REVIEW



Radiological scales predicting delayed cerebral ischemia in subarachnoid hemorrhage: systematic review and meta-analysis

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Abstract

Purpose Delayed cerebral ischemia (DCI) is a severe complication of aneurysmal subarachnoid hemorrhage (aSAH). The extent of subarachnoid blood is a strong predictor of DCI and is frequently estimated with the Fisher scale, modified Fisher scale, or Hijdra sum score. It is unclear which scale has the strongest association with clinical DCI. To evaluate this, we performed a systematic review of the literature.

Methods We performed a MEDLINE and EMBASE search from 1980 to 20th of June 2017. Radiological grade and occurrence of clinical DCI were extracted along with odds ratios (ORs) for DCI. When possible, pooled ORs with 95% confidence intervals were calculated per grade increase on the radiological scale.

Results Fifty-three studies were included. The Fisher scale was significantly associated with DCI in 62% of the studies compared to 88–100% for the other scales. In studies using the Fisher scale, Fisher 3 had the strongest association with DCI (pooled OR 3.21 (1.87–5.49)). In studies using the modified Fisher score, DCI occurred most frequently (42%) in modified Fisher 4. No pooled OR could be calculated for the other scales.

Conclusion The Fisher scale, modified Fisher scale, and Hijdra sum score are all associated with clinical DCI. The risk of DCI, however, does not increase with increasing Fisher grade as opposed to the modified Fisher scale. Furthermore, the modified Fisher scale was more commonly significantly associated with DCI than the Fisher scale, which may advocate using the modified Fisher in future SAH-related studies.

Keywords Delayed cerebral ischemia · Radiological scale · Subarachnoid hemorrhage · Systematic review

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Introduction

Delayed cerebral ischemia (DCI) is one of the most severe complications of aneurysmal subarachnoid hemorrhage (aSAH) and occurs in approximately 30% of the patients [1, 2]. The extent of subarachnoid blood on admission computed tomography (CT) scan is one of the strongest predictors of DCI [3–5]. However, it is not clear which radiological grading scale has the strongest association with DCI. Over the years, several radiological grading scales have been introduced [6]. The first scale was introduced by Fisher et al. in 1980 [7]. This four-grade scale scores the amount of blood in the cisterns as absent (grade 1), diffuse thin (<1 mm) (grade 2), thick (> 1 mm) (grade 3), or thin amount of blood in the cisterns with presence of intraventricular (IVH) or intraparenchymal (IPH) hemorrhage (grade 4). Later, an adjusted version of the Fisher scale was published: the modified Fisher scale [8, 9]. This scale introduced a separate grade for patients with both a thick



layer of blood in the cisterns and presence of IVH. An alternative, more extensive but more time consuming scale is the Hijdra sum score, which grades the amount of blood in each cistern separately [4].

Several studies have assessed the association of these radiological grading scales with the occurrence of DCI [4, 7–10]. However, prior to 2010, DCI has not been unambiguously defined [11]. When the Fisher scale was introduced, DCI was believed to be caused by vasospasm and thus angiographic vasospasm was frequently used as end point. Presently, DCI is regarded a multifactorial process, which results in neurological deterioration [12]. The question remains how well the grading scales are associated with this current clinical definition of DCI [11]. We aimed to perform a systematic review to assess the associations of the Fisher scale, the modified Fisher scale, and Hijdra sum score with clinical DCI.

Methods

Search strategy

We performed this review according to the PRISMA statement [13]. We performed a MEDLINE and EMBASE search for records published between 1980 and 20th of June 2017. The search terms "subarachnoid hemorrhage," "Fisher," "Hijdra," "score/grade," and "computed tomography," were used. Furthermore, as numerous terms for DCI are used in literature, we included the following terms for DCI: "delayed cerebral ischemia," "delayed cerebral infarction" "delayed cerebral deficit," "symptomatic vasospasm," "cerebral vasospasm," "delayed ischemic neurological deficit," "delayed ischemic neurological deficit," "felayed ischemic neurological deficit," "symptomatic vasospasm," "ferebral vasospasm," "For the full search strategy, please see the Online supplemental text 1.

Study selection

Studies that met the following criteria were included: (1) SAH proven on CT images; (2) aneurysm shown on an angiographic study; (3) amount of blood graded on admission CT by either the Fisher scale, modified Fisher scale, or Hijdra sum score; (4) outcome was clinical DCI, defined by at least the occurrence of new focal neurological signs and/or a decrease in consciousness, with or without angiographic vasospasm or new infarct on follow-up CT scan; and (5) an association between the radiological grade and DCI was reported. In case two studies used (part of) the same dataset and assessed the same radiological scale, the study with the largest patient population was included. We excluded studies that included mainly patients younger than 18 years, studies in another language than English, Dutch or German, case reports, reviews, and conference abstracts. One reviewer (W.S.) screened all titles

and abstracts for eligibility for full text review. Two reviewers (W.S. and E.L.) independently reviewed all full texts for inclusion in the review. The final decision on inclusion was made through consensus between the two reviewers.

Data extraction

Data extraction from the included studies was independently performed by two reviewers (W.S. and E.L.) using a standardized form. Crude data on radiological grade and occurrence of DCI were extracted along with, if available, the odds ratios (OR) for the occurrence of DCI. If the ORs were not available, ORs for DCI were calculated from the crude data in case these data were provided. Furthermore, we extracted whether an association between the radiological grade and DCI was found, both in univariable and multivariable analysis. Other collected variables were age, sex, and treatment modality (clipping or coiling). Differences in extracted data were evaluated by the two reviewers and resolved by consensus.

Quality assessment

Risk of bias was assessed by two reviewers independently (W.S. and D.V.) using the Newcastle-Ottawa quality assessment (NOS) scale for cohort and case control studies and the Cochrane Handbook risk of bias tool for randomized controlled trials [13, 14]. Cohort studies could be awarded a maximum of 9 points. Randomized controlled trials could be awarded a maximum of 7 points. In case an item of the scale was inapplicable, a lower maximum of points could be awarded. Points could be awarded for selection, comparability, and outcome assessment. The study population was considered unselected if no selection was made based on clinical condition, co-morbidities, and treatment of the aneurysm. A follow-up period for DCI of at least 2 weeks was considered sufficient. Follow-up was considered adequate if a DCI status (DCI or no DCI) was available for at least 80% of the included patients. Differences in risk of bias assessment between reviewers were resolved through consensus.

Statistical analyses

Mean age (standard deviation), percentage male sex, number of patients in each radiological grade, and occurrence of DCI per radiological grade were calculated using data from all studies that provided the crude data.

