Patient functional outcomes after cerebrovascular neurosurgery: a comparison of function and quality of life after conservative or surgical management of unruptured intracranial aneurysm and brain arteriovenous malformation

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Declaration of originality

I hereby declare that the work presented in this thesis has not been submitted for a higher degree to any other university or institution. To the best of my knowledge this submission contains no material previously published or written by another person, except where due reference is stated otherwise. Any contribution made to the research by others is explicitly acknowledged. Ethics Committee approvals for all patient data collected were obtained from Macquarie University (Number: 5201401165).

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Publications

Journal publications

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3. **O'Donnell, J. M.,** Al-Shahi Salman, R., Manuguerra, M., Assaad, N., & Morgan, M. K. (2018). *Quality of life and disability 12 months after surgery vs. conservative management for unruptured brain arteriovenous malformations: Scottish population-based and Australian hospital-based studies*. Acta Neurochirurgica, 160:559-66: doi:10.1007/s00701-017-3451-2
4. **O'Donnell J.M**., Morgan M.K., Manuguerra M., (2018) *Patient functional outcomes and quality of life after surgery for unruptured intracranialaneurysm*. Journal of Neurosurgery, March 2: ISSN: 0022-3085; DOI: 10.3171/2017.8.JNS171576
5. Lai, L. T., **O'Donnell J**., Morgan M.K. (2013). *The risk of seizures during the in-hospital admission for surgical or endovascular treatment of unruptured intracranial aneurysms*. Journal of Clinical Neuroscience 20(11): 1498–1502.
6. **O'Donnell J**., Morgan M.K., Savage G., Bundy A., *Measuring Functional Outcomes Following Surgery for Unruptured Intracranial Aneurysms and Brain AVM: Validity and Reliability of Past and Present Instruments* (2013). Australian Occupational Therapy Journal Supplement 60: 24.
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Results on Drivesafe Driveaware (2013). Australian Occupational Therapy Journal Supplement 60: 48.

8. **O'Donnell J.,** Morgan M.K., Savage G., Bundy A., *DriveSafe DriveAware: A Normal Population Test Retest Reliability Study* (2013). Australian Occupational Therapy Journal Supplement 60: 3.
9. **O'Donnell J**., Morgan M.K., Reply to Letter to the Editor: Quality of life of patients affected by unruptured brain AVMs. Journal of Neurosurgery Apr 2015 / Vol. 122 / No. 4 / Pages 984–986

Conference proceedings

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Declaration of contributions for papers submitted or published

Chapter 2

Patient functional outcomes after surgery for unruptured intracranial aneurysm

O'Donnell, J.M. – study design, data collection and analysis, manuscript draft
Ritson E. – data collection
Managuerra M. – data analysis advisory
Morgan M.K., – academic advisory and manuscript correction
Savage G., Bundy A. – academic advisory

Chapter 3

Patient functional outcomes after surgery for brain arteriovenous malformation

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Ritson E. – data collection
Managuerra M. – data analysis advisory
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Chapter 4

The risk of seizure following surgery for unruptured intracranial aneurysms: A prospective cohort study

O'Donnell J.M.– data analysis and manuscript draft (co-author)
Morgan, M.K. – study design, data analysis and manuscript draft (co-author)
Bervini D., – data analysis and manuscript revision

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The risk of seizures during the in-hospital admission for surgical or endovascular treatment of unruptured intracranial aneurysms

Lai, L.T. – study design, data analysis and manuscript draft (author)
O'Donnell, J.M. – section manuscript draft (co-author)
Morgan, M.K. – academic advisory and manuscript correction

Chapter 5

The risk of seizure following surgery for brain arteriovenous malformation: A prospective cohort study

O'Donnell J.M. – data analysis and manuscript draft (co-author)

Morgan, M.K. – study design, data analysis and manuscript draft (co-author)

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Chapter 6

Quality of life after conservative management or surgical treatment of unruptured brain arteriovenous malformations: A study of Scottish population and a prospective Australian cohort

O'Donnell J.M. – study design, data collection and analysis, manuscript draft

Al-Shahi Salman, R. – study design, data collection, manuscript revision

Managuerra, M., Morgan, M.K. – academic advisory and manuscript correction

Chapter 7

Comparing outcome scales after surgery for unruptured intracranial aneurysms and brain arteriovenous malformations: A prospective cohort study.

Morgan, M.K. – study design, data analysis and manuscript draft (co-author)

O'Donnell J.M. – study design, data collection and manuscript draft (co-author)

Rogers, J.M., Heller G.Z. – academic advisory and manuscript correction

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Abstract

The consequences of a haemorrhage from an intracranial aneurysm (IA) or brain arteriovenous malformation (AVM) rupture can cause a significant impact on a patient's quality of life (QOL). In addition, the knowledge of the presence of an unruptured IA (uIA) or unruptured brain AVM can also have a negative impact on such a person's QOL. The primary aim of surgery for uIA and unruptured brain AVM (AVM) is to prevent their subsequent rupture. However, studies have questioned the effectiveness of surgery for the management of uIA and unruptured AVM.(Wiebers, Whisnant et al. 2003, Mohr, Parides et al. 2014) The instrument employed in these studies for measuring success or failure of treatment is a disability scale that considers the level of function of everyday living tasks, the modified Rankin Scale (mRS).(Rankin 1957, Van Swieten 1988, Koudstaal et al. 1988) Although everyday living tasks may include driving, whether or not a patient can return to driving has hitherto been poorly defined and unstudied. This thesis examined the effectiveness of surgical management of uIA and AVM by measuring performance of self-care tasks, patients' perceived quality of life, cognitive abilities related to driving and restriction of driving due to the risk of seizures after surgery. There are two categories that may impact upon these patients returning to driving, constant persistent disabilities and the episodic events of seizures.

Section 1 of this thesis outlines investigations into the functional outcomes of surgery for uIA and AVM. Patients referred to Macquarie University (MQ) for management of uIA and AVM were assessed pre-operatively and at each follow up for 12 months using the modified Barthel Index (mBI), the modified Rankin Scale (mRS), DriveSafe DriveAware, and the Short Form 36 (SF36) Quality of Life (QOL) questionnaire. The SF36 subscales of Physical Component Score (PCS) and Mental Component Score (MCS) were used in analyses. There was no overall significant decline in function or QOL 12 months after surgery for uIA or AVM for the cohort.(O'Donnell J. 2013) There was no significant difference in the DriveSafe scores between the surgical group and the conservative group at 12months (mean 112 SD10, mean 110 SD8.7 respectively; p=0.23 mean difference 2.62 95%CI -1.7 to 6.9).There was no significant difference in function or QOL after one year between conservatively managed and surgically managed uIA patients (DriveSafe p=0.23, PCS p=0.51, MCS p=0.54). Surgically managed uIA patients experienced a temporary decline in QOL immediately after surgery, however QOL returned to pre-operative levels one year after surgery (52 SD 8.1, 46 SD 6.8

and 52 SD 7.1 respectively)(p<0.01) (paper submitted for publication). The AVM study showed surgical resection of AVM does not affect function or QOL for low-grade AVM. There was no significant difference in decline in function in conservatively managed or surgically managed AVM one year after initial presentation or surgery, respectively (p=0.43). Functional outcomes after surgery were better for lower SpetzlerPonce (SP) grade than higher grade AVMs (SP C versus B [p=0.04, mean difference -14.6, 95%CI -28.6 to -0.6] and the SP C versus A [p=0.04, mean difference -12.4, 95%CI -24.3 to -0.4]). Function and QOL were not compromised by conservative management of high grade AVM, while surgical repair of low grade AVM may improve QOL (PCS p<0.01; MCS p=0.02) without affecting function (paper submitted for publication).

The risk of seizure after discharge from hospital for surgical repair of a uIA or an AVM was examined in section 2 to determine if seizure risks would inhibit participation in work and driving.(Lai, O'Donnell et al. 2013) A neurosurgical retrospective cohort of uIA and AVM patients was analysed to examine the incidence of post-operative seizures. The risk of seizures after discharge from hospital following surgery for uIA, when there is no pre-existing risk of seizures and no complications as a result of surgery, is low (<0.1% and 1.1% at 12 months and 7 years respectively).(O'Donnell, Morgan et al. 2016) For AVM, the risk of seizures increases with the maximum diameter of the AVM and a patient history of more than two preoperative seizures.(O'Donnell, Morgan et al. 2017) The 7-year risk of developing postoperative seizures ranged from 11% for patients with AVM ≤ 4 cm and with 0 to 2 preoperative seizures, to 59% for patients with AVM >4 cm and with >2 preoperative seizures.(O'Donnell, Morgan et al. 2017)

The third section of this thesis investigated the outcomes of cerebrovascular surgery by examining QOL compared with disability ratings and function. The QOL of conservatively managed unruptured AVM was compared with surgically managed unruptured AVM in 2 separate cohorts.(O'Donnell and Morgan 2015) Results on 79 Scottish and 41 MQ patients found a significant relationship between mRS and QOL in the combined cohort (p < 0·01) but did not find significant differences in the QOL scores between conservatively and surgically managed uAVM (paper submitted for publication). The thesis concludes with the importance of using a broad range of instruments to assess patients outcomes related to disabilities and QOL following surgery for uIA and AVM. The final paper submitted for publication found poor correlation between the MCS subscale of the SF36 QOL scales and the instrument of disability commonly used to judge outcomes (mRS). This study

demonstrated that both the results of DriveSafe instrument and the PCS subscale of SF36 correlated with mRS. However, for a more comprehensive picture of a patient's recovery from surgery, QOL and Drivesafe scores should be added to the mRS.

Based on our results, we concluded that surgery can be generally effective without compromise with respect to function or QOL for the management of uIA or AVM. Functional cognitive screening is recommended prior to surgery for AVM. Consideration should be given for psychological support when individual SF36 results indicate low pre-operative MCS scores. Indicators for the restriction of driving after surgery for uIA and AVM have been identified.

Chapter 1: *Measuring function in cerebrovascular neurosurgery: An introduction*

1.1 Abstract

Traditionally, the effectiveness of surgical treatment of unruptured intracranial aneurysms (uIAs) and brain arteriovenous malformations (bAVMs) has been measured using rating scales administered by the treating surgeon. The tools are based on neurological recovery such as level of handicap rather than the ability to perform tasks related to everyday living.

Our objective was to identify the most commonly used scales to measure outcome after uIA and bAVM surgery and review their psychometric qualities. A literature search was conducted of uIA and bAVM surgery outcome studies and reviewed for scales used to report outcomes. The frequency of scales used was analysed, eliminating duplication of publications from the same patient populations. A literature search of validity and reliability of the identified scales was conducted. Thirty-five articles were identified for investigation. The modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS) are the most commonly used scales in recent studies. Not all studies stated a criterion for morbidity, and different criteria were applied to scores to define morbidity. The authors were not able to locate evidence supporting the validity of the mRS or GOS with the uIA and bAVM populations. The reliability of both scales has been investigated with varying results.

The validity of the mRS and GOS as instruments for measuring the outcome after surgery for uIA and bAVM patients is not established. Scales that measure performance of relevant functional tasks with sound psychometric qualities need to be identified and implemented in future studies.

1.1.1 Introduction

The impact of surgery for uIA and bAVM on the functional quality of life for patients is an area of increasing focus and study.(Lai, O'Donnell et al. 2013) Consistency in measuring and reporting outcomes is needed in order to compare the effectiveness of various treatments. Inconsistent results in outcome studies may be attributed to the application of different scales and criteria for morbidity.(Wiebers 1998, Towgood, Ogden et al. 2005)

The distinction between neurological and functional outcomes needs to be identified.(Sanchez, Ogilvy et al. 2007) Neurological outcome implies measurable resolution of CNS pathology, whereas functional outcome refers to the recovery of activities of daily living (ADL) without necessarily implying recovery from impairment. It is not sufficient for clinicians to be concerned with neurological recovery and not their patients' reintegration back into their former lives, as manifest in skills such as the ability to drive. The aim of surgical treatment of uIA and bAVM is to return the patient to full function with no residual symptoms. Measurement of this goal should be undertaken at one of the highest level of cognitive performance in everyday living, which in most western societies is driving a motor vehicle. The challenge is to identify functional scales that measure tasks relevant to the majority of people within cultural and environmental boundaries that have sound psychometric properties. In addition, such tasks need to be easily and efficiently administered for the benefit of the patient and clinician respectively.

With increasing variation in treatments for uIA and bAVM, reliable and valid instruments for the measurement of functional independence are necessary to judge which procedure is best .(Bederson, Awad et al. 2000, van der Schaaf, Brilstra et al. 2002) The sophistication of the information to be gleaned from an examination of the patient is increasing in complexity. Whilst assessment of gross neurological deficits has been the mainstay of assessing the outcomes for brain surgery, the functional health, arguably of at least equal importance, is less well understood. The context in which the instruments for assessing functional health are applied, as well as the relationship between the observed and observer, could influence the outcome from these scales. Therefore there is a need to demonstrate validity and reliability of such instruments in specific contexts. Such a context is the uIA and bAVM patient populations.

There have been recommendations and attempts to measure outcome by focusing on function.(King Jr, Horowitz et al. 2005, Starke, Komotar et al. 2008) Our aims are twofold: to explore the literature to identify the most commonly used scales to assess functional outcomes for the uIA and bAVM population; then to seek evidence of validity and reliability of the identified scales.

1.1.2 Methods

The Medline database was searched combining the MeSH terms “intracranial aneurysm”, “intracranial arteriovenous malformation” and “treatment outcome”, with the keyword “unruptured”. These terms were also used to search the Cochrane Database of Systematic Reviews, Scopus and Google Scholar. The bibliographies of identified manuscripts were also reviewed and used as an additional data source. No unpublished studies were included.

Inclusion criteria were English language articles and human studies. Papers reporting results for both unruptured and ruptured intracranial aneurysm or bAVM within the same study were included. Abstracts from each search were read to identify studies measuring functional outcomes for uIA or bAVM management. Papers solely reporting radiological outcomes were excluded. Where multiple articles related to the same investigated population or treatment facility, only one article was included in the final count.

From the results of this search, the reliability and validity of the most commonly used scales were then investigated to determine whether they had been applied to the uIA and bAVM populations. A literature search of Medline, Scopus and Google Scholar was conducted using the terms “validity”, “reliability”, “Rankin”, “Glasgow Outcome”.

1.1.3 Results

Thirty-five articles were identified for investigation.(Hartmann, Stapf et al. 2000, Johnston, Wilson et al. 2000, Mine, Hirai et al. 2000, Raaymakers 2000, Chyatte and Porterfield 2001, Hillman 2001, Roy, Milot et al. 2001, ApSimon, Reef et al. 2002, Nanda and Vannemreddy 2002, Wiebers, Whisnant et al. 2003, Molyneux, Cekirge et al. 2004, Kim, Haney et al. 2005, King, Kassam et al. 2005, Towgood, Ogden et al. 2005, Pollock and Brown Jr 2006, Solheim,

Eloqayli et al. 2006, Higashida, Lahue et al. 2007, Nataf, Schlienger et al. 2007, Steven, Lownie et al. 2007, Yamashiro, Nishi et al. 2007, Cantore, Santoro et al. 2008, Jayaraman, Marcellus et al. 2008, Da Costa, Thines et al. 2009, Davidson and Morgan 2010, Zhao, Yu et al. 2010, Andaluz and Zuccarello 2011, Jang, Jung et al. 2011, Laakso, Dashti et al. 2011, Panagiotopoulos, Ladd et al. 2011, Saatci, Geyik et al. 2011, Szmuda and Sloniewski 2011, van Dijk, Groen et al. 2011, Yue 2011, Seule, Stienen et al. 2012, Thines, Bourgeois et al. 2012) The International Study of Unruptured Intracranial Aneurysms (ISUIA)(Wiebers, Whisnant et al. 2003) is a multicentre study and not specified as from one institution. One study used hospital utilisation data and no measurement scales to investigate outcomes.(Higashida, Lahue et al. 2007) Overall, the methods of measuring outcomes in recent studies of uIA and bAVM outcomes show higher frequency in the use of scales with verified scientific properties than in previous decades. The Modified Rankin Scale and Glasgow Outcome Scale are the most commonly used scales in recent studies of uIA and bAVM outcomes. Investigation of the studies examining morbidity using the mRS and GOS indicate a need for consensus on the criteria used for reporting morbidity to ensure consistency in the communication of outcomes.

All studies discussed morbidity results based on the scale, yet different criteria were applied to scores to define morbidity. Not all studies stated a criterion for morbidity, and of those using the mRS, the majority stated a rating of greater than 2 (that is, 3 or higher) as the definition of morbidity (Table 1.1). However, some studies used an mRS rating of greater than 1 (2 or higher). There was no trend in morbidity criteria for studies that investigated ruptured and unruptured IA nor solely unruptured IA. Of the studies of ruptured and unruptured IA, six applied a morbidity criterion of greater than 2 and two studies applied a criterion of greater than 1. All bAVM studies in this analysis included ruptured and unruptured bAVMs. The difference in outcomes between a score of 2 or 3 is “slight” to “moderate” disability respectively. The significant functional difference is the level of assistance required to perform all previous activities independently. Other studies rated morbidity as a decline in mRS score by one or two grades, which does not allow for comparison between studies without presentation of premorbid scores.

Table 1.1: Morbidity determined by mRS

Author & year	Institution	Pathology	Patients	Ruptured and/or Unruptured	Other published scales	mRS cut off
King 2005	Yale Uni USA	aneurysm	166	both	Yes	not given
Kim 2005	Harvard Medical School USA	aneurysm	520	both	Yes	not given
Johnston 2000	Uni of California USA	aneurysm	130	unruptured	Yes	change of 2
Towgood 2005	Middlemore Hospital NZ	aneurysm	26	unruptured	Yes	>2
Molyneux 2004	Radcliffe Infirmary, UK	aneurysm	119	both		>2
Nataf 2007	St Anne Hospital France	avm	78	both		not given
Pollock 2006	Mayo Clinic USA	avm	243	both	Yes	decline of 1
Wiebers 2003	* Mayo - ISUIA	aneurysm	4060	unruptured	Yes	>2
Raaymakers 2000	Uni of Utrecht Netherlands	aneurysm	18	unruptured	Yes	>1
Yamashiro 2007	Kunamoto Uni Japan	aneurysm	149	unruptured	Yes	>2
Davidson 2010	Macq Uni, Australia	avm	640	both		>1
Jayaraman 2008	Stanford Uni USA	avm	192	both		>2
ApSimon 2002	Royal Perth Hospital Australia	avm	240	both		% each
daCosta 2009	Uni of Toronto Canada	avm	98	both		>2
Saatchi 2011	Hacettepe Uni Turkey	avm	350	both		>2
van Dijk 2011	Uni of Groningen Netherlands	aneurysm	74	both		>2
Andaluz 2011	Uni of Cincinnati USA	aneurysm	192	both		>2
Chyatte 2001	MCP Hahnemann Uni USA	aneurysm	366	unruptured		change of 1
Roy 2001	Uni of Montreal Canada	aneurysm	116	unruptured		>2
Suele 2012	Gallen Switzerland	aneurysm	42	unruptured		≥3
Panagiotopoulos 2011	Uni Hospital Essen Germany	aneurysm	30	both		>1
Cantore 2008	Uni of Rome Italy	aneurysm	130	both		decline of 1
Yue 2011	XinXiang Centre Hospital China	aneurysm	74	unruptured		>2

The criteria to define morbidity on the GOS were primarily a score of less than 4 or 5 (Table 1.2). This means a difference between “moderate” and “severe” disability. The studies that used the criterion of greater than 2 for morbidity results are stating that a poor outcome on the GOS is between “persistent vegetative state” to “good recovery” and that a good outcome score is 1 (that is, death).

Table 1.2 Morbidity determined by GOS

Author & year	Institution	Pathology	Patients	Ruptured and Unruptured	Other published scales	Own scale	GOS cut off
Towgood 2005	Middlemore Hospital NZ	aneurysm	26	unruptured	Yes		>2 (converse)
Solheim 2006	St Olav Uni Hosp Norway	aneurysm	73	unruptured	Yes		<5
Szmuda 2011	Medical Uni Gdansk Poland	aneurysm	328	both	Yes		<4
Hillman 2001	Uni Hospital Linkoping Sweden	avm	135	both			<5
Nanda 2002	Louisiana State Uni USA	aneurysm	75	unruptured			>2(converse)
Thines 2012	Lille Uni France	aneurysm	85	unruptured			change in score
Steven 2007	Uni of Western Ontario Canada	aneurysm	59	both			<4
Laakso 2011	Helsinki Uni Finland	avm	63	both			not stated
Zhao 2010	Beijing Medical University China	avm	40	both	Yes		
Higashida 2007	* Uni of California USA	aneurysm	2535	unruptured	Yes		
Mine 2000	Chiba Uni Japan	avm	55	both		Yes	
Jang 2011	Yonsei Uni Korea	aneurysm	109	unruptured		Yes	

The validity and reliability of the two most commonly used scales, the mRS and GOS, were investigated. The authors were not able to locate evidence supporting the validity of the modified Rankin Scale (or mRS) with the uIA and bAVM populations. The Rankin Scale has been used as the measure for establishing the criterion validity of other scales (King Jr, Tsevat et al. 2006, King, DiLuna et al. 2006) and a systematic review found the mRS was more responsive and sensitive to change for acute stroke patients than the Barthel Index.(Balu 2009) The construct validity and content validity of the mRS with stroke patients has been examined (Lees, Bath et al. 2012) but not confirmed.(Tilley 2012) Studies that investigated the reliability of the Rankin Scale have raised concerns of it being rated by the treating clinician and the need for a scripted interview.(Wilson, Hareendran et al. 2005, Janssen, Visser et al. 2010, Zhao, Yu et al. 2010) The Rankin Scale has been labelled as a gross measure with insufficient sensitivity to levels of deficit in this patient population. The inter-rater reliability has been shown to be poor, particularly between Grade 2 and Grade 3,(Wilson, Hareendran et al. 2005) yet this is the point of dichotomisation for most studies. Also, the rating may vary depending on which aspect of disability or handicap has been the focus. To improve the inter-rater reliability of the mRS, recommendations have been made to either use a structured interview for raters or to exclude multiple raters.(Wilson, Hareendran et al. 2005) Not all investigations have found evidence to support this recommendation.(Quinn, Dawson et al. 2009) One review of studies was not able to determine the effect of a structured interview on the reliability and found that the reliability is at best “moderate”.(Quinn, Dawson et al. 2009) Indeed, the content validity of a test is determined by high reliability.(Streiner and Norman 1996) It appears the validity of the Rankin Scale (and modified versions) has been assumed, hence it has been abundantly utilised in this population and recommended.(Cockroft 2007) Yet the literature affirming the validity of the mRS is based on studies of stroke where incidence of disability or handicap is greater.

There is evidence of the validity of the GOS, in particular the extended GOS with traumatic brain injury patients,(Levin, Boake et al. 2001) but not with the uIA and bAVM patients. A study of the GOS in a heterogeneous population found inconsistent scores in one category between genders, questioning the validity of the GOS for both genders.(LeGrand, Hindman et al. 2007)

Recent studies into the reliability of the GOS have produced similar results to those relating to the reliability of the mRS. One study found that patients' GPs tended to give more positive ratings than a psychologist or a researcher using information supplied by family members.(Anderson, Housley et al. 1993) It found the inter-rater reliability varied with the method of obtaining information and recommended implementation of the GOS by staff other than treating clinicians. Another study found good inter-rater reliability on the GOS, though with a structured interview to obtain information for rating. As with the mRS, this raises questions about the appropriateness of the GOS as an outcome measure for uIA and bAVM treatment.

1.1.4 Discussion

Guidelines for the management of uIA and bAVM are developed based on the results of published outcome studies. It is a challenge to determine the effectiveness of any treatment procedure when different instruments are used to measure outcomes. This study has shown the mRS and GOS to be the most commonly reported instruments used to measure outcomes, yet there is no consistently applied criteria with which these instruments define morbidity. In particular, the validity of the mRS and GOS to measure the outcomes with uIA and bAVM patients has not been established. Scientifically developed instruments of measurement ensure an investigation produces accurate information. Rigorous testing of psychometric properties is required and focuses on the realms of validity, reliability, specificity, sensitivity, instruction for implementation to ensure consistency of application and norms for comparison. Many scales do not have normative data because it is assumed that full independence or lack of disability is the standard in the general population. For that standard to be applied to studies of the uIA and bAVM populations, agreement is needed to establish a definition of morbidity and determine the criteria to judge a "good" or "bad" outcome.

Treatment for uIA and bAVM is aimed at preventing potential ruptures with consideration for life expectancy. Patients usually present with very minor or no symptoms, hence the goal of treatment is to maintain the patient's current level of function. Defining and identifying functional outcome instruments is necessary to accurately measure high levels of function with uIA and bAVM patients.

The term “function” has been used increasingly in clinical dialogue, yet is not well defined. This lack of definition has led to the term being used to describe measurement instruments such as neurological or disability scales as functional outcome measures. Agreement is needed on the definition of function as an underlying construct. Components of function vary for individuals according to factors such as age, culture and environment. Therefore, when comparing functional abilities within populations, it is important to determine tasks that are common activities for the group to which the subject belongs.

There are many levels of function depending on the context of the individual. Functional tasks performed daily are commonly known as ADL. Self-care tasks such as toileting and dressing, are at the simplest and lowest level of functional performance for adolescents and adults in any culture. Tasks that are more complex such as shopping or driving require higher levels of ability.

The Barthel Index is a scale commonly used to measure self-care functioning. However both the Barthel Index and the National Institutes of Health Stroke Scale (NIHSS) have been found not to be useful instruments for the uIA and bAVM patient population due to the scales’ insensitivity to change.(Kim, Haney et al. 2005) The study showed the Rankin, GOS, MMSE and SF36 showed differences in outcomes for patients with a range of clinical manifestations. However, the results also showed that the Rankin and GOS had poor correlation with the MMSE which measures cognition and the SF36 which is a quality of life questionnaire.(Kim, Haney et al. 2005) This meant that despite some patients having poor MMSE or SF36 scores, they were graded highly on the GOS and Rankin Scale. The authors concluded that cognitive status and patient perception measures should be included in future studies of patients with Subarachnoid Haemorrhage (SAH) from intracranial aneurysm. A follow-up study of 520 patients treated for SAH and intracranial aneurysm was conducted using six outcome measures, namely the GOS, Rankin Scale, Barthel Index, NIHSS, MMSE and SF36. The researchers found the measurement of tasks such as self-care is too low in level of task requirement for uIA and bAVM, hence the ineffectiveness of the Barthel Index in this study. The Barthel Index has been tested and standardised for the elderly and cerebrovascular populations.(Shah and Cooper 1993) ADL scales are effective in detecting levels of function within patients with impaired ability to perform self-care tasks, such as those suffering a SAH, however will not detect changes in function for patient groups with

high cortical deficits. Instruments need to measure functional performance at the level of functioning of which the uIA and bAVM populations are capable.

Quality of life measured by self-report questionnaire is an accepted method of examining outcomes. Whilst this is the most important outcome for the patient, and hence the treating clinician, it is a subjective concept that is difficult to substantiate in psychometric parameters such as inter-rater reliability. Quality of life measurement may provide a valuable insight of outcome from the patient's perspective following surgery for uIA and bAVM, however it is deficient as an objective measure of function.

The mRS and GOS both require the clinician to rate the patient on the scales based on information obtained from discussion with and observation of the patient. When a measurement instrument is rated by the treating clinician, it is not possible to guarantee a lack of bias for the simple reason that the clinician is trying to improve the patient's life and may want to reflect this commitment in the results of their work. There are two possible ways to overcome this dilemma: the use of non-treating clinicians or the selection of quantitative tests based on action to gain a rating, rather than relying on the judgement of the rater. To obtain such objective data, particularly for scoring function, requires the patient to "perform" one or more tasks.

Two additional aspects to gathering outcome information are access and time. Some studies have attempted to acquire more detail than just the mRS or GOS, however they have struck such problems as poor patient compliance with follow-up requirements and the often exhausting length of time taken to implement the test. One study of uIA patients used an extensive series of commonly used scales and neuropsychological tests to assess outcomes.(Towgood, Ogden et al. 2005) The results were very detailed, however the authors commented on the difficulty of patient compliance for follow-up testing after surgery. With the battery of tests taking 2–3 hours to complete, patients were prone to fatigue and loss of concentration, regardless of their medical condition. Indeed, the authors noted how the subset of patients who failed to complete the tests may have biased the results, particularly if their non-compliance was due to the effects of surgery. Another study of outcomes after treatment for ruptured aneurysms used a battery of tests given over two 90 minute periods.(Proust,

Martinaud et al. 2009) Both studies reported losing patients to follow-up or having patients refuse to participate, resulting in small sample sizes.

The frequently cited International Study of Unruptured Intracranial Aneurysms (ISUIA) study used the mRS, MMSE and the Telephone Interview for Cognitive Status (TICS).(Wiebers 1998, Wiebers, Whisnant et al. 2003) By using an instrument to rate disability supplemented by a brief cognitive assessment, the time taken to assess patients was minimal. Also, access to patients for follow-up was facilitated by the use of an instrument administered by telephone interview. The results of this study have raised several questions about the benefit of treatment over conservative management of uIAs, particularly for younger people with small aneurysms and no history of SAH. This was on the basis that the results of the cognitive outcomes showed greater cognitive morbidity than previously reported in studies of surgery for uIA.(Wiebers 1998) The ISUIA method for measuring the cognitive outcomes for uIA patients has since been investigated as the TICS was originally developed to measure cognitive decline for dementia patients who are much older as a population than the uIA population. The investigation found that performance on the TICS from the normal population declined over time for the control group but not the uIA treatment group.(Towgood, Ogden et al. 2005) This raises the question of whether the results of the morbidity in the ISUIA study were due to dementia rather than treatment of the uIA. As the authors point out, doubt is raised about the veracity of the ISUIA finding because there were no reported results of pre-treatment cognitive status and no control group with which to compare TICS scores over time. This demonstrates the importance of ensuring that the measure chosen is valid for the uIA and bAVM populations and emphasises the need for normative information to ensure that any changes are due to treatment, not age-related decline.

Return to work status is more fundamentally linked to function than judgements on degree of disability. Return to work status is objective, though categories of affirmation can be defined to include lighter duties or change in work status which does not reflect returning to pre-morbid functioning.(Towgood, Ogden et al. 2005)

In studies of uIA and bAVM, there is a need to measure function at the level at which it is affected, that is at the higher levels of cortical functioning. There have been attempts to

measure cognition at this level, however the assessments are not functional tasks, that is a person's normal action or activity. Most neuropsychological tests attempt to measure components of normal activity but are executed in an artificial manner. One functional activity commonly performed by adults in developed countries such as Australia is driving a motor vehicle. Driving requires a very high level of cortical ability and is often raised by uIA and bAVM patients as a task which, when restricted, impacts significantly on their quality of life. Measuring a person's actual on-road performance in driving is burdensome from a time, cost and accessibility perspective, though this is required for uIA and bAVM patients if advised by their clinicians. Off-road assessments have been developed with the goal of predicting on-road performance in driver rehabilitation programmes. An off-road driver assessment called DriveSafe DriveAware(Kay, Bundy et al. 2009) has been rigorously tested and found to have sound psychometric properties with excellent specificity (96%) and sensitivity (93%) to on-road driving ability.(Kay, Bundy et al. 2009, Hines and Bundy 2014) DriveSafe DriveAware has the ability to determine which patients are safe to return to driving from a neurocognitve perspective. The DriveSafe test examines the driver's awareness of the environment through a series of images of actual road conditions. The DriveAware test investigates the driver's insight into their situation and skill.(Kay, Bundy et al. 2008) The DriveSafe score is trichotomised to categories of (a) safe to drive, (b) needs further on-road assessment and (c) not safe to drive. Together with the score obtained from the DriveAware, the clinician is able to advise the patient accordingly. This test was used by the authors in the study of the outcomes of management for uIA and bAVM, along with the Medical Outcomes Study (MOS) SF36 to measure quality of life.

1.1.5 Conclusion

There is a clear need for valid and reliable measurement of the outcomes of treatment for uIA and bAVM based on function. Obstacles to achieving this have included the lack of a definition of function and problems with identifying a means of measuring function at high levels of cognitive and physical ability. Attempts have been made to measure cognition after treatment, however the methods have relied on instruments with poor psychometric qualities or which take too long to administer.

To date, the mRS and GOS have been the most cited means of measuring outcomes. However, the validity of these scales has not been verified for uIA and bAVM patients and their reliability has been questionable. Investigation of the studies examining morbidity using the mRS and GOS indicate a need for consensus on the criteria used for reporting morbidity to ensure consistency in the communication of outcomes.

The functional task most commonly performed by adults in developed countries, requiring very high levels of cognitive and physical skill, is the ability to drive a motor vehicle. We recommend that an off-road driving test that is valid, reliable and can be administered within 30 minutes, be considered as part of the repertoire of tools for outcomes measurement.

Section 1

There is divided opinion in the neurosurgical literature on whether or not to repair uIA and bAVM. The most cited study of the outcomes of management of uIA, known as the International Study of Unruptured Intracranial Aneurysms (ISUIA)(Wiebers, Whisnant et al. 2003) gathered data from treatment centres in the USA, Canada and Europe. Research from the ISUIA study suggested surgical repair of uIA may benefit only some patients, particularly depending on size, location, age, cerebrovascular history and symptoms. It found where the natural history of risk of rupture was high, the risk of poor outcome post-surgery was also high.

A non-blinded, randomised control trial of medical management of bAVM with or without intervention known as A Randomised trial of Unruptured Brain Arteriovenous malformations (ARUBA) found adverse outcomes for surgical intervention.(Mohr, Parides et al. 2014) There were significantly higher incidences of poorer outcomes in the intervention group compared with the medical management group. The intervention group included endovascular, stereotactic radiotherapy and neurosurgical treatment of bAVM alone or in combination. The ISUIA and ARUBA studies have had a profound influence on cerebrovascular surgery practice and some institutions have ceased providing surgery for uIA or bAVM.

The primary outcome of management in the ISUIA and ARUBA studies was death or stroke. The secondary outcomes were clinical impairment indicated by an mRS score of 2 or higher. Outcomes were measured using disability rating scales, primarily the mRS, quality of life (QOL) scales such as the SF36, and in the ISUIA, cognition was measured using the Mini Mental State Examination (MMSE)(Folstein, Folstein et al. 1975) and Telephone Interview for Cognitive Status (TICS)(Brandt, Spencer et al. 1988). Neither study measured functional outcomes.

Functional capacity is the ability to perform normal everyday activities, from as simple as drinking from a cup to as complex as driving a motor vehicle. No study of uIA or bAVM

management has yet measured the ability to drive. In past studies such as the ones mentioned above, function has been measured solely using a disability rating scale such as the modified Rankin Scale and, in some studies, in combination with tests such as the MMSE and TICS. These cognitive tests infer the ability to function, but do not directly measure the ability to perform a functional task, such as driving.

