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A new clinical decision rule to exclude subarachnoid hemorrhage for acute headache: a prospective, multicenter, observational study

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Key words: Computed tomography (CT), Blood pressure, Blood sugar, Serum potassium

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ABSTRACT

Objective To ensure good outcomes in the management of subarachnoid hemorrhage, accurate prediction is crucial for initial assessment of patients presenting with acute headache. We conducted this study to develop a new clinical decision rule using only objectively measurable predictors to exclude subarachnoid hemorrhage, offering higher specificity than the previous Ottawa Subarachnoid Hemorrhage Rule while maintaining comparable sensitivity.

Design Multicenter prospective cohort study

Setting Tertiary-care emergency departments of five general hospitals in Japan from April 2011 to March 2014.

Participants Enrolled patients comprised 1781 patients >15 years old with acute headache, excluding trauma or toxic causes and patients who presented in an unconscious state.

Main outcome measures Definitive diagnosis of subarachnoid hemorrhage was based on confirmation of subarachnoid hemorrhage on head computed tomography or lumbar puncture findings of non-traumatic red blood cells or xanthochromia.

Results Of the 1781 eligible patients, 277 showed subarachnoid hemorrhage. From 1561 enrolled patients, we reached a rule we called the “Ottawa-like rule”, offering

100% sensitivity when using any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion. Using the 1317 patients from whom blood samples were obtained, a new rule using any of systolic blood pressure >150 mmHg, diastolic blood pressure >90 mmHg, blood sugar >115 mg/dL, or serum potassium <3.9 mEq/L offered 100% sensitivity (95% confidence interval: 98.6-100%) and 14.5% specificity (12.5-16.9%), while the Ottwa-like rule showed the same sensitivity with a lower specificity of 8.8% (7.2-10.7%).

Conclusion While maintaining equal specificity, our new rule showed higher specificity than the Ottawa Subarachnoid Hemorrhage rule. Despite the need for blood sampling, this method can reduce unnecessary head computed tomography in acute headache patients.

Strengths and limitations of this study

- In this multicenter, cohort study, we developed a new clinical decision rule to exclude SAH (EMERALD SAH Rule) in patients presenting with acute headache at emergency department in Japan. We selected objectively measurable predictors (systolic and diastolic blood pressures and blood sugar and serum potassium) having no inter-observer differences. Keeping 100% sensitivity, the EMERALD SAH rule could show higher specificity than the previous Ottawa Subarachnoid Hemorrhage rule[8].
- The proposed rule needs to be externally validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal validation.

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a common, serious problem encountered in emergency departments (EDs), and has been reported to result in disability or even death in 40-60% of affected patients.[1-4] Good outcomes are strongly dependent on prompt diagnosis and early treatment,[1-4] while untreated patients can experience sudden clinical deterioration because of re-bleeding. “Sudden, worst headache of life” or “thunderclap headache” are widely accepted predictors of SAH, and most emergency physicians investigate patients with such characteristic headaches using head computed tomography (CT) or lumbar puncture. However, some patients with SAH do not present with such characteristic headaches, and 12% of cases are reportedly overlooked on initial assessment.[1-5] Overlooking SAH in an alert patient can lead to catastrophic disability or death[5], so the development of methods for clinical prediction with high sensitivity is very important, particularly for patients with uncharacteristic symptoms. The research group at the University of Ottawa has provided highly sensitive clinical decision rules to exclude SAH in patients presenting with acute headache.[7] Their well-organized research led to a rule including any patient ≥40 years old with neck pain or stiffness, witnessed loss of consciousness, or onset during exertion. However, a multicenter cohort validation study failed to show 100% sensitivity.[8] The group then

added “thunderclap headache” and “limited neck flexion on examination”, resulting in 100% sensitivity for the Ottawa SAH Rule.[8]

Over the last decade, we have been involved in the development of clinical predictions to exclude SAH[9-10] for patients presenting to EDs with acute headache. Several years ago, we developed the subarachnoid hemorrhage prediction score (SPS)[10] using only measurable predictors (systolic blood pressure, blood sugar, serum potassium, and white cell count) in order to minimize interobserver differences and observer biases. The SPS offered 100% sensitivity for predicting SAH in a retrospective single-center study, but recent prospective validation cohorts have failed to maintain 100% sensitivity (unpublished data).

The present study was conducted as part of the Emergency Medicine, Registry Analysis, Learning and Diagnosis (EMERALD) project, which is aimed at minimizing life-threatening diseases being overlooked at EDs in Japan. The objective of this study was to develop a new clinical decision rule using only objectively measurable predictors to exclude SAH, while maintaining 100% sensitivity and offering higher specificity than the Ottawa SAH rule. Our new rule may need blood sampling, but was aimed at further reducing unnecessary CT and lumbar puncture, thus limiting costs, exposure to radiation, and invasiveness.

METHODS

Study design

This prospective multicenter observational study was conducted through the EDs of five general hospitals in Japan from April 2011 to March 2014. The research ethics board at each participating hospital approved the study protocol, which was designed in accordance with the STROBE statement for observational studies.

Study population

Consecutive patients >15 years old with a chief complaint of acute headache and presenting within 14 days of onset were considered for enrollment. We excluded patients with headache caused by trauma, drugs, or alcohol, and those who were unconscious at the beginning of assessment. As with previous studies,[7,8] we also excluded patients with recurrent headache syndromes (history of ≥3 recurrences of headache with the same characteristics and intensity as the presenting headache over a period >6 months).

Data collection

All patient assessments were made by residents supervised by staff physicians or

attending emergency physicians. Physicians were oriented to the study and instructed to input clinical findings at the time of assessment into data collection software specially developed by the EMERALD project on a smartphone, or onto electronic charts of a hospital that showed the same data items as the smartphone device. Electronic chart data were later manually transferred to the smartphone device.

To minimize interobserver differences and observer biases, as in our previous study, we focused on objectively measurable data such as age, heart rate, systolic and diastolic blood pressures, and body temperature. We also collected a wide variety of data from blood samples, such as blood sugar, serum sodium, serum potassium, hemoglobin concentration, white blood cell counts, and platelet counts, as these factors need only a small amount of blood to determine. Special examination items for emergency patients in Japanese EDs were not used and all results were obtainable within 10 min.

All patient data were anonymized before being uploaded to the internet server via direct smartphone connection or from personal computers at EDs with Bluetooth connections to smartphone devices. Collected anonymized data were monitored and cleaned by the Joint Center for Researchers, Associates and Clinicians (JCRAC), an authorized center for quality management of data. The final data set for analyses was provided by JCRAC.

Outcome measures

The primary outcome, SAH, was defined as any of the following: SAH on unenhanced CT of the head; xanthochromia in cerebrospinal fluid; or bloody cerebrospinal fluid in the final tube sample at lumbar puncture. These findings were confirmed by an emergency physician and neurological staff (i.e., neurosurgeons or neurologists). Radiologists interpreted CT images later, and provided a final radiology report.

We performed head CT for 82.8% of the 1781 eligible patients. Discharged patients were evaluated by outpatient follow-up or by telephone interview. A total of 188 discharged patients without either CT images or follow-up evaluations were excluded, as outcome variables were not able to be confirmed.

Data analysis

Univariate analyses were used to determine the strength of association between each possible predictor variable and the outcome variables. We used a 2-sided *t* test for continuous variables and Fisher's exact test for categorical variables.

To develop the clinical decision rule, we followed previously established methodological standards.[11] We selected possible predictors as clinically important,

continuous variables showing values of $p<0.05$ on univariate analyses. The reason we used only objectively measurable variables was mentioned earlier. We performed multivariate, recursive partitioning analysis to develop rules using those possible predictors and the outcome. Cut-offs for variables were determined in the process of recursive partitioning according to the applicability to clinical settings. Sensitivity and specificity were estimated for each rule. A clinical decision rule for a life-threatening event like SAH requires 100% sensitivity with a narrow confidence interval (CI). Based on this philosophy, we selected the practical new rule with the highest specificity.

We conducted bootstrapping analysis of 1000 iterations to determine the internal stability of rules, and then calculated sensitivity and specificity of them. Analyses were performed using JMP version 11.2.0 (SAS Institute, Cary, NC) and SAS version 9.3M2 (SAS Institute).

The funding source played no role in the collection, analysis, or interpretation of data, the writing of the report, or the decision to publish.

RESULTS

Figure 1 shows the study flow for the 1781 eligible patients. Of these, 1561 patients (87·6%) were enrolled after excluding 220 patients, of whom 188 had unconfirmed

outcome variables as mentioned in the Methods and 32 were missing important information about age, onset, neck pain or stiffness, or alteration of level of consciousness. Blood test results were available for 1317 patients (84.4%).

Table 1 reports characteristics of the enrolled patients (mean age, 53 years; 58.4% women), including 277 patients (17.7%) with SAH. CT scans were performed for 94.4% of the enrolled patients, while lumbar punctures were carried out for 2.6%. The 64.7% of enrolled patients discharged from the ED. Characteristics of the 1781 eligible patients were similar to those of enrolled patients (mean age, 53 years; 58.6% women).

Table 2 shows the results of univariate analysis. Patients with SAH were older and more often showed onset during exertion, “worst headache of life”, altered level of consciousness, neck pain or stiffness, vomiting, and history of hypertension. Systolic and diastolic blood pressures were higher in patients with SAH, but surface body temperature was lower. In the 1317 patients for whom blood test results were available, blood sugar level and white cell count were higher in patients with SAH, but serum potassium was slightly lower.

From the 1561 enrolled patients, as a result of recursive partitioning analysis, we developed almost the same rule as Rule 1 from the previous literature,[7] using any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion.

This rule was termed the "Ottawa-like rule", showing 100% sensitivity (95% confidence interval (CI), 98.6-100%) and 9.1% specificity (95%CI, 7.7-10.8%). Using data from the 1317 patients for whom blood results were available, we developed a new rule using any of systolic blood pressure >150 mmHg, diastolic blood pressure >90 mmHg, blood sugar >115 mg/dL (6.9 mmol/L), or serum potassium <3.9 mEq/L (3.90 mmol/L) (Fig. 2). This new rule, which we called the "EMERALD SAH rule", offered 100% sensitivity (95%CI, 98.6-100%) and 14·5% specificity (95%CI, 12.5-16.9%). In comparison, the Ottawa-like rule showed identical sensitivity, but a lower specificity of 8.8% (95%CI, 7.2-10.7%). Moreover, the EMERALD SAH rule excluded 126 SAH-free patients among the 1225 patients with any of the predictors used in the Ottawa-like rule.

DISCUSSION

Many patients present to EDs with a primary complaint of headache.[3] Among such patients, SAH is a disease with an extremely high likelihood of death or severe impairment.[1-4] Since outcomes have been shown to improve with early diagnosis and treatment,[1-4] this is a disease that must not be overlooked in EDs. Sudden, severe headache (the worst experienced, or thunderclap headache) is considered the most

characteristic symptom of SAH, but this pathology can also be found in patients with more benign headache.[6] Other symptoms include transient loss of consciousness, nausea/vomiting, and neck pain/nuchal rigidity, but each of these is nonspecific[2,4] when present without combination and all are open to observer bias.

Over the last decade, we have been looking for rigid measurable predictors that would leave no room for interobserver disagreement. We have identified age, blood pressures, body temperature, blood sugar concentration, serum potassium concentration, and white cell count as possible predictors (Table 2). For the derivation of our new EMERALD SAH Rule, we selected systolic and diastolic blood pressures and blood sugar and serum potassium levels, as these offered relatively stronger discriminant abilities. We excluded age as a factor already used in the Ottawa SAH Rule.

Several studies have found hypertension to represent an independent risk factor for SAH.[4] Before the present study, high systolic and diastolic blood pressure had already been selected as possible predictors with similar cut-off values by the Canadian group,[7] but were not chosen as final predictors for the Ottawa SAH Rule.

We did not find any studies directly investigating the correlation between elevated blood sugar levels and SAH, but according to Douhout and colleagues,[12] higher blood sugar levels in the first 10 days after SAH are associated with worsened outcomes.

Frontera and colleagues[13] have also claimed that SAH is generally followed by hyperglycemia, suggesting some correlation between the development of SAH and elevated blood sugar levels. A recent meta-analysis[14] revealed that admission glucose levels are often high and hyperglycemia is associated with an increased risk of poor outcomes after SAH.

Serum potassium levels were also significantly decreased in patients with SAH. SAH is believed to result in accelerated catecholamine secretion and increased intracellular potassium uptake, leading to lower serum potassium levels.[15-17]

Our data demonstrated 100% sensitivity for the Ottawa-like rule, almost identical to Rule 1 with the highest sensitivity among the three rules developed by the Ottawa group.[6,7] However, specificity was lower than with our EMERALD SAH Rule. The Ottawa group proposed the more sensitive Ottawa SAH Rule to maintain 100% sensitivity, despite the lower specificity. We thus proposed a two-step decision-making rule (Fig. 3). We placed the Ottawa SAH Rule as the first screening step, because needle puncture is not needed. If the EMERALD SAH Rule is placed as the second step, we can obtain higher specificity without reducing the optimal sensitivity, thus hopefully reducing both unnecessary exposure to radiation and costs from CT, while requiring only the small blood volume needed for blood gas analysis, and also reducing the need

for invasive lumbar punctures that might result in headache even worse than the presenting symptom.

Limitations

To minimize observer biases, as we mentioned before, we have focused on objectively measurable data that do not require assessments with a κ coefficient. We did not assess interobserver agreement for non-numerical variables, so our results for the Ottawa-like rule carried a risk of interobserver differences. However, the results were not far from those of the Ottawa studies, and may be sufficient to show the superior specificity of the EMERALD SAH Rule using only four measurable variables.

We were unable to record the time to peak headache intensity for all patients, and thus did not know whether headache reached maximum intensity within 1 h for all patients. This was because patients with non-typical, relatively lighter headache experienced difficulty answering when peak intensity occurred. Moreover, many patients with acute headache are often very reluctant to answer all clinical questions from physicians. This is another reason why we chose to rely on objectively measurable findings. The EMERALD SAH Rule would be applicable regardless of the time to peak intensity.

If patients develop new neurological deficits or have a history of aneurysm or brain

tumor, precise investigations including non-enhanced and enhanced CT and routine blood testing are routinely conducted in Japanese EDs. We therefore do not emphasize the exclusion of such patients, because we can confirm the presence or absence of SAH. Our data could possibly have included a very small number of such patients. However, the negative effects of this possibility were considered to be almost zero for the derivation of the EMERALD SAH Rule.

Finally, the proposed rule needs to be properly validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal validation. This rule thus requires external validation before implementation.

Despite the necessity of blood testing, our EMERALD SAH Rule shows higher specificity than the previous Ottawa SAH Rule while maintaining equal sensitivity. It can allow further reduction of unnecessary investigations such as CT or lumbar puncture in patients showing one or more of the predictors of the Ottawa SAH Rule. The EMERALD SAH Rule can play a role as a secondary screening to exclude SAH in patients with acute headache. Further validation studies are required before the rule can be applied to routine practice in EDs.

Acknowledgments

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Competing interests: None of the authors have any conflicts of interest to declare.

Contributors: Akio Kimura has made major contributions to the conception, design, analysis, and interpretation of data in this study. Kentaro Kobayashi has made substantial contributions to the conception of this study. Hitoshi Yamaguchi, Takeshi Takahashi, Masahiro Harada, Hideki Honda, Yoshio Mori, and Keika Hirose have made substantial contributions to the acquisition of data in this study. Noriko Tanaka has made substantial contributions to the statistical analysis in this study.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics committee approval: The research ethics committee at each participating hospital approved the study protocol. Participants were informed that they might be contacted by telephone for follow-up with written consent or with verbal consent obtained at the time of telephone contact.

Clinical trial registration: UMIN 00004871

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Data sharing: No additional data available.

REFERENCES

1 Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006;354:387–96.

2 van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet* 2007;369:306–18.

3 Edlow JA, Malek AM, Ogilvy CS. Aneurysmal subarachnoid hemorrhage: update for emergency physician. *J Emerg Med* 2008;34:237–51.

4 Connolly ES, Rabinstein AA, Carthuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A guideline for healthcare professionals from the American Heart Association / American Stroke Association. *Stroke* 2012;43:1711–37.

5 Kowalski RG, Claassen J, Kreiter KT, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA* 2004;291:866–9.

6 Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998;65:791–3.

7 Perry JJ, Stiell IG, Sivilotti ML, et al. High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study.

BMJ 2010;341:c5204.

8 Perry JJ, Stiell IG, Sivilotti ML, et al. Clinical decision rules to rule out subarachnoid haemorrhage for acute headache. *JAMA* 2013;310:1248–55.

9 Kimura Y, Kimura A, Tomioka J, et al. Early diagnosis of subarachnoid hemorrhage in patients reporting headache at emergency center. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2001;12:275–81.

10 Kobayashi K, Kimura A, Hagiwara A, et al. Highly sensitive, subarachnoid hemorrhage prediction score for patients with acute headache. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2011;22:305–11.

