Acta Neurochirurgica (2023) 165:993–1000
https://doi.org/10.1007/s00701-023-05497-7

ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ANEURYSM

Propensity-adjusted analysis of ultra-early aneurysmal subarachnoid hemorrhage treatment and patient outcomes

Stefan W. Koester[1] · Joshua S. Catapano[1] · Emmajane G. Rhodenhiser[1] · Robert F. Rudy[1] · Ethan A. Winkler[1] · Dimitri Benner[1] · Tyler S. Cole[1] · Jacob F. Baranoski[1] · Visish M. Srinivasan[1] · Christopher S. Graffeo[1] · Ruchira M. Jha[1] · Ashutosh P. Jadhav[1] · Andrew F. Ducruet[1] · Felipe C. Albuquerque[1] · Michael T. Lawton[1]

Received: 29 August 2022 / Accepted: 5 January 2023 / Published online: 27 January 2023

Abstract

Background Optimal definitive treatment timing for patients with aneurysmal subarachnoid hemorrhage (aSAH) remains controversial. We compared outcomes for aSAH patients with ultra-early treatment versus later treatment at a single large center.

Method Patients who received definitive open surgical or endovascular treatment for aSAH between January 1, 2014, and July 31, 2019, were included. Ultra-early treatment was defined as occurring within 24 h from aneurysm rupture. The primary outcome was poor neurologic outcome (modified Rankin Scale score > 2). Propensity adjustment was performed for age, sex, Charlson Comorbidity Index, Hunt and Hess grade, Fisher grade, aneurysm treatment type, aneurysm type, size, and anterior location.

Results Of the 1013 patients (mean [SD] age, 56 [14] years; 702 [69%] women, 311 [31%] men) included, 94 (9%) had ultra-early treatment. Compared with the non-ultra-early cohort, the ultra-early treatment cohort had a significantly lower percentage of saccular aneurysms (53 of 94 [56%] vs 746 of 919 [81%], $P < 0.001$), greater frequency of open surgical treatment (72 of 94 [77%] vs 523 of 919 [57%], $P < 0.001$), and greater percentage of men (38 of 94 [40%] vs 273 of 919 [30%], $P = .04$). After adjustment, ultra-early treatment was not associated with neurologic outcome in those with at least 180-day follow-up (OR = 0.86), the occurrence of delayed cerebral ischemia (OR = 0.87), or length of stay (exp(β), 0.13) ($P \geq 0.60$).

Conclusions In a large, single-center cohort of aSAH patients, ultra-early treatment was not associated with better neurologic outcome, fewer cases of delayed cerebral ischemia, or shorter length of stay.

Keywords Aneurysm · Critical care · Delayed · Subarachnoid hemorrhage · Ultra-early

Abbreviations

aSAH	Aneurysmal subarachnoid hemorrhage
CCI	Charlson Comorbidity Index
DCI	Delayed cerebral ischemia
HH	Hunt and Hess
mRS	Modified Rankin Scale

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with a mortality rate of 40% to 50% [9, 18]. The usual management for patients with ruptured aneurysms is aneurysmal occlusion (which will be referred to as "treatment") within 72 h of presentation, and current guidelines call for repair of the aneurysm "as early as possible" [4]. The International Cooperative Study found that challenges associated with delayed aneurysm surgery include significant brain swelling and the potential for clinical worsening [12]. Since this study and another [11] were published, the standard at most centers has been to treat patients with ruptured aneurysms within 24 h of admission (ultra-early treatment). Some surgeons advocate for ultra-early treatment to reduce the risk of aneurysmal rebleeding, raising the potential utility of ultra-early treatment timing for these patients. With the ambiguity of a treatment timing paradigm and discrepancies

This article is part of the Topical Collection on *Vascular Neurosurgery - Aneurysm*

✉ Michael T. Lawton
Neuropub@barrowneuro.org

[1] Department of Neurosurgery, Neuroscience Publications, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd, Phoenix, AZ 85013, USA

in protocols among hospitals, the optimal definitive timing for treating patients with aSAH remains controversial. Additionally, the logistics of planning definitive surgical care within the hospital system after critical care and resuscitation may not be possible in all acute care settings, calling into question the generalizability of an ultra-early treatment recommendation.

