Lack of impact of polycystic kidney disease on the outcome of aneurysmal subarachnoid hemorrhage: a matched case-control study

Heidi J. Nurmonen, BM,^{1–3} Terhi Huttunen, MD, PhD,¹ Jukka Huttunen, MD, PhD,¹ Arttu Kurtelius, MD, PhD,^{1,2} Satu Kotikoski, BM,^{1,2} Antti Junkkari, MD, PhD,¹ Timo Koivisto, MD, PhD,^{1,2} Mikael von und zu Fraunberg, MD, PhD,^{1,2} Olli-Pekka Kämäräinen, MD, PhD,^{1,2} Maarit Lång, MD,^{2,4} Helena Isoniemi, MD, PhD,⁶ Juha E. Jääskeläinen, MD, PhD,^{1,2} and Antti E. Lindgren, MD, PhD^{1,2,5}

¹Neurosurgery of NeuroCenter, Kuopio University Hospital and University of Eastern Finland, Kuopio; ²School of Medicine, Institute of Clinical Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio; ³Kuopio Health Center, Kuopio; ⁴Neurointensive Care and ⁵Department of Clinical Radiology, Kuopio University Hospital, Kuopio; and ⁶Transplantation and Liver Surgery Clinic, Abdominal Center, Helsinki University Hospital, Helsinki, Finland

OBJECTIVE The authors set out to study whether autosomal dominant polycystic kidney disease (ADPKD), an established risk factor for intracranial aneurysms (IAs), affects the acute course and long-term outcome of aneurysmal subarachnoid hemorrhage (aSAH).

METHODS The outcomes of 32 ADPKD patients with aSAH between 1980 and 2015 (median age 43 years; 50% women) were compared with 160 matched (age, sex, and year of aSAH) non-ADPKD aSAH patients in the prospectively collected Kuopio Intracranial Aneurysm Patient and Family Database.

RESULTS At 12 months, 75% of the aSAH patients with ADPKD versus 71% of the matched-control aSAH patients without ADPKD had good outcomes (Glasgow Outcome Scale score 4 or 5). There was no significant difference in condition at admission. Hypertension had been diagnosed before aSAH in 69% of the ADPKD patients versus 27% of controls ($p < 0.001$). Multiple IAs were present in 44% of patients in the ADPKD group versus 25% in the control group ($p = 0.03$). The most common sites of ruptured IAs were the anterior communicating artery (47% vs 29%, $p = 0.05$) and the middle cerebral artery bifurcation (28% vs 31%), and the median size was 6.0 mm versus 8.0 mm ($p = 0.02$). During the median follow-up of 11 years, a second aSAH occurred in 3 of 29 (10%) ADPKD patients and in 4 of 131 (3%) controls ($p = 0.11$). A fatal second aSAH due to a confirmed de novo aneurysm occurred in 2 (6%) of the ADPKD patients but in none of the controls ($p = 0.027$).

CONCLUSIONS The outcomes of ADPKD patients with aSAH did not differ significantly from those of matched non-ADPKD aSAH patients. ADPKD patients had an increased risk of second aSAH from a de novo aneurysm, warranting long-term angiographic follow-up.

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KEYWORDS ruptured intracranial aneurysm; subarachnoid hemorrhage; polycystic kidney; autosomal dominant; vascular disorders

AUTOSOMAL dominant polycystic kidney disease (ADPKD), characterized by bilateral enlarged cystic kidneys, is a serious multisystem disease.¹ In most cases caused by a *PKD1* or *PKD2* mutation, it is carried by 1:1000–1:2500 according to population sequencing.^{2,3} In 10%–25% of patients, there is no clear family history.⁴ Clinical penetration and the course of renal disease

and other manifestations vary, even within an ADPKD family.⁵ The majority of ADPKD patients develop kidney failure requiring dialysis at a median age of 55 years,^{6,7} often followed by kidney transplantation. A vasopressin V2 antagonist may delay disease progression.⁸ Hypertension is present already in 35% of patients before the age of 18 years, and in 60% it precedes a decline in renal function.⁹

ABBREVIATIONS AComA = anterior communicating artery; ADPKD = autosomal dominant polycystic kidney disease; aSAH = aneurysmal subarachnoid hemorrhage; GOS = Glasgow Outcome Scale; IA = intracranial aneurysm; KUH = Kuopio University Hospital; MCA = middle cerebral artery.

