Surgical Neurology International

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Editor: **James I. Ausman,** MD, PhD University of California, Los Angeles, CA, USA

Original Article

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

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Received: 02 September 14 Accepted: 17 June 15 Published: 11 August 15

This article may be cited as:
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;6:135.
http://surgicalneurologyint.com/Systematic-review-of-clinical-prediction-tools-and-prognostic-factors-in-aneurysmal-subarachnoid-hemorrhage/

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 systemic 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.

Conclusions: 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.

Keywords: Aneurysmal subarachnoid hemorrhage, aneurysms, clinical outcome prediction, health research methodology, prognosis, systematic review

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.162676
Quick Response Code:

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 subarachnoid hemorrhage.

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 of at least 10 patients cases 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), 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 mortality 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 search terms aneurysmal SAH, clinical prognosis, 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 2,863 citations [Figure 1]. Screening by title and abstract and citation yielded 121 items. Of these 121 items, reviewers BL and HF reached agreement on 70 items for inclusion, 42 items for exclusion, 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).

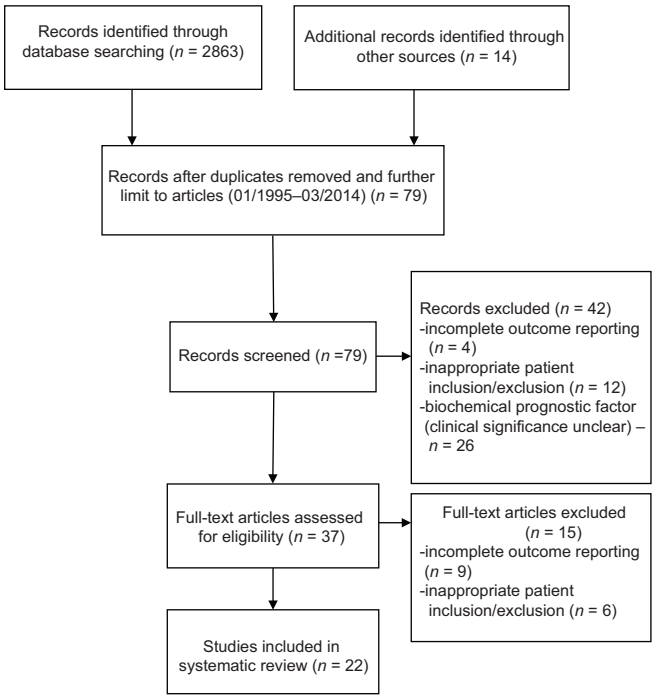

Figure 1:Flow diagram of study selection

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, and inappropriate predictor models used.

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 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.

Methodologic quality assessment

For this systematic review, we sampled the quality checklist using Delphi methods for prescriptive 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:

- Study design – Including description of study protocol, inclusion and exclusion criteria, study setting, and recruitment
- Patient population – Including representativeness of exposed cohort and ascertainment of exposure
- Candidate predictors – Including description of predictors used, selection and coding of data, inclusion of potential confounding variables
- Outcome – Including definition of outcomes, justification of outcomes, their reproducibility, length of follow-up, and outcome assessment when appropriate
- Statistical power – Ensuring effective sample size
- Statistical models – Description of mathematical methods used, and whether they are statistically sound and clinically sensible
- Bias assessment – Such as publication bias, selection bias, recall bias, and ascertainment bias
- Model performance and validation – Descriptions of any attempts to evaluate, if appropriate, model performance and validation
- 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, and 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 and 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 (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]).

Methodological quality of included studies

The included 22 studies all had thorough descriptions of study protocols, including inclusion and exclusion

Table 1: Variables investigated in existing clinical prognostic models in aneurysmal SAH

	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 re-bleeding 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 GCS 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 Re-bleeding Intraoperative cerebral swelling Postoperative GCS	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)
Juvela[14]	Clinical condition at admission (GCS) Re-bleeding 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 h) Early pulmonary infiltrates (<72 h)	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)
McGirt *et al.*[23]	Glucose level	Hunt and Hess grade Cerebral vasospasm Age Hypertension Ventriculomegaly on CT	Poor outcome (Glasgow Outcome Score 1-3)
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%

Contd...

Table 1: Contd...

	Independent variables	Independent variables controlled for during analysis	Dependent variables
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)
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 Preexisting 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 SAH 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)

Contd...

Table 1: Contd...

	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 1-3)
Van den Bergh *et al.*[37]	Magnesium level Amounts of cisternal and ventricular blood	Duration of unconsciousness Sex Re-bleeding Level of consciousness at admission	Poor outcome (WFNS grades 4 and 5)
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

WFNS: World federation of neurological surgeons; CT: Computed tomography; GCS: Glasgow coma score; SAH: Subarachnoid hemorrhage

Table 2: Methodological assessment of clinical prognostic models on aneurysmal SAH

	Chiang *et al.*[7]	Claassen *et al.*[8]	Germanson *et al.* 10	Heuer *et al.*[11]	Juvela[14]	Kahn *et al.*[15]
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 and sample size	Univariate	Univariate Multivariable	Univariate Multivariable	Univariate Multivariable	Univariate Multivariable	Univariate Multivariable
	>10 subjects per variable	>10 subjects per variable	CART >10 subjects per variable	>10 subjects per variable	>10 subjects per variable	>10 subjects per variable

Contd...

Table 2: Contd...

Validation	None	C-statistic	None	None	Hosmer-Lemeshow	Hosmer-Lemeshow
Bias	Recall bias	No major	No major	Ascertainment bias	Recall bias	No major
Funding	Not stated	Declared	Declared	Not stated	Declared	Declared
	Kramer *et al.*[17]	**Krishnamurthy *et al.*[18]**	**Lindvall *et al.*[20]**	**McGirt *et al.*[23]**	**Miss *et al.*[24]**	**Mocco *et al.*[25]**
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 and sample size	Univariate Multivariable 10 subjects per variable	Univariate Multivariable >10subjects 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	C-statistic	None	None	None
Bias	No major	Recall bias Selection bias Referral bias	No major	No major	No major	Selection bias Referral bias
Funding	Declared	Not stated	Declared	Declared	Declared	Declared
	Naidech *et al.*[26]	**Ogilvy *et al.*[28]**	**Qureshi *et al.*[29]**	**Rabinstein *et al.*[30]**	**Risselada *et al.*[32]**	**Rosengart *et al.*[33]**
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 and 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.*[34]	**van den Bergh *et al.*[37]**	**Yoshimoto *et al.*[38]**	**Karamanakos *et al.*[16]**
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 and 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

RCT: Randomized controlled trial; SAH: Subarachnoid hemorrhage; CART: Classification and regression tree

criteria. Representative patient cohorts were included in these studies. With the exception of one study (Soehle *et al*. 2007[34]), all studies had adequate patient sample sizes to ensure effective study power. 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. 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. 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.

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:

- Studies that provide clear definitions of predictor variables
- Studies with adequate study effective power and sample sizes, and
- 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 the 22 studies checked for model performance. Lack of knowledge about these model performance parameters may perpetuate one's lack of awareness about other possible entities that may influence the clinical prediction model, like potential interactions that may exist between core predictors.

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.

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