The primary focus of our research was to determine whether there is a decline in functional outcomes after cerebrovascular neurosurgery, specifically after surgical management for uIA and bAVM. The following two chapters present the results from a detailed examination into functional outcomes of surgical and conservative management for uIA and bAVM.

This study measured function and QOL before and after surgery for uIA or bAVM. Patients who were conservatively managed were included in the study and the same assessment tools used to measure their function and quality of life (Section 1 Table 1.1). Quality of life was measured using the Short Form Health Survey SF36 (licence no. QM008025)(Ware and Sherbourne 1992). Function was measured at the low level of self-care using the modified Barthel Index (mBI) to detect physical dysfunction, and at the high level in driving using DriveSafe DriveAware (DSDA) to detect cognitive dysfunction.

Section 1 Table 1.1 Scales used in the study

Scale used	Description
Quality of Life measure:SF36	Version 2 questionnaire in clinical setting or by post
SF36 Physical Component Score (PCS) subscales	Physical function
	Physical role
	Bodily pain
	General health
SF36 Mental Component Score (MCS) subscales	Social functioning
	Vitality
	Role emotional
	Mental health
Cognitive Function measure: **DriveSafe** **DriveAware**	 Original version 1; modified for use on a laptop. Measures awareness of the driving environment. Scores >95/128 indicate safe to drive. Measures awareness of own driving ability. Scores >17 indicate poor insight into driving ability and may not be safe to drive.
Physical Function measure: **Modified Barthel Index** – rates the patient's ability to perform tasks independently or with varying levels of assistance	Modified Barthel Index (mBI) rated by occupational therapist
mBI components	Feeding
	Bathing
	Grooming
	Dressing
	Bowel and bladder continence
	Toileting
	Bed-chair transfers
	Mobility levels
Optimal score	100
Sub-optimal	<100
Disability Score: **Modified Rankin Scale (mRS)**	 mRS physician rated
No symptoms at all	0
No significant disability	1
Slight disability	2
Moderate disability	3
Moderately severe disability	4
Severe disability	5
Dead	6
Optimal score	0 or 1
Sub-optimal	2 to 6

The test-retest reliability of DSDA had not been investigated prior to the commencement of this study, nor was there any normative data to enable comparison with the general population. A small test-retest reliability study of DSDA with participants from the general population was conducted as part of this study(O'Donnell J. 2013) to ensure the instrument can measure change in cognition over time (Innes, Jones et al. 2009) and provides a level of assurance that any improvement in performing the test is due to an improvement in cognitive abilities and not the practice effect of doing the test multiple times. The general population sample included people of similar age, gender and ethnicity to the uIA and bAVM populations in this study, thereby providing normative information.

Minor modifications were made to the DriveSafe and DriveAware instruments to facilitate their use in a research setting. The wording of question 1 in DriveAware was changed from "Why have you been referred for a driving assessment?" to "Why are you doing this driving assessment?". An option of "for research" with a score of 2 was included in the occupational therapy interpretation column in question 1 to enable scoring for the correct answer. A similar change was made in question 2 to accommodate answers for research participants. An option of "for research" with a score of 3 was included for research participants who answered in the negative to the question "Do you have any concerns about your driving?".

DriveSafe was originally designed to allow the subject to view images projected onto a large screen. For this study however, for the reasons of portability and access, the design was modified to enable assessments to be conducted on a laptop. A piece of calibrated string was used to maintain the original ratio of distance to image size, ensuring participants were kept the correct distance from the smaller laptop screen. All assessments were conducted in closed rooms to prevent distractions.

The total number of cerebrovascular patients invited into the study was 270: the total number of uIA patients was 209 and the total of bAVM patients was 61. From the 209 uIA patients, 34 did not participate in the study, and from the 61 bAVM patients, 16 did not participate. The uIA patients who participated were managed by five neurosurgeons at Macquarie University and the bAVM patients were managed by two neurosurgeons.

Chapter 2: *Patient functional outcomes and quality of life after surgery for unruptured intracranial aneurysm*

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https://thejns.org/view/journals/j-neurosurg/130/1/article-p278.xml

Chapter 3 *Quality of life and driving competence after surgery for unruptured brain arteriovenous malformation. A prospective cohort study.*

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O'Donnell J.M., Morgan M.K., Manuguerra M., *Quality of life and driving competence after surgery for unruptured brain arteriovenous malformations:A prospective cohort study.*

3.1 Abstract

Few studies have examined quality of life (QOL) and the cognitive ability to drive after surgical repair of unruptured brain arteriovenous malformations (bAVM). This study examined the effectiveness of surgical management of bAVM by measuring patients' QOL and their ability to safely return to driving. Between January 2011 and 2016 patients with a new diagnosis of unruptured bAVM were prospectively enrolled in a study. Assessment was performed at referral, 6 weeks after surgery and at 12-months (for both those undergoing surgery or conservative management). Assessment included: the Short Form 36 (SF36); DriveSafeDriveAware (DS); the modified Barthel Index (mBI); and the modified Rankin Scale. Continuous ordinal regression was used to examine the relationship between the outcome DS score and potential predictors. 45 patients enrolled in the study, of whom, 35 (78%) had their bAVM managed by surgery. There was a difference between those that were treated by surgery and those not treated with respect to Spetzler-Ponce class (SP). There was no significant decline in function between the initial and 12-months assessments between those that were treated by surgery and those not treated with respect to the distribution of mRS or the mean DS, mBI, PCS or MCS scores. The surgical group had significantly higher QOL of life scores from pre-surgery to 12 months post-surgery (PCS $p<0.01$; MCS $p=0.02$). Higher grade bAVM was significantly related to poorer function in the surgical group (SP C compared with SP A; $p=0.04$, mean difference -12.4, 95% CI -24.3 to -0.4). Function and QOL are not diminished after surgical repair of low grade unruptured bAVM. Surgical management of bAVM did not affect cognitive abilities relevant for returning to driving at 6 weeks or 12 months after surgery. Guidelines that restrict driving after surgery for low grade bAVM should be reconsidered.

3.1.1 Introduction

Arteriovenous malformations of the brain are vascular lesions formed by a tangle of abnormal arteries directly connected to veins without the presence of capillaries. Management options for patients with an unruptured bAVM have broadened due to advances in medical technology over the last two decades. Patients with an unruptured bAVM are able to choose whether to have treatment and what type of treatment they would prefer. Prior to the introduction of endovascular and radiosurgical management of bAVM, the only treatment option was surgical clipping. Questions have been raised of the effectiveness and necessity of the more costly and invasive surgical management for bAVM(Brinjikji, Rabinstein, Lanzino, Kallmes, & Cloft, 2011; Saatci, Geyik, Yavuz, & Cekirge, 2011). Some studies have questioned the effectiveness of any of the bAVM treatment modalities (Al-Shahi Salman et al., 2014; Mohr et al., 2014; Ross & Al-Shahi Salman, 2010). Patients seek information about the impact of the management options for bAVM on their survival, ability to function and subsequent quality of life (QOL) (Della Puppa, Rustemi, & Scienza, 2015; Proust et al., 2009; Rohn et al., 2014). An inability to return to everyday life within their normal communities as a result of surgical management for bAVM should deter patients from choosing this management option.

Studies into the outcomes of surgery on bAVM have primarily focused on survival(Britz, Salem et al. 2004, Wedderburn, van Beijnum et al. 2008, Brinjikji, Rabinstein et al. 2011, Al-Shahi Salman, White et al. 2014) or outcomes in the form of disability ratings.(ApSimon, Reef et al. 2002, Bervini, Morgan et al. 2014, Moon, Levitt et al. 2015) Some studies have investigated QOL after treatment for bAVM(Yang, Paek et al. 2012, Yamashiro, Nishi et al. 2007, Proust, Martinaud et al. 2009, Rohn, Haenggi et al. 2014) however the pre-treatment QOL status was not assessed. With no baseline function or QOL measures with which to compare post-treatment status, the voracity of statements on the outcome of treatment are weakened. A non-blinded randomised control trial of bAVM treatment known as the ARUBA trial compared conservatively managed bAVM with combined or singular treatment modalities.(Mohr, Parides et al. 2014) The trial ceased participant enrolment because of significantly higher incidences of neurological deficits in the treated group. Physical QOL was found to be better in conservatively managed bAVM in the ARUBA trial, however there

was a higher incidence of depression and anxiety in conservatively managed bAVM than in treated bAVM.(Stapf, Moy et al. 2014)

Participation in everyday activities is fundamental to a person's perception of their QOL(Gee, 2016) and one of the most common daily activities of adult Australians is driving a motor vehicle. Poor cognition after neurological deficits from bAVM treatment has been raised(Mohr et al., 2014) and previously examined (Marshall, Jonker, Morgan, & Taylor, 2003; Raghunath et al., 2016). Cognitive decline may affect the ability to drive safely,(Patomella, Tham, Johansson, & Kottorp, 2010) so driving authorities are reliant on expert opinion and published evidence to determine when restrictions should be applied for people with cognitive impairment (Office the of Superintendent of Motor Vehicles, 2014). Health professionals, particularly medical practitioners, often find themselves in a position of determining whether their patient, with whom they need to retain a level of rapport and trust, is fit to drive after a neurological disorder or procedure (Dow, 2009; Hoggarth, 2013; Thomas & Hughes, 2009). Evidence on driving after craniotomy is scarce, particularly for driving after surgical repair of a bAVM (Austroads, 2016).

The DriveSafeDriveAware test is a recently developed instrument that measures drivers' awareness of the driving environment and awareness of their driving ability, in order to predict drivers' real-life performance (Kay, Bundy & Clemson, 2009). DriveSafeDriveAware has been found to have excellent sensitivity (93%) and specificity (96%) for predicting on-road driving (Kay, Bundy & Clemson, 2009; Hines & Bundy 2014). Along with the consideration of factors such as the risk of seizures, visual field defects and disability, DriveSafeDriveAware can assist in determining a patient's fitness to drive. In this study, cognitive function was measured by the DriveSafe (DS) component of the DriveSafeDriveAware test. A DS score of > 95 predicts a satisfactory performance of driving (Kay, Bundy & Clemson, 2009).

We aim to determine if there is a decline in function and QOL after surgical management of unruptured bAVM by assessing and monitoring patients before and after surgery. The functional outcomes and QOL of surgical management will be compared with conservatively managed cases to compare rates of decline after 12 months.

3.1.2 Methods

Participants

The study was approved by the institution's Human Ethics Committee and complied with the requirements set out in the Australian National Statement on Ethical Conduct in Human Research.

Patients with recently diagnosed unruptured bAVM referred to the neurosurgery team were approached at their initial consultation from 2011 to January 2016. Consenting patients participated in follow-up assessment at six weeks following surgery, and at 12-month following surgery or initial presentation (for untreated patients). It was often not possible for regional, interstate and overseas participants to attend all follow-up appointments on-site. Correspondence from local doctors and family was monitored for changes in functional status and if sufficient information was available was incorporated in the participant's assessment. Eligible patients' flow chart is illustrated in Figure 1. One patient withdrew participation prior to commencing the pre-operative assessments. No patients withdrew from participation during the follow-up stages of the study due to neurological deficits.

Assessment Tools

The functional outcome and QOL for the management of unruptured bAVM were measured with a battery of tests and questionnaires that crossed a large cross-section of outcome performance that included: Short Form SF-36 for QOL subscales of Physical Component Score (PCS) and Mental Component Score (MCS)(Ware 2007); modified Barthel Index (mBI) as a measure of self-care performance(Mahoney 1965, Shah 1993); modified Rankin Scale (mRS)(van Swieten 1988; Rankin 1957) as a measure of disability for every day activity; and, DS (original version) as a neurocognitive evaluation of driving performance.

The DS and mBI were rated by the researcher (an occupational therapist) or an assistant researcher (general practitioner). The treating medical management team was blinded to these outcomes until analysis of the results of all patients was commenced. A contingency was instigated for a DS score indicating that driving would not likely be safe (SD<96), the score

was to be revealed to the surgeon if the patient had not been advised against driving. This action was not required during the study period. The mRS scores were allocated by the treating surgeons and the occupational therapist was blinded to these scores until analysis of the results of all patients was commenced. The Physical Component Score (PCS) and Mental Component Score (MCS) of the SF36 was extracted by factor analytic techniques.(Ware, 2007) The sequencing of assessment was planned that the SF36 was administered prior to the mBI and DS at each assessment epoch. This was to alleviate the potential impact of the DS score affecting patients' perception of their QOL.

Spetzler-Martin (SM) grades were used to group bAVMs according to level of risk of surgical outcomes(Spetzler & Martin, 1986). The SM grade was established by allocating points for size (1 for less than 3cm, 2 for size between 3 and 6 cm, and 3 for size greater than 6 cm), the presence of deep venous drainage (adding 1 point if present), and location in "eloquent" brain (adding 1 point if located in primary sensory cortex, motor cortex, language cortex, visual cortex, internal capsule, diencephalon, brainstem, deep cerebellar nuclei, or cerebellar peduncle). To facilitate analyses, SM grades were categorized into Spetzler-Ponce classes (SPC), which is a simplification of the SM grading system. SPC has been validated to predict the risk of surgery by combining SM grade 1 and 2 as Spetzler-Ponce Class A bAVM (SPC A), SM grade 3 as Spetzler-Ponce Class B bAVM (SPC B) and SM grade 4 and 5 as Spetzler-Ponce Class C bAVM (SPC C)(Spetzler & Ponce, 2011).

Statistical Analysis

Statistical analysis was performed using IBM SPSS (version 22 IBM Corp) and Prism (version 7.0; Graphpad Software Inc). Baseline characteristics were grouped into categorical variables and compared surgery and conservative management using the Pearson chi-square test or Fisher's Exact test for small groups. Continuous variables were analyzed using the t test, ordinary one-way ANOVA or repeated measures ANOVA. Continuous Ordinal Regression (Manuguerra & Heller, 2010) was used to study the relationships between the predictors and the outcome of interest, the DS score. The latter measures an intangible quantity, the driver's awareness of the driving environment, and in general cannot be easily modelled because of its inherent nonlinearity. Continuous Ordinal Regression overcomes this limitation by modeling directly the unobserved quantity of interest, the driver's awareness of

the driving environment, and then connecting it to the observed score with a link function that is estimated during the model estimation.

A statistical significance level of 5% was used throughout as multiple comparisons were executed. Dichotomization of the results, where appropriate, was any score less than 100 for the mBI and a score of greater than one for mRS scores.

3.1.3 Results

A total of 61 patients were invited to participate in this study. Of the 50 bAVM patients who consented to participate in the study, one had a change of diagnosis and four changed treatment plans (Figure 3.1). Of the remaining 45 cases, 3 did not return for follow-up, and 42 attended follow-up at least once or returned the postal questionnaire.

Figure 3.1 bAVM Participant Flowchart

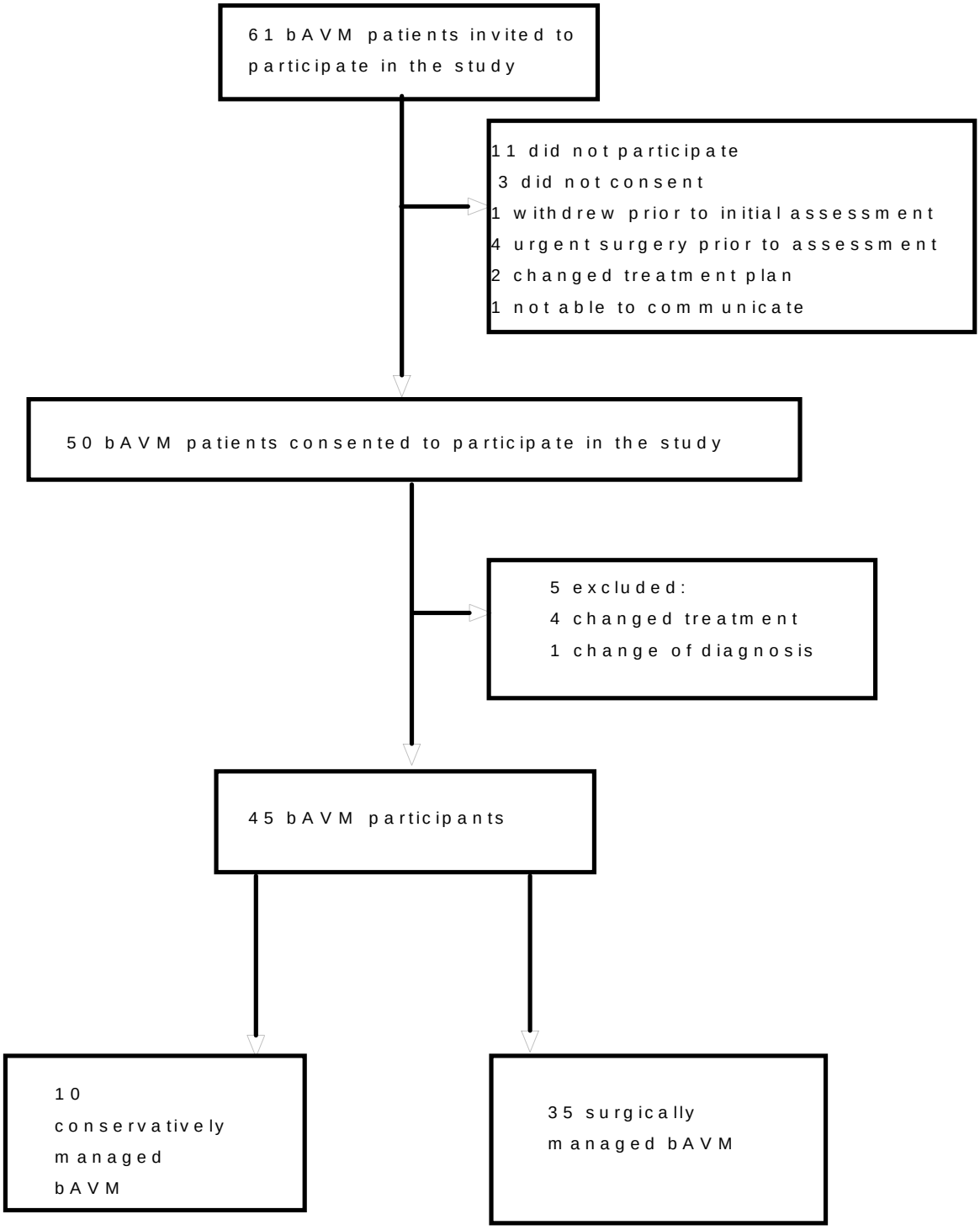

Figure 3.1 The flow chart of newly diagnosed AVM enrolled in study and those included and excluded from analysis

Table 3.1 shows the characteristics of the 45 cases in the conservative and surgical groups. The only significant differences between the groups were Spetzler-Ponce Class of bAVM (p=0.02) and the size of the bAVM (p=0.01). There was a greater proportion of SP Class A and B in the surgical group and the mean size of bAVM was larger in the conservative group.

All participants in the surgical group attended one or more follow-up assessments or returned the post-surgery postal questionnaire. Of the ten conservatively managed cases, three did not attend follow-up or return the postal questionnaire. The characteristics of the cases for which there is no follow-up information was compared to the respondent cases to detect if there could be a potential bias between the groups (Table 3.1). The respondent group tended to be younger, had significantly larger bAVM (p<0.01) and had a significantly greater proportion of SP Class C bAVM (p=0.01).

Table 3.1 Unruptured brain AVM Patient CharacteristicsTable

		Not treated	Surgically treated	Comparing surgical with no treatment cases p value of χ^2, Fisher Exact or t test	No assessments after initial presentation (not treated)
Total patients	Number (%)	10 (21%)	35 (73%)		3 (6%)
Age, years	Mean (SD)	40 (19)	38 (14)	0.60	48 (11)
<60 years	Number (%)	8 (80%)	33 (94%)	0.21	3
Female	Number (%)	5 (50%)	19 (54%)	>0.99	2
bAVM infratentorial	Number (%)	0 (0%)	2 (6%)	>0.99	0
bAVM eloquent	Number (%)	7 (70%)	16 (46%)	0.28	1
bAVM size	Mean, mm (SD)	45 (23)	30 (13)	0.01	17 (4)
Spetzler-Ponce Class	A, Number (%)	3 (30%)	25 (71%)	0.02	3
	B, Number (%)	2 (20%)	6 (17%)		
	C, Number (%)	5 (50%)	4 (11%)		
Initial DS	Median score (interquartile range)	110 (104-113)	113 (104-117)	0.43	111 (107-117)
	DS≤95; Number (%)	0 (0%)	3 (9%)	>0.99	0
Initial PCS	Mean score (SD) [patient number]	50 (9) [10]	49 (9) [33]	0.72	48 (10) [3]
	PCS<50; Number (%)	5 (50%)	18 (55%)	>0.99	2
Initial MCS	Mean score (SD) [patient number]	45 (12) [10]	40 (14) [34]	0.33	42 (19) [1]
	MCS<50; Number (%)	7 (70%)	23 (68%)	>0.99	2
Initial mRS	mRS<2; Number (%)	10 (100%)	31 (89%)	>0.56	3
	mRS>1; Number (%)	0	4 (11%)		0

DS = DriveSafe; PCS = Physical Component Score of Short Form SF-36; MCS = Mental Component Score of Short Form SF-36; mRS= modified Rankin Score.

Table 3.2. Quality of life (QOL) and outcomes scores over 12 months for surgically managed bAVM; Repeated Measures ANOVA, Chi Square or Fisher's Exact test.

	Initial		6 weeks		12-months		Comparing epochs		12-months
	No treatment	Surgery	No treatment	Surgery	No treatment	Surgery	No treatment	Surgery	Surgery vs. no treatment
Total	10	35	NA	35	10	35	2 epochs	3 epochs	1 epoch
DS, mean (SD) [patients assessed]	111 (8.5) [10]	112 (8.7) [35]	NA	113 (8.6) [35]	109 (4.9) [5]	115 (8.6) [31]	0.76	0.26	0.20
DS, number of patients with decrease between initial and 12-months by ≥9 (% of assessed)					1 (20%)	2 (8%)			0.43
PCS, mean (SD) [patients assessed]	49 (9.4) [10]	49 (9.2) [35]	NA	45 (9.2) [35]	50 (6.0) [6]	54 (6.1) [29]	0.84	**<0.01**	0.67
PCS number of patients with decrease between initial and 12-months (% of assessed)					2 (30%)	8 (28%)			0.77
MCS, mean (SD) [patients assessed]	47 (9.1) [10]	42 (13.7) [35]	NA	48 (11.6) [35]	46 (12) [6]	49 (10) [29]	0.70	0.02	0.56
MCS, number of patients with decrease between initial and 12-months (% of assessed)					3 (50%)	11 (38%)			0.66
mBI, number <100 (%)[patients assessed]	0 [7]	0 [35]	NA	3 (11%) [27]	0 [6]	3 (11%) [26]	>0.99	0.12	>0.99
mRS, number >1 (%)[patients assessed]	0 [7]	4 (11%)[35]	NA	8 (27%) [30]	1 [6]	8 (23%) [34]	0.46	0.28	>0.99

DS = DriveSafe; PCS = Physical Component Score of Short Form SF-36; MCS = Mental Component Score of Short Form SF-36; mRS= modified Rankin Score; mBI = modified Barthel Index; NA = Not applicable

There were no significant changes in function or quality of life for the conservative group from initial consultation to the 12 month follow-up (Table 3.2). There were no significant changes in function in the surgical group, however quality of life scores improved significantly from the pre-operative assessment to the post-operative assessments over the 12 month period (PCS $p<0.01$; MCS $p=0.02$). Dunnett's multiple comparison test confirmed a significant improvement in PCS scores between the pre-surgery and 12 month post-surgery scores ($p=0.02$, mean difference -4.92, 95%CI -9.15 to -0.68). These findings were confirmed when the analyses were conducted by unmatched ANOVA using all scores (PCS $p<0.01$; MCS $p=0.04$). No significant differences in decline in function or quality of life were detected between the conservatively managed and surgically managed groups (Table 3.2).

Two of 32 (2%) patients who had DS scores deemed competent to drive on initial assessment were assessed at 12-months to have a DS score deemed not competent to drive (DS<95) following surgery.

Closer examination of the SP classes of bAVM found a significant difference in the mean DS scores in the surgical group. The difference in mean DS score at 12 months post-surgery for the SP C bAVM patients was significantly lower than for the SP B patients ($p=0.04$, mean difference -14.6, 95%CI -28.6 to -0.6) and the SP A patients ($p=0.04$, mean difference -12.4, 95%CI -24.3 to -0.4). There was no significant difference in mean DS scores between the SP A and SP B bAVM patients.

Continuous Ordinal Regression was used to study the relationships between predictors (age, gender, having a driver license, management, time since assessment, mRS score, eloquence) and the outcome of interest (DS scores). The effect of repeated measures was taken into consideration by incorporating individual random effects in the model. Possessing a driver's licence, mRS score and eloquence, for either the surgical or conservative groups, had no effect on the DS scores. Younger age ($p<0.01$) and being female ($p<0.01$) were related to higher DS scores, while the decrease of awareness of the driving environment associated with age was more evident for male drivers. The time since the first assessment (p=0.01) and being managed surgically (p=0.04) were also associated with higher DS scores (Table 3.3).

Table 3.3 Continuous Ordinal Regression estimates for both surgery and untreated

	Estimate	Std Err	t value	p value
Standardised age*	0.228	0.583	0.391	0.70
Interaction Standardised age: Female	0.745	0.672	1.108	0.28
(Standardised age)^2	2.374	0.690	3.442	<0.01
Interaction (Standardised age)^2:Female	-1.699	0.736	-2.309	0.03
Female	2.438	0.793	3.073	<0.01
Possessing a licence	-0.107	0.998	-0.107	0.92
mRS of 0 at every assessment (versus >1 at least on one occasion)	-0.272	0.413	-0.658	0.52
Surgery	-1.774	0.831	-2.135	0.04
Time since first assessment	-0.002	0.001	-2.607	0.01
Eloquent	0.734	0.553	1.327	0.19

Standardized age* = (age – mean age)/standard deviation of age

3.1.4 Discussion

In this study of 45 patients with an unruptured bAVM, there was no significant decline in function or QOL after surgical or conservative management over the 12 month period after surgery or initial diagnosis. The surgical group had significant improvements in QOL from the pre-operative, 6-12 week post-operative and 12 month post-operative scores. There was no significant difference in the rate of decline in function or QOL between the conservatively and surgically managed groups.

There was no significant difference in age, gender, presentation mRS, bAVM eloquence, presentation DS or presentation QOL between conservatively and surgically managed participants. There was a significantly higher proportion of low grade bAVM and smaller size bAVM in the surgical group compared with the conservative group (p=0.02, p=0.01 respectively). This bias was due to compliance with recommendations from previous studies to prevent adverse outcomes(Davidson & Morgan, 2010). In order to account for possible bias in the conservative group from the lack of complete data, comparison of bAVM patients for whom there are no outcome scores with those who complied with follow-up found the only difference was in grade and size of bAVM. The conservatively managed patients for whom outcome scores were obtained have significantly larger bAVM and higher bAVM grades.

There was a tendency for DS scores to be higher at the 12 month follow-up consultation compared with the initial consultation in the surgical group but not the conservative group. The lower initial DS score may be due to the patient experiencing stress while performing the assessment soon after being informed of having a bAVM. The emotional stress of preparing to undergo brain surgery may have been a distraction, impacting negatively on their ability to perform the assessment in the initial consultation. This may also signal mild cognitive repression caused by harboring a bAVM, even if there has not been an event to cause neurological deficits. Other studies have also found cognition may be affected by an unruptured bAVM (Marshall et al., 2003; Raghunath et al., 2016), which emphasizes the need to do pre-operative assessments of function in order to measure outcomes of surgery.

In this study, QOL improved over the 12 month period for surgically managed bAVM patients but tended to lower for the conservatively managed patients, though not significantly. Surgically managed patients experienced a decline in their physical QOL in the first 6 to 12 weeks after surgery. This would be due to the inability to perform normal activities while recovering from surgery. The physical QOL improved significantly at 12 months after surgery and was higher than the 2008 US norm value. Mental QOL scores improved significantly between pre-operative and both post-operative time periods. There was no significant change in mental QOL for conservatively managed bAVM patients.

The functional outcomes were better for the SP A and B classes of bAVM than for the SP C class. The results of the post-operative mean DS scores across SP classes have confirmed the higher risk of surgery based on the grading of the bAVM. The purpose of categorising bAVM into SP classes is to enable the prediction of risk of surgery using factors known to be related to neurological deficits, namely size of bAVM nidus, eloquence of bAVM and deep venous drainage of the bAVM (Spetzler & Ponce, 2011). This study has shown there are significant differences in functional outcomes after surgery between the SP classes.

The participation and compliance rate of this study was high with all surgically managed patients participating in one or more follow-up assessments and only three of the ten conservatively managed patients not attending any follow-up or returning QOL questionnaires. The reason why the compliance rate was high may be that, once the risk of complications from surgery was relieved, patients had a strong desire to participate in every-day living as soon as it was deemed safe. Participating in the DS assessments provided an opportunity for patients to demonstrate their cognitive ability to perform a test related to driving a motor vehicle and gain approval to recommence driving. As explained in the consent forms, if patients' DS scores indicated they may not be safe to drive, they would be informed by the occupational therapist not to drive, their treating surgeon would be informed and a referral would be made to an occupational therapy driving assessor. If patients' DS score indicated they were cognitively safe to drive, they were informed and the surgeons were able to make decisions on safety to return to driving. Surgeons were not informed of patients' actual scores, however were able to allow driving to recommence at the post-operative follow-up. Completing QOL assessments enabled patients to express their relief of surviving major brain surgery or regret if the outcome was not as they had hoped.

Driving after surgery for bAVM is restricted for two reasons; seizures and disability preventing safe driving such as cognitive impairment or a visual field defect. We have previously reported the risks of seizure after surgery for bAVM (O'Donnell, Morgan, & Heller, 2017). The results of this study have shown there is no significant change in cognitive function required for driving after surgery for low grade unruptured bAVM. Post-surgical neurocognitive screening or referral to an occupational therapy driving assessor is recommended for high grade bAVM.

3.1.5 Conclusion

Function did not decline one year after surgical repair of bAVM. There was an improvement in QOL for surgically managed bAVM patients and no change in QOL for conservatively managed bAVM one year after initial presentation. Poorer functional outcomes after surgery were associated with higher grade bAVM. This study's results demonstrate cognition required for driving is maintained in low grade bAVM, therefore guidelines that restrict driving after surgery for low grade bAVM on the basis of potential cognitive impairment should be reconsidered.

Section 2

While the primary focus of this research is to determine the patients' functional outcomes after surgery for uIA and bAVM, it became clear in the early stages of the study that there is a need to examine all indicators of the ability to drive after surgery for uIA and bAVM. Neurosurgeons are required to advise patients about their ability to return to driving after treatment for uIA and bAVM, yet there is a paucity of information on the effect the treatment has on driving ability.(Office of the Superintendent of Motor Vehicles 2014) The Australian National Transport Commission's *Assessing Fitness to Drive* medical guidelines (2012 edition) recommends cessation of driving for six months after supratentorial surgery for private vehicle drivers and a cessation of 12 months for commercial vehicle drivers.(Austroads 2012) The inability to return to driving has a significant impact on patients' quality of life, particularly affecting patients' ability to return to work.

One concern of the Australian National Transport Commission who, with Austroads publish the Australian medical standards for licensing and clinical management guidelines, is the potential for seizures after craniotomy.(Austroads 2012) This concern has been highlighted in the latest (2016) version of the medical guidelines, which recommends future editions give consideration to appropriate circumstances where shorter non-driving periods may be permitted after intracranial surgery.(Austroads 2016)

This section's chapters will report on the risks of seizure after surgically treated uIA(O'Donnell, Morgan et al. 2016) and bAVM. The aim is to determine which patients may return to driving with little risk of post-operative seizure, and which patients should be restricted from driving. The chapters also indicate the levels of risk for periods of time in years after surgery for uIA and bAVM. The investigation of seizure risks after surgery for uIA and bAVM will provide driving authorities with further evidence for the determination of return to driving restrictions and guidelines.

Chapter 4 *The risk of seizure after surgery for unruptured intracranial aneurysms: A prospective cohort study*

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4.1 Abstract

This study aimed to identify a group of patients with a low risk of seizure following surgery for unruptured intracranial aneurysms (uIA) with the objective of determining the risk of seizure after discharge from surgery for uIA.

A consecutive prospectively collected cohort database was interrogated for all surgical uIA cases. A total of 726 cases of uIA (excluding cases proximal to the superior cerebellar artery on the vertebro-basilar system) were identified and analysed. Cox proportional hazards regression models and Kaplan-Meier life table analyses were generated assessing risk factors. Of the eleven examined, pre-operative seizure history and complication of aneurysm repair were the only risk factors found to be significant. The cumulative risk of first seizure after discharge from hospital following surgery for patients with neither pre-operative seizure, treated middle cerebral artery (MCA) aneurysm nor post-operative complications (leading to an mRS>1) was <0.1% and 1.1% at 12 months and 7 years respectively. The cumulative risk for those with pre-operative seizures was 17.3% and 66% at 12 months and 7 years respectively. The cumulative risk for seizures with either complications (leading to an mRS>1) from surgery or treated MCA aneurysm was 1.4% and 6.8% at 12 months and 7 years respectively. These differences in the three Kaplan-Meier curves were significant (log-rank $p<0.001$).

It was concluded that the risk of seizures after discharge from hospital following surgery for uIA is very low when there is no pre-existing risk of seizures. If this result can be supported by other series, guidelines restricting the return to driving because of the risk of post-operative seizures should be reconsidered.

