Original Article

Aneurysmal subarachnoid hemorrhage prognostic decision-making algorithm using classification and regression tree analysis

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Abstract

Background: Classification and regression tree analysis involves the creation of a decision tree by recursive partitioning of a dataset into more homogeneous subgroups. Thus far, there is scarce literature on using this technique to create clinical prediction tools for aneurysmal subarachnoid hemorrhage (SAH).

Methods: The classification and regression tree analysis technique was applied to the multicenter Tirilazad database (3551 patients) in order to create the decision-making algorithm. In order to elucidate prognostic subgroups in aneurysmal SAH, neurologic, systemic, and demographic factors were taken into account. The dependent variable used for analysis was the dichotomized Glasgow Outcome Score at 3 months.

Results: Classification and regression tree analysis revealed seven prognostic subgroups. Neurological grade, occurrence of post-admission stroke, occurrence of post-admission fever, and age represented the explanatory nodes of this decision tree. Split sample validation revealed classification accuracy of 79% for the training dataset and 77% for the testing dataset. In addition, the occurrence of fever at 1-week post-aneurysmal SAH is associated with increased odds of post-admission stroke (odds ratio: 1.83, 95% confidence interval: 1.56–2.45, \( P < 0.01 \)).

Conclusions: A clinically useful classification tree was generated, which serves as a prediction tool to guide bedside prognostication and clinical treatment decision making. This prognostic decision-making algorithm also shed light on the complex interactions between a number of risk factors in determining outcome after aneurysmal SAH.

Key Words: Aneurysmal subarachnoid hemorrhage, brain–body interactions, classification and regression tree analysis, prognostic decision making

INTRODUCTION

Neurologic outcome after aneurysmal subarachnoid hemorrhage (SAH) is influenced by a number of complex brain–body associations, including both non-treatment and treatment-related demographic, neurologic, and systemic factors. For bedside prognostication and clinical
decision making, a prediction tool is useful as an adjunct to complement clinical opinion and judgment.\(^\text{[6,9]}\)

One of the most frequently used measures of global function outcomes after aneurysmal SAH is the Glasgow Outcome Score (GOS). It is graded into five subgroups, including good recovery, moderate disability but functional independence, functional dependence with severe disability, persistent vegetative state, and death. This scale can be easily and accurately administered, is reliable as self or surrogate reporting tool, and correlates well with neuropsychological test measures. Subtleties to changes in function can be captured by its extended version, as well as other neuropsychological and quality of life outcome scores.\(^\text{[6,16]}\)

Classification and regression tree analysis is a statistical technique that involves creation of a decision tree by recursive partitioning of a dataset into more homogeneous subgroups. At each node, the best possible split for each variable is found by minimizing the impurity of subsequent daughter nodes. This technique prevents overfitting by pruning terminal nodes or leaves such that a decision tree is found with the smallest error rates. In addition, model performance can be enhanced by split sample validation techniques. Classification and regression tree analysis is a statistical technique that takes into account non-linear and high order interactions. It can handle large datasets with missing data, as well as high dimensionality.\(^\text{[1,2,11]}\)

**Objectives**

Using data from placebo and treatment arms of five clinical trials of Tirilazad, we aim to create a prognostic decision-making algorithm for aneurysmal SAH patients using the classification and regression tree analysis technique. In addition, model performance will be evaluated.

**MATERIALS AND METHODS**

The Tirilazad database was used to investigate prognostic subgroups for outcome prediction in aneurysmal SAH patients. The Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used to create the classification and regression tree analysis technique. In addition, model performance will be evaluated.