11 Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. *Ann Emerg Med* 1999;33:437–47.

12 Dorhout Mees SM, van Dijk GW, Algra A, et al. Glucose levels and outcome after subarachnoid hemorrhage. *Neurology* 2003;61:1132–3.

13 Frontera JA, Fernandez A, Claassen J, et al. Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. *Stroke* 2006;37:199–203.

14 Kruyt ND, Bissels GJ, de Hann RJ, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage, a meta-analysis. *Stroke* 2009;40:e424–30.

15 Fukui S, Otani N, Katoh H, et al. Female gender as a risk factor for

hypokalemia and QT prolongation after subarachnoid hemorrhage. *Neurology* 2002;59:134–6.

16 Fukui S, Katoh H, Tsuzuki N, et al. Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. *Crit Care* 2003;7:R7–12.

17 Fukui S, Katoh H, Tsuzuki N, et al. Gender disparities in serum electrolytes levels after subarachnoid hemorrhage. *J Clin Neurosci* 2004;11:606–9.

Table 1. Characteristics of Enrolled Patients (N=1561)

Characteristics	Patients	
Age, mean (SD) [range]	53 (21) [16-98]	
Women	912	58.4%
Onset during exertion	312	20.0%
Onset during rest	1131	72.5%
Headache awoke patient from sleep	55	3.5%
Duration from onset		
~60 min	297	19.0%
~24 h	863	55.3%
~7 days	342	21.9%
1 week ~	58	3.7%
Worst headache of life	274	17.6%
Thunderclap headache	37	2.4%
Alteration of consciousness level	151	9.7%
Neck pain or stiffness	1095	70.1%
Vomiting	442	28.3%
Vertigo / dizziness	206	13.2%
History of hypertension	374	24.0%
History of diabetes mellitus	118	7.6%
Heart rate, mean (SD) beats/min	79	(17)
Blood pressure, mean (SD) mmHg		
Systolic	144	(33)
Diastolic	83	(19)
Body temperature, mean (SD) °C	36.6	(0.8)
Diagnostic procedures		
CT	1474	94.4%
MRI	66	4.2%
Lumbar puncture	40	2.6%
No CT, lumbar puncture, or MRI	87	5.6%
Discharged from emergency department	1010	64.7%
Final Diagnosis		
Cerebrovascular disease (CVD)	369	23.6%
Subarachnoid hemorrhage	277	17.7%

Other CVD	92	5.9%
Other neurological disease	715	45.8%
Migraine headache	133	8.5%
Tension headache	61	3.9%
Cluster headache	12	0.8%
Unclassified benign headache	438	28.1%
Meningitis	17	1.1%
Post-seizure headache	15	1.0%
Neuralgia	10	0.6%
Brain tumor	7	0.4%
Viral illness	60	3.8%
Psychiatric disease	47	3.0%
Hypertensive crisis	38	2.4%
Peripheral vertigo	37	2.4%
Gastrointestinal disease	22	1.4%
Sinusitis	16	1.0%
Hyperventilation	16	1.0%
Urinary tract infection	16	1.0%
Dehydration	15	1.0%
Respiratory disease	14	0.9%
Syncope	10	0.6%
Cervical spondylosis	10	0.6%
Other non-neurological disease	176	11.3%

Table 2. Univariate Correlation of Valiables for Subarachnoid Hemorrhage

Characteristic	Subarachnoid Hemorrhage		*P* value
	No (n=1284)	**Yes** (n=277)	
From history			
Age, mean (SD) [range]	51 (21)	63 (15)	<0.0001
Women	56.9%	67.5%	0.0012
Onset during exertion	14.3%	54.9%	<0.0001
Worst headache of life	9.5%	54.9%	<0.0001
Thunderclap headache	2.2%	3.3%	0.279
Altered level of consciousness	3.8%	40.1%	<0.0001
Neck pain or stiffness	72.9%	86.6%	<0.0001
Vomiting	25.4%	52.7%	<0.0001
Vertigo / dizziness	15.6%	8.3%	0.0072
History of hypertension	24.0%	43.7%	<0.0001
History of diabetes mellitus	10.1%	3.6%	0.095
From physical examination			
Heart rate, mean (SD) beats/min	79 (17)	80 (17)	0.7669
Blood pressure, mean (SD) mmHg			
Systolic	139 (30)	167 (36)	<0.0001
Diastolic	81 (18)	93 (21)	<0.0001
Body temperature, mean (SD) °C	36.6 (0.8)	36.3 (0.9)	<0.0001
Diagnostic procedures			
CT	1197	277	
MRI	62	4	
Lumbar puncture	37	3	
From blood test	**No** (n=1045)	**Yes** (n=272)	
Blood sugar, mean (SD) mg/dL	127 (51)	162 (49)	<0.0001
Serum sodium, mean (SD) mEq/L	139.4 (3.4)	138.6 (3.0)	0.0016
Serum potassium, mean (SD) mEq/L	3.9 (0.5)	3.6 (0.5)	<0.0001
Hemoglobin, mean (SD) g/dL	13.6 (2.0)	13.4 (1.9)	0.1044
White cell count, mean (SD) $\times 10^3/\mu L$	7.9 (3.4)	10.3 (4.6)	<0.0001
Platelet count, mean (SD) $\times 10^4/\mu L$	21.7 (10.0)	24.0 (21.0)	0.9258

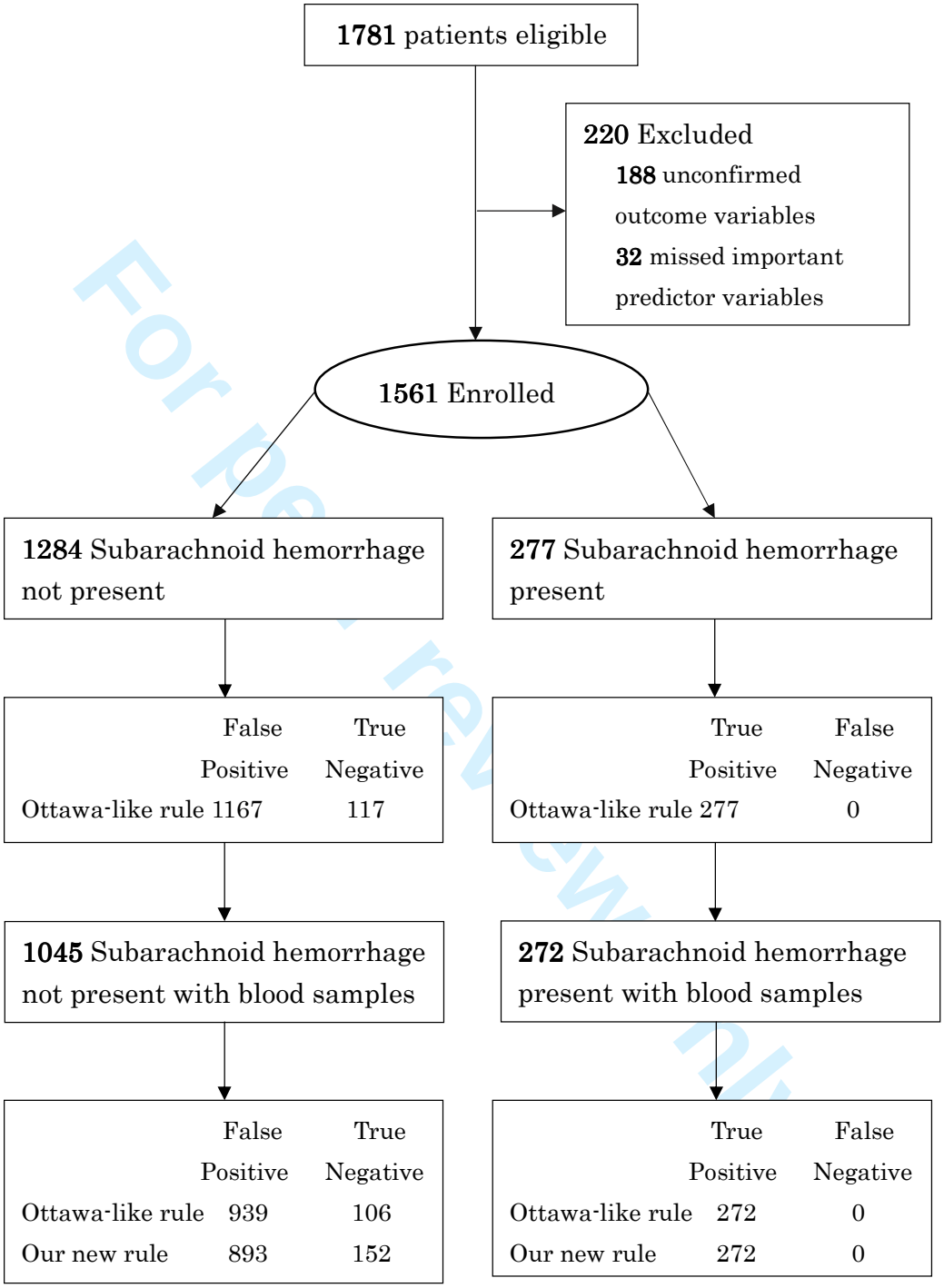

Figure 1

Details of enrollment and flow of patients in study

Ottawa-like rule, any of the following risks present:

1. Age ≥40 years

2. Neck pain or stiffness
3. Altered level of consciousness
4. Onset during exertion.

EMERALD SAH rule, any of the following risks present:

1. Systolic blood pressure >150 mmHg
2. Diastolic blood pressure >90 mmHg
3. Blood sugar >115 mg/dL (6.9 mmol/L)
4. Serum potassium <3.9 mEq/L (3.90 mmol/L)

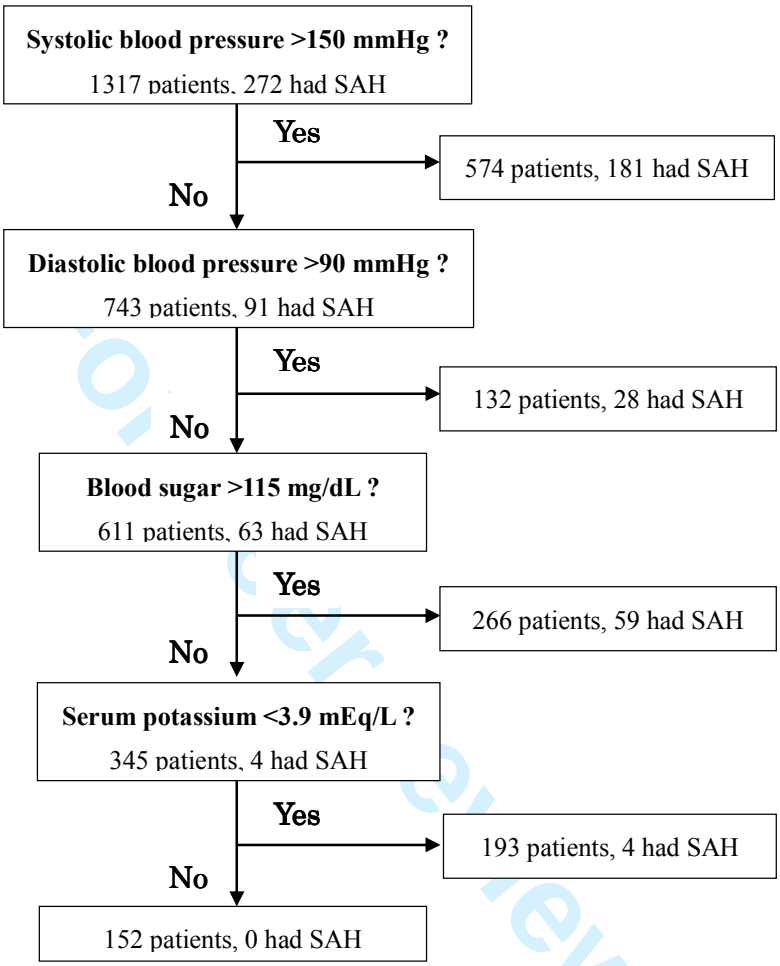

Figure 2

Example of recursive partitioning analysis with our new rule: the EMERALD SAH Rule

SAH: subarachnoid hemorrhage

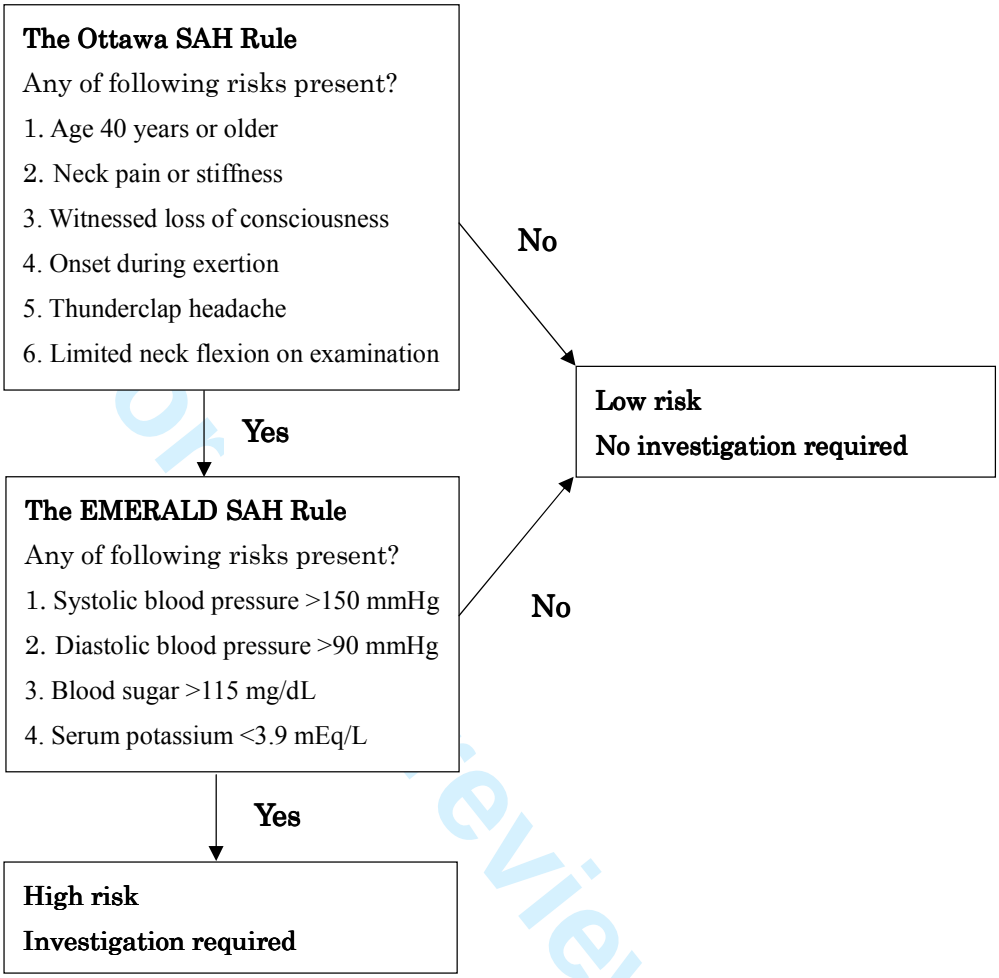

Figure 3

The proposed two-step decision-making to rule out subarachnoid hemorrhage (SAH) for adult patients with acute headache

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	① P1 P3-4	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	② **P6-7**	Explain the scientific background and rationale for the investigation being reported
Objectives	③ **P67**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	④ **P8**	Present key elements of study design early in the paper
Setting	⑤ **P8-9**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	⑥ **P8**	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	⑦ **P10**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	⑧* **P9**	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	⑨ **P9**	Describe any efforts to address potential sources of bias
Study size	⑩	Explain how the study size was arrived at
This was not written in the manuscript, but as in the previous study (Ref.7), at least 120 patients with SAH were required. Our previous study (Ref 10) reported that about 13% of patients with acute headache had SAH at our emergency department. Thus, more than 923 enrolled patient would be required. In the present study, 1317 patients with blood sample were enrolled and analysed, and among them 272 patients had SAH (Fig.1). Therefore the sample size was considered to be sufficient.		
Quantitative variables	⑪ **P9**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	⑫ **P10-11**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions

		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* **P11-12 Fig.1**	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* **P12 Table1**	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* **P12 Fig.1 Table2**	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 **P12-13 Fig2**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Using bootstrapping we calculated sensitivity and specificity for 5 rules (including the Ottwa like rule and the EMERALD rule) to select the best rule, but we didn't show them in the manuscript.		
Discussion		
Key results	18 **P15**	Summarise key results with reference to study objectives
Limitations	19 **P16-17**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 **P17**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 **P17**	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 **P19**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A new clinical decision rule to exclude subarachnoid hemorrhage for acute headache: a prospective, multicenter, observational study

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A new clinical decision rule to exclude subarachnoid hemorrhage for acute headache: a prospective, multicenter, observational study

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ABSTRACT

Objective To ensure good outcomes in the management of subarachnoid hemorrhage, accurate prediction is crucial for initial assessment of patients presenting with acute headache. We conducted this study to develop a new clinical decision rule using only objectively measurable predictors to exclude subarachnoid hemorrhage, offering higher specificity than the previous Ottawa Subarachnoid Hemorrhage Rule while maintaining comparable sensitivity.