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ADPKD predisposes patients to several cardiovascular manifestations, e.g., valve insufficiency, left ventricular hypertrophy, and aneurysms, and dissections in extracranial and intracranial arteries.⁵

Aneurysmal subarachnoid hemorrhage (aSAH), usually from rupture of a saccular intracranial aneurysm (IA), has an incidence of 9 per 100,000 patient-years¹⁰ and a peak age in the 6th decade of life.¹¹ Risk factors include smoking, hypertension, female sex, family history of saccular IA, and ADPKD.¹¹

As has been established, approximately 10% of ADPKD patients harbor unruptured IAs in their lifetime.¹² Up to 6% of ADPKD patients might die of aSAH.¹³ In a recent prospective series of 495 ADPKD patients, the incidence of SAH was 2.0 per 1000 patient-years.¹⁴ Family history of IA disease¹² and a mutation near the 5' end of *PKD1*¹⁵ are the only known risk factors for IAs within this population, and their absence does not rule out the possibility of IAs. ADPKD patients experience aSAH approximately 10 years earlier than the general population, and their aneurysms are smaller at rupture.¹⁶ These patients also seem to be at an increased risk of developing de novo aneurysms after surviving aSAH.¹⁶

The Kuopio Intracranial Aneurysm Patient and Family Database contains data on all patients with ruptured and unruptured IAs who were admitted to the Kuopio University Hospital (KUH) from a defined Eastern Finnish population since 1980. Here, we compared 32 ADPKD patients with 160 matched (age at aSAH, year of aSAH, and sex) non-ADPKD patients with their first aSAH. Our aim was to evaluate the impact of ADPKD on the acute course and long-term outcome of aSAH.

Methods

Catchment Population of KUH

Finland is divided into catchment areas of 5 publicly funded university hospitals. Kuopio Neurosurgery and Neurointensive Care have solely provided acute and elective neurosurgical care for the Eastern Finnish catchment population. Between 1980 and 2015, the population decreased from 824,823 to 815,093 while the geographic area remained unchanged; the proportion of males increased from 49% to 49.5%.¹⁶

Management Protocol of aSAH in Eastern Finland

All SAH patients, diagnosed by CT scanning or lumbar puncture, are transferred acutely to KUH for neurointensive care, 4-vessel digital subtraction angiography, and neurosurgical care, including microsurgical or endovascular IA occlusion if not moribund or very aged. Neurointensive care is provided regardless of the condition on admission, including comatose Hunt and Hess grade V patients, by a team of neurointensivists, neurosurgeons, and neuroradiologists according to international recommendations.¹⁷

The Kuopio Intracranial Aneurysm Patient and Family Database

KUH Neurosurgery maintains a database, prospective since 1990, of all cases of patients with angiographically

verified ruptured or unruptured IAs, admitted to KUH since 1980. The database is managed by a full-time coordinator, who interviews all patients and codes the data, including family history of IA, hospital periods, and follow-up visits. Clinical data, including the hospital diagnoses, prescribed medicines, and causes of death, are obtained from the national registries using unique social security numbers since 1995. The database, including 5250 IA patients at present, has been extensively studied for phenotype on admission, risk factors, concomitant diseases, outcome, and IA genetics.^{18–23}

Identification of IA Patients With ADPKD

Between 1980 and 2015, 4436 patients with IA were admitted to KUH Neurosurgery from the Eastern Finnish catchment population. In the KUH IA database, 53 IA patients with ADPKD were identified and consisted of those who 1) had been diagnosed with ADPKD before IA; 2) had ADPKD confirmed at autopsy after aSAH; 3) were diagnosed with ADPKD after IA and informed the nurse coordinator of the database of this at a control visit; and 4) have had an ICD-10 diagnosis code of either Q61.2 (polycystic kidney, adult type) or Q61.3 (polycystic kidney, nonspecified) in the Finnish national database of hospital diagnoses. Their patient records were carefully reviewed.¹⁶ Thirty-three patients presented with aSAH and 20 with an unruptured IA. One patient was excluded, giving us the final study cohort of 32 ADPKD patients with aSAH.