Pooled ORs with 95% confidence intervals for DCI were calculated for the radiological scales, both dichotomized and per grade on the radiological scale using Mantel Haenszel statistics. The Fisher and modified Fisher scale were dichotomized at grade 2 and the Hijdra sum score at grade 23. Pooled ORs were only calculated in case multiple studies reported crude data on patients for all grades of the radiological scale.



The risk for DCI was compared between all grades of each radiological scale using each grade as reference in separate analyses. A random effects model was applied to calculate the pooled ORs. Statistical heterogeneity of the studies included in the meta-analysis was assessed using the I^2 statistic. An I^2 of 0–30% was considered no relevant heterogeneity, 30–50% moderate heterogeneity, 50–75% substantial heterogeneity, and 75–100% considerable heterogeneity [14]. The possibility of publication bias was assessed by plotting the effect of the studies included in the meta-analysis by the inverse of its standard error, thus creating a funnel plot. Funnel plots were visually assessed for asymmetry which could indicate a publication bias.

A sensitivity analysis was performed comparing studies that used clinical signs only to diagnose DCI to studies that used both a radiological and clinical definition.

Analyses were performed using SPSS version 24.0.0.1 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and Review Manager 5.3.5 (RevMan, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study characteristics

The MEDLINE and EMBASE search yielded, after removal of duplicates, 6766 records. After screening of titles and abstracts, 274 full-text articles were screened for inclusion. Of the full-text articles, 221 studies were excluded. The main reasons for exclusion were the following: amount of blood not assessed with the Fisher, modified Fisher, or Hijdra sum score (n = 38), clinical DCI not one of the assessed outcomes (n = 114), and no association between amount of blood and DCI could be determined (n = 51) (Fig. 1).

Fifty-three studies were included, including 13,612 patients with a mean age of 52.4 (SD 3.5) years of which 66% was female. Table 1 shows the study characteristics of the included studies.

In total 50 cohort studies, one case—control study and two randomized controlled trials were included. DCI occurred in 29% of the patients. In 28 studies (53%), the diagnosis of DCI was based on clinical signs in combination with angiographic vasospasm. In the remaining 25 studies (47%), the diagnosis of DCI was based on clinical signs only. No sufficient uniform data could be extracted on treatment modality.

None of the included studies received the maximum score on the quality assessment scale. The mean amount of awarded points was 5.2 (SD 1.6). Items that were most often rewarded points for were comparability of the cohorts (82%) and assessment of DCI (98%). However, most studies did not use an unselected study cohort (69%), showed no demonstration that

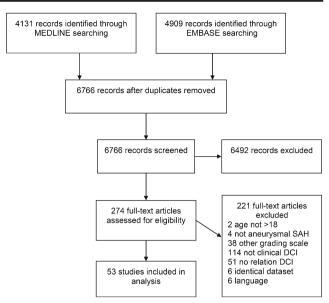


Fig. 1 PRISMA flowchart

DCI was not present at baseline (93%), and did not use a follow-up period of a least 2 weeks (56%) (Table 1).

Fisher scale

The Fisher scale was used in 42 studies (79%), including 10,429 patients. Of these 42 studies, 25 studies (5701 patients) reported patients for all Fisher grades and provided detailed data on the number of patients in each grade. A mean percentage of 6 (SD 6; range 0–23) was classified as Fisher 1, 18 (SD 9; range 0–37) as Fisher 2, 51 (SD 17; range 17–83) as Fisher 3, and 27 (SD 14; range 5–73) as Fisher 4. The distribution of patients in each Fisher grade in these studies is shown in Online supplemental Fig. 1.

Crude data on the number of patients that developed DCI in each Fisher grade was extracted from 25 studies (7222 patients), a mean percentage of 13 (SD 7; range 0–29) of patients with Fisher 1, 24 (SD 10; range 0–43) of patients with Fisher 2, 37 (SD 11; range 23–96) of patients with Fisher 3, and 30 (SD 13; range 0–70) of patients with Fisher 4 developed DCI.

The Fisher grade was significantly associated with DCI in 23 of 39 studies (62%) that performed an univariable analysis. Of the 29 studies that performed a multivariable analysis, the Fisher scale was independently associated with DCI in 16 studies (55%).

Of the 25 studies (5701 patients) that reported patients for all Fisher grades, 14 studies (4413 patients) provided data on occurrence of DCI that allowed to calculate a pooled OR by dichotomized Fisher grade and 10 studies (3939 patients) to calculate a pooled OR per Fisher grade. The pooled OR (95% CI) for DCI was 2.22 (1.54–3.19) for Fisher 3 to 4 compared to Fisher 1 to 2. Compared to Fisher 1, the pooled OR (95% CI) for DCI was 1.53 (1.01–2.32) for Fisher 2 (Fig. 2a), 3.21



