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Chapter 9

Clinical Outcome Prediction Using Bayesian Regression and Artificial Neural Networks

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Abstract

The goal of this chapter is to use a combination of traditional and Bayesian logistic regression, as well as artificial neural networks for clinical outcome prediction. Using the example of ruptured brain aneurysms, this chapter provides novel insights on specific brain-body interactions that are essential in influencing outcome in patients with ruptured brain aneurysms. Thus far, there is scarce existing literature on such important relationships. The multicenter Tirilazad database (3550 patients) was used to create this clinical outcome prediction model in order to elucidate significant brain-body interactions. Traditional logistic regression main effects model included five statistically significant single prognostic variables, namely, neurological grade, age, diastolic blood pressure, time to surgery and stroke. Logistic regression models found the significance of liver disease and hypertension in development of brain swelling, and the negative consequences of seizures in those with history of myocardial infarction and post admission fever worsening neurological outcome. Bayesian logistic regression using informative prior probability likelihoods detected a number of prognostic factors that may play a role in multiplicative interaction effects, as well as possible heterogeneity in patient subgroups. An artificial neural networks model, with similar model discrimination values as traditional logistic regression model, was created to explore the influence of non-linear relationships on the importance of prognostic factors.

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Part One – Introduction

Ruptured Brain Aneurysms and Aneurysmal Subarachnoid Hemorrhage

Patients with ruptured brain aneurysms and associated subarachnoid hemorrhage have a mortality rate of at least 45% in the first month after rupture [1-7]. Neurological damage can be from the primary injury of the aneurysm rupture itself and a number of secondary injurious processes that can further worsen the affected individual's neurological state. These secondary processes can be related to the nervous system, such as rebleeding from the ruptured aneurysm, brain swelling, occurrence of a delayed second stroke, brain blood vessel vasospasm leading to strokes, seizures and overaccumulation of brain-spinal fluid causing hydrocephalus [1-7]. In addition, other body organ systems can be affected, such as myocardial infarction, fever and overaccumulation of fluid in the lungs causing pulmonary edema. Together, these processes can lead to long term disability. Types of disability include physical, neurocognitive and psychological impairment.

The Tirilazad Database

Tirilazad was a 21-aminosteroid compound produced by Pharmacia and Upjohn, Kalamazoo, Michigan. It was originally investigated as a free radical scavenger for the potential treatment of cerebral vasospasm [8-12]. Between 1991 and 1997, 3550 patients from 162 centers in 21 countries in Europe, Australia, North America and Africa participated in five randomized, double-blind, placebo-controlled trials of Tirilazad [8-12].

Included patients were adults, with evidence of aneurysmal subarachnoid hemorrhage. The patients received either placebo or active agent (in intravenous doses of 0.6, 2, 6 or 15 mg/kg/day depending on the trial) from the third to tenth day after subarachnoid hemorrhage onset [8-12]. Excluded patients were: (1) those with traumatic subarachnoid hemorrhage, (2) infectious mycotic aneurysm, (3) severe underlying medical illness including serious cardiovascular disease, such as myocardial infarction within 6 months, uncontrolled hypertension, serious cardiac arrhythmia or congestive heart failure, (4) pregnant or lactating patients, (5) patients taking corticosteroids or calcium channel blockers other than nimodipine, (6) known intolerance to calcium channel blockers, and (7) patients whose aneurysms were treated with Gulielmi or other detachable coils [8-12].

Patients in the placebo and treatment arms were treated similarly. Over 85% of patients underwent surgical clipping (rather than coiling), and half of them were operated within the first 48 hours. Baseline demographics in both arms were balanced in terms of sex, age, number of pre-existing medical conditions, mean time to treatment, mean admission systolic blood pressure, admission neurological grade, ruptured aneurysm location, admission amount of blood. Potential confounders were accounted for in statistical analysis. Percentages of patients experiencing neurological and systemic disabilities were similar in different treatment groups [8-12].

Only one percent of patients was lost to follow up. The primary outcome measures were the patient's Glasgow Outcome Score at 3 months after aneurysm rupture. Glasgow Outcome Score is a 5-point scale, defined as: 5 – good recovery with normal life activities despite

minor deficits, 4 – moderate disability being disabled but independent, 3 – severe disability being conscious but dependent, 2 – persistent vegetative state, and 1 – death [13].

Two systematic reviews [14,15] on the five trials of Tirilazad found no substantial heterogeneity among these trials and no significant differences in the: (1) number of patients who died between treatment and placebo arms, (2) number of adverse events between the two arms, and (3) outcomes among patients who were administered different dosages of Tirilazad.

Overview of Chapter

Part Two demonstrates creation of a clinical outcome prediction model using traditional logistic regression. In our clinical example of aneurysmal subarachnoid hemorrhage, it provides novel insight on clinical prediction factors, as well as significant brain-body interactions. Multivariable binary logistic regression model will be used. Novel significant brain-body axes will be noted. They play key roles in the clinical deterioration of patients with ruptured brain aneurysms. Based on the authors' clinical expertise in neurosurgery and critical care medicine, these epidemiologic findings will be correlated to underlying pathophysiologic mechanisms.

Part Three demonstrates how Bayesian analysis and artificial neural networks can be used in a complementary way to explore findings from traditional logistic regression. Bayesian regression makes use of informative prior probability likelihoods based on the authors' shared clinical experience. The entire patient population as well as subgroups will be investigated to note any differences in odds ratios of individual prognostic variables among these groups. Furthermore, a novel artificial neural networks model will be designed to examine whether its results will complement or differ from those generated by traditional logistic regression, with consideration of possible non-linear interactions.

Part Four summarizes chapter findings and discusses future directions.

Part Two – Clinical Outcome Prediction Using Traditional Logistic Regression

Objectives

In this part, we aim to create a clinical outcome prediction model using traditional binary logistic regression. In our clinical example of aneurysmal subarachnoid hemorrhage, we aim to investigate the potential factors for outcome prediction in patients with ruptured brain aneurysms.

