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ORIGINAL ARTICLE

Outcomes following poor-grade aneurysmal subarachnoid haemorrhage: a prospective observational study

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Abstract

Background Up to 35% of aneurysmal subarachnoid haemorrhage (aSAH) cases may present as poor grade, defined as World Federation of Neurosurgical Societies (WFNS) grades IV and V. In this study, we evaluate functional outcomes and prognostic factors.

Methods This prospective study included all patients referred to a national, centralized neurosurgical service with a diagnosis of poor-grade aSAH between 01/01/2016 and 31/12/2019. Multivariable logistic regression models were used to estimate probability of poor functional outcomes, defined as a Glasgow Outcome Scale (GOS) of 1–3 at 3 months.

Results Two hundred fifty-seven patients were referred, of whom 116/257 (45.1%) underwent treatment of an aneurysm, with 97/116 (84%) treated within 48 h of referral. Median age was 62 years (IQR 51–69) with a female predominance (167/257, 65%). Untreated patients tended to be older; 123/141 (87%) had WFNS V, 60/141 (45%) unreactive pupils and 21/141 (16%) circulatory arrest. Of all referred patients, poor outcome occurred in 169/230 (73.5%). Unreactive pupils or circulatory arrest conferred a universally poor prognosis, with mortality in 55/56 (98%) and 19/19 (100%), respectively. The risk of a poor outcome was 14.1% (95% CI 4.5–23.6) higher in WFNS V compared with WFNS IV. Age was important in patients without circulatory arrest or unreactive pupils, with risk of a poor outcome increasing by 1.8% per year (95% CI 1–2.7). In patients undergoing aneurysm securement, 48/101 (47.5%) had a poor outcome, with age, rebleeding, vasospasm and cerebrospinal fluid (CSF) diversion being important prognosticators. The addition of serum markers did not add significant discrimination beyond the clinical presentation.

Conclusions The overall outcomes of WFNS IV and V aSAH remain poor, mainly due to the devastating effects of the original haemorrhage. However, in patients selected for aneurysm securement, good outcomes can be achieved in more than half of patients. Age, pre-intervention rebleeding, vasospasm, and CSF diversion are important prognostic factors.

Keywords Subarachnoid haemorrhage · Intracranial aneurysm · ASAH

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) is a devastating neurological event characterized by the rupture of an intracranial aneurysm with bleeding into the subarachnoid space [58]. SAH accounts for 5–10% of all strokes [37, 58], with an estimated worldwide incidence of 7.9 cases per 100,000 patient-years [15]. Up to 35% of cases present as poor-grade [8, 48, 56], most commonly defined via the World Federation of Neurosurgical Societies (WFNS) grade [2] as grades IV and V, corresponding to a Glasgow Coma Scale of less than 13.

This historically carries a poor prognosis, with poor functional outcomes in a majority of patients and a mortality rate

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of up to 50% [28, 33, 39, 54, 60]. While early intervention has been well established in good-grade aSAH, patients with poor-grade aSAH have been under-represented in clinical trials [67], and there remains uncertainty as to which patients, if any, will benefit from early treatment. Traditionally, patients with poor-grade presentations are often observed for improvement before definitive aneurysm treatment. However, more recent evidence has demonstrated heterogeneity in clinical presentation and subsequent outcome within this group [50]. Some series have even demonstrated improving outcomes in patients treated aggressively and early [22, 23].

Accurate prognostication of patients with poor grade aSAH would allow appropriate patient selection for early intervention, facilitating treatment of those patients likely to improve with a significant possibility of a good functional outcome. Therefore, in this study, we evaluate prognostic factors associated with longitudinal functional outcome in an unselected cohort of patients with poor-grade SAH presenting to a national, centralized neurosurgical service.

Methods

This prospective, observational study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [63] and set in a centralized neurosurgical service serving a catchment of approximately 3.9 million people. All patients with aSAH within this catchment are referred to the National Neurosurgical Centre, with most transferred for aneurysm intervention [8]. Demographic, clinical and radiological details of all patients referred to the national neurosurgical centre in Ireland between 01/01/2016 and 31/12/2019 were prospectively recorded. This included all patients referred, including those not accepted for treatment. We identified patients who died pre-hospital via the Central Statistics Office (CSO).

Participants

Patients were diagnosed with aSAH via the presence of subarachnoid blood on computed tomography (CT) and/or xanthochromic cerebrospinal fluid (CSF) on lumbar puncture. The presence of cerebral aneurysms was diagnosed with CT angiography (CTA) and/or digital subtraction angiography (DSA). Patients aged ≥ 18 years with SAH and a poor-grade presentation defined by WFNS grade IV or V at the time of referral were included.

Variables

We prospectively recorded demographic, clinical, radiological and treatment details including age, sex, WFNS grade [2], pupillary reactivity, cardiorespiratory arrest, pre-intervention aneurysm rebleeding, Fisher grade [16], aneurysm location, method of aneurysm repair, need for cerebrospinal fluid (CSF) diversion and symptomatic vasospasm. We also recorded several serum markers, including C-reactive protein (CRP), total protein and white cell count (WCC), measured on admission. Outcomes were assessed using the Glasgow Outcome Score (GOS) [30] at discharge and at 3 months by nurse specialists. The primary outcome was the GOS at 3 months. We considered a GOS of 1–3 to be a poor outcome.

Statistical analysis

All analysis was performed in *R v4.2.2* [51] (The R Foundation, Vienna, Austria). First, we fit a multivariable logistic regression model for a poor 3-month outcome in the entire cohort of patients with poor-grade ASAH. Variables included were those a priori assumed to moderate prognosis [24], including age, WFNS grade, Fisher grade, pupil reactivity, circulatory arrest and pre-intervention rebleeding. We used predictions to estimate the risk of a poor outcome under various combinations of risk factors and generated UpSet [6] plots. In these models, missing data was minimal and we considered that data may be missing not-at-random (MNAR) [46]. Therefore, this analysis used a listwise deletion approach.

We then fit a second multivariable logistic regression model in patients accepted for transfer. We included factors a priori expected to influence prognosis following admission including need for CSF diversion, symptomatic vasospasm and further rebleeding, adjusted for age, WFNS and Fisher grades. We additionally fit proportional odds models, in which the variable in question was additionally adjusted for age, WFNS grade and Fisher grade. From this, we report the common odds ratio (OR), which represents the odds ratio associated with a one-point upward shift in the GOS, and thus odds ratios > 1 indicate better outcomes [53].

