The Brain-Body Interface in Aneurysmal Subarachnoid Hemorrhage –

Outcome Prognostication and Creation of Decision Making Algorithm

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A Thesis Submitted to the Graduate School of Studies in Partial

Fulfillment of the Requirements for the Degree

Doctor of Philosophy

McMaster University

Fall 2016

DOCTOR OF PHILOSOPHY (2016)　　　　　　　　　　McMaster University

(Health Research Methodology)　　　　　　　　　　Hamilton, Ontario

TITLE:　　　The Brain-Body Interface in Aneurysmal Subarachnoid Hemorrhage:

　　　　　　　Outcome Prognostication and Creation of Decision Making

　　　　　　　Algorithm

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NUMBER OF PAGES:　　　135

Abstract

Background

Aneurysmal subarachnoid hemorrhage can lead to multi-organ disturbances as a result of central and autonomic nervous system injuries. Alterations in the brain-body interface associated with this cerebrovascular disorder have significant impact on patient morbidity and mortality. Knowledge of the most pertinent brain-body associations, as well as demographic, systemic and neurological prognostic factors on hospital admission, along with their progression during hospitalization can assist the clinician and patient family in the process of treatment decision making.

Objectives

The goals of this dissertation are to:

(1) synthesize and critically appraise the methodologic quality of existing studies that derive clinical predictor tools and clinical predictors used to determine outcome prognosis in patients with aneurysmal subarachnoid hemorrhage (SAH),

(2) synthesize and critically appraise the methodologic quality of existing studies that derive pathophysiologic mechanisms of brain-body associations in aneurysmal SAH,

(3) provide new insights into the significance of brain-body associations that are essential in influencing outcome in aneurysmal SAH, and

(4) create a decision making algorithm for aneurysmal SAH patients that is useful in bedside prognostication and clinical treatment decision making.

Methods

Existing prospective and retrospective cohort studies and randomized controlled trials were included in the systematic review investigating prognostic factors and clinical prediction tools associated with determining the neurologic outcome in adults patients with aneurysmal SAH. Existing prospective and retrospective cohorts were included in the systematic review investigating the pathophysiologic mechanisms of brain-body associations in patients with ruptured brain aneurysms. The multicenter Tirilazad database (3551 patients) was used to create the aneurysmal SAH prognostic model, in order to elucidate significant brain-body associations. Traditional binary logistic regression models were used. The classification and regression tree analysis technique is applied to the multicenter Tirilazad database in order to create a decision making algorithm.

Results

Systematic review of the literature confirmed the most frequently retained clinical outcome predictors, namely, age, neurological grade, aneurysm size and blood clot thickness. Systematic review of the literature clarified currently known

pathophysiologic mechanisms of brain-body associations in aneurysmal SAH, specifically, sympathetic activation of the cardiopulmonary system with subsequent delayed activation of neuro-cardio-endocrinological responses as part of the secondary injury cascade in response to the primary ictus of aneurysmal SAH. Logistic regression models found the significance of hepatic disease and hypertension in development of brain edema, and the negative consequences of seizures in those with history of myocardial infarction and post admission fever worsening neurological outcome. A clinically useful classification and regression tree revealed prognostic subgroups with important explanatory nodes including neurological grade, age, post admission fever and post-admission stroke.

Discussion

This dissertation clarified existing information on clinical predictors and pathophysiologic mechanisms of brain-body associations in aneurysmal SAH. It also provides novel information on brain-body associations that are essential in influencing outcome in aneurysmal SAH patients despite scarce existing literature on such important relationships. A clinically useful classification and regression tree was generated to guide both bedside prognostication and clinical treatment decision making in aneurysmal SAH patients.

Conclusions

Hospital admission prognostic factors of neurological grade and age, as well as delayed disturbances in the brain-body interface have significant impact on patient outcomes in aneurysmal subarachnoid hemorrhage. During hospitalization, development of fever can be associated with seizures and occurrence of delayed strokes, development of brain edema can be associated with underlying history of hypertension and hepatic disease, while history of myocardial infarction can predispose to seizure development. Together, these multi-organ system manifestations resulting from central and autonomic nervous system disturbances as a result of aneurysmal rupture can lead to deleterious patient outcomes.

ACKNOWLEDGEMENTS

I would like to acknowledge my PhD committee members who guided me through my PhD studies, including Professors Mitchell Levine, Forough Farrohkyar and Lehana Thabane.

I would like to thank my family members who supported me through my graduate studies.

I would also like to thank my many mentors at the McMaster University, Queen's University and University of Toronto who taught me the art and science of neurosurgery and critical care medicine. I would also like to thank my current work colleagues at the Montreal Neurological Institute and overseas in Japan and Hong Kong for their support.

PREFACE

This thesis combines four separate papers that were published or in press in peer

reviewed medical journals, including:

Lo BW, Fukuda H, Nishimura Y, Farrokhyar F, Thabane L, Levine MA. Systematic review of clinical prediction tools and prognostic factors in aneurysmal subarachnoid hemorrhage. Surg Neurol Int. 2015 Aug 11;6:135.

Lo BW, Fukuda H, Nishimura Y, Macdonald RL, Farrokhyar F, Thabane L, Levine MA. Pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms: A systematic review. Surg Neurol Int. 2015 Aug 11;6:136.

Lo BW, Fukuda H, Angle M, Teitelbaum J, Macdonald RL, Farrokhyar F, Levine MA. Clinical outcome prediction in aneurysmal subarachnoid hemorrhage – alterations in brain-body interface. Surg Neurol Int. 2016 Jun (In Press).

Lo BW, Fukuda H, Angle M, Teitelbaum J, Macdonald RL, Farrokhyar F, Levine MA. Aneurysmal subarachnoid hemorrhage prognostic decision making algorithm using classification and regression tree analysis. Surg Neurol Int. 2016 Jun (In Press).

Benjamin Lo's contributions to all the papers include: (1) developing research

questions, (2) performing literature search and reviewing relevant articles, (3)

writing up research proposal, (4) statistical analysis and interpretation, and (5)

manuscript writing and revision.

The work was performed from September 2008 to December 2015.

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Chapter One – **Introduction**

Background and Rationale

Subarachnoid hemorrhage secondary to ruptured brain aneurysms can acutely affect multiple organ systems in the brain-body interface, as a consequence of both primary and secondary injuries resulting from central and autonomic nervous system disturbances. Despite advances in the surgical treatment and neurocritical care management of aneurysmal subarachnoid hemorrhage patients, this cerebrovascular disorder is associated with significant morbidity and mortality. During the clinician and patient family's treatment decision making process, an increased awareness of altered brain-body associations is essential, as these interactions have substantial impact on patient outcomes. In addition, various demographic, systemic and neurologic factors on hospital admission and during hospitalization can influence patient outcome prognostication.

Outline of Thesis

The present thesis consists of four distinct studies.

Chapter One synthesizes and critically appraises the methodologic quality of existing studies (including prospective and retrospective cohort studies and

randomized controlled trials) that derive clinical predictor tools and clinical predictors used to determine outcome prognosis in patients with aneurysmal subarachnoid hemorrhage (SAH).

Chapter Two is a synthesis and critical appraisal of cohort studies that clarify the pathophysiologic mechanisms of brain-body associations in aneurysmal SAH. It investigates how aneurysmal SAH affects the cardiopulmonary system with subsequent neuro-cardio-endocrinological responses as part of the secondary injury cascade in response to the primary ictus of aneurysmal SAH.

Chapter Three investigates the brain-body interface in aneurysmal SAH. The brain-body interface comprises many physiological interactions which can go awry in disease states. This chapter characterizes novel brain-body associations that are essential in influencing outcome in patients with ruptured brain aneurysms.

Chapter Four uses classification and regression tree analysis techniques to create a decision making algorithm for aneurysmal SAH patients for bedside prognostication and clinical treatment decision making. This algorithm sheds light on complex interactions between a number of risk factors in determining outcome after aneurysmal SAH.

Chapter Two

Systematic review of clinical prediction tools and prognostic factors in aneurysmal subarachnoid hemorrhage

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Abstract

Background

Clinical prediction tools assist in clinical outcome prediction. They quantify the

relative contributions of certain variables and condense information that identifies

important indicators or predictors to a targeted condition. This systematic review

synthesizes and critically appraises the methodologic quality of studies that

derive both clinical predictors and clinical predictor tools used to determine

outcome prognosis in patients suffering from aneurysmal subarachnoid

hemorrhage (SAH).

Methods

This systematic review included prospective and retrospective cohort studies,

and randomized controlled trials (RCTs) investigating prognostic factors and

clinical prediction tools associated with determining the neurologic outcome in

adult patients with aneurysmal SAH.

Results

Twenty-two studies were included in this systematic review. Independent,

confounding and outcome variables were studied. Methodologic quality of

individual studies was also analyzed. Included were 3 studies analyzing

databases from RCTs, 8 prospective cohort studies and 11 retrospective cohort

studies. The most frequently retained significant clinical prognostic factors for long-term neurologic outcome prediction include age, neurological grade, blood clot thickness and aneurysm size. Methodological limitations include within and between study patient heterogeneity, regional variations in treatment protocols, patient referral biases, differences in treatment and prognosis viewpoints across different cultures.

Conclusion

Systematic review of clinical prognostic factors and clinical prediction tools in aneurysmal SAH face a number of methodological challenges. Existing methodologic limitations of epidemiologic studies on outcome prognosis in aneurysmal SAH readily influence the quality of clinical insight gained in this area.

Introduction

Clinical prediction tools assist in clinical outcome prediction. This systematic review synthesizes and critically appraises methodologic quality of studies that derive both clinical predictors and clinical predictor tools used to determine outcome prognosis in patients suffering from aneurysmal SAH.

Clinical Prediction Tools

Clinical prediction tools assist in clinical outcome prediction, in establishing the likelihood of presence or absence of a condition, as well as in determining potential therapeutic courses of action. As such, they complement clinical opinion and judgment. Clinical prediction tools quantify the relative contributions of certain variables and condense information that identifies important indicators or predictors to a targeted condition[1-6,12,19,31,35,36].

Methodologic assessment of clinical prediction tools pertains to their derivation and validation. In their development, the study from which the database is developed is critiqued for its study protocol (including inclusion and exclusion criteria, setting, patient recruitment, effective power with sample size for each predictor variable, description of patient characteristics and follow-up, report and handling of missing data, and subgroup analyses), relevance of predictor

variables and outcomes studied (justification and definition of variables and outcomes used, with attention to their coding and reproducibility), and description of mathematical models (whether these models are both statistically and clinically sensible). In terms of model performance and validation, clinical prediction tools should be presented with a discussion of the types of performance measures used, as well as the types of validation used (including internal validation techniques such as data splitting, boot-strapping, and external validation techniques, like adopting the derived rules in an external population)[1-6,12,19,31,35,36].

Aneurysmal Subarachnoid Hemorrhage

Intracranial aneurysmal subarachnoid hemorrhage (SAH) affects about 45,000 individuals in North America and 600,000 individuals worldwide annually. Aneurysmal SAH is associated with a morality rate of at least 45% in the first 30 days following rupture[22]. Apart from the primary neurological injury from the aneurysmal rupture itself, other secondary injury processes can further worsen an individual's neurological condition and eventual clinical outcome. These processes include both neurological processes (such as delayed stroke, re-bleeding, brain swelling, vasospasm induced strokes, seizures and hydrocephalus) and systemic medical complications (such as myocardial infarction, fever and pulmonary edema)[13,21,22]. Together, these processes can lead to long-term disability. Types of disability include physical, neurocognitive

and psychological impairment. Long-term reductions in health-related quality of life are common, even though the case fatality of aneurysmal SAH has slowly declined due to prompt diagnosis and repair, as well as improved critical care medical management[13,21,22].

Objectives

The purpose of this systematic review is to synthesize and critically appraise methodologic quality of studies that derive both clinical predictor tools and clinical predictors used to determine outcome prognosis in patients suffering from aneurysmal SAH, with inclusion of studies with data generated from both prospective and retrospective cohort studies, and randomized controlled trials (RCTs).

Methods

This systematic review was designed based on a predefined protocol.

Study Eligibility Criteria

We included prospective and retrospective cohort studies, and RCTs investigating clinical prediction tools and prognostic factors associated with determining neurologic outcome in adult patients with aneurysmal SAH. We

excluded prognostic studies and grading schemes based on expert opinions, those for traumatic SAH and perimesencephalic SAH. Eligible studies were limited to those published from January 1, 1995 to March 31, 2014, due to differences in diagnostic modalities and treatment prior to this point.

Literature Search

Two reviewers (Benjamin Lo [BL], Hitoshi Fukuda [HF]) independently searched a number of electronic databases. Relevant studies were identified from Ovid MEDLINE, Ovid EMBASE, Web of Science, the Cumulative Index to Nursing and Allied Health Literature, without language restrictions. To include gray literature, we also searched ProceedingsFirst and PapersFirst. . We used the following search terms:

    (1) "aneurysmal subarachnoid hemorrhage" and "clinical prognosis",

    (2) "aneurysmal subarachnoid hemorrhage" and "prediction rules".

Study Selection and Data Collection Process

Investigators (BL and HF) reviewed all titles and abstracts, and full reports of all potentially relevant trials. The initial literature search (January 1, 1995 to March 31, 2014) yielded 2863 citations (Figure 1). Screening by title andabstract yielded 121 items. Of these 121 items, reviewers BL and HF reached agreement

on 70 items for inclusion (prospective and retrospective cohort studies, and RCTs investigating clinical prediction tools and prognostic factors associated with determining neurologic outcome in adult patients with aneurysmal SAH), 42 items for exclusion (prognostic studies and grading schemes based on expert opinions, studies for traumatic SAH and perimesencephalic SAH), and were unsure on 9 items. Consensus conference was held with the assistance of a third reviewer, Yusuke Nishimura (YN). Inter-rater reliability was high (estimated kappa 0.85 (95% confidence interval [CI] 0.80-0.90) for citation and abstract screening).

Seventy-nine full-text articles were identified as potentially relevant and were assessed with further exclusion of articles due to incomplete variable and outcome reporting (n=13), inappropriate patient inclusion and exclusion criteria (n=18), and inappropriate predictor models used (n=26) [Figure 1].

Investigators BL and HF then independently applied the inclusion criteria to the full reports. Each trial report was examined carefully for its methodologic quality. As outlined in the "methodologic quality assessment" section, each article was appraised in nine areas. Of the 198 items assessed in 22 articles, BL and HF reached agreement on 160 items, disagreed on 30 items and were unsure on 8 items (kappa statistic 0.85, 95% CI 0.80-0.90). Disagreements were resolved through consensus discussions with YN, the third reviewer.

Methodologic Quality Assessment

For this systematic review, we sampled the quality checklist using Delphi methods for clinical prediction rules (QUADCPR)[9], and criteria proposed by Bouwmeester *et al.* 2012[5] for methodologic quality assessment of clinical prediction research. The following areas were used in methodologic quality assessment:

(1) study design – including description of study protocol, inclusion and exclusion criteria, study setting and recruitment,

(2) patient population – including representativeness of exposed aneurysmal subarachnoid hemorrhage patient cohort and ascertainment of exposure,

(3) candidate predictors – including description of predictors (neurologic, systemic and demographic variables) used, selection and coding of data, inclusion of potential confounding variables,

(4) outcome – including definition of outcomes (neurological and functional outcomes), justification of outcomes, their reproducibility, length of follow-up and outcome assessment when appropriate,

(5) statistical power – ensuring effective sample size,

(6) statistical models – description of mathematical methods used, and whether they are statistically sound and clinically sensible,

(7) bias assessment – such as publication bias, selection bias, recall bias, referral bias, and ascertainment bias,

(8) model performance and validation – descriptions of any attempts to

evaluate, if appropriate, model performance and validation, and

(9) statement of conflict of interest or funding.