Design Multicenter prospective cohort study

Setting Tertiary-care emergency departments of five general hospitals in Japan from April 2011 to March 2014.

Participants Enrolled patients comprised 1781 patients >15 years old with acute headache, excluding trauma or toxic causes and patients who presented in an unconscious state.

Main outcome measures Definitive diagnosis of subarachnoid hemorrhage was based on confirmation of subarachnoid hemorrhage on head computed tomography or lumbar puncture findings of non-traumatic red blood cells or xanthochromia.

Results Of the 1781 eligible patients, 277 showed subarachnoid hemorrhage. From 1561 enrolled patients, we reached a rule we called the “Ottawa-like rule”, offering

100% sensitivity when using any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion. Using the 1317 patients from whom blood samples were obtained, a new rule using any of systolic blood pressure >150 mmHg, diastolic blood pressure >90 mmHg, blood sugar >115 mg/dL, or serum potassium <3.9 mEq/L offered 100% sensitivity (95% confidence interval: 98.6-100%) and 14.5% specificity (12.5-16.9%), while the Ottwa-like rule showed the same sensitivity with a lower specificity of 8.8% (7.2-10.7%).

Conclusion While maintaining equal specificity, our new rule showed higher specificity than the Ottawa Subarachnoid Hemorrhage rule. Despite the need for blood sampling, this method can reduce unnecessary head computed tomography in acute headache patients.

Strengths and limitations of this study

- In this multicenter, cohort study, we developed a new clinical decision rule to exclude SAH (EMERALD SAH Rule) in patients presenting with acute headache at emergency department in Japan. We selected objectively measurable predictors (systolic and diastolic blood pressures and blood sugar and serum potassium) having no inter-observer differences. Maintaining 100% sensitivity, the EMERALD

SAH rule could show higher specificity than the previous rules.

- The proposed rule needs to be externally validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal validation.

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a common, serious problem encountered in emergency departments (EDs), and has been reported to result in disability or even death in 40-60% of affected patients.[1-4] Good outcomes are strongly dependent on prompt diagnosis and early treatment,[1-4] while untreated patients can experience sudden clinical deterioration because of re-bleeding. “Sudden, worst headache of life” or “thunderclap headache” are widely accepted predictors of SAH, and most emergency physicians investigate patients with such characteristic headaches using head computed tomography (CT) or lumbar puncture. However, some patients with SAH do not present with such characteristic headaches, and 12% of cases are reportedly overlooked on initial assessment.[1-5] Moreover, sudden severe headache can also be found in patients with more benign headache.[6] Overlooking SAH in an alert patient can lead to catastrophic disability or death[5], so the development of methods for clinical prediction with high sensitivity is very important, particularly for patients with uncharacteristic symptoms.

The research group at the University of Ottawa has provided highly sensitive clinical decision rules to exclude SAH in patients presenting with acute headache.[7] Their well-organized research led to a rule including any patient ≥40 years old with neck pain

or stiffness, witnessed loss of consciousness, or onset during exertion. However, a multicenter cohort validation study failed to show 100% sensitivity.[8] The group then added "thunderclap headache" and "limited neck flexion on examination", resulting in 100% sensitivity for the Ottawa SAH Rule.[8]

Over the last decade, we have been involved in the development of clinical predictions to exclude SAH[9-10] for patients presenting to EDs with acute headache. Several years ago, we developed the subarachnoid hemorrhage prediction score (SPS)[10] using only measurable predictors (systolic blood pressure, blood sugar, serum potassium, and white cell count) in order to minimize interobserver differences and observer biases. The SPS offered 100% sensitivity for predicting SAH in a retrospective single-center study, but recent prospective validation cohorts have failed to maintain 100% sensitivity (unpublished data).

The present study was conducted as part of the Emergency Medicine, Registry Analysis, Learning and Diagnosis (EMERALD) project, which is aimed at minimizing life-threatening diseases being overlooked at EDs in Japan. The objective of this study was to develop a new clinical decision rule using only objectively measurable predictors to exclude SAH, while maintaining 100% sensitivity and offering higher specificity than the Ottawa SAH rule. Our new rule may need blood sampling, but was aimed at further

reducing unnecessary CT and lumbar puncture, thus limiting costs, exposure to radiation, and invasiveness.

METHODS

Study design

This prospective multicenter observational study was conducted through the EDs of five general hospitals in Japan from April 2011 to March 2014. The research ethics board at each participating hospital approved the study protocol, which was designed in accordance with the STROBE statement for observational studies.

Study population

1899 consecutive patients >15 years old with a chief complaint of acute headache and presenting within 14 days of onset were considered for enrollment. We excluded patients with headache caused by trauma, drugs, or alcohol, and those who were unconscious at the beginning of assessment. As with previous studies,[7,8] we also excluded patients with recurrent headache syndromes (history of ≥3 recurrences of headache with the same characteristics and intensity as the presenting headache over a period >6 months).

Data collection

All patient assessments were made by residents supervised by staff physicians or attending emergency physicians. Physicians were oriented to the study and instructed to input clinical findings at the time of assessment into data collection software specially developed by the EMERALD project on a smartphone, or onto electronic charts of a hospital that showed the same data items as the smartphone device. Electronic chart data were later manually transferred to the smartphone device.

To minimize interobserver differences and observer biases, as in our previous study, we focused on objectively measurable data such as age, heart rate, systolic and diastolic blood pressures, and body temperature, which were defined as the first reading by the treating nursing staff. We also collected a variety of data from blood samples, such as blood sugar, serum sodium, serum potassium, hemoglobin concentration, white blood cell counts, and platelet counts, as these factors need only a small amount of blood to determine. However, only routine examination items for emergency patients in Japanese EDs were used and all results were obtainable within 10 min.

All patient data were anonymized before being uploaded to the internet server via direct smartphone connection or from personal computers at EDs with Bluetooth connections to smartphone devices. Collected anonymized data were monitored and cleaned by the

Joint Center for Researchers, Associates and Clinicians (JCRAC), an authorized center for quality management of data. The final data set for analyses was provided by JCRAC.

Outcome measures

The primary outcome, SAH, was defined as any of the following: SAH on unenhanced CT of the head; xanthochromia in cerebrospinal fluid; or non-traumatic, bloody cerebrospinal fluid in the final tube sample at lumbar puncture followed by either angiography or CT angiography to confirm whether an underlying pathology is causing SAH, in cooperation with neurological staff and an emergency physician. Most Japanese emergency departments in tertiary general hospitals have a 16- to 64-row multi-detector CT either within the hospital or located nearby. CT is available within 1 h even at midnight. Lumbar puncture is limited to those patients for whom plain CT seems to show negative results, but a high index of suspicion remains for SAH. Radiologists interpreted CT images later, and provided a final radiology report. We performed head CT for 82.8% of the 1781 eligible patients. Discharged patients were evaluated by outpatient follow-up or by telephone interview. A total of 188 discharged patients without either CT images or follow-up evaluations were excluded,

as outcome variables were not able to be confirmed.

Data analysis

Univariate analyses were used to determine the strength of association between each possible predictor variable and the outcome variables. We used a 2-sided *t* test for continuous variables and Fisher's exact test for categorical variables.

To develop the clinical decision rule, we followed previously established methodological standards.[11] We selected possible predictors as clinically important, continuous variables showing values of $p<0.05$ on univariate analyses. The reason we used only objectively measurable variables was mentioned earlier. We performed multivariate, recursive partitioning analysis to develop rules using those possible predictors and the outcome. Cut-offs for variables were determined in the process of recursive partitioning. Sensitivity and specificity were estimated for each rule. A clinical decision rule for a life-threatening event like SAH requires 100% sensitivity with a narrow confidence interval (CI). Based on this philosophy, we selected the practical new rule with the highest specificity.

We conducted bootstrapping analysis of 1000 iterations to determine the internal stability of rules, and then calculated sensitivity and specificity of them. Analyses were

performed using JMP version 11.2.0 (SAS Institute, Cary, NC) and SAS version 9.3M2 (SAS Institute).

The funding source played no role in the collection, analysis, or interpretation of data, the writing of the report, or the decision to publish.

RESULTS

Figure 1 shows the study flow for the 1781 eligible patients applied the exclusion criteria to the 1899 consecutive patients. Of these, 1561 patients (87·6%) were enrolled after excluding 220 patients, of whom 188 had unconfirmed outcome variables as mentioned in the Methods and 32 were missing important information about age, onset, neck pain or stiffness, or alteration of level of consciousness. Blood test results were available for 1317 patients (84.4%).

Table 1 reports characteristics of the enrolled patients (mean age, 53 years; 58.4% women), including 277 patients (17.7%) with SAH. CT scans were performed for 94.4% of the enrolled patients, while lumbar punctures were carried out for 2.6%. The 64.7% of enrolled patients discharged from the ED.

Characteristics of the 1781 eligible patients were similar to those of enrolled patients (mean age, 53 years; 58.6% women). However, 188 Patients who were not followed-up

tended to be younger (mean age 42 years) and to have lower frequencies of both onset during exertion (15%) and alteration of consciousness (2%). And their systolic blood pressure (SBP) and diastolic blood pressure (DBP) tended to be low (130 mmHg and 78 mmHg, respectively).

Table 2 shows the results of univariate analysis. Patients with SAH were older and more often showed onset during exertion, "worst headache of life", altered level of consciousness, neck pain or stiffness, vomiting, and history of hypertension. Systolic and diastolic blood pressures were higher in patients with SAH, but surface body temperature was lower. In the 1317 patients for whom blood test results were available, blood sugar level and white cell count were higher in patients with SAH, but serum potassium was slightly lower.

From the 1561 enrolled patients, as a result of recursive partitioning analysis, we developed almost the same rule as Rule 1 from the previous literature,[7] using any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion. This rule was termed the "Ottawa-like rule", showing 100% sensitivity (95% confidence interval (CI), 98.6-100%) and 9.1% specificity (95%CI, 7.7-10.8%).

Using data from the 1317 patients for whom blood results were available, we developed a new rule using any of SBP >150 mmHg, DBP >90 mmHg, blood sugar >115 mg/dL

(6.9 mmol/L), or serum potassium <3.9 mEq/L (3.90 mmol/L) (Fig. 2). This new rule, which we called the "EMERALD SAH rule", offered 100% sensitivity (95%CI, 98.6-100%) and 14·5% specificity (95%CI, 12.5-16.9%). In comparison, the Ottawa-like rule showed identical sensitivity, but a lower specificity of 8.8% (95%CI, 7.2-10.7%).

Ninety of the other 92 cardiovascular disease patients (Table 1) met the criteria of the EMERALD rule. A tiny subcortical hemorrhage and thalamic hemorrhage 1–2 cm in diameter occurred in 2 patients.

DISCUSSION

Over the last decade, we have been looking for rigid measurable predictors that would leave no room for interobserver disagreement. We have identified age, blood pressures, body temperature, blood sugar concentration, serum potassium concentration, and white cell count as possible predictors (Table 2). For the derivation of our new EMERALD SAH Rule, we selected systolic and diastolic blood pressures and blood sugar and serum potassium levels, as these offered relatively stronger discriminant abilities. We excluded age as a factor already used in the Ottawa SAH Rule.

Our data demonstrated 100% sensitivity for the Ottawa-like rule, almost identical to

Rule 1 with the highest sensitivity among the three rules developed by the Ottawa group.[6,7] However, specificity was lower than with our EMERALD SAH Rule. The Ottawa group proposed the more sensitive Ottawa SAH Rule to maintain 100% sensitivity, despite the lower specificity. We thus proposed a two-step decision-making rule (Fig. 3). We placed the Ottawa SAH Rule as the first screening step, because that is a much more clinically intuitive, and needle puncture is not needed. If the EMERALD SAH Rule is placed as the second step, we can obtain higher specificity without reducing the optimal sensitivity, thus hopefully reducing both unnecessary exposure to radiation and costs from CT, while requiring only the small blood volume needed for blood gas analysis, and also reducing the need for invasive lumbar punctures that might result in headache even worse than the presenting symptom.

Several studies have found hypertension to represent an independent risk factor for SAH.[4] Before the present study, high systolic and diastolic blood pressure had already been selected as possible predictors with similar cut-off values by the Canadian group,[7] but were not chosen as final predictors for the Ottawa SAH Rule.

We did not find any studies directly investigating the correlation between elevated blood sugar levels and SAH, but according to Douhout and colleagues,[12] higher blood sugar levels in the first 10 days after SAH are associated with worsened outcomes.

Frontera and colleagues[13] have also claimed that SAH is generally followed by hyperglycemia, suggesting some correlation between the development of SAH and elevated blood sugar levels. A recent meta-analysis[14] revealed that admission glucose levels are often high and hyperglycemia is associated with an increased risk of poor outcomes after SAH.

Serum potassium levels were also significantly decreased in patients with SAH. SAH is believed to result in accelerated catecholamine secretion and increased intracellular potassium uptake, leading to lower serum potassium levels.[15-17]

Limitations

To minimize observer biases, as we mentioned before, we have focused on objectively measurable data that do not require assessments with a κ coefficient. We did not assess interobserver agreement for non-numerical variables, so our results for the Ottawa-like rule carried a risk of interobserver differences. However, the results were not far from those of the Ottawa studies, and may be sufficient to show the superior specificity of the EMERALD SAH Rule using only four measurable variables.

We were unable to record the time to peak headache intensity for all patients, and thus did not know whether headache reached maximum intensity within 1 h for all patients.

This was because patients with non-typical, relatively lighter headache experienced difficulty answering when peak intensity occurred. Moreover, many patients with acute headache are often very reluctant to answer all clinical questions from physicians. This is another reason why we chose to rely on objectively measurable findings. The EMERALD SAH Rule would be applicable regardless of the time to peak intensity.

If patients develop new neurological deficits or have a history of aneurysm or brain tumor, precise investigations including non-enhanced and enhanced CT and routine blood testing are routinely conducted in EDs in Japan. We therefore do not emphasize the exclusion of such patients, because we can confirm the presence or absence of SAH. Our data could possibly have included a very small number of such patients. However, the negative effects of this possibility were considered to be almost zero for the derivation of the EMERALD SAH Rule.

The proposed rule needs to be properly validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal validation. This rule thus requires external validation before implementation.

Despite the necessity of blood testing, our EMERALD SAH Rule shows higher specificity than the previous Ottawa SAH Rule while maintaining equal sensitivity. It can allow further reduction of unnecessary investigations such as CT or lumbar

puncture in patients showing one or more of the predictors of the Ottawa SAH Rule. The EMERALD SAH Rule can play a role as a secondary screening to exclude SAH in patients with acute headache. Further validation studies are required, and our clinical practice will not be altered until comparable results can be confirmed from such validation.

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Competing interests: None of the authors have any conflicts of interest to declare.

Contributorship: Akio Kimura has made major contributions to the conception, design, analysis, and interpretation of data in this study. Kentaro Kobayashi has made substantial contributions to the conception of this study. Hitoshi Yamaguchi, Takeshi Takahashi, Masahiro Harada, Hideki Honda, Yoshio Mori, and Keika Hirose have made substantial contributions to the acquisition of data in this study. Noriko Tanaka has made substantial contributions to the statistical analysis in this study.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important

aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics committee approval: The research ethics committee at each participating hospital approved the study protocol. Participants were informed that they might be contacted by telephone for follow-up with written consent or with verbal consent obtained at the time of telephone contact.

Clinical trial registration: UMIN 00004871

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Data sharing: No additional data available.

REFERENCES

1 Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006;354:387–96.

2 van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet* 2007;369:306–18.

3 Edlow JA, Malek AM, Ogilvy CS. Aneurysmal subarachnoid hemorrhage: update for emergency physician. *J Emerg Med* 2008;34:237–51.

4 Connolly ES, Rabinstein AA, Carthuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A guideline for healthcare professionals from the American Heart Association / American Stroke Association. *Stroke* 2012;43:1711–37.

5 Kowalski RG, Claassen J, Kreiter KT, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA* 2004;291:866–9.

6 Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998;65:791–3.

7 Perry JJ, Stiell IG, Sivilotti ML, et al. High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study.

BMJ 2010;341:c5204.

8 Perry JJ, Stiell IG, Sivilotti ML, et al. Clinical decision rules to rule out subarachnoid haemorrhage for acute headache. *JAMA* 2013;310:1248–55.

9 Kimura Y, Kimura A, Tomioka J, et al. Early diagnosis of subarachnoid hemorrhage in patients reporting headache at emergency center. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2001;12:275–81.

10 Kobayashi K, Kimura A, Hagiwara A, et al. Highly sensitive, subarachnoid hemorrhage prediction score for patients with acute headache. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2011;22:305–11.

11 Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. *Ann Emerg Med* 1999;33:437–47.

12 Dorhout Mees SM, van Dijk GW, Algra A, et al. Glucose levels and outcome after subarachnoid hemorrhage. *Neurology* 2003;61:1132–3.