We assessed whether serum markers may be associated with poorer outcomes by adding them to our prognostic model and calculating their marginal effect [47], which reflects the percentage increase in absolute risk of a poor outcome averaged across all values of the biomarker. We additionally calculated the incremental change in the area under the receiver operating curve (iAUC), which reflects the change in AUC for a model including important clinical factors, with versus without the serum marker. We calculated the 95% CI around the iAUC using bootstraps. We took this approach to establish whether the serum marker adds incremental value to the clinical presentation. In these analyses, we assumed data were missing-at-random (MAR) and therefore performed all analyses on five multiply-imputed datasets, pooling results using Rubin's rules [40, 46]. Anonymised

datasets and statistical code are available upon reasonable request to the corresponding authors.

Results

Two hundred fifty-seven patients with poor grade aSAH were referred during the 4-year study period, of whom 154/257 (60%) were accepted for transfer and 116/257 (45.1%) underwent treatment of an aneurysm (Fig. 1). Median age was 62 years (IQR 51 to 69), with an expected female predominance (167/257, 65%). When assessing the entire cohort, poor outcomes (GOS 1–3) were observed in 169/230 (73.5%), with mortality in 139/230 (60%) (Table 1). All included patients had imaging evidence of aSAH on a CT scan. In those patients who underwent aneurysm securement, poor 3-month outcomes were observed in 48/101 (48%). The characteristics of patients undergoing aneurysm intervention are shown in Table 1.

Prognostic factors for all patients at initial presentation

The presence of unreactive pupils or circulatory arrest conferred a uniformly poor prognosis (Fig. 2). Patients presenting with unreactive pupils had an in-hospital mortality of 55/56 (98%), while patients with circulatory arrest had a mortality of 19/19 (100%). Age was not an important factor in this group (Fig. 3). While pre-intervention rebleeding also increased risk of a poor outcome (Table 2), age remained an important prognosticator (Fig. 2).

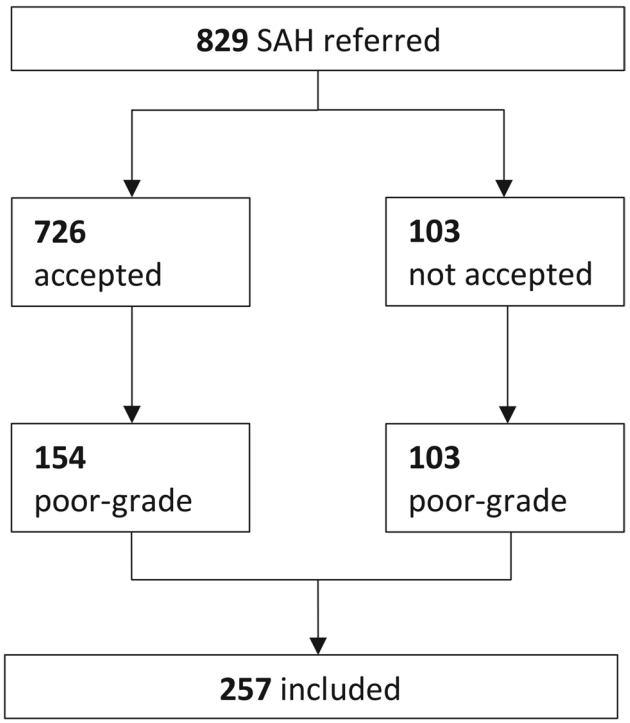

Fig. 1 Flowchart showing patient recruitment and selection

In patients without unreactive pupils, circulatory arrest or pre-intervention rebleeding, we found that age, WFNS grade and Fisher grade were important prognosticators. On average, the absolute risk of a poor outcome at 3 months was increased by 14.1% (95% CI 4.5 to 23.6) in WFNS V SAH compared with WFNS IV (Table 3). In these patients, we also found that, on average, the risk of a poor outcome increased by an average of 1.4% (95% CI 0.7 to 2) per year older in patients with WFNS V SAH (Table 2).

Prognostic factors in patients who underwent aneurysm securement

In patients undergoing aneurysm treatment, patients with WFNS V (vs. WFNS IV) aSAH had a lower GOS at 3 months (age-adjusted OR 0.51, 95% CI 0.33 to 0.98). In our cohort, Fisher IV aSAH was not strongly associated with poorer outcome (age-adjusted OR 0.63, 95% CI 0.2 to 2), though 241/257 (94%) of patients had Fisher IV aSAH. We observed a similar trend in patients who had an aneurysm secured (Fig. 4), with risk of a poor outcome increasing with age (Table 4). We found that need for CSF diversion (adjusted OR 0.49, 95% CI 0.25 to 0.99) was associated with a lower GOS at 3 months. We did not find evidence that radiological vasospasm (adjusted OR 0.65, 95% CI 0.29 to 1.45), symptomatic vasospasm (adjusted OR 0.88, 95% CI 0.38 to 2.04) or rebleeding (adjusted OR 0.38, 95% CI 0.12 to 1.21) were strongly associated with outcome (Table 5). However, there was a cumulative increased risk in patients with multiple prognostic factors (Fig. 4). For example, in a hypothetical patient aged 60 years, risk of a poor outcome increases from 43% (95% CI 25 to 62) without need for CSF diversion, rebleeding or symptomatic vasospasm to 57% (95% CI 38 to 75) with CSF diversion alone and 78% (95% CI 49 to 100) with symptomatic vasospasm, rebleeding and need for CSF diversion.

Timing of aneurysm securement

In our study, 97/116 (84%) of treated patients were treated within 48 h of ictus. Overall, we did not observe an important difference in outcomes or rebleeding in patients treated earlier (Table 6). Poor outcomes occurred in 39/84 (46%) of patients treated within 48 h compared with 9/17 (53%) of patients treated later. Adjustment for WFNS grade did not influence the outcome within 48 (OR 0.75, 95% CI 0.37 to 1.56) or 24 h (OR 0.38, 95% CI 0.14 to 1.05). Pre-intervention rebleeding occurred in 5/97 (5.2%) of patients treated within 48 h compared with 2/19 (10.5%) of patients treated later.