4.1.1 Introduction

The risk of seizure following surgery for intracranial aneurysm has been reported to be 0%(Ng, Reilly et al. 1998, Mitchell, Vindlacheruvu et al. 2005, Mori, Yamamoto et al. 2008, Lai, Gragnaniello et al. 2013, Rodriguez-Hernandez, Zador et al. 2013, Radovanovic, Abou-Hamden et al. 2014) to 15.7%.(Rabinowicz, Ginsburg et al. 1991) A variety of characteristics have been cited as increasing the risk of seizure after surgery including haemorrhagic

events(Lai, O'Donnell et al. 2013) and low aneurysm volume hospitals. (Aghakhani, Vaz et al. 2008) Some factors relate to the number of aneurysms(Rinne, Hernesniemi et al. 1996) and others are related to the aneurysm repair itself.(Sundt, Kobayashi et al. 1982, Wong, Ziewacz et al. 2012) The risk of future haemorrhage has been associated with the increased risk of seizure.(Rice, Peerless et al. 1990, Wiebers, Whisnant et al. 2003) In an analysis of the literature, two factors were commonly associated with an increased risk of future seizure: multiple aneurysms(Rinne, Hernesniemi et al. 1996) and middle cerebral artery (MCA) location.(Sundt, Kobayashi et al. 1982, Rinne, Hernesniemi et al. 1996)

Understanding which factors are associated with an increased risk of post-operative seizure, together with the cumulative risk of post-operative seizure, will assist in advising individual patients of their risk of potential seizures which will restrict their ability to resume pre-operative activities such as driving and work.(Hayashi, Hadeishi et al. 1999, Hoh, Nathoo et al. 2011) Driving after craniotomy for unruptured aneurysms is restricted for non-commercial drivers by some driving authorities for periods ranging from 3(Office of the Superintendent of Motor Vehicles 2014) to 6 months,(Austroads 2012) although no restrictions dependent on specific conditions are required by other authorities.(Rotary RehabAid Centre , Association 2011, Driver Licensing Authority 2014, Authority 2015) For commercial drivers, restrictions on returning to driving range from 6(Office of the Superintendent of Motor Vehicles 2014) to 12 months.(Austroads 2012, Driver Licensing Authority 2014, Authority 2015) The restrictions on driving after a seizure prescribed by many driving authorities specify a diversity of time periods.

Three case series, each of more than 100 patients, had reported the incidence of seizures after surgery for unruptured intracranial aneurysms (uIA) to be between 0%(Sundt, Kobayashi et al. 1982, Aghakhani, Vaz et al. 2008) and 4%(Baker, Prestigiacomo et al. 1995) during a mean follow-up period of 3 to 28 months. However, these studies were not performed with survival analysis methodologies. The overall rate of seizures for these amalgamated populations was 1.1% for an average 12 months of follow-up.

Our prospectively collected aneurysm database of the senior author (MKM) was interrogated to examine which factors, of those identified by other authors, influence the risk of first seizure following surgery for a uIA. Excluded from our analysis were aneurysms proximal to

the superior cerebellar artery on the vertebrobasilar system, as surgery that does not involve access via a supratentorial route is very unlikely to be associated with the development of seizures. Cox proportional hazards regression and Kaplan-Meier survival models were used. The purpose was to identify a group of patients with a low risk of seizures following discharge from hospital.

4.1.2 Methods

Patient Population

This study was approved by the Macquarie University Human Ethics Committee and was performed in accordance with institutional ethics committee guidelines. A prospectively collected database of the senior author (MKM) containing consecutive patients from multiple treatment centers was retrospectively analysed for the years 1989 to July 2014. The database contained demographic, clinical, radiological and treatment-related information. Due to the legal requirement in Australia for post-surgical patients to not drive if they have had a seizure, screening occurred at each post-operative consultation by the surgeon. This information was entered into the databank at the time of the consultation. Included in the records was correspondence referring to seizure events. Seizures could be either focal or generalised and were considered to have occurred if reported as such by an emergency room physician, neurosurgeon or neurologist, or upon consideration by the senior author on review of history. The study included patients confirmed to have been surgically treated for uIA and was confined to aneurysms of the anterior circulation or located distal to the level of the superior cerebellar artery (i.e. those in which surgical access was performed via a supratentorial approach). These patients were not treated with anticonvulsants during the hospital admission for surgery or during the post-operative period unless they were previously prescribed anticonvulsants for seizures occurring before the hospital admission for surgery.

Patients were excluded if they had aneurysms that did not occupy and require access via the supratentorial space or were not typical berry aneurysms (infected, dissection or traumatic aneurysms). Unruptured IA cases were excluded if they were surgically treated coincidentally with a ruptured aneurysm. Unruptured IA associated with brain arteriovenous malformations

(bAVM) were excluded due to the possibility of seizures being due to the bAVM or its surgery. Seizures that occurred during the hospital admission for aneurysm surgery were not included as the purpose of the study was to ascertain risks of seizures occurring following discharge from hospital and in the course of the patients' normal activities. There was also the additional difficulty of distinguishing these events from other neurological episodes at this time (e.g. syncope from postural hypotension).

Variables investigated

Eleven variables were selected for examination, based upon our literature review.(Sundt, Kobayashi et al. 1982, Rabinowicz, Ginsburg et al. 1991, Rodriguez-Hernandez, Zador et al. 2013, Radovanovic, Abou-Hamden et al. 2014) These variables were: aneurysm size; multiple craniotomies; gender; age (dichotomized for those less than 50 years of age and those 50 years or more); pre-existing stroke; pre-existing brain injury or brain tumor; past ruptured aneurysm (other site); pre-operative seizure; symptomatic brain compression; multiple aneurysms repaired at one surgery; MCA aneurysm treated and complication of aneurysm repair. Complication of aneurysm repair was aimed to identify stroke arising as a consequence of surgery. Because of artifact from clips, this was not possible to confirm in all cases (e.g. medial basal frontal lobe or hypothalamus in the case of anterior communicating artery repair). Therefore, we used the presence of a new neurological deficit assigned at 6 weeks with a permanent neurological deficit persisting at 12 months with an mRS>1. The patient assignment at the 6 weeks post-operative review (or if this did not occur, at the time of discharge from hospital), with the eventual mRS>1 for this complication not assigned until 12 months, allowed diplopia and eyelid ptosis (that may be responsible for an mRS of 2) to resolve and thus, not be confused with infarction. Therefore, this clinical outcome variable was used as an independent variable.

Outcome

The outcome of the study was first seizure following discharge from surgery. This required confirmation by accident and emergency room physician, neurologist or neurosurgeon. The seizure could be generalised or partial. Because of the difficulties ascribing unwitnessed events leading to alterations of consciousness in the immediate post-operative period (e.g.

narcotics, syncope and seizure), and because our specific focus was on the impact upon driving restriction, the study did not include seizures occurring during the perioperative hospital admission.

Sensitivity analysis.

To examine what impact cases excluded may have had on the outcome from primary analysis, a sensitivity analysis was performed. For this analysis, cases followed for less than 31 days with a post-operative mRS <2 excluded were modeled to have had a post-operative seizure and added to the actual number of included cases (of post-operative seizures) for the sensitivity analysis.

Statistical Analysis

Statistical analysis was performed using Prism (version 6, GraphPad Software Inc) and IBM SPSS Statistics (version 22, IBM Corporation). For the purpose of life table analysis (Kaplan-Meier estimates) and Cox regression, patients were included when reviewed on more than one occasion with the event being first seizure after discharge from surgery for uIA and censoring at last review.

The two-tailed *p* value was determined using Fisher's Exact test to identify characteristics for further review by Cox regression and Kaplan-Meier curve analysis. Because of the low number of events (cases with first post-operative seizures) a limited number of variables were selected. Multivariate Cox regression was performed for three variables; (a) pre-operative seizure; (b) MCA aneurysm treatment; and (c) complication of aneurysm repair with mRS>1 at 12 months. A statistical significance level of $p<0.05$ was used throughout. MCA aneurysm treatment and complication of aneurysm repair with mRS>1 at 12 months were combined for Kaplan-Meier analysis because of the lack of difference between these curves on first Kaplan-Meier analysis

4.1.3 Results

A total of 777 cases of uIA treated by surgery with a supratentorial exposure were identified. From this total, 51 cases were not followed for a minimum of 30 days. Failure to follow these cases was due to death or poor neurological state in 20 cases, distance to travel to follow-up (interstate or overseas) in 6, and lost to planned follow-up in 25 cases with a last mRS<4 (Figure 4.1). There were 17 cases with an mRS<2 lost to follow-up that were intended to be followed beyond 30 days. Data were collected and analysed for the remaining 726 consecutive uIA (excluding posterior circulation aneurysms proximal to the superior cerebellar artery). The mean and median time interval between initial referral and censoring or first seizure was 1,063 (SD 1,292 days) and 525 days (upper and lower 25% quartile 200 and 1,463 days) respectively. The mean follow-up from referral to last follow-up is given in Table 4.1. Post-operative complications by the definition proposed in this study were thought to be due to infarction in all cases.

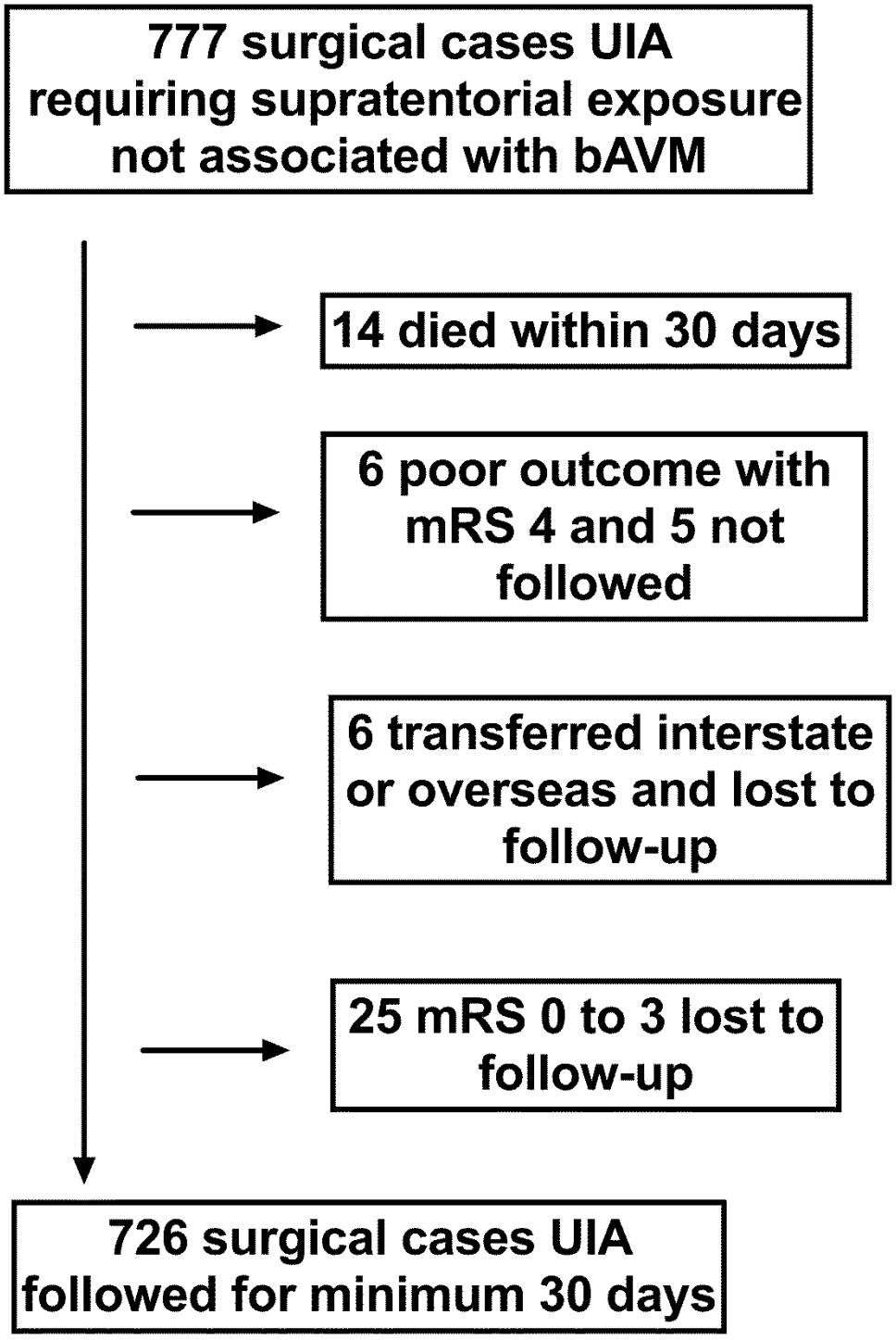


Figure 4.1 Flow chart of cases selected and followed for a minimum of 30 days after surgery from the 777 surgical cases requiring a supratentorial subarachnoid space exposure not associated with surgery for brain arteriovenous malformations (bAVM). Reasons for failure to follow included poor outcomes (modified Rankin score [mRS] greater than 3, 20 cases), patient not intended to be followed as transferred to remote locations (6 cases), and lost to- follow-up (25 cases). UIA, unruptured intracranial aneurysms

Table 4.1Characteristics of 726 patients undergoing surgery for UIA

	% Cases with characteristic identified in column 1 (number of cases with characteristic)	% Cases with characteristic identified in column 1 developing postoperative seizure. 95% CI (number of cases with characteristic developing seizure)	Fisher's Exact or Mann Whitney tests comparing group with postoperative seizures with those without (p value)
All cases: %; 95% CI (number)	726	1.9%; 1.1 to 3.2% (14)	
Characteristic examined			
Female	72% (525)	1.9%; 1.0 to 3.5% (10)	>0.99
Age 50 years or more	62% (448)	2.0%; 1.0 to 3.8% (9)	>0.99
Pre-operative seizures	2.6% (19)	21%; 4.0 to 44% (4)	<0.001
Previous craniotomy elsewhere	1.4% (10)	10%; <43% (1)	0.18
Past stroke/brain injury/brain tumor	3.6% (26)	4%; <20% (1)	0.40
Past ruptured aneurysm	3.0% (22)	5%; <24% (1)	0.35
Presentation with symptomatic brain compression	1.0% (7)	14%; <53% (1)	0.13
Maximum size (largest aneurysm) >15 mm	25% (182)	4.4%; 2.1 to 8.6% (8)	0.01
Any MCA location (includes MCA aneurysms that are not primary target)	36% (263)	3.8%; 2.0 to 7.0% (10)	<0.01
Multiple aneurysms repaired	26% (190)	1.1%; 0.04 to 4.0% (2)	0.54
Multiple craniotomies	6.9% (50)	4%; 0.3 to 14% (2)	0.25
Complication of aneurysm repair with mRS>1 at 12 month	6.9% (50)	6%; 1.4 to 17% (3)	0.07
Follow-up: Days,	**mean; SD (median; longest)** 1,082; 1,311 SD (534; 7,625)	**mean; SD (median; longest)** 2,007; 1,654 SD (1,445; 4,988)	0.015

Post-operative seizures occurred in 14 cases. Four of these 14 cases had a pre-operative seizure history and three had post-operative complications resulting in an mRS>1 at 12 months (Table 4.2). Of the twelve variables examined by Fisher's Exact test, only pre-operative seizure ($p<0.001$), maximum size >15mm ($p=0.01$), MCA treatment ($p<0.01$) and complication of surgery ($p=0.07$) were identified as potentially significant indicators of the increased risk of post-operative seizures (Table 4.1). Further investigation of these four variables by multivariate Cox regression identified pre-operative seizures ($p<0.001$, HR 17.8: 95% CI 4.5 to 70.9%), MCA treatment ($p<0.005$, HR 5.8: 95% CI 1.7 to 19.6%) and complication of aneurysm repair with mRS>1 at 12 months ($p=0{\cdot}04$, HR 4.3: 95% CI 1.04 to 17.4%) were identified as characteristics associated with a significantly increased risk of first seizure after discharge from hospital (Table 4.3). The occurrence of both pre-operative seizure and complication of repair with mRS>1 occurred in two cases. Neither of these cases was reported to have had a post-operative seizure. The occurrence of both pre-operative seizures and MCA aneurysm treatment occurred in eight cases, four of whom developed post-operative seizures.

Table 4.2:Patients experiencing first seizure undergoing surgery for UIA aneurysms.

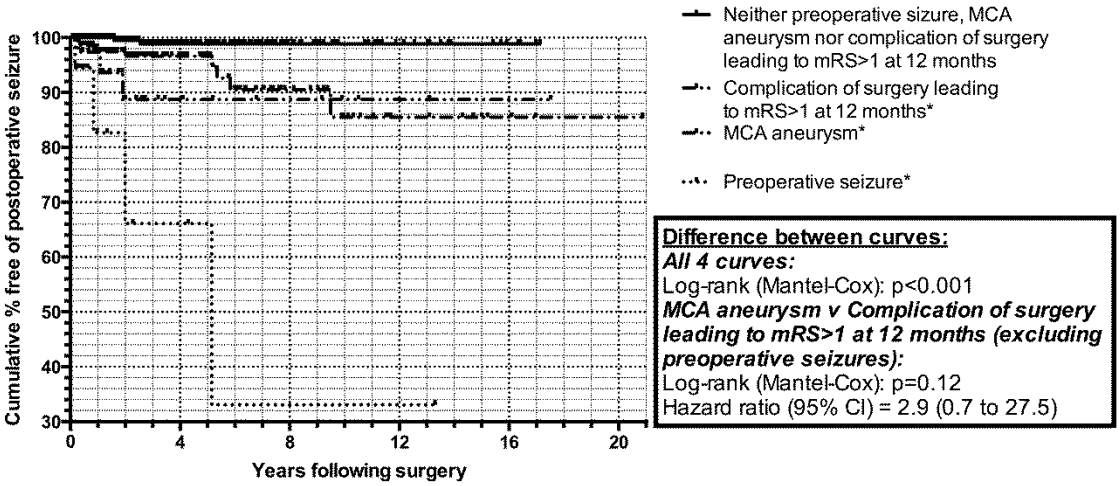
Case	Age and sex	Multiple aneurysms repaired	Aneurysm size >15mm	Pre-operative Neurological History	Neurological condition at discharge	Complications of surgery leading to mRS>1 at 12 months	MCA aneurysm treated	Days between referral and first seizure	Seizure type
1	54F	No	No	Normal	Hemiparesis	mRS=2	No	697	Simple partial
2	64F	No	Yes	Normal	Normal	Nil	Yes	1,954	Generalized
3	37F	No	Yes	Normal	Dysphasia	mRS=2	Yes	100	Generalized
4	54F	No	Yes	Normal	Normal	Nil	Yes	367	Generalized
5	34F	No	Yes	Normal	Normal	Nil	Yes	116	Generalized
6	41F	Yes	No	Normal	Normal	Nil	Yes	2129	Generalized
7	46M	No	No	Normal	Normal	Nil	No	585	Generalized
8	34F	No	No	Past meningioma resection	Normal	Nil	Yes	3,465	Generalized
9	36M	No	Yes	Normal	Normal	Nil	No	931	Generalized
10	16F	No	No	Single generalized seizure	Normal	Nil	Yes	1,884	Generalized
11	32F	No	Yes	Multiple generalized seizure	Normal	Nil	Yes	61	Generalized
12	47M	Yes	Yes	Single complex partial seizure	Normal	Nil	Yes	727	Complex partial
13	55F	No	No	Nocturnal generalized seizures	Normal	Nil	Yes	307	Nocturnal generalized
14	52M	No	Yes	Normal	Hemiparesis and dysphasia	mRS=2	No	398	Generalized
All cases						Days: mean (SD) [median: 25% and 75% quartile}		980 (1,004) [641: 259 and 1,901]	

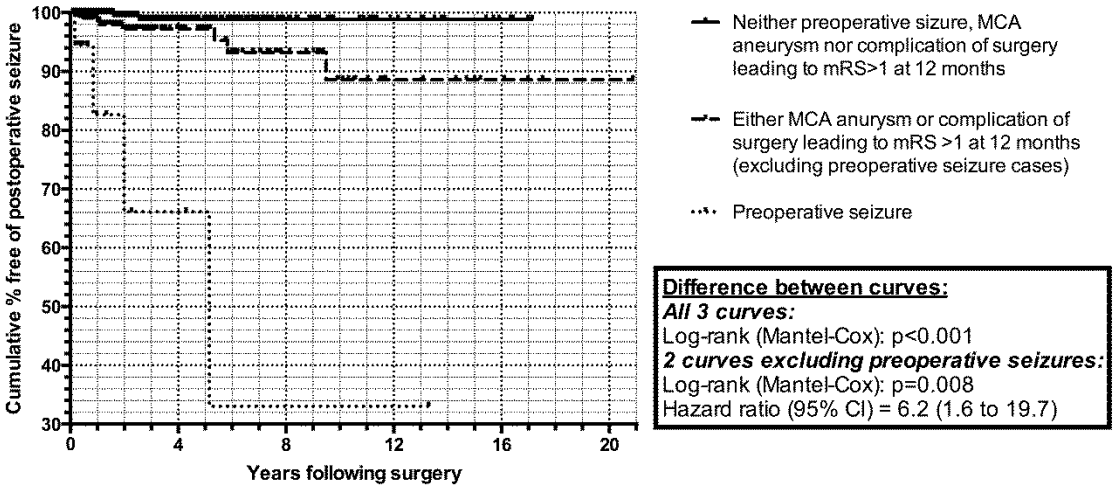
Table 4.3 Summary of Multivariate Cox regression and Kaplan-Meier analyses

Variables	Multivariate Cox regression for first post-operative seizure or Log-rank (Mantel Cox) (p value)	Hazard ratio Multivariate Cox regression, (95% CI)	Kaplan-Meier Log-rank Hazard ratio (95% CI)
Pre-operative seizures	<0.001	17.8 (4.5 to 70.9)	
Maximum size (largest aneurysm) >15 mm	0.076		
MCA location (not necessarily target aneurysm)	0.005	5.8 (1.7 to 19.6)	
Complication of aneurysm repair with mRS>1 at 12 months	0.04	4.3 (1.04 to 17.4)	
Kaplan-Meier 4 curve comparison (Pre-operative seizure, Complications of surgery leading to a mRS >1 at 12 months, MCA aneurysm and neither of the other 3 categories)	<0.001		
Kaplan-Meier curve comparing Complications of surgery leading to a mRS >1 at 12 months with MCA aneurysm (excluding preoperative seizure)	0.12		2.9 (0.7 to 27.5)
Kaplan-Meier curve comparing combined Complications of surgery leading to a mRS >1 at 12 months and MCA aneurysm (excluding preoperative seizures) with neither Complications of surgery leading to a mRS >1 at 12 months, MCA aneurysm nor preoperative seizure	<0.008		6.2 (1.6 to 19.7)

By Kaplan-Meier analysis, the cumulative risk of first post-operative seizure for cases with neither pre-operative seizures, MCA aneurysm treatment nor complications of surgery (leading to an mRS>1 at 12 months) was <0.1%, and 1.1% at 12 months and 7 years respectively (Figure 4.2). For cases with pre-operative seizures, the cumulative rate of first post-operative seizure was 17% and 66% at 12 months and 7 years respectively (Figure 2). For cases with either complications of surgery (leading to an mRS>1 at 12 months) or MCA aneurysm treatment, the cumulative risk of first post-operative seizure was 1.4% and 6.8% at 12 months and 7 years respectively (Figure 2). The difference between these three groups was significant by the Kaplan-Meier curve analysis [Log-Rank (Mantel-Cox) $p<0.001$] (Figure 2). There was no discernable difference by Log-rank (Mantel-Cox) analysis between those with complications of surgery (leading to an mRS>1 at 12 months) and MCA aneurysm treatment and these two were therefore combined for subsequent Kaplan-Meier analysis. Beyond seven years, the number at risk decreased to less than 10%, making analysis beyond this time unreliable.

There was no change in the levels of significance found in the sensitivity analysis. No variable achieved a *p* value of <0.05 after the inclusion of 17 excluded cases that were followed for less than 30 days with a last mRS<2.





Number at risk

Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
MCA	263	167	112	80	67	52	41	31	23	21	15	12	8	8	7	4	3	1	1	1	1
Complication	50	30	16	11	9	7	6	5	5	5	3	2	2	2	1	1	1	1	0	0	0
Preoperative seizures	19	6	4	3	3	2	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0
MCA excluding preoperative seizure	255	164	110	79	66	51	41	31	23	21	15	12	8	8	7	4	3	1	1	1	1
Complication excluding preoperative seizure	48	30	16	11	9	7	6	5	5	5	3	2	2	2	1	1	1	1	0	0	0
MCA or Complication excluding preoperative seizure	287	185	120	85	71	54	44	34	26	24	17	13	9	9	8	8	4	2	1	1	1
Neither preopertive seizure, MCA or complication	420	277	191	133	108	90	68	52	41	35	24	21	16	13	7	7	4	1	0	0	0
Total	726	468	315	221	182	146	113	87	68	60	42	35	25	22	15	15	8	3	1	1	1

Cumulative risk (%) of first seizure after surgery

MCA or Complication excluding preoperative seizure		1.4					6.8
Neither preopertive seizure, MCA or complication		0					1.1
Preopertive seizure		17.3					66.1

* = includes cases that may be in more than one curve

Figure 4.2 Kaplan-Meier analysis for the cumulative percentage free of postoperative seizures for 726 cases after surgical repair of unruptured intracranial aneurysms requiring a supratentorial subarachnoid space access. A, represents the 4 categories of risk identified by Cox regression (preoperative seizures, middle cerebral artery [MCA] aneurysm, complication of surgery leading to a modified Rankin score [mRS] .1 at 12 months). In this graph, some cases are represented in more than a single curve. There is a difference in the curves by log-rank, but no difference between MCA aneurysm and complication of surgery leading to a mRS .1 at 12 months. B, combines the curves of MCA aneurysm and complication of surgery leading to a mRS .1 at 12 months. There are no cases represented in more than 1 curve. There is a difference between these curves.

4.1.4 Discussion

The purpose of our investigation was to determine the level of risk of seizure after discharge from surgery for uIAs that may impact on a person's ability to return to normal activities, such as driving a motor vehicle. For the total cohort, we found that in the absence of pre-operative seizure, MCA aneurysm treatment, or complications of aneurysm repair, the cumulative risk of seizures at 7 years was 1.1%. Furthermore, in the absence of pre-operative seizure but with either MCA aneurysm treatment or complications of aneurysm repair, the cumulative risk of seizures at 7 years was 6.8%.

In theory, because the aneurysm neck is located within the subarachnoid space, microsurgical repair should be possible without significant brain damage, thus avoiding the potential for seizure development. In practice, this potential for seizure development is difficult to avoid because of a number of events that may occur during surgery, such as: surgical retraction causing brain injury; venous infarction occurring from ligation and division of veins; when the fundus of the aneurysm requires dissection from within the brain; infarction; or haemorrhage.

The risk of seizure following surgery for uIAs has important implications for driving. (Rotary RehabAid Centre , Baker, Prestigiacomo et al. 1995, Hayashi, Hadeishi et al. 1999, Beghi and Sander 2005, Association 2011, Austroads 2012, Driver Licensing Authority 2014, Office of the Superintendent of Motor Vehicles 2014, Authority 2015) The paucity of evidence has made driving authorities rely on expert opinion to develop fitness to drive guidelines.(Office of the Superintendent of Motor Vehicles 2014)

In this cohort, no patient was commenced on anticonvulsants for uIA or treatment of uIA unless they had been treated for seizures prior to their admission. We excluded from analysis aneurysm cases that did not require a supratentorial approach, as these cases do not have an obvious reason for an increased risk of seizure. From the factors that we examined (aneurysm size; multiple craniotomies; gender; age; pre-existing stroke; brain injury or brain tumor; past ruptured aneurysm; pre-operative seizure; symptomatic brain compression; multiple aneurysms repaired at one surgery; and complication of aneurysm repair) we found pre-

operative seizure and complication of aneurysm repair to be discriminators of increased risk for the development of seizure.

Although it is difficult to compare this study with the natural history of seizures occurring in a similar population, it is worth noting that the annual rate of detection of unprovoked first seizure is 23 to 61 per 100,000 population.(Hauser and Beghi 2008) This is considerably lower than was found following surgery for uIA in our series. However, our findings do suggest patients who have no pre-operative seizures, MCA aneurysm treatment or complications due to surgery can be reassured that the risk for seizure development is very low and that it is unnecessary on this account to either be prescribed preventative anticonvulsant therapy or alter daily living activities in this cohort. This study has altered our routine practice from uniformly restricting driving for a minimum of 3 months following surgery. We continue to only recommend anticonvulsants for patients with pre-operative seizures (including single seizures). We now suggest to patients that they may resume driving in the absence of pre-operative seizures or complications of surgery at the time of their six weeks post-operative follow-up. For those with complications of surgery leading to stroke, we continue to restrict their return to driving until such time as their mRS<2. If this does not occur we suggest a restriction of driving or driving with anticonvulsants providing they pass a driver assessment test. In the event that there is a post-operative seizure, these patients are recommended to commence anticonvulsants and their cases to be followed by a neurologist.

A report of a US nationwide inpatient seizure rate following surgical repair of uIA of 9.2% is comparatively high as compared with our post-discharge first seizure incidence.(Hoh, Nathoo et al. 2011) We have previously reported results from the Australian National Hospital Morbidity Database that identified an overall 2.7% incidence of perioperative seizures for uIA surgery between the years 1998 and 2008.(Lai, O'Donnell et al. 2013) For the Australian study, the incidence declined steadily from 4.2% in 1998 to 2.0% in 2008.(Lai, O'Donnell et al. 2013) The explanation for the comparatively high rate of perioperative seizures as compared with after discharge seizures reported from our cohort may well relate to greater exposure to temporary precipitants of seizure during the perioperative period that are unique to this period and not a manifestation of permanent changes of the brain that may predispose to ongoing seizures. This disconnect between early and late seizures may be similar to early

seizures after stroke not predicting long-term development of seizures (unless associated with intracerebral haemorrhage).(Serafini, Gigli et al. 2015) There are a number of possible temporary precipitants that can be suggested to increase the risk of seizure, particularly when several may be present at the same time. These include brain trauma, pneumocephalus and brain shift (as for example can occur after chronic subdural haematoma drainage)(Chen, Kuo et al. 2004), hyponatremia, orthostatic hypotension, pharmacological interaction, blood loss at the time of surgery, anaesthesia, fever, brain distortion and complications of surgery such as subdural haemorrhage and stroke. These are well recognized causes for seizures, but are may be only temporally associated with the perioperative period. Therefore, there is a reasonable expectation that for uIA, the explanation for seizures during the hospital administration may be significantly different from those resulting from permanent brain injury that will only be manifest after the acute phase has resolved and the time taken for gliosis or siderosis to commence inducing seizures.(Wang, Yang et al. 2013, Hadera, Eloqayli et al. 2015) This may also account for the long delay between surgery and first seizures identified in our cohort. However, considering the literature, there is a paucity of seizure incidence data in papers reporting the outcomes of surgery for uIAs following discharge from surgery. Few cohort series report the incidence of seizures after discharge from hospital.(Sundt, Kobayashi et al. 1982, Bidzinski, Marchel et al. 1992, Rodriguez-Hernandez, Zador et al. 2013) Those cohort studies reporting an incidence of seizure for uIA surgery have not employed survival analysis methodology in determining this incidence.

Limitations

The limitations of cohort studies are well known. There is the problem of whether the cohort treated by the authors reflects the general uIA population. These results would need to be confirmed by others to be accepted as generalisable. The patients included in our study were likely to have more surgically complex than simple aneurysms, reflecting referral bias to a centre with expertise in cerebrovascular surgery. In addition, the grading of outcomes is not independent.

A specific limitation of this study was the use of the variable complication of surgery leading to an mRS>1 at 12 months. The use of a clinical outcome variable not determined before one year following surgery in the determination of seizure outcome may at first appear to be of

limited use in assisting clinicians to determine the eligibility for return to driving. However, this clinical variable is a surrogate for stroke complicating surgery, the clinical determination of which is evident prior to discharge. The discrimination between neurological deficits responsible for outcomes with an mRS>1 caused by stroke and dissection may be made by computed tomographic scan or magnetic resonance imaging in the post-operative period. However, this cannot always be made because of clip artifact (e.g. infarcts of the hypothalamus associated with anterior communicating artery aneurysm repair) and an mRS of 2 can be caused by ptosis or diplopia (usually not caused by stroke) in the early post-operative period. Therefore, the clinical complication definition of this study was used as a surrogate for stroke caused by the surgery for aneurysm repair. As such, the determination of the advice regarding return to driving can reasonably be made early after surgery in most cases. Very few cases would require a protracted period before determining whether they fell within or outside the low risk group.

A limitation in analysis by multivariate Cox regression and Kaplan-Meier curve analysis is the low number of events (i.e. post-operative seizures) occurring, limiting the number of variables that can be analysed by these techniques. By choosing only three variables, there is a risk of missing variables that may be significant in a larger series.

4.1.5 Conclusion

Cases of uIA undergoing surgical repair with no history of pre-operative seizure and no post-operative complication or treated MCA aneurysm, had a low risk of subsequent seizure (approximately 1% over the first 7 years after surgery). If either MCA aneurysm treatment or post-operative complication has occurred, in the absence of pre-operative seizures, the risk of first seizure is no greater than 1% per year.

Chapter 5 *The risk of seizure following surgery for brain arteriovenous malformation (bAVM): A prospective cohort study*

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5.1 Abstract

Evidence for the risk of seizures following surgery for brain arteriovenous malformations (bAVM) is limited.

The objective of this study was to determine the risk of seizures after discharge from surgery for supratentorial bAVM.

A prospectively collected cohort database of 559 supratentorial bAVM patients (excluding patients where surgery was not performed with the primary intention of treating the bAVM) was analysed. Cox proportional hazards regression models (Cox regression) were generated assessing risk factors, a Receiver Operator Characteristic (ROC) curve was generated to identify a cut-point for size, and Kaplan-Meier life table curves were created to identify the cumulative freedom from post-operative seizure.

Pre-operative histories of more than two seizures and increasing maximum diameter (size, cm) of bAVM were found to be significantly ($p<0.01$) associated with the development of post-operative seizures and remained significant in the Cox regression (size as continuous variable: $p=0.01$; Hazard ratio: 1.2; 95%CI: 1.0-1.3; more than two seizures: $p=0.02$; Hazard ratio: 2.1; 95%CI: 1.1-3.8). The cumulative risk of first seizure after discharge from hospital following resection surgery for all patients with bAVM was 5.8% and 18% at 12 months and 7 years, respectively. The 7-year risk of developing post-operative seizures ranged from 11% for patients with bAVM ≤4 cm and with 0 to 2 pre-operative seizures, to 59% for patients with bAVM >4 cm and with >2 pre-operative seizures.

The risk of seizures after discharge from hospital following surgery for bAVM increases with the maximum diameter of the bAVM and a patient history of more than two pre-operative seizures.

5.1.1 Introduction

The risk of seizure following supratentorial arteriovenous malformation of the brain (bAVM) surgery has been reported to range from 4–50% and be new in onset in 3–17%.(Parkinson and Bachers 1980, Murphy 1985, Crawford, West et al. 1986, Heros, Korosue et al. 1990, Moriya, Nakamura et al. 1990, Piepgras, Sundt et al. 1993, Yeh, Tew Jr et al. 1993, Thorpe, Cordato et al. 2000, Kwon, Oh et al. 2002, Krivoshapkin and Melidy 2005, Nagata, Morioka et al. 2006, Josephson, Leach et al. 2011, Englot, Young et al. 2012, Lopez-Ojeda, Labib et al. 2013, Rohn, Haenggi et al. 2014) A variety of characteristics have been cited as increasing the risk of seizure including: age at seizure onset; duration of pre-operative seizures; bAVM size; location; previous haemorrhage; lenticulostriate arterial supply to the bAVM; fronto-temporal location; and post-operative neurological deficit.(Crawford, West et al. 1986, Yeh and Privitera 1991, Piepgras, Sundt et al. 1993, Yeh, Tew Jr et al. 1993, Kraemer and Awad 1994, Thorpe, Cordato et al. 2000) Understanding which factors are associated with an increased risk of experiencing a seizure after discharge from hospital following the surgical resection of supratentorial bAVM will assist individual patients and their doctors on the merits of continuing anti-epileptic drug (AED) therapy as well as the possibility of resuming certain pre-operative activities (e.g. driving and working with heavy machinery).

