

# Prognostication of long-term outcomes after aneurysmal subarachnoid hemorrhage: external validation of the FRESH score

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## Abstract

**Background and Objectives:** Aneurysmal subarachnoid hemorrhage (aSAH) affects 6.3 persons per 100.000 annually. Patient outcomes still vary greatly. Prognostication remains challenging and both Hunt & Hess (H&H) and World Federation of Neurosurgical Societies (WFNS) grading scales lack long term accuracy. The “Functional Recovery Expected after Subarachnoid Hemorrhage” (FRESH) scale, incorporating 4 variables - admission H&H score, Acute Physiology And Chronic Health Evaluation 2 (APACHE 2) score, patient age and aneurysmal rebleed within 48 hours – has been reported to predict long-term outcome. In this retrospective study, we assessed the external validity of this scale.

**Methods:** We retrospectively analyzed all intensive care unit (ICU) aSAH patients between Jan 1st and December 31st, 2017. 69 patients were identified. Patient baseline characteristics (age, sex, Glasgow Coma Scale (GCS), H&H, WFNS, APACHE 2 score, presence of rebleed) and outcome measures were obtained. FRESH scores were calculated accordingly. Functional outcome after 1 year was measured using the modified Rankin Scale (mRS). mRS was dichotomized into good (mRS 0-3) and poor (mRS 4-6) outcome to calculate the area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

**Results:** All patients underwent endovascular aneurysm treatment. Poor outcome was observed in 20 patients (30%); one year mortality was 24 % (16 patients). We achieved an AUC of 89% for discriminating between good and poor outcomes 12 months after hospital admission. Goodness-of-fit was calculated to be 36% using Nagelkerke R<sup>2</sup>. Sensitivity and specificity were 60% and 90% respectively.

**Conclusion:** In our retrospective analysis, the FRESH score performed well in the prediction of poor outcome (mRS 4-6) one year after aSAH. However, FRESH score calculations are cumbersome and prone to error.

**Keywords (MeSH):** Subarachnoid Hemorrhage, Aneurysmal, Prognosis, Patient Outcome Assessment, Validation Study.

## Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe type of stroke affecting 6.3 patients per 100.000 persons per year in Europe<sup>1</sup>. Despite advances in medical and interventional therapy, patient outcomes still vary greatly from full recovery to severe disability and death<sup>2</sup>. Early and accurate prognostication is

necessary to guide initial treatment and inform patients’ relatives of potential outcomes. The Hunt & Hess (H&H) scale and World Federation of Neurosurgeons Society (WFNS) scale are often used for long-term prognostication, however being based on only neurological parameters, they lack long-term accuracy. The recently developed “Functional Recovery Expected after Subarachnoid Hemorrhage” (FRESH)

*Ethical review: This study is a retrospective non-interventional trial with already existing data that were collected through patient file review. These data were presented to the local ethical committee (Ziekenhuis Oost-Limburg Genk, Belgium, chairman Dr. P Noyens). Given the retrospective nature of the study, ethics committee approval was not necessary.*

score includes both neurological and physiological parameters obtained during the first 48 hours of hospital admission<sup>3</sup>. The FRESH score incorporates 4 parameters (admission H&H, APACHE 2 or Acute Physiology And Chronic Health Evaluation 2 score, patient age and aneurysmal rebleed within 48 hours) to predict mortality and functional outcome one year after aSAH. The FRESH score has already shown an excellent score performance in an external validation study.<sup>4</sup> Since both the original and validation FRESH studies were performed in the United States, we aimed to externally validate the FRESH score in a European patient population pilot study.

## Methods

### *Ethical review*

This study is a retrospective non-interventional trial with already existing data that were collected through patient file review. These data were presented to the local ethical committee (ZOL Genk, chairman Dr. P Noyens). Given the retrospective nature of the study, ethics committee approval was not necessary.

### *Fresh score calculation*

The FRESH prognostication score is the result of the analyses of a prospective registry of more than 1500 patients suffering from non-traumatic subarachnoid hemorrhage and being admitted to a single tertiary-care center between 1996 and 2014. A selection of 35 variables including age, past medical history (myocardial infarction, congestive heart failure, hypertension, diabetes mellitus), admission H&H, Glasgow Coma Scale (GCS) and APACHE 2 physiology scores, admission pupillary reactivity, features of brain imaging (infarction, SAH blood volume, hydrocephalus, cerebral edema, intraventricular hemorrhage, location and size of the aneurysm), mode of aneurysm treatment (clipping versus coiling) and aneurysm rebleed within 48 hours were analyzed. The combination of age, H&H scale, APACHE 2 physiology score (without the GCS component) and aneurysmal rebleed was found to predict outcome best. After assigning score values to the 4 items to allow a final sum score between 1 and 9, the FRESH formula was constructed (figure 1)<sup>3</sup>.

### *Patient selection and data collection*

We retrospectively analyzed all patients with aSAH admitted to our intensive care unit (ICU) in a 12-month period between January 1st and December 31st, 2017. We identified a total of 69 patients. In one patient outcome at one year could not be determined.