13 Frontera JA, Fernandez A, Claassen J, et al. Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. *Stroke* 2006;37:199–203.

14 Kruyt ND, Bissels GJ, de Hann RJ, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage, a meta-analysis. *Stroke* 2009;40:e424–30.

15 Fukui S, Otani N, Katoh H, et al. Female gender as a risk factor for

hypokalemia and QT prolongation after subarachnoid hemorrhage. *Neurology* 2002;59:134–6.

16 Fukui S, Katoh H, Tsuzuki N, et al. Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. *Crit Care* 2003;7:R7–12.

17 Fukui S, Katoh H, Tsuzuki N, et al. Gender disparities in serum electrolytes levels after subarachnoid hemorrhage. *J Clin Neurosci* 2004;11:606–9.

Table 1. Characteristics of Enrolled Patients (N=1561)

Characteristics	Patients	
Age, mean (SD) [range]	53 (21) [16-98]	
Women	912	58.4%
Onset during exertion	312	20.0%
Onset during rest	1131	72.5%
Headache awoke patient from sleep	55	3.5%
Duration from onset		
~60 min	297	19.0%
~24 h	863	55.3%
~7 days	342	21.9%
1 week ~	58	3.7%
Worst headache of life	274	17.6%
Thunderclap headache	37	2.4%
Alteration of consciousness level	151	9.7%
Neck pain or stiffness	1095	70.1%
Vomiting	442	28.3%
Vertigo / dizziness	206	13.2%
History of hypertension	374	24.0%
History of diabetes mellitus	118	7.6%
Heart rate, mean (SD) beats/min	79	(17)
Blood pressure, mean (SD) mmHg		
Systolic	144	(33)
Diastolic	83	(19)
Body temperature, mean (SD) °C	36.6	(0.8)
Diagnostic procedures		
CT	1474	94.4%
MRI	66	4.2%
Lumbar puncture	40	2.6%
No CT, lumbar puncture, or MRI	87	5.6%
Discharged from emergency department	1010	64.7%
Final Diagnosis		
Cerebrovascular disease (CVD)	369	23.6%
Subarachnoid hemorrhage	277	17.7%

Other CVD	92	5.9%
Other neurological disease	715	45.8%
Migraine headache	133	8.5%
Tension headache	61	3.9%
Cluster headache	12	0.8%
Unclassified benign headache	438	28.1%
Meningitis	17	1.1%
Post-seizure headache	15	1.0%
Neuralgia	10	0.6%
Brain tumor	7	0.4%
Viral illness	60	3.8%
Psychiatric disease	47	3.0%
Hypertensive crisis	38	2.4%
Peripheral vertigo	37	2.4%
Gastrointestinal disease	22	1.4%
Sinusitis	16	1.0%
Hyperventilation	16	1.0%
Urinary tract infection	16	1.0%
Dehydration	15	1.0%
Respiratory disease	14	0.9%
Syncope	10	0.6%
Cervical spondylosis	10	0.6%
Other non-neurological disease	176	11.3%

Table 2. Univariate Correlation of Valiables for Subarachnoid Hemorrhage

Characteristic	Subarachnoid Hemorrhage		*P* value
	No (n=1284)	**Yes** (n=277)	
From history			
Age, mean (SD) [range]	51 (21)	63 (15)	<0.0001
Women	56.9%	67.5%	0.0012
Onset during exertion	14.3%	54.9%	<0.0001
Worst headache of life	9.5%	54.9%	<0.0001
Thunderclap headache	2.2%	3.3%	0.279
Altered level of consciousness	3.8%	40.1%	<0.0001
Neck pain or stiffness	72.9%	86.6%	<0.0001
Vomiting	25.4%	52.7%	<0.0001
Vertigo / dizziness	15.6%	8.3%	0.0072
History of hypertension	24.0%	43.7%	<0.0001
History of diabetes mellitus	10.1%	3.6%	0.095
From physical examination			
Heart rate, mean (SD) beats/min	79 (17)	80 (17)	0.7669
Blood pressure, mean (SD) mmHg			
Systolic	139 (30)	167 (36)	<0.0001
Diastolic	81 (18)	93 (21)	<0.0001
Body temperature, mean (SD) °C	36.6 (0.8)	36.3 (0.9)	<0.0001
Diagnostic procedures			
CT	1197	277	
MRI	62	4	
Lumbar puncture	37	3	
From blood test	**No** (n=1045)	**Yes** (n=272)	
Blood sugar, mean (SD) mg/dL	127 (51)	162 (49)	<0.0001
Serum sodium, mean (SD) mEq/L	139.4 (3.4)	138.6 (3.0)	0.0016
Serum potassium, mean (SD) mEq/L	3.9 (0.5)	3.6 (0.5)	<0.0001
Hemoglobin, mean (SD) g/dL	13.6 (2.0)	13.4 (1.9)	0.1044
White cell count, mean (SD) $\times 10^3/\mu L$	7.9 (3.4)	10.3 (4.6)	<0.0001
Platelet count, mean (SD) $\times 10^4/\mu L$	21.7 (10.0)	24.0 (21.0)	0.9258

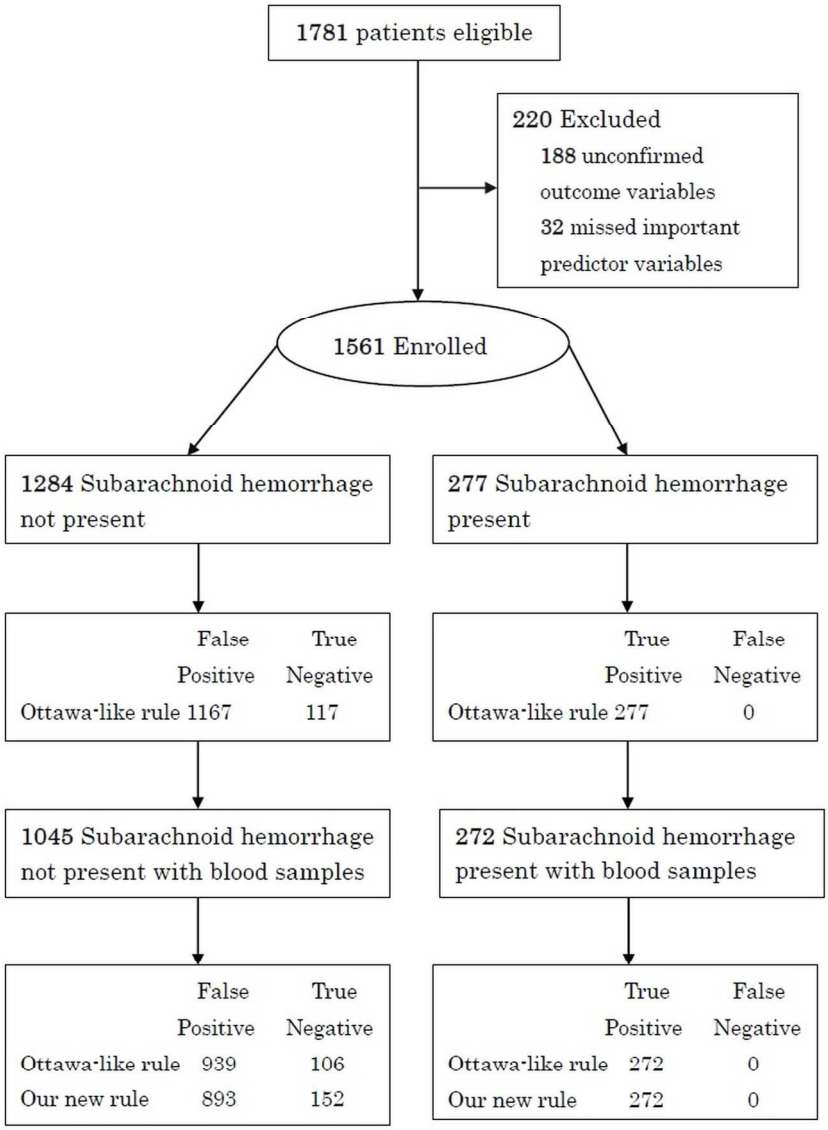

Figure 1
Details of enrollment and flow of patients in study

Ottawa-like rule, any of the following risks present:
1. Age ≧40 years
2. Neck pain or stiffness
3. Altered level of consciousness
4. Onset during exertion.

EMERALD SAH rule, any of the following risks present:
1. Systolic blood pressure >150 mmHg
2. Diastolic blood pressure >90 mmHg
3. Blood sugar >115 mg/dL (6.9 mmol/L)
4. Serum potassium <3.9 mEq/L (3.90 mmol/L)

233x274mm (300 x 300 DPI)

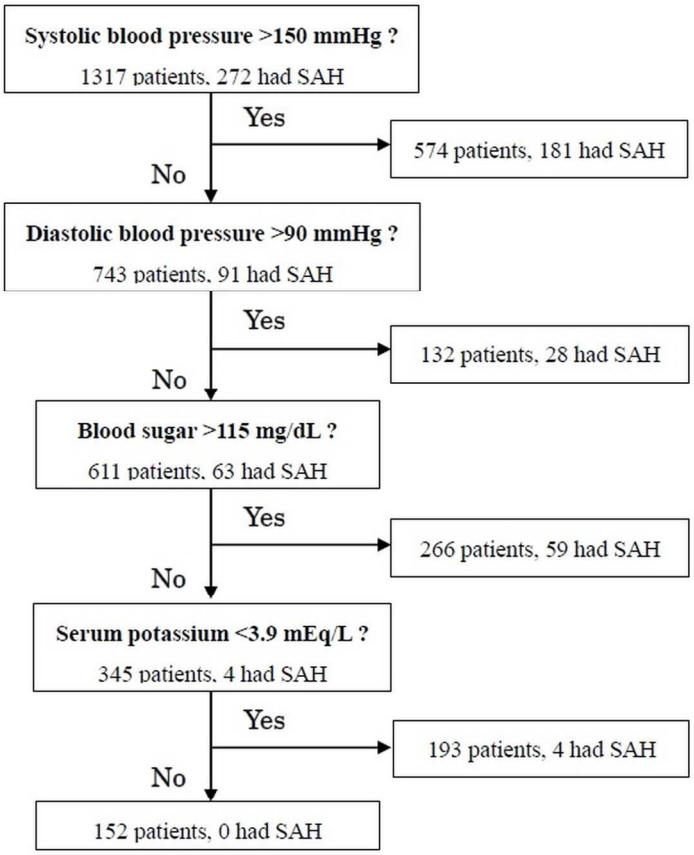

Figure 2
Example of recursive partitioning analysis with our new rule: the EMERALD SAH Rule
SAH: subarachnoid hemorrhage

210x191mm (300 x 300 DPI)

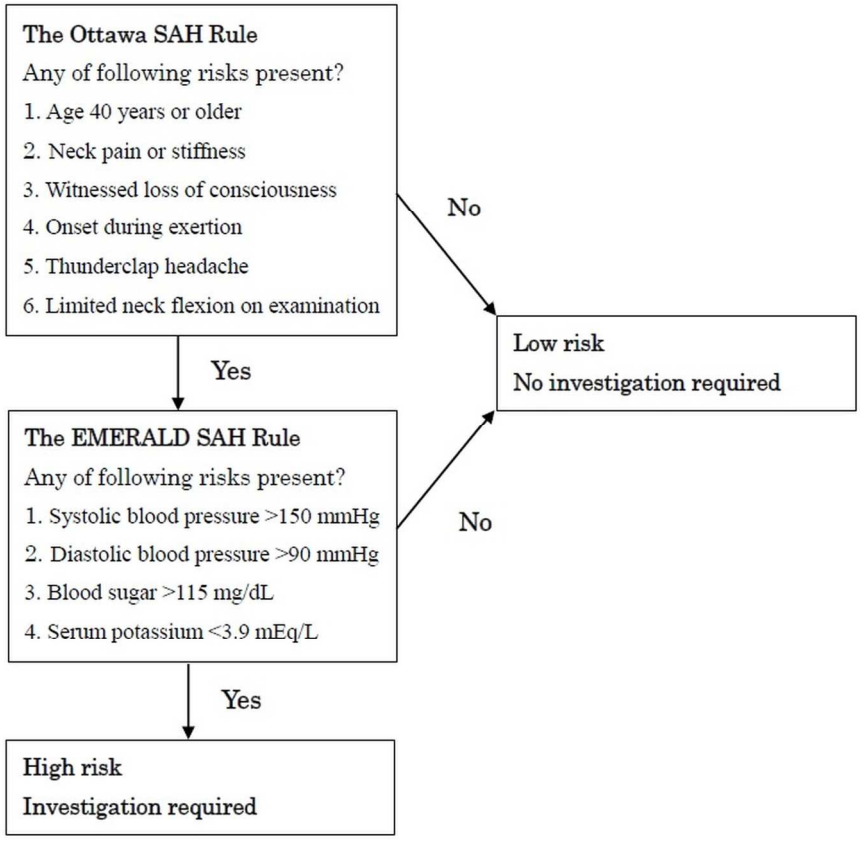

Figure 3
The proposed two-step decision-making to rule out subarachnoid hemorrhage (SAH) for adult patients with acute headache

217x186mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	① P1 P3-4	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	② **P6-7**	Explain the scientific background and rationale for the investigation being reported
Objectives	③ **P67**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	④ **P8**	Present key elements of study design early in the paper
Setting	⑤ **P8-9**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	⑥ **P8**	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	⑦ **P10**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	⑧* **P9**	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	⑨ **P9**	Describe any efforts to address potential sources of bias
Study size	⑩	Explain how the study size was arrived at
This was not written in the manuscript, but as in the previous study (Ref.7), at least 120 patients with SAH were required. Our previous study (Ref 10) reported that about 13% of patients with acute headache had SAH at our emergency department. Thus, more than 923 enrolled patient would be required. In the present study, 1317 patients with blood sample were enrolled and analysed, and among them 272 patients had SAH (Fig.1). Therefore the sample size was considered to be sufficient.		
Quantitative variables	⑪ **P9**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	⑫ **P10-11**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions

		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* **P11-12 Fig.1**	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* **P12 Table1**	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* **P12 Fig.1 Table2**	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 **P12-13 Fig2**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Using bootstrapping we calculated sensitivity and specificity for 5 rules (including the Ottwa like rule and the EMERALD rule) to select the best rule, but we didn't show them in the manuscript.		
Discussion		
Key results	18 **P15**	Summarise key results with reference to study objectives
Limitations	19 **P16-17**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 **P17**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 **P17**	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 **P19**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A new clinical decision rule to exclude subarachnoid hemorrhage for acute headache: a prospective, multicenter, observational study

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A new clinical decision rule to exclude subarachnoid hemorrhage for acute headache: a prospective, multicenter, observational study

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ABSTRACT

Objective To ensure good outcomes in the management of subarachnoid hemorrhage, accurate prediction is crucial for initial assessment of patients presenting with acute headache. We conducted this study to develop a new clinical decision rule using only objectively measurable predictors to exclude subarachnoid hemorrhage, offering higher specificity than the previous Ottawa Subarachnoid Hemorrhage Rule while maintaining comparable sensitivity.

Design Multicenter prospective cohort study

Setting Tertiary-care emergency departments of five general hospitals in Japan from April 2011 to March 2014.

Participants Enrolled patients comprised 1781 patients >15 years old with acute headache, excluding trauma or toxic causes and patients who presented in an unconscious state.

Main outcome measures Definitive diagnosis of subarachnoid hemorrhage was based on confirmation of subarachnoid hemorrhage on head computed tomography or lumbar puncture findings of non-traumatic red blood cells or xanthochromia.

Results Of the 1781 eligible patients, 277 showed subarachnoid hemorrhage. From 1561 enrolled patients, we reached a rule we called the “Ottawa-like rule”, offering

100% sensitivity when using any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion. Using the 1317 patients from whom blood samples were obtained, a new rule using any of systolic blood pressure >150 mmHg, diastolic blood pressure >90 mmHg, blood sugar >115 mg/dL, or serum potassium <3.9 mEq/L offered 100% sensitivity (95% confidence interval: 98.6-100%) and 14.5% specificity (12.5-16.9%), while the Ottwa-like rule showed the same sensitivity with a lower specificity of 8.8% (7.2-10.7%).

Conclusion While maintaining equal sensitivity, our new rule seemed to offer higher specificity than the previous rules proposed by the Ottawa group. Despite the need for blood sampling, this method can reduce unnecessary head computed tomography in acute headache patients.

Strengths and limitations of this study

- In this multicenter, cohort study, we developed a new clinical decision rule to exclude SAH (EMERALD SAH Rule) in patients presenting with acute headache at emergency department in Japan. We selected objectively measurable predictors (systolic and diastolic blood pressures and blood sugar and serum potassium)

having no inter-observer differences. Maintaining 100% sensitivity, the EMERALD SAH rule could show higher specificity than the previous rules.

- The proposed rule needs to be externally validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal validation.