Table 1 Characteristics of patients transferred and treated versus those not treated

Characteristic	Overall, $N=257$[1]	Treated, $N=116$[1]	Not treated, $N=141$[1]	p-value[2]
Age	62 (51, 69)	58 (49, 64)	64 (55, 73)	<0.001
Sex				0.011
Female	167 (65%)	85 (73%)	82 (58%)	
Male	90 (35%)	31 (27%)	59 (42%)	
WFNS grade				<0.001
IV	92 (36%)	74 (64%)	18 (13%)	
V	165 (64%)	42 (36%)	123 (87%)	
Circulatory arrest	21 (8.4%)	0 (0%)	21 (16%)	<0.001
Unreactive pupils	60 (24.1%)	0 (0%)	60 (45%)	<0.001
Fisher grade				0.7
III	16 (6.2%)	8 (6.9%)	8 (5.7%)	
IV	241 (94%)	108 (93%)	133 (94%)	
Aneurysm location				<0.001
Anterior	136 (74%)	96 (83%)	40 (62%)	
Posterior	19 (10%)	20 (17%)	10 (14%)	
Unknown	30 (16%)	0 (0%)	19 (28%)	
Treatment of aneurysm				<0.001
Endovascular	101 (39%)	101 (87%)	0 (0%)	
Surgical	15 (5.8%)	15 (13%)	0 (0%)	
None	141 (55%)	0 (0%)	141 (100%)	
CSF diversion				<0.001
EVD	72 (28%)	54 (47%)	18 (13%)	
Lumbar drain	9 (3.5%)	6 (5%)	3 (2%)	
None	176 (68.5%)	56 (48%)	120 (85%)	
Rebleed				0.072
None	227 (88%)	105 (91%)	122 (87%)	
Pre-operative	26 (10%)	7 (6.0%)	19 (13%)	
Peri-operative	2 (0.8%)	2 (1.7%)	NA	
Post-operative	2 (0.8%)	2 (1.7%)	NA	
Time to treatment (days)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	NA	
Time to treatment				
<24 h	24 (21%)	24 (21%)	NA	
24–48 h	73 (63%)	73 (63%)	NA	
>48 h	19 (16%)	19 (16%)	NA	
GOS at discharge				<0.001
1	135 (55%)	22 (19%)	113 (86%)	
2	14 (5.7%)	8 (6.9%)	6 (4.6%)	
3	64 (26%)	59 (51%)	5 (3.8%)	
4	26 (11%)	22 (19%)	4 (3.1%)	
5	8 (3.2%)	5 (4.3%)	3 (2.3%)	
GOS at 3 months				<0.001
1	139 (60%)	23 (23%)	116 (90%)	
2	5 (2.2%)	2 (2.0%)	3 (2.3%)	
3	25 (11%)	23 (23%)	2 (1.6%)	
4	24 (10%)	22 (22%)	2 (1.6%)	
5	37 (16%)	31 (31%)	6 (4.7%)	

[1]Median (IQR); *n* (%)

[2]Wilcoxon rank sum test; Pearson's chi-squared test; Fisher's exact test

Incomplete proportions are due to missing data

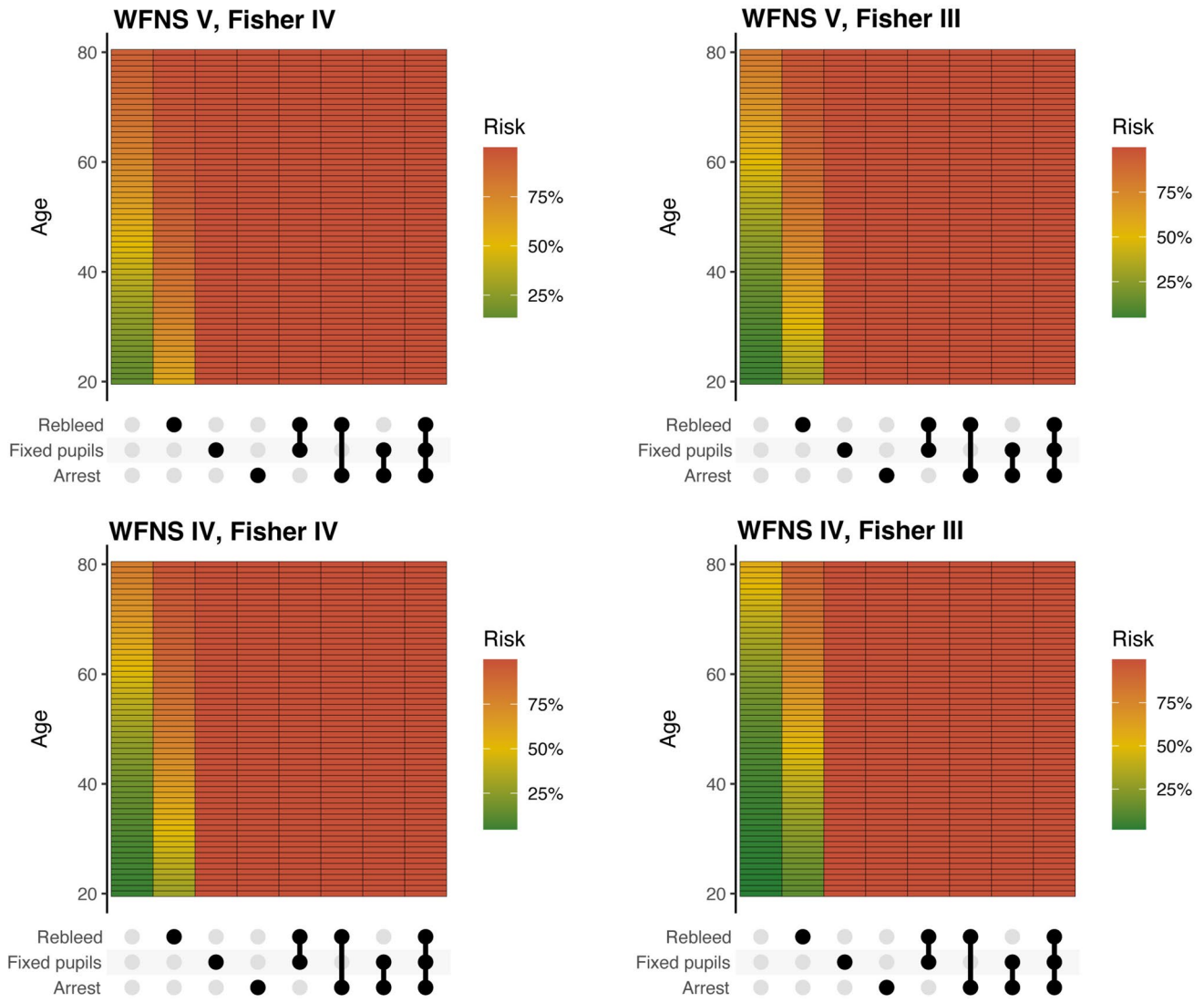

Fig. 2 Modified UpSet plots showing the risk of a poor outcome with age and various combinations of risk factors. A black dot indicates that a risk factor is present, whereas a grey dot indicates that it is not