With regards to the cumulative incidence of patients free of seizures following bAVM surgery, there are major differences between series reporting absolute proportion of patients experiencing seizures (over a defined period) and that calculated by Kaplan-Meier curves. As an example, the hitherto largest surgical series of supratentorial bAVM treated by surgery reported 20% of patients experiencing a seizure in a mean follow-up of 20.7 months. However, from their Kaplan-Meier curve, the estimate of the 5-year cumulative incidence of patients experiencing seizure appears to be greater than 30% at five years.(Englot, Young et al. 2012) The method of estimating the seizure incidence by absolute proportion may provide an overly optimistic view of the proportion of patients experiencing seizures following surgery. This is because there are usually variable lengths of follow-up of patients (often resulting in a short median length of time) during which a small proportion of patients are detected with seizures. The length of follow-up for which bAVM management series reported seizures was typically short, 21(Englot, Young et al. 2012) to 147(Von Der Brelie, Simon et al. 2015) months (if they are reported at all). For the absolute proportion to be accurate, considerably longer periods of follow-up of all patients are required. On the other hand, the Kaplan-Meier method of establishing cumulative incidence of patients free of seizures may be more accurate given the technique's ability to adjust for the variability in

time to last follow-up free of seizure, and time-to-first seizure. This is generally considered a reasonable estimate of outcome in large cohorts until fewer than 10% of those initially at risk remain among the patients followed.(Peacock 2007)

There are a number of different and important foci on the development of post-operative seizures. Most series have concentrated either on improvement in seizure control,(Piepgras, Sundt et al. 1993, Yeh, Tew Jr et al. 1993, Englot, Young et al. 2012) or on comparing management pathways.(Hoh, Chapman et al. 2002, Hyun, Kong et al. 2012, Wang, Yang et al. 2013) Both are important, the former in patients who undergo bAVM surgery with a seizure disorder (and the potential for improved control or cure) and the latter for influencing a management decision on selecting treatments. However, another important focus is the development of any post-operative seizure. This is because the occurrence of any seizure will impact on the patient's activities (e.g. driving and working with heavy machinery) and hence, on a patient's quality of life.(Rohn, Haenggi et al. 2014, Della Puppa, Rustemi et al. 2015) To this point in time, the decision on restriction of activities, and the role of prophylactic AED, following surgery for bAVM remains weakly supported by evidence.(Josephson, Sauro et al. 2016)

The aim of this study was to determine factors associated with patients experiencing a first post-operative seizure following supratentorial bAVM resection and to determine the cumulative risk of first post-operative seizures. This was in order to provide greater understanding of both the role of bAVM alone (in the absence of the impact of haemorrhage) as well as the combination of bAVM presenting with haemorrhage, on the risk of post-operative seizures.

5.1.2 Methods

Patient Population

This study was approved by, and performed in accordance with, the Macquarie University Human Ethics Committee (HEC). Patient consent was not required for our HEC approval. A prospectively collected database of the senior author (MKM) containing all consecutive patients undergoing surgery for brain arteriovenous malformations (bAVM), for years 1989 to July 2014, was retrospectively analysed. The database contained demographic, clinical, radiological and treatment-related information. Entry into the database was prospective and documented at the time that the information was available. Demographic and clinical data were entered at the date of referral. Digital subtraction angiography (DSA) information was entered prior to treatment and grading of the bAVM was similarly recorded prior to surgery. The Spetzler-Martin grade (SMG) was established by allocating points for size (1 for less than 3cm, 2 for size between 3 and 6 cm, and 3 for size greater than 6 cm), the presence of deep venous drainage (adding 1 point if present), and location in "eloquent" brain (adding 1 point if located in primary sensory cortex, motor cortex, language cortex, internal capsule, diencephalon, brainstem, deep cerebellar nuclei, or cerebellar peduncle).(Spetzler and Martin 1986) The Spetzler-Ponce Class categories (SPC) are derived from combining SMG 1 and 2 for SPC A, SMG 3 for SPC B and combining SMG 4 and 5 for SPC C.(Spetzler and Ponce 2011)

A legal requirement in Australia is for post-surgical patients to refrain from driving if a seizure occurs. Furthermore, at the time of motor vehicle licence renewal, a medical clearance is required from the treating specialist if seizures are disclosed, and is reviewed annually. This responsibility and obligation encourages screening for seizures at each post-operative consultation by the neurosurgeon. This information was recorded in the database at the time of each consultation. Included in the records was correspondence referring to seizure events. Seizures could be either focal or generalised and considered to have occurred if reported as such by an emergency room physician, neurosurgeon or neurologist or were considered to be by the senior author on review of history. Patients were included if they were treated by surgery for supratentorial bAVM (Figure 5.1).

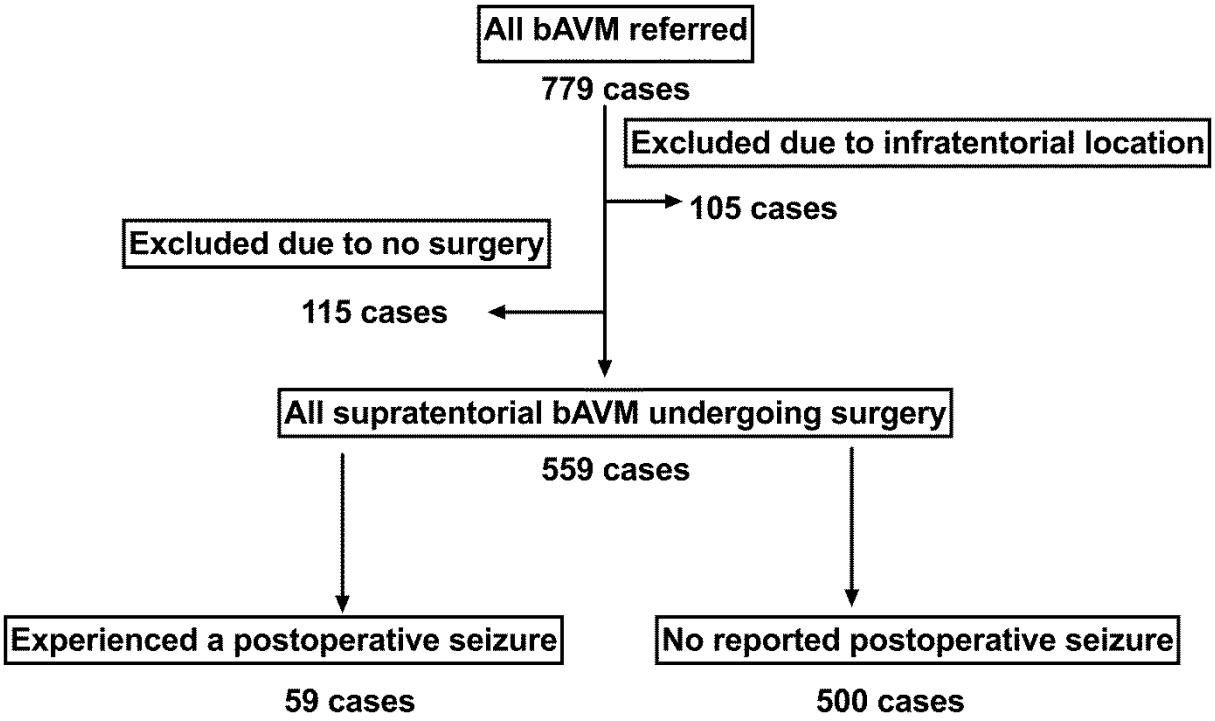

Figure 5.1 The flow chart of bAVM included and excluded from analysis.

Patients were excluded if they had bAVM treated in infratentorial locations or were treated by surgery that was not intended for attempted bAVM excision (e.g. evacuation of associated haematoma or repair of aneurysms without an attempt to excise the bAVM).

The responsibility for entry into the database was that of the senior author. However, the database was accessible to Residents, Fellows and Occupational Therapists at the time of assessment and follow-up.

Routine post-operative seizure prophylaxis over the cohort study period

The AED protocol was the continuation of previously prescribed AED or, in the absence of previous AED treatment, commencement of monotherapy at the time of bAVM resection and continued for 12 months. If no seizure had occurred in the 12 months following bAVM resection, the AED therapy was stopped. However, for patients that were being pre-operatively managed by neurologist for epilepsy, or at the request of patients who were

dependent upon their ability to drive (e.g commercial drivers, living in remote locations with no alternative method of transport), AEDs were continued beyond 12 months. Monitoring of compliance was transferred to the care of the patient's primary care physician after discharge from hospital for bAVM surgery. We did not have the relevant clinical and blood level data to know whether there was concordance between intention-to-treat with AEDs and treatment received with AED at the time of any post-operative seizures.

Variables investigated

Our prospectively collected bAVM database of the senior author (MKM) was interrogated to examine which factors influenced the onset of first seizure for supratentorial bAVM following ablative surgery. Fifteen variables were selected for examination, based upon our literature review. These were: sex; age; mode of presentation; largest diameter of bAVM (cm); eloquent cortex; deep venous drainage; Spetzler Ponce Class; brain location; side; modified Rankin Scale score (mRS) before surgery; arterial supply; pre-operative embolisation; complications (leading to an mRS>1 and mRS>2 at 12 months); AED treatment; and aneurysm repair. Mode of presentation was further broken down into presentation by: haemorrhage; seizures; more than two pre-operative seizures; nature of seizure (generalised versus partial) and neurological deficits unrelated to haemorrhage. Patients who experienced both partial and generalised seizures or partial seizures secondarily generalised were classified with the generalised group. Patients who had seizures (or a seizure-like event) as a consequence of haemorrhage were not included in the patients classified as presenting with seizure. Because patients with a presentation with intracranial haemorrhage may also present with seizures, and because the mechanism for the seizure genesis in these patients may be unrelated to the presence of bAVM but rather the haemorrhage, patients presenting with both haemorrhage and pre-operative seizures were considered separately and not included in the group classified as presenting with seizures. This was in order to have a greater understanding of the role of bAVM alone on the presentation with seizures and the risk of post-operative seizures after surgery to eliminate the bAVM.

Seizures that occurred during the hospital admission for bAVM surgery were not included for three reasons:

1. The purpose of the study was to ascertain the risk for seizures following hospital discharge, during the course of normal activities for patients and not perioperative seizures.

2. There is difficulty in distinguishing unobserved seizures from the differential diagnosis of syncope from postural hypotension immediately after surgery. This is particularly a problem for patients managed with prolonged sedation in intensive care.
3. The collection of data on in-hospital seizure was not collected in the bAVM database and would therefore need to be retrospectively collected. All other variables examined in the database are entered prospectively. The retrospective collection of this data is made more problematic as the method of hospital detection and recording of seizures has changed over the 25 years of the database. More recently, it has been the hospital practice of detection and recording of all seizure-like events as "code blue" at Macquarie University Hospital. This makes the quality of in-hospital information of seizures inconsistent over the study period.

Outcome

The outcome variable of the study was the occurrence of first seizure following discharge from hospital after surgery. This required confirmation by an accident and emergency room physician, neurologist or neurosurgeon. The seizure could be generalised or partial. Post-operative seizures occurring during the in-patient post-operative admission for bAVM resection were not included as an outcome variable (see above for explanation).

Statistical Analysis

The two-tailed *p* value was determined using Fisher's Exact test, χ^2 test, *t* test or Mann Whitney test. From the univariate analysis, employing those pre-operative factors with the greatest likelihood to have an association with seizure occurrence as well as selecting variables identified from the literature as being associated with the occurrence of post-operative seizures, a multivariable Cox proportional hazard regression (Cox regression) was performed. Variable selection was performed using the backward stepwise Wald technique (as some of the variables included were determined by pre-selection from variables identified in the literature). The event was first seizure after discharge from surgery for bAVM, and censoring occurred at last review.

To quantify the cumulative risk of first seizure for an identifiable group of patients with the

lowest risk, a group of patients was selected from characteristics identified from the Cox regression, for presentation by Kaplan-Meier curves. For continuous variables, the cut-point for the Kaplan-Meier curve was selected from a Receiver Operator Characteristic (ROC) curve by maximising the sum of sensitivity and specificity. Differences between Kaplan-Meier curves were assessed by a Mantel-Cox log-rank test and log-rank test for trends.

Because of the large number of variables examined, a statistical significance level of 1% was used throughout for the univariate analysis from which variables were identified and selected for inclusion in the Cox regression. A statistical significance level of 5% was used for the Cox regression analysis. Statistical analysis was performed using Prism (version 6, GraphPad Software Inc) and IBM SPSS Statistics (version 22, IBM corporation) software.

5.1.3 Results

Data were collected and analysed for 559 consecutive supratentorial bAVM undergoing surgical resection (Figure 5.1). Fifty-nine of these patients were identified to have a post-discharge seizure. The characteristics for those with and without seizures are reported in detail in Table 5.1. Patients with seizures were followed on average for 15 months longer than those without seizures. However, seizures occurred on average 15 months earlier than the length of follow-up for those identified as having no seizure. This suggested that the time difference in follow-up between the two groups was not important. A greater proportion of those experiencing seizures were prescribed antiepileptic drugs (AED), suggesting that the absence of AED prescription was not important in the occurrence of first seizure.

The post-operative detection rate of seizures was: 14% (95% CI: 9.3-20%) (24 of 176 patients) for patients presenting with pre-operative seizures (in the absence of coincidental presentation with haemorrhage); 10% (95% CI: 6.8-15%) (24 of 240 patients) presenting with haemorrhage; 18% (95% CI: 11-27%) (14 of 80 patients) presenting with neurological deficit not due to haemorrhage; and 7.8% (95% CI: 3.8-15%) (8 of 102 patients) presenting other than haemorrhage, seizure or neurological deficit (Table 5.1). Within the presentation with haemorrhage group, the post-operative detection rate of seizures for those also having pre-operative seizures was 25% (95% CI: 12-45%) (6 of 24 patients) and for those without pre-operative seizures it was 8.3% (95% CI: 4.5-15%) (18 of 216 patients) (Table 5.1). This difference was not significant at the 1% level (p=0.02).

The nature of the post-operative seizures was at least one generalised seizure in 76% (95% CI: 64-85%) of patients identified with post-operative seizures. Patients who experienced a partial seizure that did not secondarily generalise occurred in 24% (95% CI: 15-36%) of patients identified with the first post-operative seizure.

Table 5.1 Characteristics of 559 patients undergoing surgery for supratentorial bAVM resection

Characteristics	No Postoperative Seizure	Postoperative Seizure	Fisher's Exact, t* or Mann Whitney tests** comparing group with postoperative seizures with those without (p value)
All: %; 95% CI (number)	500	59	
Preoperative data:			
Demographic			
Female: %; 95% CI (number)	50%; 45-54% (n=249)	41%; 29-53% (n=24)	0.22
Age years, mean (SD)	37 (15)	34 (14)	0.09*
Clinical presentation			
mRS before surgery >1	34%; 30-38% (n=168)	32%; 22-45% (n=19)	0.88
Preoperative hemorrhage (all cases): %; 95% CI (number)	43%; 39-48% (n=216)	41%; 29-53% (n=24)	0.78
Preoperative hemorrhage and no preoperative seizures: %; 95% CI (number)	39%; 34-43% (n=193)	31%; 20-43% (n=18)	0.26
Preoperative hemorrhage and preoperative seizures: %; 95% CI (number)	4.6%; 3.1-6.8% (n=23)	10%; 4.4-21% (n=6)	0.11
Preoperative hemorrhage and 1 or 2 seizures preoperative seizures: %; 95% CI (number)	3.2%; 1.9-5.2% (n=16)	5.1%; 1.2-14% (n=3)	0.44
Preoperative hemorrhage and >2 seizures preoperative seizures: %; 95% CI (number)	1.4%; 0.6-2.9% (n=7)	5.1%; 1.2-14% (n=3)	0.08
Any preoperative seizure (all patients): %; 95% CI (number)	34%; 30-38% (n=170)	51%; 38-63% (n=30)	0.01
No preoperative seizures (all patients): %; 95% CI (number)	66%; 62-70% (n=330)	49%; 37-62% (n=29)	0.01
Preoperative seizures (excluding patients presenting with hemorrhage): %; 95% CI (number)	30%; 27-35% (n=152)	41%; 29-53% (n=24)	0.14
Preoperative 1 or 2 seizures (excluding patients presenting with hemorrhage): %; 95% CI (number)	16%; 13-20% (n=82)	10%; 4.4-21% (n=6)	0.26
Preoperative 1 or 2 seizures (including patients presenting with hemorrhage): %; 95% CI (number)	35%; 31-39% (n=175)	51%; 38-63% (n=30)	0.02
Preoperative >2 seizures (excluding patients presenting with hemorrhage): %; 95% CI (number)	15%; 12-18% (n=73)	34%; 23-47% (n=20)	<0.01
Preoperative generalized seizure: %; 95% CI (number)	22%; 18-26% (n=109)	24%; 15-36% (n=14)	0.74
Preoperative partial seizure only: %; 95% CI (number)	8.6%; 6.4-11% (n=43)	17%; 9.3-29% (n=10)	0.06
Preoperative neurological deficit not due to hemorrhage: %; 95% CI (number)	13%; 11-17% (n=66)	24%; 15-36% (n=14)	0.05
Presentation other than hemorrhage, seizure or neurological deficit: %; 95% CI (number)	19%; 16-22% (n=94)	14%; 6.8-25% (n=8)	0.38
Angioarchitectural features			
For a subgroup analysis of location see Table 3			
Size mm, mean (SD)	3.3 (1.6)	4.3 (2.1)	<0.01*
Deep venous drainage: %; 95% CI (number)	33%; 29-38% (n=167)	31%; 20-30% (n=18)	0.77
Eloquent: %; 95% CI (number)	42%; 38-46% (n=209)	46%; 34 to 58% (n=27)	0.58
SPC A: %; 95% CI (number)	60%; 55-64% (n=298)	32%; 22-45% (n=19)	<0.01
SPC B: %; 95% CI (number)	28%; 24-32% (n=138)	53%; 40-65% (n=31)	<0.01
SPC C: %; 95% CI (number)	13%; 10-16% (n=64)	15%; 8-27% (n=9)	0.55
Left: %; 95% CI (number)	51%; 46-55% (n=253)	56%; 43-68% (n=33)	0.49
Distal ACA supply: %; 95% CI (number)	34%; 30-39% (n=172)	48%; 35-60% (n=28)	0.06
MCA supply distal to lenticulostriate; %; 95% CI (number)	68%; 63-72% (n=338)	78%; 66-87% (n=46)	0.14
Proximal ACA supply: %; 95% CI (number)	2.6%; 1.5-4.4% (n=13)	3.4%; 0.3-12% (n=2)	0.67
Anterior choroidal and lenticulostriate; %; 95% CI (number)	21%; 18-25% (n=107)	20%; 12-32% (n=12)	>0.99
PCA supply; %; 95% CI (number)	44%; 40-49% (n=221)	61%; 48-72% (n=36)	0.02
Location in exclusively parietal lobe or straddling both frontal and parietal lobes; %; 95% CI	19%; 15-22% (n=93)	27%; 17-40% (n=16)	0.02

(number) (see table 4)			
Ancillary Treatment			
Preoperative embolization; %; 95% CI (number)	13%; 10-16% (n=65)	22%; 13-34% (n=13)	0.07
Postoperative data:			
Clinical			
Follow-up between surgery and last follow-up: months, mean; SD (median; longest)	37.4; 44.5 (21.4; 242)	52.6; 39.6 (44.3; 203.7)	<0.01**
Interval between surgery and censor or event: months, mean; SD (median; longest)	37.4; 44.5 (21.4; 242)	22.7; 24.4 (13.0; 101.8)	0.05**
Complication of bAVM repair with mRS>1 at 12 month: %; 95% CI (number)	23%; 19-27% (n=113)	25%; 16-38% (n=15)	0.62
Complication of bAVM repair with mRS>2 at 12 month: %; 95% CI (number)	10%; 8-13% (n=51)	19%; 11-31% (n=11)	0.08
Postoperative generalized seizure: %; 95% CI (number)	NA	76%; 64-85% (n=45)	
Postoperative partial seizure only: %; 95% CI (number)	NA	24%; 15-36% (n=14)	
Angioarchitectural features			
Residual bAVM identified after surgery	1%; 0.4-2.4% (n=5)	0%; 0-7.3% (n=0)	>0.99
Ancillary Treatment			
Anticonvulsant treatment at censor or event: %; 95% CI (number)	17%; 14-21% (n=86)	64%; 52-75% (n=38)	<0.01
Addition and separate aneurysm repair; %; 95% CI (number)	10%; 8-13% (n=50)	10%; 4-21% (n=6)	>0.99

Three factors were identified to be highly significant ($p<0.01$) in association with the development of post discharge seizures. These were: bAVM size; more than two pre-operative seizures; and SPC B and C bAVM (Table 5.2). Because of the absence of either deep venous drainage or eloquent location as being significantly associated with the development of post-operative seizures (critical elements contributing to the SMG, and hence SPC, classification), and the interdependence between size and SMG, size was incorporated into the Cox regression, and SMG or SPC were not included. Therefore, from variables that we identified, we included bAVM size and more than two pre-operative seizures into the Cox regression analysis. In addition, previous reports have identified SMG, lenticulostriate arterial feeders and specific bAVM locations as increasing the risk of post-operative seizures. For this reason, eloquent location, deep venous drainage (as the two other variables contributing to SMG grouping), bAVM supply from anterior choroidal and lenticulostriate arteries, and location straddling parietal and frontal lobes or parietal lobe (as the regions identified in our study to have the greatest association with seizures – see below) were included in the initial variables examined in the multivariate Cox regression analysis.

Table 5.2 Summary of Multivariate Cox regression.

Variables	Multivariate Cox regression for first post-operative seizure (p value)	Hazard ratio Multivariate Cox regression, (95% CI)
More than 2 preoperative seizures*	0.02	2.1 (1.1 - 3.8)
Maximum bAVM size (continuous variable)*	0.01	1.2 (1.0 - 1.3)
Eloquent location	0.06	1.1 (0.6 – 1.8)
Deep venous drainage	0.48	1.0 (0.5 – 1.8)
Lenticulostriate or anterior choroidal feeding artery	0.28	1.5 (0.7 – 2.8)
Location straddling parietal and frontal lobes or parietal lobe	0.26	1.4 (0.8 – 2.5)

*Remained at last step of regression equation

The nature of seizures at presentation (partial or generalised) was not significantly associated with the development of post-operative seizures. Of the 176 patients with seizures, 70% of patients had at least one generalised seizure and 30% experienced partial seizure without any episodes of generalised seizures (Table 5.1).
Of all the factors examined from the multivariate Cox regression, only more than two pre-operative seizures (p=0.02; Hazard ratio of 2.1: 95% CI 1.1 to 3.8), and size, cm (continuous variable; p=0.01; Hazard ratio of 1.2: 95% CI 1.0 to 1.3) remained in the Cox regression at step 5 and were significant in explaining the occurrence of seizure after discharge (Table 5.2).

The cut-point for the Kaplan-Meier analysis for size was derived from the ROC curve (area under the curve 0.664; 95% CI 0.58-0.75; p<0.01) (Figure 5.2). The size maximizing the addition of sensitivity and specificity was 4.0 cm (sensitivity 60%, specificity 70%). This was then used in the Kaplan-Meier curves. The Kaplan-Meier curves are demonstrated in Figure 3. Combining the number of pre-operative seizures with bAVM (zero, one or two seizures versus more than two seizures) with maximum bAVM diameter size (≤ 4 cm versus >4 cm) generated four Kaplan-Meier curves (Figure 5.3). The number of patients at risk for the first 7 years following surgery remained greater than 10% of the initial number and thus, was considered a reliable length of follow-up for the calculation of the cumulative proportion experiencing seizures. From these curves, the overall cumulative risk of first seizure occurring after discharge from hospital for resection of supratentorial bAVM was: 5.8%, 16% and 18% at 12 months, 5 years and 7 years respectively. For patients with bAVM no greater than 4 cm and with zero, one or two pre-operative seizures the cumulative occurrence of first seizure was 4.4%, 11% and 11% at 12 months, 5 years and 7 years respectively (Figure 5.3). For patients with bAVM no greater than 4 cm and who reported more than two pre-operative seizures the cumulative occurrence of first seizure was 3.0%, 6.4% and 17% at 12 months, 5 years and 7 years respectively (Figure 5.3). For patients with bAVM greater than 4 cm and with zero, one or two pre-operative seizures the cumulative occurrence of first seizure was 1.1%, 27% and 27% at 12 months, 5 years and 7 years respectively (Figure 3). For patients with bAVM greater than 4 cm and who reported more than two pre-operative seizures the cumulative occurrence of first seizure was 33%, 48% and 59% at 12 months, 5 years and 7 years respectively (Figure 5.3 and Table 5.3). These four Kaplan-Meier curves were significantly different (p<0.01; log rank) (Figure 5.3).

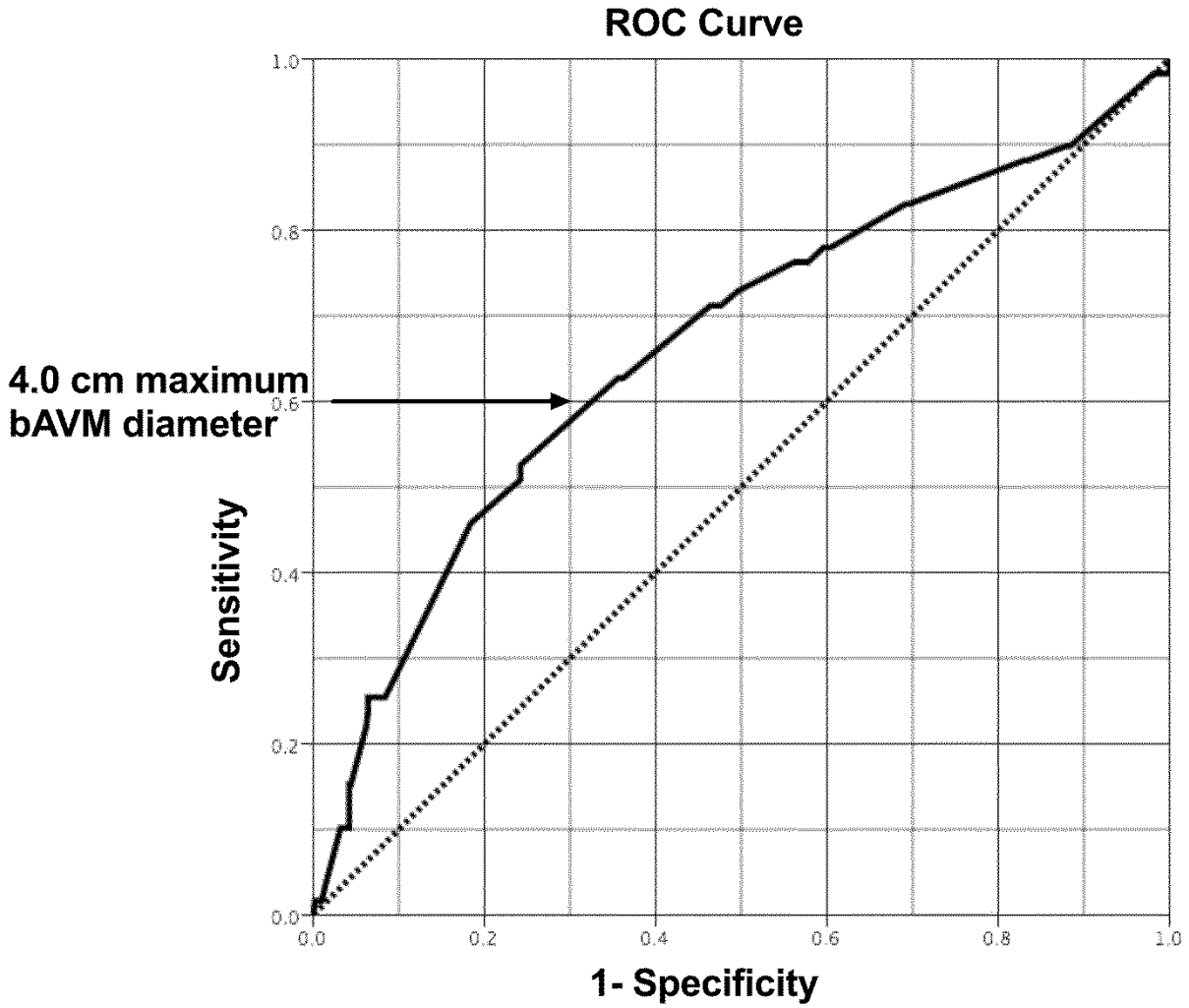

Figure 5.2 Receiver Operator Characteristic (ROC) curve for bAVM size and the occurrence of a first postoperative seizure (area under the curve 0.664; 95% CI 0.58-0.75; p<0.01). The size maximizing the addition of sensitivity and specificity was 4.0 cm (sensitivity 60%, specificity 70%).

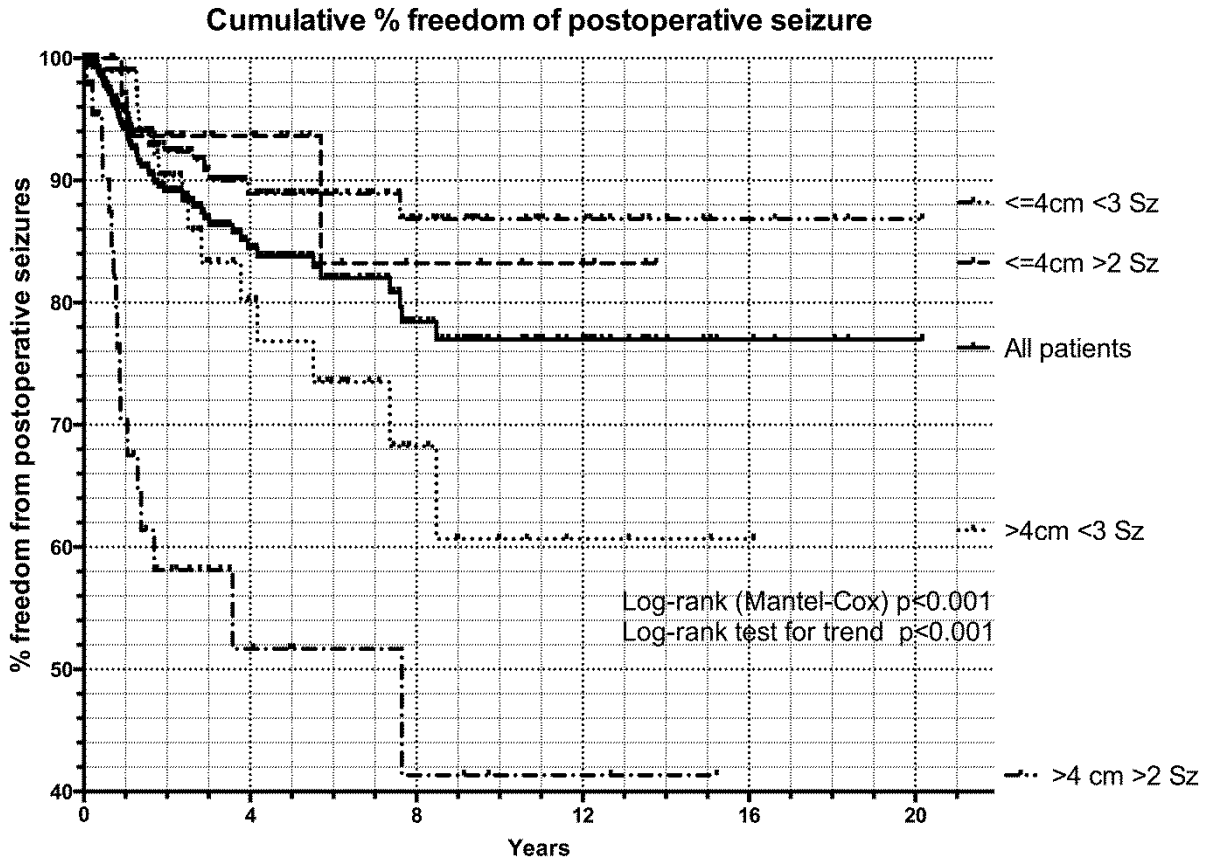

Figure 5.3 Kaplan-Meier curves generated by the combination of the number of preoperative seizures (zero, one or two versus more than two) with maximum bAVM diameter size (less than or equal to four cm versus greater than four cm). Greater than 10% of those initially at risk were followed for 7 years for each of these two curves. The curves were statistically significantly different (p<0.01; log-rank Mante-Cox and long-rank for trend). Symbols of groups: Patients with bAVM no greater than 4 cm in maximum diameter presenting with a history of 0, 1 or 2 preoperative seizures (<=4cm <3 Sz); Patients with bAVM no greater than 4 cm in maximum diameter presenting with a history of more than 2 preoperative seizures (<=4cm >2 Sz); Patients with bAVM greater than 4 cm in maximum diameter presenting with a history of 0, 1 or 2 preoperative seizures (>4cm <3 Sz); Patients with bAVM greater than 4 cm in maximum diameter presenting with a history of more than 2 preoperative seizures (>4cm >2 Sz). The number at risk for each year can be seen in Table 3.

Whilst the proportional hazards assumption was not tested, neither the Kaplan-Meier curves for pre-operative seizures (zero, one or two versus greater than two pre-operative seizures), nor the Kaplan-Meier curves for bAVM size (no greater than 4 cm versus greater than 4 cm) crossed. Therefore, we considered the proportional odds assumption to be satisfied.

Subgroup analysis of SPC

Because both SPC and the number of pre-operative seizures were associated with the risk for

the development of post-operative seizures and the importance that SPC makes in segmenting the bAVM population, the subgroup analysis of the number of seizures with SPC was analysed and presented in Table 5.4. For patients without pre-operative seizures, the detection rate of post-operative seizures by SPC was: 6.0% (95%CI: 3.8-9.2%) for SPC A; 16% (95%CI: 10-24%) for SPC B; and 12% (95%CI: 6.4-22%) for SPC C. For those experiencing one or two pre-operative seizures, the detection rate of post-operative seizures by SPC was: 6.8% (95%CI: 2.2-17%) for SPC A; 13% (95%CI: 4.4-29%) for SPC B; and 0% (95%CI: 0-49%) for SPC C. For those experiencing more than two pre-operative seizures, the detection rate of post-operative seizures by SPC was: 3.5% (95%CI: 18-50%) for SPC A; 32% (95%CI: 18-50%) for SPC B; and 30% (95%CI: 14-52%) for SPC C. This difference did not reach significance by our criteria ($p=0.03$) amongst the SPC groups in the detection rate of post-operative seizures for patients with more than two pre-operative seizures.