Methods

Using the Tirilazad database, the identified independent variables included:

1. patient's neurological grade at hospital admission,

2. age (in years),
3. sex,
4. patient's weight (kg),
5. aneurysm size (mm),
6. presence of vasospasm at the time of hospital admission as noted on the admission angiogram (admission vasospasm),
7. presence of hemorrhage within the brain's ventricles (intraventricular hemorrhage),
8. presence of blood clot within the brain at the time of hospital admission (intracerebral hematoma),
9. location of aneurysm (anterior or posterior circulation in the brain),
10. thickness of subarachnoid hemorrhage (thin as 1 mm or less of blood clot, thick as more than 1 mm of blood clot),
11. systolic blood pressure on admission (mmHg),
12. diastolic blood pressure on admission (mmHg),
13. temperature on admission (degree Celsius),
14. occurrence of fever one week after hospital admission,
15. presence of prior episode of subarachnoid hemorrhage,
16. history of migraines,
17. history of hypertension,
18. history of angina,
19. history of myocardial infarction,
20. history of diabetes mellitus,
21. history of hepatic disease,
22. history of thyroid disease,
23. time to surgical treatment (hours),
24. treatment arm (investigational agent Tirilazad versus placebo),
25. development of hydrocephalus,
26. development of brain swelling (cerebral edema),
27. occurrence of stroke post admission,
28. development of vasospasm during course of treatment,
29. development of severe vasospasm requiring balloon angioplasty to dilate constricted vessels,
30. development of seizures requiring use of anti-seizure medication, and
31. development of fluid accumulation in the lungs (pulmonary edema) after admission.

The dependent variable used for analysis is the dichotomized Glasgow Outcome Score at three months. Good outcome represents functional independence (GOS 5 and GOS 4). Poor outcome represents functional dependence (GOS 3), persistent vegetative state (GOS 2) or death (GOS 1).

Using IBM SPSS Version 19.0™, independent variables were entered into univariate models in which chi square analyses were used to investigate for associations with poor neurologic outcome. Two-way interaction terms that included brain and body (systemic) prognostic factors were examined. Variables that reached a probability of 0.10 were then entered into a multivariable binary logistic regression model. Significance of this model was set at a probability of 0.05. In both our univariate and multivariable binary logistic models, there were at least 10 to 15 subjects per independent variable. In the multivariable logistic

regression model, both independent risk factors as well as two-way interaction terms were investigated for their cumulative predictor effects for poor neurologic outcome. In addition, the following diagnostics were performed:

1. correlation matrix to rule out multicollinearity among predictor variables,
2. Hosmer and Lemeshow test to ensure good data fit to model and model calibration,
3. c statistic and classification to examine model discrimination, and
4. split sample analysis (70% training and 30% testing) to examine model generalizability [16].

Results

Correlation matrix of the included 31 independent variables was examined to ensure that there were no correlated variables. Single prognostic variables found to be statistically significant in univariate analyses included the following: (1) neurological grade, (2) age, (3) time to surgical treatment, (4) presence of fever one week post admission, (5) aneurysm size, (6) angiographic vasospasm on admission, (7) presence of intraventricular hemorrhage, (8) development of cerebral edema, (9) presence of intracerebral hematoma, (10) history of hypertension, (11) history of myocardial infarction, (12) development of stroke post admission, (13) history of previous episode of subarachnoid hemorrhage, (14) location of aneurysm, (15) development of vasospasm, and (16) development of seizures requiring use of anti-epileptic medications.

Interaction terms found to be statistically significant in univariate analyses included the following: (1) fever by aneurysm size, (2) fever by intraventricular hemorrhage, (3) fever by seizures, (4) intraventricular hemorrhage by aneurysm size, (5) hepatic disease by brain edema, (6) hypertension by brain edema, (7) hepatic disease by hydrocephalus, (8) hydrocephalus by aneurysm size, (9) myocardial infarction by blood clot thickness, (10) seizures by myocardial infarction, and (11) seizures by aneurysm size.

The above significant single prognostic variables and interaction terms were entered into a multivariable binary logistic regression model. The final model comprised 5 significant single prognostic variable terms and 4 significant interaction terms.

Statistically significant terms in the final model are shown below.

The Omnibus Tests of Model Coefficients indicated that this model was statistically significant (chi square = 887.9, $p < 0.001$). This model showed a large significant reduction in -2 log likelihood (-2LL from 2240 to 1699, $p < 0.001$). Nagelkerke R Square statistic indicated that approximately 47% of the variance in poor neurologic outcome could be predicted from the combination of the significant terms. In terms of model discrimination (Figure 1), the c statistic was 0.87 (95% confidence interval of 0.86-0.89).

Classification Table indicated that 84% of subject outcomes were predicted correctly. In terms of model calibration, the Hosmer and Lemeshow test showed a chi square of 11.38, $p = 0.181$, suggesting that the model appeared to fit the data reasonably well. Generalizability of model findings was supported by split sample validation (70% training, 30% testing), whereby the following criteria were met: (1) no multicollinearity (standard errors less than 2 for significant terms), (2) classification accuracy (84.5%) was greater than 1.25 times chance accuracy (82.5%), (3) individual relationship Wald statistic significance less than alpha level

of 0.05, and (4) classification accuracy rate for training sample was 84.5%, whereas classification accuracy rate for testing sample was 82.5%, both satisfying minimum requirement for holdout sample (0.9*84.5%=76%).

Variable	β coefficient	Standard Error	Odds Ratio (e^{β})	95% Confidence Interval	Significance (p value)
Neurological Grade	0.72	0.06	2.06	1.83-2.32	<0.001
Age (per year) [For every Δ5 years]	0.05 [0.25]	0.005	1.06 [1.28]	1.05-1.07 [1.22-1.42]	<0.001
Diastolic Blood Pressure (mmHg) [For Δ5 mmHg]	0.01 [0.05]	0.004	1.01 1.05	1.00-1.02 [1.05-1.10]	0.02
Time to Surgery (hour)	0.01	0.004	1.01	1.00-1.02	0.02
Stroke	1.39	0.33	4.03	2.11-7.69	<0.001
Seizures by Fever on Day 8	0.87	0.13	2.39	1.86-3.06	<0.001
Brain Edema by Hepatic Disease	1.70	0.80	5.47	1.13-26.46	0.03
Brain Edema by Hypertension	0.98	0.26	2.66	1.59-4.45	<0.001
Seizures by Myocardial Infarction	1.12	0.41	3.05	1.35-6.87	0.007

Interpretation of Results

There has been scarce epidemiologic literature to attempt to characterize complex brain-body interactions in those with ruptured brain aneurysms. Our analyses included both non-treatment and treatment related prognostic factors, as well as significant two-way interactions that captured clinically relevant brain-body associations in aneurysmal subarachnoid hemorrhage. Traditional significant prognostic variables including stroke, neurological grade and age were confirmed through the main effects logistic regression model.

