Stroke

RESEARCH LETTER

Early Brain Injury and Soluble ST2 After Nontraumatic Subarachnoid Hemorrhage

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Following nontraumatic subarachnoid hemorrhage (SAH), secondary brain injury resulting from delayed cerebral ischemia and cerebral vasospasm negatively impacts patient outcomes.[1] Unfortunately, efforts to treat delayed cerebral ischemia and cerebral vasospasm pharmacologically have thus far been unsuccessful in improving outcomes,[2] highlighting the need to explore additional injury mechanisms. Accordingly, injury to the brain within the first 72 hours of symptom onset, termed early brain injury (EBI), is hypothesized to play an important role in SAH pathogenesis.[3] However, there is limited understanding of the contributing features and biological markers that are linked to EBI. Given the importance of EBI in mediating neurological injury after SAH, we sought to identify EBI markers that predict neurological outcome, to evaluate the relationship of inflammatory biomarker soluble ST2 (sST2)[4,5] level to these markers and to utilize our findings to derive and validate an EBI risk score.

METHODS AND RESULTS

This was a retrospective observational study including nontraumatic SAH patients from the Massachusetts General Hospital (n=190; discovery cohort) and Rigshospitalet Copenhagen (n=50; validation cohort). Clinical markers of EBI included early loss of consciousness, symptomatic hydrocephalus (as indicated by external ventricular drainage placement), Glasgow Coma Scale score at 24 hours, and early neuroworsening (defined as a decrease in Glasgow Coma Scale ≥2 points within the first 72 hours). Radiographic markers included global cerebral edema and bicaudate index. In the discovery cohort, we assessed sST2 level using serial plasma samples drawn at early, intermediate, and late sampling time points. The three time points corresponded to 3.5±1.2, 7.8±1.3, and 13±2.3 days post-hemorrhage, respectively. In the validation cohort, plasma samples were collected daily between posthemorrhage days 1 through 8. Poor functional outcome was defined as a 90-day modified Rankin Scale score ≥3. Further rationale for the selection of these variables is provided in the Data Supplement.

To derive an EBI risk score, EBI markers were sequentially added into a multivariable logistic regression model adjusted for age, sex, and admission Hunt-Hess grade. Classification was assessed by a comparison of receiver operating characteristic curves. β-coefficients in the discovery cohort were used to compute integer point values for each risk factor, and internal validation was performed using the bootstrap procedure with 500 replications. The sensitivity, specificity, and accuracy were calculated for the risk model at 4 categories (0–1, 2–3, 4–5, and 6–7). For external validation of the EBI risk score's performance, the weighted regressions from the discovery cohort were applied to the validation cohort, and the sensitivity, specificity, and accuracy for predicting 90-day modified Rankin Scale were determined.

In a multivariable logistic regression model including all EBI markers with sST2 and adjusting for age, sex, and admission Hunt-Hess, 24-hour Glasgow Coma Scale, symptomatic hydrocephalus, sST2 level, age, and sex were independent predictors of outcome ($P<0.05$ for all). These markers were sequentially added into a multivariable logistic regression to generate the EBI risk score. Discrimination was evaluated using receiver operating characteristic analysis, where the baseline model (age and sex) had an area under the curve of 0.658. The sequential addition of each feature to the model led to improvement in

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model performance at each step, as shown in the Figure (A) ($P<0.05$ for each). The final model in the discovery cohort had an area under the curve of 0.910 (95% CI, 0.864–0.956). The components and weights of the EBI risk score are shown in the Figure (B). This score had a sensitivity of 93% (95% CI, 84%–98%), a specificity of 75% (95% CI, 67%–83%), and an accuracy of 82%. The distribution of 90-day modified Rankin Scale in patients with a higher EBI risk score versus lower risk patients is shown in the Figure (C).

The EBI risk score was further validated in a second cohort, utilizing the weighted regressions from the discovery cohort. The model performed similarly to that in the discovery cohort, with an area under the curve of 0.846, a sensitivity of 86% (95% CI, 57%–98%), a specificity of 83% (95% CI, 67%–94%), and an accuracy of 84%. The Figure (D) shows the distribution of modified Rankin Scale by risk score in the validation cohort.

SUMMARY

In this study, we derived and validated a composite EBI risk score. In addition to confirming the importance of EBI in determining long-term SAH recovery, the risk score could be used for patient selection or risk stratification in future clinical trials. The score was derived and validated in 2 independent cohorts, highlighting its ability to perform across separate patient populations. Future studies should focus on validating the application of EBI in clinical settings, examining other biomarkers in addition to sST2, and deepening our understanding of the pathophysiologic factors that lead to EBI and impact patient outcomes.

ARTICLE INFORMATION

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Disclosures

Dr Rubin serves as a scientific advisory board member for Celgene. Dr Rosenthal receives funding from UCB Pharma, Inc, as a member of its scientific advisory board and from Ceribell, Inc, as a member of its scientific advisory board and has received grants from Sage Therapeutics outside the submitted work. Dr Bevers has received grants and personal fees from Biogen and personal fees from Atlas Ventures outside the submitted work. Dr Patel reports personal fees from Microvention, Medtronic, and Penumbra outside the submitted work. Dr Møller has received grants from the Lundbeck Foundation and Rigshospitalet Research Board during the conduct of the study. Dr Kimberly has received grant support and consulting fees from Biogen, Inc, and from NControl Therapeutics, Inc, and has patent 16/486687 pending and licensed. Dr Kimberly serves as a scientific advisory board member for Biogen, Inc, and NControl Therapeutics, Inc.