Current Study Groups

The study group includes the ADPKD patients admitted alive to KUH between 1980 and 2015 with their first aSAH. The control group includes 5 non-ADPKD control patients admitted alive to KUH between 1980 and 2015 with their first aSAH for each ADPKD aSAH patient, matched by sex, age at aSAH, and year of aSAH (Fig. 1). In case-control matching (IBM SPSS Statistics version 22.0, IBM Corp.), priority was given to exact matches, but a range of 3 years in age and 5 years for the year of aSAH were allowed for a sufficient number of controls. The records of the controls were rereviewed to exclude ADPKD and family history of ADPKD.

Variables

The variables used to compare the groups are presented in Tables 1–3. Familial saccular IA disease was defined as ≥ 2 affected first-degree relatives. Hypertension was defined as one of the following: diagnosis of hypertension, antihypertensive medication started before aSAH, or self-reported diagnosis. Kidney function was defined by the glomerular filtration rate, estimated using the CKD-EPI (Chronic Kidney Disease–Epidemiology Collaboration) formula.²⁴ Data on dialysis or kidney transplantation, before or after aSAH, were obtained from the medical records and national clinical data, including the Finnish National Transplantation Registry.

Statistical Analysis

Categorical variables are expressed as proportions and continuous variables as medians, IQRs, and ranges. The 2

FIG. 1. Flowchart of patient inclusion in the present study.

groups were compared using the chi-square test, Fisher's exact test, Mood's median test, and Mann-Whitney U-test, as appropriate; $p \leq 0.05$ was considered significant. Multivariate analysis was not performed due to the small num-

ber of ADPKD patients. Kaplan-Meier analysis with the log-rank test was used to compare the cumulative mortality rates after aSAH. In survival analysis, follow-up was calculated from the date of SAH until death or the last date of follow-up. IBM SPSS Statistics (version 22.0, IBM Corp.) was used for statistical analyses.

Ethical Issues

This study was approved by the ethics committee of KUH. The study was conducted according to the Declaration of Helsinki, and all patients provided informed consent. Data fusion from the Finnish nationwide registries was approved by the Ministry of Social Affairs and Health of Finland.

Results

Patient Groups

There were 32 ADPKD patients with aSAH, 16 females and 16 males (1:1), with median ages of 44 years and 39 years, respectively (Fig. 1 and Table 1). The patients were compared with the 160 matched non-ADPKD control aSAH patients. Hypertension was diagnosed before aSAH in 69% (22/32) of the ADPKD patients and in 27% (43/160) of the controls ($p < 0.001$). Among the 32 ADPKD patients, 19% (6/32) had moderately to severely decreased kidney function at aSAH, none were on dialysis, and 1 patient already had received a donor kidney. Twenty-seven percent of the ADPKD patients had normal kidney function at the time of admission for aSAH, and in 56%, the serum creatinine level was within the normal range.

Clinical Condition on Admission

The ruptured aneurysms of ADPKD patients were sig-

TABLE 1. Baseline characteristics of the 32 study patients and the 160 matched control patients

Variable	aSAH Patients w/ ADPKD (n = 32)	Matched aSAH Patients w/o ADPKD (n = 160; 5:1)	p Value
Female sex, n (%)	16 (50)	80 (50)	Matched
Median age on admission, yrs (IQR)	43 (34–51)	43 (34–51)	Matched
Familial sIA disease, n (%)	0 (0)	18 (11)	0.047
Smoking, current or former, n (%)	10 (31)	63 (39)	NS
Hypertension diagnosed before aSAH, n (%)	22 (69)	43 (27)	<0.001
Diabetes diagnosed before aSAH, n (%)	0 (0)	8 (5)	NS
Median age at ADPKD diagnosis, yrs (IQR)*	42 (30–53)		
Kidney function on admission†			
Median eGFR, ml/min (IQR)	83 (61–98)	98 (85–108)	0.005
Normal function (≥ 90), n (%)	7 (27)	86 (67)	<0.001
Mild decrease (60–89), n (%)	13 (50)	39 (30)	
Moderate decrease (30–59), n (%)	5 (19)	3 (2)	
Severe decrease (15–29), n (%)	1 (4)	0 (0)	
Kidney failure (<15), n (%)	0 (0)	0 (0)	
Kidney transplantation/dialysis before aSAH, n	1/0	0/0	

eGFR = estimated glomerular filtration rate; NS = not significant; sIA = saccular IA.

* Data were missing in 15 patients.

† Data were missing in 6 and 32 patients in the ADPKD and non-ADPKD groups, respectively.