In patients with ruptured brain aneurysms, excessive activation of the sympathetic nervous system as well as systemic inflammatory response can lead to deleterious effects on the internal regulatory mechanisms of multiple organ systems [17-22]. These body systems include the cardiovascular, pulmonary, temperature regulation, immune and neuro-gut axes. Overstimulation of the insular cortex and amygdala of the dominant brain can trigger both seizures and cardiac arrhythmias. This epidemiologic study confirms the negative effects of the combination of seizures and history of cardiovascular disease (in the form myocardial injury) on neurologic outcome (OR 3.05, 95% CI 1.35-6.87, p=0.007).

Excessive activation of the sympathetic nervous system also leads to a surge of catecholamine release. This catecholamine surge acts on the postganglionic fibers to the heart and blood vessels. In turn, autonomic control over blood pressure regulation and vascular resistance is lost [1-7,17-22]. Disrupted blood brain barrier is the end result as fluid and

proteins leak into worsening areas of brain edema [1-7,17-22]. Epidemiologically, our database captured the interdependent brain-body association of the development of brain edema in those with hypertension. Specifically, in those with poorly controlled blood pressure who develop brain swelling as a result of ruptured brain aneurysms, the odds ratio of poor neurologic outcome is 2.66 (95% CI 1.59-4.45, p<0.001).

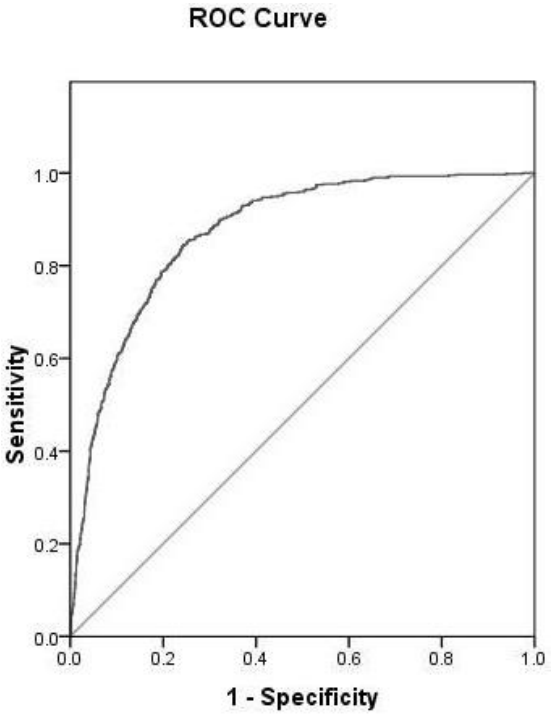

Figure 1. ROC curve to analyze binary logistic regression model discrimination. Output figure generated by IBM SPSS Version 19.0™ (Armonk, NY).

Fevers markedly increase cerebral metabolic rate and can worsen secondary injurious processes in the brain, such as brain swelling [1-7,17-22]. They must be recognized in a timely fashion and treated aggressively. Early onset fevers can be secondary to dysfunction of the temperature regulation centers in the hypothalamus [21]. Late onset fevers are more likely to be infectious, but can include fevers secondary to drugs and pulmonary embolism [17-22]. In those with fever at one week after aneurysm rupture and seizures, the odds ratio for poor neurologic outcome can be as high as 2.39 fold (95% CI 1.86-3.06, p<0.001).

Original insights are given in this chapter to attempt to delineate the significance of hepatic component of the neuro-gut axis in influencing neurologic outcome in aneurysmal subarachnoid hemorrhage. Through our epidemiologic data, we propose that liver disease can lead to significantly worse neurologic outcome via the development of brain swelling. Scarce published literature on this area captures the incidence of hepatic failure at 1.9% after aneurysmal subarachnoid hemorrhage [1,17]. Yet, the incidence of hepatic enzyme elevation is common in patients with ruptured brain aneurysms, and can be as high as 24% [1,17]. Possible liver dysfunction related mechanisms on neurologic outcome include: (1) altered

blood flow to the brain, (2) release of chemicals which are toxic to the nervous system, (3) altered blood clotting cascade, and (4) overall systemic inflammatory states [1, 17].

In systemic inflammatory states after aneurysm rupture, inflammatory markers are released (such as cytokines, leukotrienes, prostaglandins and endothelins) [1-7, 17-22]. These chemicals interfere with the liver's ability to remove neurotoxic substances from blood [1-7, 17-22]. In turn, these neurotoxic substances (such as glutamate, manganese, mercaptans and ammonia) can leak across the disrupted blood brain barrier [1-7, 17-22]. This is especially common in those with alcoholic liver disease [1-7, 17-22]. The end result is a viscous cycle of neuron swelling and death, marked increase in brain blood flow (cerebral hyperemia) and brain swelling (cerebral edema) [1-7, 17-22]. In those with chronic liver disease, there are usually states of decreased cerebral blood flow because of blood shunting into the liver's portal circulation [1-7, 17-22]. However, rupture of brain aneurysms can predispose these patients to decompensated states with acute marked increases in brain blood flow (luxuriant perfusion) and decreased differences in the oxygen content between the arterial blood vessels and jugular veins [1-7, 17-22]. As shown in this epidemiologic study, development of brain swelling in the face of liver disease may predispose the aneurysmal subarachnoid hemorrhage patient to poor neurologic outcome by 5.5 fold, and can be as high as 26 fold (OR 5.47, 95% CI 1.13-26.46, p=0.03).

Limitations and Future Directions

Further delineation can be done in future studies to investigate the impact of other body systems, such as the kidney and immune systems, on neurologic outcome. Furthermore, the Tirilazad database did not capture some important variables, such as smoking and alcohol consumption.

In the next section of this chapter, informative prior probability likelihoods will be incorporated in Bayesian logistic regression analysis to investigate their effects on the odds ratios of prognostic variables on the entire group and subgroups of Tirilazad trial patients. In addition, an artificial neural networks model will be designed to examine whether its results will complement or differ from those generated by traditional logistic regression model, with consideration of possible non-linear interactions.