Results

Study Search and Selection

The initial literature search (January 1, 1995 – March 31, 2014) yielded 2863

citations (Figure 1). These were screened by title and abstract. Seventy-nine

full-text articles were identified as potentially relevant and were assessed with the

further exclusion of articles due to an incomplete variable and outcome reporting,

inappropriate patient inclusion and exclusion criteria, an inappropriate predictor

models used. Twenty-two studies were included in this systemic review, with

Table 1 examining the independent, confounding and outcome variables, and

Table 2 examining their methodologic quality.

Study Results & Synthesis of Results

This systemic review of both clinical prediction tools and prognostic factors in
patients with aneurysmal SAH comprised 3 studies analyzing databases from
RCTs, 8 prospective cohort studies, and 11 retrospective cohort studies. The
most frequently retained significant clinical prognostic factors for long-term
neurologic outcome prediction include age (n = 7: Germanson *et al.* 1998[10],
McGirt *et al.* 2007[23], Ogilvy *et al.* 2006[28], Rabinstein *et al.* 2004[30], Risselada *et al.*
2010[32], Rosengart *et al.* 2007[33], Karamanakos *et al.* 2012[16]), neurological grade
(n=6: Germanson *et al.* 1998[10], Kahn *et al.* 2006[15], McGirt *et al.* 2007[23], Ogilvy *et
al.* 2006[28], Rabinstein *et al.* 2004[30], Risselada *et al.* 2010[32], Karamanakos *et al.*
2012[16]), blood clot thickness on CT imaging (n = 4: Ogilvy *et al.* 2006[28],
Rabinstein *et al.* 2004[30], Risselada *et al.* 2010[32], Rosengart *et al.* 2007[33]), and
aneurysm size (n = 2: Rosengart *et al.* 2007[33], Risselada *et al.* 2010[32]). Table 1
describes the aforementioned variables depicted in individual studies.

Methodological Quality of Included Studies

The included 22 studies all had thorough descriptions of study protocols,
including inclusion and exclusion criteria. Representative patient cohorts were
included in these studies. 4 of the 22 studies included multicenter cohorts. With
the exception of one study (Soehle *et al.* 2007[34]), all studies had adequate patient
sample sizes to ensure effective study power, ensuring 10 outcome events per
variable investigated. Predictor variables were adequately defined in all studies.

Patients were followed from 1 to 12 months after aneurysmal rupture for assessment of neurological outcomes, with small proportions of patients lost to follow-up. Neurologic and functional outcome assessments were performed in 15 of 22 studies. In addition, most studies (19 of 22 studies) accounted for potential confounding variables and stratification in their analyses (Tables 1 and 2). Univariate and multivariable logistic regression analyses were used for most studies (21 of 22 studies). However, only 6 of 22 studies checked for model performance including good calibration (agreement between predicted probabilities and observed outcome frequencies) and good discrimination (ability to distinguish between patients with and without the outcome)[2-4]. Finally, studies of clinical predictors and prediction models in aneurysmal SAH are prone to patient selection and referral biases, as well as recall bias in outcome assessments (Table 2).

Discussion

This systematic review was conducted to synthesize current evidence on prognostic factors affecting the outcome in aneurysmal SAH and to appraise the methodologic quality of studies investigating these clinical outcome prediction tools.

Methodological Issues

Systematic reviews for clinical prognostic factors and clinical prediction tools in aneurysmal SAH face a number of methodological challenges. These include within and between study patient heterogeneity, regional variations in treatment protocols, patient referral biases, and differences in treatment and prognosis viewpoints across different cultures.

Between-center differences in treatment and patient populations influence patient prognosis and clinical outcomes[7,8,10,11,14-18,20,22-30,32-34,37,38]. These center cluster effects should be taken into account when determining the effect sizes of individual prognostic factors. In addition, prognostic variables may be co-dependent[7,8,10,11,14-18,20,22-30,32-34,37,38]. Exploration of interactions between variables is important as they reflect the interrelated pathophysiologic mechanisms of brain-body associations in aneurysmal SAH.

Unlike a recently performed systematic review on clinical prediction models in aneurysmal SAH[13], this systematic review included:

(1) studies that provide clear definitions of predictor variables,

(2) studies with adequate study effective power and sample sizes, and

(3) methodological assessment based on standardized guidelines for quality

assessment of clinical prediction tools.

This systematic review also attempted to overcome other methodological

limitations by including high quality cohort studies and RCTs in prognosis fulfilling

a number of quality assessment criteria, namely, those proposed by QUADCPR[9],

and criteria proposed by Bouwmeester *et al.* 2012[5]. In addition, all included

studies had clearly defined predictor and outcome variables, effective study

power, as well as clinically and statistically sensible prediction tools and

prognostic factors.

Across most studies, the core and most frequently retained clinical outcome

predictors in aneurysmal SAH include age[10,16,23,28,30,32,33], neurological

grade[10,15,16,23,28,30,32], aneurysm size[32,33] and blood clot thickness[28,30,32,33]. Yet, a

number of other systemic, physiologic and neurologic parameters may also turn

out to be important clinical outcome predictors. These factors are usually not as

frequently included in clinical outcome prognostic studies on aneurysmal SAH.

For instance, even though the majority of studies (n = 20) used univariate and

multivariable logistic regression analyses for determination of significant

prognostic factors and clinical prediction tools, only 6 of 22 studies checked for

model performance.   In addition, model performance may be affected by

interactions between core predictors, as well as latent variables not accounted for during analysis.

Conclusion

Studies attempting to elucidate prognostic factors in aneurysmal SAH are affected by a number of methodologic limitations. This systematic review attempted to overcome some of these methodologic limitations by synthesizing high-quality RCTs and cohort studies. Yet, these synthesized epidemiologic studies did not attempt to clarify underlying mechanisms of how ruptured brain aneurysms influence other body systems. Brain-body associations carry a significant impact on patients' clinical outcomes. Together, existing methodologic limitations of epidemiologic studies on outcome prognosis in aneurysmal SAH readily influence the quality of clinical insight gained in this area.

Figure 1. Flow diagram of study selection

Records identified through database searching (n = 2863)	Additional records identified through other sources (n = 14)

Records after duplicates removed and further limit to articles (01/1995-03/2014) (n = 79)

Records screened (n =79)

Records excluded (n =42)
-incomplete outcome reporting (n = 4)
-inappropriate patient inclusion/exclusion (n = 12)
-biochemical marker as prognostic factor (clinical significance unclear) [n = 26]

Full-text articles assessed for eligibility (n = 37)

Full-text articles excluded (n = 15)
-incomplete outcome reporting (n = 9)
-inappropriate patient inclusion/exclusion (n = 6)

Studies included in systematic review (n = 22)

Table 1. Variables investigated in existing clinical prognostic models in aneurysmal subarachnoid hemorrhage.

	Independent Variables	Independent Variables Controlled for during Analysis	Dependent Variables
Chiang et al. [7]	-worst clinical grade (WFNS, Hunt and Hess) before treatment	-age	-outcome (Glasgow Outcome Scale, Karnofsky scale)
Claassen et al. [8]	-hypoxia (arterio-alveolar gradient > 125 mmHg) -metabolic acidosis (bicarbonate < 20 mmol/L) -hyperglycemia (glucose > 180 mg/dL) -cardiovascular instability (mean arterial pressure < 70 or > 130 mmHg)	-in hospital rebleeding -aneurysm size -intraventricular hemorrhage -level of consciousness at onset -age	-poor outcome (modified Rankin Score > 3)
Germanson et al. [10]	-age -sex -preexisting hypertension -aneurysm size and location -CT clot thickness -serum glucose -Glasgow Coma Score -level of consciousness	-none	-outcome (Glasgow Outcome Score at 3 months)
Heuer et al. [11]	-neurological grade (Hunt and Hess grade, GCS motor score) -intracerebral hemorrhage -intraventricular hemorrhage -rebleeding -intraoperative cerebral swelling -postoperative GCS score	-age -aneurysm size -vasospasm -intraoperative aneurysm rupture -secondary cerebral insults	-increased intracranial pressure -lack of correlation between intracranial pressure and poor neurological outcome (Hunt and Hess grades 4 and 5)

	Independent Variables	Independent Variables Controlled for during Analysis	Dependent Variables
Juvela [14]	-clinical condition at admission (GCS) -rebleeding -delayed cerebral ischemia -surgical clipping -heavy consumption of alcohol	-sex -age	-poor outcome (Glasgow Outcome Score 1-3)
Kahn et al. [15]	-severity of illness -clinical grade of hemorrhage -red blood cell transfusions -severe sepsis	-intracranial pressure -cerebral perfusion pressure -Hunt and Hess grade	-acute lung injury -mortality
Kramer et al. [17]	-late pulmonary infiltrates (> 72 hours) -early pulmonary infiltrates (< 72 hours)	-age -initial WFNS grade -amount of blood on initial CT -presence of symptomatic vasospasm	-poor outcome (Glasgow Outcome Score 1-3) -mortality
Krishnamurthy et al. [18]	-smoking	-age -sex -Hunt and Hess grade -amount of blood on initial CT (Fisher grade) -medical comorbidities	-poor outcome (Glasgow Outcome Score 1-3) -delayed neurological deterioration
Lindvall et al. [20]	-amount of blood of CT (Fisher grade) -Hunt and Hess grade	-age	-poor outcome (Glasgow Outcome Score 1-3)

	Independent Variables	Independent Variables Controlled for during Analysis	Dependent Variables
McGirt e al. [23]	-glucose level	-Hunt and Hess grade -cerebral vasospasm -age -hypertension -ventriculomegaly on CT	-poor outcome (Glasgow Outcome Score 1 to 3)
Miss et al. [24]	-aneurysm coiling -aneurysm clipping	-hemodynamic factors -mechanical ventilation -phenylephrine doses	-cardiac troponin I > 1.0 mcg/L -regional wall motion abnormalities -left ventricular ejection fraction < 50%
Mocco et al. [25]	-age -hyperglycemia -worst preoperative Hunt and Hess grades (4 and 5) -aneurysm size (> 13 mm)	-sex -medical history (obesity, hypertension, myocardial infarction, coronary artery disease, congestive heart failure, arrhythmia, diabetes, renal disease, stroke, depression, anxiety disorder, smoking) -hemoglobin level -leukocytosis -sodium level -acute pulmonary disease -aneurysm coiling -aneurysm clipping -acute hydrocephalus -global cerebral edema -intracerebral hemorrhage	-poor neurologic outcome (Hunt and Hess grade 5, mortality)
Naidech et al. [26]	-hemoglobin level	-Hunt and Hess grade -age -angiographic vasospasm	-cerebral infarction -poor outcome (Hunt and Hess grades 4 and 5)

	Independent Variables	Independent Variables Controlled for during Analysis	Dependent Variables
Ogilvy et al. [28]	-Hunt and Hess grade -Fisher grade -aneurysm size -age -anterior circulation aneurysms	-aneurysm clipping -aneurysm coiling -posterior circulation aneurysms	-poor outcome (Hunt and Hess grades 4 and 5)
Qureshi et al. [29]	-sodium level	-age -sex -pre-existing hypertension -admission neurological grade (GCS score) -initial mean arterial pressure -subarachnoid clot thickness -intraventricular blood -intraparenchymal hematoma -ventricular dilation -aneurysm size and location	-outcome (Glasgow Outcome Scale, mortality rate)
Rabinstein et al. [30]	-age -initial WFNS grade -coiling	-anterior aneurysm location -global deficits -diffuse vasospasm -number of affected vessels -number of endovascular treatments	-poor outcome (WFNS grades 4 and 5)
Risselada et al. [32]	-age -sex -prior subarachnoid hemorrhage -Fisher grade -lumbar puncture finding -WFNS grade -number of aneurysms -size and aneurysm location -vasospasm on admission	-randomization group	-outcome (Modified Rankin Scale, death at 2 months)

	Independent Variables	Independent Variables Controlled for during Analysis	Dependent Variables
Rosengart et al. [33]	-age -admission neurological grade -clot thickness -aneurysm location -aneurysm size -systolic blood pressure -prior SAH -history of hypertension -intraventricular hemorrhage -anticonvulsant use -induced hypertension, hypervolemia, hypervolemia -symptomatic vasospasm -fever at day 8 -cerebral infarction		-outcome (Glasgow Outcome Scale)
Soehle et al. [34]	-poor initial neurologic grade (Hunt and Hess grade 4 or 5) -amount of blood on CT (Fisher grade) -pulsatility index -resistance index	-mean arterial blood pressure -intracranial pressure -middle cerebral artery flow velocity	-poor outcome (Glasgow Outcome Score 1 to 3)
Van den Bergh et al. [37]	-magnesium level -amounts of cisternal and ventricular blood	-duration of unconsciousness -sex -rebleeding -level of consciousness at admission	-poor outcome (WFNS grades 4 and 5)

	Independent Variables	Independent Variables Controlled for during Analysis	Dependent Variables
Yoshimoto et al. [38]	-systemic inflammation (> 2 criteria)	-age -aneurysm location -amount of blood on CT (Fisher grade) -age -Hunt and Hess grade -glucose concentration	-poor outcome (Glasgow Outcome Score grades 1, 2 and 3)
Karamanakos et al. [16]	-age -Hunt and Hess grade -hydrocephalus	-gender -family history of saccular aneurysms -time period of aneurysmal SAH -intracerebral hemorrhage -intraventricular hemorrhage -subdural hematoma	-mortality at 1-3 days, mortality at 4-30 days, mortality at 1-12 months period

Table 2. Methodological assessment of clinical prognostic models on aneurysmal subarachnoid hemorrhage.

	Chiang et al.[7]	*Claassen et al.*	*Germanson*	*Heuer et al.*	*Juvela*	*Kahn et al.*
Study Design	Retrospective cohort	Retrospective cohort	Analysis of RCT database	Retrospective cohort	Prospective cohort	Retrospective cohort
Representativeness of cohort	Yes	Yes	Yes	Yes	Yes	Yes
Confounding	No adjustment	Adjusted	No adjustment	Adjusted	Adjusted	Adjusted
Blinding of assessors	No	Yes	Yes	Yes	No	Yes
Stratification	No	Yes	Yes	Yes	Yes	Yes
Statistical Methods & Sample Size	Univariate > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable	Univariate Multivariable CART > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable
Model Performance	None	C-statistic	None	None	Hosmer-Lemeshow	Hosmer-Lemeshow
Bias	Recall bias	No major	No major	Ascertainment bias	Recall bias	No major
Conflict of Interest	Not stated	Declared	Declared	Not stated	Declared	Declared

Statement						
	Kramer et al.	*Krishnamurthy*	*Lindvall et al.*	*McGirt et al.*	*Miss et al.*	*Mocco et al.*
Study Design	Retrospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort
Representativeness of cohort	Yes	Yes	Yes	Yes	Yes	Yes
Confounding	Adjusted	Adjusted	No adjustment	Adjusted	Adjusted	Adjusted
Blinding of assessors	Yes	No	Yes	Yes	Yes	Yes
Stratification	Yes	Yes	No	Yes	Yes	Yes
Statistical Methods & Sample Size	Univariate Multivariable 10 subjects per variable	Univariate Multivariable > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable	Univariate Multivariable > 10 subjects per variable
Model Performance	None	None	C-statistic	None	None	None
Bias	No major	Recall bias Selection bias Referral bias	No major	No major	No major	Selection bias Referral bias
Conflict of Interest	Declared	Not stated	Declared	Declared	Declared	Declared

Statement						

	Naidech et al.	*Ogilvy et al.*	*Qureshi et al.*	*Rabinstein et al.*	*Risselada et al.*	*Rosengart et al.*
Study Design	Retrospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Analysis of RCT database	Analysis of RCT database
Representativeness of cohort	Yes	Yes	Yes	Yes	Yes	Yes
Confounding	Adjusted	Adjusted	Adjusted	Adjusted	Adjusted	Adjusted
Blinding of assessors	Yes	Yes	Yes	Yes	Yes	Yes
Stratification	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Methods & Sample Size	Univariate Multivariable >10 subjects per variable	Univariate Multivariable >10 subjects per variable	Univariate Multivariable >10 subjects per variable	Univariate Multivariable 10 subjects per variable	Univariate Multivariable >10 subjects per variable	Univariate Multivariable >10 subjects per variable
Validation	None	None	None	None	Bootstrap Hosmer-Lemeshow C-statistic	Goodness of fit - McFadden R squared
Bias	No major	No major	No major	No major	No major	No major
Funding	Declared	Not stated	Not stated	Not stated	Declared	Declared

	Soehle et al.	*van den Bergh et al.*	*Yoshimoto et al.*	*Karamanakos et al.*
Study Design	Prospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort
Representativeness of cohort	Yes	Yes	Yes	Yes
Confounding	Adjusted	Adjusted	Adjusted	Adjusted
Blinding of assessors	No	Not stated	Not stated	No
Stratification	No	Yes	Yes	Yes
Statistical Methods & Sample Size	Univariate Multivariable <10 subjects per variable	Univariate Multivariable >10 subjects per variable	Univariate Multivariable >10 subjects per variable	Univariate Multivariable >10 subjects per variable
Validation	None	None	None	None
Bias	No major	No major	Selection bias Referral bias	No major
Funding	Declared	Not stated	Not stated	Declared

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Chapter Three

**Pathophysiologic mechanisms of brain-body associations in ruptured brain
aneurysms: a systematic review**

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Abstract

Background

Patients with ruptured brain aneurysms and aneurysmal subarachnoid hemorrhage (SAH) suffer neurological damage from primary injury of the aneurysmal rupture itself, as well as a number of secondary injurious processes that can further worsen the affected individual's neurological state. In addition, other body systems can be affected in a number of brain-body associations.