Utility of serum markers

We did not find evidence that addition of serum markers including CRP, WCC and total protein improved discrimination of outcomes when added to a model adjusting for clinical prognosticators. We found only marginal increases in the AUC for CRP (+ 1%, 95% CI − 1.1 to 3.2), WCC (+ 0.1%, 95% CI − 1 to 1.2) and total protein (+ 1.8%, 95% CI − 1.2 to 4.9), with only adjusted increases in risk with increases in serum markers (Table 6). Any degree of discrimination observed appeared to be most pronounced in patients without clinical prognosticators (Fig. 5). However, in a subgroup of patients who had an aneurysm secured, the addition of CRP to a model adjusted for clinical factors resulted in a small increase in AUC of 8.7% (95% CI 0.8 to 17) (Table 7).

Pre-hospital mortality

In addition to the patients included this study, data suggested an additional 184 patients with pre-hospital mortality due to spontaneous SAH during the study period. If we assume that the cause of SAH in all these patients was a ruptured aneurysm and include them in the present study, poor outcomes would have been observed in 353/414 (85.3%) and mortality in 323/414 (78%).

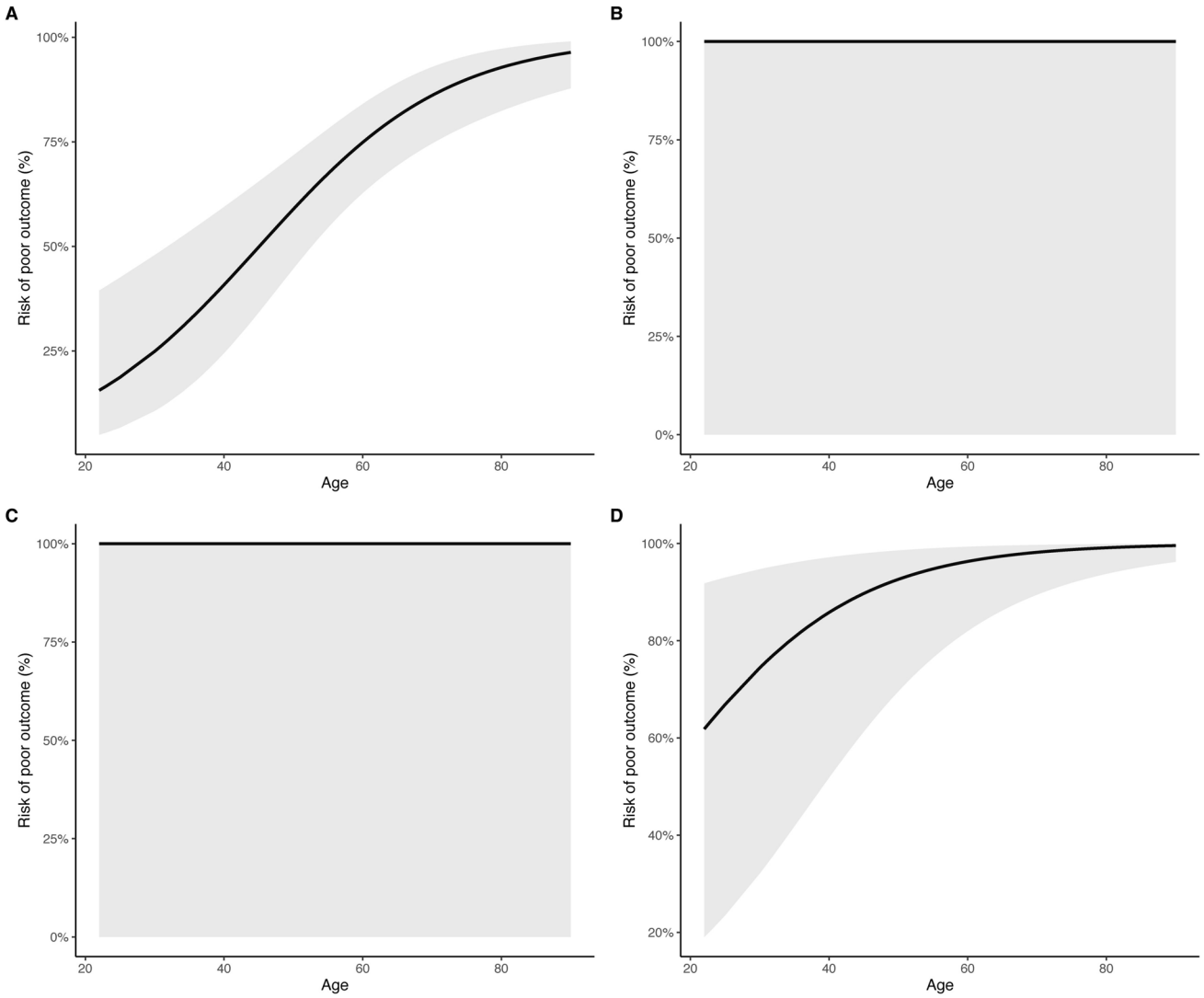

Fig. 3 Line plots showing the risk of a poor outcome at three months in relationship to age, in patients with WFNS grade V and Fisher grade IV ASAH. **A** Patients with reactive pupils, no arrest and no rebleeding, **B** patients with unreactive pupils, **C** patients with an arrest and **D** patients with a rebleed, but reactive pupils and no arrest

Discussion

Multiple recent publications have suggested that good outcomes may be achievable in patients with poor grade aSAH, attributing this improvement to endovascular techniques and/or earlier aneurysm treatment [1, 5, 7, 11, 12, 25, 31, 36, 39, 59, 65, 66]. Some studies have suggested that good outcomes may be achieved in 30–40% of patients [1, 26, 31, 65, 66] and mortality in less than 20% [31]. Our data suggests that, unfortunately, the outcomes of poor-grade aSAH remain poor, with mortality observed in 60% of patients and poor outcome (GOS 1–3) in 73.5% at 3 months. Our findings are consistent with other published data in unselected patients, showing similar risks of mortality and poor outcomes [28, 33, 39, 54]. This suggests that better outcomes in more recent publications may be at least partly attributable to selection bias, with exclusion of patients with factors such as unreactive pupils or circulatory arrest [17, 29, 49, 64]. Another important factor is the exclusion of untreated patients, who make up a large proportion of patients in unselected cohorts and have a universally poor outcome [20, 27].