Although SPC grouping was important in predicting complications, the occurrence of complications within each SPC was not statistically significantly associated with the development of post-operative seizures (Table 5.4).

Table 5.3 Subgroup analysis of the number of patients developing postoperative seizures by Spetzler-Ponce Class (SPC).

	SPC A patients developing postoperative seizures	SPC B patients developing postoperative seizures	SPC C patients developing postoperative seizures	χ^2 comparing SPC groups (p value)
All: %; 95% CI (number)	6.0%; 3.8-9.2% (19 of 317)	18%; 13-25% (31 of 169)	12%; 6.4-22% (9 of 73)	<0.01
Presentation with seizure (no presentation with hemorrhage)				
Any preoperative seizure: %; 95% CI (number)	5.7%; 2.1-13% (5 of 88)	22%; 14-34% (14 of 63)	24%; 11-44% (6 of 25)	0.01
No preoperative seizure: %; 95% CI (number)	6.1%; 3.6-10% (14 of 229)	16%; 10-24% (17 of 106)	6.3%; 1.5-17% (3 of 48)	0.01
1 or 2 seizure prior to presentation: %; 95% CI (number)	6.8%; 2.2-17% (4 of 59)	13%; 4.4-29% (4 of 32)	0%; 0-49% (0 of 5)	0.53
>2 seizure prior to presentation: %; 95% CI (number)	3.5%; <0.1-19% (1 of 29)	32%; 18-50% (10 of 31)	30%; 14-52% (6 of 20)	0.03
χ^2 comparing no seizures, 1 or 2 seizures and >2 seizure presentation groups (p value)	0.84	0.11	0.03	
Presentation with both hemorrhage and seizure				
All cases: %; 95% CI (number)	11%; 1.7-33% (2 of 19)	75%; 30-97% (3 of 4)	20%; 10-60% (1 of 6)	0.04
1 or 2 seizure prior to presentation: %; 95% CI (number)	13%; 2.2-37% (2 of 16)	100%; 20-100% (1 of 1)	0%; 0-70% (0 of 2)	0.09
>2 seizure prior to presentation: %; 95% CI (number)	0%; 0-62% (0 of 3)	70%; 20-94% (2 of 3)	25%; 3-70% (1 of 4)	0.32
χ^2 comparing no seizures, 1 or 2 seizures and >2 seizure presentation groups (p value)	0.83	0.95	0.78	
Presentation other than seizure				
Presenting with hemorrhage: %; 95% CI (number)	6.3%; 3.2-12% (9 of 144)	19%; 12-31% (13 of 67)	6.9%; 0.9-23% (2 of 29)	0.02
Presenting with neither hemorrhage or seizure: %; 95% CI (number)	5.9%; 2.2-13% (5 of 85)	10%; 3.5-24% (4 of 39)	5.3%; <0.01-26% (1 of 19)	0.66
χ^2 comparing seizures, hemorrhage, and neither seizure nor hemorrhage presentation (p value)	0.98	0.38	0.12	
Development of complication				
Complication leading to a mRS>1 at 12 months; %; 95% CI (number)	0%; 0-55% (0 of 4)	23%; 12-41% (7 of 30)	14%; 5.1-32% (4 of 28)	0.49
No complication leading to a mRS>1 at 12 months; %; 95% CI (number)	6.0%; 3.9-9.3% (19 of 313)	17%; 12-24% (24 of 139)	11%; 4.4-24% (5 of 45)	<0.01
Fisher exact test comparing development of complications versus no complications (p value)	>0.99	0.44	0.73	

Subgroup analysis of location

Because the incidence of presentation by seizure may vary with differences in anatomical location of bAVM, a subgroup analysis of the proportion of presentation with seizure (excluding seizures in association with haemorrhage) was made with respect to bAVM location (Table 5.5). The location had a significant impact upon the proportion of patients that presented with seizures ($p<0.01$). The range in the proportion of patients presenting with seizures was from 48% (95% CI: 34-62%) for bAVM located straddling both frontal and parietal lobes, to 7.7% (95% CI: 5.7-10%) for bAVM located in the corpus callosum, basal ganglia, ventricle or diencephalon (Table 5.5).

For patients presenting with causes other than seizure, the proportion who subsequently developed post-operative seizures was 8.9% (95% CI: 6.4-12%) and ranged from 17% (95% CI: 6.4-38%) for bAVM located straddling both frontal and parietal lobes, to 5.9% (95% CI: 1.9-15%) for bAVM located in the occipital lobe inclusive of adjacent lobes (Table 5.5). This difference was not found to be significant ($p=0.50$). For patients presenting with seizures (not associated with presentation by haemorrhage), the proportion who subsequently develop post-operative seizures was 14% (95% CI: 9.8-20%) and ranged from 17% (95% CI: 6.4-38%), for bAVM located straddling both frontal and parietal lobes, to 5.9% (95% CI: 1.9-15%), for bAVM located in the occipital lobe inclusive of adjacent lobes (Table 5.5). This difference was not found to be significant ($p=0.16$).

Table 5.4Subgroup analysis of the number of patients with preoperative seizures (excluding presentation by hemorrhage) developing postoperative seizures by anatomical location.

	% Patients with bAVM in anatomical location (n)	Preoperative seizure presentation not related to hemorrhage % (n)	% Patients with postoperative seizure with no preoperative seizures (n)	% Patients with postoperative seizure with preoperative seizures (n)	Fisher exact test comparing those presenting with to those without preoperative seizures that develop postoperative seizures. (p value)
All: where relevant: %; 95% CI (number)	(559)	31; 28-35 (176)	8.9; 6.4-12 (34 of 383)	14; 9.8-20 (25 of 176)	0.07
Location					
Frontal lobe exclusive of adjacent lobe: %; 95% CI (number)	32; 29-36 (181)	31; 25-39 (57 of 181)	8.1; 4.3-14 (10 of 124)	11; 4.6-21 (6 of 57)	0.58
Straddling both frontal and parietal lobe: %; 95% CI (number)	7.9; 5.9-10 (44)	48; 34-62 (21 of 44)	17; 6.4-38 (4 of 23)	9.5; 1.2-30 (2 of 21)	0.66
Parietal lobe exclusive of adjacent lobe: %; 95% CI (number)	12; 9.2-15 (65)	37; 26-49 (24 of 65)	15; 6.5-29 (6 of 41)	17; 6.1-36 (4 of 24)	>0.99
Temporal lobe exclusive of adjacent lobe: %; 95% CI (number)	24; 21-28 (134)	36; 28-44 (48 of 134)	8.1; 3.8-16 (7 of 86)	10; 4.1-23 (5 of 48)	0.76
Occipital lobe inclusive of adjacent lobe: %; 95% CI (number)	16; 14-20 (92)	14; 8.3-23 (13 of 92)	5.9; 1.9-15 (4 of 68)	8.7; 4.3-16 (8 of 92)	0.56
Corpus callosum-basal ganglia-ventricular-diencephalon: %; 95% CI (number)	7.7; 5.7-10 (43)	4.7; 0.4-16 (2 of 43)	7.3; 1.8-20 (3 of 41)	0; 0-9.8 (0 of 43)	0.11
χ^2 comparing allocation to brain region (p value)		<0.01	0.50	0.16	

5.1.4 Discussion:

The analysis of our results found that bAVM maximum diameter and the reporting of more than two pre-operative seizures (unassociated with presentation by haemorrhage) were significantly associated with the occurrence of post-operative seizures. In our study, the cumulative 7-year risk of first seizure following surgery for supratentorial bAVM was found to be 18% for all patients (Figure 5.3 and Table 5.6). For patients with bAVM no greater than 4 cm and with zero, one or two pre-operative seizures, the cumulative occurrence of first seizure was 11% at 7 years. For patients with bAVM no greater than 4 cm and who reported more than two pre-operative seizures, the cumulative occurrence of first seizure was 17% at 7 years. For patients with bAVM greater than 4 cm and with zero, one or two pre-operative seizures, the cumulative occurrence of first seizure was 27% at 7 years. For patients with bAVM greater than 4 cm and who reported more than two pre-operative seizures, the cumulative occurrence of first seizure was 59% at 7 years. The survival-curve analysis was stratified by size dichotomized at 4 cm and the number of pre-operative seizures (less than three versus more than two). However, because of the likely interest in the cumulative first seizure risk for patients with no seizures prior to surgery and not presenting with haemorrhage, we did look at this in a *post hoc* analysis and found for patients with bAVM no greater than 4 cm, the cumulative occurrence of first seizure was 12% at 7 years and for patients with bAVM greater than 4 cm and who reported more than two pre-operative seizures, the cumulative occurrence of first seizure was 21% at 7 years (Table 5.6). Our overall results fall into the range of previous reports.(Hoh, Chapman et al. 2002, Kwon, Oh et al. 2002, Rohn, Haenggi et al. 2014) Our results can be considered reliable for our study population because 10% of the cohort remained in the Kaplan-Meier analysis for the first 7 years. By contrast, the cumulative 5-year risk of first seizure for untreated unruptured bAVM has been reported to be 8%.(Al-Shahi Salman 2012) This is similar to our treated bAVM seizure risk for small bAVM that have had zero, one or two pre-operative seizures. The nature of the first seizure detected in the post-operative period was generalised in 76% and partial seizures in 24%.

Table 5.5 Cumulative postoperative seizures at 12 months, 5 years and 7 years as calculated from Kaplan-Meier curves.

Combination of Preoperative seizure number and bAVM maximum diameter	Initial number of patients	Cumulative postoperative seizures at 12 months	Cumulative postoperative seizures at 5 years	Cumulative postoperative seizures at 7 years
0, 1 or 2 preoperative seizures and no greater than 4 cm (number of patients at risk)	365	4.4% (249)	11% (68)	11% (47)
0 preoperative seizures, no hemorrhage and no greater than 4 cm (number of patients at risk)	240	3.1% (163)	12% (42)	12% (29)
More than 2 preoperative seizures and no greater than 4 cm (number of patients at risk)	42	3.0% (30)	6.4% (11)	17% (7)
0, 1 or 2 preoperative seizures and greater than 4 cm (number of patients at risk)	101	1.1% (75)	27% (23)	27% (15)
0 preoperative seizures, no hemorrhage and greater than 4 cm (number of patients at risk)	114	2.1% (79)	17% (26)	21% (14)
More than 2 preoperative seizures and greater than 4 cm (number of patients at risk)	51	33% (24)	48% (6)	59% (5)
All cases	559	5.8% (378)	16% (108)	18% (74)

Factors associated with presentation with seizures

Our study was confined to patients undergoing surgery and hence excluded 17% (115 patients) of all bAVM enrolled. From previous studies of our cohort, the results of surgery for SPC A and SPC B can be generalised due to the large proportion of such patients undergoing surgery.(Korja, Bervini et al. 2014) The large proportion of patients excluded from surgery with SPC C patients shares similar selection bias with other centres (e.g. excluded asymptomatic and older patients from surgery with SPC C bAVM). Therefore, our series is fit-for-purpose to investigate the cumulative incidence of, and characteristics associated with, seizures after discharge from surgery for supratentorial bAVM. However, because of the exclusion of many patients from surgery, it is not a study appropriate to assess factors associated with presentation with seizures. Therefore, the significance of these results is limited and the purpose of reporting factors associated with presentation in our study is to provide context that will facilitate comparisons with others.

Presentation with haemorrhage occurred in 43% of our patients with supratentorial bAVM and 33% presented with seizures (in the absence of haemorrhage). This is similar to the 30% reported by Englot and colleagues in their large series of supratentorial bAVM.(Englot, Young et al. 2012) This is to be expected with the exclusion of infratentorial bAVM (which have a high proportion of patients presenting with haemorrhage and a low proportion of

patients presenting with seizure). Pre-operatively, 70% of patients had at least one generalised seizure and 30% experienced partial seizure without any episodes of generalised seizures.

The propensity for seizures induced by supratentorial bAVM is clear. Strong associations have been reported between presenting seizures and bAVM in the temporal lobe.(Hoh, Chapman et al. 2002, Nagata, Morioka et al. 2006, Galletti, Costa et al. 2014) We found a greater incidence of patients presenting with seizures for bAVM located in the cortex straddling both the frontal and parietal lobes (48%: 95%CI: 34-62%), parietal lobe (37%: 95%CI: 26-49%) and temporal lobe (36%: 95%CI: 28-44%).

Factors associated with post-operative seizures

We found the association between presentation with greater than two pre-operative seizures (in the absence of haemorrhage), and increasing maximum diameter of bAVM, with the development of post-operative seizures. When any number of pre-operative seizures was investigated, this was not associated with an association with post-operative seizures. This is a similar finding to Englot and colleagues' study.(Englot, Young et al. 2012) With regards to the number of pre-operative seizures, unless a significant seizure disorder is established pre-operatively, the risk of post-operative seizure may be no higher than for other patients with bAVM undergoing surgery. We have previously reported that our series did not find a higher incidence of seizures associated with the temporal lobe than other supratentorial locations.(Thorpe, Cordato et al. 2000) This was again studied and reconfirmed. Although there were differences in presentation with seizures dependent upon location of the bAVM, specific locations were not associated with the development of different post-operative seizure incidence. This was a similar finding to that of Englot and colleagues.(Englot, Young et al. 2012)

Kaplan-Meier curves have previously been used to determine the cumulative incidence of post-operative seizures with contrasting results.(Englot, Young et al. 2012, Wang, Yang et al. 2013) Studies by Wang and colleagues,(Wang, Yang et al. 2013) and Englot and colleagues,(Englot, Young et al. 2012) utilised Kaplan-Meier curves of cumulative freedom from seizures following treatment. An important difference with our cohort and those of both Wang and colleagues,(Wang, Yang et al. 2013) and Englot and colleagues,(Englot, Young et al. 2012) is that for our patients defined as presenting with seizures, there were patients who did not have a coincidental presentation with haemorrhage. This creates a slight difference in

the interpretation of results. Furthermore, the primary purpose of the Wang and colleagues cohort of 164 patients was to compare the difference in post-operative seizures between surgical and radiosurgical treatment of bAVM rather than to identify the cumulative incidence of first seizure or identify characteristics associated with the occurrence of first post-operative seizure. The primary purpose of Englot and colleagues cohort of 440 patients was, in part, similar to our present study to determine factors associated with post-operative freedom from seizures in patients with surgically resected supratentorial bAVM. Englot and colleagues identified deep perforating arteries as the only significant factor associated with the occurrence of post-operative seizures.(Englot, Young et al. 2012) Many of the factors examined by Englot and colleagues found not to be associated with the occurrence of post-operative seizures, were also found in our series (sex, side, lobe, deep venous drainage, eloquent location, at least one pre-operative seizure and pre-operative embolisation). However, we could not confirm their finding of an association with deep perforating artery supply with our examination of anterior choroidal and lenticulostriate arteries. Furthermore, Englot and colleagues did not confirm our finding that increasing maximum diameter of bAVM was associated with an increasing incidence of post-operative seizures. To be comparable to our analysis, we recalculated the incidence of post-operative seizures in Englot and colleagues series into those with SPC A (19% of 214 patients) and those without (23% of 162 patients). This remained a non-significant difference (p=0.38). The other factor that we found to be significantly associated with an increased proportion of patients with post-operative seizures was that of having greater than two pre-operative seizures. Greater than two pre-operative seizures was not examined in the Englot and colleagues series, although, interestingly, at least one pre-operative seizure was close to being significant in the Englot and colleagues series, raising the possibility that, had they examined for multiple seizures pre-operatively, they may have confirmed our finding.

The influence of SPC on the development of post-operative seizures needs to be considered. There are a number of observations that deserve consideration. Due to the impact of size on SPC and the association between SPC and complications leading to mRS greater than one at 12 months, we need to consider whether our findings of the association of increasing size/increasing risk for post-operative seizures is a surrogate for complications of surgery. Our findings found that patients developing complications were not more likely to develop post-operative seizures (whether looking at the total cohort or within individual SPC categories).

Role of surgery in the control of post-operative seizures

Resection of bAVM for the management of refractory seizures is effective in improving seizure control.(Lopez-Ojeda, Labib et al. 2013, Baranoski, Grant et al. 2014) However, there is a considerable difference between achieving improved seizure control by bAVM surgery for those who have a significant seizure disorder, and curing epilepsy by bAVM surgery. These should not be confused. Our results suggest that following bAVM resection, a significant proportion of patients are not cured of the risk for the development of seizures. Even in the group of patients identified as having the lowest risk for the development of seizure (i.e. SPC A with no more than two pre-operative seizures), 13% will have experienced at least one post-operative seizure within the first 7 years after surgery. Therefore, recommendations on restricting activities such as returning to work and driving need to reflect the potential for post-operative seizures following surgery for bAVM.(Association 2011, Austroads 2012, Driver Licensing Authority 2014, Office of the Superintendent of Motor Vehicles 2014)

Considering the potential for the impact of bias on the characteristics that predisposed to seizures, it can be seen that, for our cohort, those with first seizures were more likely to be prescribed AED (although with unknown compliance). That is, both SPC B and C and those with a history of more than two pre-operative seizures were more likely to be prescribed AED. Therefore, it is unlikely that these characteristics were associated with an increased risk of developing seizures because of any planned intention-not-to-treat with AED. Furthermore, the senior author (MKM) previously identified that post-operative neurological deficits and pre-operative seizures were associated with an increased risk of seizures influencing the prescribing recommendations.(Thorpe, Cordato et al. 2000) There is a strong correlation between SPC grade greater than A, and the development of post-operative deficits.(Davidson and Morgan 2010, Korja, Bervini et al. 2014) Therefore, it is unlikely that cases with such characteristics (i.e. SPC B and C, pre-operative seizures) would be preferentially considered not to be treated with AED therapy because of our previous reported experience.(Thorpe, Cordato et al. 2000)

Limitations

Limitations of the study include a bias amongst those recommended for AED therapy and a lack of knowledge of patient compliance. There was a bias of the senior author (MKM) that those with multiple pre-operative seizures, large bAVMs, poor neurological outcomes and

those who felt an acute dependency on returning to driving be continued on AEDs in the absence of seizures beyond 12 months.(Thorpe, Cordato et al. 2000) Knowledge of compliance of AEDs was limited because the primary responsibility for this was transferred to the primary care physicians. These physicians were expected to consult with the patient at more frequent intervals than was required for routine post-operative consultations with the senior author (MKM), for whom planned reviews were routinely scheduled for 6 weeks and then annually following surgery. Many patients experiencing a seizure or other unexpected problems did return for review by MKM at these times, but due to distance and available expertise, not all presented immediately after the seizure to the neurosurgical team. Management of post-operative seizures often occurred without the senior author's involvement.

Further bias and limitations relate to the reporting of seizures and time of recognition of seizures. Because of the mandatory restriction on driving, patients with seizures may be reluctant to admit to having experienced an event that may impact upon driving privileges. This is less likely to be the case for generalised seizures due to the normally dramatic nature of their presentation, but may occur with partial seizures. Furthermore, the recognition of a seizure event may not always be accurate, causing some error in reporting. However, because of the medico-legal responsibility of treating physicians to follow government guidelines with regards driving recommendations, we believe that the reporting from clinicians does capture most first seizure events.

An analysis decision that needs to be explained is the separation of patients that presented with haemorrhage who also had experienced pre-operative seizures from being analysed with the group presenting with seizures (in the absence of haemorrhage). The reason for this distinction was because the mechanism for the seizure genesis in patients with haemorrhage may be due to the haemorrhage itself, rather than to the presence of bAVM. Therefore, patients presenting with both haemorrhage and pre-operative seizures were considered separately and not included in the group classified as presenting with seizures. This was in order to get a greater understanding of the role of bAVM alone on the presentation with seizures and the risk of post-operative seizures after surgery to eliminate the bAVM.

The results showing that those with low risk factors for the development of post-operative seizures had a significant risk of seizures (11% over 7 years) came as a surprise to us. This has prompted a change in our recommendations to patients with regards to the discontinuation of AED at the 12 months review. We now recommend that even in the absence of post-operative seizures, no one discontinue AEDs unless an EEG, no less than 12 months after

surgery and at the time of the decision, confirms the absence of spike activity that might suggest a risk of epilepsy. We also now emphasise the importance of ensuring compliance until this test is performed. Whether this practice change will reduce the proportion of patients experiencing post-operative seizure remains to be seen.

5.1.5 Conclusion

Patients with small (no greater than 4 cm maximum diameter) bAVM undergoing surgical repair,and with a history of no more than two pre-operative seizures, had risk of subsequent seizure of approximately 11% over the first 7 years after surgery. For other patients, the cumulative occurrence of post-operative seizure was significantly greater (up to 59% for bAVM greater than 4 cm and those reporting more than two pre-operative seizures). Recommendations for driving after surgery should consider bAVM grade and history of pre-operative seizures.

Section 3

The previous chapters investigated the effectiveness of cerebrovascular neurosurgery with regard to functional outcomes, quality of life and risk of seizures. A closer examination of whether there is a relationship between functional outcomes and QOL after cerebrovascular neurosurgery was needed. The results of the uIA study showed no decline in function after surgery and hence, no decline in quality of life. However, there was no such clear connection between function post-surgery and quality of life in the bAVM group. For this group, there was a higher likelihood of poorer functional outcomes and inability to return to driving. The patient knowing that there is an abnormality in their brain for which they have to make decisions on management options and try to maintain premorbid lifestyles, may affect the quality of life of people with a bAVM.(O'Donnell and Morgan 2015) The following chpaters explored the relationship between QOL and function after surgery, and endevoured to detemine if the risk of surgery as measured by a Minimally Important Change (MIC) was predictive of QOL after cerebrovascular surgery.

The multicentre, non-blinded randomised trial of unruptured bAVM management (ARUBA) found medical management to be superior to interventional therapy (endovascular, radiosurgery, surgery or a combination of therapies) for the prevention of death or stroke.(Mohr, Parides et al. 2014) This study commenced in 2007 and has reported on the clinical outcomes over the initial five-year period. QOL scales have been used as part of the outcome measurement armamentarium during the initial five-year period and the ongoing five-year follow-up period since patient recruitment ceased. The outcome of QOL in the ARUBA trial has yet to be reported. However, the small number of cases included in ARUBA suggests that, when the results do become known, they will not unequivocally apply to outcomes from surgery.

To explore this affect in more detail, a study was conducted in conjunction with the University of Edinburgh to compare the quality of life of Scottish residents diagnosed with a bAVM, with our Australian bAVM cohort. The aim was to establish the effect of differing management of bAVM on quality of life. The following chapter presents the findings from the joint study.

The Medical Outcomes Study Form-36 Health Survey Questionnaire (SF36) was used in both cohorts and is a measure that provides an eight-item profile of scores across physical, mental and emotional aspects of subjective health.(Ware and Sherbourne 1992) Factor analytic techniques have been used to produce summary scores from the eight subscales: the Physical Component Score (PCS) and Mental Component Score (MCS).(Ware 2002) Formulas for z-score standardizations, estimating aggregate component scores and T-score transformation of component scores were used to convert raw scores from SF36 version 1 to PCS and MCS scores using 1998 general U.S. population means, standard deviations and 1990 factor score coefficients.(Ware 2002) This enabled comparison of PCS and MCS scores within the SIVMS and MQ cohorts.

Studies have been conducted in the United Kingdom (UK) and Australia to investigate the appropriate application of the SF36 to the respective populations.(Jenkinson, Layte et al. 1997, Jenkinson 1999, Hawthorne, Osborne et al. 2007) The studies have been conducted to determine whether the US norms for the eight item scales or two component summary scores can be applied to the UK and Australian general populations in order to compare the QOL for medical condition subgroups. The studies found the means and standard deviations derived from the 1998 US general population study differed from the respective UK and Australian general populations' means and standard deviations. The QOL unique to each general population may affect the calculated PCS and MCS scores inhibiting the use of the US norms as the point of comparison.

There were relatively similar distributions of SP classes of bAVM in the two cohorts. There was a significant difference in the age and presentation mRS between the SIVMS and MQ cohorts, the latter particularly for the surgical groups. There was no significant difference for the conservative or surgical groups in the BI or mRS scores between the SIVMS and MQ cohorts after 12 months. There were significantly higher scores in the PCS ($p<0{\cdot}01$) and in the MCS ($p<0{\cdot}01$) in the MQ cohort compared with the SIVMS cohort at 12 months for conservative and surgically managed groups. However this anomaly may be due to cultural differences or problems using the US 1998 norms in algorithms in order to compare data from differing SF36 versions.

Continuous Ordinal Regression was used to examine age, gender, bAVM management, SP class, time from initial presentation, initial mRS, 12 month mRS and QOL (PCS and MCS). A

significant relationship was only found between 12 month mRS and QOL (PCS $p<0{\cdot}01$; MCS $p<0{\cdot}01$).

Chapter 6 *Quality of life with unruptured brain arteriovenous malformations: Scottish population and Australian hospital studies.*

Published paper:

O'Donnell, J. M., Al-Shahi Salman, R., Manuguerra, M., Assaad, N., & Morgan, M. K. (2018). Quality of life and disability 12 months after surgery vs. conservative management for unruptured brain arteriovenous malformations: Scottish population-based and Australian hospital-based studies. *Acta Neurochirurgica*, 1-8. doi:10.1007/s00701-017-3451-2

Pages 117-124 of this thesis have been removed as they contain published material. Please refer to the following citation for details of the article contained in these pages.

O'Donnell, J.M., Al-Shahi Salman, R., Manuguerra, M. et al. Quality of life and disability 12 months after surgery vs. conservative management for unruptured brain arteriovenous malformations: Scottish population-based and Australian hospital-based studies. Acta Neurochir 160, 559–566 (2018).

DOI: 10.1007/s00701-017-3451-2

Chapter 7 *Comparing outcome scales after surgery for unruptured intracranial aneurysms and brain arteriovenous malformations: A prospective cohort study*

Paper submitted for publication as:

Morgan M.K., O'Donnell J.M., Rogers J.M., Heller G.Z. (2017*), Comparing outcome scales after surgery for unruptured intracranial aneurysms and brain arteriovenous malformations: A prospective cohort study*.

7.1 Abstract

The modified Rankin Scale (mRS) has not been previously assessed against quality of life instruments (QoL) [e.g. Short Form 36 (SF36)] in the evaluation of surgical outcomes for unruptured intracranial aneurysms (uIA) and unruptured brain arteriovenous malformations (ubAVM). We investigated the relationship between QoL scores, mRS and the perceived risk of management in the outcome of surgery of uIA and ubAVM.

Between January 2011 and January 2016 patients with a new diagnosis of uIA and ubAVM were prospectively enrolled in a study in which assessment was performed at referral and at 12-months. Assessment included: Physical Component Score (PCS) and Mental Component Score (MCS) of the Quality Metric Short Form 36 (SF36); off-road driver screening instrument DriveSafe (DS); and mRS. The administrator of the QoL scores, and the treating surgeon assigning mRS, were blinded to each other's assessments. Minimally Important Change (MIC) for each outcome measure was used to identify adverse outcomes from surgery for individual patients. The MIC for: mRS was defined as a new neurological deficit with a mRS >1 at 12-months; MCS and PCS as a decline in each of these score of ≥6.5 points; and DS as a decline in DS score of ≥6 points.

166 patients completed the minimal dataset for analysis. Of these patients, 131 were treated by surgery and 35 remained untreated. There was no difference in any QoL outcome at 12-months after surgery compared with the initial outcomes for either surgical or untreated patients. MIC for mRS, DS, PCS and MCS occurred in 8.4%, 14%, 21% and 20% of patients, respectively. The perceived risk of surgery as calculated in this study was relevant for the MIC for mRS (p=0.047; OR: 1.04, 95% CI: 1.00-1.09) and MIC for PCS (p=0.02; OR: 1.05, 95% CI: 1.01-1.09). An initial lower PCS was associated with an MIC for mRS (p=0.01; OR: 0.91, 95% CI: 0.85-0.98) and an MIC for DS (p=0.01; OR: 0.93, 95% CI: 0.87-0.98). An initial higher PCS was associated with an MIC for PCS (p<0.01; OR: 1.13, 95% CI: 1.05-1.22). The factors associated with an MIC for MCS were a higher initial MCS (p<0.01; OR: 1.11, 95% CI: 1.05-1.17) and a lower initial DS (p=0.05; OR: 0.96, 95% CI: 0.91-1.00). No outcome measures in this study significantly highly correlated with each other.

Prediction of adverse outcomes from surgery relate to outcomes of mRS and PCS, both domains that reflect disability, one, independently rated, and the other, self-rated. To obtain a more complete representation of patient outcomes requires separate administration of QoL scales. The high degree of MIC for MCS suggests vigilance in following patients for the potential need for early postoperative psychological intervention.

Introduction.

Management of unruptured intracranial aneurysms (uIA) is controversial. Although no randomized control trial (RCT) of aneurysms has been conducted, the results of three large audits suggest that many small aneurysms can be left untreated with an annual risk of first hemorrhage of near zero.(Wiebers, Whisnant et al. 2003, Sonobe, Yamazaki et al. 2010, Morita, Kirino et al. 2012) However, bias in selecting patients for treatment, by excluding cases from these cohorts, has created doubt that such aneurysms should remain untreated in all circumstances.(Wiebers, Whisnant et al. 2003, Sonobe, Yamazaki et al. 2010, Morita, Kirino et al. 2012, Etminan, Brown et al. 2015, Korja and Kaprio 2016)

Similarly, controversy exists in the management of unruptured brain arteriovenous malformations (ubAVM). The outcomes from an RCT of ubAVM management suggest an advantage for conservative treatment in comparison to intervention.(Mohr, Parides et al. 2014) Again, the conclusion from the authors of this RCT has been challenged, due to a number of methodological concerns(Korja, Hernesniemi et al. 2014, Cenzato, Boccardi et al. 2017) The instrument used in these assessments, evaluating the advantages and disadvantages of various management pathways, was the modified Rankin Scale (mRS). Therefore, it is important to understand the extent to which we can apply this outcome measure to the studied patients. The mRS is one of the most common measures employed in stroke trials and clinical assessment.(Chyatte and Porterfield 2001, Wilson, Hareendran et al. 2005, Kasner 2006, Quinn, Dawson et al. 2008, Quinn, Dawson et al. 2009a, Quinn, Dawson et al. 2009c, Fearon, McArthur et al. 2012, Lees, Bath et al. 2012, Tilley 2012) However, it is not without its limitations and the method of application of the instrument is important in the meaningfulness of the results.(Wilson, Hareendran et al. 2005, Kasner 2006, Quinn, Dawson et al. 2008, Quinn, Dawson et al. 2009a, Quinn, Dawson et al. 2009c, Fearon, McArthur et al. 2012, Lees, Bath et al. 2012, Tilley 2012)

The mRS is not the only method of evaluating outcomes from either cerebrovascular neurosurgery or stroke. Indeed, more than 40 instruments have been used to measure outcomes in stroke studies.(Lyden, Lu et al. 2001, Quinn, Dawson et al. 2009a, Lees, Bath et al. 2012) One important consideration in outcomes, in addition to disability (the most common focus for clinicians), is the quality of life (QoL), most commonly the focus of the patients.(van der Schaaf, Brilstra et al. 2002, Marshall, Jonker et al. 2003, Otawara, Ogasawara et al. 2004, Otawara, Ogasawara et al. 2005, Towgood, Ogden et al. 2005a, Yang, Paek et al. 2012, Della Puppa, Rustemi et al. 2015) It cannot be assumed that following

treatment of uIA or ubAVM the mRS reflects the patient's QoL. Although QoL to some degree has been evaluated following treatment for uIA and ubAVM,(Marshall, Jonker et al. 2003, Brilstra, Rinkel et al. 2004, Otawara, Ogasawara et al. 2004, Towgood, Ogden et al. 2005a, King Jr, Tsevat et al. 2006, Coert, Chang et al. 2007, Proust, Martinaud et al. 2009, O'Donnell J. 2013a, O'Donnell J. 2013b) these studies have limited application because of small size, recruitment biases or failure to include baseline measurement. Moreover, mRS has not been validated or compared in the treatment of uIA and ubAVM with other instruments of outcome that reflect a patient's quality of life (QoL) prospectively with baseline evaluation at the commencement of management decisions. The importance of understanding the relationship between mRS and measures of QoL is that in the absence of a correlation, reporting by mRS alone is limited in capturing the patient's outcome experience.

An instrument commonly utilized to measure QoL is the Medical Outcomes Study Questionnaire Short Form-36 Health Survey (SF-36).(Ware and Sherbourne 1992, Ware Jr, Bayliss et al. 1996, Ware 2002, Bayliss, Bayliss et al. 2004, O'Donnell J. 2013a) The SF-36 provides scores across physical, mental and emotional aspects of subjective health.(Ware and Sherbourne 1992, Ware Jr, Bayliss et al. 1996, Ware 2002, Bayliss, Bayliss et al. 2004) Summary scores can be computed for two subscales, the Physical Component Score (PCS) and Mental Component Score (MCS). A measure of functional activity, the DriveSafe (DS) component of the DriveSafeDriveAware test, is a recently developed computerized instrument that simulates decision-making relevant to driving, in order to predict drivers' real-life performance.(Dow 2009, Kay, Bundy et al. 2009, O'Donnell J. 2013a, O'Donnell J. 2013b, O'Donnell J. 2013c, Hines and Bundy 2014) DS score of $\leq$ 95 predicts an unsatisfactory performance of driving.(O'Donnell J. 2013a, O'Donnell J. 2013b, O'Donnell J. 2013c, Vargus-Adams and Majnemer 2014) Both the SF-36 and DSDA have established norms and high degrees of inter-observer and test-retest reliability.(Ware and Sherbourne 1992, Ware Jr, Bayliss et al. 1996, Ware 2002, Bayliss, Bayliss et al. 2004, Ware 2007, Kay, Bundy et al. 2012, O'Donnell J. 2013c, Hines and Bundy 2014)

Three major influences on a patient's perception of QoL may include: the realized disability from surgery or the natural history untreated; the potential for disability from future surgery or the natural history untreated; and the patient's concerns, anxieties and coping mechanisms regarding these outcomes realized and potential if untreated. Therefore, a patient's awareness of the perceived threat of an untreated uIA or ubAVM, and how the outcome expectations from surgery have been met, may also have a role in determining QoL.(Van Swieten,

Koudstaal et al. 1988, Towgood, Ogden et al. 2005a) Risks of surgery identifies outcome in terms of mRS with respect to aneurysm size, aneurysm location, patient age, for uIA and mode of presentation and Spetzler-Martin grade [SMG] for bAVM.(Spetzler and Martin 1986, Spetzler and Ponce 2011, Bervini, Morgan et al. 2014, Korja, Bervini et al. 2014, Kim, Abla et al. 2015, Morgan, Wiedmann et al. 2016a, Morgan, Wiedmann et al. 2016b, Morgan, Davidson et al. 2017) In addition, the 10-year risk of non-treatment (or treatment by any other management pathway) can be estimated from the literature.(Wiebers, Whisnant et al. 2003, Juvela, Poussa et al. 2013, Morgan, Davidson et al. 2017) Both the risk of surgery and the risk of hemorrhage untreated influences the neurosurgical recommendations and patients' awareness of the outcomes. Regardless of the patient's outcome, these discussions remain with the patient for a considerable time and may continue to impact upon a patient's perception of health.(Towgood, Ogden et al. 2005a)

Our aim was to prospectively recruit a cohort of patients with newly diagnosed uIA and ubAVM referred to a neurosurgical consultation clinic and evaluate their outcomes at 12-months after treatment or initial consultation with respect to mRS, SF-36 and DS scales. The purpose was to determine the correlation between various outcome scales and the association of perceived risks with these outcomes.