TABLE 2. Clinical condition on admission to neurointensive care of 32 ADPKD patients and 160 matched control patients with aSAH

Variable	aSAH Patients w/ ADPKD (n = 32)	Matched aSAH Patients w/o ADPKD (n = 160)	p Value
Hunt & Hess grade, n (%)			
I	4 (12)	17 (11)	NS
II	13 (41)	72 (45)	NS
III	8 (25)	29 (18)	NS
IV	6 (19)	31 (19)	NS
V	1 (3)	10 (6)	NS
Acute CT findings, n (%)			
Subdural hematoma	2 (6)	7 (4)	NS
Intracerebral hemorrhage	6 (19)	45 (28)	NS
Intraventricular hemorrhage	8 (25)	53 (34)	NS
Hydrocephalus	13 (41)	72 (46)	NS
Extraventricular drainage, n (%)	11 (34)	51 (32)	NS
Meningitis treated, n (%)	1 (3)	21 (13)	NS
Delayed cerebral ischemia, n (%)			
Vasospasm on angiography	5 (16)	37 (23)	NS
Delayed cerebral ischemia clinically	7 (22)	38 (24)	NS
Both of the above	4 (12)	25 (16)	NS
Site of ruptured IA, n (%)			
ACoMA	15 (47)	47 (29)	0.054
A ₂ –A ₅	1 (3)	7 (4)	NS
MCA bifurcation	9 (28)	49 (31)	NS
Other MCA segments	3 (9)	10 (6)	NS
ICA	3 (9)*	12 (8)	NS
PCoMA	0 (0)	17 (11)	0.054
BA bifurcation	0 (0)	5 (3)	NS
Other	1 (3)	13 (8)†	NS
Size of ruptured IA, mm‡			
Median	6.0	8.0	0.022
<5, n (%)	10 (32)	24 (16)	0.032
5–10, n (%)	17 (55)	84 (55)	NS
>10, n (%)	4 (13)	44 (29)	NS
Multiple IAs, n (%)	14 (44)	40 (25)	0.031
Ruptured IA etiology, n (%)			NS
Saccular	31	158	
Fusiform	1	2	
Wall, n (%)			NS
Irregular	29 (91)	146 (91)	
Smooth	2 (6)	11 (7)	
Not available	1 (3)	3 (2)	
Treatment of ruptured IA, n (%)			
Open microsurgery	25 (78)	120 (75)	NS
Endovascular	4 (12)	29 (18)	NS
Conservative	3 (9)	11 (7)	NS

BA = basilar artery; ICA = internal carotid artery; PCoMA = posterior communicating artery.

* One IA was fusiform.

† Two IAs were fusiform.

‡ Size was not known in 1 patient in the ADPKD group and 8 in the non-ADPKD group.

TABLE 3. Outcome of 32 ADPKD patients and 160 matched control patients after aSAH

Variable	aSAH Patients w/ ADPKD (n = 32)	Matched aSAH Patients w/o ADPKD (n = 160)	p Value
Mortality, n (%)			
at 1 mo	3 (9)	22 (14)	NS
at 12 mos	3 (9)	29 (18)	NS
at 5 yrs	5 (16)	34 (21)	NS
at 10 yrs	8 (25)	44 (28)	NS
Leading causes of death, n (%)			
aSAH w/ late effects	6 (19)	32 (20)	
Cancer		10 (6)	
ADPKD	3 (9)		
Cardiovascular disease	2 (6)	8 (5)	
Good outcome (GOS 4 or 5) at 12 mos, n (%)	24 (75)	114 (71)	NS
Poor outcome (GOS 1–3) at 12 mos, n (%)	8 (25)	46 (29)	NS
Second SAH after surviving 12 mos, n (%)	3/29 (9)	4/131 (3)	0.092
Returned to previous profession, n (%)*	18 (60)	78 (54)	NS
Median age at death, yrs (range)	64 (33–82)	58 (20–92)	NS

* Of those who were working before the ictus.

nificantly smaller than those of the control patients (median 6.0 vs 8.0 mm, $p = 0.022$) (Table 2). There were more small (< 5 mm) ruptured IAs in the ADPKD patients than in the control group (32% vs 16%, $p = 0.032$). Presenting with multiple aneurysms at initial diagnosis was more common among the ADPKD patients (44% vs 25%, $p = 0.031$). There were no statistically significant differences in aneurysm location or aneurysm shape between the groups. Distribution of saccular and fusiform aneurysms was similar.