Part Three – Comparative Analyses Using Bayesian Regression and Artificial Neural Networks

Objectives

In this part, we aim to perform a comparative analysis of prognostic factors in aneurysmal subarachnoid hemorrhage using Bayesian logistic regression and artificial neural networks, with results generated from frequentist logistic regression. Informative prior probability likelihoods will be incorporated in Bayesian logistic regression analysis to investigate their effects on the odds ratios of prognostic variables on the entire group and

subgroups of Tirilazad trial patients. In addition, an artificial networks model will be designed to examine whether its results will complement or differ from those generated by frequentist logistic regression model, with consideration of possible non-linear interactions.

Methods

Our analyses made use of the Tirilazad database, as well as the same independent and dependent variables as those from the previous section. To explore clinical prognostic factors for aneurysmal subarachnoid hemorrhage, the following statistical analyses were performed:

1. Bayesian logistic regression with WinBUGS 1.4.3, on both the entire patient population and 5 subgroups of 710 patients. Informative priors, odds ratios for each independent variable were estimated to lie between 0.01 and 100, with mean of 1 and precision of 0.189. Two chains of initial values were used, with 1000 iterations as burn-in and 100,000 total iterations. Convergence diagnostics were examined [23-28].
2. Artificial neural networks with IBM SPSS Version 19.0™, using 3 partitions for split sample validation technique (60% training, 20% testing and 20% holdout). Model discrimination was examined with the c statistic. The most robust clinical prediction model was presented with estimates of the relative importance of each prognostic variable [29-32].

Results

Bayesian Logistic Regression

Bayesian logistic regression made use of informative priors, with odds ratios for each independent variable estimated to lie between 0.01 and 100, with mean of 1 and precision of 0.189. The final Bayesian logistic regression model took into account Markov Chain Monte Carlo (MCMC) sampling. That is, Markov chains were used to generate Monte Carlo samples from probability distributions. In order to ensure that the resultant chain was a representative sample from the distributions, two chains of initial values were used with 1000 iterations used as burn in, with a total of 100 000 iterations. Kernel density probability distributions were smooth in contour. They represented posterior probability distributions for beta coefficients of clinical prognostic variables. Brooks-Gelman-Rubin (BGR) diagnostics showed that the two chains converged, thus, ensuring that sampling was from the same distribution as convergence occurred. Auto correlation plots showed that beta coefficients for age, diastolic blood pressure, systolic blood pressure, temperature and weight did not demonstrate rapid drop off, demonstrating correlation of simulation values to previous values for beta coefficients of these variables. Comparison of Bayesian and frequentist logistic regression results is demonstrated below.

Comparison of Bayesian and Frequentist Logistic Regression Results

Neurological Grade

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.84, 1.72-1.98
GROUP 1 (1-710):	1.83, 1.54-2.18
GROUP 2 (711-1420):	1.77, 1.53-2.07
GROUP 3 (1421-2130):	2.03, 1.72-2.41
GROUP 4 (2131-2840):	2.08, 1.74-2.51
GROUP 5 (2841-3550):	1.91, 1.63-2.25
Frequentist Logistic Regression:	2.06, 1.83-2.32, **p < 0.001**

Age (years)

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.04, 1.03-1.05
GROUP 1 (1-710):	1.04, 1.02-1.06
GROUP 2 (711-1420):	1.03, 1.02-1.05
GROUP 3 (1421-2130):	1.04, 1.03-1.07
GROUP 4 (2131-2840):	1.05, 1.03-1.07
GROUP 5 (2841-3550):	1.05, 1.03-1.07
Frequentist Logistic Regression:	1.06, 1.05-1.07, **p < 0.001**

Diastolic blood pressure on admission (mmHg)

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.00, 1.00-1.01
GROUP 1 (1-710):	1.01, 1.00-1.03
GROUP 2 (711-1420):	1.00, 0.98-1.02
GROUP 3 (1421-2130):	1.01, 1.00-1.03
GROUP 4 (2131-2840):	1.00, 0.98-1.01
GROUP 5 (2841-3550):	0.99, 0.97-1.01
Frequentist Logistic Regression:	1.00, 0.99-1.01, p=0.42

Systolic blood pressure on admission (mmHg)

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.00, 1.00-1.01
GROUP 1 (1-710):	0.99, 0.98-1.00
GROUP 2 (711-1420):	1.01, 1.00-1.02
GROUP 3 (1421-2130):	1.01, 1.00-1.02
GROUP 4 (2131-2840):	1.01, 1.00-1.02
GROUP 5 (2841-3550):	1.02, 1.00-1.03
Frequentist Logistic Regression:	1.00, 0.99-1.01, p=0.27

Temperature on admission (degrees Celsius)

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.11, 0.96-1.26

GROUP 1 (1-710):	1.03, 0.83-1.25
GROUP 2 (711-1420):	1.08, 0.82-1.38
GROUP 3 (1421-2130):	1.14, 0.90-1.44
GROUP 4 (2131-2840):	1.24, 0.99-1.69
GROUP 5 (2841-3550):	1.25, 0.96-1.68
Frequentist Logistic Regression:	1.08, 0.93-1.24, p=0.32

Time to surgical treatment (hours)

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.00, 1.00-1.00
GROUP 1 (1-710):	1.00, 1.00-1.01
GROUP 2 (711-1420):	1.00, 1.00-1.00
GROUP 3 (1421-2130):	1.00, 1.00-1.00
GROUP 4 (2131-2840):	1.00, 0.99-1.00
GROUP 5 (2841-3550):	1.00, 1.00-1.00
Frequentist Logistic Regression:	1.01, 1.00-1.01, **p=0.03**

Weight (kg)

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.00, 1.00-1.00
GROUP 1 (1-710):	1.00, 0.99-1.02
GROUP 2 (711-1420):	0.97, 0.95-0.99
GROUP 3 (1421-2130):	1.00, 1.00-1.02
GROUP 4 (2131-2840):	0.99, 0.98-1.01
GROUP 5 (2841-3550):	0.98, 0.97-1.00
Frequentist Logistic Regression:	0.99, 0.98-1.00, p=0.07

Presence of fever one week post admission

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.10, 0.92-1.33
GROUP 1 (1-710):	1.20, 0.76-1.89
GROUP 2 (711-1420):	1.00, 0.67-1.50
GROUP 3 (1421-2130):	0.99, 0.65-1.53
GROUP 4 (2131-2840):	1.64, 1.07-2.53
GROUP 5 (2841-3550):	0.82, 0.54-1.26
Frequentist Logistic Regression:	1.94, 1.51-2.49, **p<0.001**

