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Predictive model for poor grade subarachnoid haemorrhage patients in 30-day observation - a 9 year cohort study.

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Abstract

Objective: The purpose of this study was to identify prognostic factors and to create the predictive model based on poor-grade subarachnoid hemorrhage (SAH) population received only supportive symptomatic treatment.

Design: Prospective observational cohort study.

Setting: Intensive care unit at Clinical Department of Neurology.

Participants: A total of 101 spontaneous SAH patients disqualified from neurosurgical operative treatment due to poor clinical condition. Data were collected in nine years period.

Outcome measures: Unfavorable outcome was defined as a modified Rankin Score >=5 at 30 days of observation.

Results: Multivariable logistic regression analysis indicated the World Federation of Neurosurgical Societies Scale score, increasing age, Fisher grade and admission leukocytosis as independent predictive factors. Proposed scale subdivides the study population into four prognostic groups with significantly different outcomes: grade I: probability of favorable outcome 89.9%; grade II: 47.5%; grade III: 4.2%; grade IV: 0%. The ROC curve for the prediction of outcome performed by the new scale had an AUC=0,910 (excellent accuracy).

Conclusions: Unfavorable outcome in non-operated poor-grade SAH patients is strongly predicted by traditional unmodifiable factors like age, amount of bleeding in CT, level of consciousness as well as leukocytosis. A new predictive scale created on above parameters seems to reliably predict the outcome and may contribute to more effective planning of therapeutic management in patients with poor-grade SAH.

Strengths and limitations of this study

- There is lack of studies analyzing population of the poor-grade SAH patients, which indeed represent a special cohort of patients, particularly due to different clinical course with extremely high mortality and morbidity rates as well as undefined clear treatment protocol.
- Proposed model provide an opportunity for easy use and early outcome prediction among poor clinical condition SAH patients which may contribute to more effective planning of therapeutic management.
- One potentially uncontrolled confounder that was not adjusted for is appropriate evaluation of morphological parameter of aneurysm.

Introduction

Bleeding into the subarachnoid space (SAH) is a serious medical condition with complex pathogenesis and variable clinical presentation. Surgery or endovascular treatment is a key component for the proper management of SAH patients. However, the implementation of definitive therapy for patients in poor grade SAH remains controversial due to its association with the high morbidity and mortality rates.[1,2] These patients are usually managed conservatively and those who survive and show clinical improvement are selected for definitive therapy. In recent years, there have been several studies indicating an improved outcome with the early treatment of the ruptured aneurysm in selected subgroup of patients with the poor-grade aneurysmal SAH.[1,2,3] Undoubtedly, early aneurysm occlusion prevents recurrent hemorrhage and vasospasm can be treated more effectively, yet nothing can be done about irreversible brain damage. Moreover, severe cerebral insult is not directly expressed in neurological condition at admission. Clinical presentation of poor grade SAH is a highly complex process caused by intracerebral hemorrhage, cerebral swelling, intraventricular hemorrhage, acute hydrocephalus, microcirculatory disturbances, decreased global cerebral perfusion, increased intracranial pressure and neurogenic cardiac or pulmonary dysfunction.[4] Therefore, more comprehensive evaluation of clinical condition is essential for the proper outcome prediction, especially in regard to this cohort. There has been an enormous effort to work out the prognostic models predicting an outcome in SAH patients over many years.[5] This was largely complicated by heterogeneity of study populations and treatment procedures as well as approaches having been used, which all influenced the outcome. Those studies included different subgroups of patients exposed to various treatment procedures with the majority of subjects in good-grade SAH who qualified for surgical treatment. Only few patients in these cohorts were not operated and they were

exposed only to supportive symptomatic treatment. Indeed, poor grade SAH patients received no surgical treatment, represent a special population, which deserves particular attention especially from the view of neurological wards.

In this study we focused on such non-operated, poor grade SAH population, treated in neurological intensive care unit (NICU) so as to identify predictive factors and build the prognostic model for such population.

Materials and methods

The study was conducted on a group of patients who had been admitted and treated with diagnosed spontaneous SAH (i.e., bleeding into subarachnoid space confirmed by a CT scan). The research protocol was planned for the prospective observational clinical study carried out in the period from January 2001 to December 2010. After completion of the data collection, the retrospective analysis was performed.

The study group only included patients disqualified from neurosurgical clipping or endovascular coiling due to poor clinical condition (i.e., World Federation of Neurological Surgeons Grades IV and V).

Exclusion criteria included: 1) patients aged <18 years; 2) admission criteria >24 h; 3) patients who were admitted in poor grades to NICU but after initial treatment were qualified to the operative treatment – only patients managed conservatively during the observation period were included in analysis; 4) posttraumatic hemorrhage, intoxication and the presence of any other serious medical conditions (active cancer, infectious, systemic, hematologic, cardiovascular diseases, etc.) that had existed prior to the occurrence of SAH and could otherwise have led to the significant disruption of the correct assessment of the clinical status and outcome among patients with SAH.

The study was approved by the hospital's institutional review board.