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a common, serious problem encountered in emergency departments (EDs), and has been reported to result in disability or even death in 40-60% of affected patients.[1-4] Good outcomes are strongly dependent on prompt diagnosis and early treatment,[1-4] while untreated patients can experience sudden clinical deterioration because of re-bleeding. “Sudden, worst headache of life” or “thunderclap headache” are widely accepted predictors of SAH, and most emergency physicians investigate patients with such characteristic headaches using head computed tomography (CT) or lumbar puncture. However, some patients with SAH do not present with such characteristic headaches, and 12% of cases are reportedly overlooked on initial assessment.[1-5] Moreover, sudden severe headache can also be found in patients with more benign headache[6]. Overlooking SAH in an alert patient can lead to catastrophic disability or death[5], so the development of methods for clinical prediction with high sensitivity is very important, particularly for patients with uncharacteristic symptoms.

The research group at the University of Ottawa has provided highly sensitive clinical decision rules to exclude SAH in patients presenting with acute headache.[7] Their well-organized research led to a rule including any patient ≥40 years old with neck pain

or stiffness, witnessed loss of consciousness, or onset during exertion. However, a multicenter cohort validation study failed to show 100% sensitivity.[8] The group then added "thunderclap headache" and "limited neck flexion on examination", resulting in 100% sensitivity for the Ottawa SAH Rule.[8]

Over the last decade, we have been involved in the development of clinical predictions to exclude SAH[9-10] for patients presenting to EDs with acute headache. Several years ago, we developed the subarachnoid hemorrhage prediction score (SPS)[10] using only measurable predictors (systolic blood pressure, blood sugar, serum potassium, and white cell count) in order to minimize interobserver differences and observer biases. The SPS offered 100% sensitivity for predicting SAH in a retrospective single-center study, but recent prospective validation cohorts have failed to maintain 100% sensitivity (unpublished data).

The present study was conducted as part of the Emergency Medicine, Registry Analysis, Learning and Diagnosis (EMERALD) project, which is aimed at minimizing life-threatening diseases being overlooked at EDs in Japan. The objective of this study was to develop a new clinical decision rule using only objectively measurable predictors to exclude SAH, while maintaining 100% sensitivity and offering higher specificity than the Ottawa SAH rule. Our new rule may need blood sampling, but was aimed at further

reducing unnecessary CT and lumbar puncture, thus limiting costs, exposure to radiation, and invasiveness.

METHODS

Study design

This prospective multicenter observational study was conducted through the EDs of five general hospitals in Japan from April 2011 to March 2014. The research ethics board at each participating hospital approved the study protocol, which was designed in accordance with the STROBE statement for observational studies.

Study population

1899 consecutive patients >15 years old with a chief complaint of acute headache and presenting within 14 days of onset were considered for enrollment. We excluded patients with headache caused by trauma, drugs, or alcohol, and those who were unconscious at the beginning of assessment. As with previous studies,[7,8] we also excluded patients with recurrent headache syndromes (history of ≥3 recurrences of headache with the same characteristics and intensity as the presenting headache over a period >6 months).

Data collection

All patient assessments were made by residents supervised by staff physicians or attending emergency physicians. Physicians were oriented to the study and instructed to input clinical findings at the time of assessment into data collection software specially developed by the EMERALD project on a smartphone, or onto electronic charts of a hospital that showed the same data items as the smartphone device. Electronic chart data were later manually transferred to the smartphone device.

To minimize interobserver differences and observer biases, as in our previous study, we focused on objectively measurable data such as age, heart rate, systolic and diastolic blood pressures, and body temperature, which were defined as the first reading by the treating nursing staff. We also collected a variety of data from blood samples, such as blood sugar, serum sodium, serum potassium, hemoglobin concentration, white blood cell counts, and platelet counts, as these factors need only a small amount of blood to determine. However, only routine examination items for emergency patients in Japanese EDs were used and all results were obtainable within 10 min.

All patient data were anonymized before being uploaded to the internet server via direct smartphone connection or from personal computers at EDs with Bluetooth connections to smartphone devices. Collected anonymized data were monitored and cleaned by the

Joint Center for Researchers, Associates and Clinicians (JCRAC), an authorized center for quality management of data. The final data set for analyses was provided by JCRAC.

Outcome measures

The primary outcome, SAH, was defined as any of the following: SAH on unenhanced CT of the head; xanthochromia in cerebrospinal fluid; or non-traumatic, bloody cerebrospinal fluid in the final tube sample at lumbar puncture (LP) followed by either angiography or CT angiography to confirm whether an underlying pathology is causing SAH, in cooperation with neurological staff and an emergency physician. All participating hospitals have 64-row, multidetector row (MD) CT scanners either within the ED or located nearby. CT is available within 1 h, even at midnight. Even if results seem negative on plain CT, LP is only performed for those patients showing equivocal results on subsequent MRI or CT angiography, but for whom a high index of suspicion for SAH remains. Radiologists interpreted CT images later, and provided a final radiology report.

Discharged patients were evaluated by outpatient follow-up or by telephone interview. A total of 188 discharged patients without either CT images or follow-up evaluations were

excluded, as outcome variables were not able to be confirmed.

Data analysis

Univariate analyses were used to determine the strength of association between each possible predictor variable and the outcome variables. We used a 2-sided *t* test for continuous variables and Fisher's exact test for categorical variables.

To develop the clinical decision rule, we followed previously established methodological standards.[11] We selected possible predictors as clinically important, continuous variables showing values of $p<0.05$ on univariate analyses. The reason we used only objectively measurable variables was mentioned earlier. We performed multivariate, recursive partitioning analysis to develop rules using those possible predictors and the outcome. Cut-offs for variables were determined in the process of recursive partitioning. Sensitivity and specificity were estimated for each rule. A clinical decision rule for a life-threatening event like SAH requires 100% sensitivity with a narrow confidence interval (CI). Based on this philosophy, we selected the practical new rule with the highest specificity.

We conducted bootstrapping analysis of 1000 iterations to determine the internal stability of rules, and then calculated sensitivity and specificity of them. Analyses were

performed using JMP version 11.2.0 (SAS Institute, Cary, NC) and SAS version 9.3M2 (SAS Institute).

The funding source played no role in the collection, analysis, or interpretation of data, the writing of the report, or the decision to publish.

RESULTS

Figure 1 shows the study flow for the 1781 eligible patients applied the exclusion criteria to the 1899 consecutive patients. Of these, 1561 patients (87·6%) were enrolled after excluding 220 patients, of whom 188 had unconfirmed outcome variables as mentioned in the Methods and 32 were missing important information about age, onset, neck pain or stiffness, or alteration of level of consciousness. Blood test results were available for 1317 patients (84.4%).

Table 1 reports characteristics of the enrolled patients (mean age, 53 years; 58.4% women), including 277 patients (17.7%) with SAH. CT scans were performed for 94.4% of the enrolled patients, while lumbar punctures were carried out for 2.6%. The 64.7% of enrolled patients discharged from the ED.

Characteristics of the 1781 eligible patients were similar to those of enrolled patients (mean age, 53 years; 58.6% women). However, 188 Patients who were not followed-up

tended to be younger (mean age 42 years) and to have lower frequencies of both onset during exertion (15%) and alteration of consciousness (2%). And their systolic blood pressure (SBP) and diastolic blood pressure (DBP) tended to be low (130 mmHg and 78 mmHg, respectively).

Table 2 shows the results of univariate analysis. Patients with SAH were older and more often showed onset during exertion, "worst headache of life", altered level of consciousness, neck pain or stiffness, vomiting, and history of hypertension. Systolic and diastolic blood pressures were higher in patients with SAH, but surface body temperature was lower. In the 1317 patients for whom blood test results were available, blood sugar level and white cell count were higher in patients with SAH, but serum potassium was slightly lower.

From the 1561 enrolled patients, as a result of recursive partitioning analysis, we developed almost the same rule as Rule 1 from the previous literature,[7] using any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion. This rule was termed the "Ottawa-like rule", showing 100% sensitivity (95% confidence interval (CI), 98.6-100%) and 9.1% specificity (95%CI, 7.7-10.8%).

Using data from the 1317 patients for whom blood results were available, we developed a new rule using any of SBP >150 mmHg, DBP >90 mmHg, blood sugar >115 mg/dL

(6.9 mmol/L), or serum potassium <3.9 mEq/L (3.90 mmol/L) (Fig. 2). This new rule, which we called the "EMERALD SAH rule", offered 100% sensitivity (95%CI, 98.6-100%) and 14·5% specificity (95%CI, 12.5-16.9%). In comparison, the Ottawa-like rule showed identical sensitivity, but a lower specificity of 8.8% (95%CI, 7.2-10.7%).

Ninety of the other 92 cerebrovascular disease patients (Table 1) met the criteria of the EMERALD rule. A tiny subcortical hemorrhage and thalamic hemorrhage 1–2 cm in diameter occurred in 2 patients.

DISCUSSION

Over the last decade, we have been looking for rigid measurable predictors that would leave no room for interobserver disagreement. We have identified age, blood pressures, body temperature, blood sugar concentration, serum potassium concentration, and white cell count as possible predictors (Table 2). For the derivation of our new EMERALD SAH Rule, we selected systolic and diastolic blood pressures and blood sugar and serum potassium levels, as these offered relatively stronger discriminant abilities. We excluded age as a factor already used in the Ottawa SAH Rule.

Our data demonstrated 100% sensitivity for the Ottawa-like rule, almost identical to

Rule 1 which has the highest sensitivity among the three rules developed by the Ottawa group.[7] Prospective validation was provided for those three rules,[8] showing that Rule 1 had the highest sensitivity of 98.5% and 27.5% specificity. However, 100% sensitivity was not achieved. From this result, the Ottawa group proposed the Ottawa SAH Rule[8] with 100% sensitivity, adding "thunderclap headache" and "limited neck flexion", despite making the specificity 12.2% lower than that of Rule 1. This represented an even lower specificity than the EMERALD SAH Rule in our study.

We thus proposed a two-step decision-making rule (Fig. 3). We placed the Ottawa SAH Rule as the first screening step, because that is a much more clinically intuitive, and needle puncture is not needed. We can exclude SAH without unnecessary blood sampling for some patients with acute headache. However, if the EMERALD SAH Rule is placed as the second step, we can obtain higher specificity without reducing the optimal sensitivity, thus hopefully reducing both unnecessary exposure to radiation and costs from CT, while requiring only the small blood volume needed for blood gas analysis, and also reducing the need for invasive LPs that might result in headache even worse than the presenting symptom.

Several studies have found hypertension to represent an independent risk factor for SAH.[4] Before the present study, high systolic and diastolic blood pressure had already

been selected as possible predictors with similar cut-off values by the Canadian group,[7] but were not chosen as final predictors for the Ottawa SAH Rule.

We did not find any studies directly investigating the correlation between elevated blood sugar levels and SAH, but according to Douhout and colleagues,[12] higher blood sugar levels in the first 10 days after SAH are associated with worsened outcomes. Frontera and colleagues[13] have also claimed that SAH is generally followed by hyperglycemia, suggesting some correlation between the development of SAH and elevated blood sugar levels. A recent meta-analysis[14] revealed that admission glucose levels are often high and hyperglycemia is associated with an increased risk of poor outcomes after SAH.

Serum potassium levels were also significantly decreased in patients with SAH. SAH is believed to result in accelerated catecholamine secretion and increased intracellular potassium uptake, leading to lower serum potassium levels.[15-17]

Our study cohort contained a higher proportion (17.7%) of positive SAH than the Ottawa SAH Rule cohort. One contributor to the high rate of SAH in this study may have been the higher percentage of patients referred from smaller hospitals or clinics to EDs of tertiary general hospitals, like those participating in this study in Japan, compared to those in EDs of hospitals in North America. Walk-in patients with

headaches may attend smaller, secondary hospitals or clinics. Patients with a strong index of suspicion for SAH may be taken by ambulance to bigger general hospitals.

We should also discuss why the LP rate was very low, at 2.6%. If results from non-contrast CT are negative, LP follow-up seems to represent a standard of care[18]. However, LP is very invasive, requiries patient cooperation, and might causes further headache. Among member countries of the Organization for Economic Co-operation and Development, Japan has the largest number of CT scanners per million people, and the same situation can also be seen in the number of MRI scanners. Easy access to fifth-generation imaging, MDCT, which seems to identify SAH with almost 100% sensitivity[19], is assured at any time in all participating hospitals. Moreover, in patients with negative results on non-contrast CT, but still with a high suspicion of SAH, Japanese emergency physicians prefer to perform less invasive CT angiography[20] or MRI[21,22] before LP, and LP is indicated if the results are equivocal. The costs of radiological examinations are covered by the National Health Insurance system of Japan. These were considered the major reasons for the very low frequency of LP.

Limitations

To minimize observer biases, as we mentioned before, we have focused on objectively measurable data that do not require assessments with a κ coefficient. We did not assess

interobserver agreement for non-numerical variables, so our results for the Ottawa-like rule carried a risk of interobserver differences. However, the results were not far from those of the Ottawa studies, and may be sufficient to show the superior specificity of the EMERALD SAH Rule using only four measurable variables.

We were unable to record the time to peak headache intensity for all patients, and thus did not know whether headache reached maximum intensity within 1 h for all patients. This was because patients with non-typical, relatively lighter headache experienced difficulty answering when peak intensity occurred. Moreover, many patients with acute headache are often very reluctant to answer all clinical questions from physicians. This is another reason why we chose to rely on objectively measurable findings. The EMERALD SAH Rule would be applicable regardless of the time to peak intensity.

If patients develop new neurological deficits or have a history of aneurysm or brain tumor, precise investigations including non-enhanced and enhanced CT and routine blood testing are routinely conducted in EDs in Japan. We therefore do not emphasize the exclusion of such patients, because we can confirm the presence or absence of SAH. Our data could possibly have included a very small number of such patients. However, the negative effects of this possibility were considered to be almost zero for the derivation of the EMERALD SAH Rule.

The proposed rule needs to be properly validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal validation. This rule thus requires external validation before implementation.

Despite the necessity of blood testing, our EMERALD SAH Rule shows higher specificity than the previous Ottawa SAH Rule while maintaining equal sensitivity. It can allow further reduction of unnecessary investigations such as CT or LP in patients showing one or more of the predictors of the Ottawa SAH Rule. The EMERALD SAH Rule can play a role as a secondary screening to exclude SAH in patients with acute headache. However, further validation studies providing comparable results are required before making alterations to clinical practice.

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Competing interests: None of the authors have any conflicts of interest to declare.

Contributorship: Akio Kimura has made major contributions to the conception, design, analysis, and interpretation of data in this study. Kentaro Kobayashi has made substantial contributions to the conception of this study. Hitoshi Yamaguchi, Takeshi Takahashi, Masahiro Harada, Hideki Honda, Yoshio Mori, and Keika Hirose have made substantial contributions to the acquisition of data in this study. Noriko Tanaka has made substantial contributions to the statistical analysis in this study.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important

aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics committee approval: The research ethics committee at each participating hospital approved the study protocol. Participants were informed that they might be contacted by telephone for follow-up with written consent or with verbal consent obtained at the time of telephone contact.

Clinical trial registration: UMIN 00004871

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Data sharing: No additional data available.

REFERENCES

1 Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006;354:387–96.

2 van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet* 2007;369:306–18.

3 Edlow JA, Malek AM, Ogilvy CS. Aneurysmal subarachnoid hemorrhage: update for emergency physician. *J Emerg Med* 2008;34:237–51.

4 Connolly ES, Rabinstein AA, Carthuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A guideline for healthcare professionals from the American Heart Association / American Stroke Association. *Stroke* 2012;43:1711–37.

5 Kowalski RG, Claassen J, Kreiter KT, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA* 2004;291:866–9.

6 Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998;65:791–3.

7 Perry JJ, Stiell IG, Sivilotti ML, et al. High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study.

BMJ 2010;341:c5204.

8 Perry JJ, Stiell IG, Sivilotti ML, et al. Clinical decision rules to rule out subarachnoid haemorrhage for acute headache. *JAMA* 2013;310:1248–55.

9 Kimura Y, Kimura A, Tomioka J, et al. Early diagnosis of subarachnoid hemorrhage in patients reporting headache at emergency center. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2001;12:275–81.

10 Kobayashi K, Kimura A, Hagiwara A, et al. Highly sensitive, subarachnoid hemorrhage prediction score for patients with acute headache. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2011;22:305–11.

11 Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. *Ann Emerg Med* 1999;33:437–47.

12 Dorhout Mees SM, van Dijk GW, Algra A, et al. Glucose levels and outcome after subarachnoid hemorrhage. *Neurology* 2003;61:1132–3.

13 Frontera JA, Fernandez A, Claassen J, et al. Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. *Stroke* 2006;37:199–203.

14 Kruyt ND, Bissels GJ, de Hann RJ, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage, a meta-analysis. *Stroke* 2009;40:e424–30.

15 Fukui S, Otani N, Katoh H, et al. Female gender as a risk factor for

hypokalemia and QT prolongation after subarachnoid hemorrhage. *Neurology* 2002;59:134–6.