Aneurysm size (mm)

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.34, 1.10-1.64
GROUP 1 (1-710):	1.31, 0.78-2.19
GROUP 2 (711-1420):	1.02, 0.67-1.55
GROUP 3 (1421-2130):	1.34, 0.83-2.16
GROUP 4 (2131-2840):	1.18, 0.73-1.90
GROUP 5 (2841-3550):	**2.20, 1.41-3.41**

Frequentist Logistic Regression: 1.37, 1.04-1.80, **p=0.02**

History of angina

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.13, 0.69-1.82
GROUP 1 (1-710): 1.14, 0.38-3.31
GROUP 2 (711-1420): 1.53, 0.40-5.69
GROUP 3 (1421-2130): 0.85, 0.29-2.28
GROUP 4 (2131-2840): 1.10, 0.43-2.79
GROUP 5 (2841-3550): 3.14, 0.72-14.06
Frequentist Logistic Regression: 1.13, 0.58-2.21, p=0.72

Presence of angiographic vasospasm on admission

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.54, 1.16-2.05
GROUP 1 (1-710): 0.68, 0.31-1.41
GROUP 2 (711-1420): 1.50, 0.81-2.74
GROUP 3 (1421-2130): **2.52, 1.34-4.78**
GROUP 4 (2131-2840): **2.58, 1.31-5.10**
GROUP 5 (2841-3550): 1.22, 0.62-2.39
Frequentist Logistic Regression: 1.54, 1.04-2.30, **p=0.03**

Presence of intraventricular hemorrhage on admission

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.50, 1.25-1.81
GROUP 1 (1-710): 1.24, 0.81-1.91
GROUP 2 (711-1420): **2.27, 1.50-3.44**
GROUP 3 (1421-2130): **1.88, 1.22-2.92**
GROUP 4 (2131-2840): 1.16, 0.74-1.81
GROUP 5 (2841-3550): 1.26, 0.83-1.92
Frequentist Logistic Regression: 1.33, 1.02-1.73, **p=0.04**

Development of cerebral edema

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.86, 1.42-2.42
GROUP 1 (1-710): 1.96, 1.16-3.32
GROUP 2 (711-1420): 1.29, 0.71-2.34
GROUP 3 (1421-2130): **2.78, 1.44-5.42**
GROUP 4 (2131-2840): 1.98, 0.97-4.03
GROUP 5 (2841-3550): **2.71, 1.40-5.28**
Frequentist Logistic Regression: 1.84, 1.29-2.62, **p<0.001**

History of diabetes mellitus

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.45, 0.94-2.24

GROUP 1 (1-710):	0.81, 0.30-2.08
GROUP 2 (711-1420):	2.28, 0.84-6.27
GROUP 3 (1421-2130):	1.36, 0.47-3.78
GROUP 4 (2131-2840):	2.32, 0.81-6.71
GROUP 5 (2841-3550):	1.71, 0.62-4.82
Frequentist Logistic Regression:	1.00, 0.99-1.01, p=0.42

Presence of intracerebral hematoma on admission

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.35, 1.09-1.65
GROUP 1 (1-710):	0.92, 0.53-1.56
GROUP 2 (711-1420):	1.23 0.79-1.91
GROUP 3 (1421-2130):	1.78, 1.10-2.88
GROUP 4 (2131-2840):	1.03, 0.61-1.73
GROUP 5 (2841-3550):	1.97, 1.25-3.12
Frequentist Logistic Regression:	1.39, 1.04-1.87, **p=0.03**

History of hepatic disease

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.17, 0.75-1.79
GROUP 1 (1-710):	1.39, 0.46-3.78
GROUP 2 (711-1420):	0.84, 0.26-2.39
GROUP 3 (1421-2130):	1.18, 0.43-2.95
GROUP 4 (2131-2840):	1.29, 0.49-3.30
GROUP 5 (2841-3550):	1.08, 0.40-2.74
Frequentist Logistic Regression:	1.76, 0.90-3.45, p=0.10

Development of hydrocephalus

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.68, 1.45-1.95
GROUP 1 (1-710):	1.40, 0.97-1.99
GROUP 2 (711-1420):	1.90, 1.36-2.66
GROUP 3 (1421-2130):	1.49, 1.04-2.13
GROUP 4 (2131-2840):	**2.09, 1.48-2.96**
GROUP 5 (2841-3550):	1.56, 1.09-2.21
Frequentist Logistic Regression:	0.95, 0.73-1.23, p=0.68

History of hypertension

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.62, 1.38-1.89
GROUP 1 (1-710):	1.74, 1.22-2.48
GROUP 2 (711-1420):	1.80, 1.26-2.57
GROUP 3 (1421-2130):	1.43, 0.98-2.09
GROUP 4 (2131-2840):	1.52, 1.06-2.18
GROUP 5 (2841-3550):	**2.00, 1.36-2.94**

Frequentist Logistic Regression: 1.37, 1.05-1.79, **p=0.02**

History of myocardial infarction

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.76, 1.06-2.89
GROUP 1 (1-710): 2.10, 0.76-5.75
GROUP 2 (711-1420): 0.92, 0.15-4.40
GROUP 3 (1421-2130): **2.52, 1.02-6.39**
GROUP 4 (2131-2840): 2.32, 0.81-6.90
GROUP 5 (2841-3550): 1.00, 0.15-6.07
Frequentist Logistic Regression: 2.07, 1.01-4.27, **p=0.05**

Occurrence of stroke post admission

Bayesian Logistic Regression:
ALL (1-3552): Exp(B) 6.14, 5.08-7.44
GROUP 1 (1-710): **10.74, 6.86-17.13**
GROUP 2 (711-1420): **7.20, 4.63-11.4**
GROUP 3 (1421-2130): 5.38, 3.48-8.46
GROUP 4 (2131-2840): **7.70, 4.92-12.30**
GROUP 5 (2841-3550): 5.40, 3.50-8.48
Frequentist Logistic Regression: 4.03, 2.11-7.69, **p<0.001**

Development of pulmonary edema post admission

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.00, 0.77-1.29
GROUP 1 (1-710): 1.26, 0.81-1.94
GROUP 2 (711-1420): 1.12, 0.51-2.35
GROUP 3 (1421-2130): 0.77, 0.39-1.45
GROUP 4 (2131-2840): 1.13, 0.62-2.03
GROUP 5 (2841-3550): **2.74, 1.07-7.11**
Frequentist Logistic Regression: 0.83, 0.56-1.23, p=0.37