 Table 1
 Study characteristics

Fisher et al. [7]	Author	Study type	Study type Radiological scale		Mean age (± SD)	Male sex (%)	DCI (%)	Study quality
Adams et al. [16]	Fisher et al. [7]	Pc		47	48 (n/a)	30	49	2 of 9*
Grosset et al. [17] Pc Fisher 121 47 (2.6) n/a 39 2 0 69 Rabb et al. [18] Rc Fisher 178 45 (n/a) 40 21 4 0 79 Rabb et al. [18] Pc Fisher 170 498 (13.6) 37 29 5 67 9 Murayam et al. [20] Rc Fisher 170 498 (13.6) 37 29 3 4 0 77 8 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1					46 (n/a)			
Rabbe et al. [18] Rec Fisher 178 45 (m/s) 40 21 4 of 9° Lasner et al. [19] Pe Fisher 70 49 X (13.6) 37 29 5 of 9° Mumyama et al. [20] Re Fisher 60 52 (m/s) 26 23 4 of 7° Obredia et al. [21] Pe Fisher 24 n/m 40 19 7 of 9° Juvela et al. [22] Pe Fisher 28 50 (m/s) 51 41 6 of 9° McGirt et al. [23] Pe Fisher 98 50 (m/s) 36 22 3 of 9° Simplal et al. [26] Pe Fisher 151 55 (14) 29 29 7 of 9° Reilly et al. [27] Re Fisher 75 51 (4) 27 35 3 of 8° Reilly et al. [28] Re Fisher 15 52 (11) 27 35 3 of 8° Bribar 15 51 (4) 27 35 3 of 8°	Adams et al. [16]	Rc	Fisher	934	n/a	n/a	32	8 of 9*
Lasner et al. [19] Pe Fisher 69 52 (m/s) 26 23 4 of 7*	Grosset et al. [17]	Pc	Fisher	121	47 (2.6)	n/a	39	2 of 9*
Murayama er al. [20] Re (Fisher Pisher Pisher) 69 (S) (S) (Na) 26 (S)	Rabb et al. [18]	Rc	Fisher	178	45 (n/a)	40	21	4 of 9*
Charpentier et al. [21] Rc Fisher 7.04 46 (m/a) 40 19 7 of 9° Juvela et al. [23] Pc Fisher 7.0 46 (m/a) 51 41 66 of 9° McGiri et al. [23] Rc Fisher 223 53 (m/a) 46 22 3 of 9° Elimo et al. [25] Pc Fisher 167 53 (m/a) n/a 35 56 of 8° Rilly et al. [27] Rc Fisher 514 55 (14) 29 29 7 of 9° Reilly et al. [27] Rc Fisher 75 51 (14) 29 29 7 of 9° Hirshima et al. [28] Pc Fisher 155 54 (14) 29 29 7 of 9° Hirshima et al. [28] Rc Fisher 115 54 (14) 29 29 7 of 9° Birth et al. [31] Pc Fisher 135 54 (14) 32 23 3 of 8° Smith et al. [31] Rc Fisher 115 52 (11)		Pc	Fisher	70	49.8 (13.6)	37	29	5 of 9*
Juvela et al. [22] Pc Fisher 70 46 (n/a) 51 41 6 of 9° McGirt et al. [23] Rc Fisher 223 53 (15) 44 45 60 69° McGirt et al. [24] Pc Fisher 98 50 (n/a) 36 22 3 of 9° Klimo et al. [25] Pc Fisher 167 53 (n/a) n/a 35 5 of 8° Singhal et al. [26] Pc Fisher 514 55 (14) 29 29 7 of 9° Reilly et al. [27] Rc Fisher 75 51 (14) 27 35 3 of 8° Hoh et al. [28] Pc Fisher 515 54 (14) 29 29 7 of 9° Hirashima et al. [29] Rc Fisher 134 59 (3) (3) 30 28 60 f9° Hirashima et al. [29] Rc Fisher 134 54 (n/a) 30 21 8 of 9° Oertel et al. [31] Pc Fisher 134 54 (n/a) 30 21 8 of 9° Oertel et al. [31] Pc Fisher 135 54 (14) 32 43 3 of 8° Oertel et al. [31] Rc Fisher 135 54 (14) 32 43 3 of 8° Oertel et al. [31] Rc Fisher 135 54 (14) 32 43 3 of 8° Ohe tal. [32] Rc Fisher 135 54 (14) 32 43 3 of 8° Ohe tal. [33] Rc Fisher 155 54 (14) 32 43 3 of 8° Ohe tal. [34] Rc Fisher 158 51 (10) 38 29 4 of 9° Orralez et al. [37] Rc Fisher 158 51 (10) 38 29 4 of 9° Orralez et al. [37] Rc Fisher 158 51 (10) 38 29 4 of 9° Orralez et al. [38] Rc Fisher 158 55 (146) 31 43 3 of 9° Orralez et al. [39] Rc Fisher 276 55 (146) 31 43 3 of 9° Orralez et al. [39] Rc Fisher 276 55 (146) 31 43 40 (14) Orralez et al. [38] Rc Fisher 164 52 (n/a) 36 25 6 of 9° Orralez et al. [39] Rc Fisher 164 52 (n/a) 36 25 6 of 9° Orralez et al. [40] Rc Hijdra 91 54 (13) 25 36 7 of 8° Orralez et al. [41] Rc Hijdra 91 54 (13) 25 36 7 of 8° Orralez et al. [41] Rc Hijdra 91 54 (13) 37 40 (19) 40 (19) Orralez et al. [41] Rc Hijdra 413 n/a 29 n/a 4 of 8° Orralez et al. [41] Rc Hijdra 413 n/a 29 n/a 4 of 8°	Murayama et al. [20]	Rc	Fisher	69	52 (n/a)	26	23	4 of 7*
McCirt et al. [23] Rc Fisher 98 50 (n/a) 36 22 30 of 9° Dehdishit et al. [24] Pc Fisher 98 50 (n/a) 36 22 30 of 9° Kilimo et al. [25] Pc Fisher 167 35 (n/a) n/a 35 5 of 8° Singhal et al. [26] Pc Fisher 514 55 (14) 29 29 7 of 9° Beilly et al. [27] Rc Fisher 155 54 (14) 29 29 7 of 9° Hirashima et al. [29] Rc Fisher 115 54 (14) 20 29 7 of 9° Bilirashima et al. [29] Rc Fisher 115 54 (14) 30 21 8 of 9° Orrel et al. [31] Rc Fisher 115 52 (11) 39 51 5 of 9° Fonter at al. [31] Rc Fisher 115 54 (14) 32 43 30 of 8° McCirr et al. [33] Rc Fisher 158 51 (10)	Charpentier et al. [21]	Rc	Fisher	244	n/a	40	19	7 of 9*
Dehdashin et al. [24] Pc Fisher 98 50 (n/a) 36 22 3 of 9° Klimo et al. [25] Pc Fisher 167 35 (n/a) n/a 35 5 of 8° Singhal et al. [26] Pc Fisher 514 55 (14) 29 29 7 of 9° Reilly et al. [27] Rc Fisher 75 51 (14) 27 35 3 of 8° Hoh et al. [28] Pc Fisher 155 54 (14) 29 29 7 of 9° Hirsshims et al. [29] Rc Fisher 155 54 (14) 29 29 7 of 9° Smith et al. [30] Rc Fisher 155 54 (14) 29 30 21 8 of 9° Smith et al. [30] Rc Fisher 134 54 (n/a) 30 21 8 of 9° Smith et al. [30] Rc Fisher 113 52 (11) 39 51 5 of 9° Frontera et al. [9] Rc Fisher 115 54 (14) 32 43 3 of 8° McGirt et al. [32] Rc Fisher 115 54 (14) 32 43 3 of 8° McGirt et al. [33] Rc Fisher 115 54 (14) 32 43 3 of 8° McGirt et al. [33] Rc Fisher 158 51 (10) 38 29 4 of 9° Gonzalez et al. [35] Rc Fisher 158 59 (13) 30 43 6 of 9° Gonzalez et al. [35] Rc Fisher 276 559 (13) 36 24 7 of 9° Starke et al. [37] Pc Fisher 276 559 (13) 36 24 7 of 9° Kramer et al. [38] Rc Fisher 276 559 (13) 36 25 6 of 9° Rivero-Arias et al. [39] Rc Fisher 164 52 (n/a) 36 25 6 of 9° Dumont et al. [40] Rc Fisher 149 53.8 (1.1) 37 4 of 9° Kramer et al. [41] Rc Hijdra 138 n/a n/a 29 n/a 4 of 8° Kramer et al. [41] Rc Hijdra 143 n/a 29 n/a 4 of 8° Wousef et al. [43] Rc Fisher 210 54 (13) 22 4 of 9° Wilson et al. [44] Pc Fisher 30 43, 31, 31 30 43, 31 30 Wolfried Fisher 276 55 (13) 26 28 50 (7) Wilson et al. [48] Rc Fisher 30 44, 31 3 of 8° Wolfried Fish	Juvela et al. [22]	Pc	Fisher	70	46 (n/a)	51	41	6 of 9*