**RESULTS**

Patient selection and participation in the Tirilazad trials are summarized in Figure 1. In the Tirilazad patient populations, unfavorable outcome (functional dependence, persistent vegetative state, and death) at 3 months after aneurysmal SAH was observed in 1061 (30%) patients. Classification trees describing the relationships between neurological outcome and explanatory factors in aneurysmal SAH were generated using the training dataset [Figure 2] and testing dataset [Figure 3]. Figures 2 and 3 demonstrate seven terminal prognostic subgroups with the same node ranking order according to the percentages of unfavorable outcomes,
with percentage differences between the two decision trees ranging from 1.3 to 7.8%. Seven terminal prognostic subgroups are illustrated as follows:

1. Good admission neurological grade (Hunt and Hess grades 1 or 2), absent post-admission stroke (Node #3)—8.7% unfavorable outcome (training dataset) and 7.4% unfavorable outcome (testing dataset),

2. Poor admission neurological grades (Hunt and Hess grades 3 or 4), absent post-admission stroke, absent post-admission fever (Node #10)—33.6% unfavorable outcome (training dataset) and 37.4% unfavorable outcome (testing dataset),

3. Good admission neurological grades, post-admission stroke, age <58.5 years (Node #7)—38.3% unfavorable outcome (training dataset) and 43.8% unfavorable outcome (testing dataset),
4. Poor admission neurological grades, absent post-admission stroke, development of post-admission fever (Node #12)—44.6% unfavorable outcome (training dataset) and 48.6% unfavorable outcome (testing dataset),

5. Good admission neurological grades, post-admission stroke, age >58.5 years (Node #8)—59.4% unfavorable outcome (training dataset) and 54.7% unfavorable outcome (testing dataset),

6. Poor admission neurological grade (Hunt and Hess grade 5), absent post-admission stroke, development of post-admission fever (Node #11)—69.7% unfavorable outcome (training dataset) and 61.9% unfavorable outcome (testing dataset), and

7. Poor admission neurological grades, post-admission stroke (Node #6)—75.4% unfavorable outcome (training dataset) and 72.9% unfavorable outcome (testing dataset).

The classification and regression tree model generated using the training dataset had a classification accuracy of 79%, risk estimate of 0.21, with a standard error of 0.008. The model generated using the testing dataset had a classification accuracy of 77%, risk estimate of 0.23, and a standard error of 0.01. The occurrence of fever at 1 week post-aneurysmal rupture is associated with increased odds of post-admission stroke (odds ratio (OR): 1.83, 95% confidence interval (CI): 1.56–2.45, $P < 0.01$).
Table 1 shows a clinical prognostic decision-making algorithm for aneurysmal SAH patients with prognostic subgroups based on the classification and regression tree derived from the Tirilazad database.

DISCUSSION

Clinical prediction tools facilitate the process of prognostication and clinical decision making for both clinicians and patient families. The current classification and regression tree has seven terminal prognostic subgroups and makes use of the two most frequently retained clinical prognostic factors for long term neurologic outcome, namely, neurological grade\(^3,4,10,12,13,14,15\) and age.\(^3,5,10,12,13,14,15\) It also demonstrates the significance of both post-admission stroke and fever in outcome prediction.

In the present study, the occurrence of post-admission stroke increases the proportion of unfavorable neurologic outcome in aneurysmal SAH patients originally presenting with favorable admission neurological grades by 30%. In our prior analysis of the Tirilazad database, multivariable logistic regression analysis demonstrated that post-admission stroke increases the odds of poor neurological outcome in aneurysmal SAH patients by four fold (OR: 4.03, 95% CI: 2.11–7.69, \(P < 0.01\)). Patients experiencing vasospasm are at an increased risk of post-admission strokes. In addition, several secondary injury cascade events may predispose these patients to post-admission strokes. In addition, several secondary injury cascade events may predispose these patients to post-admission strokes, including: (1) Microthrombi formation, (2) cortical spreading depression, (3) microvascular constriction, (4) proliferation of pro-inflammatory cascade, (5) presence of blood–brain barrier disruption, and (6) inadequate collateral circulation.\(^7,9\) Several contemporary neurocritical care strategies are used to decrease the likelihood of post-admission strokes. They include: (1) The use of milrinone, an inotropic vasodilator with anti-inflammatory properties, to prevent and treat vasospasm, (2) early decompressive craniectomy in patients with refractory increased intracranial pressures associated with cerebral edema, and (3) monitoring and treating seizures.