Electronic patient records were queried for baseline characteristics such as age, sex and GCS score upon admission. The H&H score was derived from emergency and critical care department notes where the H&H had been scored by the treating physician. In case the H&H had not been scored upon admission, an experienced ICU physician reviewed the admission charts and clinical exam notes to estimate the H&H scale. In this way, the H&H score was assigned for every single included patient. The occurrence of rebleed within 48 hours was assessed by review of radiology reports and images from head computer tomography (CT) scans performed within this time window by the same ICU physician. APACHE 2 physiology score was calculated as the worst APACHE score using the worst available clinical and laboratory data within 24 hours after admission.

### *Outcomes*

Functional outcome at one year was assessed by the modified Rankin Scale (mRS) which scores global disability from 0 (no symptoms) to 6 (death)<sup>5</sup>. Since mRS scores had been collected earlier in patient follow up and quality improvement projects, these scores were obtained from electronic charts.

### *Statistical analysis*

Statistical analyses were performed using JMP version 15 (SAS Institute, Marlow, Buckinghamshire, UK). In alignment with the original paper and the FRESH validation paper, mRS scores were dichotomized into a good outcome (mRS 0-3) and a poor outcome (mRS 4-6).<sup>3,4</sup> Also a sensitivity analysis with the dichotomization good outcome (mRS 0-2) versus poor outcome (mRS 3-6) was done to test the validity of the FRESH score. In the ischemic stroke literature mRS 0-2 is often regarded as good or acceptable outcome<sup>5,6</sup>.

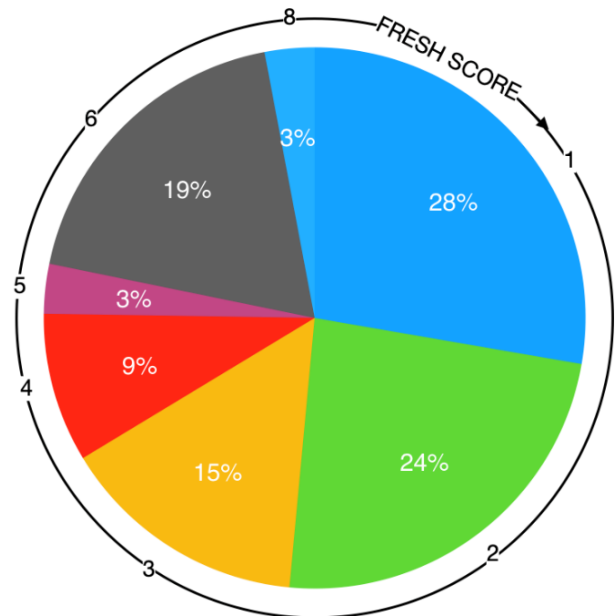
The nominal logistic regression model with the FRESH score targeting poor outcome (mRS 4-6) versus good outcome (mRS 0-3) is described by means of the overall performance using Nagelkerke R<sup>2</sup>, discrimination using the c-statistic with area under the receiver-operating characteristic (ROC) curve (AUROC), calibration (goodness-of-fit) through the HosmerLemeshow test and misclassification rate by describing the difference between observed and predicted events.

## Results

The medical records of 69 patients were examined. One patient was excluded due to missing data. Patient baseline characteristics are shown in Table I. 72% of patients was female; mean age was

**Table I.** — Patient characteristics.

n	68
Age, year, mean (SD)	58 (14.6)
Female, no. (%)	49 (72)
Hunt & Hess grade (%)	
1	23 (34)
2	20 (30)
3	7 (10)
4	3 (4)
5	15 (22)
GCS (%)	
13-15	47 (69)
9-12	2 (3)
3-8	19 (28)
APACHE-2 phys, median (IQR)	10 (7-14)
FRESH score, median (IQR)	2.3 (1.5-4.6)



*Fig. 2* — FRESH score distribution.

58 years (SD 14,6; IQR 49-68). Approximately 3 out of 4 patients had mild to moderate aSAH (H&H grade 1-3), while 1 in 4 patients had severe aSAH (H&H grade 4-5). In our patient population, FRESH scores ranged from 1 to 8, while the full range of FRESH scores is 1 to 9. FRESH score distribution is shown in figure 2. Good outcome (mRS 0-3) was observed in 48 patients (71%), while 20 patients (29%) had a poor outcome (mRS 4-6). The observed poor outcome was mainly due to patient death: 4 patients had a mRS score of 4, while 16 patients had died (mRS 6).

The nominal logistic regression model with the FRESH score targeting poor outcome (mRS 4-6) versus good outcome (mRS 0-3) showed a Nagelkerke R<sup>2</sup> of 0.32. The HosmerLemeshow p-value was 0.69, revealing good calibration. We achieved an AUROC AUC of 86% at discriminating between good and poor outcome at one year (figure 3). The misclassification rate was 11/68 (16%). The accuracy of the FRESH score was 84% (95%CI 73% to 92%). Sensitivity and specificity were 65% (95%CI 41% to 85%) and 92% (95%CI 80% to 98%) respectively.