Klimo et al. [25] Pe Fisher 167 53 (m/a) m/a 35 5 of 8°	McGirt et al. [23]	Rc	Fisher	223	53 (15)	44	45	6 of 9*
Singhal et al. [26] Pc Fisher 514 55 (14) 29 29 7 of 9* Rellly et al. [27] Rc Fisher 515 51 (14) 27 35 3 of 8* Hoh et al. [28] Pc Fisher 115 54 (14) 29 29 7 of 9* Hirashima et al. [29] Rc Fisher 145 59.3 (13.3) 30 28 6 of 9* Smith et al. [31] Pc Fisher 134 54 (n/a) 30 21 8 c0 9* Ocrel et al. [31] Pc Fisher 135 52 (11) 30 21 8 c0 9* McCiff et al. [32] Rc Fisher 135 54 (14) 32 43 3 of 8* Oh et al. [33] Rc Fisher 135 51 (10) 38 29 4 of 9* Krishnamurthy et al. [34] Rc Fisher 126 85.0 (13.2) 40 27 5 of 8* Ohar et al. [35] Rc Fisher 276 55.9 (13.5)		Pc	Fisher	98	50 (n/a)	36	22	3 of 9*
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Hohet al. [28]	Singhal et al. [26]	Pc	Fisher	514	55 (14)	29	29	7 of 9*
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Smith et al. [30] Re Fisher 134 54 (n/a) 30 21 8 of 9* Oertel et al. [31] Pe Fisher 51 52 (11) 39 51 5 of 9* Frontera et al. [9] Re Fisher 115 52 (11) 39 51 5 of 9* McGirt et al. [32] Re Fisher 115 54 (14) 32 43 3 of 8* Oh et al. [33] Re Fisher 158 51 (10) 38 29 4 of 9* Krishamurthy et al. [34] Re Fisher 320 53.5 (14.6) 31 43 6 of 9* Onzalez et al. [35] Re Fisher 68 58.0 (13.2) 40 27 5 of 8* Dhar et al. [36] Pe Fisher 77 54 (12) 36 30 6 of 9* Starke et al. [37] Pe Fisher 13 53 (n/a) 32 26 6 of 9* Starke et al. [48] Re Fisher 13 53 (n/a)	Hoh et al. [28]	Pc	Fisher	515	54 (14)	29	29	7 of 9*
Octrel et al. [31] Pc Fisher 51 52 (11) 39 51 5 of 9* Frontera et al. [9] Re Fisher, Modified Fisher 1355 n/a n/a 33 7 of 9* McGirt et al. [32] Re Fisher 115 54 (14) 32 43 3 of 6* Oh et al. [33] Re Fisher 115 54 (10) 38 29 4 of 9* Krishnamurthy et al. [34] Re Fisher 320 53.5 (14.6) 31 43 6 of 9* Gonzalez et al. [35] Re Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [37] Pe Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [38] Re Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [39] Re Fisher 113 53.8 (1.1) 37 37 4 of 9* Rivero-Arias et al. [40] Re Hijdra 113 </td <td>Hirashima et al. [29]</td> <td>Rc</td> <td>Fisher</td> <td>145</td> <td>59.3 (13.3)</td> <td>30</td> <td>28</td> <td>6 of 9*</td>	Hirashima et al. [29]	Rc	Fisher	145	59.3 (13.3)	30	28	6 of 9*
Frontera et al. [9] Rc Fisher, Modified Fisher 1355 n/a n/a 33 7 of 9* McGirt et al. [32] Rc Fisher 115 54 (14) 32 43 3 of 8* Oh et al. [33] Rc Fisher 158 51 (10) 38 29 4 of 9* Krishnamurthy et al. [34] Rc Fisher 320 53.5 (14-6) 31 43 6 of 9* Gonzalez et al. [35] Rc Fisher 68 58.0 (13.2) 40 27 5 of 8* Dhar et al. [36] Pc Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [37] Pc Fisher 77 54 (12) 36 30 6 of 8* Kramer et al. [38] Rc Fisher 1644 52 (n/a) 36 25 6 of 9* Rivero-Arias et al. [39] Rc Fisher 113 53.8 (1.1) 37 37 4 of 9* Kramer et al. [40] Rc Hijdra 138 n/a n/a 28 6 of 9* Krainer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Krainer et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher 149 53.8 (10.5) 31 48 6 of 9* Oliveira et al. [44] Pc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher 149 53.8 (10.5) 31 48 6 of 9* Oliveira et al. [44] Pc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [45] Pc Modified Fisher 210 51 (2.5) 26 28 5 of 7† Oliveira et al. [46] RCT Modified Fisher 303 43.9 (12.4) 43 43 5 of 9* Wilson et al. [48] Rc Fisher 55 (6 (n/a) 27 22 6 of 9* Oliveira et al. [49] Pc Modified Fisher 29 55 (13) 26 36 6 of 8* Romero et al. [50] Pc Fisher 55 (31) 26 31 22 4 of 8* Oliveira dandani et al. [51] Rc Modified Fisher 29 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 50 (47 50 (n/a) 30 21 7 of 9* Dandapani et al. [54] Pc Fisher 57 49 (n/a) 52 29 4 of 9* Dandapani	Smith et al. [30]	Rc	Fisher	134	54 (n/a)	30	21	8 of 9*
McGirt et al. [32] Rc Fisher 115 54 (14) 32 43 3 of 8* Oh et al. [33] Rc Fisher 158 51 (10) 38 29 4 of 9* Krishnamurhy et al. [34] Rc Fisher 320 53.5 (14.6) 31 43 6 of 9* Conzalez et al. [35] Rc Fisher 68 58.0 (13.2) 40 27 5 of 8* Dhar et al. [36] Pc Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [37] Pc Fisher 77 54 (12) 36 30 6 of 8* Kramer et al. [43] Rc Fisher Modified Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [40] Rc Hijdra 138 n3k (11) 37 37 4 of 9* Kramer et al. [41] Rc Hijdra 138 n3k n.0 28 6 of 9* Kasius et al. [42] Rc Hijdra 13	Oertel et al. [31]	Pc	Fisher	51	52 (11)	39	51	5 of 9*
Oh et al. [33] Rc Fisher 158 51 (10) 38 29 4 of 9* Krishnamurthy et al. [34] Rc Fisher 320 53.5 (14.6) 31 43 6 of 9* Gonzalez et al. [35] Rc Fisher 68 58.0 (13.2) 40 27 5 of 8* Dhar et al. [36] Pc Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [37] Pc Fisher 277 54 (12) 36 30 6 of 8* Kramer et al. [38] Re Fisher, Modified Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [49] Re Fisher 164 52 (n/a) 36 25 6 of 9* Dumont et al. [40] Re Fisher 114 53.8 (10.5) 37 37 4 of 9* Kramer et al. [41] Re Hijdra 91 54 (13) 25 36 7 of 8* Vousef et al. [42] Re Fisher 149	Frontera et al. [9]	Rc	Fisher, Modified Fisher	1355	n/a	n/a	33	7 of 9*