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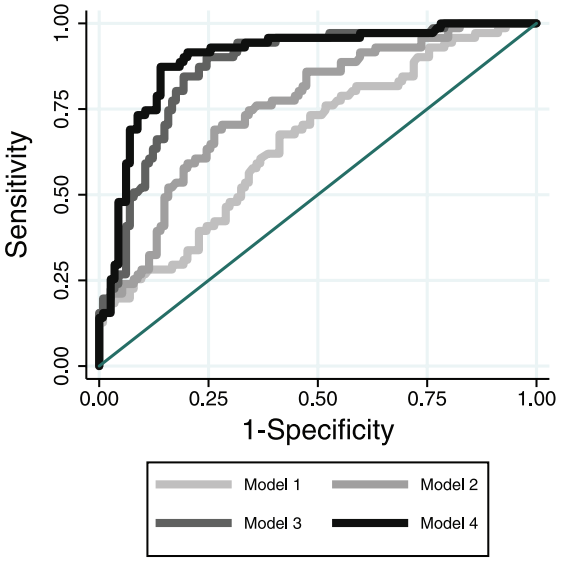
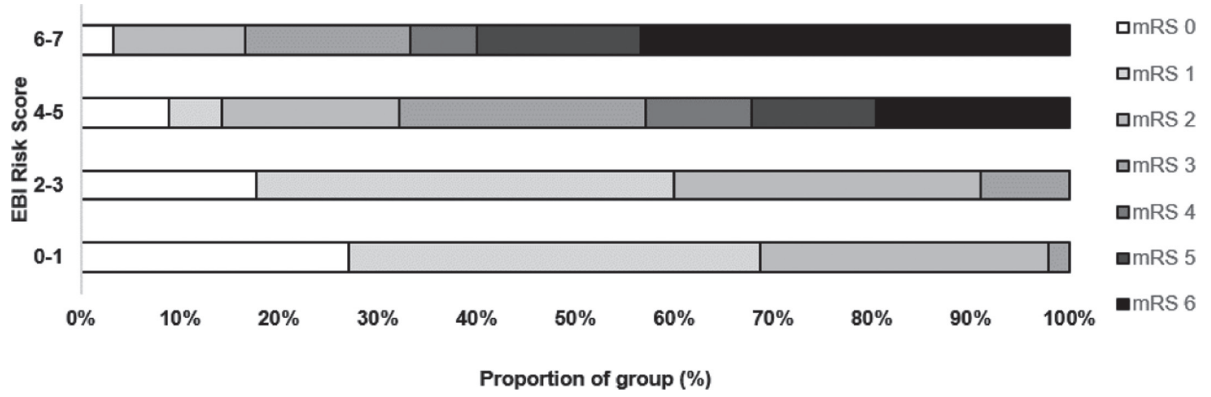
A



B

EBI Risk Factor	β Coeff.	Outcome	Point Value
Age	1.19	≤ 60 yrs	0
		> 60 yrs	1
Sex	0.977	Female	0
		Male	1
Symptomatic Hydrocephalus	2.19	No	0
		Yes	2
24hr Glasgow Coma Score	2.14	> 12	0
		≤ 12	2
sST2	0.986	< 66 ng/mL	0
		≥ 66 ng/mL	1
Total Points			7

C



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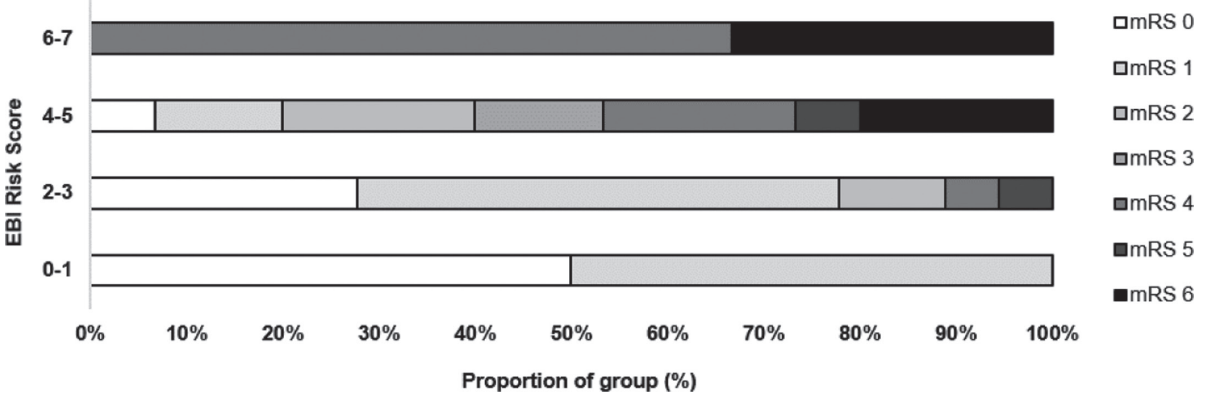

Figure. An early brain injury (EBI) risk score adds predictive value for outcome in 2 independent cohorts.
A, Receiver operating characteristic curves are shown for sequential logistic regression models. Model 1=age+sex; model 2=model 1+soluble ST2 (sST2); model 3=model 2+symptomatic hydrocephalus; model 4=model 3+24-h Glasgow Coma Scale (GCS). Each model had improved discrimination compared with the prior ($P<0.05$ for all). **B**, EBI risk score components and points. **C**, The distribution of 90-d modified Rankin Scale (mRS) scores in the discovery cohort is shown, where higher EBI risk score categories predict worse outcome ($P<0.0001$). **D**, Validation of the risk score categories is shown in an independent cohort ($P<0.001$).