Twenty-seven patients (39.7%) had a poor outcome at 1 year when poor outcome was defined as mRS 3-6. The nominal logistic regression model with the FRESH score targeting poor outcome as mRS 3-6 versus good outcome (mRS 0-2) showed a Nagelkerke R<sup>2</sup> of 0.19. The Hosmer-Lemeshow p-value was 0.12, revealing good calibration. We

achieved an AUROC of 78%. The misclassification rate was 18/68 (26%). The accuracy of the FRESH score in this model was 74% (95%CI 61% to 84%). Sensitivity, and specificity were 59% (95% CI 39% to 78%) and 83% (95% CI 68% to 93%), respectively.

## Discussion

The aim of this study was to externally validate the ability of the FRESH score to predict clinical patient outcome one year after aSAH in a European patient population. Considering an area under the ROC curve of almost 90% to discriminate between good and poor outcomes, we confirm the FRESH score to be an excellent scoring modality in aSAH.

Our study differs from the original validation study with respect to geographical location, patient demographics and type of SAH. The original study was performed in Connecticut, all patients were US citizens with a case mix of Caucasian (80%), black (10%), Hispanic (6%) and Asian patients (2%) while in our study all patients were Caucasian. Mean age (58 yo versus 59.5 yo) was comparable in both validation studies. Male to female ratio, however, was different: 50% of patients were female in the original validation study while in our study 72% of patients were female. The main difference, however, lies in the fact that in our study only patients with aneurysmal SAH were evaluated, while in the original trial 70% of patients suffered from aneurysmal SAH and 30% had non-aneurysmal non-traumatic SAH. All patients in our cohort underwent endovascular treatment, opposed to only 80% of aSAH patients in the original validation study. The obvious differences in the populations of both

$$\text{FRESH score} = \frac{(\text{H\&H})^2 + \frac{\text{APACHE phys}}{10} + a + r}{5} + 1$$

H&H = Hunt & Hess score on admission  
a = age (> 70 yo = 9; = 70 yo = 0)  
r = rebleed (yes = 4; no = 0)  
APACHE phys = APACHE w/o GCS

*Fig. 1* — FRESH score calculation.

studies makes our study very valuable in confirming the generalizability of the FRESH score.

The model performed worse when good outcome was defined as a mRS 0 to 2. Notably the misclassification rate increased significantly.

The strength of using the FRESH score for prognostication of long-term outcome after SAH lies in the fact that it incorporates not only the clinical neurological picture upon admission (as quantified by the H&H score), but also the physiological condition of the patient, (as assessed by the APACHE 2 physiology score). The integrated physiological and neurological score appears to be superior to using only neurological parameters (H&H or WFNS scale) or physiological parameters (such as the SAH Physiological Derangement Score or SAH-PDS) in the prediction of outcome after SAH.

There are certain limitations to our study. First, both the retrospective nature in the grading of variables in our study and the limited number of patients that were analyzed pose a certain risk of bias. Second, the patient group with poor outcome was mainly determined by patient death rather than by poor neurological outcome. In the patients that had died, we were unable to analyze the exact cause of death, i.e., whether death was due to medical issues refractory to therapy or rather due to futility and consequent therapy withdrawal?

Despite the limitations of our trial, we're convinced that the FRESH score is a useful tool for both clinical and research settings. In a clinical setting, the FRESH score can be used to inform about treatment and shape realistic expectations when interacting with patients and relatives. The relative distribution of mRS by respective score values at 12 months after SAH in the original derivation cohort study is shown in figure 3. In a research setting, the FRESH score could be used as a stratification tool in randomized controlled trials to compare treatment modalities for SAH. However, it must be taken into account that the FRESH score contains a multitude of variables, making the calculation rather laborious and prone to error. This might prove to be a limiting

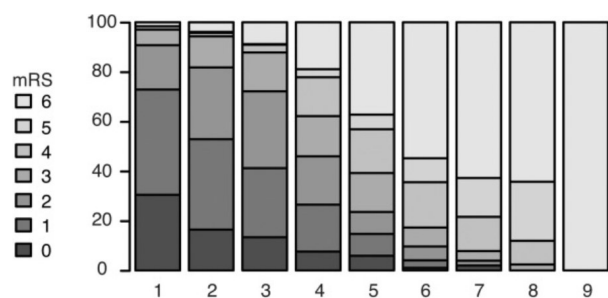


Fig. 3 — Relative distribution of mRS by respective score values at 12 months after SAH in the original derivation cohort study<sup>3</sup>.

factor for using the FRESH score. To tackle the latter issue, however, it is noteworthy to mention that the authors of the original papers have created a free smartphone application that can be downloaded from <https://itunes.apple.com/us/app/fresh-score/id1015675236>.

## Summary and Conclusions

This analysis is the first external validation of the FRESH score, a tool for prognostication of long-term outcome after spontaneous SAH, outside the USA. The FRESH score performed very well in predicting outcomes after aSAH. The potential widespread use of the FRESH score in both clinical and research context is therefore suggested by these results.

*Conflicts of interest:* The authors have no conflicts of interest to declare.

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[doi.org/10.56126/73.S1.25](https://doi.org/10.56126/73.S1.25)