Krishnamthy et al. [34] Rc Fisher 320 53.5 (14.6) 31 43 6 of 9* Gonzalez et al. [35] Rc Fisher 68 58.0 (13.2) 40 27 5 of 8* Dhar et al. [36] Pc Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [37] Pc Fisher 77 54 (12) 36 30 6 of 8* Kramer et al. [38] Rc Fisher, Modified Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [39] Rc Fisher 1644 52 (n/a) 36 25 6 of 9* Dumont et al. [40] Rc Hijdra 138 n/a n/a 28 6 of 9* Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kramer et al. [42] Rc Hijdra 138 n/a n/a 28 6 of 9* Kasius et al. [42] Rc Hijdra 13 5	McGirt et al. [32]	Rc	Fisher	115	54 (14)	32	43	3 of 8*
Gonzalez et al. [35] Rc Fisher 68 58.0 (13.2) 40 27 5 of 8* Dhar et al. [36] Pc Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [37] Pc Fisher 77 54 (12) 36 30 6 of 8* Kramer et al. [38] Rc Fisher, Modified Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [39] Rc Fisher 1644 52 (n/a) 36 25 6 of 9* Dumont et al. [40] Rc Modified Fisher 113 53.8 (1.1) 37 37 4 of 9* Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kasius et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Hijdra 413 <td>Oh et al. [33]</td> <td>Rc</td> <td>Fisher</td> <td>158</td> <td>51 (10)</td> <td>38</td> <td>29</td> <td>4 of 9*</td>	Oh et al. [33]	Rc	Fisher	158	51 (10)	38	29	4 of 9*
Dhar et al. [36] Pc Fisher 276 55.9 (13.5) 36 24 7 of 9* Starke et al. [37] Pc Fisher 77 54 (12) 36 30 6 of 8* Kramer et al. [38] Rc Fisher, Modified Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [39] Rc Fisher 1644 52 (n/a) 36 25 6 of 9* Kramer et al. [40] Rc Modified Fisher 113 53.8 (1.1) 37 37 4 of 9* Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kasius et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 9* Kasius et al. [42] Rc Hijdra 413 n/a n/a 28 6 of 9* Vousef et al. [43] Rc Fisher, modifed Fisher 2	Krishnamurthy et al. [34]	Rc	Fisher	320	53.5 (14.6)	31	43	6 of 9*
Starke et al. [37] Pc Fisher 77 54 (12) 36 30 6 of 8* Kramer et al. [38] Rc Fisher, Modified Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [39] Rc Fisher 1644 52 (n/a) 36 25 6 of 9* Dumont et al. [40] Rc Modified Fisher 113 53.8 (1.1) 37 37 4 of 9* Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kramer et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [45] Pc Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamimi et al. [46] RCT Modified Fisher 210<	Gonzalez et al. [35]	Rc	Fisher	68	58.0 (13.2)	40	27	5 of 8*
Kramer et al. [38] Rc Fisher, Modified Fisher 237 53 (n/a) 32 26 6 of 9* Rivero-Arias et al. [39] Rc Fisher 1644 52 (n/a) 36 25 6 of 9* Dumont et al. [40] Rc Modified Fisher 113 53.8 (1.1) 37 37 4 of 9* Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kasius et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Vousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher, modifed Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [45] Pc Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamimi et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fish	Dhar et al. [36]	Pc	Fisher	276	55.9 (13.5)	36	24	7 of 9*
Rivero-Arias et al. [39] Rc Fisher 1644 52 (n/a) 36 25 6 of 9* Dumont et al. [40] Rc Modified Fisher 113 53.8 (1.1) 37 37 4 of 9* Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kasius et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher, modifed Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [45] Pe Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamini et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7* Zhu et al. [47] Cc Modified Fisher 210 51 (2.5) 26 28 5 of 9* Wilson et al. [48] Rc Fisher <	Starke et al. [37]	Pc	Fisher	77	54 (12)	36	30	6 of 8*
Dumont et al. [40] Rc Modified Fisher 113 53.8 (1.1) 37 37 4 of 9* Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kasius et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher, modifed Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [44] Pc Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamimi et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fisher 210 51 (2.5) 26 28 5 of 7† Wilson et al. [48] Rc Fisher 218 54 (12) 26 21 4 of 9* de Rooij et al. [49] Pc Modified Fisher, Hijdra <td>Kramer et al. [38]</td> <td>Rc</td> <td>Fisher, Modified Fisher</td> <td>237</td> <td>53 (n/a)</td> <td>32</td> <td>26</td> <td>6 of 9*</td>	Kramer et al. [38]	Rc	Fisher, Modified Fisher	237	53 (n/a)	32	26	6 of 9*
Kramer et al. [41] Rc Hijdra 138 n/a n/a 28 6 of 9* Kasius et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 9* Oliveira et al. [44] Pc Fisher, modifed Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [45] Pc Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamimi et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fisher 303 43.9 (12.4) 43 43 5 of 9* Wilson et al. [48] Rc Fisher 218 54 (12) 26 21 4 of 9* Wilson et al. [49] Pc Modified Fisher, Hijdra 255 56 (n/a) 27 22 6 of 9* Ohnishi et al. [50] Pc Fisher	Rivero-Arias et al. [39]	Rc	Fisher	1644	52 (n/a)	36	25	6 of 9*