Evidence supporting a higher incidence of rebleeding events among those not receiving treatment immediately after admission has been provided by Park et al. [20], who demonstrated a higher rate of rebleeding among those who were treated within 72 h as opposed to immediately (7.4% vs 2.1%, $P=0.003$) in an analysis of 576 total patients. The same study also showed that immediate treatment led to better outcomes [20]. Since then, studies have reported varying findings regarding rebleeding and outcomes after immediate treatment [3, 7, 16, 19, 22, 27]. A recent retrospective study of 575 patients by Buscot et al. [2] showed that early treatment (within 12.5 h of presentation) was associated with discharge home and aSAH survival at 12 months. Critical care advances, such as blood pressure control, coagulopathy reversal, neurologic intensive care unit services, and pain and emesis control at admission, may reduce rebleeding events and, therefore, the morbidity and mortality associated with these events. This analysis compared outcomes for aSAH patients with ultra-early treatment versus later treatment at a single large center.

Methods

This retrospective cohort study was approved by the St. Joseph's Hospital and Medical Center Institutional Review Board, Phoenix, Arizona, with the requirement for informed consent waived due to the low risk to patients and the study's retrospective nature. All patients in the Post–Barrow Ruptured Aneurysm Trial (PBRAT) database treated for an aSAH from January 1, 2014, to July 31, 2019, at a single quaternary-care center were retrospectively analyzed. Patients who experienced rerupture or died before transfer or transport were not included in the analysis. Inclusion criteria included the availability of initial rupture time and variables necessary to diagnose delayed cerebral ischemia (DCI). DCI-related infarction was defined as a cerebral infarction identified by computed tomography or magnetic resonance imaging or proven on autopsy after ruling out infarctions directly related to the procedure [25]. Delay of treatment was defined as the difference between the time of rupture and time of definitive treatment (open microsurgery or endovascular). Patients who did not receive definitive treatment were excluded; this excluded patients with a Glasgow Coma Scale score of 3 without brainstem reflexes or those from whom treatment was withheld on the basis of family request. An external ventricular drain was placed in patients with any sign of hydrocephalus.

Patients were grouped into two cohorts on the basis of whether treatment was received within 24 h of rupture (ultra-early treatment) or more than 24 h after rupture (non-ultra-early treatment). Information gathered included patient age, sex, Hunt and Hess (HH) grade, Fisher grade, Charlson Comorbidity Index (CCI), Glasgow Coma Scale score at patient presentation, aneurysm size, aneurysm location, and treatment type. The Fisher grade used in this case is the Barrow Neurological Institute (BNI) Fisher grade [28]. The primary outcome was poor neurologic outcome, defined as a modified Rankin Scale (mRS) score greater than 2 at last follow-up. The mRS score was determined by in-patient visits, follow-up phone-communication, or patient letters by a single senior member of the research faculty. This group was also examined for those with at least 180 days of follow-up. Secondary outcomes included DCI-related infarction occurrence, length of hospital stay, and vasospasm. Mortality was defined as death during hospital stay or at follow-up. Vasospasm was defined as sudden constriction of a vessel evidenced by angiography, transcranial doppler, and computed tomography or magnetic resonance imaging. The data that support the findings of this study are available from the corresponding author upon reasonable request and institutional review board approval, as applicable.

Data are presented as a mean with standard deviation (SD) or number of patients with percentage. Statistical analyses, including data aggregation, analysis, and propensity adjustment, were performed using R, version 4.0.1 (R Foundation for Statistical Computing). Interval variables, such as demographic and clinical characteristics of patients, were analyzed with an independent 2-sample t test, and categorical variables were calculated using a χ^2 test. Variables that compared medians were calculated using Mood's median test. A 2-sided $P<0.05$ was considered statistically significant. A propensity score was computed from baseline covariates, including age, sex, treatment type (open surgery versus endovascular treatment), CCI ≥ 4, HH grade ≥ 4, Fisher grade ≥ 4, aneurysm type, aneurysm size, and anterior location.

Results

During the study period, 1013 patients met the inclusion criteria and were included in the final analysis. Among these patients, 94 (9%) were treated in an ultra-early fashion, and 919 (97%) were treated more than 24 h after rupture (Table 1). A significantly greater proportion of patients were male in the ultra-early treatment group (38 of 94 [40%]) compared with the non-ultra-early treatment group (273 of 919 [30%]) ($P=0.04$).