7.1.1 Methods

This study was approved by the institutional ethics committee and performed in accordance with their guidelines.

Inclusion

Between January 2011 and January 2016 consecutive patients with newly diagnosed uIA and ubAVM, referred to the neurosurgeons at Macquarie Health, Macquarie University (Macquarie University) and seen in out-patient consultations, were identified.

Exclusion

Exclusions included those: non-English speaking; declined or withdrew consent; found to have an incorrect diagnosis of uIA or ubAVM; or failed to complete the minimal dataset collection. The minimal dataset collection for both the initial and the 12-months assessment

included the mRS score and an SF-36 completion sufficient to allow either a PCS or MCS score to be calculated. Patients treated by other means, such as gamma knife or endovascular intervention, were not followed at the neurosurgical center and thus did not have the requisite minimal data set. Therefore, the treatment was dichotomized between that of microsurgery and conservative management (untreated). In addition, patients with uIA were excluded if this was thought to have arisen as a consequence of infection, dissection, trauma or the aneurysm was located outside the subarachnoid space. The full patient selection process is illustrated in Figure 7.1.

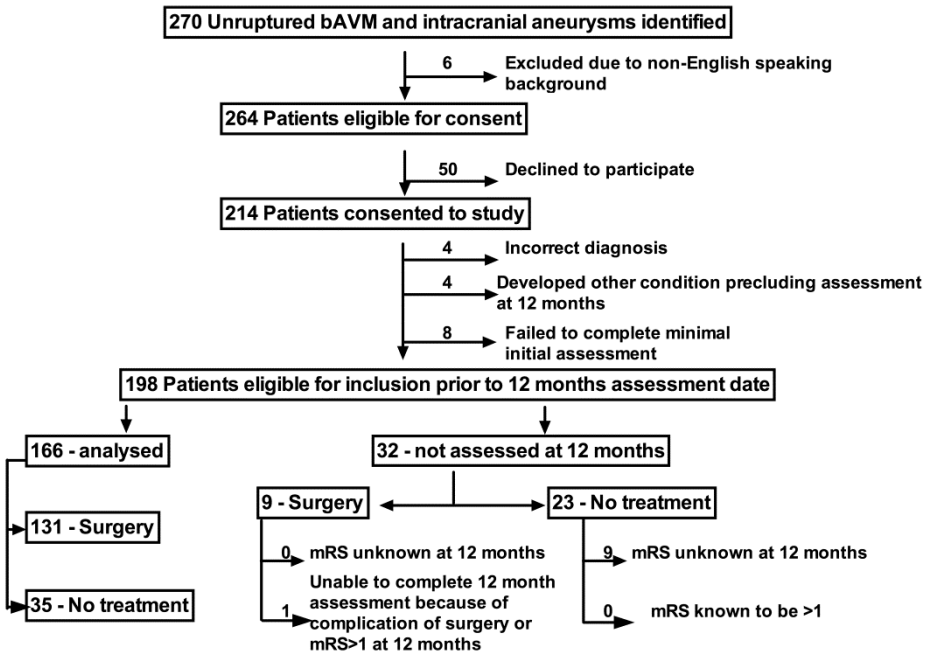

Figure 7.1 The flow chart of newly diagnosed uIA and ubAVM enrolled in study and those included and excluded from analysis.

Baseline demographic, angioarchitectural and clinical data

Demographic, angioarchitectural and clinical data was collected prospectively for each patient. These have been described in detail in previous publications.(Bervini, Morgan et al. 2014, Korja, Bervini et al. 2014) These data included age, sex and mode of presentation. In addition, the following was recorded: for uIA the aneurysm maximum diameter (mm) and

location; and for the ubAVM patients, the Spetzler-Martin (SMG) grade was recorded by allocating points for size (1 for less than 3cm, 2 for size between 3 and 6 cm, and 3 for size greater than 6 cm), the presence of deep venous drainage (adding 1 point if present), and location in “eloquent” brain (adding 1 point if located in primary sensory cortex, motor cortex, language cortex, internal capsule, diencephalon, brainstem, deep cerebellar nuclei, or cerebellar peduncle).(Spetzler and Martin 1986) Analysis was simplified by allocating SMG grades into Spetzler-Ponce classes (SPC). The SPC is a simplification of the SMG, that has been validated to predict the risk of surgery,(Spetzler and Martin 1986, Bervini, Morgan et al. 2014, Korja, Bervini et al. 2014) and combines SMG I and II as Spetzler-Ponce Class A bAVM (SPC A), SMG III as Spetzler-Ponce Class B bAVM (SPC B) and SMG IV and V as Spetzler-Ponce Class C bAVM (SPC C).

Measuring outcomes

The following outcome scales were administered at the time of the initial consultation and at 12-months after either the initial consultation (for untreated patients) or surgery (12-month follow-up).

i. The SF-36 was administered by a single occupational therapist. The patients were made aware that these results would not be made known to the treating surgeons. Factor analytic techniques were used to produce summary scores from the PCS and MCS subscales scores.(Ware 2002) For regional, interstate and overseas participants who were unable to attend follow-up appointments on-site (only necessary for a small number of ubAVM patients), the SF-36 questionnaires were posted. Questionnaires were also posted to all participants who had not completed the instrument at the time of their 12-month follow-up appointment. The treating medical management team was blinded to these outcomes until analysis of the results of all patients was commenced. For the purpose of dichotomizing outcomes, significant adverse outcomes for PCS and MCS were considered to be a decline in score by 6.5, based upon standards used by Ware and colleagues and Bayliss and colleagues of the minimally important change for an individual studied longitudinally.(Ware Jr, Bayliss et al. 1996, Bayliss, Bayliss et al. 2004) These are termed Minimally Important Change (MIC for PCS and MIC for MCS).

ii. The original version of the DS was administered at the time of initial consultation and at 12-month follow-up, with higher scores reflecting better performance. The patients were aware that these results would not be made known to the treating medical management team (unless the performance indicated that a DS score indicated that driving should not be permitted). The treating medical management team was blinded to these outcomes until analysis of the results of all patients was commenced. However, there was a contingency for patients that failed to demonstrate a competent performance of DS>95 and who were assessed eligible to drive by the treatment team that the occupational therapist would inform the treatment team of the discordance and recommend that the patient be referred for an on-road occupational therapy driving assessment. This scenario did not occur. For the purpose of dichotomizing outcomes, an MIC for DS was considered to be a decline in DS score by 6, paralleling the degree of change used for PCS and MCS relative to the standard deviation, as the minimally important change for an individual studied longitudinally (MIC for DS).

iii. The patient's treating surgeon recorded the mRS score at the time of initial assessment as well as at the 12-month follow-up. This was recorded by the neurosurgeon in the presence of the patient. The administrator of the DS and SF-36 results was blinded to the mRS until analysis of the results of all patients was commenced. An MIC for the mRS was regarded as a decline in mRS due to complications of surgery, with a mRS greater than 1 at 12-months (MIC for mRS).

Measuring risk of unfavorable outcome

A favorable outcome for untreated patients was considered to be a future free of hemorrhage. A favorable outcome following treatment by surgery was considered to include a future free of hemorrhage, an absence of disability from treatment, confirmed obliteration of the pathology (uIA or ubAVM) and an absence of retreatment. The risk of an unfavorable outcome from these two management pathways was calculated as follows.

i. *Risk untreated:*,

ii. The 10 year risk of untreated uIA and ubAVM was calculated from estimation of the annual risks of hemorrhage reported in the literature adjusted for age. These were calculated for each year of age of the patient at diagnosis. The basis for estimating

these risks was adjusted for pathology (uIA or ubAVM) and, in the case of uIA, aneurysm size. The following 10-year risk of rupture were used: 9% for anterior circulation aneurysms less than 12 mm and posterior circulation aneurysms less than 7 mm; 27% for anterior circulation aneurysms 13-24 mm and posterior circulation aneurysms 7-12 mm; 33% for posterior circulation aneurysms 13-24 mm; 63% for anterior circulation giant aneurysms; 75% for posterior giant aneurysms; and 16% for ubAVM. The derivation of these data was from the reports of Juvela and colleagues for small anterior circulation aneurysms, ISUIA for other aneurysms and Hernesniemi and colleagues for ubAVM.(Wiebers, Whisnant et al. 2003, Juvela, Poussa et al. 2013, Morgan, Davidson et al. 2017) Although the natural history is less certain than these figures suggest, these were the data prevalent at the time used by the neurosurgeons discussing management options with this patient cohort. The selection of these three studies in the estimation of risk of future hemorrhage was based on the subjects of these studied cohorts being derived from a time during which surgery was seldom offered (therefore, minimizing selection bias) and a mean length of follow-up greater than 10-years. Because there were insufficient data for larger uIA from Juvela and colleagues(Juvela, Poussa et al. 2013) ISUIA II was used. ISUIA II was not used for small anterior circulation aneurysms because the majority of small anterior circulation aneurysm patients were censored to surgery during the ISUIA II audit period and therefore, may not reflect the natural history. The annualized risk of rupture was projected by the decay function for 10 years (i.e. 100 – 100.e-annual proportion risk x10 = 10 year risk %). Further discounting was performed for age by multiplying the risk by the proportion of patients expected to be alive in the next ten years as estimated by the Australian life-table 2013 (Figure 7.2).

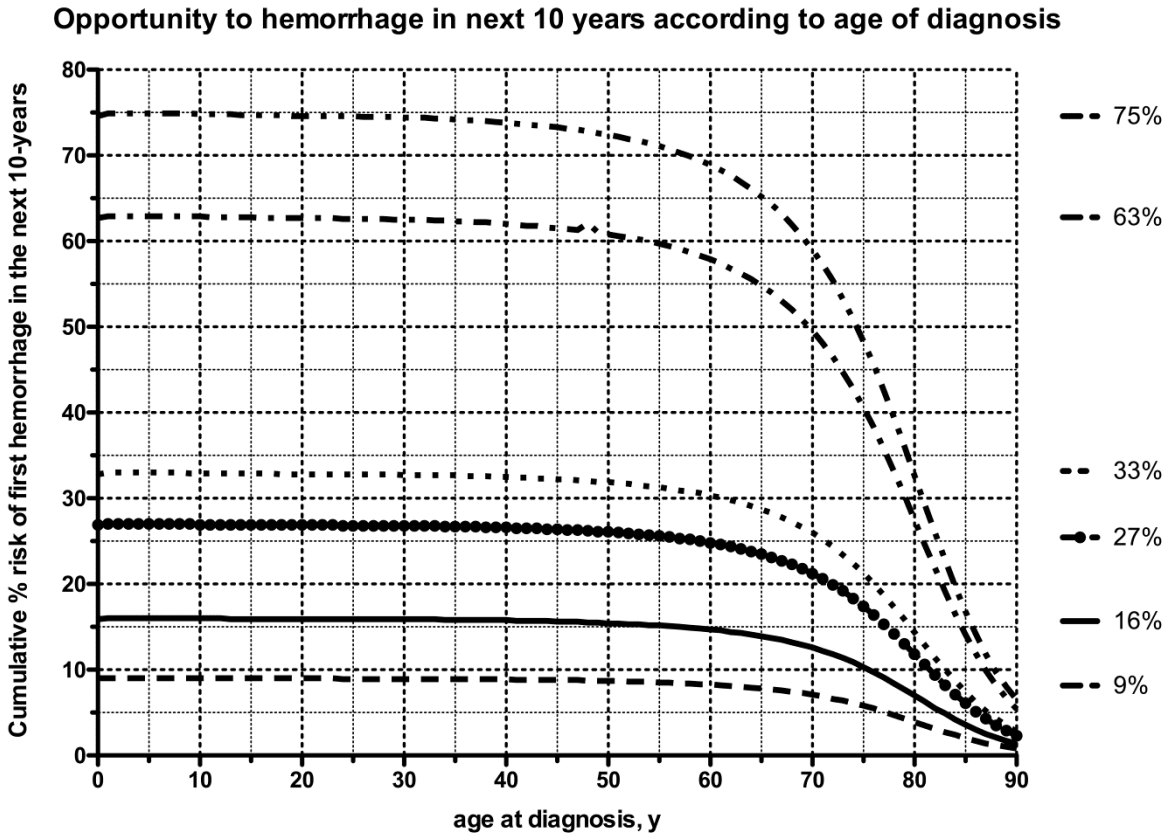

Figure 7.2 The cumulative risk of the opportunity for first hemorrhage in untreated uIA and bAVM over the next 10-years adjusted for age at first diagnosis in years (y) with the 10-year risk of 9% (anterior circulation aneurysms less than 12 mm and posterior circulation aneurysms less than 7 mm)(Juvela, Poussa et al. 2013); 27% (anterior circulation aneurysms 13-24 mm and posterior circulation aneurysms 7-12 mm)(Wiebers, Whisnant et al. 2003); 33% (posterior circulation aneurysms 13-24 mm); 63% (anterior circulation giant aneurysms)(Wiebers, Whisnant et al. 2003); 75% (posterior giant aneurysms)(Wiebers, Whisnant et al. 2003); and 16% (ubAVM)(Morgan, Davidson et al. 2017a).

iii. *Risk of surgery:* These were calculated at eight years as the risk of an unfavorable outcome (defined above) from a mathematical construct of previously published risk scores.(Morgan, Wiedmann et al. 2016a, Morgan, Wiedmann et al. 2016b) Eight years was selected because this was the longest length of follow-up from which the authors were able to reliably report the risk of unfavorable outcomes from surgery.(Morgan, Wiedmann et al. 2016a, Morgan, Wiedmann et al. 2016b) We have assumed that because most of the complications of surgery occur early, the 8 years represents the long-term risk of unfavorable outcome following surgery. For ubAVM surgery, the equation for the risk of unfavorable outcome is:

$$Risk\ of\ ubAVM\ surgery = \left(\frac{e^{exponent}}{1 + e^{exponent}}\right).100$$

where the exponent = - 5.076 + (0.473 x maximum diameter in cm) + 1.488 (if located in eloquent brain) + 1.679 (if deep venous drainage is present).(Morgan, Wiedmann et al. 2016b)

For uIA surgery, the 8-year risk of unfavorable outcome is:

$$Risk\ of\ uIA\ surgery = \left(\frac{e^{exponent}}{1 + e^{exponent}}\right).103$$

where the exponent = - 6.031 + (0.113 x maximum diameter in mm) + (0.04 age, years) + 1.08 (if posterior circulation).(Morgan, Wiedmann et al. 2016a)

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY). Baseline characteristics were compared using Fisher's exact test, *t* test and Mann-Whitney U test, where relevant. For the surgically managed patients, the associations between QoL factors along with perceived risk of surgery were examined with Pearson's bivariate correlation. A statistical significance level of 5% was used throughout.

Four regression analyses were performed to establish significant factors and their odds ratio (OR) for the dependent variables of the following outcomes: MIC for mRS; MIC for DS; MIC for PCS; and MIC for MCS. The factors explored included a combination of clinical, demographic and predictors of outcome data. Because the focus of attention was deterioration, the MIC was utilized in the regression analysis. Univariate followed by forward (Wald) stepwise multivariate logistic regressions were performed.

7.1.2 Results

Of 270 patients presenting with uIA and ubAVM between January 2011 and January 2016, 198 patients were eligible for inclusion (Figure 7.1). The major reason for non-participation (decline to participate) was treatment by some other means (e.g. endovascular treatment) not provided by the neurosurgeons of Macquarie University and not able to be followed in this study. From the 198 patients eligible for inclusion with complete initial assessment, 166 completed the 12-month assessment and were included in the analyses.

Thirty-two were not assessed at 12 months and were not included in the analyses (Figure 7.1). Of these who had surgery (9 patients) one was known to have a complication of surgery with a mRS greater than 1 at 12 months (mRS score of 3) and the remaining 8 had mRS of 0 or 1. Of these who had no treatment (23 patients) 12 were known not to have had an unfavorable event leading to a mRS greater than 1 at 12 months and for 9 the mRS was unknown.

Comparing surgery and non-surgical groups

The baseline characteristics for the 166 analyzed patients comparing those that were treated by surgery (131 patients) and those not treated by surgery (35 patients) is reported in Table 7.1. No patient in the series died or had an mRS>3. Comparing the surgical group with the untreated group, there was a significant difference in mean age (untreated patients were older) and median 10-years perceived risk of hemorrhage (untreated patients had a perceived lower risk of hemorrhage). At initial assessment, there was no significant difference in these two groups in terms of mean PCS, MCS, DS, distribution of mRS scores or median perceived risk of surgery (Table 7.1).

For those undergoing surgery, the proportion experiencing an MIC in mRS, DS, PCS and MCS was 8.4%, 14%, 21% and 20% respectively. For those undergoing no treatment, the proportion experiencing an MIC in mRS, DS, PCS and MCS was 3.6%, 11%, 14% and 25% respectively (Table 7.1). There was no statistically significant difference between those undergoing surgery and no treatment with respect to each of these 12-month MIC results (Table 7.1). The time interval between initial evaluation and surgery was a median 4 days (with an upper 75% quartile of 20 days).

Table 7.1 Comparison between patients undergoing surgery and non-treatment.

		Surgery	No treatment	p-value
Total patients		131	35	
Preoperative data	AVM patients (%)	33 (25)	7 (20)	0.66
	Age, y (SD)	48 (14)	56 (17)	**<0.01**
	Female (%)	92 (70)	23 (66)	0.68
	Initial PCS score, mean (SD)	51 (8.3)	51 (7.2)	0.98
	Initial MCS score, mean (SD)	46 (12)	49 (11)	0.14
	Initial DS score, mean (SD)	109 (10)	107 (11)	0.32
	Initial patients with mRS>1 (%)	5 (3.8)	0	0.34
	Perceived 10-year risk of hemorrhage untreated. Median % (range)	8.8 (6.1-63)	8.2 (2.0-16)	**<0.01**
	Perceived risk of surgery. Median % (range) [mean: 95% CI of mean]	4.0 (0.4-67) [7.2: 5.4-9]	4.7 (1.5-87)	0.35
	Days initial assessment until surgery. Median (upper 75% quartile)	4 (20)	NA	
12-month data	12-month PCS. Mean (SD) [Comparing initial with 12-month PCS (p-value)]	50 (7.9) [0.75]	51 (7.9) [0.98]	0.82
	12-month MCS. Mean (SD) [Comparing initial with 12-month MCS (p-value)]	49 (11) **[0.03]**	50 (11) [0.66]	0.54
	12-month DS. Mean (SD) [Comparing initial with 12-month DS (p-value)]	112 (10) **[0.02]**	109 (8.7) [0.45]	0.16
	MIC mRS (%) 12-month mRS 2 12-month mRS 3	11 (8.4) 9 2	1 of 28 (3.6) 1 0	0.69
	MIC PCS (%)	27 (21)	4 of 28 (14)	0.60
	MIC MCS (%)	26 (20)	7 of 28 (25)	0.61
	MIC DS (%)	18 of 126 (14)	3 of 27 (11)	>0.99

MIC=minimally important change; MIC mRS = complication of surgery leading to a new permanent neurological deficit and mRS >1; MIC PCS = Decline in PCS of greater than 6.5; MIC MCS = Decline in MCS of greater than 6.5; MIC DS = Decline in DS component of DSDA ≥ 6; NA= not applicable.

With regards the 10-year perceived risk of hemorrhage and the perceived risk of surgery, an ROC curve was constructed to identify whether a break-point could be identified at which treatment by surgery was favored (Figure 7.3). It can be appreciated from the curves that there was no identifiable bias favoring surgery associated with preoperative estimates of risk of surgery (area under the curve of 0.45, 95% CI: 0.35-0.55, *p*=0.35) (Figure 3). However, there was an identifiable bias favoring surgery associated with increasing preoperative estimates of risk of subsequent hemorrhage (area under the curve of 0.69, 95% CI: 0.59-0.80, *p*<0.01) (Figure 7.3) with a cut-point at 8.3% at 10-years.

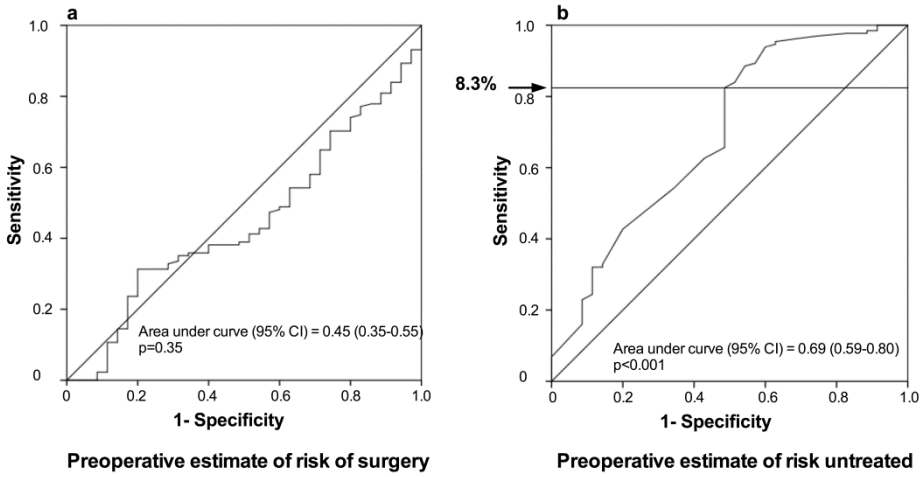

Figure 7.3 Receiver Operator Characteristic (ROC) curve for (a), uIA and ubAVM preoperative estimate of perceived risk of surgery, and the decision to undergo treatment by surgery (area under the curve 0.45; 95% CI 0.35-0.55; p=0.35). The ROC curve for (b), uIA and ubAVM preoperative estimate of 10-year risk of hemorrhage untreated, and the decision to undergo treatment by surgery (area under the curve 0.69; 95% CI 0.59-0.80; p<0.001). The 10-year risk of hemorrhage if untreated maximizing the addition of sensitivity and specificity was 8.3%.

Outcomes of surgery

For the 131 patients undergoing surgery, there was no difference in means between the initial and the 12-month scores for PCS (51 c.f. 50, respectively) and a statistically significant small increase in mean scores for MCS (46 c.f. 49, respectively *p*=0.03) and DS (109 c.f. 112, respectively *p*=0.02) (Table 7.2). Outcomes for mRS, DS, PCS and MCS are reported in Table 7.2. Correlations of outcomes related to PCS, MCS and DS at 12-month following surgery are shown in Figure 7.4. There was only one significant correlation, that of DS with PCS with a Pearson r of 0.23.

Table 7.2 Minimally Important Change (MIC) from surgery as measured by mRS, PCS, MCS, and DS

Outcome	Characteristic	No MIC	Yes MIC	P value
mRS	Total (%)	120	11 (8.4)	
	AVM (%)	28 (23)	5 (45)	0.15
	Age, years, mean (SD)	48 (14)	52 (10)	0.36
	Female (%)	83 (69)	9 (82)	0.50
	Initial PCS, mean (SD)	51 (7.9)	44 (11)	**<0.01**
	Initial MCS, mean (SD)	46 (12)	40 (11)	0.09
	Initial DS, mean (SD)	109 (10)	108 (7.0)	0.67
	Perceived 10 year risk untreated, median % (range)	8.8 (6.1-63)	15 (8.3-22.7)	0.36
	Perceived risk of surgery, median % (range)	4.0 (0.4-61)	6.6 (1.8-67)	**0.03**
	12-month PCS, mean (SD)	51 (7.9)	44 (11)	**<0.01**
	12-month MCS, mean (SD)	46 (12)	40 (11)	0.09
	12-month DS, mean (SD)	113 (10)	108 (13)	0.67
DS	Total (%)	108	18 (14)	
	AVM (%)	27 (25)	4 (22)	>0.99
	Age, years, mean (SD)	48 (14)	54 (10)	0.06
	Female (%)	79 (73)	12 (67)	0.58
	Initial PCS, mean (SD)	52 (8.1)	46 (9.5)	**<0.01**
	Initial MCS, mean (SD)	46 (12)	44 (11)	0.64
	Initial DS, mean (SD)	109 (9.8)	112 (7.9)	0.16
	Perceived 10 year risk untreated, median % (range)	8.8 (6.1-63)	8.8 (7.9-59)	0.71
	Perceived risk of surgery, median % (range)	3.6 (0.9-67)	4.4 (1.6-38)	0.15
	12-month PCS, mean (SD)	51 (8.0)	47 (6.7)	**0.048**
	12-month MCS, mean (SD)	49 (10)	47 (13)	0.44
	12-month DS, mean (SD)	115 (8.0)	99 (13)	**<0.01**
PCS	Total (%)	103	27 (21)	
	AVM (%)	26 (25)	6 (23)	>0.99
	Age, years, mean (SD)	48 (14)	51 (14)	0.11
	Female (%)	72 (70)	19 (70)	>0.99
	Initial PCS, mean (SD)	50 (8.3)	56 (6.8)	**<0.01**
	Initial MCS, mean (SD)	46 (12)	44 (12)	0.42
	Initial DS, mean (SD)	109 (10)	110 (10)	0.45
	Perceived 10 year risk untreated, median % (range)	8.8 (6.1-62)	8.6 (6.9-63)	0.58
	Perceived risk of surgery, median % (range)	3.9 (0.4-61)	4.4 (1.3-67)	0.41
	12-month PCS, mean (SD)	52 (6.3)	44 (9.6)	**<0.01**
	12-month MCS, mean (SD)	49 (11)	47 (12)	0.54
	12-month DS, mean (SD)	112 (10)	112 (13)	0.74
MCS	Total (%)	105	26 (20)	
	AVM (%)	28 (27)	5 (19)	0.61
	Age, years, mean (SD)	44 (12)	53 (8.0)	0.10
	Female (%)	77 (73)	15 (58)	0.15
	Initial PCS, mean (SD)	51 (8.4)	50 (8.6)	0.72
	Initial MCS, mean (SD)	44 (12)	53 (8.0)	**<0.01**
	Initial DS, mean (SD)	110 (9.7)	106 (11)	0.07
	Perceived 10 year risk untreated, median % (range)	8.8 (6.1-63)	8.8 (6.1-26)	0.58
	Perceived risk of surgery, median % (range)	3.9 (0.4-67)	4.2 (0.9-30)	0.41
	12-month PCS, mean (SD)	50 (8.0)	51 (7.6)	0.60
	12-month MCS, mean (SD)	51 (9.2)	39 (12)	**<0.01**
	12-month DS, mean (SD)	113 (10)	110 (11)	0.16

MIC=minimally important change; MIC mRS = complication of surgery leading to a new permanent neurological deficit and modified Rankin Score (mRS) >1; MIC PCS = Decline in Physical Component Score (PCS) of greater than 6.5; MIC MCS = Decline in Mental Component Score (MCS) of greater than 6.5; MIC DS = Decline in DriveSafe (DS) component of DSDA ≥ 6.

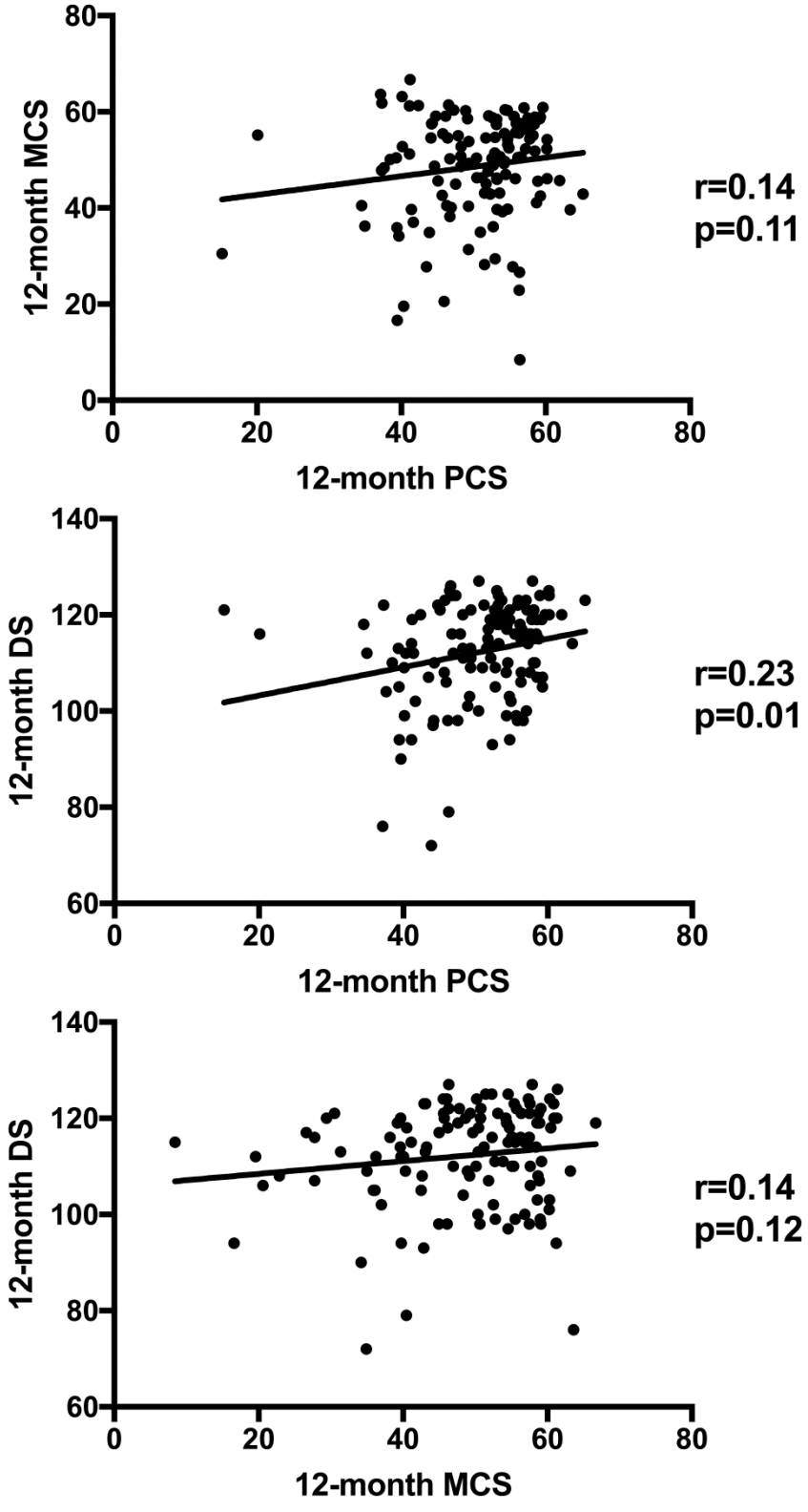

Figure 7.4 Correlation plots of 12-month outcomes following surgery reported by Mental Component Score (MCS) of the Quality Metric Short Form 36 (SF36), Physical Component score (PCS) of SF36 and the DriveSafe (DS) score. This demonstrates no r correlation between these different MCS and PCS and no correlation between MCS and DS. There is correlation but with a low Pearson r between DS and PCS.

Binary logistic regression was performed for MIC for mRS, PCS, MCS and DS (Table 7.3). These results found for:

i. *MIC for mRS* (11 events): There was an association with a greater perceived risk of surgery (odds ratio 1.04, 95% CI: 1.00-1.09, p=0.047) and initial lower PCS (odds ratio 0.91, 95% CI: 0.85-0.98, p=0.01).

ii. *MIC for DS* (18 events): There was an association with a initial lower PCS (odds ratio 0.93, 95% CI: 0.87-0.98, p=0.01).

iii. *MIC for PCS* (27 events): There was an association with a greater perceived risk of surgery (odds ratio 1.05, 95% CI: 1.01-1.09, p=0.02) and initial greater PCS (odds ratio 1.13, 95% CI: 1.05-1.22, p<0.01).

iv. *MIC for MCS* (26 events): There was an association with an initial lower DS (odds ratio 0.96, 95% CI: 0.91-1.00, p=0.054) and an initial greater MCS (odds ratio 1.11, 95% CI: 1.05-1.17, p<0.01).

Table 7.3 Outcome at 12-months after surgery for binary logistic regression.

	MIC mRS			MIC DS			MIC PCS			MIC MCS		
Number of events (%)	11 of 129 with complete data			18 of 125 with complete data			27 of 129 with complete data			26 of 129 with complete data		
Characteristic	Uni-variate (p-value)	Multi-variate (p-value)	Odds ratio (95% CI)	Uni-variate (p-value)	Multi-variate (p-value)	Odds ratio (95% CI)	Uni-variate (p-value)	Multi-variate (p-value)	Odds ratio (95% CI)	Uni-variate (p-value)	Multi-variate (p-value)	Odds ratio (95% CI)
AVM	0.10			0.85			0.73			0.46		
Age	0.37			0.07			0.38			0.11		
Female	0.36			0.59			0.94			0.13		
Perceived 10 year risk untreated	0.76			0.24			0.85			0.61		
Perceived risk of surgery	**<0.01**	**0.047**	**1.04 (1.00 -1.09)**	0.27			**0.049**	**0.02**	**1.05 (1.01-1.09)**	0.70		
Initial mRS >1	0.49			0.72			0.29			0.99		
Initial PCS	**<0.01**	**0.01**	**0.91 (0.85-0.98)**	**<0.01**	**0.01**	**0.93 (0.87-0.98)**	**<0.01**	**<0.01**	**1.13 (1.05-1.22)**	0.68		
Initial MCS	0.10			0.66			0.43			**<0.01**	**<0.01**	**1.11 (1.05-1.17)**
Initial DS	0.67			0.16			0.44			**0.07**	**0.054**	**0.96 (0.91-1.00)**

MIC=minimally important change; MIC mRS = complication of surgery leading to a new permanent neurological deficit and mRS >1; MIC PCS = Decline in PCS of greater than 6.5; MIC MCS = Decline in MCS of greater than 6.5; MIC DS = Decline in DS component of DSDA ≥ 6.

