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Non-cerebral vasospasm factors and cerebral vasospasm predict delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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Aneurysmal subarachnoid hemorrhage (aSAH) is a typical neurosurgical emergency. The patient's prognosis is related to the severity of the initial illness and post-operative complications, especially delayed cerebral ischemia (DCI). DCI, which occurs in up to 30% of patients with subarachnoid hemorrhage (SAH), usually 2 weeks after hemorrhage, is one of the leading causes of death and disability in aSAH. Currently, it is generally accepted that DCI is primarily associated with cerebral vasospasm (CVS). However, after aggressive anti-CVS therapy, a subset of patients still develop DCI, suggesting that CVS is not the entire DCI cause.[1]

Microcirculatory spasm, microthrombosis, cortical diffusion depolarization, and cerebral autonomic dysregulation have been associated with DCI development. However, these factors are generally difficult to measure and difficult to use in the clinical setting. Therefore, we attempted to screen the prognostic factors of DCI from some common clinical data, establish a predictive model of DCI with non-CVS elements and combine it with CVS to improve DCI's diagnosis rate and improve patient outcomes.

We designed this study according to the guidelines outlined in the *Declaration of Helsinki* and approved by the local ethics committee of the First Affiliated Hospital of Fujian Medical University (Fujian, China, Approval No. MRCTA, ECFAH of FMU [2020] 005). The informed consent form was signed by the patient or his or her authorized legal representative. If the patients could not sign the form themselves, we obtained informed consent from the patient's authorized legal representative. Patient management was performed following the American Heart Association/American Stroke Association "Guidelines for the Treatment of aSAH." Depending on the patient's condition and autonomous preference, craniotomy or endovascular treatment may be indicated.

Retrospective clinical data were obtained from 711 aSAH patients (from 2013 to 2018) who underwent surgical treatment at the Department of Neurosurgery, The First Affiliated Hospital of Fujian Medical University. Patient inclusion criteria were (1) patient >18 years and <60 years; (2) the patient had confirmed SAH caused by an intracranial aneurysm by computed tomography angiography (CTA) or digital subtraction angiography (DSA); (3) the patient had completed pre-operative laboratory testing at our institution. Exclusion criteria were (1) patients ≤18 years or ≥60 years; (2) the patient had been diagnosed with DCI before admission; (3) the patient had a history of neurological diseases, such as an intracranial tumor, stroke, and severe craniocerebral injury; (4) patients with uremia, cirrhosis, renal dysfunction, malignancy, and other systemic diseases.

DCI was defined as clinical deterioration or a new infarct on computerized tomography (CT) (but not visible on admission or immediate postoperative scan). Criteria for CVS diagnosis were persistent arterial spasm visible on DSA or CTA, excluding other causes.[2]

General conditions of the patient on admission include but are not limited to fever (axillary temperature >37.3°C), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg), loss of consciousness

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(LOC), mechanical ventilation (MV) therapy immediately after admission (admission MV), and significant past medical history. These indicators were collected by the nurses on the ward at the time of admission and recorded in the nursing record.

Based on the previous reports, in addition to the routine laboratory tests performed on admission to the hospital, we calculated the following variables, which were considered to be related to the inflammatory response. They are as follows: neutrophil-to-lymphocyte ratio (NLR) = neutrophils/lymphocytes; systemic inflammation response index (SIRI) = neutrophils × monocytes/lymphocytes; platelet-to-lymphocyte ratio (PLR) = platelets/lymphocytes; lymphocyte-to-monocyte ratio (LMR) = lymphocytes/monocytes; glucose to potassium ratio (GPR) = glucose/potassium.