Table 1 Characteristics of patients treated for aneurysmal subarachnoid hemorrhage by time to treatment

Characteristic	Non-ultra-early treatment ($N=919$)	Ultra-early treatment ($N=94$)	P value*
Age, year, mean (SD)	56 (14)	56 (15)	.84
Sex			.04
Male	273 (30)	38 (40)	
Female	646 (70)	56 (60)	
Anterior aneurysm location	733 (80)	66 (71)	.06
Aneurysm location, artery			> .99
Internal carotid	74 (8)	18 (19)	
Middle cerebral	135 (15)	12 (13)	
Vertebral	32 (4)	8 (9)	
Anterior choroidal	8 (1)	0 (0)	
Anterior cerebral	40 (4)	8 (9)	
Anterior communicating	299 (33)	15 (16)	
Posterior communicating	177 (19)	13 (14)	
Posterior cerebral	23 (3)	2 (2)	
Superior cerebellar	15 (2)	4 (4)	
Basilar	61 (7)	5 (5)	
Anterior inferior cerebellar	0 (0)	1 (1)	
Posterior inferior cerebellar	52 (6)	7 (8)	
Aneurysm size, mm, mean (SD)	6.4 (3.6)	5.3 (4.1)	
Aneurysm type			< .001
Unknown, other	4 (0.4)	2 (2.1)	
Saccular	746 (81)	53 (56)	
Fusiform	110 (12)	10 (11)	
Dissecting	42 (4.6)	15 (16)	
Blister	17 (1.8)	14 (15)	
Glasgow Coma Scale score at admission, mean (SD)	11.7 (3.8)	11.6 (3.9)	.70
Hunt and Hess grade, median (IQR)	3 (2–4)	2 (2–3.75)	.91
Hunt and Hess grade			.60
1	71 (7.7)	7 (7.4)	
2	317 (34)	35 (37)	
3	286 (31)	28 (30)	
4	153 (17)	11 (12)	
5	92 (10)	13 (14)	
Hunt and Hess grade ≥ 4	245 (27)	24 (26)	.91
Fisher grade, median (IQR)	4 (3–4)	4 (4–4)	.99
Fisher grade			.82
0	1 (0.1)	0 (0)	
1	22 (2.4)	3 (3.2)	
2	83 (9.0)	6 (6.4)	
3	137 (15)	14 (15)	
4	675 (73)	71 (76)	
5	1 (0.1)	0 (0)	
Fisher grade ≥ 4	676 (74)	71 (76)	.77
Charlson Comorbidity Index, mean (SD)	1.64 (1.50)	1.80 (1.96)	.67
Charlson Comorbidity Index ≥ 4	104 (11)	11 (12)	> .99
External ventricular drain	757 (82)	76 (81)	.71
Intraparenchymal hemorrhage	211 (23)	18 (19)	.38
Rerupture	27 (2.9)	3 (3.2)	.75
Length of stay, day, mean (SD)	19 (9)	19 (9)	.89
Open surgical treatment	523 (57)	72 (77)	< .001

Table 1 (continued)

Characteristic	Non-ultra-early treatment ($N=919$)	Ultra-early treatment ($N=94$)	P value*
Days to last follow-up, mean (SD)	737 (1201)	708 (1200)	.73
Follow-up > 180 days	355 (39)	36 (38)	> .99
Delayed cerebral ischemia	333 (36)	34 (36)	> .99
Vasospasm	651 (71)	64 (68)	.66
Retreatment	48 (5)	2 (2)	.31
Modified Rankin Scale score			
At discharge, median (IQR)	4 (3–5)	4 (3–5)	.99
At last follow-up, median (IQR)	3 (1–5)	3 (1–4)	.85
> 2 at last follow-up	460 (50)	49 (52)	.78
> 2 in those with at least 180 days follow-up	85/355 (24)	8/36 (22)	.98
Mortality	127 (14)	10 (11)	.39

Data are presented as number (%) of patients unless otherwise noted

*Statistical tests performed: Wilcoxon rank-sum test, χ^2 test of independence, Mood's Median test, and Fisher's exact test

The frequency of anterior circulation aneurysms was similar for the ultra-early and non-ultra-early treatment groups (66 of 94 [71%] vs 733 of 919 [80%], $P=0.06$). However, the ultra-early treatment group had a significantly lower proportion of saccular aneurysms (53 [56%] vs 746 [81%], $P<0.001$), and a significantly greater proportion of the ultra-early treatment group received open microsurgical treatment (72 [77%] vs 523 [57%], $P<0.001$). Hunt and Hess grade, Fisher grade, CCI, and length of follow-up were comparable between the two cohorts ($P\geq0.60$). No significant difference was seen in the proportion of intraparenchymal hemorrhage between the two treatment groups ($P=0.38$; Table 1).