Differences between the *p*-values obtained in the comparison of the data in Table 7.2 and that of the univariate analyses performed in the regression analyses can be explained by excluded cases in the regression analysis with incomplete data (e.g. absent PCS or DSDA scores) that were included in the summary of data in Table 7.2.

7.1.3 Discussion

From this cohort of 166 patients analyzed with newly diagnosed uIA or ubAVM, utilizing the most common scale reported measuring adverse outcome (mRS), 8.4% sustained an adverse outcome 12-months following surgery as compared with 3.7% untreated. In addition, the proportions of patients having an MIC for PCS, MCS and DS following surgery were 21%, 20% and 14%, respectively. For untreated patients these MIC outcomes were 14%, 25% and 11% and were not significantly different to the surgery group. Considering the relationship between the various 12-month outcome scores following surgery, there was an association of a downgrade in outcome as measured by mRS (as used in this study, mRS greater than one due to complications of surgery) with a lower mean PCS score at 12-months. Furthermore, there was an association of a MIC for DS with a lower mean PCS score at 12-months (although this was not reciprocated with an MIC for PCS associated with lower DS scores at 12-months). However, there was no relationship between any of the outcome scores with an MIC in MCS. Therefore, the various outcome instruments do not converge and hence, they provide different information about outcomes. This highlights the narrow bounds within which reporting of outcomes by mRS can be applied when discussing with patients expectations of outcomes. Discussion of outcomes based upon mRS should be specifically confined to expectation of disability and audits of surgical performance (given the reliability of the scale and its popularity of use).(Lees, Bath et al. 2012) Adverse QoL outcome (as measured by SF-36) may occur in the absence of an adverse mRS outcome or in the absence of a loss of activity function in relation to driving as measured by the DS. This needs to be considered when discussing the outcomes of surgery. Furthermore, the relatively high proportion of patients with a significant MIC in MCS (20% of treated patients and 25% of untreated patients) suggests a potential role for psychological support during the first 12 months following identification of uIA or ubAVM.

As the outcome assessment tools do not converge, it is necessary to explore what information at the initial assessment predicts the likelihood of an adverse outcome for each of these instruments and scales. The perceived risk of surgery (higher) and the initial PCS are

associated with MIC for both mRS and PCS. However, for initial PCS, a lower score is associated with an MIC for mRS and a higher score for MIC for PCS. The initial PCS (lower) is also associated with a MIC for DS. An MIC for MCS is neither associated with perceived risk of surgery nor initial PCS. The associations of an MIC for MCS are an initial MCS (higher) and initial DS (lower). Therefore, the predictors of adverse outcomes vary and depend on the outcome assessment tool utilized.

The MIC of mRS of 8.4% (complication rate realized) (Table 7.2) was within the 95% confidence interval boundary of the 7.2% mean of the perceived risk of surgery score (5.4 to 9.0 %) (complication rate predicted) (Table 7.1). Therefore, the perceived risk of surgery score appears to be valid for the purpose to which it is used, the prediction of disability related to everyday activity. This is also reflected in the fact that an increased perceived risk of surgery is also associated with an increased likelihood of an MIC for PCS, a domain that could be expected to relate to disability. However, perceived risk of surgery is unrelated to an MIC for MCS.

With a recent RCT questioning the role for treatment for patients with ubAVM and audit studies questioning the role treatment of small anterior circulation uIA,(Wiebers, Whisnant et al. 2003, Sonobe, Yamazaki et al. 2010, Morita, Kirino et al. 2012, Mohr, Parides et al. 2014) it is important to consider the scope of outcomes measured and the time period that outcomes were monitored for these studies. As an example, the 8.4% of patients with an MIC of mRS following surgery in our study is a similar proportion of patients that are predicted to have a hemorrhage if left untreated over a 10-year period (8.8%, Table 7.1). This suggests a time course to yield a benefit from surgery is likely to be considerably longer than the median and mean follow-ups in the recent RCT for treatment for patients with ubAVM and audit studies of uIA. (Wiebers, Whisnant et al. 2003, Sonobe, Yamazaki et al. 2010, Morita, Kirino et al. 2012, Mohr, Parides et al. 2014)

Although patients treated by surgery and those untreated differed in age at diagnosis and perceived risk of hemorrhage over the next 10-years, they were comparable with regards perceived risk of surgery, initial PCS, MCS, DS and mRS scores. Generally speaking, with regards the whole cohort, there were broad similarities in outcomes for each of these outcome instruments at 12-months comparing those treated by surgery with those untreated. Therefore, we believe our results from those undergoing surgery are generalizable to all patients with uIA and ubAVM at Macquarie University. However, this is a single hospital-based center that

excludes patients treated by means other than surgery. The results must be reconfirmed in other centers and for other treatments to be generalizable to all patients managed for uIA and ubAVM.

Limitations.

There are a number of difficulties and limitations in applying and interpreting each of the outcome instruments used in this study. These include: the absence of a gold-standard against which each of the instruments can be judged; the application of the instruments; the point of dichotomization to define the MIC; the estimation of the risk of surgery; the estimation of the risk of untreated lesions; and the combination in the study of patients with both uIA and ubAVM.

The mRS, an ordinal hierarchical scale that measures the degree of disability or dependence in daily activity,(Rankin 1957, van der Schaaf, Brilstra et al. 2002)[j] is easily administered, is valid for the concept that is measured, is reasonably reliable and is one of the most common measures employed in stroke trials and clinical assessment.(Chyatte and Porterfield 2001, Wilson, Hareendran et al. 2005, Kasner 2006, Quinn, Dawson et al. 2009a, Quinn, Dawson et al. 2009b, Quinn, Dawson et al. 2009c, Fearon, McArthur et al. 2012, Lees, Bath et al. 2012, Tilley 2012) However, the method of application of the instrument is important in the meaningfulness of the results. (Wilson, Hareendran et al. 2005, Kasner 2006, Quinn, Dawson et al. 2008, Quinn, Dawson et al. 2009a, Quinn, Dawson et al. 2009c, Fearon, McArthur et al. 2012, Lees, Bath et al. 2012, Tilley 2012) Two important considerations need to be discussed in detail regarding our study with resect to mRS, the raters of the mRS and the point of dichotomization of outcomes between an mRS score of 1 and 2. There is a greater reliability for raters with greater training and experience and fewer raters. There were five neurosurgeons participating in this study, each experienced with applying mRS ratings, and each patient was assessed by the same neurosurgeon at the initial and the 12-month follow-up assessment.(Bervini, Morgan et al. 2014, Korja, Bervini et al. 2014) Dichotomization of the mRS score between mRS score of 1 and 2 (as used in this study), is likely to be of greater reliability than between 2 and 3(common in many stroke outcome studies).(Wilson, Hareendran et al. 2005) Furthermore, for the purpose of analyzing patients who are mostly an mRS score of 0 prior to surgery, dichotomization between a score of 1 and 2 allows the greatest number of patients with disability to be captured without confusion, for example as to whether postoperative scalp or wound paresthesia should be rated as 1 (non disabling

symptoms) or 0.(Morgan, Wiedmann et al.) Therefore, we believe that for MIC for mRS following surgery, dichotomization between mRS score of 1 and 2 is appropriate.

The two subscales, PCS and MCS, of the Medical Outcomes SF-36 are measures that provide scores across physical and mental aspects of subjective health.(Ware and Sherbourne 1992, Ware 2002) These scores have established population norms (mean scores for a normal population of 50 and SD 10) within which our cohort could be seen to fit (both at the initial assessment and at the postoperative assessment). However, for greater validity in terms of individual patient outcomes, we have utilized MIC.(Ware Jr, Bayliss et al. 1996, Bayliss, Bayliss et al. 2004) MIC has been previously reported for longitudinal health studies utilizing 6.5 for both PCS and MCS as the point of dichotomization.(Ware Jr, Bayliss et al. 1996, Bayliss, Bayliss et al. 2004) However, although the face validity appears to be reasonable, the lack of a gold-standard for which to test this MIC, and the lack of correlation with each of the outcome instruments, creates some uncertainty of both the validity and reliability of the application of MIC for PCS and MCS to individual patients. This may be reflected in the association between higher initial scores for both PCS and MCS with the development of MIC for PCS and MCS, respectively. By comparison, an MIC for DS was associated with a lower initial DS score. Such an effect with PCS and MCS might be explained by an overestimation of health at the initial assessment due to some systematic differences in expectations or reporting bias. Such an effect suggests that whilst additional measures such as SF-36 are integral to gaining an holistic picture of an individual patient's health, there remains a role for measures that are moderated by an observer (such as DS and mRS) to control for self-reporting bias.(Dow 2009, Fearon, McArthur et al. 2012, Crane, Rissel et al. 2016)

Similarly, the DS version 1 is a recently introduced screening instrument that is an off-road assessment of awareness of the driving environment. The DS has a high sensitivity (93%) and specificity (96%) for predicting driving performance.(Kay, Bundy et al. 2009, Hines and Bundy 2014) The DS can also be interpreted more broadly than its application to driving competence. The skills necessary to perform this test include a measure of speed and accuracy of decision-making important in performing everyday tasks. The standard deviation of DS is similar to the standard deviation for both PCS and MCS. Although no standards have yet been set for what constitutes an MIC for DS in the literature, a decline in score of 6 is a reasonable cut-point given the adoption of 6.5 for PCS and MCS both with similar SD to that of DS. This differs from the DS score of >95 to be considered safe to drive. However,

this cut-point of competent driving fails to capture patients in whom a significant decline in DS score occurs that had a high score initially. Therefore, we regard a decline of 6 from the initial assessment score as reasonable for the cut-point defining MIC for DS. This cut-point identified 18 patients with an MIC for DS, a number intermediate between that found for mRS and either PCS or MCS.

Influence of perceived risk of future hemorrhage untreated.

In common with both uIA and ubAVM is the future risk of hemorrhage. From the patient's perspective, the event of hemorrhage is the critical problem and not whether the cause is either an uIA or ubAVM. The perceived future risk of hemorrhage must enter the discussion to inform the decision as to whether or not surgery is recommended. Therefore, it is reasonable to utilize the perceived risk of future hemorrhage (irrespective of cause) as a factor in the analysis. However, these risks are uncertain and depend on angioarchitectural features and age (affecting the opportunity to rupture). The surgeon needs to ultimately make a recommendation and therefore, make a "best guess" as to what is a reasonable risk of future hemorrhage. For the risk construct used in this study, it has been found to be consistent with the recommendation to treat.

Influence of perceived risk of treatment by surgery.

With regards the perceived risk of surgery, these models were developed from an analysis of a larger cohort of cases (1080 uIA craniotomies and 562 Spetzler-Martin Grade I to III bAVM patients) based upon mRS and therefore the association between MIC for mRS and risk of surgery in this study is not surprising.(Morgan, Wiedmann et al. 2016a, Morgan, Wiedmann et al. 2016b) This risk model allows an estimation of long-term outcomes (including permanent new neurological deficits, effective treatment, retreatment and hemorrhage) following surgery. (Morgan, Wiedmann et al. 2016a, Morgan, Wiedmann et al. 2016b) The current results confirm the validity of the scoring system with regards the development of disability for everyday activity based upon the role of aneurysm size, aneurysm location (anterior or posterior circulation) and patient age for uIA, and ubAVM maximum size, deep venous drainage (DVD) and location (eloquent versus non-eloquent) for ubAVM. Very few of the patients from this present prospective study were in the previous studies that led to the development of these risk constructs ,(Morgan, Wiedmann et al. 2016a, Morgan, Wiedmann et al. 2016b) and, therefore, this study is validation for these risk equations. Furthermore, the

risks are calculated on a broadly similar basis for both uIA and ubAVM and therefore, both pathologies can be combined. From the patient's point of view, the pathology is of less relevance than the expected outcomes from each management pathway (including untreated management). Therefore, it is reasonable to combine these two pathological entities.

The perceived risk for surgery was not found to be associated with an MIC for MCS. This is of importance as the factors that are used to construct the perceived risk of surgery in this study are generally regarded as the factors of importance for adverse outcome following surgery. For uIAs; size, anterior versus posterior location, and patient age and for AVM; maximum size, deep venous drainage and eloquent location are generally reported as predicting outcome from surgery.(Spetzler and Ponce 2011, Bervini, Morgan et al. 2014, Korja, Bervini et al. 2014, Kim, Abla et al. 2015) Therefore, factors other than these contribute to patient QoL captured by the MCS following surgery.

7.1.4 Conclusions

There are a number of instruments that can be used to assess patient outcome. When comparing treatments, utilizing a common measure of outcomes is essential. These must be easily administered, relevant and reliable. No single instrument can encompass all aspects of outcomes. To measure effectiveness of eliminating uIA and ubAVM, imaging (e.g. digital subtraction angiography) is considered the gold standard. By comparison, clinical outcome is more difficult to measure. We found that at 12-months following surgery, the combined cohort of patients had minimal difference in outcomes in comparison with their initial assessment when measured against the QoL scores of PCS and MCS or activity function of DS, and fell within the range expected for population norms. When focusing on individual outcome following surgery, 8.4%, 14%, 20% and 21% of patients measured by mRS, DS, MCS and PCS respectively were found to have sustained an MIC as defined by this study. Furthermore, there was little correlation between the different instruments of outcome and hence, no single instrument can be utilized that provides a comprehensive outcome score. Further research is required to validate instruments that predict broad QoL outcomes of uIA and ubAVM management. Of particular importance is that the risk factors for surgical outcomes are relevant for predicting disability for everyday activity but not for predicting QoL outcome (other than that associated with disability). Furthermore, the frequency with which a decline in MCS occurs in the absence of disability, and the lack of a valid instrument to predict the development of a decline in mental health, suggests vigilance is necessary in

monitoring the mental health of all newly diagnosed patients with uIA or ubAVM, regardless of management pathways and recommending early psychological intervention when appropriate. Additional measures like the SF-36 are integral to gaining a holistic picture of patients' health and outcomes from surgery. In addition, the inclusion of objective health measures will remain critical for understanding outcomes and controlling self-reporting bias for outcomes reported by SF-36.

Chapter 8 *Discussion and Conclusion*

8.1 Summation of thesis results

The primary purpose of this study was to determine the effectiveness of surgery for uIA and bAVM based on functional outcomes. The study was conducted in three sections: outcomes of surgery, risk of post-operative seizure, and the effect of bAVM management on QOL. Function and QOL after 12 months of conservative management or one year after surgery for uIA or bAVM were examined. Function was defined as maintaining pre-operative performance on a cognitive driving test, self-care measure and disability rating scale. QOL was determined by changes in scores on a QOL questionnaire and the rating of relief or regret for uIA or bAVM management decisions. The outcomes in this study were measured with instruments scored by raters from three different perspectives. The QOL was rated by the patient diagnosed with a uIA or bAVM, which provided subjective and insightful information on the experience of having these conditions. The function was scored by a non-treating occupational therapist or general practitioner using objective assessment tools. Levels of disability were scored by the treating surgeon using the mRS which was part of their standard practice.

The unique design of this study has facilitated the exploration of secondary issues for uIA and bAVM management. No other studies have focused on the ability to return to driving after surgery for uIA or bAVM. The primary reason for assessing cognition required for driving was to measure performance at the highest possible level of function for a common everyday activity using a standardised instrument. The issues of restrictions on returning to driving after craniotomy were highlighted and the study parameters were widened to investigate seizure risk which would also restrict returning to drive. The indicators of safety for driving after surgery for uIA and bAVM have been identified as a result of this study.

8.1.1 Outcomes

The first section of this thesis focused on the outcomes of surgery for uIA and bAVM. In Chapter 2, patients' function and QOL were investigated to determine whether the outcomes one year after surgery were worse than after a year of no treatment for a uIA. There was no loss of function or QOL after surgery for uIA. In comparison, there was also no loss of function or QOL for uIA that was conservatively managed. Surgically managed uIA patients

experienced a temporary decline in QOL immediately after surgery, however QOL returned to pre-operative levels one year after surgery. There was no significant difference in function or QOL after one year between conservatively managed and surgically managed uIA patients.

Careful consideration must be given to the instruments employed to measure outcomes and the timing of the outcome assessments. There was no correlation between the disability scale rated by the treating surgeon (mRS) or the QOL scale rated by the patient (SF36) with the performance score on the cognitive driver screening test (DriveSafe) assessed by the occupational therapist. Each measure provides an important perspective on outcomes, therefore each instrument needs to be included in the measurement armamentarium for determining outcomes after uIA surgery. The improvement in physical QOL over the months after surgery shows the importance of considering recovery time in outcome studies. Determining outcomes premature to complete recovery provides a false result on the effectiveness of treatment.

In Chapter 3, the outcomes of surgery for bAVM showed surgical resection of bAVM does not affect function or QOL for low grade bAVM. There was no significant decline in function in conservatively managed or surgically managed bAVM one year after initial presentation or surgery respectively. Functional outcomes after surgery were better for SPA and SPB than SPC class bAVMs. There was no significant change over the initial 12 month period in QOL for patients whose bAVM was conservatively managed. There was a significant improvement from before surgery to one year after surgery in physical and mental QOL for patients whose bAVM was surgically managed. These results indicate function and QOL are not compromised by conservative management of high grade bAVM, while surgical repair of low grade bAVM may improve QOL without affecting function. Overall, the results have signalled a possibility of poorer cognitive function in bAVM patients, emphasising the importance of pre-operative baseline measures of function before determining effectiveness of interventions.

8.1.2 Risk of post-operative seizures

In chapter 4, we investigated the risk of seizure after discharge from hospital for surgical repair of a uIA. We found the cumulative risk was low at 1.1% at 7 years if there was no pre-operative seizure, the repaired aneurysm was not MCA aneurysm and there were no complications of aneurysm repair. Conversely, we have been able to provide a guide for

decisions on returning to high risk activities such as driving by identifying predictors of risk of post-operative seizure.(Walcott and Lawton 2016) Higher risks of post-operative seizure were indicated by pre-operative seizure, MCA aneurysm treatment and complications of aneurysm repair. These findings have meant that, for the identified subgroup of patients for whom the seizure risk is very low, it is not necessary to prescribe preventive anticonvulsive therapy and earlier advice can be given regarding driving after uIA surgery.

In chapter 5, we identified the risk of seizures after surgical repair of bAVM. The factors of a maximum diameter of 4 cm and more than two pre-operative seizures were associated with increased risk of post-operative seizures. A history of zero, one or two pre-operative seizures and a maximum diameter of less than 4 cm were found to have a cumulative 7-year risk of first seizure at 11% following surgery. Specific locations of the bAVM and post-operative complications were not associated with development of post-operative seizure. The risk of seizure after surgery for bAVM was found to be relatively higher than for the general population which should be considered before work and driving activities are resumed.

8.1.3 Quality of life after cerebrovascular neurosurgery

The results of chapters 3 and 5 indicate the impact of having a bAVM may be heavy, and with this cerebrovascular condition more likely to affect younger people, we decided to further examine the resultant QOL from management of bAVM. Chapter 6 presents the results of our investigation of QOL after conservative or surgical management of bAVM in two different cohorts; a population based cohort (SIMVS) and our single institution cohort (MQ). Biases in management strategies and data collection methods were identified. In the SIVMS cohort, there were non-significant better mental QOL scores for conservatively managed bAVM compared with surgically managed bAVM. In the MQ cohort, where there is a bias toward surgical repair, there was a significant improvement in QOL after surgical excision of the unruptured bAVM. This study shows further studies are needed to determine the effect on QOL of knowingly harbouring an unruptured bAVM compared with surgical repair of an unruptured bAVM.(Lo Buono, Bonanno et al. 2016) It could be assumed there is a relationship between the surgeons' rating of disability and the patients' self reported QOL. In chapter 7 we examined this relationship and investigated the perceived risk of management in the outcome of surgery of uIA and unruptured bAVM. The results showed there was minimal difference in patient outcomes at 12 months follow up in comparison with initial assessment when measured against the QoL scores of PCS and MCS or activity function of DS. An MIC

in the mRS, DS, MCS and PCS outcome measures was found in 8.4%, 14%, 20% and 21% of patients respectively. There was little correlation in the outcome measures and QOL scores, and risk factors for surgery were found to predict disability but not QOL. Despite the absence of a disability, the QOL results showed there was a trend for mental health to decline, indicating a need to monitor mental health after surgery for cerebrovascular conditions.

8.2 Future Directions

This study has shown there was no loss of function or QOL after surgery for uIA and bAVM over a 6-year period at our institution, however these results may not be replicated if this study were to be conducted at institutions where surgery to repair cerebrovascular conditions is less frequently performed. Registries of management and outcomes for cerebrovascular conditions would facilitate the monitoring of outcomes of intervention, highlighting areas where skill acquisition needs improvement and determining the risk versus effectiveness of new technologies and management strategies as they are introduced.(Cenzato, Boccardi et al. 2017)

The strong desire to return to normal living inspired participants to comply with the outcome data collection for this study. Study participants were highly motivated to perform the post-operative driving assessments in order to be able to return to driving and their everyday lives. The version of the test used in this study took approximately 20 to 30 minutes with an occupational therapist scoring the test. The more recently developed version of the DriveSafe DriveAware test is performed by touchscreen technology using an iPad and can be administered within 15 minutes.(Cheal 2015) Future studies investigating the outcomes of cerebrovascular surgery should use objective, standardised functional performance measures that convey information pertinent to the everyday lives of the study population that can be administered swiftly and at low cost in order to maximise participant compliance.

Further comparative observational studies are needed to ascertain the association between unruptured bAVM treatment and QOL. In the absence of dramatic treatment effects on QOL in our observational data and other studies, QOL outcomes in the ARUBA trial (and other ongoing randomised trials such as TOBAS, NCT02098252) are keenly awaited.

8.3 Thesis conclusion

Based on function and QOL, surgery is effective for the management of uIA or bAVM. There was no decline in function or QOL after surgical repair of uIA and bAVM. In the absence of pre-operative seizure, MCA aneurysm treatment or complications of aneurysm repair, guidelines that restrict driving for more than 12 weeks after surgery for uIA need to be reviewed. Restriction of driving after surgery is recommended for high-grade bAVM with the maximum diameter greater than 4 cm and a history of more than two pre-operative seizures.

References

Aghakhani, N., G. Vaz, P. David, F. Parker, P. Goffette, A. Ozan and C. Raftopoulos (2008). "Surgical management of unruptured intracranial aneurysms that are inappropriate for endovascular treatment: experience based on two academic centers." Neurosurgery **62**(6): 1227-1234; discussion 1234-1225.

Al-Shahi Salman, R. (2012). "The outlook for adults with epileptic seizure(s) associated with cerebral cavernous malformations or arteriovenous malformations." Epilepsia **53 Suppl 4**: 34-42.

Al-Shahi Salman, R., P. M. White, C. E. Counsell, J. du Plessis, J. van Beijnum, C. B. Josephson, T. Wilkinson, C. J. Wedderburn, Z. Chandy, E. J. St George, R. J. Sellar, C. P. Warlow and C. Scottish Audit of Intracranial Vascular Malformations (2014). "Outcome after conservative management or intervention for unruptured brain arteriovenous malformations." JAMA **311**(16): 1661-1669.

Andaluz, N. and M. Zuccarello (2011). "Treatment strategies for complex intracranial aneurysms: Review of a 12-year experience at the University of Cincinnati." Skull Base **21**(4): 233-241.

Anderson, S. I., A. M. Housley, P. A. Jones, J. Slattery and J. D. Miller (1993). "Glasgow outcome scale: An inter-rater reliability study." Brain Injury **7**(4): 309-317.

ApSimon, H. T., H. Reef, R. V. Phadke and E. A. Popovic (2002). "A population-based study of brain arteriovenous malformation: Long-term treatment outcomes." Stroke **33**(12): 2794-2800.

Austroads (2012). Assessing fitness to drive - Commercial and private vehicle drivers. 4th edn. Sydney, Austroads Ltd. Australia

Austroads (2016). Assessing Fitness to Drive for Commercial and Private Vehicle Drivers (2016 Edition). Sydney, Austroads Ltd. Australia

Road Safety Authority (2015). Medical fitness to drive guidelines; 4th edition. National Programme Office for Traffic Medicine. Dublin, Republic of Ireland

Backes, D., G. J. Rinkel, I. C. van der Schaaf, J. A. Nij Bijvank, B. H. Verweij, J. M. Visser-Meily, M. W. Post, A. Algra and M. D. Vergouwen (2015). "Recovery to Preinterventional Functioning, Return-to-Work, and Life Satisfaction After Treatment of Unruptured Aneurysms." Stroke **46**(6): 1607-1612.

Baker, C. J., C. J. Prestigiacomo and R. A. Solomon (1995). "Short-term perioperative anticonvulsant prophylaxis for the surgical treatment of low-risk patients with intracranial aneurysms." Neurosurgery **37**(5): 863-870; discussion 870-861.

Balu, S. (2009). "Differences in psychometric properties, cut-off scores, and outcomes between the Barthel Index and Modified Rankin Scale in pharmacotherapy-based stroke trials: Systematic literature review." Current Medical Research and Opinion **25**(6): 1329-1341.

Baranoski, J. F., R. A. Grant, L. J. Hirsch, P. Visintainer, J. L. Gerrard, M. Gunel, C. C. Matouk, D. D. Spencer and K. R. Bulsara (2014). "Seizure control for intracranial arteriovenous malformations is directly related to treatment modality: a meta-analysis." Journal of neurointerventional surgery **6**(9): 684-690.

Bayliss, E. A., M. S. Bayliss, J. E. Ware Jr and J. F. Steiner (2004). "Predicting declines in physical function in persons with multiple chronic medical conditions: What we can learn from the medical problem list." Health and Quality of Life Outcomes **2 (no pagination)**(47).

Bederson, J. B., I. A. Awad, D. O. Wiebers, D. M. Piepgras, E. C. J. Haley, T. Brott, G. P. Hademenos, D. Chyatte, R. Rosenwasser and C. M. Caroselli (2000). "Recommendations for the Management of Patients With Unruptured Intracranial Aneurysms: A Statement for Healthcare Professionals From the Stroke Council of the American Heart Association." Stroke **31**(11): 2742-2750.

Beghi, E. and J. W. Sander (2005). "Epilepsy and driving." BMJ (Clinical research ed.) **331**(7508): 60-61.

Bervini, D., M. K. Morgan, E. A. Ritson and G. Heller (2014). "Surgery for unruptured arteriovenous malformations of the brain is better than conservative management for selected cases: A prospective cohort study." Journal of Neurosurgery **121**(4): 878-890.

Bidzinski, J., A. Marchel and A. Sherif (1992). "Risk of epilepsy after aneurysm operations." Acta neurochirurgica **119**(1-4): 49-52.

Brandt, J., M. Spencer and M. Folstein (1988). "The telephone interview for cognitive status." Neuropsychiatry, Neuropsychology and Behavioral Neurology **1**(2): 111-117.

Brilstra, E. H., G. J. Rinkel, Y. van der Graaf, M. Sluzewski, R. J. Groen, R. T. Lo and C. A. Tulleken (2004). "Quality of life after treatment of unruptured intracranial aneurysms by neurosurgical clipping or by embolisation with coils. A prospective, observational study." Cerebrovasc Dis **17**(1): 44-52.

Brinjikji, W., A. A. Rabinstein, G. Lanzino, D. F.Kallmes and H. J. P. Cloft (2011). "Effect of Age on Outcomes of Treatment of Unruptured Cerebral Aneurysms: A Study of the National Inpatient Sample 2001-2008." Stroke **42**(5): 1320-1324.

Britz, G. W., L. Salem, D. W. Newell, J. Eskridge and D. R. Flum (2004). "Impact of Surgical Clipping on Survival in Unruptured and Ruptured Cerebral Aneurysms: A Population-Based Study." Stroke **35**(6): 1399-1403.

Buijs, J. E., P. Greebe and G. J. E. Rinkel (2011). "Quality of life, anxiety and depression in patients with an unruptured intracranial aneurysm with or without aneurysm occlusion." Neurosurgery.

Cantore, G., A. Santoro, G. Guidetti, C. P. Delfinis, C. Colonnese and E. Passacantilli (2008). "Surgical treatment of giant intracranial aneurysms: current viewpoint." Neurosurgery **63**(4 Suppl 2): 279-289; discussion 289-290.

Cenzato, M., E. Boccardi, E. Beghi, P. Vajkoczy, I. Szikora, E. Motti, L. Regli, A. Raabe, S. Eliava, A. Gruber, T. R. Meling, M. Niemela, A. Pasqualin, A. Golanov, B. Karlsson, A. Kemeny, R. Liscak, B. Lippitz, M. Radatz, A. la Camera, R. Chapot, C. Islak, L. Spelle, A. Debernardi, E. Agostoni, M. Revay and M. K. Morgan (2017). "European consensus

conference on unruptured brain AVMs treatment (Supported by EANS, ESMINT, EGKS, and SINCH)." Acta Neurochirurgica: 1-6.

Cheal, B., Kuang, H. (2015). DriveSafe DriveAware for Touch Screen Administration Manual. Sydney, Australia:, Pearson Clinical.

Chen, C.W., J.R. Kuo, H.J. Lin, C.H. Yeh, B.S. Wong, C.H. Kao and C.C. Chio (2004). "Early post-operative seizures after burr-hole drainage for chronic subdural hematoma: correlation with brain CT findings." Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia **11**(7): 706-709.

Chyatte, D. and R. Porterfield (2001). "Functional outcome after repair of unruptured intracranial aneurysms." Journal of Neurosurgery **94**(3): 417-421.

Cockroft, K. M. (2007). "Unruptured brain arteriovenous malformations should be treated conservatively: no." Stroke; a journal of cerebral circulation **38**(12): 3310-3311.

Coert, B. A., S. D. Chang, H. M. Do, M. P. Marks and G. K. Steinberg (2007). "Surgical and endovascular management of symptomatic posterior circulation fusiform aneurysms." Journal of Neurosurgery **106**(5): 855-865.

Crane, M., C. Rissel, S. Greaves and K. Gebel (2016). "Correcting bias in self-rated quality of life: an application of anchoring vignettes and ordinal regression models to better understand QoL differences across commuting modes." Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation **25**(2): 257-266.

Crawford, P. M., C. R. West, M. D. Shaw and D. W. Chadwick (1986). "Cerebral arteriovenous malformations and epilepsy: factors in the development of epilepsy." Epilepsia **27**(3): 270-275.

Da Costa, L. D., L. Thines, A. R. Dehdashti, M. C. Wallace, R. A. Willinsky, M. Tymianski, M. L. Schwartz and G. T. Ter Brugge (2009). "Management and clinical outcome of Posterior fossa arteriovenous malformations: Report on a single centre 15-year experience." Journal of Neurology, Neurosurgery and Psychiatry **80**(4): 376-379.

Davidson, A. S. and M. K. Morgan (2010). "How safe is arteriovenous malformation surgery? A prospective, observational study of surgery as first-line treatment for brain arteriovenous malformations." Neurosurgery **66**(3): 498-504.

Della Puppa, A., O. Rustemi and R. Scienza (2015). "Letter to the editor: quality of life of patients affected by unruptured brain AVMs." Journal of neurosurgery **122**(4): 984-985.

Dow, J. (2009). "Commentary: Evaluation of Driver Fitness—The Role of Continuing Medical Education." Traffic Injury Prevention **10**(4): 309 - 311.

Driver Licensing Authority (2014). For medical practitioners: At a glance guide to the current medical standards of fitness to drive. Swansea, United Kingdom.

Englot, D. J., W. L. Young, S. J. Han, C. E. McCulloch, E. F. Chang and M. T. Lawton (2012). "Seizure predictors and control after microsurgical resection of supratentorial arteriovenous malformations in 440 patients." Neurosurgery **71**(3): 572-580; discussion 580.

Etminan, N., R. D. Brown, Jr., K. Beseoglu, S. Juvela, J. Raymond, A. Morita, J. C. Torner, C. P. Derdeyn, A. Raabe, J. Mocco, M. Korja, A. Abdulazim, S. Amin-Hanjani, R. Al-Shahi Salman, D. L. Barrow, J. Bederson, A. Bonafe, A. S. Dumont, D. J. Fiorella, A. Gruber, G. J. Hankey, D. M. Hasan, B. L. Hoh, P. Jabbour, H. Kasuya, M. E. Kelly, P. J. Kirkpatrick, N. Knuckey, T. Koivisto, T. Krings, M. T. Lawton, T. R. Marotta, S. A. Mayer, E. Mee, V. M. Pereira, A. Molyneux, M. K. Morgan, K. Mori, Y. Murayama, S. Nagahiro, N. Nakayama, M. Niemela, C. S. Ogilvy, L. Pierot, A. A. Rabinstein, Y. B. Roos, J. Rinne, R. H. Rosenwasser, A. Ronkainen, K. Schaller, V. Seifert, R. A. Solomon, J. Spears, H. J. Steiger, M. D. Vergouwen, I. Wanke, M. J. Wermer, G. K. Wong, J. H. Wong, G. J. Zipfel, E. S. Connolly, Jr., H. Steinmetz, G. Lanzino, A. Pasqualin, D. Rufenacht, P. Vajkoczy, C. McDougall, D. Hanggi, P. LeRoux, G. J. Rinkel and R. L. Macdonald (2015). "The unruptured intracranial aneurysm treatment score: a multidisciplinary consensus." Neurology **85**(10): 881-889.

Fearon, P., K. S. McArthur, K. Garrity, L. J. Graham, G. McGroarty, S. Vincent and T. J. Quinn (2012). "Prestroke modified Rankin stroke scale has moderate interobserver reliability and validity in an acute stroke setting." Stroke **43**(12): 3184-3188.

Folstein, M. F., S. E. Folstein and P. R. McHugh (1975). ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician." Journal of Psychiatric Research **12**(3): 189-198.

Galletti, F., C. Costa, L. M. Cupini, P. Eusebi, M. Hamam, N. Caputo, S. Siliquini, C. Conti, E. Moschini, P. Lunardi, S. Carletti and P. Calabresi (2014). "Brain arteriovenous malformations and seizures: an Italian study." Journal of neurology, neurosurgery, and psychiatry **85**(3): 284-288.

Gee, E. (2016). Reinventing Emma. Melbourne, Kew, A : Dennis Jones & Associates.

Hadera, M. G., H. Eloqayli, S. Jaradat, A. Nehlig and U. Sonnewald (2015). "Astrocyte-neuronal interactions in epileptogenesis." Journal of neuroscience research **93**(7): 1157-1164.

Hartmann, A., C. Stapf, C. Hofmeister, J. P. Mohr, R. R. Sciacca, B. M. Stein, A. Faulstich and H. Mast (2000). "Determinants of neurological outcome after surgery for brain arteriovenous malformation." Stroke **31**(10): 2361-2364.