Methods

This systematic review synthesizes prospective and retrospective cohort studies that investigate brain-body associations in patients with ruptured brain aneurysms. The methodologic quality of these studies will be appraised.

Results

Six cohort studies were included in this systematic review. The methodologic quality of each study was assessed. They had representative patient populations, clear selection criteria and clear descriptions of study designs. Reproducible study protocols with ethics board approval were present. Clinical results were described in sufficient detail and were applicable to aneurysmal SAH patients in clinical practice. There were few withdrawals from the study. Limitations included small sample sizes and between-study differences in diagnostic tests

and clinical outcome endpoints. Several pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms were clarified through this systematic review. Sympathetic activation of the cardiovascular system in aneurysmal SAH not only triggers the release of atrial and brain natriuretic peptides, it can also lead to increased pulmonary venous pressures and permeability causing hydrostatic pulmonary edema. Natriuretic states can herald the onset or worsening of clinical vasospasm as the renin-angiotensin-aldosterone system is activated in a delayed manner.

Conclusion

This systematic review synthesizes the most current evidence of underlying mechanisms of brain related associations with body systems in aneurysmal SAH. Results gained from these studies are clinically useful and shed light on how ruptured brain aneurysms affect the cardiopulmonary system. Subsequent neuro-cardio-endocrine responses then interact with other body systems as part of the secondary responses to primary injury.

Introduction

Brain Injury Spectrum after Aneurysmal Subarachnoid Hemorrhage

Patients with ruptured brain aneurysms and aneurysmal subarachnoid hemorrhage (SAH) suffer neurological damage from primary injury of the aneurysm rupture itself, as well as a number of secondary injurious processes that can further worsen the affected individual's neurological state. Secondary injurious processes can be related to the nervous system such as re-bleeding from the ruptured aneurysm, brain swelling, occurrence of a delayed stroke, brain blood vessel vasospasm leading to seizures, strokes and an increase in brain-spinal fluid causing hydrocephalus. Figure 1 illustrates the spectrum of primary and secondary neurological injuries after aneurysmal SAH.

Brain-Body Associations in Aneurysmal Subarachnoid Hemorrhage

When brain aneurysms rupture, other body systems can be affected in a number of brain-body associations. Previous literature attempted to characterize cardiac and pulmonary manifestations in aneurysmal SAH[2]. Aneurysmal SAH triggers catecholamine release resulting in:

1. stunned myocardium and contraction band necrosis, and

2. altered pulmonary capillary permeability and pulmonary edema.

Yet, patients with ruptured brain aneurysms manifest clinical observations to show the involvement of other body organs including endocrine and renal abnormalities.

Objectives

The purpose of this systematic review is to synthesize studies that investigate the pathophysiologic mechanisms of brain-body associations in patients with ruptured brain aneurysms. This systematic review also critically appraises the methodologic quality of studies that attempt to derive brain-body associations in aneurysmal SAH.

Methods

This systematic review was designed based on a predefined protocol.

Study Eligibility Criteria

Studies that were eligible for this systematic review included:

1. studies of adult patients with ruptured brain aneurysms,

2. these patients received diagnostic tests to investigate pathophysiologic mechanisms of brain-body associations in aneurysmal SAH,

3. these patients also received reference standard investigations to document multi-organ deteriorations after brain aneurysm rupture, and

4. prospective and retrospective cohort studies and randomized controlled trials investigating pathophysiologic mechanisms of brain-body associations in aneurysmal SAH.

We excluded the following studies:

1. those that do not characterize pathophysiologic mechanisms of brain-body associations,

2. those that do not distinguish between aneurysmal and non-aneurysmal SAH, and

3. studies based on expert opinions.

Eligible studies were limited to those published from January 1, 2000 to March 31, 2014. We truncated eligible studies to this time period because of advancements in:

1. investigations to diagnose aneurysmal SAH, such as computed tomography (CT) angiogram,

2. diagnostic tests to investigate pathophysiologic mechanisms of brain-body associations, such as advanced pulse contour analysis for cardiopulmonary parameters and blood assays for neuroendocrine markers, and

3. surgical and neurocritical care treatment differences such as availability of minimally invasive endovascular techniques.

Literature Search

Two reviewers (Benjamin Lo [BL], Hitoshi Fukuda [HF]) independently searched a number of electronic databases. Relevant studies were identified from Ovid MEDLINE, Ovid EMBASE, Web of Science, the Cumulative Index to Nursing and Allied Health Literature, without language restrictions. To include gray literature, we also searched ProceedingsFirst and PapersFirst. We used the search terms:

1. "aneurysmal subarachnoid hemorrhage" and "cardiopulmonary",

2. "aneurysmal subarachnoid hemorrhage" and "renal",

3. "aneurysmal subarachnoid hemorrhage" and "gastrointestinal",

4. "aneurysmal subarachnoid hemorrhage" and "immune" and "hematologic", and

5. "aneurysmal subarachnoid hemorrhage" and "brain-body associations".

Study Selection and Data Collection Process

Both investigators (BL and HF) reviewed all titles and abstracts, and full reports of all potentially relevant trials. The initial literature search (January 1, 2000 – March 31, 2014) yielded 150 citations (Figure 2). Screening by title and abstract

and citation yielded 88 items. Of these 88 items, reviewers BL and HF reached

agreement on 41 items for inclusion, 38 items for exclusion and were unsure on 9

items. A consensus conference was held with the assistance of a third reviewer,

Yusuke Nishimura (YN). Interrater reliability was high (estimated kappa 0.81 (95%

CI 0.76-0.87) for citation and abstract screening). Fifty full text articles were

identified as potentially relevant, and were assessed, with further exclusion of

articles due to:

1. inappropriate patient inclusion and exclusion criteria,

2. inadequate outcome reporting, and

3. discussions lacking pathophysiologic mechanisms of brain-body

    associations in aneurysmal SAH.

Investigators BL and HF then independently applied the inclusion criteria to the

full reports. Each trial report was examined carefully for its methodologic quality.

As outlined in the "methodologic quality assessment" section, each article was

appraised in nine areas. Of the 54 items assessed in six articles, BL and HF

reached agreement on 43 items, disagreed on 8 items and were unsure on 3

items (kappa statistic = 0.82, 95% CI 0.71-0.93). Disagreements were resolved

through consensus discussions and YN, the third reviewer.

For data collection, the reviewers (BL, HF) extracted relevant data using a data

extraction form, piloted on a sample of included studies. Disagreements were

resolved by consensus discussions and YN, the third reviewer.

Assessment of Pathophysiologic Mechanisms of Brain-Body Associations in Aneurysmal Subarachnoid Hemorrhage

For this systematic review, the following items were reviewed in order to clarify pathophysiologic mechanisms of brain-body associations in aneurysmal SAH:

1. study design – including description of study protocol, study setting and recruitment,

2. patient population – including representativeness of cohort, inclusion and exclusion criteria, and sample size,

3. investigations – including reference tests to document organ dysfunction and diagnostic tests to document how ruptured brain aneurysms affect other organs,

4. outcome – including discussions on pathophysiologic mechanisms of brain-body associations in aneurysmal SAH, and

5. ethical conduct of study – including institutional ethics board approval and funding declarations.

Methodologic Quality Assessment

For this systematic review, we sampled the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies Tool – Revised Version[12]. The following areas

were used in methodologic quality assessment as they would apply to pathophysiologic mechanisms of brain-body associations in aneurysmal SAH:

1. whether subjects included are representative of those treated in clinical practice,

2. clear study designs and descriptions of study protocols, inclusion and exclusion criteria, study settings and recruitment,

3. inclusion of study findings with adequate discussions of pathophysiologic mechanisms of brain-body associations in aneurysmal SAH,

4. clear descriptions of reference standards to document multi-organ dysfunction,

5. whether diagnostic tests to investigate brain-body associations were described in sufficient detail to permit test replication,

6. whether clinical data for study subjects are reproducible for those treated in clinical practice,

7. reporting of non-interpretable test results,

8. explanation of study withdrawals, and

9. whether the measure is clinically useful.

Results

Study Search and Selection

The initial literature search (January 1, 2000 – March 31, 2014) yielded 150 citations (Figure 2). These were screened by title and abstract. Fifty full text articles were identified as potentially relevant, and were assessed, with further exclusion of articles due to inappropriate patient inclusion and exclusion criteria, inadequate outcome reporting, and discussions lacking pathophysiologic mechanisms of brain-body associations in aneurysmal SAH. Six studies were included in this systematic review.

A meta-analysis was not feasible in this review to statistically pool outcomes obtained from the included studies clarifying pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms. Marked between-study differences were noted in the included studies with: (1) differing diagnostic tests and reference value ranges, (2) differing clinical outcome endpoint measures, and (3) scarcity of studies investigating each type of diagnostic investigation. Diagnostic tests of serum and cerebrospinal fluid markers were studied in four out of six studies, radiographic investigations in two out of six studies, and invasive pulmonary artery thermodilution parameters in two out of six studies. In addition, there is no standardization of diagnostic tests between investigating centers.

Study Results and Synthesis of Results

This systematic review identified five prospective cohort studies and one

retrospective study for inclusion in the analysis. Of the six methodologically

rigorous studies identified for this systematic review, pathophysiologic

mechanisms were clarified between the brain and the following organ systems:

1. cardiac system – six out of six studies,

2. pulmonary system – three out of six studies,

3. endocrine system – three out of six studies,

4. renal system (including electrolyte and fluid balance) – three out of six

    studies,

5. immune and hematologic systems – zero studies, and

6. gastrointestinal system – zero studies.

Assessment of Pathophysiologic Mechanisms of Brain-Body Associations

in Aneurysmal Subarachnoid Hemorrhage for Included Studies

Article 1: Endocrine response after severe subarachnoid hemorrhage related to

sodium and blood volume regulation

In this prospective cohort study, Audibert *et al.* investigated endocrinologic

responses, as well as sodium and water regulation after severe aneurysmal SAH[1].

Over a period of 2 years, 19 adults with aneurysmal SAH were included (average

47 years old). Totally, 12 patients were excluded because of the history of renal

insufficiency, cardiac disease, chronic treatment with diuretics, angiotensin-

converting enzyme inhibitors and steroids. Clear study protocols were described

with the maintenance of euvolemia and sodium balance. Reference standard

tests that documented multi-organ involvement included an electrocardiogram,

cardiac enzymes, echocardiography and transcranial Doppler ultrasound.

Diagnostic tests performed to clarify brain-body associations included daily

sodium excretion fraction, glomerular filtration rate, creatinine clearance, plasma

levels of brain natriuretic peptide, atrial natriuretic peptide, aldosterone, renin,

angiotensin II and vasopressin. This study found the following:

1. with maintenance of euvolemia and salt balance, only 1 out of 19 patients

   experienced severe clinical vasospasm,

2. levels of brain natriuretic peptide increased between days 1 and 3 after

   aneurysmal rupture,

3. levels of atrial natriuretic peptide increased between days 4 and 6 after

   aneurysmal rupture, with associated increases in levels of renin,

   aldosterone and angiotensin II, and

4. levels of vasopressin increased between days 10 and 12 after aneurysmal

   rupture.

This study clearly describes the relationship between brain aneurysmal rupture and delayed activation of renin-angiotensin-aldosterone system. It had institutional ethics board approval, and clear declaration of funding sources. However, its main weaknesses included smalls study sample size, patient selection and center referral biases.

Article 2: Neuro-cardio-endocrine response to acute subarachnoid hemorrhage

In this prospective cohort study, Espiner *et al.* investigated relationships between neurologic, cardiac and endocrine responses after severe aneurysmal SAH[5]. Over a period of 2 years, 18 adults with aneurysmal SAH were included (average 54 years old). Exclusion criteria included history of renal, hepatic, cardiac, endocrine diseases and history of diuretic and angiotensin converting enzyme inhibitor use prior to hospitalization. Clear study protocols were described. Patients were prescribed tapering doses of dexamethasone on admission. Reference standard tests that documented multi-organ involvement included an electrocardiogram, cardiac enzymes, chest radiographs. Diagnostic tests performed to clarify brain-body associations included plasma levels of cardiac enzymes, endothelin, brain natriuretic peptide and atrial natriuretic peptide, cerebrospinal fluid levels of brain natriuretic peptide, and atrial natriuretic peptide. This study found the following:

1. Brain natriuretic peptide and atrial natriuretic peptide levels in plasma increased in the first 3 days post-aneurysmal rupture. They returned to normal levels by day 7. Cerebrospinal fluid levels of brain natriuretic peptide and atrial natriuretic peptide did not show any changes. Abnormal electrocardiograms were noted in 6 out of 7 patients.

2. Urinary sodium levels increased within the first 3 days then remained stable. Plasma sodium levels gradually decreased.

3. Plasma vasopressin levels were increased on presentation then fell to normal levels after 2 days. Plasma aldosterone and renin levels increased at day 10-12. Cortisol levels fell abruptly on day 3 and maintained low levels to day 10.

4. Initial elevations of epinephrine, norepinephrine and endothelin fell by day 3 and remained at subnormal levels.

This study thoroughly describes the various relationships between the brain, neuroendocrine and renal systems. It had institutional ethics board approval and clear declaration of funding sources. However, its main weakness is the treatment of patients with admission dose of dexamethasone which further delayed activation of the renin-angiotensin-aldosterone system. Patients also demonstrated depressed adrenal-hypothalamic cortisol axis. This study also had small study sample size. Other weaknesses included patient selection and center referral biases.

Article 3: Subarachnoid hemorrhage complicated with neurogenic pulmonary edema and Tako-tsubo-like cardiomyopathy

In this retrospective cohort study, Inamasu *et al.* characterized cardiopulmonary dysfunctions in aneurysmal SAH. Over a period of 5 years, 16 adults with aneurysmal SAH and neurogenic pulmonary edema were included (average 63 years). Exclusion criteria included patients with non-aneurysmal SAH. Clear study protocols were described. Patients were maintained euvolemic and had spinal catheters for clot clearance. Reference standard tests included electrocardiogram and chest radiograph. Diagnostic tests included a transthoracic echocardiogram. This study found the following:

1. Of 16 patients with neurogenic pulmonary edema, 14 had Tako-tsubo-like cardiomyopathy. All exhibited electrocardiographic changes (including ST segment abnormalities, QT prolongation and T-wave inversions). They were all intubated and were on vasopressors.

2. Neurogenic pulmonary edema was significantly associated with posterior circulation aneurysms (p = 0.004). 9 out of 16 patients died (7 from the primary aneurysmal rupture, 1 from rebleeding and 1 from vasospasm-induced strokes).