History of migraines

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)0.74, 0.61-0.89
GROUP 1 (1-710): 0.72, 0.49-1.05
GROUP 2 (711-1420): 0.71, 0.47-1.07
GROUP 3 (1421-2130): 0.86, 0.55-1.30
GROUP 4 (2131-2840): 0.81, 0.53-1.22
GROUP 5 (2841-3550): 0.85, 0.52-1.38
Frequentist Logistic Regression: 0.93, 0.70-1.25, p=0.65

Presence of previous episode of subarachnoid hemorrhage

Bayesian Logistic Regression:
ALL (1-3552): Exp(B)1.66, 1.30-2.10

GROUP 1 (1-710):	1.61, 0.85-2.94
GROUP 2 (711-1420):	**2.01, 1.17-3.42**
GROUP 3 (1421-2130):	**2.23, 1.26-3.90**
GROUP 4 (2131-2840):	1.32, 0.73-2.35
GROUP 5 (2841-3550):	1.91, 1.12-3.23
Frequentist Logistic Regression:	1.60, 1.07-2.39, **p=0.02**

Location of aneurysm

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.00, 0.96-1.01
GROUP 1 (1-710):	1.00, 0.97-1.03
GROUP 2 (711-1420):	1.25, 0.77-1.99
GROUP 3 (1421-2130):	1.04, 0.62-1.71
GROUP 4 (2131-2840):	1.12, 0.68-1.84
GROUP 5 (2841-3550):	1.48, 0.78-2.78
Frequentist Logistic Regression:	1.72, 1.18-2.51, **p=0.005**

Thickness of subarachnoid hemorrhage

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.00, 0.99-1.02
GROUP 1 (1-710):	1.00, 0.98-1.02
GROUP 2 (711-1420):	**1.64, 1.13-2.40**
GROUP 3 (1421-2130):	**2.60, 1.75-3.94**
GROUP 4 (2131-2840):	**2.82, 1.91-4.24**
GROUP 5 (2841-3550):	**2.64, 1.78-3.98**
Frequentist Logistic Regression:	1.02, 0.99-1.05, p=0.13

Sex

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.01, 0.83-1.24
GROUP 1 (1-710):	3.25, 0.04-234.39
GROUP 2 (711-1420):	2.35, 0.03-165.2
GROUP 3 (1421-2130):	1.27, 0.81-2.02
GROUP 4 (2131-2840):	0.92, 0.64-1.35
GROUP 5 (2841-3550):	1.22, 0.84-1.78
Frequentist Logistic Regression:	0.73, 0.51-1.04, p=0.09

History of thyroid disease

Bayesian Logistic Regression:	
ALL (1-3552):	Exp(B)1.10, 0.82-1.46
GROUP 1 (1-710):	1.09, 0.62-1.88
GROUP 2 (711-1420):	1.21, 0.69-2.11
GROUP 3 (1421-2130):	1.13, 0.53-2.30
GROUP 4 (2131-2840):	0.96, 0.41-2.11
GROUP 5 (2841-3550):	1.21, 0.54-2.66

Frequentist Logistic Regression: 0.98,0.62-1.54, p=0.92

Development of vasospasm during course of treatment

Bayesian Logistic Regression:

ALL (1-3552):	Exp(B)1.73, 1.47-2.04
GROUP 1 (1-710):	1.70, 1.16-2.50
GROUP 2 (711-1420):	1.80, 1.25-2.60
GROUP 3 (1421-2130):	1.82, 1.24-2.64
GROUP 4 (2131-2840):	1.17, 0.79-1.73
GROUP 5 (2841-3550):	**2.44, 1.65-3.61**
Frequentist Logistic Regression:	1.58, 1.21-2.06, **p<0.001**

Treatment Group

Bayesian Logistic Regression:

ALL (1-3552):	Exp(B)1.00, 0.96-1.04
GROUP 1 (1-710):	1.06, 0.97-1.16
GROUP 2 (711-1420):	1.05, 0.96-1.15
GROUP 3 (1421-2130):	0.88, 0.72-1.07
GROUP 4 (2131-2840):	1.18, 1.00-1.38
GROUP 5 (2841-3550):	0.95, 0.83-1.08
Frequentist Logistic Regression:	0.74, 0.48-1.13, p=0.17

Development of severe vasospasm requiring balloon angioplasty

Bayesian Logistic Regression:

ALL (1-3552):	Exp(B)1.34, 0.95-1.89
GROUP 1 (1-710):	1.71, 0.88-3.29
GROUP 2 (711-1420):	0.42, 0.10-1.50
GROUP 3 (1421-2130):	1.44, 0.68-3.03
GROUP 4 (2131-2840):	**2.27, 1.21-4.29**
GROUP 5 (2841-3550):	1.20, 0.24-5.56
Frequentist Logistic Regression:	1.31, 0.77-2.20, p=0.32

Development of seizures requiring use of anti-epileptic medications

Bayesian Logistic Regression:

ALL (1-3552):	Exp(B)1.25, 1.06-1.47
GROUP 1 (1-710):	**2.11, 1.27-3.64**
GROUP 2 (711-1420):	1.47, 1.02-2.11
GROUP 3 (1421-2130):	1.61, 1.04-2.65
GROUP 4 (2131-2840):	1.19, 0.81-1.77
GROUP 5 (2841-3550):	1.42, 1.00-2.01
Frequentist Logistic Regression:	1.68, 1.28-2.21, **p<0.001**