16 Fukui S, Katoh H, Tsuzuki N, et al. Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. *Crit Care* 2003;7:R7–12.

17 Fukui S, Katoh H, Tsuzuki N, et al. Gender disparities in serum electrolytes levels after subarachnoid hemorrhage. *J Clin Neurosci* 2004;11:606–9.

18 Perry JJ, Spacek A, Forbes M, et al. Is the combination of negative computed tomography result and negative lumbar puncture result sufficient to rule out subarachnoid hemorrhage? *Ann Emerg Med* 2008; 51:707-13.

19 Boesiger BM, Schiber JR. Subarachnoid hemorrhage diagnosis by computed tomography and lumber puncture: Are fifth generation CT scanners better at identifying subarachnoid hemorrhage? *J Emerg Med* 2005; 29:23-27.

20. McCormack RF, Huston A. Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan? *Acad Emerg Med* 2010: 17;444-51.

21. Verma RK, Kottke R, Andereggen L et al. Detecting subarachnoid hemorrhage: Comparioson of combined FLAIR/SWI versus CT. *Europ J Radiol* 2013; 82:1539–45.

22. Farzad A, Radian B, Oh JS et al. Emergency diagnosis of subarachnoid hemorrhage: an evidence-based debate. *J Emerg Med* 2013; 44:1045-53.

Table 1. Characteristics of Enrolled Patients (N=1561)

Characteristics	Patients	
Age, mean (SD) [range]	53 (21) [16-98]	
Women	912	58.4%
Onset during exertion	312	20.0%
Onset during rest	1131	72.5%
Headache awoke patient from sleep	55	3.5%
Duration from onset		
~60 min	297	19.0%
~24 h	863	55.3%
~7 days	342	21.9%
1 week ~	58	3.7%
Worst headache of life	274	17.6%
Thunderclap headache	37	2.4%
Alteration of consciousness level	151	9.7%
Neck pain or stiffness	1095	70.1%
Vomiting	442	28.3%
Vertigo / dizziness	206	13.2%
History of hypertension	374	24.0%
History of diabetes mellitus	118	7.6%
Heart rate, mean (SD) beats/min	79	(17)
Blood pressure, mean (SD) mmHg		
Systolic	144	(33)
Diastolic	83	(19)
Body temperature, mean (SD) °C	36.6	(0.8)
Diagnostic procedures		
CT	1474	94.4%
MRI	66	4.2%
Lumbar puncture	40	2.6%
No CT, lumbar puncture, or MRI	87	5.6%
Discharged from emergency department	1010	64.7%
Final Diagnosis		
Cerebrovascular disease (CVD)	369	23.6%
Subarachnoid hemorrhage	277	17.7%

Other CVD	92	5.9%
Other neurological disease	715	45.8%
Migraine headache	133	8.5%
Tension headache	61	3.9%
Cluster headache	12	0.8%
Unclassified benign headache	438	28.1%
Meningitis	17	1.1%
Post-seizure headache	15	1.0%
Neuralgia	10	0.6%
Brain tumor	7	0.4%
Viral illness	60	3.8%
Psychiatric disease	47	3.0%
Hypertensive crisis	38	2.4%
Peripheral vertigo	37	2.4%
Gastrointestinal disease	22	1.4%
Sinusitis	16	1.0%
Hyperventilation	16	1.0%
Urinary tract infection	16	1.0%
Dehydration	15	1.0%
Respiratory disease	14	0.9%
Syncope	10	0.6%
Cervical spondylosis	10	0.6%
Other non-neurological disease	176	11.3%

Table 2. Univariate Correlation of Valiables for Subarachnoid Hemorrhage

Characteristic	Subarachnoid Hemorrhage		*P* value
	No (n=1284)	**Yes** (n=277)	
From history			
Age, mean (SD) [range]	51 (21)	63 (15)	<0.0001
Women	56.9%	67.5%	0.0012
Onset during exertion	14.3%	54.9%	<0.0001
Worst headache of life	9.5%	54.9%	<0.0001
Thunderclap headache	2.2%	3.3%	0.279
Altered level of consciousness	3.8%	40.1%	<0.0001
Neck pain or stiffness	72.9%	86.6%	<0.0001
Vomiting	25.4%	52.7%	<0.0001
Vertigo / dizziness	15.6%	8.3%	0.0072
History of hypertension	24.0%	43.7%	<0.0001
History of diabetes mellitus	10.1%	3.6%	0.095
From physical examination			
Heart rate, mean (SD) beats/min	79 (17)	80 (17)	0.7669
Blood pressure, mean (SD) mmHg			
Systolic	139 (30)	167 (36)	<0.0001
Diastolic	81 (18)	93 (21)	<0.0001
Body temperature, mean (SD) °C	36.6 (0.8)	36.3 (0.9)	<0.0001
Diagnostic procedures			
CT	1197	277	
MRI	62	4	
Lumbar puncture	37	3	
From blood test	**No** (n=1045)	**Yes** (n=272)	
Blood sugar, mean (SD) mg/dL	127 (51)	162 (49)	<0.0001
Serum sodium, mean (SD) mEq/L	139.4 (3.4)	138.6 (3.0)	0.0016
Serum potassium, mean (SD) mEq/L	3.9 (0.5)	3.6 (0.5)	<0.0001
Hemoglobin, mean (SD) g/dL	13.6 (2.0)	13.4 (1.9)	0.1044
White cell count, mean (SD) $\times 10^3/\mu L$	7.9 (3.4)	10.3 (4.6)	<0.0001
Platelet count, mean (SD) $\times 10^4/\mu L$	21.7 (10.0)	24.0 (21.0)	0.9258

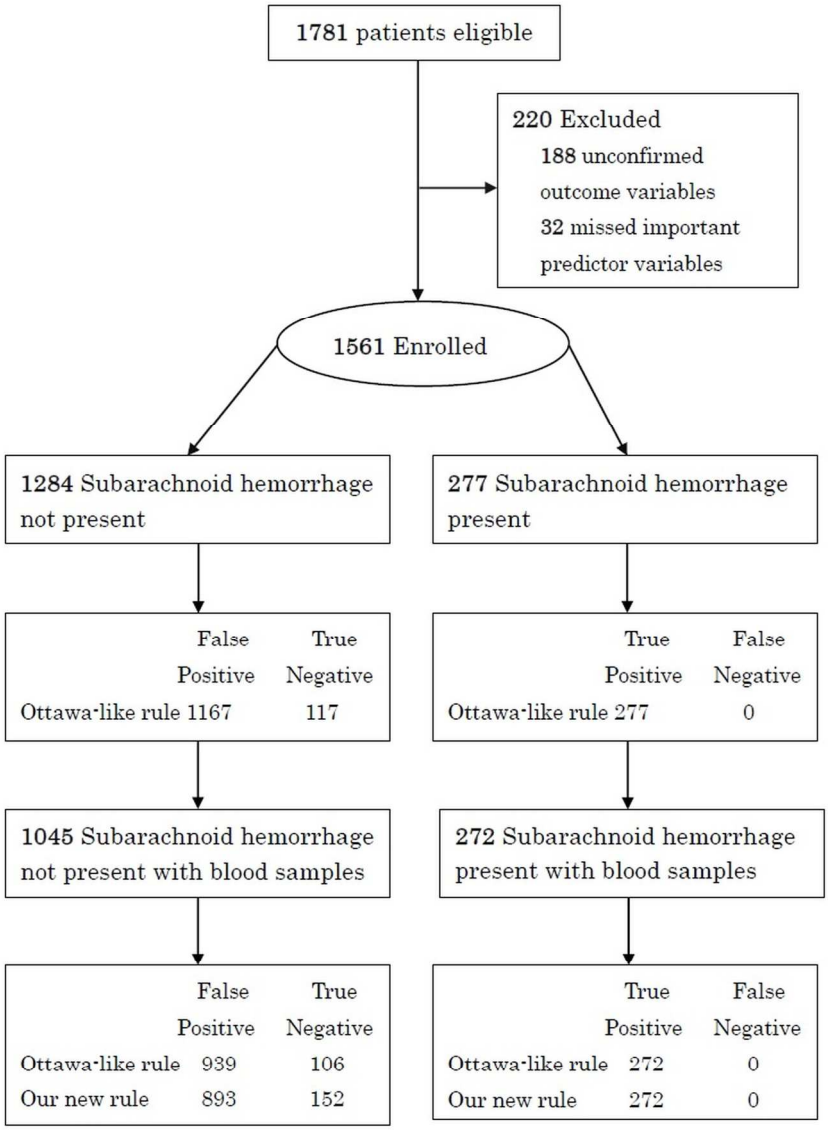

Figure 1\r\nDetails of enrollment and flow of patients in study\r\n\r\nOttawa-like rule, any of the following risks present:\r\n1. Age ≧40 years\r\n2. Neck pain or stiffness\r\n3. Altered level of consciousness\r\n4. Onset during exertion.\r\n\r\nOur new rule (namely, the EMERALD SAH rule), any of the following risks present:\r\n1. Systolic blood pressure >150 mmHg\r\n2. Diastolic blood pressure >90 mmHg\r\n3. Blood sugar >115 mg/dL (6.9 mmol/L)\r\n4. Serum potassium <3.9 mEq/L (3.90 mmol/L)\r\n

233x274mm (300 x 300 DPI)

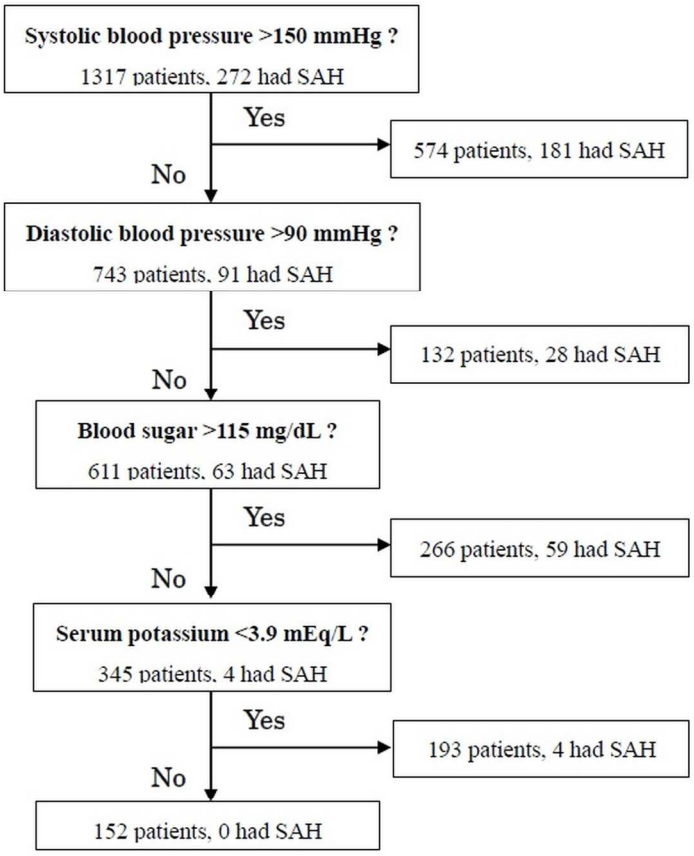

Figure 2
Example of recursive partitioning analysis with our new rule: the EMERALD SAH Rule
SAH: subarachnoid hemorrhage

210x191mm (300 x 300 DPI)

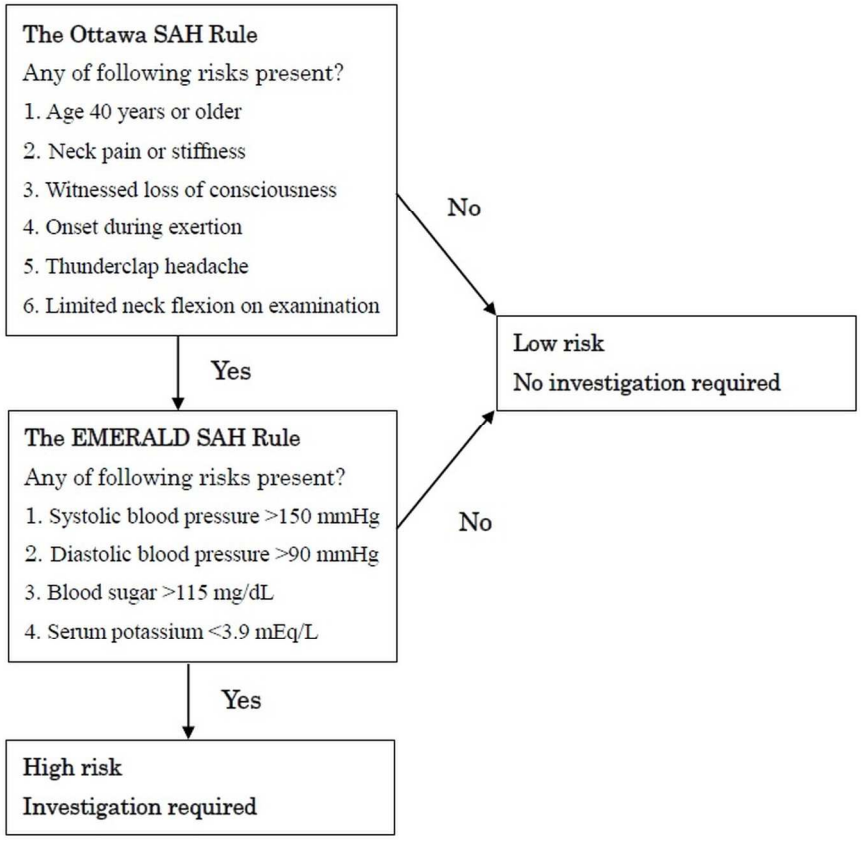

Figure 3
The proposed two-step decision-making to rule out subarachnoid hemorrhage (SAH) for adult patients with acute headache

217x186mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	① P1 P3-4	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	② **P6-7**	Explain the scientific background and rationale for the investigation being reported
Objectives	③ **P67**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	④ **P8**	Present key elements of study design early in the paper
Setting	⑤ **P8-9**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	⑥ **P8**	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	⑦ **P10**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	⑧* **P9**	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	⑨ **P9**	Describe any efforts to address potential sources of bias
Study size	⑩	Explain how the study size was arrived at
This was not written in the manuscript, but as in the previous study (Ref.7), at least 120 patients with SAH were required. Our previous study (Ref 10) reported that about 13% of patients with acute headache had SAH at our emergency department. Thus, more than 923 enrolled patient would be required. In the present study, 1317 patients with blood sample were enrolled and analysed, and among them 272 patients had SAH (Fig.1). Therefore the sample size was considered to be sufficient.		
Quantitative variables	⑪ **P9**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	⑫ **P10-11**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions

		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* **P11-12 Fig.1**	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* **P12 Table1**	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* **P12 Fig.1 Table2**	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 **P12-13 Fig2**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Using bootstrapping we calculated sensitivity and specificity for 5 rules (including the Ottwa like rule and the EMERALD rule) to select the best rule, but we didn't show them in the manuscript.		
Discussion		
Key results	18 **P15**	Summarise key results with reference to study objectives
Limitations	19 **P16-17**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 **P17**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 **P17**	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 **P19**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A new clinical decision rule to exclude subarachnoid hemorrhage for acute headache: a prospective, multicenter, observational study

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Keywords:	Computed tomography (CT), Blood pressure, Blood sugar, Serum potassium

A new clinical decision rule to exclude subarachnoid hemorrhage for acute headache: a prospective, multicenter, observational study

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ABSTRACT

Objective To ensure good outcomes in the management of subarachnoid hemorrhage (SAH), accurate prediction is crucial for initial assessment of patients presenting with acute headache. We conducted this study to develop a new clinical decision rule using only objectively measurable predictors to exclude SAH, offering higher specificity than the previous Ottawa SAH Rule while maintaining comparable sensitivity.

Design Multicenter prospective cohort study

Setting Tertiary-care emergency departments of five general hospitals in Japan from April 2011 to March 2014.

Participants Eligible patients comprised 1781 patients >15 years old with acute headache, excluding trauma or toxic causes and patients who presented in an unconscious state.

Main outcome measures Definitive diagnosis of SAH was based on confirmation of SAH on head computed tomography or lumbar puncture findings of non-traumatic red blood cells or xanthochromia.

Results A total of 1561 patients were enrolled in this study, of whom 277 showed SAH. Using these enrolled patients, we reached a rule with mainly categorical predictors used in previous reports, called the “Ottawa-like rule”, offering 100% sensitivity when using

any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion. Using the 1317 patients from whom blood samples were obtained, a new rule using any of systolic blood pressure >150 mmHg, diastolic blood pressure >90 mmHg, blood sugar >115 mg/dL, or serum potassium <3.9 mEq/L offered 100% sensitivity (95% confidence interval: 98.6-100%) and 14.5% specificity (12.5-16.9%), while the Ottwa-like rule showed the same sensitivity with a lower specificity of 8.8% (7.2-10.7%).

Conclusion While maintaining equal sensitivity, our new rule seemed to offer higher specificity than the previous rules proposed by the Ottawa group. Despite the need for blood sampling, this method can reduce unnecessary head computed tomography in acute headache patients.