Aneurysmal SAH Presentation

The median Hunt and Hess grade at admission among both groups was II: 41% among the ADPKD patients and 45% among the controls. We found no statistically significant differences in the prevalence of aSAH complications, such as intracerebral hematoma or delayed ischemic complication. Clinical characteristics of aSAH in the 2 groups are presented in Table 2.

Outcome at 12 Months

At 12 months, 9% in the ADPKD group versus 18% in the non-ADPKD group had died ($p = 0.23$), while 75% versus 71% had good functional outcome (Glasgow Outcome Scale [GOS] score 4 or 5) (Table 3). Outcome was poor (GOS score 1–3) in 25% versus 29% ($p = 0.67$); 60% versus 54% of the individuals working before aSAH returned to their previous occupation.

Recurrent Hemorrhage

In total, a second SAH occurred in 3 ADPKD (2, 7, and 10 years after the initial hemorrhage) and 4 control (2, 6, 10, and 22 years) patients ($p = 0.06$), which was in 2 ADPKD patients (patients A and B) but in none of the control patients from a confirmed de novo aneurysm ($p = 0.03$). The recurrent SAH was fatal in 5 of the 7 (71%) patients.

Patient A was a female with normal kidney function, a smoker, with no hypertension, who experienced aSAH at the age of 22 years due to an 8-mm aneurysm in the middle cerebral artery (MCA). Ten years later, the patient had a second aSAH due to a 5-mm de novo aneurysm of the anterior communicating artery (AComA). She also had 2 new unruptured de novo IAs (basilar artery and internal carotid artery). She survives and works in her previous profession. Patient B was a female with normal kidney function, a smoker with hypertension who had aSAH at the age of 26 years due to an MCA aneurysm. She recovered well apart from epilepsy and returned to her previous profession. Seven years later, now with end-stage kidney failure, she had a second aSAH due to a 4-mm de novo aneurysm of the pericallosal artery, and also an unruptured de novo IA (AComA). The second aSAH was fatal.

Outcome After 12 Months

The median follow-up time was 15 years (447 patient-years) for the 29 ADPKD patients and 17 years (2266 patient-years) for the 131 non-ADPKD patients alive at 12 months (Table 3). At 10 years, the cumulative survival rates were 80% versus 85% (Fig. 2). Shunt-dependent hydrocephalus developed in 6% versus 11% of patients. Nine (31%) ADPKD patients had a kidney transplant at a median of 10 years after aSAH (range 3–23 years).

Discussion

In this matched case-control study, we found no difference in aSAH outcome between ADPKD aSAH patients and their matched controls. This is the first study to compare the phenotype and outcome of aSAH between ADPKD patients and a 5-fold matched population control group of aSAH patients without ADPKD.

In our study, case fatality in ADPKD patients with first aSAH was 9% at 12 months. In previous cohorts,

case fatalities ranging from 10% at 3 months²⁵ to 55% at 6 months²⁶ have been reported. In a meta-analysis of 160 aSAH patients, 43% were dead and 21% were dependent.²⁷ Aneurysmal SAH is diverse in presentation, and the best predictor of outcome is the level of consciousness on admission.^{28,29} In our cohort of young (median age 43 years) aSAH patients, the median Hunt and Hess grade was II in both groups, and only 22% of the ADPKD patients versus 26% of the controls had a Hunt and Hess grade of IV or V. In this study, ADPKD patients had aSAH from smaller aneurysms than matched controls (6.0 mm vs 8.0 mm). This is in line with previous data.^{16,25,26}

In our study, ADPKD patients fared similarly to their matched controls. Previously, occurrences of preexisting medical conditions worsening aSAH prognosis have been reported, such as coronary artery disease and chronic obstructive airway disease.³⁰ Chronic kidney disease is associated with a higher incidence of stroke and is a risk factor for poor outcome in both ischemic and hemorrhagic stroke;³¹ however, data on SAH as a separate entity from hemorrhagic stroke, including intracerebral hemorrhage, are sparse. According to an analysis on 1.1 million patients from the Nationwide Inpatient Sample, the adjusted OR for in-hospital death when hospitalized with SAH was 1.93 for chronic kidney disease patients.³² None of our ADPKD patients was in terminal kidney failure at aSAH, which is likely related to their younger age at aSAH¹⁶ than that at which they reach end-stage renal failure.^{6,7} One ADPKD patient experienced aSAH despite having already received a donor kidney, but even so their outcome was excellent. These results indicate that kidney failure is usually not a major factor in ADPKD patients with SAH, and other factors are more important in determining the outcome. Surprisingly, life expectancy after aSAH was not different between ADPKD patients and matched controls. This is the first study on this subject.