Kasius et al. [42] Rc Hijdra 91 54 (13) 25 36 7 of 8* Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher, modifed Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [45] Pc Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamimi et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [49] Rc Fisher 218 54 (12) 26 21 4 of 9* Wilson et al. [48] Rc Fisher 95 62.1 (n/a) 27 22 6 of 9* Wilson et al. [49] Pc Fisher 95	Dumont et al. [40]	Rc	Modified Fisher	113	53.8 (1.1)	37	37	4 of 9*
Yousef et al. [43] Rc Fisher 149 53.8 (10.5) 31 48 6 of 8* Oliveira et al. [44] Pc Fisher, modifed Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [45] Pc Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamimi et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fisher 303 43.9 (12.4) 43 43 5 of 9* Wilson et al. [48] Rc Fisher 218 54 (12) 26 21 4 of 9* de Rooij et al. [49] Pc Modified Fisher, Hijdra 255 56 (n/a) 27 22 6 of 9* Ohnishi et al. [50] Pc Fisher 95 62.1 (n/a) 44 23 5 of 9* Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc	Kramer et al. [41]	Rc	Hijdra	138	n/a	n/a	28	6 of 9*
Oliveira et al. [44] Pc Fisher, modifed Fisher 24 54 (11) 21 42 6 of 9* Ibrahim et al. [45] Pc Hijdra 413 n/a 29 n/a 4 of 8* Al-Tamimi et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fisher 303 43.9 (12.4) 43 43 5 of 9* Wilson et al. [48] Rc Fisher 218 5 4 (12) 26 21 4 of 9* de Rooij et al. [49] Pc Modified Fisher, Hijdra 255 56 (n/a) 27 22 6 of 9* Ohnishi et al. [50] Pc Fisher 95 62.1 (n/a) 44 23 5 of 9* Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc	Kasius et al. [42]	Rc	Hijdra	91	54 (13)	25	36	7 of 8*
Bibrahim et al. [45] Pc Hijdra 413 n/a 29 n/a 4 of 8*	Yousef et al. [43]	Rc	Fisher	149	53.8 (10.5)	31	48	6 of 8*
Al-Tamimi et al. [46] RCT Modified Fisher 210 51 (2.5) 26 28 5 of 7† Zhu et al. [47] Cc Modified Fisher 303 43.9 (12.4) 43 43 5 of 9* Wilson et al. [48] Rc Fisher 218 54 (12) 26 21 4 of 9* de Rooij et al. [49] Pc Modified Fisher, Hijdra 255 56 (n/a) 27 22 6 of 9* Ohnishi et al. [50] Pc Fisher 95 62.1 (n/a) 44 23 5 of 9* Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 75 3 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	Oliveira et al. [44]	Pc	Fisher, modifed Fisher	24	54 (11)	21	42	6 of 9*
Zhu et al. [47] Cc Modified Fisher 303 43.9 (12.4) 43 43 5 of 9* Wilson et al. [48] Rc Fisher 218 54 (12) 26 21 4 of 9* de Rooij et al. [49] Pc Modified Fisher, Hijdra 255 56 (n/a) 27 22 6 of 9* Ohnishi et al. [50] Pc Fisher 95 62.1 (n/a) 44 23 5 of 9* Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* Yousef et al. [53] Rc Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et	Ibrahim et al. [45]	Pc	Hijdra	413	n/a	29	n/a	4 of 8*
Wilson et al. [48] Rc Fisher 218 54 (12) 26 21 4 of 9* de Rooij et al. [49] Pc Modified Fisher, Hijdra 255 56 (n/a) 27 22 6 of 9* Ohnishi et al. [50] Pc Fisher 95 62.1 (n/a) 44 23 5 of 9* Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 753 53 (14) 34 11 6 of 9* <	Al-Tamimi et al. [46]	RCT	Modified Fisher	210	51 (2.5)	26	28	5 of 7†
de Rooij et al. [49] Pc Modified Fisher, Hijdra 255 56 (n/a) 27 22 6 of 9* Ohnishi et al. [50] Pc Fisher 95 62.1 (n/a) 44 23 5 of 9* Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc <	Zhu et al. [47]	Cc	Modified Fisher	303	43.9 (12.4)	43	43	5 of 9*
Ohnishi et al. [50] Pc Fisher 95 62.1 (n/a) 44 23 5 of 9* Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al.	Wilson et al. [48]	Rc	Fisher	218	54 (12)	26	21	4 of 9*
Karamchandani et al. [51] Rc Modified Fisher 259 55 (13) 26 36 6 of 8* Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	de Rooij et al. [49]	Pc	Modified Fisher, Hijdra	255	56 (n/a)	27	22	6 of 9*
Romero et al. [52] Pc Fisher 100 48 (n/a) 56 n/a 4 of 9* Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	Ohnishi et al. [50]	Pc	Fisher	95	62.1 (n/a)	44	23	5 of 9*
Yousef et al. [53] Rc Fisher 164 54 (n/a) 28 57 6 of 8* de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	Karamchandani et al. [51]	Rc	Modified Fisher	259	55 (13)	26	36	6 of 8*
de Oliveira Manoel et al. [54] Pc Modified Fisher 693 53 (12) 31 22 4 of 8* Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	Romero et al. [52]	Pc	Fisher	100	48 (n/a)	56	n/a	4 of 9*
Calviere et al. [55] Pc Fisher 30 45 (12) 37 20 5 of 9* Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	Yousef et al. [53]	Rc	Fisher	164	54 (n/a)	28	57	6 of 8*
Dhandapani et al. [56] Pc Fisher 75 49 (n/a) 52 29 4 of 9* Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	de Oliveira Manoel et al. [54]	Pc	Modified Fisher	693	53 (12)	31	22	4 of 8*
Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*	Calviere et al. [55]	Pc	Fisher	30	45 (12)	37	20	5 of 9*
Rodriguez-Régent et al. [57] Pc Fisher 47 50 (n/a) 30 21 7 of 9* Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*		Pc		75		52	29	4 of 9*
Malinova et al. [58] Pc Fisher 753 53 (14) 34 11 6 of 9* Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*		Pc		47	50 (n/a)	30	21	7 of 9*
Kozak et al. [59] Rc Fisher 457 47.2 (11) 41 23 7 of 9* Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*		Pc		753	53 (14)		11	
Behrouz et al. [60] Rc Fisher 135 43 (15) 41 24 5 of 8*		Rc		457		41	23	7 of 9*
		Rc	Fisher	135		41	24	5 of 8*
	Mijiti et al. [61]	Rc	Modified Fisher	343	n/a	39	29	7 of 9*