When the analysis was restricted to patients receiving open microsurgical treatment ($n=595$, Supplemental Table 1) or to patients undergoing endovascular treatment ($n=418$, Supplemental Table 2), the results were similar to those obtained for the total population. Among patients with open microsurgical treatment, clipped aneurysms were significantly smaller in the ultra-early treatment group ($n=72$, mean 5.2 [4.5] mm) than in the non-ultra-early treatment group ($n=523$, 6.3 [4.0] mm) ($P<0.001$). Among patients undergoing open microsurgery, the proportion of intraparenchymal hemorrhage was significantly greater among those with non-ultra-early treatment versus those with ultra-early treatment (150 [29%] vs 12 [17%], $P=0.03$). Among those with endovascular treatment, the mean (SD) aneurysm size was 5.4 (3.0) mm in the ultra-early treatment group ($n=22$) vs 6.6 (3.0) mm in the non-ultra-early treatment group ($n=396$) ($P=0.06$). Within the endovascular treatment group, 4 of 22 (18%) patients with ultra-early treatment and 159 of 396 (40%) patients without ultra-early treatment had follow-up greater than 180 days ($P=0.07$).

The rates of vasospasm, DCI-related infarction, length of hospital stay, and retreatment were not significantly different between the ultra-early and non-ultra-early treatment cohorts (Table 1, $P\geq0.23$), and no differences in these parameters were found when patients were stratified by treatment type (Supplemental Tables 1 and 2). Ultra-early treatment was not associated with a greater median (IQR) mRS score at last follow-up (3 [4, 3, 2, 1] vs 3 [4, 3, 2, 1, 5], $P=0.85$) or greater proportion of patients with poor neurologic outcome (mRS > 2) at last follow-up (49 of 94 [52%] vs 460 of 919 [50%], $P=0.78$).

After propensity adjustment, ultra-early treatment was not associated with poor neurologic outcome (mRS score > 2) at final follow-up (odds ratio [OR], 1.05 [95% CI, 0.63–21.74], $P=0.85$) or in those with at least 180-day follow-up (OR, 0.86 [95% CI, 0.31–2.15], $P=0.76$) (Table 2), frequency of DCI-related infarction (OR, 0.87 [95% CI, 0.53–1.42],

Table 2 Propensity-adjusted outcome for mRS score greater than 2 in those with at least 180-day follow-up

Characteristic	OR	95% CI	P value
Ultra-early treatment	0.86	0.31–2.15	.76
Age, year	1.01	0.98–1.03	.59
Male sex	0.99	0.51–1.90	.98
CCI ≥ 4	6.26	2.56–15.9	< .001
HH ≥ 4	1.93	1.06–3.49	.031
FG ≥ 4	1.19	0.62–2.33	.61
Open surgical treatment	0.95	0.43–2.14	.89
Aneurysm type	1.10	0.44–2.63	.84
Aneurysm size	1.03	0.95–1.11	.52
Anterior location	0.51	0.26–0.97	.041
Propensity score	0.82	0.00–5.50	.97

CCI, Charlson Comorbidity Index; *CI*, confidence interval; *FG*, Fisher grade; *HH*, Hunt and Hess grade; *mRS*, modified Rankin Scale; *OR*, odds ratio

Table 3 Propensity-adjusted outcome for delayed cerebral ischemia occurrence

Characteristic	OR	95% CI	*P* value
Ultra-early treatment	0.87	0.53–1.42	.60
Age, year	1.00	0.98–1.01	.48
Male sex	0.77	0.54–1.08	.14
CCI ≥ 4	0.94	0.58–1.51	.80
HH ≥ 4	2.53	1.86–3.45	< .001
FG ≥ 4	1.63	1.15–2.33	.007
Open surgical treatment	0.93	0.62–1.39	.72
Aneurysm type	0.91	0.56–1.47	.76
Aneurysm size	1.05	1.01–1.10	.03
Anterior location	0.91	0.64–1.30	.58
Propensity score	15.9	0.15–1.68	.27

CCI, Charlson Comorbidity Index; *CI*, confidence interval; *FG*, Fisher grade; *HH*, Hunt and Hess grade; *OR*, odds ratio

Table 4 Propensity-adjusted outcome for length of hospital stay

Characteristic	Exp(**β**)	95% CI	*P* value
Ultra-early treatment	0.13	− 1.85 to 2.12	.90
Age, year	− 0.03	− 0.08 to 0.02	.20
Male sex	− 1.33	− 2.70 to 0.04	.052
CCI ≥ 4	− 1.39	− 3.34 to 0.56	.16
HH ≥ 4	1.76	0.46–3.06	.007
FG ≥ 4	3.97	2.62–5.31	< .001
Open surgical treatment	1.09	− 0.56 to 2.73	.20
Aneurysm type	0.21	− 1.78 to 2.20	.87
Aneurysm size	− 0.06	− 0.24 to 0.12	.54
Anterior location	− 0.65	− 2.12 to 0.81	.39
Propensity score	− 1.98	− 21.3 to 17.4	.87