Post-admission clinical assessments included Glasgow Coma Score (admission GCS), Hunt and Hess grade (HH), World Federation of Neurological Surgeons Scale (WFNS), modified Fisher score (mFisher), and VASOGRADE.[3] These assessments were adjudicated by the primary neurosurgeon, verified by the supervising physician, and recorded in the computerized medical record system. The patient's responsible physician assessed the post-operative GCS score (postGCS) on the first post-operative day. All patients underwent DSA or CTA within 2 days of surgery to determine whether the aneurysm was occluded entirely or embolized and assessed for vasospasm. Image data were stored in the "Picture Archiving and Communication Systems" to ensure traceability. Clinical intervention information included the surgical procedure (clipping or coiling), the surgical time, the number of arteries, and the use of post-operative MV (postMV).

Patients began to receive documentation of their neurological conditions immediately after surgery. In the hospital, the patient was observed during routine rounds. After discharge, patients were asked to return to the hospital for another review within 1 month. The endpoint of observation was 30 days after surgery or the appearance of DCI.

We investigated the relationship between the DCI and the collected parameters. The normality of the data was assessed using the Shapiro–Wilk test. The Student's *t* test was used to compare normally distributed continuous variables. Continuous variables are shown as mean ± standard deviation. Mann–Whitney *U* tests were used to compare variables that were not normally distributed and presented as median (Q_1, Q_3). Categorical variables were expressed as counts (percentages) and analyzed by the χ^2 test or Fisher exact test. Kruskal–Wallis rank-sum test was used to compare ordered variables. Variables associated with DCI ($P < 0.05$) in univariate analysis were included in the multivariate analysis. Logistic regression analysis was used to calculate the hazard ratio (HR) and 95% confidence intervals (CI). Backward logistic regression was used to remove the least essential variables from the initial model at a time until $P < 0.05$ for all remaining variables, resulting in a non-CVS prediction model of DCI (non-CVS model). Further analysis compared the predictive performance of the non-CVS model, CVS, and the combined non-CVS and CVS model (combined model) for DCI. The discriminatory power of the models was assessed using the sensitivity, specificity, Youden index, and C-statistic, and the differences in C-statistic between the three models were evaluated using the DeLong test. Calibration plots were used to evaluate the calibration of the three models and internal validation was performed using the bootstrap method. A clinically available nomogram was then created. Statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA) and R statistical software (R version 4.0.3, R Project, www.r-project.org). $P < 0.05$ was considered statistically significant.

Among the 711 aSAH patients who underwent surgical treatment, DCI occurred in 57 patients. We included as many variables related to disease as possible in the analysis. In the pre-analysis, we analyzed the number of aneurysms, HH, WFNS, mFisher, and postMV days, as ordered variables and found that the percentages of patients with aneurysms >3, HH ≥ grade 2, WFNS ≥ grade 3, mFisher ≥ grade 3, and postMV ≥3 days in the DCI group were significantly higher than those in the non-DCI group (all $P < 0.05$) [Supplementary Table 1, http://links.lww.com/CM9/A813]. Therefore, a bicategorical transformation of the above variables was performed. Similarly, for the ordered variables, admission GCS and postGCS, because their values ranged from 3 to 15, which may be detrimental to the analysis and construction of prediction models, we conventionally transformed the GCS into three levels of ordered variables: GCS 15–13 as grade 1, GCS 12–9 as grade 2, and GCS 8–3 as grade 3.

The stepwise backward multivariate logistic analysis showed that only LOC (HR: 3.466, 95% CI: 1.085–11.074, $P = 0.036$), hypertension (HR: 2.227, 95% CI: 1.203–4.123, $P = 0.011$), VASOGRADE (HR: 1.582, 95% CI: 1.163–2.150, $P = 0.029$), number of aneurysms (HR: 11.533, 95% CI: 2.318–57.384, $P = 0.003$), surgical procedures (HR: 0.364, 95% CI: 0.137–0.965, $P = 0.042$), postMV(HR: 3.074, 95% CI: 1.281–7.374, $P = 0.012$), and postGCS (HR: 0.832, 95% CI: 0.779–0.889, $P < 0.001$) remained meaningful indicators. Based on these results, we developed a predictive model of DCI for non-CVS factors, the non-CVS model.