Strengths and limitations of this study

- In this multicenter, cohort study, we developed a new clinical decision rule to exclude SAH (EMERALD SAH Rule) in patients presenting with acute headache at emergency department in Japan. We selected objectively measurable predictors (systolic and diastolic blood pressures and blood sugar and serum potassium)

having no inter-observer differences. Maintaining 100% sensitivity, the EMERALD SAH rule could show higher specificity than the previous rules.

- The proposed rule needs to be externally validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal validation.

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a common, serious problem encountered in emergency departments (EDs), and has been reported to result in disability or even death in 40-60% of affected patients.[1-4] Good outcomes are strongly dependent on prompt diagnosis and early treatment,[1-4] while untreated patients can experience sudden clinical deterioration because of re-bleeding. “Sudden, worst headache of life” or “thunderclap headache” are widely accepted predictors of SAH, and most emergency physicians investigate patients with such characteristic headaches using head computed tomography (CT) or lumbar puncture. However, some patients with SAH do not present with such characteristic headaches, and 12% of cases are reportedly overlooked on initial assessment.[1-5] Moreover, sudden severe headache can also be found in patients with more benign headache[6]. Overlooking SAH in an alert patient can lead to catastrophic disability or death[5], so the development of methods for clinical prediction with high sensitivity is very important, particularly for patients with uncharacteristic symptoms.

The research group at the University of Ottawa has provided highly sensitive clinical decision rules to exclude SAH in patients presenting with acute headache.[7] Their well-organized research led to a rule including any patient ≥40 years old with neck pain

or stiffness, witnessed loss of consciousness, or onset during exertion. However, a multicenter cohort validation study failed to show 100% sensitivity.[8] The group then added "thunderclap headache" and "limited neck flexion on examination", resulting in 100% sensitivity for the Ottawa SAH Rule.[8]

Over the last decade, we have been involved in the development of clinical predictions to exclude SAH[9-10] for patients presenting to EDs with acute headache. Several years ago, we developed the subarachnoid hemorrhage prediction score (SPS)[10] using only measurable predictors (systolic blood pressure, blood sugar, serum potassium, and white cell count) in order to minimize interobserver differences and observer biases. The SPS offered 100% sensitivity for predicting SAH in a retrospective single-center study, but recent prospective validation cohorts have failed to maintain 100% sensitivity (unpublished data).

The present study was conducted as part of the Emergency Medicine, Registry Analysis, Learning and Diagnosis (EMERALD) project, which is aimed at minimizing life-threatening diseases being overlooked at EDs in Japan. The objective of this study was to develop a new clinical decision rule using only objectively measurable predictors to exclude SAH, while maintaining 100% sensitivity and offering higher specificity than the Ottawa SAH rule. Our new rule may need blood sampling, but was aimed at further

reducing unnecessary CT and lumbar puncture, thus limiting costs, exposure to radiation, and invasiveness.

METHODS

Study design

This prospective multicenter observational study was conducted through the EDs of five general hospitals in Japan from April 2011 to March 2014. The research ethics board at each participating hospital approved the study protocol, which was designed in accordance with the STROBE statement for observational studies.

Study population

Eighteen hundred ninety-nine patients >15 years old with a chief complaint of acute headache and presenting within 14 days of onset were considered for enrollment. We excluded patients with headache caused by trauma, drugs, or alcohol, and those who were unconscious at the beginning of assessment. As with previous studies,[7,8] we also excluded patients with recurrent headache syndromes (history of ≥3 recurrences of headache with the same characteristics and intensity as the presenting headache over a period >6 months).

Data collection

All patient assessments were made by residents supervised by staff physicians or attending emergency physicians. Physicians were oriented to the study and instructed to input clinical findings at the time of assessment into data collection software specially developed by the EMERALD project on a smartphone, or onto electronic charts of a hospital that showed the same data items as the smartphone device. Electronic chart data were later manually transferred to the smartphone device.

To minimize interobserver differences and observer biases, as in our previous study, we focused on objectively measurable data such as age, heart rate, systolic and diastolic blood pressures, and body temperature, which were defined as the first reading by the treating nursing staff. We also collected a variety of data from blood samples, such as blood sugar, serum sodium, serum potassium, hemoglobin concentration, white blood cell counts, and platelet counts, as these factors need only a small amount of blood to determine. However, only routine examination items for emergency patients in Japanese EDs were used and all results were obtainable within 10 min.

All patient data were anonymized before being uploaded to the internet server via direct smartphone connection or from personal computers at EDs with Bluetooth connections

to smartphone devices. Collected anonymized data were monitored and cleaned by the Joint Center for Researchers, Associates and Clinicians (JCRAC), an authorized center for quality management of data. The final data set for analyses was provided by JCRAC.

Outcome measure

The primary outcome, SAH, was defined as any of the following: SAH on unenhanced CT of the head; xanthochromia in cerebrospinal fluid; or non-traumatic, bloody cerebrospinal fluid in the final tube sample at lumbar puncture (LP) followed by either angiography or CT angiography to confirm whether an underlying pathology is causing SAH, in cooperation with a neurological staff (neurologist or neurosurgeon) and emergency physicians. All participating hospitals had 64-row, multidetector row (MD) CT scanners either within the ED or located nearby. CT is available within 1 h, even at midnight. Even if results seemed negative on plain CT, LP was only performed for those patients showing equivocal results on subsequent MRI or CT angiography, but for whom a high index of suspicion for SAH remained. Radiologists interpreted CT images later, and provided a final radiology report. Radiologists checked CT misinterpretations of negative SAH. When radiologists found a very subtle SAH on CT, they contacted the

emergency department. If emergency physicians recognized a mistake after discharge, they contacted the patient to come back to the ED as soon as possible. Discharged patients were evaluated by outpatient follow-up or by telephone interview. A total of 188 discharged patients without either CT images or follow-up evaluations were excluded, as outcome variables were not able to be confirmed.

Data analysis

Univariate analyses were used to determine the strength of association between each possible predictor variable and the outcome variable. We used a 2-sided *t* test for continuous variables and Fisher's exact test for categorical variables.

To develop the clinical decision rule, we followed previously established methodological standards.[11] Firstly, we selected categorical variables showing values of $p<0.05$ on univariate analyses. Then, we selected possible predictors as clinically important, continuous variables showing values of $p<0.05$ on univariate analyses. The reason we used objectively measurable variables was mentioned earlier. Setting presence (1) or absence (0) of SAH as the outcome variable, we performed multivariate, recursive partitioning analyses to develop rules using only the selected categorical variables and age and using only the selected, objectively measurable predictors.

Cut-offs for variables were determined in the process of recursive partitioning. Sensitivity and specificity were estimated for each rule. A clinical decision rule for a life-threatening event like SAH requires 100% sensitivity with a narrow confidence interval (CI). Based on this philosophy, we selected the practical new rule with the highest specificity.

We conducted bootstrapping analysis of 1000 iterations to determine the internal stability of rules, and then calculated sensitivity and specificity of them. Analyses were performed using JMP version 11.2.0 (SAS Institute, Cary, NC) and SAS version 9.3M2 (SAS Institute).

The funding source played no role in the collection, analysis, or interpretation of data, the writing of the report, or the decision to publish.

RESULTS

Figure 1 shows the study flow for the 1781 eligible patients applied the exclusion criteria to the 1899 consecutive patients. Of these, 1561 patients (87·6%) were enrolled after excluding 220 patients, of whom 188 had unconfirmed outcome variables as mentioned in the Methods and 32 were missing important information about age, onset, neck pain or stiffness, or alteration of level of consciousness. Blood test results were

available for 1317 patients (84.4%).

Table 1 reports characteristics of the enrolled patients (mean age, 53 years; 58.4% women), including 277 patients (17.7%) with SAH. CT scans were performed for 94.4% of the enrolled patients, while lumbar punctures were carried out for 2.6%. The 64.7% of enrolled patients discharged from the ED.

Characteristics of the 1781 eligible patients were similar to those of enrolled patients (mean age, 53 years; 58.6% women). However, 188 Patients who were not followed-up tended to be younger (mean age 42 years) and to have lower frequencies of both onset during exertion (15%) and alteration of consciousness (2%). And their systolic blood pressure (SBP) and diastolic blood pressure (DBP) tended to be low (130 mmHg and 78 mmHg, respectively).

Table 2 shows the results of univariate analysis. Patients with SAH were older and more often showed onset during exertion, “worst headache of life”, altered level of consciousness, neck pain or stiffness, vomiting, and history of hypertension. Systolic and diastolic blood pressures were higher in patients with SAH, but surface body temperature was lower. In the 1317 patients for whom blood test results were available, blood sugar level and white cell count were higher in patients with SAH, but serum potassium was slightly lower.

From the 1561 enrolled patients, as a result of recursive partitioning analysis, we developed almost the same rule as Rule 1 from the previous literature,[7] using any of age ≥40 years, neck pain or stiffness, altered level of consciousness, or onset during exertion. This rule was termed the "Ottawa-like rule", showing 100% sensitivity (95% confidence interval (CI), 98.6-100%) and 9.1% specificity (95%CI, 7.7-10.8%).

Using data from the 1317 patients for whom blood results were available, we developed a new rule using any of SBP >150 mmHg, DBP >90 mmHg, blood sugar >115 mg/dL (6.9 mmol/L), or serum potassium <3.9 mEq/L (3.90 mmol/L) (Fig. 2). This new rule, which we called the "EMERALD SAH rule", offered 100% sensitivity (95%CI, 98.6-100%) and 14·5% specificity (95%CI, 12.5-16.9%). In comparison, the Ottawa-like rule showed identical sensitivity, but a lower specificity of 8.8% (95%CI, 7.2-10.7%).

Ninety of the other 92 cerebrovascular disease patients (Table 1) met the criteria of the EMERALD rule. A tiny subcortical hemorrhage and thalamic hemorrhage 1–2 cm in diameter occurred in 2 patients.

DISCUSSION

Over the last decade, we have been looking for rigid measurable predictors that would

leave no room for interobserver disagreement. We have identified age, blood pressures, body temperature, blood sugar concentration, serum potassium concentration, and white cell count as possible predictors (Table 2). For the derivation of our new EMERALD SAH Rule, we selected systolic and diastolic blood pressures and blood sugar and serum potassium levels, as these offered relatively stronger discriminant abilities. We excluded age as a factor already used in the Ottawa SAH Rule.

Our data demonstrated 100% sensitivity for the Ottawa-like rule, almost identical to Rule 1 which has the highest sensitivity among the three rules developed by the Ottawa group.[7] Prospective validation was provided for those three rules,[8] showing that Rule 1 had the highest sensitivity of 98.5% and 27.5% specificity. However, 100% sensitivity was not achieved. From this result, the Ottawa group proposed the Ottawa SAH Rule[8] with 100% sensitivity, adding "thunderclap headache" and "limited neck flexion", despite making the specificity 12.2% lower than that of Rule 1. This represented an even lower specificity than the EMERALD SAH Rule in our study.

We thus proposed a two-step decision-making rule (Fig. 3). We placed the Ottawa SAH Rule as the first screening step, because that is a much more clinically intuitive, and needle puncture is not needed. We can exclude SAH without unnecessary blood sampling for some patients with acute headache. However, if the EMERALD SAH

Rule is placed as the second step, we can obtain higher specificity without reducing the optimal sensitivity, thus hopefully reducing both unnecessary exposure to radiation and costs from CT, while requiring only the small blood volume needed for blood gas analysis, and also reducing the need for invasive LPs that might result in headache even worse than the presenting symptom.

Several studies have found hypertension to represent an independent risk factor for SAH.[4] Before the present study, high systolic and diastolic blood pressure had already been selected as possible predictors with similar cut-off values by the Canadian group,[7] but were not chosen as final predictors for the Ottawa SAH Rule.

We did not find any studies directly investigating the correlation between elevated blood sugar levels and SAH, but according to Douhout and colleagues,[12] higher blood sugar levels in the first 10 days after SAH are associated with worsened outcomes. Frontera and colleagues[13] have also claimed that SAH is generally followed by hyperglycemia, suggesting some correlation between the development of SAH and elevated blood sugar levels. A recent meta-analysis[14] revealed that admission glucose levels are often high and hyperglycemia is associated with an increased risk of poor outcomes after SAH.

Serum potassium levels were also significantly decreased in patients with SAH. SAH is

believed to result in accelerated catecholamine secretion and increased intracellular potassium uptake, leading to lower serum potassium levels.[15-17]

Limitations

Our study cohort contained a higher proportion (17.7%) of positive SAH than the Ottawa SAH Rule cohort. One contributor to the high rate of SAH in this study may have been the higher percentage of patients referred from smaller hospitals or clinics to EDs of tertiary general hospitals, like those participating in this study in Japan, compared to those in EDs of hospitals in North America. Walk-in patients with headaches may attend smaller, secondary hospitals or clinics. Patients with a strong index of suspicion for SAH may be taken by ambulance to bigger general hospitals. Another issue warranting attention was the fact that the LP rate was very low, at 2.6%. If results from non-contrast CT are negative, LP follow-up seems to represent a standard of care[18]. However, LP is very invasive, requires patient cooperation, and might causes further headache. Among member countries of the Organization for Economic Co-operation and Development, Japan has the largest number of CT scanners per million people, and the same situation can also be seen in the number of MRI scanners. Easy access to fifth-generation or later imaging by MDCT, which seems to detect SAH with sensitivity approaching 100% [19], are routinely assured not only at all hospitals

participating in the present study, but also at almost every general hospital in Japan. This allows CT to be obtained within 1 h from arrival in the ED. Moreover, easy access to EDs is provided all over Japan, so most patients with acute headache will present to hospitals within a few hours of onset. Among patients with negative results on non-contrast CT, as confirmed by emergency physicians, neurological doctors and radiologists, but still show a high suspicion of SAH, Japanese emergency physicians prefer to perform the less invasive and more specific CT angiography[20] or MRI[21,22] before LP, and LP is indicated only if the results of imaging are equivocal. The costs of radiological examinations are covered by the National Health Insurance system of Japan. These were considered the major reasons for the very low frequency of LP.

Although we have explained the Japanese situation for the higher proportion of SAH and low LP rate, the findings might imply that some headaches at risk of representing SAH were not being captured by this study. Careful application of our results to EDs with a lower prevalence of SAH appears warranted.

To minimize observer biases, as we mentioned before, we have focused on objectively measurable data that do not require assessments with a κ coefficient. We did not assess interobserver agreement for non-numerical variables, so our results for the Ottawa-like rule carried a risk of interobserver differences. However, the results were not far from

those of the Ottawa studies, and may be sufficient to show the superior specificity of the EMERALD SAH Rule using only four measurable variables.

We were unable to record the time to peak headache intensity for all patients, and thus did not know whether headache reached maximum intensity within 1 h for all patients. This was because patients with non-typical, relatively lighter headache experienced difficulty answering when peak intensity occurred. Moreover, many patients with acute headache are often very reluctant to answer all clinical questions from physicians. This is another reason why we chose to rely on objectively measurable findings. The EMERALD SAH Rule would be applicable regardless of the time to peak intensity.

If patients develop new neurological deficits or have a history of aneurysm or brain tumor, precise investigations including non-enhanced and enhanced CT and routine blood testing are routinely conducted in EDs in Japan. We therefore do not emphasize the exclusion of such patients, because we can confirm the presence or absence of SAH. Our data could possibly have included a very small number of such patients. However, the negative effects of this possibility were considered to be almost zero for the derivation of the EMERALD SAH Rule.

The proposed rule needs to be properly validated before being fully incorporated into clinical practice, because we only undertook bootstrapping analysis for internal

validation. This rule thus requires external validation before implementation.

Despite the necessity of blood testing, our EMERALD SAH Rule shows higher specificity than the previous Ottawa SAH Rule while maintaining equal sensitivity. It can allow further reduction of unnecessary investigations such as CT or LP in patients showing one or more of the predictors of the Ottawa SAH Rule. The EMERALD SAH Rule can play a role as a secondary screening to exclude SAH in patients with acute headache. However, further validation studies providing comparable results are required before making alterations to clinical practice.

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Competing interests: None of the authors have any conflicts of interest to declare.

Contributorship: Akio Kimura has made major contributions to the conception, design, analysis, and interpretation of data in this study. Kentaro Kobayashi has made substantial contributions to the conception of this study. Hitoshi Yamaguchi, Takeshi Takahashi, Masahiro Harada, Hideki Honda, Yoshio Mori, and Keika Hirose have made substantial contributions to the acquisition of data in this study. Noriko Tanaka has made substantial contributions to the statistical analysis in this study.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important

aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics committee approval: The research ethics committee at each participating hospital approved the study protocol. Participants were informed that they might be contacted by telephone for follow-up with written consent or with verbal consent obtained at the time of telephone contact.

Clinical trial registration: UMIN 00004871

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Data sharing: No additional data available.

REFERENCES

1 Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006;354:387–96.

2 van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet* 2007;369:306–18.