CCI, Charlson Comorbidity Index; *CI*, confidence interval; *FG*, Fisher grade; *HH*, Hunt and Hess grade

P = 0.60) (Table 3), or length of stay (exp(β), 0.13 [95% CI, − 1.85 to 2.12], *P* = 0.90) (Table 4).

Discussion

Although guidelines recommend that a ruptured aneurysm be treated as early as possible for all grades of aSAH [4, 23], it remains unclear what treatment timeline is best for patient outcomes. This study found no association between ultra-early treatment of ruptured aneurysms, defined as treatment within 24 h of reported hemorrhage, and neurologic outcome, occurrence of DCI-related infarction, or length of hospital stay. If ultra-early treatment is not associated with better outcomes, it may be possible to allocate more time to surgical planning before aSAH treatment, which should be tailored to patient and aneurysm characteristics and hospital resources.

Evidence in support of early treatment

Extensive work suggests better outcomes at either discharge or clinical follow-up for patients treated early with respect to the time of rupture. Oudshoorn et al. [19] found ultra-early treatment (within 24 h) associated with better outcomes at clinical follow-up in a literature review but not in their own clinical cohort of 1238 patients. Sonig et al. [22] found better outcomes at discharge and lower hospital costs among 17,412 patients treated within 24 h using the National (Nationwide) Inpatient Sample database, even after a multivariate regression. Chen et al. [3] reported that, among 18 patients with poor-grade aneurysms and intracerebral hematoma, 4 of 15 patients treated within 24 h had improved outcomes, compared to 0 of 3 patients treated after 24 h, as measured by Glasgow Outcome Scale score at follow-up. Wong et al. [29] found improved clinical outcomes among patients treated within 24 h in a cohort of 96 patients with poor-grade aneurysms (OR, 2.4). Rawal et al. [21] found better outcomes associated with ultra-early endovascular treatment of aSAH. He et al. [8] analyzed 60 patients and found that, although patients who received ultra-early treatment had higher World Federation of Neurosurgical Societies grade and brain herniation, postoperative complications and outcomes (as measured by mRS at follow-up) were similar to those among non-early patients, which suggested a benefit of treatment within 24 h. Zhao et al. [30] conducted a meta-analysis and found that treatment within 48 h was associated with improved clinical outcomes among patients with poor-grade aSAHs.

Evidence against early treatment

On the other hand, some studies have questioned the benefits of ultra-early aSAH treatment because of its association with increased risks, especially increased periprocedural risks [14, 31]. Notably, Wan et al. [27] analyzed 5362 patients treated for aSAH with concurrent intracranial hemorrhage and found worse outcomes among patients treated within 6 h of rupture. Han et al. [7] conducted a review and meta-analysis of ultra-early treatment for poor-grade aSAH (as defined by HH grade IV or V) across 14 studies. They evaluated the effect of ultra-early treatment on death and functional outcomes (as defined by mRS or Glasgow Outcome Scale scores) and found no significant difference in functional outcomes or mortality associated with ultra-early treatment. However, ultra-early treatment did prevent preoperative rebleeding [16]. Because rebleeding is a predictor of poor outcome following aSAH [6, 24, 26] and occurs more commonly among patients with poor HH grade [14], this

hints at a benefit of ultra-early treatment. Interestingly, ultra-early treatment has been associated with poor HH grade at admission [29, 8]. Han et al. [7] noted that patients with brain herniation are more likely to receive ultra-early treatment, and therefore a selection bias may have prevented a statistically significant favorable finding. Although Han et al. [7] excluded patients with lower HH grades (I, II, and III), our study accounts for HH scores as part of our propensity adjustment to address this selection bias. Although our study did not find a significant benefit associated with ultra-early treatment, we do not advocate a substantial delay in treating patients with rupture. The mean (SD) time from rupture to treatment in our cohort was 1.68 (3.32) days. Additional analysis on the optimal timeline for treatment of ruptured aneurysms is needed to help elucidate practice guidelines.