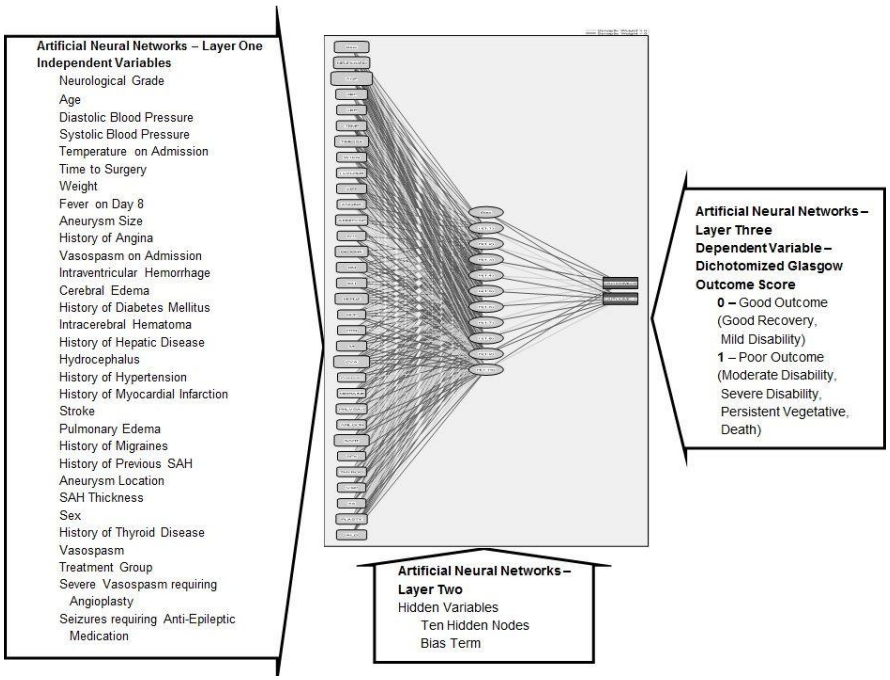

Figure 2. Artificial neural networks output using the dichotomized Glasgow Outcome Score with insets for each layer. Output figure generated by IBM SPSS Version 19.0™ (Armonk, NY).

Artificial Neural Networks

The most robust artificial neural networks for clinical prediction in aneurysmal subarachnoid hemorrhage was found using the multilayer perceptron model with 3 partitions (training sample 60%, testing sample 20%, holdout sample 20%), as shown in Figure 2.

The network architecture had 1 hidden layer and 10 latent variables. The sigmoid function was specified as the activation function from input to hidden layers, and from hidden to output layers. Training criteria made use of periodic synaptic weight optimization, with the error optimization function using gradient descent.

Training time required 53 seconds. Model classification showed 84% correct predictions in the training sample, 81% correct predictions in the testing sample and 85% correct predictions in the holdout sample. C statistic was used to examine discrimination, with area under the ROC curve being 0.870, for both favourable and unfavourable outcomes (Figure 3). The predicted-by-observed chart showed ability of the model to predict both favourable and unfavourable outcomes (Figure 4).

Variables in order of magnitude of relative importance are shown as follows:

1. age - 0.132,
2. neurological grade - 0.082,
3. occurrence of stroke post admission - 0.079,
4. thickness of subarachnoid hemorrhage - 0.069,
5. time to surgical treatment - 0.060,

6. history of hepatic disease - 0.054,
7. development of cerebral edema - 0.049,
8. presence of angiographic vasospasm on admission - 0.044,
9. diastolic blood pressure - 0.038,
10. development of severe vasospasm requiring angioplasty - 0.034,

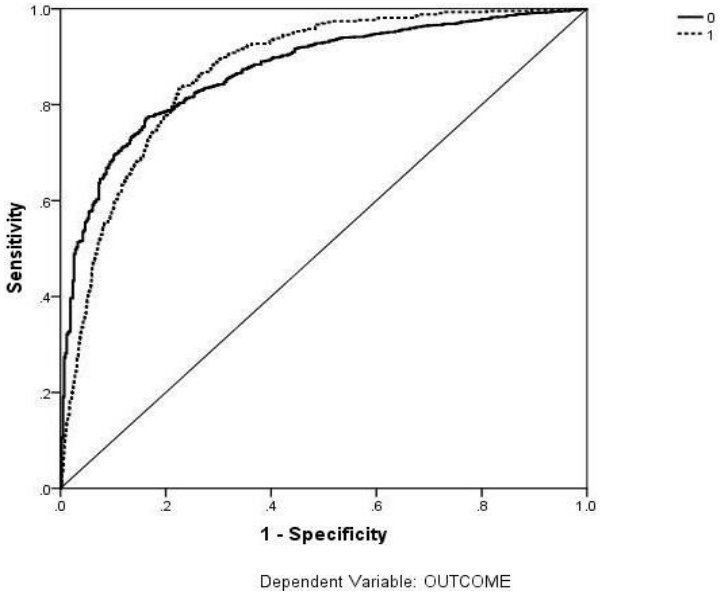

Figure 3. ROC curve to analyze model performance. Output figure generated by IBM SPSS Version 19.0™ (Armonk, NY).

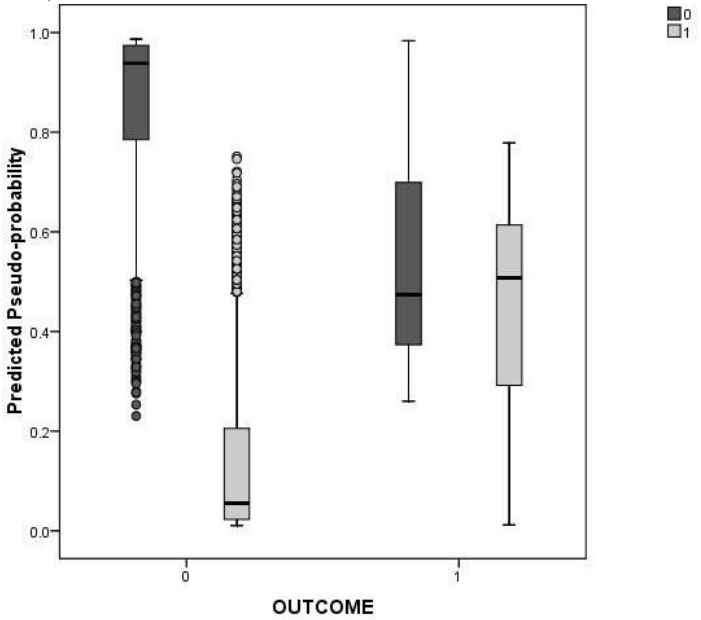

Figure 4. Predicted-by-Observed Chart showing ability to predict both favourable and unfavourable outcomes. Output figure generated by IBM SPSS Version 19.0™ (Armonk, NY).

