneurysmal SAH. However, score performance did not substantially change in this subgroup (Table 2).

DISCUSSION

Here, we externally validated the FRESH score, a tool to prognosticate long-term outcome after spontaneous SAH. Score performance in this prospective study cohort was excellent.

A crude but pragmatic first step in assessing performances of different scores is to compare them with the H&H or WFNS scores. If consistently applied the H&H score can achieve an AUC of 85% at discriminating between favorable and unfavorable long-term outcome.[6] Apart from the FRESH score few prognostic SAH models outperform this number.[6,9] In this independent cohort FRESH performed with similar discriminatory ability and slightly better goodness of fit.

The Yale validation cohort differed from the original derivation cohort in many ways, a circumstance that is

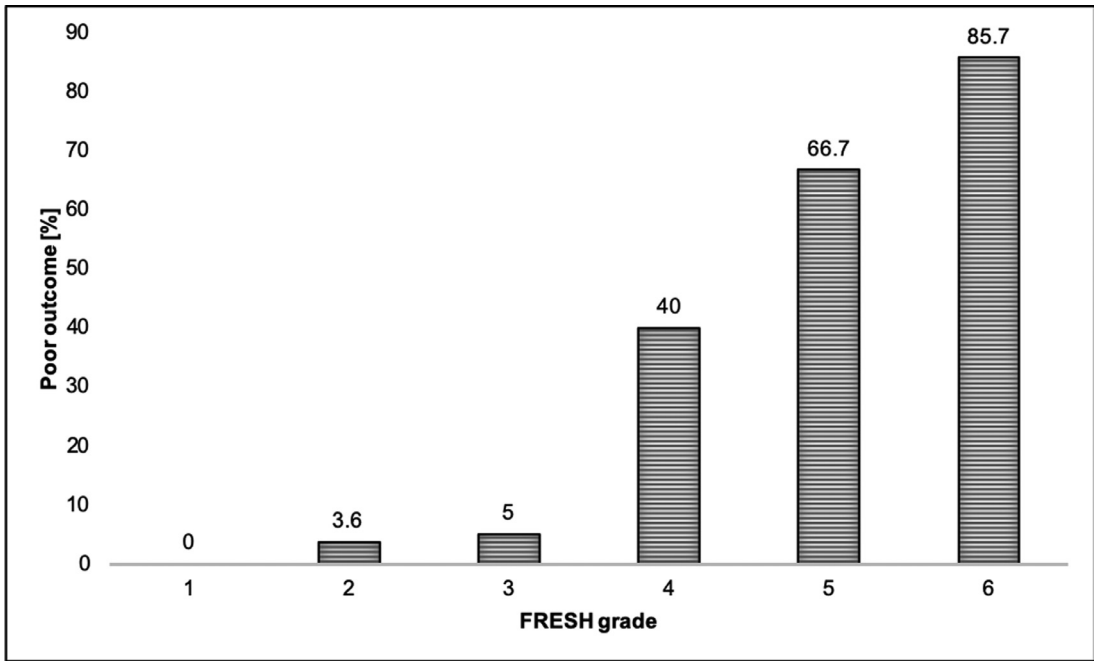

Figure 2. *Unfavorable outcome (modified Rankin score 4-6) by FRESH grade.*

desirable for external validation as it illustrates the generalizability of the score if the validation is successful. Even though both derivation and validation cohorts were collected at medical centers in the North East of the United States, ethnic composition and clinical variables of the cohorts were markedly different. For example, the external cohort had a higher percentage of white (80% versus 45%) and a lower percentage of Hispanic patients (6% versus 30%) than the derivation cohort. Patients in the external cohort had a lower percentage of high H&H grades (16% versus 31%). Coiling as aneurysm treatment was by far more commonly used than in the derivation cohort (80% versus 20%). The validation cohort was considerably smaller than the derivation cohort. However, while patient data in the derivation cohort had been collected over 2 decades, a time during which SAH therapy underwent many changes, all patients in the Yale cohort were treated according to the same recent guidelines.[8] In summary, because of these cohort differences and despite the geographic proximity of the 2 medical centers, we consider this external validation meaningful.