In this study, ADPKD patients were at an increased risk of having a second aSAH from a de novo aneurysm. In a large international cohort of European ADPKD aSAH patients, 3 of 47 (6.4%) experienced a second aSAH from a de novo aneurysm during a mean follow-up of 8.3 years.²⁵ This is also in line with our previous finding that the rate of de novo aneurysm formation is 1.3% per patient-year among ADPKD patients after surviving aSAH and 0.2% per patient-year in the general Eastern Finnish aSAH population (HR 7.7).¹⁶ A recent systematic review suggested that the de novo formation rate in ADPKD patients is as high as 1.4% per patient-year.³³ Our results again highlight the importance of angiographic follow-up in this subgroup of aSAH patients.

This study has several strengths derived from the universal and publicly funded healthcare system in Finland. The country is divided into mutually exclusive catchment populations between the 5 university hospitals, allowing unselected and minimally biased disease databases. The Kuopio Intracranial Aneurysm Patient and Family Database, with clinical data integrated from the national registries, using the personal identification codes, allows for retrospective construction of complete clinical lifelines of aSAH patients from Eastern Finland from birth to death or last follow-up.^{34–38}

This is a retrospective study, and as such is subject to se-

FIG. 2. Kaplan-Meier survival curve after aSAH in 32 ADPKD patients and 160 matched controls.

lection bias. However, the unselected database from which the study population is derived, along with the 1:5 matched control group, compensates for this. Furthermore, to minimize the possibility of incorrect diagnoses of ADPKD, the files of the 192 patients were rereviewed.

ADPKD is a rare disease and subsequently the study population is relatively small, which could have contributed to our negative finding. However, we feel that this is unlikely, given the fact that control patients in fact had a slightly higher mortality and percentage of poor outcome. To reach 5 matched control patients for each ADPKD patient (median age 43 years), a range of 5 years in the year of admission and a range of 3 years in age at aSAH had to be allowed, which may cause bias if the treatment of aSAH had significantly improved within that time range. There was no statistically significant difference in the proportion of endovascular versus microsurgical aneurysm occlusion. Even if there was a bias due to this, this is unlikely to be systematic, especially when priority was given to exact matches in the case-control matching.

It is possible that some aSAH patients with ADPKD have been missed, if they died before reaching the hospital or had not been admitted to KUH due to poor condition or presumed poor prognosis due to ADPKD.

In Finland, all kidney transplant candidates are screened for cerebral aneurysms before the operation; it is possible that the patients who reach uremia at a young age have had their aneurysms prophylactically treated. It should be noted that our results may not be directly applicable to other populations. Also, the impact of kidney failure on aSAH outcome should be addressed in larger cohorts.

Conclusions

There is no significant difference in aSAH prognosis in

patients with ADPKD in comparison with matched population controls. The risk of recurrent aSAH from a de novo aneurysm is increased in ADPKD patients, indicating the need for long-term angiographic follow-up.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Nurmonen, Jääskeläinen, Lindgren. Acquisition of data: Nurmonen, Isoniemi. Analysis and interpretation of data: Nurmonen. Drafting the article: Nurmonen.

Critically revising the article: Nurmonen, T Huttunen, J Huttunen, Kurtelius, Kotikoski, Junkkari, Koivisto, von und zu Fraunberg, Kämäräinen, Lång, Isoniemi, Lindgren. Reviewed submitted version of manuscript: all authors. Statistical analysis: Nurmonen. Study supervision: von und zu Fraunberg, Jääskeläinen, Lindgren.

Supplemental Information

Previous Presentations

A portion of the results was presented as an oral presentation at the 15th International Conference on Subarachnoid Hemorrhage, Amsterdam, the Netherlands, June 25–28, 2019.

Correspondence

Heidi J. Nurmonen: Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland. heidi.nurmonen@kuh.fi.