In our study, unreactive pupils were associated with mortality in 98% and poor functional outcome in 100%, along with 100% mortality in patients with circulatory arrest. This is broadly consistent with previous publications [13, 35, 44, 52], and some authors have suggested a modification of the WFNS grading scale to account for the absence of brainstem reflexes [50]. Occasional good outcomes in patients with unreactive pupils have been reported [26], and therefore, some may argue that the poor outcomes in such patients

Table 2 Illustrative risks of a poor outcome at 3 months, defined as a Glasgow Outcome Scale of 1–3

WFNS V				
Age	None[a]	Unreactive pupils	Cardiac arrest	Rebleed
20	13 (0–28.1)	100 (99.98–100)	100 (99.97–100)	57 (8.88–100)
30	23.8 (5.1–42.4)	100 (99.99–100)	100 (99.99–100)	73.4 (38–100)
40	39.4 (21.2–57.6)	100 (100–100)	100 (99.99–100)	85.2 (63.5–100)
50	57.6 (43.4–71.8)	100 (100–100)	100 (100–100)	92.3 (80.3–100)
60	73.9 (62.9–85)	100 (100–100)	100 (100–100)	96.2 (89.8–100)
70	85.5 (76.3–94.8)	100 (100–100)	100 (100–100)	98.1 (94.7–100)
80	92.5 (85.5–99.5)	100 (100–100)	100 (100–100)	99.1 (97.3–100)
Marginal effect[b]	*+1.4% (0.7 to 2)*	*<0.01% (−<0.01 to<0.01)*	*<0.01% (−<0.01 to<0.01)*	*+0.3% (0.1 to 0.7)*
WFNS IV				
Age	None[a]	Unreactive pupils	Cardiac arrest	Rebleed
20	5 (0–12)	100 (99.95–100)	100 (99.92–100)	31.8 (−10.84 to 74.5)
30	9.9 (0–20.2)	100 (99.97–100)	100 (99.96–100)	49.3 (4.65–94)
40	18.7 (5.6–31.7)	100 (99.99–100)	100 (99.98–100)	67 (30.28–100)
50	32.4 (18.9–45.8)	100 (99.99–100)	100 (99.99–100)	80.9 (56.2–100)
60	50 (37.3–62.6)	100 (100–100)	100 (100–100)	89.8 (75.14–100)
70	67.6 (54.2–80.9)	100 (100–100)	100 (100–100)	94.9 (86.6–100)
80	81.3 (68.4–94.2)	100 (100–100)	100 (100–100)	97.5 (92.94–100)
Marginal effect[b]	*+1.8% (1 to 2.7)*	*<0.01% (−<0.01 to<0.01)*	*<0.01% (−<0.01 to<0.01)*	*+0.7% (0 to 1.5)*

[a]Refers to patients with reactive pupils, no rebleed and no circulatory arrest

[b]The marginal effect refers to the change in risk of a poor outcome per year increase in age, *averaged* across all ages. Positive values indicate an increased risk of a poor outcome

Risks are the absolute risk of a poor outcome, with the 95% confidence interval in parentheses, derived as predictions from multivariable logistic regression models

Table 3 Marginal increased absolute risks associated with increasing WFNS and Fisher grade

Prognostic factors	WFNS (V vs. IV)	Fisher (IV vs. III)
None[a]	+20.3% (6.5 to 34)	+22.4% (−7.8 to 52.6)
Rebleed	+8% (−1.5 to 17.6)	+11.3% (−10.5 to 33.1)
Unreactive pupils	+ <0.01% (−<0.01 to<0.01)	+ <0.01% (−<0.01 to<0.01)
Circulatory arrest	+ <0.01% (−<0.01 to<0.01)	+ <0.01% (−<0.01 to<0.01)
Overall	*+14.1% (4.5 to 23.6)*	*+15.8 (−5.1 to 36.7)*

[a]Refers to patients with reactive pupils, no rebleeding and no circulatory arrest

Marginal risks are presented as estimates both for the overall population and for patients with significant prognostic factors. In all cases, risks are estimated a counterfactual grid of all possible factor combinations and averaged

may be because they were not accepted for active management and therefore the result of a self-fulfilling prophecy. As we did not treat these patients actively, we cannot comment on what the outcome might have been if they had been accepted for neurocritical care and neurosurgical management. However, in one study examining early and aggressive intervention in patients thought to have a poor prognosis, even some patients with bilaterally unreactive pupils, outcomes remained poor with a 1-year mortality of 65.8% [38].

We found that in patients selected for aneurysm intervention, good outcomes (GOS 4–5) were achieved with 53% of cases being independent at 3 months. This further improved in younger patients aged less than 65 years old to 63%, which highlights that good outcomes are achievable in carefully selected patients. In addition, patients with poor grade aSAH, particularly younger patients, may continue to improve functionally beyond our 3-month timeframe [4], and thus, the proportion achieving good longer term outcomes may be higher than our study suggests. It is also worth noting that a very small proportion of patients (2% in the treated group and 2.3% in the untreated group) survived in a vegetative state (GOS2). In patients who did not have unreactive pupils, circulatory arrest or pre-intervention rebleeding, we found that WFNS grade,