Ultra-early patient demographics

The percentage of patients treated within 24 h varies between studies, as does the presentation of these patients. In our study, 9% (94 of the 1013) were treated within 24 h. This percentage is similar to that given in Akinci et al. [1], who reported that, among 580 patients studied, 12.1% of patients were treated ultra-early, but it is much smaller than the percentage given in the National (Nationwide) Inpatient Sample database, which reported that 36.4% of patients were treated within 24 h [22]. Koopman et al. [13] found that irregular aneurysm shape was an independent predictor of rebleeding within 24 h. Similarly, our analysis found a lower percentage of saccular aneurysms in the ultra-early treatment group.

Vasospasm

We did not observe a relationship between ultra-early treatment and decreased vasospasm, as seen by D'Andrea et al. [5], but this may be because the relationship exists only for a shorter time frame. D'Andrea and colleagues observed a lower incidence of vasospasm among patients treated within 6 h compared to more than 6 h after rupture [5]. They conducted a retrospective analysis of patients treated within 6 h and patients treated within 12 h and found significant differences in the incidence of postoperative vasospasm, incidence of postoperative hydrocephalus, and clinical outcomes (as measured by Glasgow Outcome Scale–Extended score) at 1-year follow-up, but they found no differences between the cohorts at discharge. Although it should be noted that D'Andrea et al. [5] did not adjust for HH grade, CCI, or other potential confounding variables, their results suggest a potential explanation of why our results showed no significant difference between patients treated within 24 h and more than 24 h after rupture, which is that the 24-h timeframe is not specific enough. A prior study by Latorre et al. has shown that asymptomatic vasospasm in ruptured aneurysm patients is not associated with an increase in poor outcome (mRS > 3) in 175 consecutive patients [15]. Detection of vasospasm is still of importance as it is not clear which vasospasm events could precipitate DCI, and a significant possibility remains that vasospasm could lead to subclinical deficits that standard neurological exams do not detect.

Future directions

The discordance among the literature on the ideal treatment timeline for aSAH patients, including the insignificant results of the present study, suggest that factors difficult to quantify could be responsible for outcomes associated with treatment timeline. The results of this study emphasize immediate stabilization and optimization of the airway, breathing, and circulation of the patient followed by management of intracranial pressure, which may involve placement of an external ventricular drain or decompressive surgery. Once the patient is stable, prompt transfer to a neurosurgical center for definitive treatment should be undertaken. The circumstances that delay the process to ultra-fast treatment may include intraparenchymal hemorrhage with mass effect and poor neurological examination results, prompting more intensive critical care.

Limitations

Numerous studies at multiple centers have investigated the relationship between ultra-early and early aneurysm treatment and patient outcomes. The most recent literature and our study classify ultra-early treatment as occurring within 24 h [7, 16, 1, 8]. However, it should be noted that some studies define ultra-early treatment as occurring within 48 h [30, 17] and early treatment as occurring within 72 h [1], whereas others define ultra-early treatment as occurring within 6 h [27, 5, 10] and define early treatment as occurring within12 h [5]. Studies also vary with respect to the timeline for evaluating outcome; some studies evaluate outcomes at hospital discharge, whereas others assess follow-up outcomes. There is no protocolized fashion that guides our determination of timing of definitive surgical treatment, so treatment timing was made by the on-call physician for patients in this study. If a bypass was needed as part of definitive treatment and the patient was admitted during the weekend, treatment was delayed until the primary team could be present. This factor is a major limitation to this study and inherent to its retrospective design. The critical care of patients is individualized, and no specific protocol exists at our institution that would systematically deviate from stabilization and optimization of the airway, breathing, and circulation along with management

of intracranial pressure with an external ventricular drain or decompression surgery.

Because of its retrospective nature, this study has limitations inherent in reviewing previously collected data, including both observer bias and interpretation bias. Analysis was not performed on medical comorbidities or hospital complications. The actual timing of rupture is nearly impossible to know, and the best estimation was made using the patient's or family's description of precipitating events and symptoms to determine the ictus. Data pertaining to patients who experienced rerupture and died before transfer or transport were not included in this study, leading to selection bias. Bias may also be introduced by not having a standardized follow-up period. Although this is difficult to achieve, the statistically insignificant follow-up periods between cohorts may show that this is not a major confounding variable in the analyses, but it still very well could be. To further explore this, we analyzed how many patients had at least 180 days of follow-up. Additionally, the percentage of patients in our cohort who received ultra-early treatment (9%) is relatively small, and open surgical treatment is more heavily represented among such cases, leading to a potential bias in treatment type. Oftentimes, higher intracranial pressures have an effect on whether surgical intervention is done more urgently versus not, and we were not able to account for this in our cohorts.