This study clearly demonstrated relationships between neurogenic pulmonary edema and Tako-tsubo-like cardiomyopathy. It had institutional ethics board approval and clear declaration of funding sources. However, its main

weaknesses included small study sample size, patient selection and center referral biases.

Article 4 – Cardiac troponin elevation, cardiovascular morbidity and outcome after subarachnoid hemorrhage

In this retrospective cohort study, Naidech *et al.* investigated relationships between cardiac troponin rise after aneurysmal SAH and its association with cardiopulmonary complications, delayed cerebral ischemia and death[7]. Over a period of 4 years, 253 patients with SAH and electrocardiographic abnormalities were included (average 55 years). Exclusion criteria included patients with traumatic SAH and hemorrhage from arteriovenous malformations. Clear study protocols were described. Patients were maintained euvolemic. Reference standard tests included an electrocardiogram. Diagnostic tests included cardiac enzymes and chest radiographs. This study found the following:

1. Cardiac enzyme elevation was noted in patients who were older (average age 55 years), worse admission neurologic status, more blood on CT scan on admission, more physiologic dysfunction and hypertensive therapy.

2. Cardiac enzyme elevation was associated with risk of hypotension requiring vasopressors, left ventricular systolic dysfunction on echocardiogram, delayed cerebral ischemia from vasospasm and death.

This study demonstrated associations between cardiac troponin elevation and cardiovascular-related morbidity and mortality after aneurysmal SAH. It had institutional ethics board approval and clear declaration of funding sources. However, this study did not distinguish between aneurysmal and non-aneurysmal SAH. Furthermore, it did not discuss pathophysiologic mechanisms of brain-body associations in detail.

Article 5 – Clinical significance of elevated natriuretic peptide levels and cardiopulmonary parameters after subarachnoid hemorrhage

In this prospective cohort study, Nakamura *et al.* investigated the relationships between natriuretic peptides and changes in cardiopulmonary parameters[10]. Over a period of 2 years, 20 adults with aneurysmal SAH were included (average 65 years). Exclusion criteria included patients with a history of acute myocardial infarction, arrhythmia and congestive heart failure. Clear study protocols were described. Patients were maintained euvolemic. Reference standard tests included electrocardiograph, chest radiograph, echocardiograph and transcranial Doppler. Diagnostic tests included plasma levels of atrial natriuretic peptide and brain natriuretic peptide and pulse contour analysis to measure cardiopulmonary parameters. This PiCCO system measured cardiac index, systemic vascular resistance index, intrathoracic blood volume index and extravascular lung water index. This study found the following:

1. Plasma levels of brain natriuretic peptides peaked on post-aneurysm rupture day 1. Plasma levels of atrial natriuretic peptide peaked on post-aneurysm rupture day 2, and remained increased up to day 6.

2. Natriuretic peptides caused sodium and water loss with plasma sodium levels falling between days 3 and 10.

3. There were no changes in cardiac indices and slight increases in extravascular lung water indices. There were no changes in intrathoracic blood volume indices.

This study thoroughly discussed relationships between elevated natriuretic peptides and cardiopulmonary parameters after aneurysmal SAH. It had institutional ethics board approval and clear declaration of funding sources. However, its main weaknesses included small study sample size, patient selection and center referral biases.

Article 6 – Circulatory characteristics of normovolemia and normotension therapy after subarachnoid hemorrhage, focusing on pulmonary edema

In this prospective cohort study, Sato *et al.* characterized circulatory parameters after several aneurysmal SAH to reveal mechanisms of pulmonary edema[11]. Over a period of 2 years, 49 adults with aneurysmal SAH were included (average 59 years). Exclusion criteria included patients with brainstem dysfunction and

lack of study consent. Clear study protocols were described. Patients were

maintained euvolemic. Reference standard tests included chest radiograph and

arterial blood gases. Diagnostic tests included pulse contour analysis to measure

cardiopulmonary parameters. This study found the following:

1. 7 out of 49 patients experienced neurogenic pulmonary edema.

2. Patients with neurogenic pulmonary edema had a lower cardiac function

   index and lower global ejection fraction. They had higher global end

   diastolic volume index.

3. Even though neurogenic pulmonary edema patients had net negative

   water balance and low central venous pressures, they had higher

   extravascular lung water index.

This study thoroughly discussed circulatory changes in aneurysmal SAH patients

with neurogenic pulmonary edema. It had institutional ethics board approval, and

clear declaration of funding sources. However, its main weaknesses included

small study sample size, patient selection, and center selection biases.

Methodological Quality of Included Studies

In summary, all six studies have strong methodologic quality (Table 1).

They had representative patient populations, clear selection criteria and clear

descriptions of study designs. Reproducible study protocols with ethics board

approval were present. Clinical results were described in sufficient detail and were applicable to aneurysmal SAH patients in clinical practice. There were few study withdrawals. These cases were medical deteriorations and deaths precluding study completion. The main methodologic weakness in all studies included small sample size, patient selection and center referral biases.

Results gained from these studies are clinically useful and shed light on how ruptured brain aneurysms affect the cardiopulmonary system. Subsequent neuro-cardio-endocrine responses then interact with other body systems, including the renal system, as part of the secondary responses to primary injury.

Discussion

This systemic review gathers the most current methodologically rigorous evidence on known pathophysiologic mechanisms of brain-body associations in aneurysmal SAH. The following pathophysiologic discussion summarizes this current state of knowledge[1,3-11,13,14].

Rupture of brain aneurysms can lead to over activity of the sympathetic nervous system. This triggers a sympathetic surge of catecholamine release from the thoracic spinal cord's paravertebral chain. Catecholamine release from sympathetic surge is associated with neurologic and systemic sequelae which

affect survival and functional outcome. Pathologically, the cardiac ventricle is stunned[2]. This manifests as electrographic changes and troponin elevations[6,9,10]. Troponin changes are more commonly found in those with poor neurological grade, intraventricular hemorrhage, cerebral edema, loss of consciousness at ictus, and multisystem physiological derangements[9]. They are associated with adverse events including left ventricular systolic dysfunction, pulmonary edema, hypotension requiring vasopressors, delayed strokes and death[9]. Troponin release, however, are not usually as high as levels observed after myocardial infarction secondary to lack of coronary blood flow[6,9,10]. Indeed, cardiac stunning refers to cardiac beta receptor hyper activation and hyper contraction where contraction band necrosis can result. An extreme case of this is the observation of stunned apical and mid-ventricular segments in Tako-tsubo-like cardiomyopathy[6]. Electrocardiographic, troponin and echocardiographic evidence correlate with blood measurement of brain natriuretic peptide, a protein released from the cardiac ventricle with peak values on post-rupture day 1[1,5,10,11]. The brain site of brain natriuretic peptide production does not seem to be as affected, as cerebrospinal fluid levels of brain natriuretic peptide are not elevated[1,5,10,11]. Further physiologic evidence from pulse contour analysis point to a global decrease in cardiac ejection fraction, with a subsequent increase in extravascular lung water index by post-rupture day 3[10,11]. This is consistent with increased catecholamines in peripheral arterioles which can increase pulmonary venous pressures and enhance pulmonary vascular permeability[1,3-11,13,14]. The

combination of increased pulmonary vascular permeability, increased pulmonary vascular pressures, decreased cardiac contractility and increased volume from resuscitation can lead to hydrostatic pulmonary edema where hydrostatic pressures favouring edema formation overwhelms the opposing oncotic pressures. As a result of the apparent increased preload, the cardiac atrium is stretched[1,5,10,11]. Plasma atrial natriuretic peptide levels peak at post-rupture day 2 after aneurysmal rupture. Cerebrospinal fluid levels of atrial natriuretic peptides remain normal suggesting that the primary source of atrial natriuretic peptide release is the cardiac atrium and not the brain.

Together, atrial and brain natriuretic peptides then act on renal tubules triggering sodium and volume loss. Without appropriate resuscitation, plasma sodium levels can fall drastically by post-rupture day 4-6[10,11]. This drop can be attenuated with pre-emptive judicious volume and salt replacement. With this treatment, the incidence of severe clinical vasospasm can be lowered[1]. Natriuretic and diuretic states in aneurysmal SAH often herald the onset of clinical vasospasm. Between days 4 and 6, the renin-angiotensin-aldosterone system is activated[1,3-11,13,14]. Figure 3 shows pathophysiologic mechanisms of brain-body associations after aneurysmal SAH, as well as interrelationships, between the neuro-cardio-endocrine and the renin-angiotensin-aldosterone systems. This system is activated in a delayed manner as a compensatory mechanism for prior sodium and water loss. Waiting for this mechanism alone to

compensate for sodium and water balance in the aneurysmal SAH patient will have severe negative consequences because the onset of vasospasm can lead to delayed strokes and further secondary neurological damage.

Clinical Implications

This systematic review elucidates mechanisms of how ruptured brain aneurysms affect neuroendocrine, heart, lung, as well as fluid and electrolyte balance in the affected patients. Recognition of pathophysiologic mechanisms of brain-body associations is essential in preventing complications after treatment of ruptured brain aneurysms. The clinician should be vigilant about:

1. Maintenance of sodium and water balance,

2. Potential negative impact of agents which interfere with the renin-angiotensin-aldosterone system (including corticosteroids and angiotensin-converting enzyme inhibitors),

3. ventilatory support to overcome pulmonary edema, and

4. inotropic and vasopressor support for the stunned myocardium.

Limitations

This systematic review included studies with small sample sizes. Highly selected patient populations were included, with short-term follow-up. Differing diagnostic

tests were used to clarify pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms, with no standardization of diagnostic tests between investigating centers. Because of these limitations, individual patient variability in physiologic responses may not be adequately captured. Patients with underlying comorbidities such as gastrointestinal diseases were not included to clarify the effects of other comorbidities on pathophysiologic mechanisms of brain-body associations in aneurysmal SAH patients. In addition, there is scarce epidemiologic evidence to demonstrate the clinical associations between ruptured brain aneurysms and the gastrointestinal, immune and hematologic systems.

Conclusion

This systematic review synthesizes the most current evidence of underlying mechanisms of brain related associations with body systems in aneurysmal SAH. However, literature is still lacking on some key mechanisms including the reasons for early-onset cerebral edema in the aneurysmal SAH patient, which is an important cause of early hospital associated mortality. In addition, the mechanisms of late hospital associated mortality are not well described in large epidemiologic aneurysmal SAH populations. There is also insufficient epidemiologic evidence of associations between the brain-gastrointestinal and brain-immune systems.

Figure 1. Spectrum of primary and secondary neurologic injuries after aneurysmal subarachnoid hemorrhage.
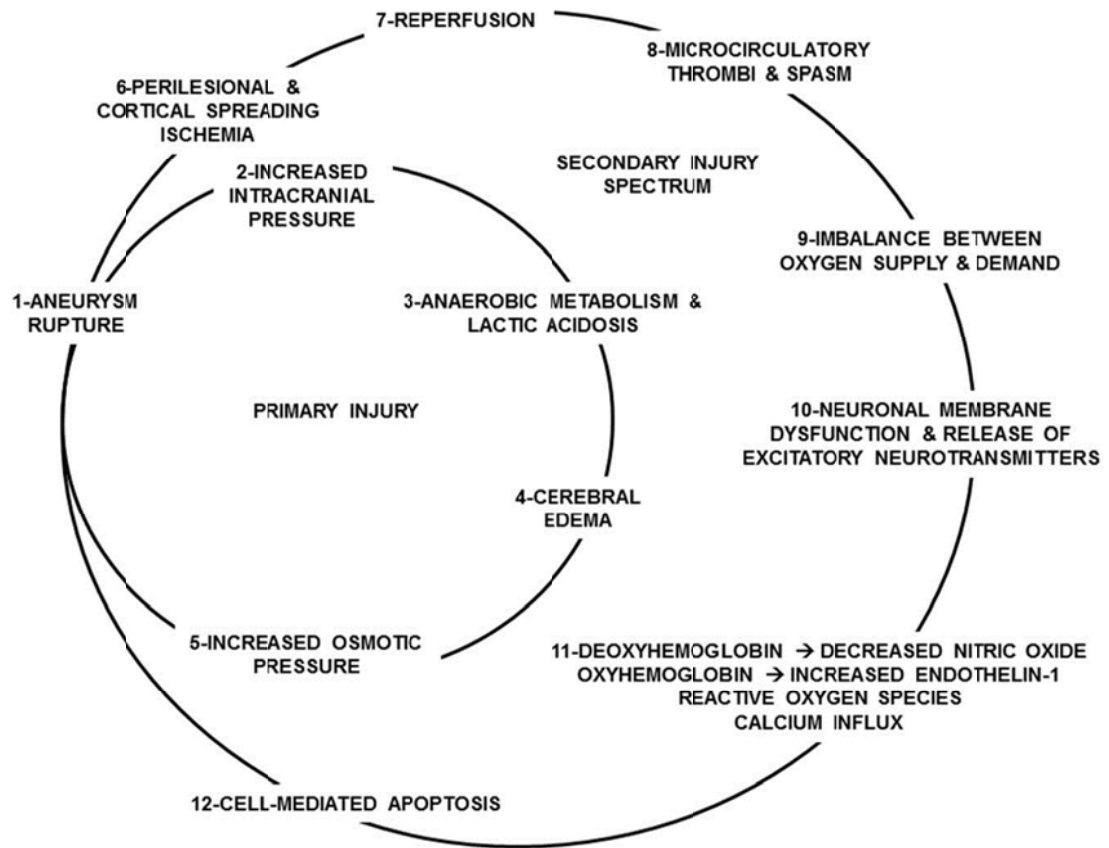
Explanations for each step are given below:

1. rupture of a brain aneurysm,

2. increased intracranial pressure results in decreased blood flow to the brain,

3. metabolism under lack of oxygen leading to formation and release of lactic acid,

4. brain swelling as a result of increased intracranial pressure and anaerobic metabolism,

5. fluid leaks across disrupted blood-brain barrier,

6. lack of blood flow and oxygen spread from site of aneurysm rupture to across the entire brain,

7. injurious process when brain attempts to re-supply blood and oxygen to involved areas,

8. clotting is triggered in small vessels, along with induced constriction of vessels of different sizes (vasospasm),

9. inadequate oxygen is supplied via brain blood flow to meet the metabolic requirements of the damaged brain areas,

10. nerve cell membranes are disrupted, and further damage is caused with release of a number of chemicals that are toxic to the injured regions, and

11. products (including reactive oxygen species, endothelin-1, decreased nitric oxide, calcium) trigger deleterious processes (such as seizures, vasospasm, delayed strokes), and the process of programmed cell death is triggered.