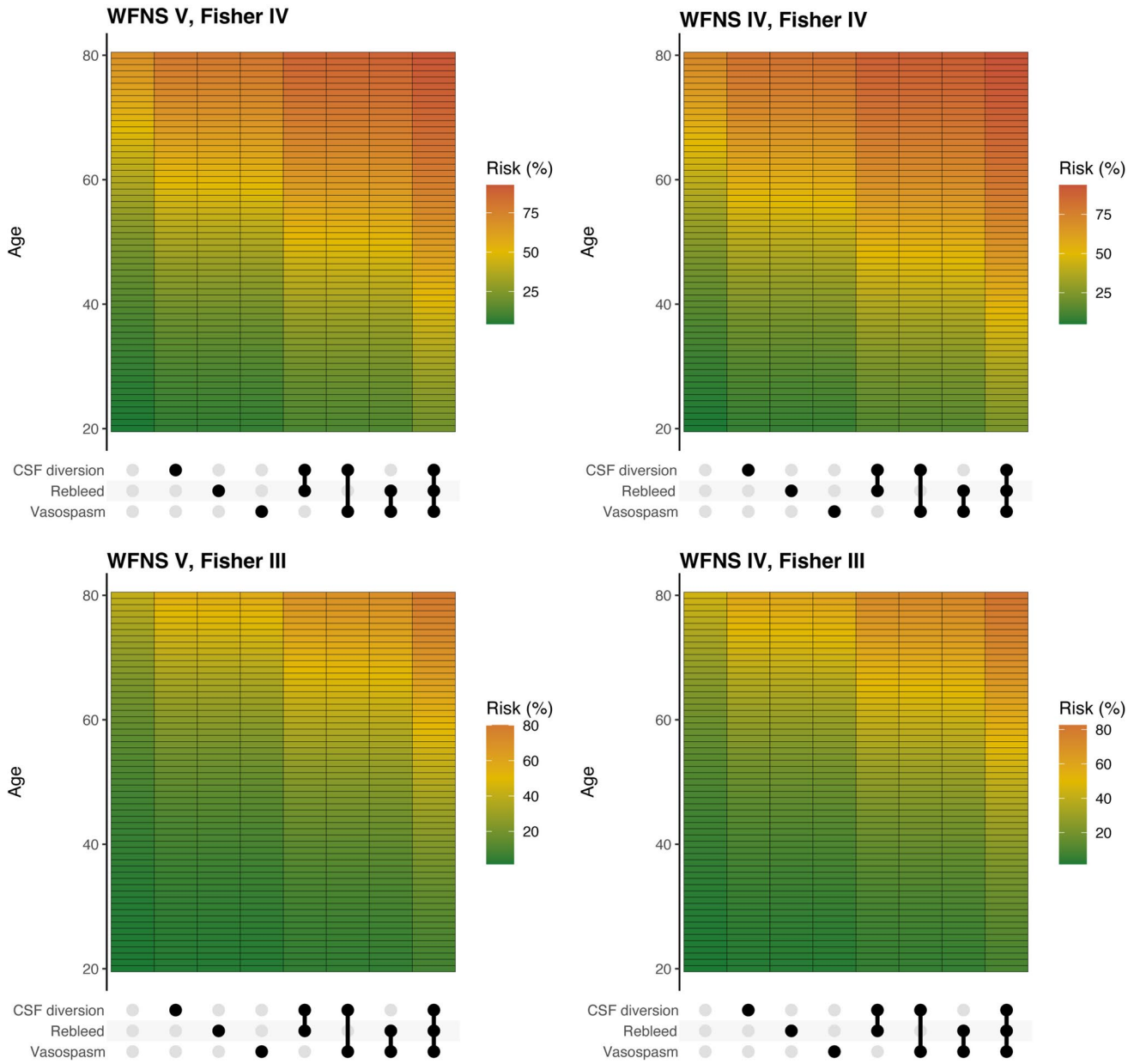

Fig. 4 Modified UpSet plots showing the risk of a poor outcome with age and additional risk factors in patients who underwent treatment of an intracranial aneurysm. A black dot indicates that a risk factor is present, whereas a grey dot indicates that it is not

Fisher grade and age were important prognostic factors. In those who underwent aneurysm securement, the need for CSF diversion was also an important factor. However, it is important to note that good outcomes were observed in 8/141 (6.3%) of untreated patients, which highlights the need for refinement of the current patient selection criteria.

Our finding that increasing age is associated with an escalating risk of a poor outcome is consistent with previous studies, which have demonstrated poor outcomes in the elderly [13, 19], even in good-grade SAH [62]. However, an important caveat is that age may be acting as a surrogate for general comorbidity burden. The applicability of this finding to otherwise healthy older adults with a good functional baseline is unclear.

Need for CSF diversion was the only factor that appeared to be an important prognosticator in our cohort, which likely reflects the presence of hydrocephalus [69]. While symptomatic vasospasm or rebleeding did not influence risk of poor outcomes in isolation, their effects appeared to be cumulative, especially in older patients (Fig. 4). Pre-intervention rebleeding occurred in 26/257 (10%) of our patients with

Table 4 Illustrative risks of a poor outcome at 3 months in patients who had aneurysm securement, stratified by several risk factors

WFNS V				
Age	None[a]	Symptomatic vasospasm	CSF diversion	Rebleed
20	4.9 (0–13.9)	8.4 (0–24.7)	8.2 (0–22.5)	8.4 (0–27.1)
30	9.2 (0–21.8)	15.2 (0–37.9)	14.8 (0–33.8)	15.1 (0–42.3)
40	16.6 (0.9–32.2)	25.9 (0–54)	25.4 (3.9–46.9)	25.9 (0–61.1)
50	28 (10.9–45.1)	40.7 (10.6–70.7)	40 (19.5–60.4)	40.6 (1.1–80)
60	43.2 (24.6–61.7)	57.3 (28.4–86.1)	56.6 (37.9–75.2)	57.2 (19.3–95)
70	59.8 (37.8–81.7)	72.4 (46.8–98)	71.8 (53.3–90.4)	72.3 (40.5–100)
80	74.4 (51–97.8)	83.7 (63–100)	83.3 (66.2–100)	83.6 (59.7–100)
WFNS IV				
Age	None[a]	Symptomatic vasospasm	CSF diversion	Rebleed
20	4.3 (0–11.8)	7.3 (0–21.2)	7.2 (0–18.8)	7.3 (0–23.4)
30	8.1 (0–18.9)	13.4 (0–33.4)	13.1 (0–28.8)	13.4 (0–37.4)
40	14.7 (0.3–29.1)	23.3 (0–49.4)	22.8 (4.1–41.4)	23.2 (0–56)
50	25.2 (6.8–43.5)	37.2 (6.2–68.2)	36.6 (16.4–56.7)	37.2 (0–76.8)
60	39.7 (15.8–63.5)	53.7 (20.5–87)	53 (30.8–75.2)	53.6 (12.1–95.2)
70	56.3 (26.7–85.8)	69.4 (37.8–100)	68.8 (44.8–92.8)	69.4 (31.9–100)
80	71.6 (40.7–100)	81.6 (55.3–100)	81.2 (59–100)	81.6 (52.1–100)