11. presence of previous episode of subarachnoid hemorrhage - 0.032,
12. history of diabetes mellitus - 0.028,
13. temperature on admission - 0.027,
14. presence of intracerebral hematoma on admission - 0.027,
15. presence of fever one week post admission - 0.026,
16. development of seizures requiring use of anti-epileptic medications - 0.025,
17. history of myocardial infarction - 0.024,
18. aneurysm size - 0.023,
19. patient's weight - 0.021,
20. systolic blood pressure on admission - 0.021,
21. history of thyroid disease - 0.019,
22. location of aneurysm - 0.018,
23. history of angina - 0.014,
24. presence of intraventricular hemorrhage on admission - 0.011,
25. history of migraines - 0.009,
26. treatment group - 0.008,
27. development of vasospasm during course of treatment - 0.007,
28. development of pulmonary edema post admission - 0.006,
29. history of hypertension - 0.006,
30. sex - 0.006, and
31. development of hydrocephalus - 0.004.

Interpretation of Results

Comparative analyses of clinical prognostic factors for aneurysmal subarachnoid hemorrhage using Bayesian regression and artificial neural networks demonstrated that these techniques complemented results generated by frequentist logistic regression.

Bayesian Logistic Regression Analysis

Beta coefficients for prognostic variables were similar in magnitude using frequentist multivariable logistic regression and Bayesian logistic regression with informative prior likelihoods, using the entire patient population group. However, dissimilar odds ratios for patient subgroups were noted, with increased magnitudes of odds ratios for the following independent variables: (1) aneurysm size, (2) presence of angiographic vasospasm on admission, (3) presence of intraventricular hemorrhage on admission, (4) development of cerebral edema, (5) development of hydrocephalus, (6) history of hypertension, (7) history of myocardial infarction, (8) occurrence of stroke post admission, (9) development of pulmonary edema post admission, (10) previous episode of subarachnoid hemorrhage, (11) thickness of subarachnoid hemorrhage, (12) sex, (13) development of vasospasm during course of treatment, (14) development of severe vasospasm requiring balloon angioplasty, and (15) development of seizures requiring use of anti-epileptic medications.

The aforementioned observations point to different effect sizes across patient subgroups, suggesting possibility of heterogeneity in patient characteristics, multiplicative interactions between prognostic variables, as well as non-linear relationships.

In this section, Bayesian analyses carry advantages of enabling the investigator to: (1) incorporate informative prior likelihoods based on known knowledge, (2) examine effect sizes across patient subgroups, (3) hypothesize on possibility of divergent subgroups, (4) examine variability in treatment responses, and (5) examine multiplicative interaction effects between prognostic variables.

Artificial Neural Networks

The most robust artificial neural networks for clinical prediction in aneurysmal subarachnoid hemorrhage was found using the multilayer perceptron model with sigmoid activation functions, mean square error and gradient descent, with 10 latent variables in one layer. Model classification showed large percentage (84%) of correct predictions in the training sample, which is retained across the testing and holdout samples. Model discrimination value was demonstrated with area under the ROC curve being 0.870, for both favourable and unfavourable outcomes.

The ten predictors with the highest normalized importance values include age, neurological grade, occurrence of stroke post admission, thickness of subarachnoid hemorrhage, time to surgical treatment, history of hepatic disease, development of cerebral edema, presence of angiographic vasospasm on admission, diastolic blood pressure and development of severe vasospasm requiring angioplasty.

In comparison with frequentist logistic regression presented in the previous section, both models had similar model discrimination values. In general, the significant variables generated with logistic regression were similar to those from artificial neural networks. The effects of non-linear relationships were noted in the clinically robust artificial neural networks model. This resulted in a different ordering of the variables' relative importance estimates when compared with their beta coefficients from traditional logistic regression. For example, age exhibited the highest relative importance in the artificial neural networks model as the likelihood of unfavourable outcome markedly increased with age in a non-linear fashion.

In this section, artificial neural networks were shown to have the advantages of being able to take into account non-linear relationships, as well as model discrimination values that were comparable to those generated with frequentist logistic regression. However, they were shown to have the disadvantages of not being able to provide details on the various higher order interactions and specific non-linear relationships for variables. In addition, it is difficult to clinically interpret the variables' relative importance estimates.

Limitations and Future Directions

Insight gained from Bayesian analyses and artificial neural networks models may be used by the investigator in order to improve the design of the traditional logistic regression model. These techniques, therefore, play a complementary role to frequentist methods. More sophisticated models can be explored with development of more advanced statistical

softwares that can both specify and process high order interactions and non-linear relationships in Bayesian analyses and artificial neural networks. In addition, Bayesian principles can be integrated into artificial neural networks which allow investigators to incorporate prior likelihood probabilities while designing elements of a particular artificial neural network.

Part Four – Conclusion

This chapter represents the first paper to analyze both non-treatment and treatment related prognostic factors, as well as two way brain-body interactions. It provided a number of important novel findings, which are key in elucidating the mechanisms of neurological deterioration in aneurysmal subarachnoid hemorrhage patients. This is also the first paper to elucidate epidemiologic links of brain interactions across multiple organ systems, namely: (1) the neuro-gut and cardiovascular axes in pathogenesis of brain edema, which can be deleterious in those with ruptured brain aneurysms, as well as (2) the cardiovascular and temperature regulation axes in combination with seizures, which can also be deleterious in those with ruptured brain aneurysms.

This chapter also used both Bayesian regression and artificial neural networks in an innovative way to complement results from frequentist logistic regression models. Using informative prior likelihoods, both entire group and subgroup analyses were performed. It is hypothesized that subgroup heterogeneity, multiplicative interactions and non-linear relationships can affect the magnitudes of odds ratios across patient subgroups. The effects of such non-linear relationships were noted in the clinically robust artificial neural networks model.

Future Directions

The techniques of frequentist logistic regression, Bayesian regression and artificial neural networks were applied to the Tirilazad database. Since the conduct of the Tirilazad trials, there have been advancements in both medical and surgical treatment of cerebral aneurysms. These include aneurysm coiling and neurocritical care of aneurysmal subarachnoid hemorrhage patients. In addition, the Tirilazad database did not capture variables such as smoking, alcohol consumption, and other systematic complications including renal and hematologic complications.

The prognostication system described in this chapter made use of a combination of techniques that are generalizable and applicable to development of clinical prediction rules in other areas of medicine. Most importantly, this chapter has detailed novel brain-body associations which significantly influence clinical outcome in aneurysmal subarachnoid hemorrhage. Recognition and treatment of these factors are essential in optimizing outcome and preventing deterioration in those with ruptured brain aneurysms.

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