Figure 2. Flow diagram of study selection.

```
┌─────────────────────────────┐      ┌─────────────────────────────┐
│  Records identified through │      │ Additional records identified│
│      database searching     │      │    through other sources    │
│         (n = 147)           │      │          (n = 3)            │
└─────────────────────────────┘      └─────────────────────────────┘
               │                                    │
               ▼                                    ▼
     ┌───────────────────────────────────────────────────┐
     │         Records after duplicates removed          │
     │  and further limit to articles (01/2000-03/2014)  │
     │                    (n = 50)                       │
     └───────────────────────────────────────────────────┘
                            │
                            ▼
          ┌──────────────────────────┐        ┌──────────────────────────────────┐
          │    Records screened      │───────▶│ Records excluded (n = 38)        │
          │       (n = 50)           │        │ -inappropriate patient           │
          └──────────────────────────┘        │ inclusion/exclusion (n = 19)     │
                       │                       │ -incomplete outcome reporting    │
                       ▼                       │ with no pathophysiologic         │
                                               │ mechanisms (n = 17)              │
                                               │ -biochemical markers with        │
                                               │ clinical significance being      │
                                               │ unclear (n = 2)                  │
                                               └──────────────────────────────────┘

          ┌──────────────────────────┐        ┌──────────────────────────────────┐
          │ Full-text articles assessed│──────▶│ Full-text articles excluded      │
          │     for eligibility      │        │          (n = 6)                 │
          │       (n = 12)           │        │ -inappropriate patient           │
          └──────────────────────────┘        │ inclusion/exclusion (n = 2)      │
                       │                       │ -inadequate outcome reporting    │
                       ▼                       │ (inadequate discussions on       │
          ┌──────────────────────────┐        │ pathophysiologic mechanisms)     │
          │   Studies included in    │        │ (n = 4)                          │
          │    systematic review     │        └──────────────────────────────────┘
          │        (n = 6)           │
          └──────────────────────────┘
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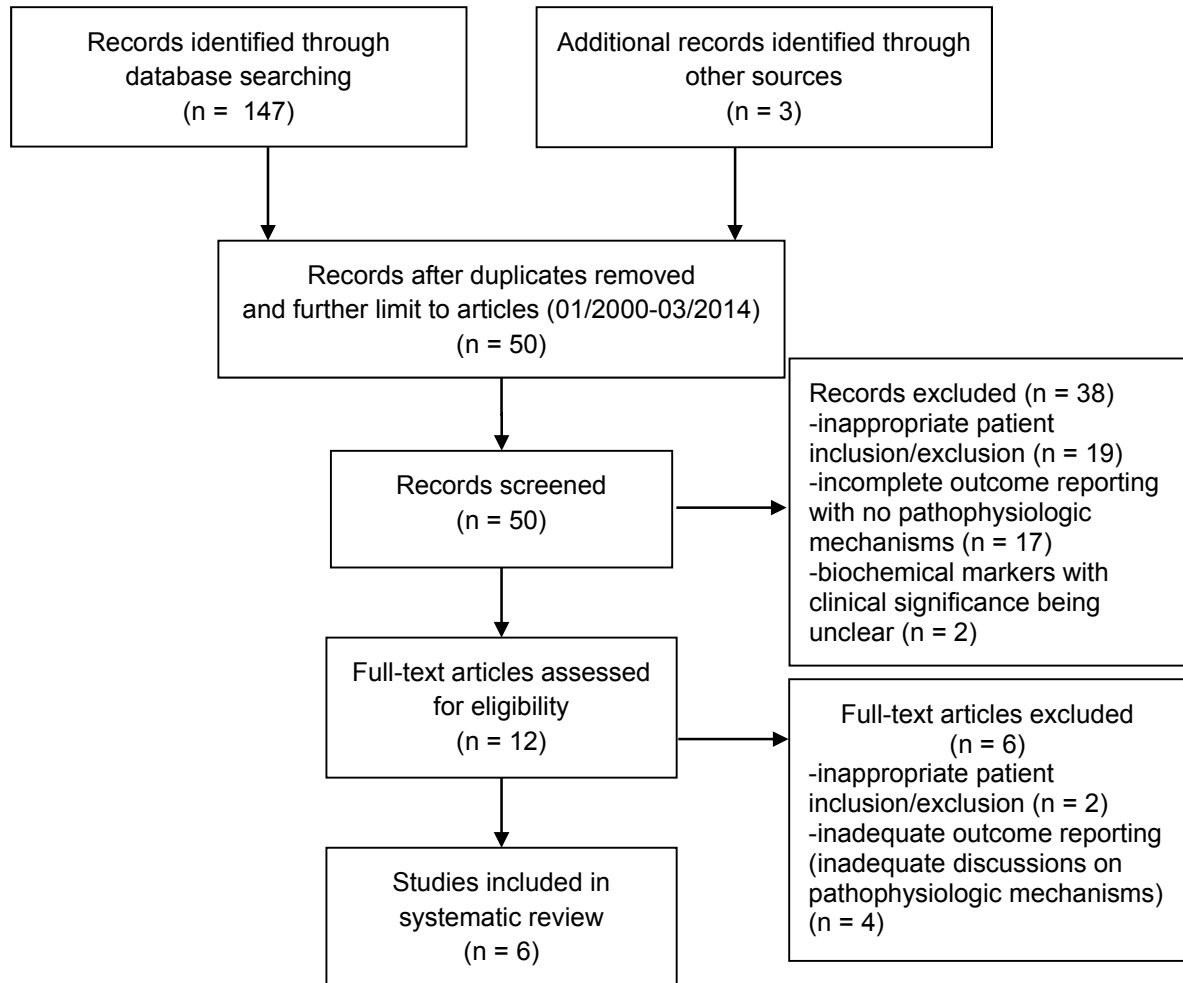
Figure 3. Pathophysiologic mechanisms of brain-body associations after aneurysmal subarachnoid hemorrhage and delayed activation of the renin-angiotensin-aldosterone system.
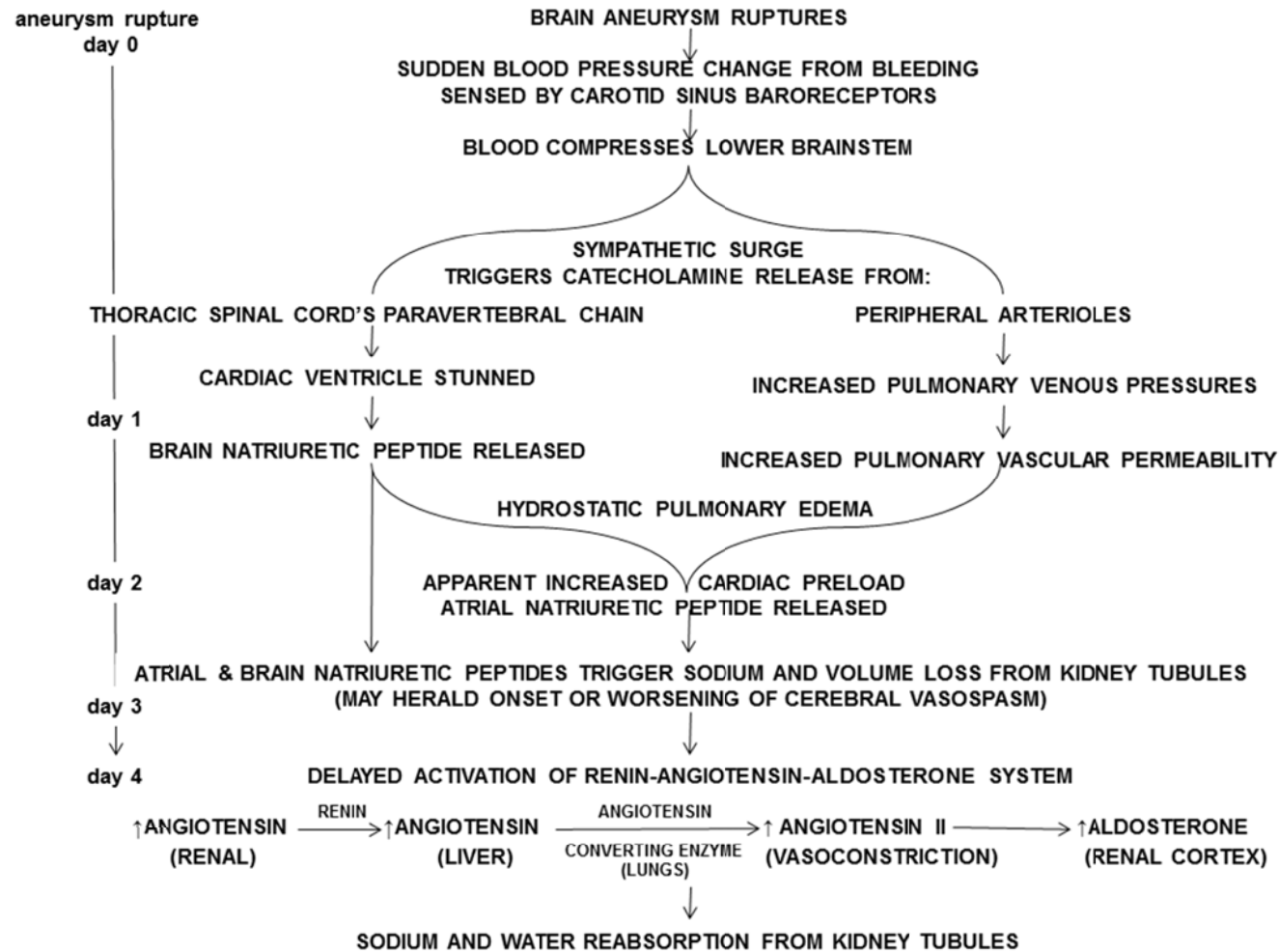
Table 1. Methodological assessment of articles on brain-body associations in aneurysmal subarachnoid hemorrhage.

	Audibert et al.[1]	*Espiner et al.*[5]	*Inamasu et al.*[6]	*Naidech et al.*[9]	*Nakamura et al.*[10]	*Sato et al.*[11]
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort
Representativeness of cohort	Yes	Yes	Yes	Yes	Yes	Yes
Selection criteria	Clear	Clear	Clear	Clear	Clear	Clear
Reference standard used?	Yes	Yes	Yes	Yes	Yes	Yes
Index test reproducible?	Yes	Yes	Yes	Yes	Yes	Yes
Clinical data applicable to clinical practice?	Yes	Yes	Yes	Yes	Yes	Yes
Non-interpretable test results reported?	Yes	Yes	Yes	Yes	Yes	Yes
Withdrawals explained?	Yes	Yes	Yes	No study withdrawals	Yes	No study withdrawals
Measure clinically useful?	Yes	Yes	Yes	Yes	Yes	Yes

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Chapter Four

Clinical Outcome Prediction in Aneurysmal Subarachnoid Hemorrhage –

Alterations in Brain-Body Interface

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Abstract

Background

Brain-body associations are essential in influencing outcome in patients with

ruptured brain aneurysms. Thus far, there is scarce existing literature on such

important relationships.

Methods

The multicenter Tirilazad database (3551 patients) was used to create this clinical

outcome prediction model in order to elucidate significant brain-body associations.

Traditional binary logistic regression models were used.

Results

Binary logistic regression main effects model included four statistically significant

single prognostic variables, namely, neurological grade, age, stroke and time to

surgery. Logistic regression models demonstrated the significance of

hypertension and liver disease 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.

Conclusion

Using the aforementioned results generated from binary logistic regression

models, one can identify potential patients who are in the high risk group of

neurological deterioration. Specific therapies can be tailored to prevent these

detriments, including treatment of hypertension, seizures, early detection and

treatment of myocardial infarction and prevention of hepatic encephalopathy.

Introduction

The brain-body interface comprises many physiological interactions which can go awry in disease states. Under conditions of normal homeostasis, brain-body associations are frequently characterized as interactions between the human nervous system and the cardiovascular, respiratory, endocrinological and gastrointestinal systems.

The Brain-Body Interface

Cardiovascular-Nervous System Associations

Direct and indirect projections of the autonomic nervous system control the cardiovascular system. These projections act via the parabrachial nucleus of the midbrain and pons. The parabrachial nucleus is a relay station that transmits signals between the cerebral cortex (especially limbic cortex), amygdala, hypothalamic paraventricular nucleus, vasomotor area of the lower brainstem (including the ventrolateral medulla, medullary raphe, nucleus of the solitary tract) and the thoracolumbar interomediolateral gray column of the spinal cord[2,3,10].

The autonomic nervous system mediates heart rate (chronotrophy), rate of nervous impulse transmission through the cardiac conductive tissue (dromotropy)

and force of contraction (inotropy). Blood vessel diameter and tone are also mediated via the autonomic nervous system.

Counter-regulatory feedback with the sympathetic nervous system predominates. An example of such counter-regulatory feedback is the Cushing reflex. Increases in intracranial pressure from disease states such as intracerebral hemorrhage lead to decreased levels of oxygen and increased local levels of hydrogen ions and carbon dioxide around the vasomotor regions of the lower brainstem secondary to anaerobic metabolism. As a counter-regulatory measure, the systemic blood pressure is elevated in an attempt to increase blood flow to the brain. With this increase in blood pressure, heart rate is reflexively decreased via the arterial baroreceptors[26,27,44,46].

Other factors also affect the amount of autonomic nervous output from the vasomotor regions of the brainstem. They include:

1. blood oxygen level,

2. blood carbon dioxide level,

3. pain stimulus,

4. chemoreceptors and baroreceptors in the carotid, pulmonary and aortic vessels sense corresponding changes,

5. nerve impulse feedback from the lungs secondary to lung inflation and deflation, and

6. regulatory signals between the cerebral cortex and brainstem.

Respiratory-Nervous System Associations

Pacemaker cells in the medulla are responsible for the autonomic control of respiration. Their rhythmic discharges are modified by pneumotaxic neurons in the pons, as well as limbic and hypothalamic resions[2,3,10.] Other contributions include:

1. impulses from afferent pulmonary vagal fibers with lung inflation and deflation,

2. spinal reflexes from cervical and thoracic spinal cord to the diaphragm and intercostal muscles,

3. changes in the cerebrospinal fluid concentrations of carbon dioxide and hydrogen ions sensed by medullary chemoreceptors, and

4. changes in oxygen tension sensed by baroreceptors in the aorta, cardiac atrium and ventricle, as well as pulmonary arteries.

Endocrinological-Nervous System Associations

The hypothalamic-pituitary axis regulates key aspects of homeostasis, temperature control and endocrinological functions. This system integrates

inputs from both the limbic system and brainstem in order to modulate both emotional and instinctual reactions to changes in the internal milieu[2,10,41].

Gastrointestinal-Nervous System Associations

The gastrointestinal autonomic nervous system regulates central nervous system inputs to the enteric system regarding gut motility and secretory functions. It works in conjunction with local paracrine pathways[2,10].

Aneurysmal Subarachnoid Hemorrhage & Alterations in Brain-Body Associations

Patients with ruptured brain aneurysms and associated SAH have a mortality rate of at least 45% in the first month after rupture[30]. 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, over accumulation of brain spinal fluid causing hydrocephalus. In addition, other body organ systems can be affected, such as myocardial infarction and over accumulation of fluid in lungs causing pulmonary edema.

Together, these processes can lead to long term disability. Types of disability include physical, neurocognitive and psychological impairment. Table 1 summarizes alterations in physiological interactions in the brain-body interface.

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. Between 1991 and 1997, 3551 patients from 171 centers in 22 countries in North America, Europe, Australia, New Zealand and Africa participated in five randomized, double-blind, placebo-controlled trials of Tirilazad[11,12,20,24,25].

Included patients were adults with evidence of aneurysmal SAH. 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 onset of SAH. Excluded patients were:

1. those with traumatic SAH,

2. those with infectious mycotic aneurysms,

3. severe underlying medical illnesses including serious cardiovascular disease, such as myocardial infarction within the previous 6 months,

       uncontrolled hypertension, serious cardiac arrthymias 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 Guglielmi or other detachable coils.

Patients in the placebo and treatment arms were otherwise treated similarly. Over 85% of patients underwent surgical clipping, 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, amount of blood visualized on admission CT scan (measured by the Fisher scale taking into account thickness of blood clot with or without intraventricular component). The potential confounder of patient sex was accounted for in statistical analysis in the North American Tirilazad trial where fewer female patients were randomized to the treatment arm[12]. The percentages of patients experiencing neurological and systemic disabilities were similar in different treatment groups[11,12,20,24,25].

Only one percent of patients were lost to follow up. The primary outcome measure was the patient`s Glasgow Outcome Score at 3 months after aneurysmal 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[18].

Two systematic reviews involving the five Tirilazad trials found no substantial heterogeneity among these trials, and no significant differences between treatment and placebo arms, or amongst patients who were administered different dosages of Tirilazad regarding the number of patients who died, the number of adverse events or neurological outcome at 3 months follow up[16,47].

Objectives

Using data from the placebo and Tirilazad arms of the five clinical trials, I aim to create a clinical outcome prediction model using binary logistic regression and investigate the potential factors for outcome prediction in patients with ruptured brain aneurysms. In particular, I will assess the interaction of potential factors and explore the role for possible associations between the brain and other organ systems.

Methods

The Tirilazad database was used to investigate the potential factors for outcome prediction in aneurysmal SAH and to assess interactions of factors between the brain and other organ systems.

Table 2 summarizes the independent variables recorded in the Tirilazad database.

The dependent variable used for statistical analysis is the dichotomized Glasgow Outcome Score at three months, that is good or poor outcome. Good outcome represents functional independence (GOS 5 or 4). Poor outcome represents functional dependence (GOS 3), persistent vegetative state (GOS 2) or death (GOS 1)[15].

Table 3 summarizes neurologic and systemic factors, as well as *a priori* hypotheses investigated regarding possible interactions between brain and other organ systems.

Using IBM SPSS Version 19.0[TM], independent variables were entered into univariate models in which chi-square analyses were performed to investigate associations with poor outcome. Two-way interaction terms that included