3 Edlow JA, Malek AM, Ogilvy CS. Aneurysmal subarachnoid hemorrhage: update for emergency physician. *J Emerg Med* 2008;34:237–51.

4 Connolly ES, Rabinstein AA, Carthuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. A guideline for healthcare professionals from the American Heart Association / American Stroke Association. *Stroke* 2012;43:1711–37.

5 Kowalski RG, Claassen J, Kreiter KT, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA* 2004;291:866–9.

6 Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998;65:791–3.

7 Perry JJ, Stiell IG, Sivilotti ML, et al. High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study.

BMJ 2010;341:c5204.

8 Perry JJ, Stiell IG, Sivilotti ML, et al. Clinical decision rules to rule out subarachnoid haemorrhage for acute headache. *JAMA* 2013;310:1248–55.

9 Kimura Y, Kimura A, Tomioka J, et al. Early diagnosis of subarachnoid hemorrhage in patients reporting headache at emergency center. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2001;12:275–81.

10 Kobayashi K, Kimura A, Hagiwara A, et al. Highly sensitive, subarachnoid hemorrhage prediction score for patients with acute headache. (in Japanese) *Journal of the Japanese Association for Acute Medicine* 2011;22:305–11.

11 Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. *Ann Emerg Med* 1999;33:437–47.

12 Dorhout Mees SM, van Dijk GW, Algra A, et al. Glucose levels and outcome after subarachnoid hemorrhage. *Neurology* 2003;61:1132–3.

13 Frontera JA, Fernandez A, Claassen J, et al. Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. *Stroke* 2006;37:199–203.

14 Kruyt ND, Bissels GJ, de Hann RJ, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage, a meta-analysis. *Stroke* 2009;40:e424–30.

15 Fukui S, Otani N, Katoh H, et al. Female gender as a risk factor for

hypokalemia and QT prolongation after subarachnoid hemorrhage. *Neurology* 2002;59:134–6.

16 Fukui S, Katoh H, Tsuzuki N, et al. Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. *Crit Care* 2003;7:R7–12.

17 Fukui S, Katoh H, Tsuzuki N, et al. Gender disparities in serum electrolytes levels after subarachnoid hemorrhage. *J Clin Neurosci* 2004;11:606–9.

18 Perry JJ, Spacek A, Forbes M, et al. Is the combination of negative computed tomography result and negative lumbar puncture result sufficient to rule out subarachnoid hemorrhage? *Ann Emerg Med* 2008; 51:707-13.

19 Boesiger BM, Schiber JR. Subarachnoid hemorrhage diagnosis by computed tomography and lumber puncture: Are fifth generation CT scanners better at identifying subarachnoid hemorrhage? *J Emerg Med* 2005; 29:23-27.

20. McCormack RF, Huston A. Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan? *Acad Emerg Med* 2010: 17;444-51.

21. Verma RK, Kottke R, Andereggen L et al. Detecting subarachnoid hemorrhage: Comparioson of combined FLAIR/SWI versus CT. *Europ J Radiol* 2013; 82:1539–45.

22. Farzad A, Radian B, Oh JS et al. Emergency diagnosis of subarachnoid hemorrhage: an evidence-based debate. *J Emerg Med* 2013; 44:1045-53.

Table 1. Characteristics of Enrolled Patients (N=1561)

Characteristics	Patients	
Age, mean (SD) [range]	53 (21) [16-98]	
Women	912	58.4%
Onset during exertion	312	20.0%
Onset during rest	1131	72.5%
Headache awoke patient from sleep	55	3.5%
Duration from onset		
~60 min	297	19.0%
~24 h	863	55.3%
~7 days	342	21.9%
1 week ~	58	3.7%
Worst headache of life	274	17.6%
Thunderclap headache	37	2.4%
Alteration of consciousness level	151	9.7%
Neck pain or stiffness	1095	70.1%
Vomiting	442	28.3%
Vertigo / dizziness	206	13.2%
History of hypertension	374	24.0%
History of diabetes mellitus	118	7.6%
Heart rate, mean (SD) beats/min	79	(17)
Blood pressure, mean (SD) mmHg		
Systolic	144	(33)
Diastolic	83	(19)
Body temperature, mean (SD) °C	36.6	(0.8)
Diagnostic procedures		
CT	1474	94.4%
MRI	66	4.2%
Lumbar puncture	40	2.6%
No CT, lumbar puncture, or MRI	87	5.6%
Discharged from emergency department	1010	64.7%
Final Diagnosis		
Cerebrovascular disease (CVD)	369	23.6%
Subarachnoid hemorrhage	277	17.7%

Other CVD	92	5.9%
Other neurological disease	715	45.8%
Migraine headache	133	8.5%
Tension headache	61	3.9%
Cluster headache	12	0.8%
Unclassified benign headache	438	28.1%
Meningitis	17	1.1%
Post-seizure headache	15	1.0%
Neuralgia	10	0.6%
Brain tumor	7	0.4%
Viral illness	60	3.8%
Psychiatric disease	47	3.0%
Hypertensive crisis	38	2.4%
Peripheral vertigo	37	2.4%
Gastrointestinal disease	22	1.4%
Sinusitis	16	1.0%
Hyperventilation	16	1.0%
Urinary tract infection	16	1.0%
Dehydration	15	1.0%
Respiratory disease	14	0.9%
Syncope	10	0.6%
Cervical spondylosis	10	0.6%
Other non-neurological disease	176	11.3%

Table 2. Univariate Correlation of Valiables for Subarachnoid Hemorrhage

Characteristic	Subarachnoid Hemorrhage		*P* value
	No (n=1284)	**Yes** (n=277)	
From history			
Age, mean (SD) [range]	51 (21)	63 (15)	<0.0001
Women	56.9%	67.5%	0.0012
Onset during exertion	14.3%	54.9%	<0.0001
Worst headache of life	9.5%	54.9%	<0.0001
Thunderclap headache	2.2%	3.3%	0.279
Altered level of consciousness	3.8%	40.1%	<0.0001
Neck pain or stiffness	72.9%	86.6%	<0.0001
Vomiting	25.4%	52.7%	<0.0001
Vertigo / dizziness	15.6%	8.3%	0.0072
History of hypertension	24.0%	43.7%	<0.0001
History of diabetes mellitus	10.1%	3.6%	0.095
From physical examination			
Heart rate, mean (SD) beats/min	79 (17)	80 (17)	0.7669
Blood pressure, mean (SD) mmHg			
Systolic	139 (30)	167 (36)	<0.0001
Diastolic	81 (18)	93 (21)	<0.0001
Body temperature, mean (SD) °C	36.6 (0.8)	36.3 (0.9)	<0.0001
Diagnostic procedures			
CT	1197	277	
MRI	62	4	
Lumbar puncture	37	3	
From blood test	**No** (n=1045)	**Yes** (n=272)	
Blood sugar, mean (SD) mg/dL	127 (51)	162 (49)	<0.0001
Serum sodium, mean (SD) mEq/L	139.4 (3.4)	138.6 (3.0)	0.0016
Serum potassium, mean (SD) mEq/L	3.9 (0.5)	3.6 (0.5)	<0.0001
Hemoglobin, mean (SD) g/dL	13.6 (2.0)	13.4 (1.9)	0.1044
White cell count, mean (SD) $\times 10^3/\mu L$	7.9 (3.4)	10.3 (4.6)	<0.0001
Platelet count, mean (SD) $\times 10^4/\mu L$	21.7 (10.0)	24.0 (21.0)	0.9258

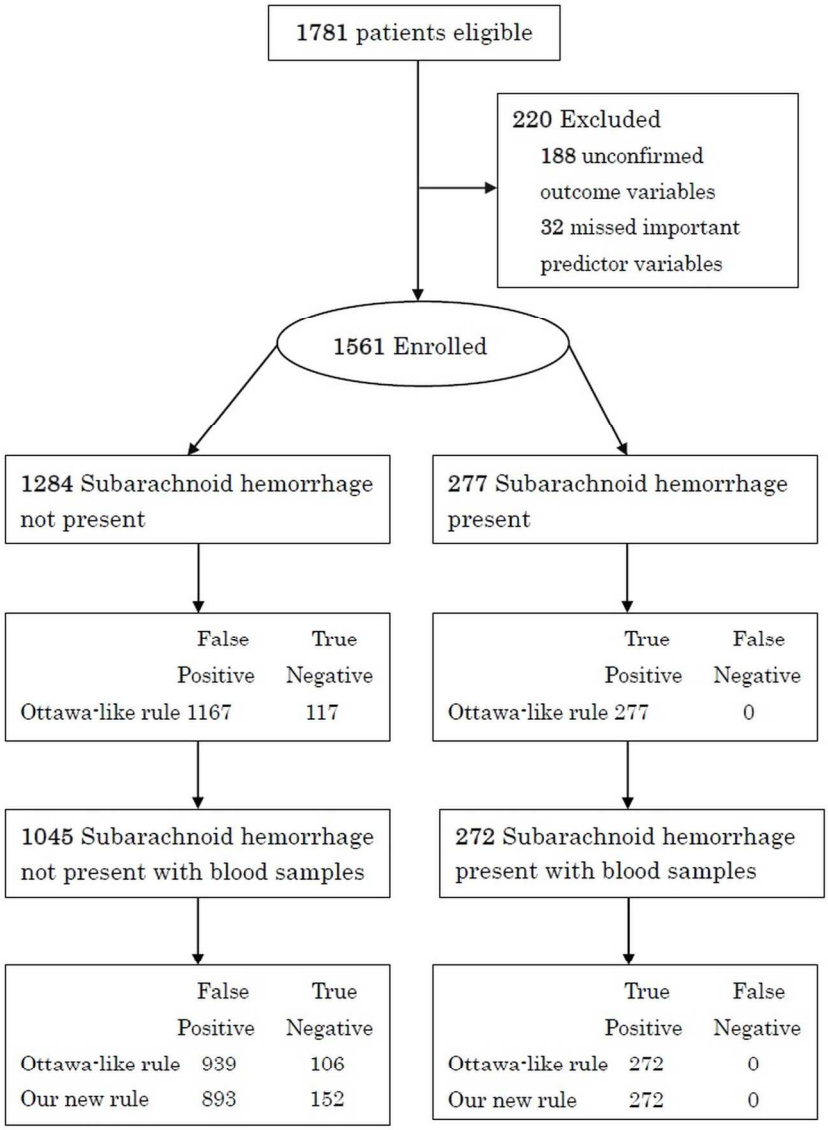

Figure 1\r\nDetails of enrollment and flow of patients in study\r\n\r\nOttawa-like rule, any of the following risks present:\r\n1. Age ≧40 years\r\n2. Neck pain or stiffness\r\n3. Altered level of consciousness\r\n4. Onset during exertion.\r\n\r\nOur new rule (namely, the EMERALD SAH rule), any of the following risks present:\r\n1. Systolic blood pressure >150 mmHg\r\n2. Diastolic blood pressure >90 mmHg\r\n3. Blood sugar >115 mg/dL (6.9 mmol/L)\r\n4. Serum potassium <3.9 mEq/L (3.90 mmol/L)\r\n

233x274mm (300 x 300 DPI)

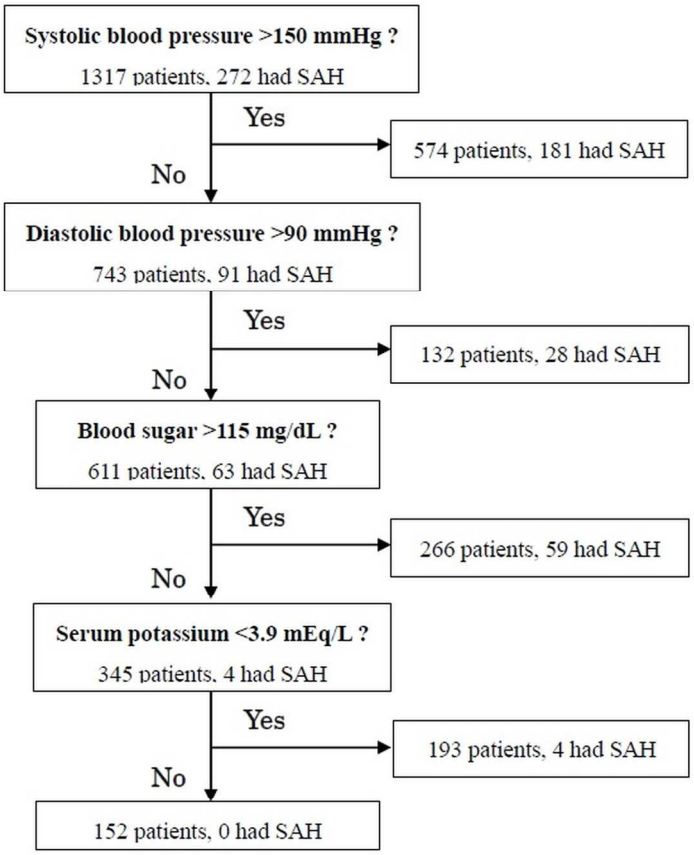

Figure 2
Example of recursive partitioning analysis with our new rule: the EMERALD SAH Rule
SAH: subarachnoid hemorrhage

210x191mm (300 x 300 DPI)

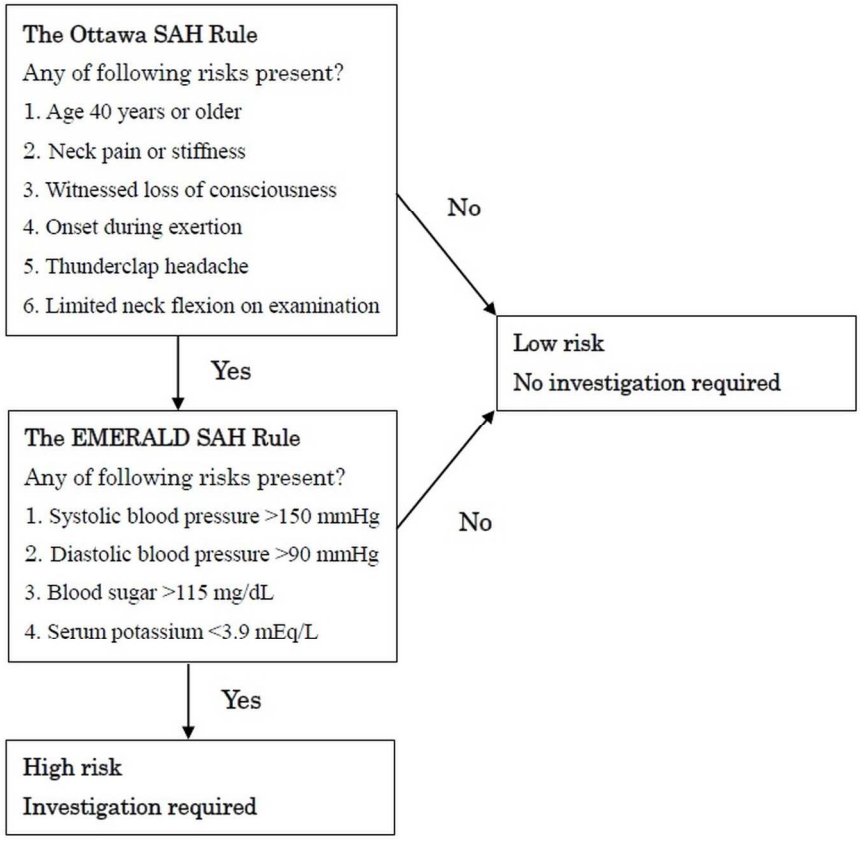

Figure 3
The proposed two-step decision-making to rule out subarachnoid hemorrhage (SAH) for adult patients with acute headache

217x186mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	① P1 P3-4	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	② **P6-7**	Explain the scientific background and rationale for the investigation being reported
Objectives	③ **P67**	State specific objectives, including any prespecified hypotheses
Methods		
Study design	④ **P8**	Present key elements of study design early in the paper
Setting	⑤ **P8-9**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	⑥ **P8**	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	⑦ **P10**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	⑧* **P9**	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	⑨ **P9**	Describe any efforts to address potential sources of bias
Study size	⑩	Explain how the study size was arrived at
This was not written in the manuscript, but as in the previous study (Ref.7), at least 120 patients with SAH were required. Our previous study (Ref 10) reported that about 13% of patients with acute headache had SAH at our emergency department. Thus, more than 923 enrolled patient would be required. In the present study, 1317 patients with blood sample were enrolled and analysed, and among them 272 patients had SAH (Fig.1). Therefore the sample size was considered to be sufficient.		
Quantitative variables	⑪ **P9**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	⑫ **P10-11**	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions

		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13* **P11-12 Fig.1**	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* **P12 Table1**	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* **P12 Fig.1 Table2**	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 **P12-13 Fig2**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Using bootstrapping we calculated sensitivity and specificity for 5 rules (including the Ottwa like rule and the EMERALD rule) to select the best rule, but we didn't show them in the manuscript.		
Discussion		
Key results	18 **P15**	Summarise key results with reference to study objectives
Limitations	19 **P16-17**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 **P17**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 **P17**	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 **P19**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.