Conclusion

The association between ultra-early treatment of aSAH and rebleeding and patient outcomes has been controversial in the literature. Patients who received ultra-early treatment at our center experienced no differences in outcome compared with those who did not receive ultra-early treatment. Because our study found a lack of beneficial effect of ultra-fast treatment on outcomes in aSAH, stabilization should be prioritized with subsequent transfer to a tertiary center for definitive care.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00701-023-05497-7.

Acknowledgements We thank the staff of Neuroscience Publications at Barrow Neurological Institute for assistance with manuscript preparation.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by S. W. Koester and E. G. Rhodenhiser. The first draft of the manuscript was written by S. W. Koester and E. G. Rhodenhiser, and all authors commented on further versions of the manuscript. All authors read and approved the final manuscript.

Data Availability The data utilized for this study consist of individual patient data from a single center and are not publicly available. A release of the de-identified data may be requested if the authors are contacted directly.

Declarations

Ethical approval This retrospective cohort study was approved by the St. Joseph's Hospital and Medical Center Institutional Review Board, Phoenix, Arizona, with the requirement for informed consent waived due to the low risk to patients and the study's retrospective nature.

Conflict of interest The authors declare no competing interests.

References

1. Akinci AT, Akturk Y, Tutunculer B, Orakdogen M, Simsek O (2021) The effects of the early and ultra-early intervention on the outcome in aneurysmatic subarachnoid hemorrhage. Ulus Travma Acil Cerrahi Derg 27:449–456
2. Buscot MJ, Chandra RV, Maingard J, Nichols L, Blizzard L, Stirling C, Smith K, Lai L, Asadi H, Froelich J, Reeves MJ, Thani N, Thrift A, Gall S (2022) Association of onset-to-treatment time with discharge destination, mortality, and complications among patients with aneurysmal subarachnoid hemorrhage. JAMA Netw Open 5:e2144039
3. Chen J, Zhu J, He J, Wang Y, Chen L, Zhang C, Zhou J, Yang L (2016) Ultra-early microsurgical treatment within 24 h of SAH improves prognosis of poor-grade aneurysm combined with intracerebral hematoma. Oncol Lett 11:3173–3178
4. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P, Stroke AHA, C, Council on Cardiovascular R, Intervention, Council on Cardiovascular N, Council on Cardiovascular S, Anesthesia, Council on Clinical C, (2012) Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 43:1711–1737
5. D'Andrea G, Picotti V, Familiari P, Barbaranelli C, Frati A, Raco A (2020) Impact of early surgery of ruptured cerebral aneurysms on vasospasm and hydrocephalus after SAH: our preliminary results. Clin Neurol Neurosurg 192:105714
6. Galea JP, Dulhanty L, Patel HC, Uk IS, Hemorrhage Database C (2017) Predictors of outcome in aneurysmal subarachnoid hemorrhage patients: observations from a multicenter data set. Stroke 48:2958–2963
7. Han Y, Ye F, Long X, Li A, Xu H, Zou L, Yang Y, You C (2018) Ultra-early treatment for poor-grade aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. World Neurosurg 115:e160–e171
8. He JQ, Chen JH, Zhu J, Chen L, Zhang CL, Yang LK, Wang YH, Zou J, Hu X (2015) Prognosis of ultra-early microsurgery combined with extraventricular drainage in patients with poor-grade aneurysms. Int J Clin Exp Med 8:9723–9729
9. Hop JW, Rinkel GJ, Algra A, van Gijn J (1997) Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke 28:660–664
10. Kaneko J, Tagami T, Unemoto K, Tanaka C, Kuwamoto K, Sato S, Tani S, Shibata A, Kudo S, Kitahashi A, Yokota H (2019) Functional outcome following ultra-early treatment for ruptured aneurysms in patients with poor-grade subarachnoid hemorrhage. J Nippon Med Sch 86:81–90