Hauser, W. A. and E. Beghi (2008). "First seizure definitions and worldwide incidence and mortality." Epilepsia **49 Suppl 1**: 8-12.

Hawthorne, G., R. H. Osborne, A. Taylor and J. Sansoni (2007). "The SF36 Version 2: Critical analyses of population weights, scoring algorithms and population norms." Quality of Life Research **16**(4): 661-673.

Hayashi, T., H. Hadeishi, S. Kawamura, Y. Nonoyama, A. Suzuki and N. Yasui (1999). "Postoperative anticonvulsant prophylaxis for patients treated for cerebral aneurysms." Neurologia Medico-Chirurgica **39**(12): 828-833; discussion 833-824.

Heros, R. C., K. Korosue and P. M. Diebold (1990). "Surgical excision of cerebral arteriovenous malformations: late results." Neurosurgery **26**(4): 570-577; discussion 577-578.

Higashida, R. T., B. J. Lahue, M. T. Torbey, L. N. Hopkins, E. Leip and D. F. Hanley (2007). "Treatment of unruptured intracranial aneurysms: A nationwide assessment of effectiveness." American Journal of Neuroradiology **28**(1): 146-151.

Hillman, J. (2001). "Population-based analysis of arteriovenous malformation treatment." Journal of Neurosurgery **95**(4): 633-637.

Hines, A. and A. C. Bundy (2014). "Predicting driving ability using DriveSafe and DriveAware in people with cognitive impairments: a replication study." Australian occupational therapy journal **61**(4): 224-229.

Hoggarth, P. A. (2013). "Diagnosis of cognitive impairment and the assessment of driving safety in New Zealand: A survey of canterbury GPs." New Zealand Medical Journal **126**(1387): 87-97.

Hoh, B. L., P. H. Chapman, J. S. Loeffler, B. S. Carter and C. S. Ogilvy (2002). "Results of multimodality treatment for 141 patients with brain arteriovenous malformations and seizures: factors associated with seizure incidence and seizure outcomes." Neurosurgery **51**(2): 303-309; discussion 309-311.

Hoh, B. L., S. Nathoo, Y.-Y. Chi, J. Mocco and F. G. Barker, 2nd (2011). "Incidence of seizures or epilepsy after clipping or coiling of ruptured and unruptured cerebral aneurysms in the nationwide inpatient sample database: 2002-2007." Neurosurgery **69**(3): 644-650; discussion 650.

Hyun, S. J., D. S. Kong, J. I. Lee, J. S. Kim and S. C. Hong (2012). "Cerebral arteriovenous malformations and seizures: differential impact on the time to seizure-free state according to the treatment modalities." Acta Neurochirurgica **154**(6): 1003-1010.

Innes, C. R. H., R. D. Jones, T. J. Anderson, S. G. Hollobon and J. C. Dalrymple-Alford (2009). "Performance in normal subjects on a novel battery of driving-related sensory-motor and cognitive tests." Behavior Research Methods **41**(2): 284-294.

Jang, E. W., J. Y. Jung, C. K. Hong and J. Y. Joo (2011). "Benefits of surgical treatment for unruptured intracranial aneurysms in elderly patients." Journal of Korean Neurosurgical Society **49**(1): 20-25.

Janssen, P. M., N. A. Visser, S. M. Dorhout Mees, C. J. M. Klijn, A. Algra and G. J. E. Rinkel (2010). "Comparison of telephone and face-to-face assessment of the modified Rankin Scale." Cerebrovascular Diseases **29**(2): 137-139.

Jayaraman, M. V., M. L. Marcellus, S. Hamilton, H. M. Do, D. Campbell, S. D. Chang, G. K. Steinberg and M. P. Marks (2008). "Neurologic complications of arteriovenous malformation embolization using liquid embolic agents." American Journal of Neuroradiology **29**(2): 242-246.

Jenkinson, C. (1999). "Comparison of UK and US methods for weighting and scoring the SF-36 summary measures." Journal of Public Health Medicine **21**(4): 372-376.

Jenkinson, C., R. Layte and K. Lawrence (1997). "Development and Testing of the Medical Outcomes Study 36-Item Short Form Health Survey Summary Scale Scores in the United Kingdom: Results from a Large-Scale Survey and a Clinical Trial." Medical Care **35**(4): 410-416.

Johnston, S. C., C. B. Wilson, V. V. Halbach, R. T. Higashida, C. F. Dowd, M. W. McDermott, C. B. Applebury, T. L. Farley and D. R. Gress (2000). "Endovascular and

surgical treatment of unruptured cerebral aneurysms: Comparison of risks." Annals of Neurology **48**(1): 11-19.

Josephson, C. B., J. P. Leach, R. Duncan, R. C. Roberts, C. E. Counsell, R. Al-Shahi Salman, c. Scottish Audit of Intracranial Vascular Malformations steering and collaborators (2011). "Seizure risk from cavernous or arteriovenous malformations: prospective population-based study." Neurology **76**(18): 1548-1554.

Josephson, C. B., K. Sauro, S. Wiebe, F. Clement and N. Jette (2016). "Medical vs invasive therapy in AVM-related epilepsy." Neurology **86**(1): 64-71.

Juvela, S., K. Poussa, H. Lehto and M. Porras (2013). "Natural history of unruptured intracranial aneurysms: A long-term follow-up study." Stroke **44**(9): 2414-2421.

Kasner, S. E. (2006). "Clinical interpretation and use of stroke scales." Lancet Neurology **5**(7): 603-612.

Kay, L. G., A. Bundy and L. Clemson (2009). "Validity, reliability and predictive accuracy of the Driving Awareness Questionnaire." Disability and Rehabilitation **31**(13): 1074-1082.

Kay, L. G., A. C. Bundy and L. M. Clemson (2008). "Predicting fitness to drive using the visual recognition slide test (USyd)." American Journal of Occupational Therapy **62**(2): 187-197.

Kay, L. G., A. C. Bundy and L. M. Clemson (2009). "Predicting Fitness to Drive in People With Cognitive Impairments by Using DriveSafe and DriveAware." Archives of Physical Medicine and Rehabilitation **90**(9): 1514-1522.

Kay, L. G., A. C. Bundy, L. Clemson, B. Cheal and T. Glendenning (2012). "Contribution of off-road tests to predicting on-road performance: A critical review of tests." Australian Occupational Therapy Journal **59**(1): 89-97.

Kim, H., A. A. Abla, J. Nelson, C. E. McCulloch, D. Bervini, M. K. Morgan, C. Stapleton, B. P. Walcott, C. S. Ogilvy, R. F. Spetzler and M. T. Lawton (2015). "Validation of the supplemented Spetzler-martin grading system for brain Arteriovenous malformations in a Multicenter cohort of 1009 surgical patients." Neurosurgery **76**(1): 25-31.

Kim, D. H., C. L. Haney and G. Van Ginhoven (2005). "Utility of outcome measures after treatment for intracranial aneurysms: a prospective trial involving 520 patients." Stroke **36**(4): 792-796.

King Jr, J. T., M. B. Horowitz, A. B. Kassam, H. Yonas and M. S. Roberts (2005). "The Short Form-12 and the measurement of health status in patients with cerebral aneurysms: Performance, validity, and reliability." Journal of Neurosurgery **102**(3): 489-494.

King Jr, J. T., J. Tsevat and M. S. Roberts (2006). "The Physical Performance Test and the evaluation of functional status in patients with cerebral aneurysms." Journal of Neurosurgery **104**(4): 525-530.

King, J. T., A. B. Kassam, H. Yonas, M. B. Horowitz and M. S. Roberts (2005). "Mental health, anxiety, and depression in patients with cerebral aneurysms." Journal of Neurosurgery **103**(4): 636-641.

King, J. T. J., M. L. DiLuna, D. V. Cicchetti, J. M. Tsevat and M. S. Roberts (2006). "Cognitive Functioning in Patients with Cerebral Aneurysms Measured with the Mini Mental State Examination and the Telephone Interview for Cognitive Status." Neurosurgery **59**(4): 803-811.

Korja, M., D. Bervini, N. Assaad and M. K. Morgan (2014). "Role of surgery in the management of brain arteriovenous malformations: Prospective cohort study." Stroke **45**(12): 3549-3555.

Korja, M., J. Hernesniemi, M. T. Lawton, R. F. Spetzler and M. K. Morgan (2014). "Is cerebrovascular neurosurgery sacrified on the altar of RCTs?" Lancet **384**(9937): 27-28.

Korja, M. and J. Kaprio (2016). "Controversies in epidemiology of intracranial aneurysms and SAH." Nature Reviews Neurology **12**(1): 50-55.

Kraemer, D. L. and I. A. Awad (1994). "Vascular malformations and epilepsy: clinical considerations and basic mechanisms." Epilepsia **35 Suppl 6**: S30-43.

Krivoshapkin, A. L. and E. G. Melidy (2005). "Microsurgery for cerebral arteriovenous malformation management: a Siberian experience." Neurosurgical review **28**(2): 124-130.

Kwon, O. K., C.-W. Oh and D. H. Han (2002). "Postoperative seizure outcome in patients with cerebral arteriovenous malformations." Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia **9 Suppl 1**: 1-2.

Laakso, A., R. Dashti, S. Juvela, P. Isarakul, M. Niemela and J. Hernesniemi (2011). "Risk of hemorrhage in patients with untreated Spetzler-Martin grade IV and V arteriovenous malformations: a long-term follow-up study in 63 patients." Neurosurgery **68**(2): 372-377; discussion 378.

Lai, L. T., C. Gragnaniello and M. K. Morgan (2013). "Outcomes for a case series of unruptured anterior communicating artery aneurysm surgery." Journal of Clinical Neuroscience **20**(12): 1688-1692.

Lai, L. T., J. O'Donnell and M. K. Morgan (2013). "The risk of seizures during the in-hospital admission for surgical or endovascular treatment of unruptured intracranial aneurysms." Journal of Clinical Neuroscience **20**(11): 1498-1502.

Lees, K. R., P. M. Bath, P. D. Schellinger, D. M. Kerr, R. Fulton, W. Hacke, D. Matchar, R. Sehra, D. Toni and G. European Stroke Organization Outcomes Working (2012). "Contemporary outcome measures in acute stroke research: choice of primary outcome measure." Stroke **43**(4): 1163-1170.

LeGrand, S. A., B. J. Hindman, F. Dexter, L. G. Moss and M. M. Todd (2007). "Reliability of a telephone-based Glasgow Outcome Scale assessment using a structured interview in a heterogenous population of patients and examiners." Journal of Neurotrauma **24**(9): 1437-1446.

Levin, H. S., C. Boake, J. Song, S. McCauley, C. Contant, P. Diaz-Marchan, S. Brundage, H. Goodman and K. J. Kotrla (2001). "Validity and sensitivity to change of the extended Glasgow Outcome Scale in mild to moderate traumatic brain injury." Journal of Neurotrauma **18**(6): 575-584.

Lo Buono, V., L. Bonanno, F. Corallo, A. Sidoti, P. Bramanti and S. Marino (2016). "Evaluation of Qualitative Outcomes after Surgical Intervention on Patients Affected by Arteriovenous Malformations." Journal of Stroke and Cerebrovascular Diseases **25**(12): 2947-2952.

Lopez-Ojeda, P., M. Labib, J. Burneo and S. P. Lownie (2013). "Temporal lobe arteriovenous malformations: surgical outcomes with a focus on visual field defects and epilepsy." Neurosurgery **73**(5): 854-862; discussion 862; quiz 862.

Lyden, P. D., M. Lu, S. R. Levine, T. G. Brott and J. Broderick (2001). "A modified national institutes of health stroke scale for use in stroke clinical trials preliminary reliability and validity." Stroke **32**(6): 1310-1316.

Mahoney, F. I. and D. W. Barthel (1965). "Functional Evaluation: The Barthel Index." Maryland state medical journal **14**: 61-65.

Manuguerra, M. and G. Z. Heller (2010). "Ordinal regression models for continuous scales." The International Journal of Biostatistics **6**(1): Article 14.

Marshall, G. A., B. P. Jonker, M. K. Morgan and A. J. Taylor (2003). "Prospective study of neuropsychological and psychosocial outcome following surgical excision of intracerebral arteriovenous malformations." Journal of Clinical Neuroscience **10**(1): 42-47.

Mine, S., S. Hirai, J. Ono and A. Yamaura (2000). "Risk factors for poor outcome of untreated arteriovenous malformation." Journal of Clinical Neuroscience **7**(6): 503-506.

Mitchell, P., R. R. Vindlacheruvu, K. Mahmood, R. D. Ashpole, A. Grivas and A. D. Mendelow (2005). "Supraorbital eyebrow minicraniotomy for anterior circulation aneurysms." Surgical Neurology **63**(1): 47-51; discussion 51.

Mohr, J. P., M. K. Parides, C. Stapf, E. Moquete, C. S. Moy, J. R. Overbey, R. Al-Shahi Salman, E. Vicaut, W. L. Young, E. Houdart, C. Cordonnier, M. A. Stefani, A. Hartmann, R. von Kummer, A. Biondi, J. Berkefeld, C. J. Klijn, K. Harkness, R. Libman, X. Barreau, A. J. Moskowitz and A. i. international (2014). "Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial." Lancet **383**(9917): 614-621.

Molyneux, A. J., S. Cekirge, I. Saatci and G. Gál (2004). "Cerebral Aneurysm Multicenter European Onyx (CAMEO) Trial: Results of a Prospective Observational Study in 20 European Centers." American Journal of Neuroradiology **25**(1): 39-51.

Moon, K., M. R. Levitt, R. O. Almefty, P. Nakaji, F. C. Albuquerque, J. M. Zabramski, J. E. Wanebo, C. G. McDougall and R. F. Spetzler (2015). "Safety and Efficacy of Surgical Resection of Unruptured Low-grade Arteriovenous Malformations From the Modern Decade." Neurosurgery **77**(6): 948-952.

Morgan, M. K., A. S. Davidson, N. N. A. Assaad and M. A. Stoodley (2017a). "Critical review of brain AVM surgery, surgical results and natural history in 2017." Acta Neurochirurgica: 1-22.

Morgan, M. K., M. Wiedmann, N. N. Assaad and G. Z. Heller (2016a). "Complication-effectiveness analysis for unruptured intracranial aneurysm surgery: A prospective cohort study." Neurosurgery **78**(5): 648-659.

Morgan, M. K., M. Wiedmann, N. N. Assaad and G. Z. Heller (2016b). "Complication-effectiveness analysis for brain arteriovenous malformation surgery: A prospective cohort study." Neurosurgery **79**(1): 47-57.

Morgan, M. K., M. K. H. Wiedmann, M. A. Stoodley and G. Z. Heller (2017b)."Microsurgery for Spetzler-Ponce Class A and B arteriovenous malformations utilizing an outcome score adopted from Gamma Knife radiosurgery: a prospective cohort study." Journal of Neurosurgery **0**(0): 1-12.

Mori, K., T. Yamamoto, Y. Nakao, K. Oyama, T. Esaki, M. Watanabe, S. Nonaka, T. Hara and K. Honma (2008). "Lateral supraorbital keyhole approach to clip unruptured anterior communicating artery aneurysms." Minimally Invasive Neurosurgery **51**(5): 292-297.

Morita, A., T. Kirino, K. Hashi, N. Aoki, S. Fukuhara, N. Hashimoto, T. Nakayama, M. Sakai, A. Teramoto, S. Tominari and T. Yoshimoto (2012). "The natural course of unruptured cerebral aneurysms in a Japanese cohort." New England Journal of Medicine **366**(26): 2474-2782.

Moriya, N., K. Nakamura, T. Asakura, M. Niiro and K. Kadota (1990). "Arteriovenous malformations and epilepsy--natural history and surgical results with associated seizure." The Japanese journal of psychiatry and neurology **44**(2): 381-382.

Murphy, M. J. (1985). "Long-term follow-up of seizures associated with cerebral arteriovenous malformations. Results of therapy." Archives of neurology **42**(5): 477-479.

Nagata, S., T. Morioka, K. Matsukado, Y. Natori and T. Sasaki (2006). "Retrospective analysis of the surgically treated temporal lobe arteriovenous malformations with focus on the visual field defects and epilepsy." Surgical neurology **66**(1): 50-55; discussion 55.

Nanda, A. and P. Vannemreddy (2002). "Surgical management of unruptured aneurysms: prognostic indicators." Surgical Neurology **58**(1): 13-19; discussion 19-20.

Nataf, F., M. Schlienger, M. Bayram, M. Ghossoub, B. George and F. X. Roux (2007). "Microsurgery or radiosurgery for cerebral arteriovenous malformations? A study of two paired series." Neurosurgery **61**(1): 39-49.

Ng, P. Y., P. L. Reilly, B. P. Brophy and S. Halcrow (1998). "Distal anterior cerebral artery aneurysms: a clinical series." British Journal of Neurosurgery **12**(3): 209-212.

O'Donnell, J. and M. K. Morgan (2015). "Response." J Neurosurg **122**(4): 985-986.

O'Donnell J., M. M. K., Savage G., Bundy A. (2013a). "Measuring functional outcomes following surgery for unruptured, intracranial aneurysms and brain AVM's: Vailidity and reliability of past and present instruments. ." Aust Occupational Therapy Journal Suppl. **60 Suppl 1**: 24.

O'Donnell J., M. M. K., Savage G., Bundy A. (2013c). "DriveSafe DriveAware: A Normal Population Test Retest Reliability Study " Australian Occupational Therapy Journal Supplement **60**: 3.

O'Donnell, J. M., M. K. Morgan, D. Bervini, G. Z. Heller and N. Assaad (2016). "The risk of seizure after surgery for unruptured intracranial aneurysms: A prospective cohort study." Neurosurgery **79**(2): 222-229.

O'Donnell, J. M., M. K. Morgan and G. Z. Heller (2017). "The Risk of Seizure Following Surgery for Brain Arteriovenous Malformation: A Prospective Cohort Study." Neurosurgery. **29**.

O'Donnell J., M. M. K., Savage G., Bundy A. (2013b). "Fitness to Drive After Surgery for Unruptured Intracranial Aneurysms and Brain AVMs: Pre and Post Treatment Results on Drivesafe Driveaware " Australian Occupational Therapy Journal Supplement **60**: 48.

Office of the Superintendent of Motor Vehicles. (2014). British Columbria driver fitness handbook for medical professionals. Victoria BC, Canada, Ministry of Justice.

Otawara, Y., K. Ogasawara, Y. Kubo, N. Tomitsuka, M. Watanabe, A. Ogawa, M. Suzuki and K. Yamadate (2004). "Anxiety before and after surgical repair in patients with asymptomatic unruptured intracranial aneurysm." Surgical Neurology **62**(1): 28-31.

Otawara, Y., K. Ogasawara, A. Ogawa and K. B. Yamadate (2005). "Cognitive Function Before and After Surgery in Patients With Unruptured Intracranial Aneurysm." Stroke **36**(1): 142-143.

Panagiotopoulos, V., S. C. Ladd, E. Gizewski, S. Asgari, E. I. Sandalcioglu, M. Forsting and I. Wanke (2011). "Recovery of ophthalmoplegia after endovascular treatment of intracranial aneurysms." Ajnr: American Journal of Neuroradiology **32**(2): 276-282.

Parkinson, D. and G. Bachers (1980). "Arteriovenous malformations. Summary of 100 consecutive supratentorial cases." Journal of neurosurgery **53**(3): 285-299.

Patomella, A. H., K. Tham, K. Johansson and A. Kottorp (2010). "P-drive on-road: internal scale validity and reliability of an assessment of on-road driving performance in people with neurological disorders." Scandinavian Journal of Occupational Therapy **17**(1): 86-93.

Peacock, J. K., S. (2007). Presenting medical statistics from proposal to publication. Oxford, Oxford University Press.

Piepgras, D. G., T. M. Sundt, Jr., A. T. Ragoowansi and L. Stevens (1993). "Seizure outcome in patients with surgically treated cerebral arteriovenous malformations." Journal of Neurosurgery **78**(1): 5-11.

Pollock, B. E. and R. D. Brown Jr (2006). "Use of the modified Rankin Scale to assess outcome after arteriovenous malformation radiosurgery." Neurology **67**(9): 1630-1634.

Proust, F., O. Martinaud, E. Gérardin, S. Derrey, S. Levèque, S. Bioux, E. Tollard, E. Clavier, O. Langlois, O. Godefroy, D. Hannequin and P. Fréger (2009). "Quality of life and brain damage after microsurgical clip occlusion or endovascular coil embolization for ruptured anterior communicating artery aneurysms: neuropsychological assessment." Journal of Neurosurgery **110**(1): 19-29.

Quinn, T. J., J. Dawson, M. R. Walters and K. R. Lees (2008). "Variability in modified rankin scoring across a large cohort of international observers." Stroke **39**(11): 2975-2979.

Quinn, T. J., J. Dawson, M. R. Walters and K. R. Lees (2009a). "Reliability of the modified Rankin Scale: a systematic review." Stroke **40**(10): 3393-3395.

Quinn, T. J., J. Dawson, M. R. Walters and K. R. Lees (2009b). "Exploring the reliability of the modified rankin scale." Stroke **40**(3): 762-766.

Quinn, T. J., J. Dawson, M. R. Walters and K. R. Lees (2009c). "Functional outcome measures in contemporary stroke trials." International Journal of Stroke **4**(3): 200-205.

Rankin, J. (1957). "Cerebral vascular accidents in patients over the age of 60, II: prognosis." Scottish Medical Journal **2**(5): 200-215

Raaymakers, T. W. (2000). "Functional outcome and quality of life after angiography and operation for unruptured intracranial aneurysms. On behalf of the MARS Study Group." J Neurol Neurosurg Psychiatry **68**(5): 571-576.

Rabinowicz, A. L., D. L. Ginsburg, C. M. DeGiorgio, P. S. Gott and S. L. Giannotta (1991). "Unruptured intracranial aneurysms: seizures and antiepileptic drug treatment following surgery." Journal of Neurosurgery **75**(3): 371-373.

Radovanovic, I., A. Abou-Hamden, S. Bacigaluppi and M. Tymianski (2014). "A safety, length of stay, and cost analysis of minimally invasive microsurgery for anterior circulation aneurysms." Acta Neurochirurgica **156**(3): 493-503.

Raghunath, A., N. Bennett, A. Arimappamagan, D. I. Bhat, D. Srinivas, K. Thennarasu, R. Jamuna and S. Somanna (2016). "Impact on cognitive functions following gamma knife radiosurgery for cerebral arteriovenous malformations." Journal of Neurosciences in Rural Practice **7**(1): 28-35.

Raymond, J., T. E. Darsaut and A. J. Molyneux (2011). "A trial on unruptured intracranial aneurysms (the TEAM trial): Results, lessons from a failure and the necessity for clinical care trials." Trials **12**.

Rice, B. J., S. J. Peerless and C. G. Drake (1990). "Surgical treatment of unruptured aneurysms of the posterior circulation." Journal of Neurosurgery **73**(2): 165-173.

Rinne, J., J. Hernesniemi, M. Niskanen and M. Vapalahti (1996). "Analysis of 561 patients with 690 middle cerebral artery aneurysms: anatomic and clinical features as correlated to management outcome." Neurosurgery **38**(1): 2-11.

Rodriguez-Hernandez, A., Z. Zador, R. Rodriguez-Mena and M. T. Lawton (2013). "Distal aneurysms of intracranial arteries: application of numerical nomenclature, predilection for cerebellar arteries, and results of surgical management." World Neurosurgery **80**(1-2): 103-112.

Rohn, B., D. Haenggi, N. Etminan, M. Kunz, B. Turowski and H. J. Steiger (2014). "Epilepsy, headache, and quality of life after resection of cerebral arteriovenous malformations." Journal of Neurological Surgery **75**(4): 282-288.

Ross, J. and R. Al-Shahi Salman (2010). "Interventions for treating brain arteriovenous malformations in adults." Cochrane database of systematic reviews (Online) **7**.

Rotary RehabAid Centre. Guidelines for medical practitioners in determining fitness to drive: revised second edition. Hospital Authority. Hong Kong.

Roy, D., G. Milot and J. Raymond (2001). "Endovascular treatment of unruptured aneurysms." Stroke **32**(9): 1998-2004.

Saatci, I., S. Geyik, K. Yavuz and H. S. Cekirge (2011). "Endovascular treatment of brain arteriovenous malformations with prolonged intranidal Onyx injection technique: long-term results in 350 consecutive patients with completed endovascular treatment course." Journal of Neurosurgery **115**(1): 78-88.

Sanchez, C. E., C. S. Ogilvy and B. S. Carter (2007). "Outcomes studies in cerebrovascular neurosurgery." Neurosurgical Focus **22**(3): E11.

Serafini, A., G. L. Gigli, G. Gregoraci, F. Janes, I. Cancelli, S. Novello and M. Valente (2015). "Are Early Seizures Predictive of Epilepsy after a Stroke? Results of a Population-Based Study." Neuroepidemiology **45**(1): 50-58.

Seule, M. A., M. N. Stienen, O. P. Gautschi, H. Richter, L. Desbiolles, S. Leschka and G. Hildebrandt (2012). "Surgical treatment of unruptured intracranial aneurysms in a low-volume hospital--outcome and review of literature." Clinical Neurology & Neurosurgery **114**(6): 668-672.

Shah, S. and B. Cooper (1993). "Issues in the choice of activities of daily living assessment." Australian Occupational Therapy Journal **40**(2): 77-82.

Singapore Medical Association (2011). Medical guidelines on fitness to drive; second edition.

Solheim, O., H. Eloqayli, T. B. Muller and G. Unsgaard (2006). "Quality of life after treatment for incidental, unruptured intracranial aneurysms." Acta Neurochirurgica **148**(8): 821-830.

Sonobe, M., T. Yamazaki, M. Yonekura and H. Kikuchi (2010). "Small unruptured intracranial aneurysm verification study: SUAVe study, Japan." Stroke **41**(9): 1969-1977.
Spetzler, R. F. and N. A. Martin (1986). "A proposed grading system for arteriovenous malformations." Journal of Neurosurgery **65**(4): 476-483.

Spetzler, R. F. and N. A. Martin (1986). "A proposed grading system for arteriovenous malformations." Journal of Neurosurgery **65**(4): 476-483.

Spetzler, R. F. and F. A. Ponce (2011). "A 3-tier classification of cerebral arteriovenous malformations." Journal of Neurosurgery **114**(3): 842-849.

Stapf, C., C. S. Moy, J. Overbey, E. Moquete, M. Parides, E. Vicaut, A. J. Moskowitz and J. P. Mohr (2014). "Health-related quality of life in patients with unruptured brain avm managed with or without interventional therapy - The aruba trial." Stroke. Conference **45**(no pagination).

Starke, R. M., R. J. Komotar, B. Y. Hwang, L. E. Fischer, M. L. Otten, M. B. Merkow, M. C. Garrett, S. R. Isaacson and E. S. Connolly Jr (2008). "A comprehensive review of radiosurgery for cerebral arteriovenous malformations: Outcomes, predictive factors, and grading scales." Stereotactic and Functional Neurosurgery **86**(3): 191-199.

Steven, D. A., S. P. Lownie and G. G. Ferguson (2007). "Aneurysms of the distal anterior cerebral artery: Results in 59 consecutively managed patients." Neurosurgery **60**(2): 227-233.
Streiner, D. L. and G. R. Norman (1996). Health Measurment Scales: a practical guide to their development and use Oxford, Oxford University Press.

Sundt, T. M., Jr., S. Kobayashi, N. C. Fode and J. P. Whisnant (1982). "Results and complications of surgical management of 809 intracranial aneurysms in 722 cases. Related and unrelated to grade of patient, type of aneurysm, and timing of surgery." Journal of neurosurgery **56**(6): 753-765.

Szmuda, T. and P. Sloniewski (2011). "Early and long-term outcome of surgically treated giant internal carotid artery aneurysms-comparison with smaller aneurysms." Acta Neurochirurgica **153**(8): 1611-1619.

Thines, L., P. Bourgeois and J. P. Lejeune (2012). "Surgery for unruptured intracranial aneurysms in the ISAT and ISUIA era." Canadian Journal of Neurological Sciences **39**(2): 174-179.

Thomas, R. H. and T. A. T. Hughes (2009). ""Can I drive, doctor?" LEAN thinking may help us answer the question." Practical Neurology **9**(2): 71-79.

Thorpe, M. L., D. J. Cordato, M. K. Morgan and G. K. Herkes (2000). "Postoperative seizure outcome in a series of 114 patients with supratentorial arteriovenous malformations." Journal of Clinical Neuroscience **7**(2): 107-111.

Tilley, B. C. (2012). "Contemporary outcome measures in acute stroke research: choice of primary outcome measure and statistical analysis of the primary outcome in acute stroke trials." Stroke **43**(4): 935-937.

Towgood, K., J. A. Ogden and E. Mee (2005). "Neurological, neuropsychological, and functional outcome following treatment for unruptured intracranial aneurysms." Journal of the International Neuropsychological Society **11**(5): 522-534.

Towgood, K., J. A. Ogden and E. Mee (2005). "Psychosocial effects of harboring an untreated unruptured intracranial aneurysm." Neurosurgery **57**(5): 858-856; discussion 858-856.

van der Schaaf, I. C. M., E. H. M. D. Brilstra, G. J. E. M. D. Rinkel, P. M. P. Bossuyt and J. M. F. F. van Gijn (2002). "Quality of Life, Anxiety, and Depression in Patients With an Untreated Intracranial Aneurysm or Arteriovenous Malformation." Stroke **33**(2): 440-443.

van Dijk, J. M. C., R. J. M. Groen, M. Ter Laan, J. R. Jeltema, J. J. A. Mooij and J. D. M. Metzemaekers (2011). "Surgical clipping as the preferred treatment for aneurysms of the middle cerebral artery." Acta Neurochirurgica: 1-7.

Van Swieten, J. C., P. J. Koudstaal, M. C. Visser, H. J. A. Schouten and J. Van Gijn (1988). "Interobserver agreement for the assessment of handicap in stroke patients." Stroke **19**(5): 604-607.

Vargus-Adams, J. N. and A. Majnemer (2014). "International Classification of Functioning, Disability and Health (ICF) as a framework for change: revolutionizing rehabilitation." Journal of child neurology **29**(8): 1030-1035.

Von Der Brelie, C., M. Simon, J. Esche, J. Schramm and A. Bostrom (2015). "Seizure outcomes in patients with surgically treated cerebral arteriovenous malformations." Neurosurgery **77**(5): 762-768.

Walcott, B. P. and M. T. Lawton (2016). "The risk of seizure after surgery for unruptured intracranial aneurysms: A prospective cohort study: Comment." Neurosurgery **79**(2): 229-230.

Wang, J. Y., W. Yang, X. Ye, D. Rigamonti, A. L. Coon, R. J. Tamargo and J. Huang (2013). "Impact on seizure control of surgical resection or radiosurgery for cerebral arteriovenous malformations." Neurosurgery **73**(4): 648-655.

Ware, J. E., Kosinski, M., Bjorner, J.B., Turner-Bowker, D.M., Gandek, B., & Maruish, M.E. (2007). User's manual for the SF-36v2™ Health Survey (2nd ed.). Lincoln, RI: . Chapter 7, pp81-84, QualityMetric Incorporated.

Ware Jr, J. E., M. S. Bayliss, W. H. Rogers, M. Kosinski and A. R. Tarlov (1996). "Differences in 4-year health outcomes for elderly and poor, chronically III patients treated in HMO and fee-for-service systems: Results from the medical outcomes study." Journal of the American Medical Association **276**(13): 1039-1047.

Ware, J. E., Jr. and Kosinski, M.A. (2002). SF-36 Physical and Mental Health Summary Scales: a manual for users of Version 1. Lincoln, Rhode Island, USA, QualityMetric Incorporated.

Ware, J. E., Jr. and C. D. Sherbourne (1992). "The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection." Medical Care **30**(6): 473-483.

Wedderburn, C. J., J. van Beijnum, J. J. Bhattacharya, C. E. Counsell, V. Papanastassiou, V. Ritchie, R. C. Roberts, R. J. Sellar, C. P. Warlow and R. Al-Shahi Salman (2008). "Outcome after interventional or conservative management of unruptured brain arteriovenous malformations: a prospective, population-based cohort study." The Lancet Neurology **7**(3): 223-230.

Wiebers, D. O. (1998). "Unruptured intracranial aneurysms - Risk of rupture and risks of surgical intervention." New England Journal of Medicine **339**(24): 1725-1733.

Wiebers, D. O., J. P. Whisnant, J. Huston, 3rd, I. Meissner, R. D. Brown, Jr., D. G. Piepgras, G. S. Forbes, K. Thielen, D. Nichols, W. M. O'Fallon, J. Peacock, L. Jaeger, N. F. Kassell, G. L. Kongable-Beckman, J. C. Torner and I. International Study of Unruptured Intracranial Aneurysms (2003). "Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment." Lancet **362**(9378): 103-110.

Wilson, J. T. L., A. Hareendran, A. Hendry, J. Potter, I. Bone and K. W. Muir (2005). "Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview." Stroke **36**(4): 777-781.

Wong, J. M., J. E. Ziewacz, A. L. Ho, J. R. Panchmatia, A. H. Kim, A. M. Bader, B. G. Thompson, R. Du and A. A. Gawande (2012). "Patterns in neurosurgical adverse events: open cerebrovascular neurosurgery." Neurosurgical Focus **33**(5): E15.

Yamashiro, S., T. Nishi, K. Koga, T. Goto, D. Muta, J.-i. Kuratsu and S. Fujioka (2007). "Postoperative quality of life of patients treated for asymptomatic unruptured intracranial aneurysms." Journal of Neurosurgery **107**(6): 1086-1091.

Yamashiro, S., T. Nishi, K. Koga, T. Goto, D. Muta, J. I. Kuratsu and S. Fujioka (2007). "Postoperative quality of life of patients treated for asymptomatic unruptured intracranial aneurysms." Journal of Neurosurgery **107**(6): 1086-1091.

Yang, S. Y., S. H. Paek, D. G. Kim and H. T. (2012) Chung "Quality of life after radiosurgery for cerebral arteriovenous malformation patients who present with seizure." European Journal of Neurology.

Yeh, H. S. and M. D. Privitera (1991). "Secondary epileptogenesis in cerebral arteriovenous malformations." Archives of neurology **48**(11): 1122-1124.

Yeh, H. S., J. M. Tew Jr and M. Gartner (1993). "Seizure control after surgery on cerebral arteriovenous malformations." Journal of Neurosurgery **78**(1): 12-18.

Yue, W. (2011). "Endovascular treatment of unruptured intracranial aneurysms." Interventional Neuroradiology **17**(4): 420-424.

Zhao, J., T. Yu, S. Wang, Y. Zhao and W. Y. Yang (2010). "Surgical treatment of giant intracranial arteriovenous malformations." Neurosurgery **67**(5): 1359-1370.