We compared the C-statistic values of non-CVS, CVS, and combination models and further assessed their discriminatory power by sensitivity, specificity, and Youden index. The C-statistic values for the three models, non-CVS, CVS, and combined model, were 0.805, 0.851, and 0.933, respectively. For the non-CVS model, its specificity was 0.632, sensitivity was 0.855, and Youden index was 2.659. For the CVS model, its specificity was 0. 913, sensitivity was 0.789, and Youden index was 2.072. For the combined model, its specificity was 0.829, sensitivity was 0.945, and Youden index was 3.086. The CVS model seemed to have a better C-statistic than the non-CVS model, but less sensitivity than the non-CVS model. However, results of the DeLong test showed no difference between the C-statistics of the non-CVS model and the

CVS model ($P = 0.316$), but after the two models were combined, the combination model had better C-statistics than the non-CVS model ($P < 0.001$) and the CVS model ($P < 0.001$).

Besides, we used calibration curves to describe the accuracy of the model when predicting DCI and validated it with the bootstrap method. The mean squared error was used to evaluate the fit of the non-CVS, CVS, and combination models, and the mean squared error was 0.00094, 0.00018, and 0.00066, respectively, with no overfitting. A decision model was developed to assess the possible clinical benefit of the three models. The analysis found that the combination model outperformed the other two models by providing services at an almost 10%–70% risk range. Therefore, we established clinical impact curves to evaluate the application of the combination model in DCI diagnosis. The combination model was in good agreement with the actual clinical observations. Finally, we established the nomogram of the combination model [Supplementary Figure 1, http://links.lww.com/CM9/A813].

We analyzed the relationship between clinically common non-CVS factors and DCI after aSAH, screening for multivariate factors consisting of LOC, hypertension, VASOGRADE, number of aneurysms >3, surgical approach, postMV ≥ 3 days, and postGCS. The non-CVS model and the CVS model have comparable prediction abilities for DCI. Also, combining the non-CVS model with the CVS model can significantly improve the prediction of DCI.

DCI is one of the major causes of poor outcomes in aSAH. Many clinical studies have evaluated predictors of DCI. However, there are not widely accepted and used predictors for DCI other than CVS. CVS is not a complete predictor of DCI, and there is a risk of overtreatment or missed diagnosis with CVS. Some reports use some laboratory indices to predict DCI, but these indices are not standard clinical laboratory indices, and their "availability" limits their further clinical use. Therefore, there is a need to develop a prediction model for DCI based on standard clinical indices.[4]

Regarding the variables included in the predictive model, some factors have been suggested to be associated with DCI. The impact of LOC and surgical procedures on DCI has been reported.[5] Others reported were found in the pre-analysis, such as the "number of aneurysms" and "number of days postMV used." Most patients with postMV ≥3 days are in a state of central respiratory dysfunction, characterizing by early and severe brain dysfunction that may be an early precursor to DCI. VASOGRADE is a grading scale constructed with mFisher and WFNS developed by de Oliveira Manoel *et al*[3] published in 2015. The VASOGRADE was the only graded scale retained after multivariate screening, demonstrating its importance in the prediction of DCI. The exclusion of some inflammatory indicators, represented by the NLR, from the multifactorial model may imply that local factors are more important than systemic factors in DCI development.

Our study also has some shortcomings, such as the fact that our study is a retrospective study, and there is selection bias. Besides, our sample size is not large enough for further collection and analysis. Also, the lack of external validation of our study may limit the generalization of our findings. We consider continuing this work in a further prospective cohort study.

The non-CVS model, based on typical clinical indices, can achieve similar DCI prediction to the CVS model, and when combined with the CVS model, it dramatically improves the prediction of DCI and is extremely easy to use.

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Conflicts of interest

None.

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