11. Kassell NF, Torner JC (1983) Aneurysmal rebleeding: a preliminary report from the cooperative aneurysm study. Neurosurg 13:479–481
12. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL (1990) The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: overall management results. J Neurosurg 73:18–36
13. Koopman I, Greving JP, van der Schaaf IC, van der Zwan A, Rinkel GJ, Vergouwen MD (2019) Aneurysm characteristics and risk of rebleeding after subarachnoid haemorrhage. Eur Stroke J 4:153–159
14. Laidlaw JD, Siu KH (2003) Poor-grade aneurysmal subarachnoid hemorrhage: outcome after treatment with urgent surgery. Neurosurg 53:1275–1280
15. Latorre JG, Lodi Y, El-Zammar Z, Devasenapathy A (2011) Is asymptomatic vasospasm associated with poor outcome in subarachnoid hemorrhage? Neurohospitalist 1:165–171
16. Linzey JR, Williamson C, Rajajee V, Sheehan K, Thompson BG, Pandey AS (2018) Twenty-four-hour emergency intervention versus early intervention in aneurysmal subarachnoid hemorrhage. J Neurosurg 128:1297–1303
17. Liu A, Peng T, Qian Z, Li Y, Jiang C, Wu Z, Yang X (2015) Enterprise stent-assisted coiling for wide-necked intracranial aneurysms during ultra-early (48hours) subarachnoid hemorrhage: a single-center experience in 59 consecutive patients. J Neuroradiol 42:298–303
18. Lovelock CE, Rinkel GJ, Rothwell PM (2010) Time trends in outcome of subarachnoid hemorrhage: population-based study and systematic review. Neurol 74:1494–1501
19. Oudshoorn SC, Rinkel GJ, Molyneux AJ, Kerr RS, Dorhout Mees SM, Backes D, Algra A, Vergouwen MD (2014) Aneurysm treatment <24 versus 24–72 h after subarachnoid hemorrhage. Neurocrit Care 21:4–13
20. Park J, Woo H, Kang DH, Kim YS, Kim MY, Shin IH, Kwak SG (2015) Formal protocol for emergency treatment of ruptured intracranial aneurysms to reduce in-hospital rebleeding and improve clinical outcomes. J Neurosurg 122:383–391
21. Rawal S, Alcaide-Leon P, Macdonald RL, Rinkel GJ, Victor JC, Krings T, Kapral MK, Laupacis A (2017) Meta-analysis of timing of endovascular aneurysm treatment in subarachnoid haemorrhage: inconsistent results of early treatment within 1 day. J Neurol Neurosurg Psychiatry 88:241–248
22. Sonig A, Shallwani H, Natarajan SK, Shakir HJ, Hopkins LN, Snyder KV, Siddiqui AH, Levy EI (2018) Better outcomes and reduced hospitalization cost are associated with ultra-early treatment of ruptured intracranial aneurysms: a US nationwide data sample study. Neurosurg 82:497–505
23. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G, European Stroke Organization (2013) European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis 35:93–112
24. Stienen MN, Germans M, Burkhardt JK, Neidert MC, Fung C, Bervini D, Zumofen D, Rothlisberger M, Marbacher S, Maduri R, Robert T, Seule MA, Bijlenga P, Schaller K, Fandino J, Smoll NR, Maldaner N, Finkenstadt S, Esposito G, Schatlo B, Keller E, Bozinov O, Regli L, Swiss SOSSG (2018) Predictors of in-hospital death after aneurysmal subarachnoid hemorrhage: analysis of a nationwide database (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemorrhage]). Stroke 49:333–340
25. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, Macdonald RL, Diringer MN, Broderick JP, Dreier JP, Roos YB (2010) Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke 41:2391–2395
26. Vergouwen MD, Jong-Tjien-Fa AV, Algra A, Rinkel GJ (2016) Time trends in causes of death after aneurysmal subarachnoid hemorrhage: a hospital-based study. Neurol 86:59–63
27. Wan A, Jaja BN, Schweizer TA, Macdonald RL, on behalf of the SAHIT collaboration (2016) Clinical characteristics and outcome of aneurysmal subarachnoid hemorrhage with intracerebral hematoma. J Neurosurg 125:1344–1351
28. Wilson DA, Nakaji P, Abla AA, Uschold TD, Fusco DJ, Oppenlander ME, Albuquerque FC, McDougall CG, Zabramski JM, Spetzler RF (2012) A simple and quantitative method to predict symptomatic vasospasm after subarachnoid hemorrhage based on computed tomography: beyond the Fisher scale. Neurosurg 71:869–875
29. Wong GK, Boet R, Ng SC, Chan M, Gin T, Zee B, Poon WS (2012) Ultra-early (within 24 hours) aneurysm treatment after subarachnoid hemorrhage. World Neurosurg 77:311–315
30. Zhao B, Rabinstein A, Murad MH, Lanzino G, Panni P, Brinjikji W (2017) Surgical and endovascular treatment of poor-grade aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurosurg Sci 61:403–415
31. Zipfel GJ (2015) Ultra-early surgery for aneurysmal subarachnoid hemorrhage. J Neurosurg 122:381–382