Of note, our cohort included patients with both aneurysmal and nonaneurysmal etiologies of their SAH, mirroring the methodology of the original FRESH score. However, nonaneurysmal spontaneous SAH should likely be regarded as a separate entity with a clinical course and outcome different from aneurysmal SAH.[10] Furthermore, "aneurysmal rebleed" is a variable contained in the score. Therefore, FRESH will likely perform better in populations of only aneurysmal SAH patients – and has done so in our respective subgroup analysis. Future investigators may consider using FRESH preferably for prognostication after aneurysmal SAH.

Clinical scores are abundant and the constant production of more scores contrasts with their infrequent use in clinical practice. Until recently about 11 SAH prediction models had been published, none of which is frequently used.[5,11] A recent large-scale study in the multicenter

Table 2. *FRESH score performance*

	Validation cohort	Derivation cohort	Validation cohort – aneurysmal SAH
Discrimination			
AUC	90.8% (81.9-96.5%)	89.8% (88.1-91.6)	89.7 (79.1-96.4)
Goodness of Fit			
Nagelkerke's R square	.54	.50	.53
Cox & Snell R square	.35	.35	.36

Abbreviations: AUC, area under the curve.

Prognostication of unfavorable functional outcome 12 months after spontaneous subarachnoid hemorrhage. Unfavorable functional outcome is defined as modified Rankin scale 4-6.

SAHIT cohort, which includes the cohort from which the FRESH score was derived, generated the SAHIT score for prognostication of disability 3 months after SAH.[12] The score was internally and externally validated. Score performance indicated good results, which however, did not reach the performance level of the FRESH score.[12,13] These performance differences are likely due to different methodological approaches in the 2 studies. Large pooled cohorts, such as the SAHIT cohort, have the advantage of suppressing confounding factors through averaging, but this comes at the expense of being restricted to fewer variables that can be added to the prediction model, namely those variables that are available in all contributing data sets. For example the APACHE II score is typically not available in many SAH cohorts, but as a marker of the physiologic (nonneurologic) condition of the patient, has consistently shown to be a powerful predictor of outcome.[6,7,14] Deriving a score from a single-center prospective cohort with many available clinical and imaging variables, and then validating the score in multiple external cohorts, may ultimately yield the more promising results as compared to deriving the score from a large multicenter cohort.

Even though validity of the FRESH score in African, Asian, and European cohorts still remains to be shown, the results of our paper support the generalizability of FRESH and will possibly aide its implementation as a clinical decision-making tool in patients with spontaneous SAH. Moreover, FRESH may serve as a stratification tool in randomized controlled trials. In the past, trial stratification has often been based on the WFNS score, which may have contributed to the negative results in some of these trials.[15-17] We know from the positive thrombectomy trials in patients with ischemic stroke that selective patient inclusion may lead to the establishment of new therapies despite prior negative trials.[18] Thus FRESH may, in addition to its clinical purpose, fill the gap and be used as a stratification tool for randomized trials investigating interventions in patients with SAH.[19]

Our study has several limitations. First, the validation cohort was relatively small and the percentage of patients with unfavorable 12 months outcome was smaller compared to the derivation cohort, limiting the statistical power of this study. During the first phase of enrollment subjects were required to sign consent forms upon admission in order to be enrolled in the prospective database. The concern that patients during the first enrollment phase had lower neurological baseline severity was shown to be unsubstantiated in a selection bias analysis, comparing patients before and after this change in enrollment procedure (no significant difference in H&H or Glasgow coma scale scores). Second, H&H as well as APACHE II scores were graded retrospectively. Third, 19.6% of our patients did not have complete follow-up data. This is a comparatively low lost-to-follow-up rate but nevertheless may have skewed study results. Fourth, our cohort was lacking patients with high FRESH grades (grades 7-9). This is not surprising given that in the original score derivation cohort, which had a higher morbidity burden – as indicated by higher H&H and APACHE II score values on admission – only 7% had high FRESH grades. And fifth, we were only able to validate the disability (main) portion of the FRESH score, because variables necessary to calculate the cognition and quality of life subscores of FRESH were not available in this data set.

Summary and Conclusions

This study constitutes the first external validation of FRESH, a score to prognosticate outcome after spontaneous SAH, using the original four score variables. External score performance was excellent. These results confirm the generalizability of FRESH for its clinical and research use.

Conflict of Interest

The authors warrant that they have no financial or other relationships with commercial parties that might pose a conflict of interest with regard to this manuscript.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.06.038.

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