Fever is often a clinical indicator of neurological deterioration because it also triggers events in the secondary cascade of neurological injury. An epileptic aneurysmal SAH patient who develops post-admission fever has an increased odds of poor outcome by a factor of 2.4 (OR: 2.4, 95% CI: 1.86–3.06, \(P < 0.01\)). The various causes of post-admission late onset fevers, including nosocomial infections, central neurological injury, thromboembolic events, and drug–drug interactions, can also lead to neurological complications, including increased intracranial pressures, cerebral edema, and post-admission strokes.\(^7,9\) The occurrence of fever at 1 week post-hospital admission is associated with increased odds of post-admission strokes (OR: 1.83, 95% CI: 1.56–2.15, \(P < 0.01\)), including vasospasm-induced delayed strokes. Aggressive symptomatic control and rigorous search for underlying etiology are, therefore, warranted.

Limitations

The decision tree algorithm presented in this study was created using the Tirilazad database whereby prospective data was gathered to test an intervention, rather than for clinical prognostic purposes. Since the conduct

| Admission neurological grade | Age=58.5 years | Post-admission fever | Post-admission stroke | Unfavorable outcome (%) | Unfavorable outcome category |
|------------------------------|----------------|----------------------|-----------------------|-------------------------|-----------------------------|
| Poor Old-- | Present | Present | 75.9 | >75% very high |
| Poor Older | Present | Present | 73.6 | 50-75% high |
| Poor Younger | Present | Present | 66.9 | |
| Good Older | Present | Present | 63.2 | |
| Poor Older | Present | Absent | 56.6 | |
| Poor Younger | Present | Absent | 55.4 | |
| Good Older | Absent | Present | 44.0 | 25-50% intermediate |
| Poor Older | Absent | Absent | 41.5 | |
| Good Younger | Present | Present | 39.0 | |
| Poor Younger | Present | Absent | 39.0 | |
| Good Younger | Absent | Present | 25.7 | |
| Good Older | Present | Absent | 18.5 | <25% low |
| Poor Younger | Absent | Absent | 17.4 | |
| Good Older | Absent | Absent | 14.3 | |
| Good Younger | Present | Absent | 7.9 | |
| Good Younger | Absent | Absent | 2.0 | |
of the clinical trials of Tirilazad, there have been advances in the surgical treatment and neurocritical care management of aneurysmal SAH patients. Despite variations in management at different centers, terminal prognostic subgroups depicted remain clinically relevant in a contemporary setting because they encompass frequently encountered factors including neurological grade, age, post-admission stroke, and fever. In this study, split validation technique was used to enhance model generalizability. Further investigations can make use of the classification and regression technique with external patient cohorts to further examine model generalizability.

**CONCLUSIONS**

Clinical outcome after aneurysmal SAH may be influenced by interactions among a number of brain–body associations. Classification tree algorithm serves as a useful tool for prognostic decision making. The prognostic subgroups demonstrated the interplay of various underlying pathophysiologic mechanisms which, together, may adversely influence long-term neurologic outcome after aneurysmal SAH.

The classification tree generated in this article increases clinician and patient family awareness of the various demographic, neurologic, and systemic prognostic factors, which are pertinent for initial prognostication, namely, admission neurological grade and patient age. It also alerts the clinician regarding two important brain–body associations, including the occurrence of fever and delayed strokes, which may arise during hospitalization severely affecting patient outcomes. The clinician is, then, encouraged to tailor various treatment efforts to prevent and treat these, as well as other alterations in the brain–body interface in order to maximize the chances of survival and recovery after aneurysmal subarachnoid hemorrhage.

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**Conflicts of interest**

There are no conflicts of interest.

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