neurologic and systemic prognostic factors were examined (Table 3). Variables that reached a probability of 0.10 were then entered into a multivariable binary logistic regression model. Variables that reached p value $\leq$ 0.05 were deemed significant. For Hosmer and Lemeshow test for goodness of fit of the model, p $\geq$ 0.05 was deemed significant[14,42.] Multivariable analyses had at least 10 subjects per independent variable, which is the minimum number required for a stable multivariable model using logistic regression[14,42].

In the multivariable logistic regression model, 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 ,

3. c statistic and classification to examine model discrimination, and

4. split-sample analysis (70% training and 30% testing) to examine model generalizability.

Results

Patient selection and participation in the Tirilazad trials are summarized in Figure 1. Characteristics of the study patient population are summarized in Table 4.

Correlated matrix of the included independent variables was examined to ensure that there were no correlated variables. Variables and interaction terms that reached a probability of 0.10 were entered into the multivariable binary logistic regression model. These variables and interaction terms are summarized in Table 5. Significant single prognostic variables and interaction terms were entered into a multivariable binary logistic regression model. The final model includes significant single prognostic variables and interaction terms summarized in Table 6.

The multivariable binary logistic regression model found four statistically significant single prognostic variables, namely, admission neurological grade, age, time to surgery and post-admission stroke, and four significant interaction terms. These observations are listed as follows:

1. the odds of poor outcome associated with one unit increase in neurological grade is increased by a factor of 2.06,

2. the odds of poor outcome associated with one unit (every 5 years) increase in age is increased by a factor of 1.28,

3. the odds of poor outcome associated with one unit (every hour) increase in time to surgery is increased by a factor of 1.01, and

4. the odds of poor outcome is increased by a factor of 4.0 when the aneurysmal SAH patient experiences post hospital admission stroke.

The multivariable binary logistic regression model also found four statistically significant interaction terms. These observations are listed as follows:

1. the odds of poor outcome is increased by a factor of 2.39 when the aneurysmal SAH patient experiences fever one week post hospital admission and seizures,

2. the odds of poor outcome is increased by a factor of 5.47 when the aneurysmal SAH patient with history of hepatic disease develops cerebral edema,

3. the odds of poor outcome is increased by a factor of 2.66 when the aneurysmal SAH patient with history of hypertension develops cerebral edema, and

4. the odds of poor outcome is increased by a factor of 3.05 when the aneurysmal SAH patient with history of myocardial infarction develops seizures.

The Omnibus Tests of Model Coefficients indicated that this model was statistically significant (chi square = 887.90, $p < 0.01$) [Table 6]. This model showed a large significant reduction in -2 log likelihood (-2 LL from 2240 to 1699, $p < 0.01$). 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 2), the c statistic was 0.87 (95% confidence interval 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 = 0.18, suggesting that the model appeared to fit the data well. Generalizability of model findings was supported by split sample validation (70% training and 30% testing). The following are the findings:

1. no multicollinearity (standard errors for beta coefficients less than 2),

2. individual relationship Wald statistic significance less than alpha level of 0.05, and

3. 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%), and

4. classification accuracy (84.5%) was 1.025 times chance accuracy (82.5%).

Discussion

There has been scarce literature to attempt to characterize complex brain-body associations in patients with ruptured brain aneurysms. This analysis included both non-treatment and treatment related prognostic factors, as well as two-way interactions, which described clinically relevant brain-body associations in aneurysmal SAH.

The main effects logistic regression model confirmed the significance of

neurological grade, age, stroke and time to surgery in outcome prognosis in

aneurysmal SAH.

This study also demonstrates that the odds of poor neurological outcome is

increased by a factor of four in aneurysmal SAH patients who develop post-

admission strokes (OR 4.03, 95% CI 2.11-7.69, p<0.01). With modern modalities

of routine cerebral surveillance imaging over the course of treatment, up to half of

aneurysmal SAH patients have observed non-resolving hypodensities, and

persistent areas of cerebral perfusion deficits, consistent with stroke. It is

increasingly recognized that cerebral infarction after aneurysmal SAH may occur

early after aneurysmal rupture or in a delayed manner. Factors associated with

development of cerebral infarction include admission neurological status,

treatment related complications and occurrence of symptomatic vasospasm[22,39].

Secondary injury cascade events predisposing aneurysmal SAH patients to post

admissions strokes include: (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 circulations.

In addition, this study found that timing to surgical treatment of ruptured

aneurysms is significant in determining neurological outcome. This is supported

from the observation that shorter time interval to treatment is associated with reduction in aneurysmal rebleeding rates[36].

I also make the observation that development of cerebral edema, in the context of history of hypertension and liver disease, has significant impact on neurologic outcome deterioration in aneurysmal SAH.

By itself, development of cerebral edema may predispose the aneurysmal SAH to poor neurological outcome (OR 1.84, 95% CI 1.29-2.62, p<0.01, univariate analysis). Further examination of systemic factors revealed that aneurysmal SAH patients with a history of hypertension and development of cerebral edema have 2.7 fold increased odds of poor neurologic outcome (OR 2.66, 95% CI 1.59-4.45, p<0.01). Patients with a history of hypertension are more prone to defective cerebral autoregulation. When cerebral dysautoregulation is present after aneurysmal SAH, brain engorgement can occur as plasma proteins leak from capillaries with increased permeability. Extracellular vasogenic edema may follow as a result of increased hydrostatic pressures, with predilection for posterior cerebral circulation territories[37,38]. it is important, therefore, to recognize that chronic hypertensive patients have altered elevated blood pressure ranges for autoregulation. It is also essential to monitor for development of cerebral edema in these patients.

This study also makes the novel observation that development of cerebral edema in aneurysmal SAH patients with history of liver dysfunction markedly increases likelihood for poor outcome (OR 5.47, 95% CI 1.13-26.46, p=0.03). Similar to patients with hypertensive history, patients with chronic liver disease have been shown to have altered cerebral autoregulation and cerebral blood flow with decreased cerebral blood flow in the anterior cingulum and increased blood flow in the basal ganglia and occipital lobes at baseline. In acute states of ruptured cerebral aneurysms, these patients' blood brain barriers become disrupted with marked increased cerebral blood flow secondary to luxuriant perfusion, thus, predisposing them to development of vasogenic edema. In addition, cytotoxic osmoregulatory mechanisms are involved whereby astrocytes swell secondary to the toxic effects of ammonia and glutamate. The end result is a vicious cycle of neuronal swelling and death, marked increased in cerebral blood flow (cerebral hyperemia) and cerebral edema[4,7,34,35]. It is important, therefore, to prevent development of hepatic encephalopathy and monitor for cerebral edema in aneurysmal SAH patients who have chronic liver dysfunction.

Seizures post aneurysmal SAH increase mortality. The observed incidence of seizures can be as high as 15% in the aneurysmal SAH patient population[45]. In this study, I observed that seizures increase the odds of poor outcome by a factor of 1.68 (95% CI 1.28-2.21,p<0.01, univariate analysis). However, occurrence of seizures in the clinical settings of post admission fever and background history of

myocardial infarction significantly increases morbidity and mortality. The epileptic

aneurysmal SAH patient who develops post admission fever is predisposed to

poor outcome (OR 2.39, 95% CI 1.86-3.06,p<0.01). Fevers increase cerebral

metabolic rate and can exacerbate secondary injury. Early onset fevers can be

secondary to dysfunction of temperature regulation centers in the hypothalamus

whereas late onset fevers are more likely to be infectious, but can include fevers

secondary to drugs and pulmonary embolism[26,27,33,46]. Exogenous and

endogenous pyrogens increase the propensity for fevers and seizure

development. In febrile states, inflammatory cytokines increase neuronal

excitability via temperature sensitive ion channels leading to increased likelihood

of synchronized neuronal activity[8,19,31]. Not only is it essential to monitor and

treat both seizures and fevers themselves, it is also important to search for

underlying etiologies, including infections, pulmonary embolism, drug-drug

interactions and delayed strokes which may alter seizure thresholds in the febrile

aneurysmal SAH patient.

Finally, our analysis makes the observation that seizures in the setting of history

of myocardial infarction increase the odds of poor outcome by a factor of 3.05 (95%

CI 1.35-6.87, p=0.01). Repetitive autonomic stimulation can occur in the actively

seizing aneurysmal SAH patient in a lock step phenomenon which can trigger the

development of cardiac ictal arrthymias[5,17,28]. Continuous cardiac sympathetic

discharges and cortical epileptiform activity can occur in a synchronized time-

locked manner. These repetitive synchronized autonomic sympathetic discharges lead to cardiac ischemia and structural damage to the myocardium[23]. In aneurysmal SAH patients with preexisting coronary artery disease and seizures, the propensity of cardiac ischemia is increased, along with potentially fatal multi-systemic complications, including development of neurogenic pulmonary edema and respiratory suppression associated with fatal cardiac tachy- or bradyarrthymias, or cardiac asystole. Multi-system critical care cardiovascular and respiratory supports, therefore, are essential in these epileptic aneurysmal SAH patients in order to maximize their chances of survival.

Methodologic Strengths

Our analyses made use of a large multicenter database of aneurysmal SAH patients. I investigated both single prognostic factors and explored brain-body interactions. In so doing, several novel observations were found which significantly influence clinical outcome in aneurysmal SAH patients. Furthermore, I examined model discrimination, calibration and validity.

Limitations

This is a retrospective observational study which included heterogeneous clusters of patients from different geographical regions. Patients of various

genetic backgrounds may exhibit different clinical responses to treatments, such as pharmacokinetic profiles to medications. In addition, the Tirilazad database did not capture important modifiable variables of behaviours including smoking and alcohol consumption. Referral and selection biases are also present as these patients were admitted to and treated at specialized centers with neurosurgical and critical care capabilities. Furthermore, statistical analyses did not take into account non-linear effects and three-way interactions.

Future Directions

Further studies can be carried out to generalize these observations to other aneurysmal SAH patient populations. Further delineation can also be carried out to investigate the impact of brain interactions with other body systems, such as renal system, on neurological outcome in aneurysmal SAH patients.

Acknowledgements

Article Contributions

Conception and design: Lo. Acquisition of data, analysis and interpretation: Lo.

Article writing and revision according to feedback: Lo. Article feedback: Fukuda,

Angle, Teitelbaum, Macdonald, Farrokhyar, Thabane, Levine. Database

provision: Macdonald.

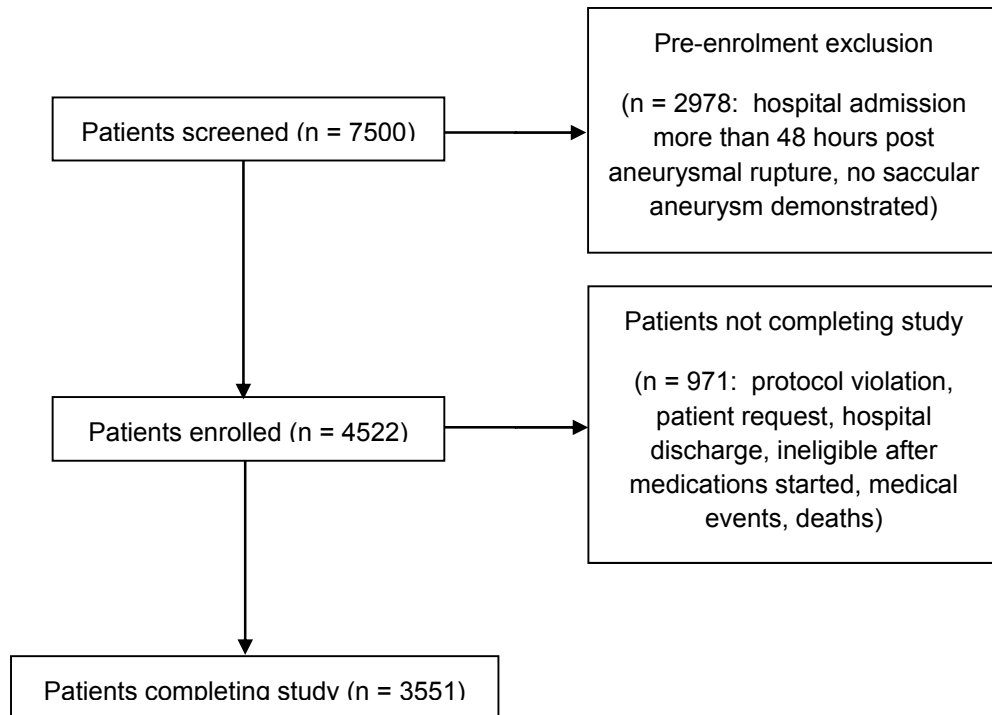Figure 1. Patient selection and participation in the Tirilazad trials.

Figure 2. ROC curve to analyze logistic regression model discrimination. Output
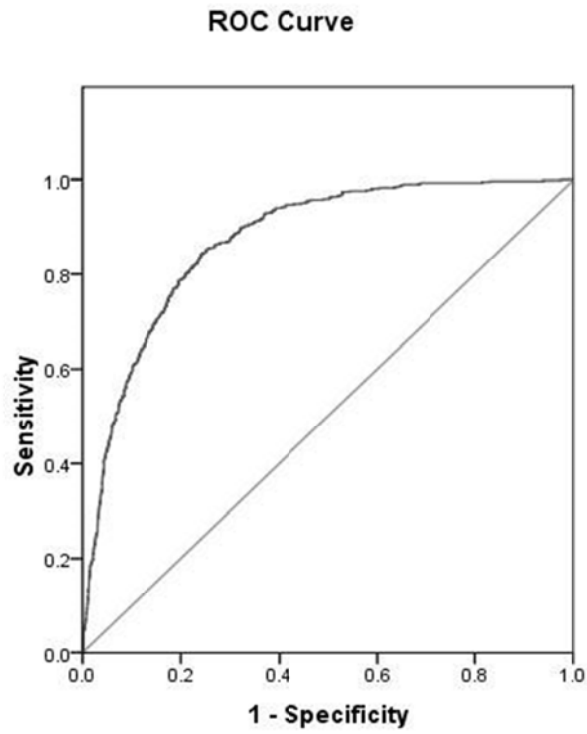figure generated by IBM SPSS Version 19.0[TM] (Armonk NY).

Table 1. Brain-body interface under normal homeostasis and after aneurysmal subarachnoid hemorrhage.

Brain-Body Interface Under Normal Homeostasis	Alterations in Aneurysmal Subarachnoid Hemorrhage