[a]Refers to patients with no vasospasm, no requirement for CSF diversion and no rebleeding

CSF, cerebrospinal fluid

Table 5 Results of univariable proportional odds regressions

Variable	OR	95% CI
WFNS V (vs. IV)[a]	0.51	(0.33 to 0.98)
Fisher IV (vs. III)[a]	0.63	(0.2 to 2)
Radiological vasospasm[b]	0.65	(0.29 to 1.45)
Symptomatic vasospasm[b]	0.88	(0.38 to 2.04)
Hypertension[b]	0.62	(0.29 to 1.33)
IHD[b]	3	(0.29 to 30.8)
Smoker[b]	0.79	(0.3 to 2.1)
Posterior circulation[b]	0.46	(0.18 to 1.17)
CSF diversion[b]	0.49	(0.25 to 0.99)
Rebleeding[b]	0.38	(0.12 to 1.21)
Aneurysm treatment within 48 h[c,d]	0.75	(0.37 to 1.56)

IHD, ischaemic heart disease

[a]Adjusted for age

[b]Adjusted for age, WFNS grade and Fisher grade

[c]Adjusted for WFNS grade

[d]Excludes patients five patients undergoing early surgical decompression for mass effect

Lower odds ratios (< 1) indicate a *higher* likelihood of a *lower* GOS at 3 months, which relates to a poorer outcome. Therefore, odds ratios less than 1 suggest that the variable is negatively prognostic while odds ratios greater than 1 suggest it is positively prognostic

poor grade aSAH. In the treated group, data was captured on a daily basis prospectively, and therefore, it is unlikely for rebleeds to have been missed in this group. Rebleeding may have been missed from unsecured aneurysms in the untreated group of patients as these patients were not transferred to the neurosurgical centre. The prognostic importance of rebleeding in the overall patient cohort with poor-grade aSAH therefore remains unclear in our study.

The timing of aneurysm treatment in poor-grade aSAH has been the subject of much debate with some advocating early treatment to minimize risk of rebleeding [10], delaying treatment until after the vasospasm period and selecting patients who recover well [32]. Traditionally, delayed aneurysm treatment was performed at our centre, but there has been a shift towards early treatment [8]. During the study period, our centre's approach has been to secure the aneurysm early (within 48 h of ictus) in poor-grade aSAH patients. There were some variations in practice between different neurosurgeons. For example, some neurosurgeons would lighten sedation and assess the patient's neurological function prior to a decision regarding intervention, whereas others would proceed with aneurysm securement without this neurological assessment. However, despite these variations, 84% of our patients underwent treatment within 48 h. Patients with poor-grade SAH are thought to be at particularly high risk of early rebleeding [14], which makes early treatment appealing in this group [68]. Rebleeding was uncommon in our cohort, which may be partially attributable to the aforementioned shift towards earlier treatment, although underreporting in patients not accepted for treatment may also be a factor.

In our cohort, treatment within 48 h was not associated with outcome. This is likely a consequence of few undergoing late treatment after 48 h (19/116, 16%) and the selected

Table 6 Absolute risk of a poor 3-month outcome and rebleeding, stratified by time to aneurysm securement

Characteristic	Overall, $N=101$[1]	Poor outcome		p-value[2]	Overall, $N=116$[1]	Rebleeding		p-value[3]
		No, $N=53$[1]	Yes, $N=48$[1]			No, $N=109$[1]	Yes, $N=7$[1]	
Time to aneurysm securement				0.3				0.4
<24 h	24 (24%)	10 (19%)	14 (29%)		24 (21%)	22 (20%)	2 (29%)	
24–48 h	60 (59%)	35 (66%)	25 (52%)		73 (63%)	70 (64%)	3 (43%)	
>48 h	17 (17%)	8 (15%)	9 (19%)		19 (16%)	17 (16%)	2 (29%)	

[1] *n* (%)