Table 1 (continued)

Author	Study type	Radiological scale	Patients	Mean age (± SD)	Male sex (%)	DCI (%)	Study quality
Aldakkan et al. [62]	Pc	Fisher	191	51 (13)	15	41	5 of 9*
Oda et al. [63]	Rc	Fisher, Hijdra	151	61 (14)	30	23	5 of 8*
Griessenauer et al. [64]	Pc	Fisher, Modified Fisher, Hijdra	149	55 (13)	24	23	6 of 9*
Rostami et al. [65]	Pc	Fisher	30	58.9 (n/a)	17	30	3 of 7*

Pc prospective cohort, RCT randomized controlled trial, Rc retrospective cohort, Cc case—control study, n/a not available

(1.87–5.49) for Fisher 3 (Fig. Fig. 2b), and 2.21 (1.49–3.28) for Fisher 4 (Fig. Fig. 2c), respectively. Patients with Fisher 4 had a significantly lower risk of DCI compared to patients with Fisher 3 (OR (95% CI) 0.60 (0.37–0.97)) (Table 2).

There was no relevant statistical heterogeneity between the studies: the l^2 ranged between 0 and 20%. Visual inspection of the funnel plot showed a symmetrical distribution of the study effects (Online supplemental Fig. 2).

Modified Fisher scale

The modified Fisher scale was used in 11 studies (21%), including 3941 patients. Seven studies (2476 patients) included patients for all modified Fisher grades and provided data on the number of patients in each grade (Online supplemental Fig. 1). The majority of the studies grouped modified Fisher 0 and 1 together. A mean percentage of 20 (SD 4; range 11–29) was classified as modified Fisher 0–1, 11 (SD 4; range 0–20) as modified Fisher 2, 30 (SD 7; range 14–46) as modified Fisher 3, and 39 (SD 10; range 34–61) as modified Fisher 4.

Crude data on the number of patients that developed DCI in each modified Fisher grade was extracted from 5 studies (2085 patients). A mean percentage of 21 (SD 7; range 5–24) of patients with modified Fisher 0–1, 26 (SD 9; range 0–33) of patients with modified Fisher 2, 30 (SD 9; range 5–36) of patients with modified Fisher 3, and 42 (SD 9; range 34–83) of patients with modified Fisher 4 developed DCI.

The modified Fisher grade was significantly associated with DCI in 7 of 8 (88%) of studies that performed a univariable analysis and in 8 of 9 (89%) studies that performed a multivariable analysis.

Of the 5 studies that reported patients for all modified Fisher grades, 4 (1959 patients) provided data on occurrence of DCI that allowed to calculate a pooled OR by dichotomized modified Fisher grade. The pooled OR (95% CI) for DCI was 2.31 (1.40–3.81) for modified Fisher 3–4 compared to modified Fisher 0–2. No pooled OR per grade increase on the modified Fisher was calculated; as of three studies (1616 patients) that provided data for the occurrence of DCI in all

modified Fisher grades, one study included 84% of the patients.

Hijdra sum score

The Hijdra sum score was used in 6 studies (11%), including 1197 patients. Mean Hijdra score in 4 studies (1048 patients) was 19 (SD 2; range 17–23). In two studies (289 patients) that reported the mean Hijdra score stratified by occurrence of DCI, mean Hijdra score was 24 (SD 2; range 22–26) in patients with DCI and 14 (SD 1; range 15–15) in patients without DCI.

The Hijdra score was significantly associated with DCI in both studies that performed univariable analysis and in all four studies that performed multivariable analysis. None of the studies provided crude data that allowed for calculating a pooled OR.

Sensitivity analysis

A sensitivity analysis was performed in the meta-analysis of the Fisher scale. Four studies (3254 patients) diagnosed DCI using clinical signs only, whereas the other 6 studies (673 patients) combined clinical signs with angiographic vasospasm. In studies that used clinical signs only to diagnose DCI, both Fisher 3 (OR (95%CI) 2.48 (1.70–3.60)) and Fisher 4 (OR (95%CI) 2.11 (1.23–3.61)) were significantly associated with DCI. In studies combining clinical signs with angiographic vasospasm to diagnose DCI, Fisher 3 (OR (95%CI) 8.79 (2.08–37.12)) was significantly associated with DCI (Online supplemental Table 1).

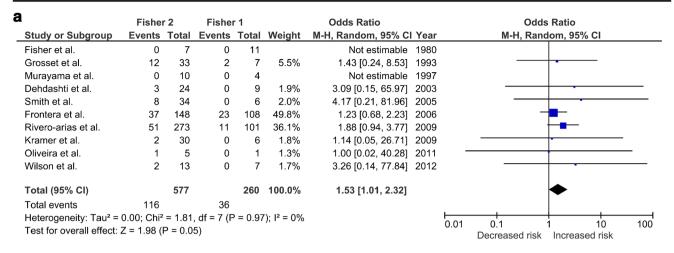
Discussion

In this systematic review, pooled analysis of the Fisher scale showed that all Fisher grades have an increased risk of clinical DCI compared to Fisher 1, with Fisher 3 patients having the highest risk of DCI. Nevertheless, the highest rate of DCI was seen in patients with modified



^{*}Scored on the NOS scale

[†]Scored on the Cochrane Handbook risk of bias tool for randomized controlled trials scale



	Fishe	r 3	Fisher	· 1		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yo	ear	M-H, Random, 95% CI
Fisher et al.	23	24	0	11	2.6%	360.33 [13.59, 9551.34] 19	980	
Grosset et al.	27	53	2	7	8.3%	2.60 [0.46, 14.59] 19	993	-
Murayama et al.	13	47	0	4	3.1%	3.52 [0.18, 69.94] 19	997	-
Dehdashti et al.	10	31	0	9	3.2%	9.28 [0.49, 175.17] 20	003	-
Smith et al.	7	25	0	6	3.0%	5.27 [0.26, 105.75] 20	005	
Frontera et al.	339	917	23	108	39.6%	2.17 [1.34, 3.50] 20	006	
Kramer et al.	53	151	0	6	3.3%	7.06 [0.39, 127.77] 20	009	-
Rivero-arias et al.	187	692	11	101	31.4%	3.03 [1.58, 5.79] 20	009	
Oliveira et al.	2	7	0	1	2.2%	1.36 [0.04, 46.65] 20	011	-
Wilson et al.	42	182	0	7	3.3%	4.54 [0.25, 81.09] 20	012	-
Total (95% CI)		2129		260	100.0%	3.21 [1.87, 5.49]		•
Total events	703		36					
Heterogeneity: Tau ² =	0.13; Chi ²	= 11.3	2, df = 9 (P = 0.2	$(25); I^2 = 20$)%	<u> </u>	.01 0.1 1 10 1
Test for overall effect:	Z = 4.25 (P < 0.0	001)				U.	.01 0.1 1 10 1 Decreased risk Increased risk

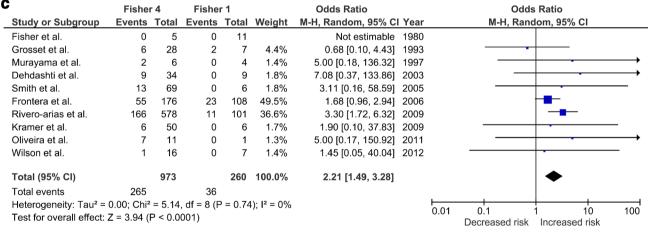


Fig. 2 a Forest plot comparing risk of DCI of Fisher 2 with Fisher 1 patients. b Forest plot comparing risk of DCI of Fisher 3 with Fisher 1 patients. c Forest plot comparing risk of DCI of Fisher 4 with Fisher 1 patients

Fisher 4. For the modified Fisher and Hijdra sum score, no pooled ORs per individual grade could be calculated. Fisher grades were significantly associated with DCI in less studies compared to the other radiological grades. The results of this review should be interpreted with care as the risk of bias was high in the included studies.