Cardiovascular System -autonomic nervous control of cardiovascular system: 1. counter-regulatory feedback with sympathetic nervous system, and 2. primary relay station being vasomotor regions of the lower brainstem	**Cardiovascular System Dysfunction** -altered autonomic nervous control of cardiovascular system: 1. sympathetic nervous system activation, 2. blood pressure changes sensed by carotid sinus baroreceptors, and 3. blood around lower brainstem triggers catecholamine release from thoracic paravertebral chain
Pulmonary System -automatic control of respiration by lower brainstem's pacemaker cells with additional modifications by: 1. brainstem chemoreceptors and vascular baroreceptors, 2. brain (limbic, hypothalamic and brainstem) inputs and spinal (cervical and thoracic cord) reflexes, and 3. pulmonary local volume and vascular controls	**Pulmonary System Dysfunction** -altered autonomic control of respiration with sympathetic surge: 1. blood oxygen, carbon dioxide and pH levels change and sensed by chemoreceptors and baroreceptors, 2. altered brain and spinal inputs trigger hyperventilation and ataxic breathing patterns, and 3. increased pulmonary vascular permeability and venous pressures leading to hydrostatic pulmonary edema.
Endocrine System -hypothalamic-pituitary axis coordinates key aspects of homeostasis 1. counter-regulatory feedback with target end organs including the adrenal glands	**Endocrinological System Dysfunction** -altered hypothalamic-pituitary axis: 1. sodium and water imbalance triggered by early altered levels of natriuretic peptides and later compensation by the renin-angiotensin-aldosterone system

Table 2. Independent variables recorded in the Tirilazad database.

Demographic Factors	Neurological Factors	Systemic Factors

1. sex
2. age (years)
3. patient's weight (kg)
	Non-Treatment Related Factors
	
	1. hospital admission neurological grade (Hunt and Hess)
	    1 – asymptomatic
	    2 – headaches, cranial nerve palsy
	    3 – mild focal deficit, confusion
	    4 – stupor, moderate to severe hemiparesis
	    5 – deep coma, moribund
	2. aneurysm size ($\leq$ 12 mm or > 12 mm)
	3. presence of angiographic vasospasm on hospital admission
	4. presence of intraventricular hemorrhage
	5. presence of intracerebral hemorrhage
	6. location of aneurysm (anterior or posterior circulation)
	7. thickness of subarachnoid hemorrhage ($\leq$ 1 mm or > 1 mm)
	8. prior episode of subarachnoid hemorrhage
	9. history of migraines
	10. presence of hydrocephalus
	11. development of cerebral edema
	12. occurrence of stroke post admission
	13. development of vasospasm during
		1. systolic blood pressure (mmHg)
		2. diastolic blood pressure (mmHg)
		3. temperature on admission (degree Celsius)
		4. occurrence of fever one week after hospital admission
		5. history of hypertension
		6. history of angina
		7. history of myocardial infarction
		8. history of diabetes mellitus
		9. history of hepatic disease
		10. history of thyroid disease
		11. development of pulmonary edema

| | course of treatment
14. seizures requiring antiepileptic medications

Treatment Related Factors

1. time to surgical treatment (hours)
2. treatment arm
3. severe vasospasm requiring balloon angioplasty | |

Table 3. *A priori* hypotheses for brain-body interactions and their rationale.

Systemic Factors and Rationale for Investigating Brain-Body Interactions
1. age Age, along with clinical pre-operative grade and CT findings are associated with poor neurological outcome in aneurysmal SAH[13,40]. Both cerebral and systemic atherosclerotic changes occur as one ages. 2. hypertension Hypertension is associated with poor neurological outcome in aneurysmal SAH as it predisposes to hemodynamic related structural damage in cerebral blood vessels, including endothelial damage and decreased elasticity of blood vessel wall[1,29]. 3. history of diabetes Diabetes and poor glycemic control are associated with symptomatic vasospasm[9]. Insulin resistance is associated with dysfunction of vascular resistance vessels, including endothelial hypertrophy and altered contractile properties. 4. history of liver disease Hepatic dysfunction is associated with poor clinical grade at hospital admission. During the course of treatment, liver dysfunction is observed in up to 25% of aneurysmal SAH patients[3]. 5. history of thyroid disease Sick euthyroid syndrome may be observed in aneurysmal SAH patients with previously normal functioning thyroid gland. During acute physiological stress, these patients may have decreased amounts of thyroid hormone, and inhibition of thyroxine production by elevated cortisol levels[6,31].

6. occurrence of fever at one week post admission

   Fevers are associated with increased cerebral metabolic rates. Even one episode of fever after aneurysmal SAH can be associated with poor outcome[43].

7. history of myocardial infarction

   Patients with a history of myocardial infarction are prone to troponin elevations and decompensated heart failure after SAH[21]. Those with elevated troponin levels and heart failure are more likely to have significant morbidity and mortality.

Neurologic Factors and Specific *A Priori* Hypotheses

1. neurological grade

   I will investigate the degree by which admission neurological grade influences clinical outcome if the aneurysmal SAH patients also have the following conditions, as they are prone to complications arising from them:
   (1) increasing age (age and neurological grade),
   (2) hypertension (hypertension and neurological grade),
   (3) diabetes (diabetes and neurological grade),
   (4) liver disease (liver disease and neurological grade),
   (5) thyroid disease (thyroid disease and neurological grade),
   (6) fever (fever and neurological grade), and
   (7) myocardial infarction (myocardial infarction and neurological grade).

2. occurrence of stroke post admission

   I hypothesize that aneurysmal SAH patients who experience post admission stroke may have poor clinical outcome if they also have the following conditions:
   (1) increasing age (age and stroke),

(2) hypertension (hypertension and stroke),
(3) diabetes (diabetes and stroke),
(4) liver disease (liver disease and stroke),
(5) fever (fever and stroke), and
(6) myocardial infarction (myocardial infarction and stroke).

Aneurysmal SAH patients with post admission stroke and the aforementioned systemic conditions are predisposed to related complications including rebleeding, seizures, cerebral edema, delayed stroke and vasospasm.

3. development of vasospasm during course of treatment

Aneurysmal SAH patients who experience vasospasm may be predisposed to poor clinical outcome as they are more likely to experience complications including delayed stroke and rebleeding if they concomitantly have the following conditions:
(1) hypertension (hypertension and vasospasm),
(2) diabetes (diabetes and vasospasm),
(3) liver disease (liver disease and vasospasm),
(4) fever (fever and vasospasm), and
(5) myocardial infarction (myocardial infarction and vasospasm).

4. seizures requiring antiepileptic medications

I hypothesize that aneurysmal SAH patients with the following systemic conditions who experience seizures may be predisposed to poor clinical outcome arising from complications including status epilepticus, cerebral edema, vasospasm and delayed stroke:
(1) increasing age (age and seizures),
(2) hypertension (hypertension and seizures),
(3) diabetes (diabetes and seizures),
(4) liver disease (liver disease and seizures),
(5) fever (fever and seizures), and
(6) myocardial infarction (myocardial infarction and seizures).

5. aneurysm size

   Aneurysmal SAH patients with hypertension (hypertension and aneurysm size) and myocardial infarction (myocardial infarction and aneurysm size) may experience rebleeding complicating their clinical course leading to poor clinical outcome.

6. presence of intraventricular hemorrhage

   I hypothesize that aneurysmal SAH patients with intraventricular hemorrhage and the following systemic conditions are more likely to experience complications including hydrocephalus and rebleeding which may lead to poor clinical outcome:
   (1) increasing age (age and intraventricular hemorrhage),
   (2) hypertension (hypertension and intraventricular hemorrhage),
   (3) diabetes (diabetes and intraventricular hemorrhage),
   (4) liver disease (liver disease and intraventricular hemorrhage),
   (5) fever (fever and intraventricular hemorrhage), and
   (6) myocardial infarction (myocardial infarction and intraventricular hemorrhage).

7. presence of intracerebral hemorrhage

   Aneurysmal SAH patients with post admission intracerebral hemorrhage are prone to poor clinical outcome arising from complications including rebleeding, seizures, cerebral edema and vasospasm, if they also have the following conditions:
   (1) increasing age (age and intracerebral hemorrhage),
   (2) hypertension (hypertension and intracerebral hemorrhage),
   (3) diabetes (diabetes and intracerebral hemorrhage),
   (4) liver disease (liver disease and intracerebral hemorrhage),
   (5) fever (fever and intracerebral hemorrhage), and
   (6) myocardial infarction (myocardial infarction and intracerebral hemorrhage).

8. development of cerebral edema

I hypothesize that aneurysmal SAH patients who develop post rupture cerebral edema and, concomitantly, have the following conditions, may be prone to poor clinical outcome:
(1) increasing age (age and cerebral edema),
(2) hypertension (hypertension and cerebral edema),
(3) diabetes (diabetes and cerebral edema),
(4) liver disease (liver disease and cerebral edema),
(5) fever (fever and cerebral edema), and
(6) myocardial infarction (myocardial infarction and cerebral edema).
These patients may experience seizures and delayed stroke as possible related complications.

Table 4. Characteristics of the study patient population.

Characteristic (n = 3551)			
Demographic Factors			
Mean age (years)	51.7 ± 13.2		
Female sex (percent)	2933 (82.6)		
Patient weight (kilogram)	69.5 ± 15.0		
Neurological Factors (Non-Treatment Related)		**Neurological Factors (Treatment Related)**	
Hospital admission neurological grade		Seizures requiring antiepileptic medications (%)	2313 (65.1)
Hunt and Hess Grade 1 (%)	1289 (36.3)		
Hunt and Hess Grade 2 (%)	1045 (29.4)	Mean time to surgical treatment (hours)	0.9 ± 1.9
Hunt and Hess Grade 3 (%)	417 (11.7)	Treatment arm receiving Tirilazad (%)	2173 (61.2)
Hunt and Hess Grade 4 (%)	355 (10.0)	Severe vasospasm needing balloon	158 (4.4)
Hunt and Hess Grade 5 (%)	445 (12.5)	angioplasty (%)	
Aneurysm size ≤ 12 mm (%)	2594 (73.0)		
Presence of admission angiographic vasospasm (%)	412 (11.6)		
Presence of intraventricular hemorrhage (%)	1588 (44.7)		
Presence of intracerebral hematoma (%)	818 (23.0)		
Posterior circulation location of aneurysm (%)	498 (14.0)		
Subarachnoid hemorrhage thickness ≤ 1 mm (%)	1214 (34.2)		
Prior episode of SAH (%)	340 (9.6)		
History of migraines (%)	915 (25.8)		
Presence of hydrocephalus (%)	1497 (42.2)		
Development of cerebral edema (%)	381 (10.7)		
Occurrence of post admission stroke (%)	979 (27.6)		
Development of vasospasm during treatment (%)	1059 (29.8)		

Systemic Factors	
Mean systolic blood pressure (mmHg)	141.2 ± 24.7
Mean diastolic blood pressure (mmHg)	76.6 ± 15.2
Mean temperature on admission (degree Celsius)	37.0 ± 0.9
Occurrence of fever one week after admission (%)	1753 (49.4)
History of hypertension (%)	1217 (34.3)
History of angina (%)	129 (3.6)
History of myocardial infarction (%)	87 (2.5)
History of diabetes mellitus (%)	155 (4.4)
History of hepatic disease (%)	127 (3.6)
History of thyroid disease (%)	291 (8.2)
Development of pulmonary edema (%)	313 (8.8)
Data are presented as the mean ± standard deviation, or as the number of patients (%).	

Table 5. Univariate analysis main effects variables and interaction terms.

Variable Terms	Odds Ratios	95% Confidence Intervals	p value
Main Effects Variables			
Neurological grade	2.06	1.82-2.31	<0.01
Age (years)	1.05	1.04-1.07	<0.01
Time to surgery (hours)	1.00	1.00-1.01	0.03
Fever on day 8	1.94	1.51-2.49	<0.01
Aneurysm size	1.37	1.04-1.80	0.02
Admission vasospasm	1.54	1.04-2.30	0.03
Intraventricular hemorrhage	1.33	1.02-1.73	0.04
Brain Edema	1.84	1.29-2.62	<0.01
Intracerebral hemorrhage	1.39	1.04-1.87	0.03
History of hypertension	1.37	1.05-1.79	0.02
History of myocardial infarction	2.07	1.01-4.27	0.06
Post admission stroke	6.35	4.90-8.24	<0.01
Previous subarachnoid hemorrhage	1.60	1.07-2.39	0.02
Aneurysm location	1.72	1.18-2.51	0.01
Vasospasm	1.58	1.21-2.06	<0.01
Seizures	1.68	1.28-2.21	<0.01

Variable Terms	Odds Ratios	95% Confidence Intervals	p value
Interaction Terms			
Fever on day 8 by aneurysm size	2.63	2.10-3.31	<0.01
Fever on day 8 by intraventricular hemorrhage	3.21	2.68-3.83	<0.01
Fever on day 8 by seizures	2.66	2.24-3.14	<0.01
Brain edema by hepatic disease	3.50	1.24-9.86	0.02
Brain edema by history of hypertension	4.18	2.96-5.91	<0.01
Hydrocephalus by hepatic disease	1.82	1.02-3.23	0.04
History of myocardial infarction by subarachnoid hemorrhage thickness	2.63	1.53-4.53	<0.01
History of myocardial infarction by seizures	3.35	1.86-6.05	<0.01

Table 6. Statistically significant terms in the final binary logistic regression model.

Variable Terms	Odds Ratios	95% Confidence Intervals	p value
Neurological grade	2.06	1.83-2.32	<0.01
Age (per year) [For every Δ5 years]	1.06 [1.28]	1.05-1.07 [1.22-1.42]	<0.01