[2] Pearson's chi-squared test

[3] Fisher exact test

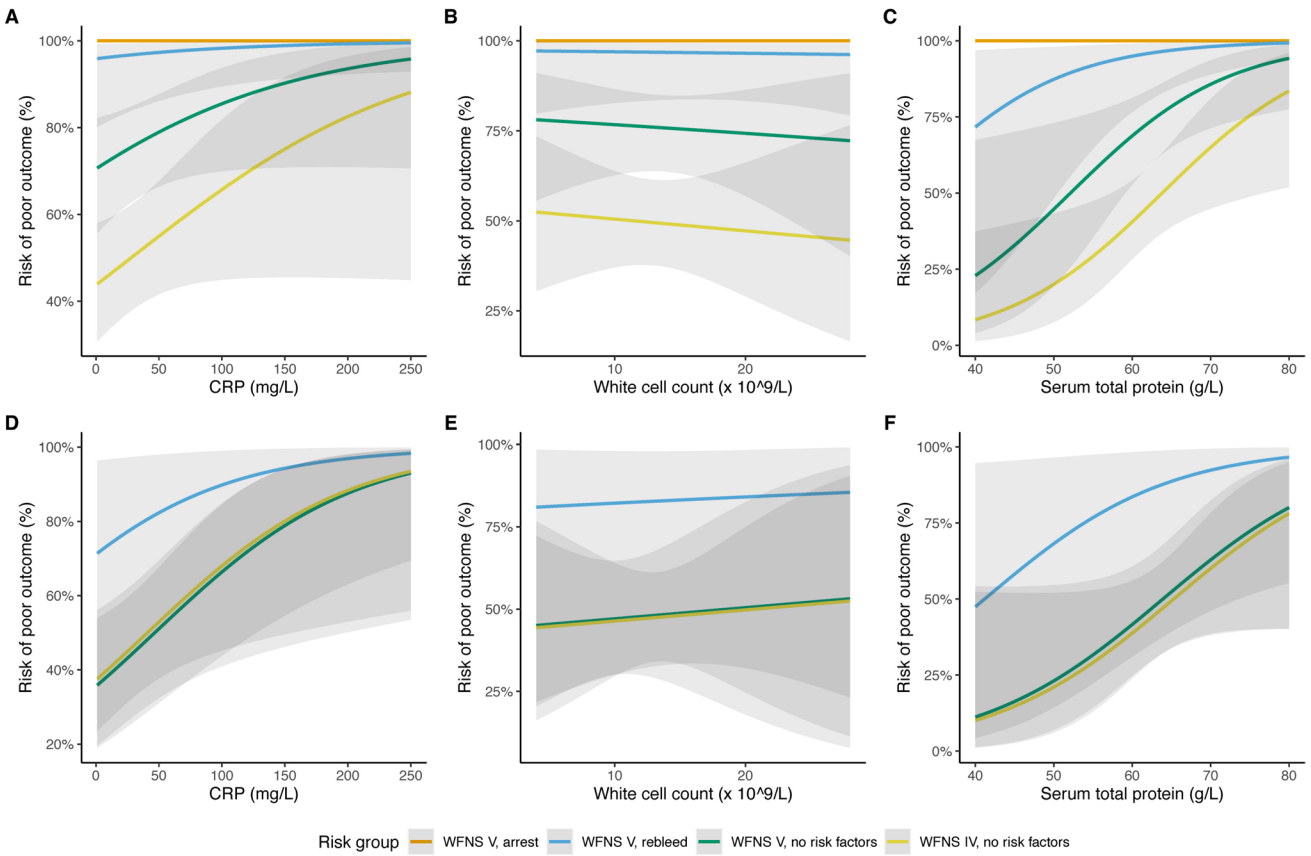

Fig. 5 Association of serum markers with absolute risk of a poor outcome, stratified by clinical risk factors, derived from logistic regression models adjusted for age, WFNS grade, Fisher grade and the presence of rebleeding, unreactive pupils or circulatory arrest. Shaded areas represent the 95% confidence interval of the estimate. **A–C** The entire cohort of patients. **D–F** Patients undergoing treatment of an aneurysm only

nature of this group. Patients treated late are likely those who improved after referral, with late intervention [32, 67]. Improvement prior to treatment is associated with an improved prognosis [13], and thus, this cohort may provide a false inverse association between prolonged time to treatment and improved outcome. As a result, any benefit of early treatment may not be reflected in our study in this cohort of patients. It is important to additionally note, however, that our findings do not preclude a benefit of much earlier (for example within 6 h) treatment.

An array of serum biomarkers have been proposed as prognostic in SAH including CRP [3, 18, 61], WCC [21,

Table 7 Incremental change in the area under the receiver operating curve (AUC) with the addition of each serum marker to a model containing important clinical variables

Marker	iAUC (95% CI)	Marginal effect (95% CI)
All patients[a]		
CRP (mg/L)	+1% (−1.1 to 3.2)	+0.1% (−0.01 to 0.2)
WCC ($\times 10^9$/L)	+0.1% (−1 to 1.2)	−0.2% (−1.4 to 1)
Serum total protein (g/L)	+1.8% (−1.2 to 4.9)	+1.2% (−0.4 to 2)
Aneurysm secured[b]		
CRP (mg/L)	+8.7% (0.8 to 17)	+0.4% (0.2 to 0.6)
WCC ($\times 10^9$/L)	+2.9% (−5 to 11)	+0.7% (−2 to 3)
Serum total protein (g/L)	+3.4% (−3 to 10)	+1.5% (−0.3 to 3.2)

CRP, C-reactive protein; *WCC*, white cell count

[a]Base model adjusted for age, WFNS grade, Fisher grade, pupillary reactivity, circulatory arrest and rebleeding

[b]Base model adjusted for age, WFNS grade, Fisher grade, need for CSF diversion, vasospasm and rebleeding

Incremental AUC > 0 suggests that the model is improved by addition of the marker in question, while < 0 suggests it is made worse by inclusion of the marker. The marginal effect is also reported, which reflects the expected change in absolute risk of a poor outcome with each one unit change in the serum marker level, in a model adjusted for clinical factors

42, 45] and haemoglobin [41, 55]. Studies to date have primarily assessed these markers in univariable models. In our study, there was no incremental benefit of serum markers over clinical presentation alone. Our results suggest that any benefit is likely too small to be clinically useful. However, our study cannot comment on their utility in the wider population with SAH. We observed marginally increasing benefit in patients with better clinical presentation. In particular, the addition of CRP appeared to slightly improve prognostication in patients undergoing aneurysm securement.

An important issue when considering outcomes of poor-grade SAH is in relation to pre-hospital mortality. These patients are typically not counted in studies examining poor grade SAH but account for 15–25% of all SAH cases [9, 34, 43, 57]. In one large study examining over 79 million person-years of follow-up, sudden deaths accounted for 26% of all SAH cases [34]. These cases are liable to be missed in studies examining aSAH referred to neurosurgical centres, and thus, the true incidence and mortality attributable to poor-grade aSAH is likely underestimated. In our study, inclusion of patients who died pre-hospital would have increased the risk of poor outcomes and mortality to 85.3% and 78%, respectively.

Limitations

This is observational and is therefore subject to confounding despite our efforts to include as unselected sample as possible. One source of bias in our study is that patients with factors associated with a very poor prognosis such as unreactive pupils or circulatory arrest were typically not treated.

Generalizability

This study is an unselected cohort and thus may be expected to generalize reasonably to areas with similar population structure. The neurosurgical service in Ireland is highly centralized with only 2 neurosurgical centres for the entire population of 5 million people. Our centre provides neurosurgery to three-quarters of Ireland and receives all neurosurgical referrals from the hospitals within this catchment area (with a population of 3.8 million people). We additionally accounted for pre-hospital mortalities. Therefore, we are confident that very few, if any, cases of aSAH would have been missed.

Conclusion

Unfortunately, despite the many advances in aSAH treatment, the overall outcomes of poor-grade SAH remain poor due to the high mortality and irreversible brain injury at the time of initial haemorrhage. However, in selected patients who undergo aneurysm securement, good outcomes (GOS 4–5 at 3 months) can be achieved in 53% of patients. Increasing age, WFNS grade V, rebleeding, vasospasm and need for CSF diversion were risk factors for poor outcome. In patients with poor-grade SAH, the use of CRP, total protein and WCC adds only minimal predictive discrimination beyond of the clinical presentation.

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Acquisition of data: MOD, DK, PC, DN, DC, JT, AOH, SP, DR.
Interpretation of data: JH, MOD, MJ, JT, AOH, SP, DR.
Statistical analysis: JH.

Drafting of the manuscript: JH, MJ.

Critical revision of the manuscript for important intellectual content: all authors.

Supervision: MJ.

All authors reviewed the manuscript prior to final submission.

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Declarations

Ethical approval This study was approved by the local institutional review board (CA248) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided informed consent to all treatment.

Competing interests The authors declare no competing interests.

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