To our knowledge, this is the first systematic review assessing the association of radiological scales for grading SAH with DCI. One narrative review reported an overview of all available radiological scales for predicting vasospasm until 2006; however, no associations with DCI were presented in this review [6]. A recent systematic review assessed all risk



 Table 2
 Pooled odds ratios for development of delayed cerebral ischemia

	Fisher 1	Fisher 2	Fisher 3
Fisher 1	Reference		
Fisher 2	1.53 (1.01–2.32)	Reference	
Fisher 3	3.21 (1.87–5.49)	2.10 (1.40–3.15)	Reference
Fisher 4	2.21 (1.49–3.28)	1.38 (0.93–2.05)	0.60 (0.37-0.97)

factors for DCI showing that smoking is an established predictor of DCI; however, the radiological scales were not assessed in this review [49].

Fisher et al. showed that patients with Fisher 3 had the highest risk of vasospasm, a well-known cause of DCI [7]. Our review showed that patients with Fisher 3 also have the highest risk of clinical DCI (OR 3.2). The pooled analysis further showed that patients with Fisher 4 have a significantly lower risk of DCI compared to Fisher 3 patients. The main difference between Fisher 3 and Fisher 4 is the presence of blood outside the subarachnoid space in Fisher 4 with extension to the ventricles (IVH) or parenchyma (IPH). The thickness of SAH does not play a role in the scale difference. Habitually, most Fisher 4 patients will have a larger quantity of SAH and part of this blood is "escaping" to the ventricular system. However, even in patients with a perimesencephalic hemorrhage, blood can migrate into the 4th ventricle, upgrading these patients with a low tendency to develop DCI to a Fisher grade 4. This might explain the lower rate of DCI in Fisher grade 4 versus grade 3 patients. Furthermore, due to the presence of an IPH, Fisher 4 patients may be in poorer clinical condition which masks clinical deterioration [66]. The Fisher scale lacks a separate grade for patients with both thick SAH and IVH, which the modified Fisher does have. As such, patients with both thick SAH and IVH cannot be categorized in a Fisher grade.

In our sensitivity analysis, we analyzed if the strength of the association between the Fisher scale and DCI is dependent on the definition of DCI. The OR for DCI in Fisher 3 patients was higher in studies that used clinical deterioration and angiographic vasospasm to diagnose DCI, compared to those using clinical signs only. However, this high OR may be largely due to the inclusion of the results from the original paper by Fisher et al., in which patients were included with angiographic vasospasm as part of the definition of DCI. In this study all patients that developed DCI were graded as Fisher 3 [7]. Furthermore, confidence intervals were broad so no firm conclusions can be drawn based on this data.

We could not collect sufficient comparable data to calculate pooled ORs per grade of the modified Fisher scale and Hijdra sum score. We believe there are several reasons for this. There were a considerably lower number of studies using these scales. Even after the introduction of the modified Fisher in 2006, the Fisher scale was the most frequently used scale in the studies included in this review. As this was also the case for studies published in the last 5 years, this is not only due to later introduction of the scale. The Hijdra sum score may be too extensive and cumbersome for widespread usage, as this score requires grading of the amount of blood in ten basal cisterns and four ventricles separately. Another reason for not pooling the data is the large variability in data reporting. The usage of a wide range of definitions for DCI resulted in the exclusion of many studies that did not use a clinical definition of DCI. Furthermore, various categories of radiological grades were frequently grouped together, and a variety of effect estimates was used.

One of the most important strengths of this review is the presentation of the first formal meta-analysis on the association of the Fisher scale with DCI. The usage of clinical DCI as end point resulted in more homogeneous outcome data. The use of clinical DCI as endpoint is also a limitation of this study. This diagnosis may be more subjective and have a higher interobserver variation compared to radiological DCI. Furthermore, clinical DCI cannot be diagnosed in comatose patients. However, as follow-up imaging is frequently not routinely made, the clinical relevance of radiological DCI remains questionable. Finally, as not for all studies the risk of publication bias could be evaluated by a funnel plot, a publication bias may have occurred.

This review shows several advantages of the modified Fisher scale over the Fisher scale for clinical practice. Firstly, even though no pooled OR could be calculated, modified Fisher 4 patients had the highest rate of DCI. This may show that this scale identifies the group which has the highest risk of DCI. Secondly, the modified Fisher scale shows an increasing risk of DCI per grade increase on the scale, whereas the Fisher scale does not. This is counter-intuitive for a scale that is developed to predict DCI and makes the scale less suitable for clinical practice. Thirdly, the Fisher scale was in just over half of the included studies significantly associated with DCI. This may show the limited ability of the Fisher scale to differentiate between patients with a high and a low risk of DCI. In contrast, the other scales were more frequently associated with DCI. For the Hijdra sums score, not enough comparable data could be collected. Thus, the possibility that the Hijdra score has a higher association to DCI as the Fisher and modified Fisher score cannot be ruled out. Recently, new radiological scales like the Barrow Neurological Institute SAH Grading Scale, incorporation of the Modified Graeb score to the modified Fisher, and quantification of SAH volume have been introduced [67, 68–71]. These scales measure the amount of blood in a more quantitative manner and have shown high associations with DCI and reduced interobserver variability.



Conclusion

This review shows that the Fisher scale, modified Fisher scale, and Hijdra sum score are all associated with clinical DCI. The risk of DCI, however, does not increase with increasing Fisher scale as opposed to the other grading scales. Furthermore, the modified Fisher scale was more commonly significantly associated with clinical DCI than the Fisher scale, which may advocate the use of the modified Fisher in future SAH-related studies.

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Compliance with ethical standards

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Competing interests The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Statement of informed consent was not applicable since the authors did not collect any patient data.

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