Time to surgery (hour)	1.01	1.00-1.02	0.02
Stroke	4.03	2.11-7.69	<0.01
Seizures by fever on day 8	2.39	1.86-3.06	<0.01
Brain edema by hepatic disease	5.47	1.13-26.46	0.03
Brain edema by hypertension	2.66	1.59-4.45	<0.01
Seizures by myocardial infarction	3.05	1.35-6.87	0.01

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Chapter Five

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 SAH.

Objectives

The goal of this chapter is to use classification and regression tree analysis

technique to create a prognostic decision making algorithm for aneurysmal SAH

patients.

Methods

The classification and regression tree analysis technique is applied to the

multicenter Tirilazad database (3551 patients) in order to create this 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 is 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

one week post aneurysmal SAH is associated with increased odds of post

admission stroke (OR 1.83, 95% CI 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.

Introduction

Neurologic outcome after aneurysmal 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[8,9].

One of the most frequently used measures of global function outcomes after aneurysmal SAH is the Glasgow Outcome Score. 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[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[1,2,11].

Objectives

Using data from the placebo and treatment arms of the five clinical trials of Tirilazad, I 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.

Methods

The Tirilazad database was used to investigate prognostic subgroups for outcome prediction in aneurysmal SAH patients. The Tirilazad clinical trial study design and patient populations were described in Chapter Four. IBM SPSS Version 23.0[TM] was used to create the CART decision tree.

Candidate predictors included independent variables that reached a probability of
0.10 in univariate logistic regression analysis (refer to Chapter Four). They
include:

1. hospital admission neurological (Hunt and Hess) grade [1 – asymptomatic,
   2 – headaches, cranial nerve palsy, 3 – mild focal deficit, 4 – stupor,
   moderate to severe hemiparesis, 5 – deep coma],

2. age (years),

3. time to surgery (hours),

4. occurrence of post admission fever on day 8,

5. aneurysm size (≤ 12 mm or > 12 mm),

6. presence of angiographic vasospasm on hospital admission,

7. presence of intraventricular hemorrhage,

8. development of cerebral edema,

9. presence of intracerebral hemorrhage,

10. history of hypertension,

11. history of myocardial infarction,

12. occurrence of stroke post admission,

13. prior episode of SAH,

14. location of aneurysm,

15. development of vasospasm during course of treatment, and

16. development of seizures requiring antiepileptic medications.

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

Statistical power was ensured by having effective sample size of more than 10 subjects per variable, and at least 10 patients per final subgroup[1,2,11,17]. For decision tree growing, the Gini index splitting rule was used to decrease variance between classes through reduction of entropy where the largest categories were split into separate subgroups. Overfitting was avoided by using tree pruning[1,2,11,17]. Decision trees were generated with training and testing datasets, with percentages of favourable outcome reported in each terminal prognostic subgroup. Split sample analysis (70% training and 30% testing) was used to examine model performance, with reports of classification accuracy, risk estimate and standard error for each decision tree. Univariate models using chi-square analyses were performed to investigate the associations between explanatory variables generated in the classification trees.

Results

Patient selection and participation in the Tirilazad trials are summarized in Figure 1. In the Tirilazad patient populations, unfavourable outcome (functional

dependence, persistent vegetative state and death) at three months after
aneurysmal SAH was observed in 1061 (30%) of 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 demonstrated seven terminal
prognostic subgroups with the same node ranking order according to
percentages of unfavourable 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% unfavourable outcome (training
    dataset) and 7.4% unfavourable 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%
    unfavourable outcome (training dataset) and 37.4% unfavourable outcome
    (testing dataset),

3. good admission neurological grades, post-admission stroke, age < 58.5
    years (Node #7) – 38.3% unfavourable outcome (training dataset) and
    43.8% unfavourable outcome (testing dataset),

4. poor admission neurological grades, absent post-admission stroke,
    development of post-admission fever (Node #12) – 44.6% unfavourable

outcome (training dataset) and 48.6% unfavourable outcome (testing dataset),

5. good admission neurological grades, post-admission stroke, age > 58.5 years (Node #8) – 59.4% unfavourable outcome (training dataset) and 54.7% unfavourable 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% unfavourable outcome (training dataset) and 61.9% unfavourable outcome (testing dataset), and

7. poor admission neurological grades, post-admission stroke (Node #6) – 75.4% unfavourable outcome (training dataset) and 72.9% unfavourable 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 standard error of 0.008. The model generated using the testing dataset had a classification accuracy of 77%, risk estimate of 0.23 and standard error of 0.01.

The occurrence of fever at one week post-aneurysmal rupture is associated with increased odds of post admission stroke (OR 1.83, 95% CI 1.56-2.45, p<0.01).

Table 1 shows a clinical prognostic decision making algorithm for aneurysmal

subarachnoid hemorrhage 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 unfavourable neurologic outcome in aneurysmal SAH patients

originally presenting with favourable 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) [Refer to Chapter Four]. Patients experiencing vasospasm

are at increased risk of post-admission strokes. Additionally, 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) 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, as it also triggers events in the secondary cascade of neurological injury. The 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) [refer to Chapter Four]. 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 one 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 in order to test an intervention, rather than for clinical prognostic purposes. Since the conduct 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, as 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 chapter 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 to 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.

Acknowledgements

Article Contributions

Conception and design: Lo. Acquisition of data, analysis and interpretation: Lo.

Article writing and revision according to feedback: Lo. Article feedback: Fukuda,

Angle, Teitelbaum, Macdonald, Farrokhyar, Thabane, Levine. Database

provision: Macdonald.

Figure 1 – Patient selection and participation in the Tirilazad trials.

Patients screened (n = 7500)

Pre-enrolment exclusion

(n = 2978: hospital admission more than 48 hours post aneurysmal rupture, no saccular aneurysm demonstrated)

Patients enrolled (n = 4522)

Patients not completing study

(n = 971: protocol violation, patient request, hospital discharge, ineligible after medications started, medical events, deaths)
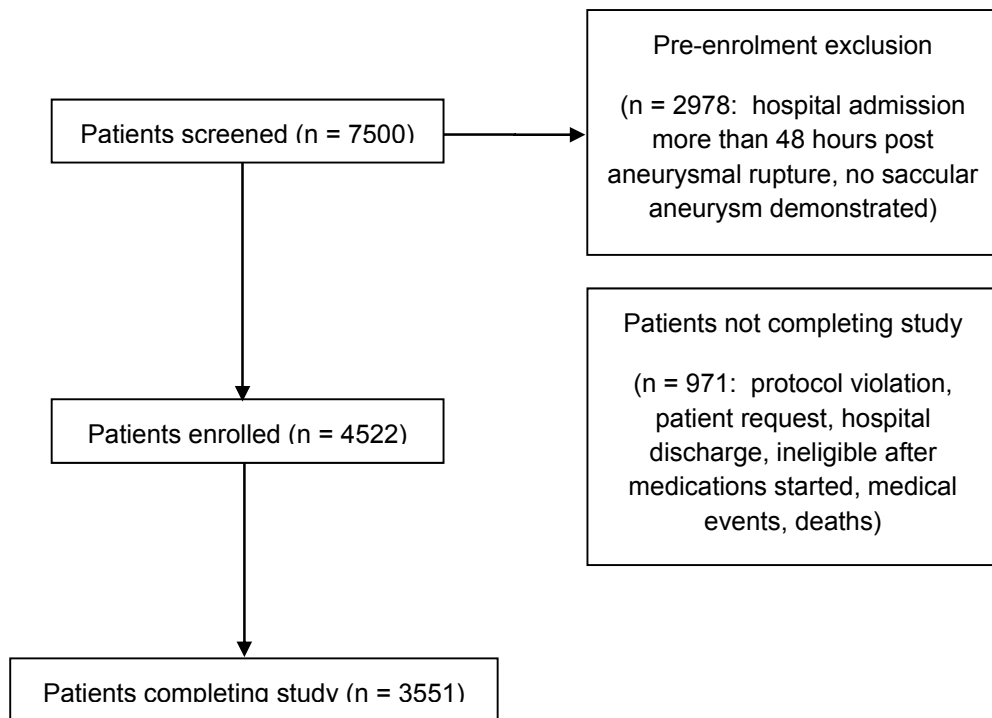
Patients completing study (n = 3551)

Figure 2 – Classification tree describing the relationships between neurological outcome and explanatory factors in aneurysmal subarachnoid hemorrhage (training data set). [For Node 0 (Outcome), 0 = favourable outcome (GOS 5 and 4), 1 = unfavourable outcome (GOS 3,2 and 1). For Nodes 1-12, 0 = absent, 1 = present.]
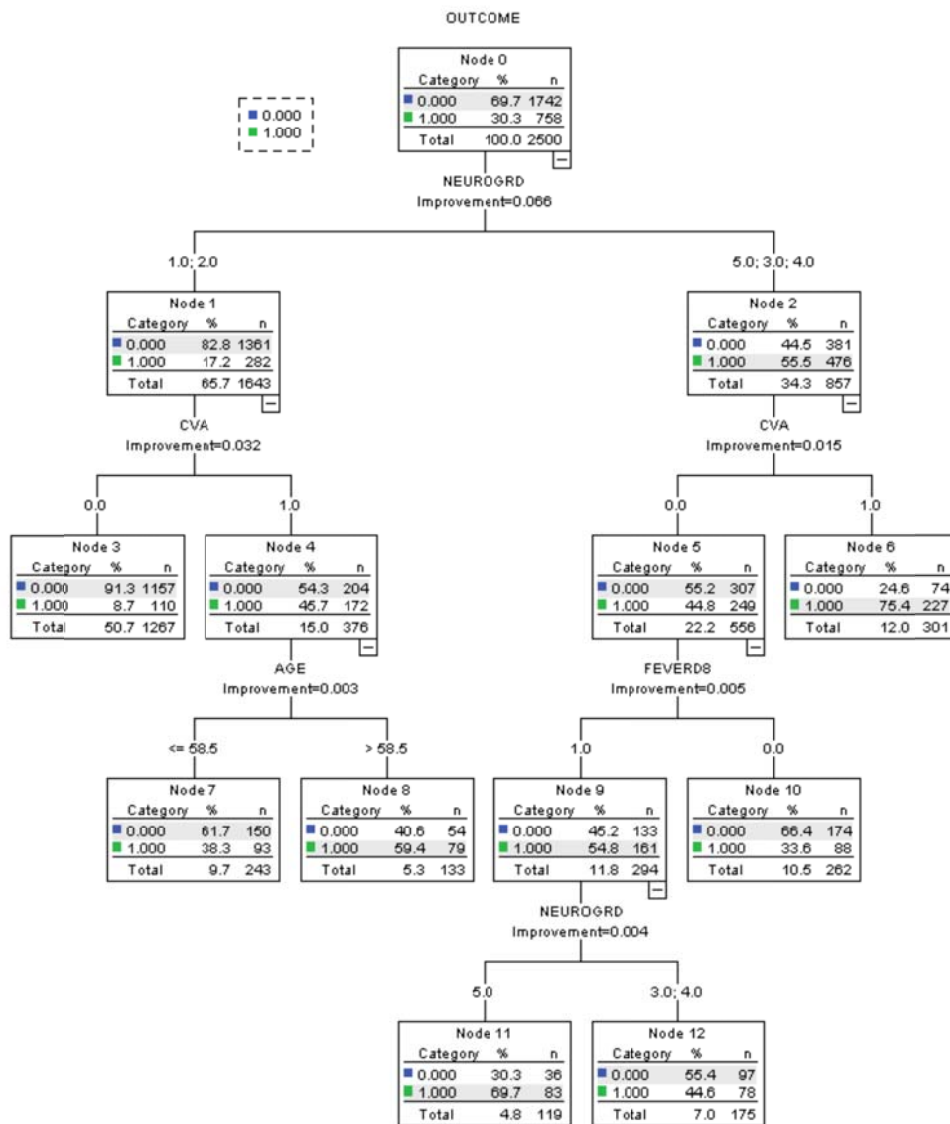
Figure 3 – Classification tree describing the relationships between neurological outcome and explanatory factors in aneurysmal subarachnoid hemorrhage (testing data set). [For Node 0 (Outcome), 0 = favourable outcome (GOS 5 and 4), 1 = unfavourable outcome (GOS 3,2 and 1). For Nodes 1-12, 0 = absent, 1 = present.]
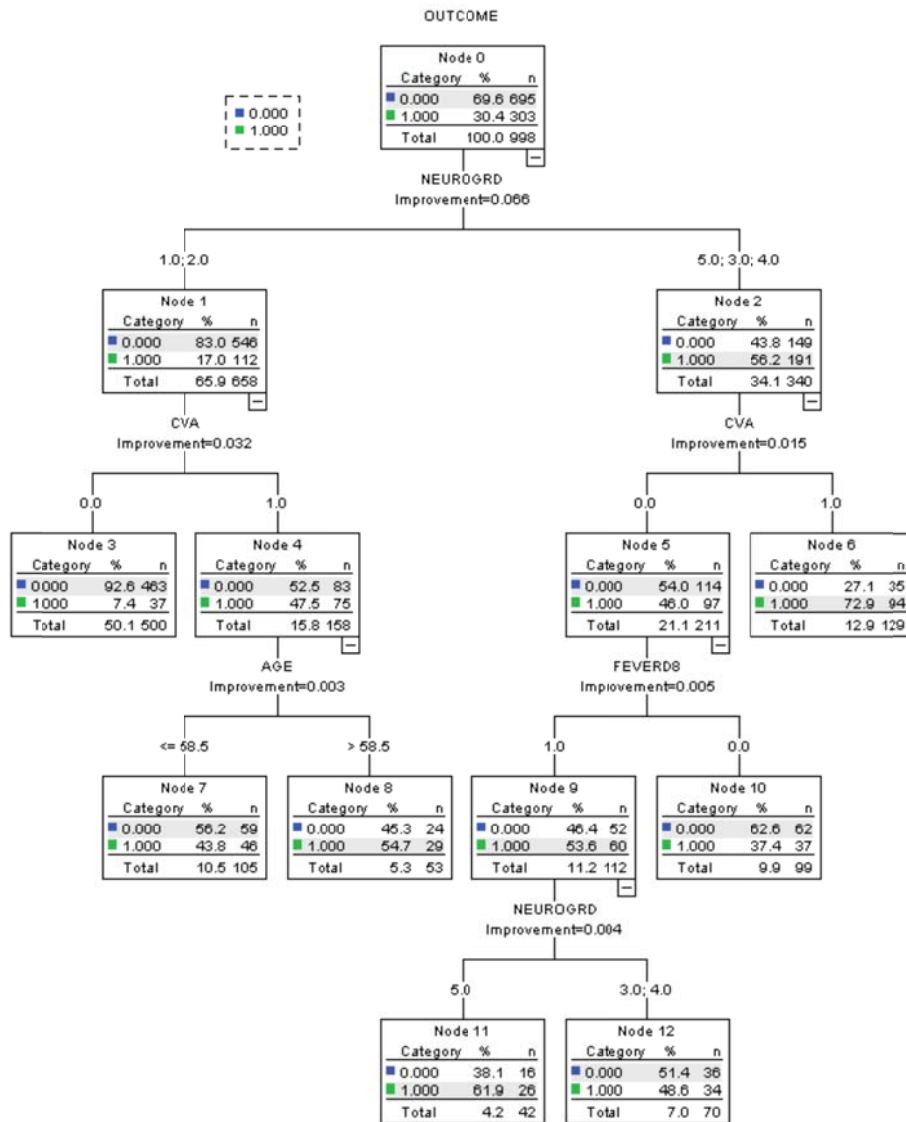
Table 1 – Clinical prognostic decision making algorithm in aneurysmal

subarachnoid hemorrhage, with prognostic subgroups based on classification

and regression tree derived from the Tirilazad database

Admission neurological grade	Age = 58.5 years	Post-admission fever	Post-admission stroke	Unfavourable outcome (%)	
Poor	Older	Present	Present	75.9%	>75% very high
Poor	Older	Absent	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	Absent	Present	55.4%	
Good	Older	Absent	Present	44.0%	25-50% inter-mediate
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%	

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Chapter Six

Conclusions

This chapter summarizes key findings from this dissertation, and discusses future directions.

Chapter Two presented a systematic review and critical appraisal of methodologic quality of existing studies that derive clinical predictor tools and clinical predictors used to determine outcome prognosis in patients with aneurysmal SAH. The most frequently retained significant clinical prognostic factors for long-term neurologic outcome prediction include age and neurological grade. Yet, systematic reviews for clinical prognostic factors and clinical prediction tools in aneurysmal SAH have a number of methodological challenges. Several factors should be taken into account when determining the effect sizes of individual prognostic factors, including within and between study patient heterogeneity, variations in treatment, patient referral biases and prognostic viewpoints across different cultures.

Chapter Three presented a systematic review and critical appraisal of cohort studies that attempt to clarify pathophysiologic mechanisms of brain-body associations in aneurysmal SAH. Aneurysmal SAH affects the cardiopulmonary

system with subsequent neuro-cardio-endocrinological responses as part of the secondary injury cascade in response to the primary ictus of aneurysmal SAH. Sympathetic activation of the cardiovascular system in aneurysmal SAH not only triggers the release of atrial and brain natriuretic peptide, it can also lead to increased pulmonary venous pressures and permeability causing hydrostatic pulmonary edema. Natriuretic states can herald the onset or worsening of clinical vasospasm as the renin-angiotensin-aldosterone system is activated in a delayed manner.

The brain-body interface comprises many physiological interactions which can go awry in disease states. Chapter Four characterizes brain-body associations that are essential in influencing outcome in patients with ruptured brain aneurysms. The main effects logistic regression model in this chapter demonstrated the significance of neurological grade, age, stroke and time to surgery in outcome prognosis in aneurysmal SAH patients. Interactions analyses demonstrated that aneurysmal SAH patients with history of hypertension and liver disease are predisposed to poor neurological outcome if they have concomitant cerebral edema. These patients have impaired cerebral autoregulation with disrupted blood brain barriers and altered collateral circulations. In addition, the epileptic aneurysmal SAH patient who develops post admission fever and myocardial infarction are predisposed to poor neurological outcome. Fevers increase cerebral metabolic rate and exacerbate secondary injury, including vasospasm-

induced delayed strokes. Repetitive synchronized autonomic sympathetic discharges lead to cardiac ischemia and structural damage of the myocardium.

Chapter Five uses classification and regression tree technique to create a decision making algorithm for aneurysmal SAH patients, a tool which can aid bedside prognostication and clinical treatment decision making. The decision tree revealed seven prognostic subgroups with important explanatory nodes including neurological grade, age, post admission fever and post admission stroke. In addition, post admission fever is demonstrated to be associated with increased odds of post admission strokes, including vasospasm-induced cerebral ischemia.

Future Directions

Given the rapid advances in diagnosis and treatment of aneurysmal SAH, future studies should aim to generalize brain-body associations as well as decision making algorithms to other aneurysmal SAH patient populations, particularly those who undergo endovascular treatment of aneurysms and those treated in specialized neurocritical care units. Additional studies on pathophysiologic mechanisms of brain-body interactions in aneurysmal SAH will further shed light on how the brain communicates with other body systems under states of physiologic stress. Furthermore, investigations will be performed to see whether

these associations in an altered brain-body interface are observed in patients

with other acute cerebrovascular disorders, including ischemic and hemorrhage

strokes.