Collected data

After admission, the patients were managed in accordance with a standardized protocol used in our hospital. We considered all patient characteristics that could be collected reliably within the first hours after hospital admission. The clinical status of the patients was evaluated by World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage (WFNS).[6] At the same time blood samples were collected and basic laboratory tests were performed. Based on routinely collected data, potential predicting factors of unfavorable outcome were analyzed according to strict definitions. They included: 1) age (age tertiles were rounded to the nearest decade of age: <=50, 51-65, >65 years) and sex; 2) medical history (cardiac arrhythmia, hypertension, ischemic heart disease, diabetes); 3) admission laboratory findings; leukocytosis (white blood cells (WBC) >15 × 10(9)/L),[7,8] anemia (hemoglobin <9.0 g/l), hyperglycemia (blood glucose >=7.8 mmol/l),[9] hyponatremia (serum sodium <=130 mmol/l); 4) clinical factors; fever (body temperature >=38.0°C), tachycardia (heart rate >100/min.), bradycardia (heart rate <60/min.), systolic blood pressure (categories: <130, 130-139, 140-159, 160-179, 180-209, >=210 mm Hg) and diastolic blood pressure (categories:<85, 85-89, 90-99, 100-109, 110-119, >=120 mm Hg); 5) radiologic variables (Fisher scale).[10] The disease and its consequences were evaluated by means of a modified six-point Rankin scale (mRS) during a 30-day long hospital observation in the local clinic.

Statistical methods

The analysis was conducted on the basis of 17 factors and with the help of the univariate logistic regression depending on the dichotomous division of the study group into a favorable outcome group (mRS 0-4) and an unfavorable outcome group (mRS 5-6). Continuous variables were categorized to aid in a clinical application. The statistical analysis

allowed to determine five factors that are correlated with the prognosis. Thereafter, a multivariate logistic regression analysis was carried out using backward elimination to identify independent predictors ($p < 0.05$). The relative weighting of each individual component was determined from the relative change of the odds ratio (OR) of the variables. On the basis of the collected data a 9 grades prognostic model was developed. Subsequently, the grading system was compressed to four grades for simplification of tool. New scale then was analyzed in terms of sensitivity and specificity, and the result has allowed to determine the reliability of the diagnostic test by ROC curve. In addition, to test prediction value of the new scale in relation to mortality, the Kaplan-Meier survival curves were performed. Statistical analyses were performed using MedCalc 12.2 (MedCalc Software, Ostend, Belgium) or Stata 11 (StataCorp, College Station, Texas).

Results

Baseline demographic and clinical data

A group of 101 patients out of 231 (114 women and 117 men) fulfilled the inclusion criteria for the study. Demographic and clinical features classified by the outcome are shown in Table 1. The age of the patients ranged from 21 to 87 years with a mean at the age of 57, which presented a linear relationship with the outcome. Male to female ratio was 1.4:1 (58 men and 43 women). According to medical history, hypertension was present in a half of the cases whereas other cardiovascular diseases were less frequent (cardiac arrhythmia 9%, coronary artery disease 6% and diabetes mellitus 7%). However, no chronic disease that was analyzed affected the outcome. Out of a total number of poor-grade patients, 27 (27%) were in the WFNS Grade IV and 74 (73%) were in Grade V. Having assessed the CT scans on arrival of those patients, most patients (94 %) were in Fisher garde III (31%) and IV (63%). Digital subtraction angiography (DSA) was our standard protocol for examination of SAH patients in

our center. However, in 67 cases DSA was not performed because of a poor clinical condition. Other 34 patients underwent DSA; intracranial aneurysms were confirmed in 27 cases, in five cases they were negative and in two cases were identified an arteriovenous malformation.

Out of those who were admitted to our department and subsequently analyzed, 21 individuals (21%) were found in an improved clinical condition after 30 days of the SAH treatment. Unfortunately, 80 patients (79%) had an unfavorable outcome, including in-hospital mortality that occurred in 74 cases (73%). Out of these deaths, 52 were due to the initial hemorrhage, 14 deaths were due to rebleeding documented by computer tomography, five deaths were due to vasospasm, two deaths were due to medical complication and there was one sudden death (unknown cause) .

Outcome predictors

The conducted multivariate analysis, which incorporates all five predictors that are relevant in simple models, has identified four independent predictors. The level of consciousness by WFNS score (OR=16.52; p<0.0001), increasing age (OR=4,9; p=0.0053), the amount of bleeding in CT estimated by the Fisher scale (OR=4.23; p=0.0051) and admission leukocytosis (OR=6,16; p=0.0186) achieved the strongest predictive value. Hosmer-Lemeshow test (chi-square goodness-of-fit=3.0342; p=0.9322) has indicated good calibration of multivariate logistic model (Table 2).

Proposed prognostic scale

On the basis of the analysis, a prognostic model was designed (Table 3). The total score is the sum of the points of the various characteristics. WFNS grade was strongest associated with the outcome, it was given the most weight on the scale. Others predictors had relatively the same association with the outcome and were therefore weighted relatively similar. The proposed scale had 9 theoretical grades, and was collapsed to four

grades (risk groups) for simplification. Grades were compressed when differences in poor outcomes were minimal or absent (Table 4). The ROC curve for the prediction of unfavorable outcome performed by the new scale had an AUC=0,910 (excellent accuracy). Figure 1 shows a survival curve during the period of observation – the patients classified in the four risk groups had different survival experience (log-rank chi-square = 25.11; p<0.0001), with a median survival of 5 days for group IV, 7 days for group III, and 11 days for group II.

Discussion

Owing to the advancement of diagnostics and the treatment of patients with SAH, the prognoses for these patients have significantly improved in recent decades. Notwithstanding, current epidemiological data still indicate a high percentage of disability (33%) and deaths (44%) among patients with SAH.[11] Patients who receive only conservative treatment due to a poor clinical condition are an important population that to a great extent predetermines the data.

Both current research conducted on the group of patients who receive only conservative treatment during a 30-day long monitoring and previously-published papers that analyse the patients who are surgically treated, indicate that level of consciousness, patient's age and the amount of bleeding in CT neuroimaging – all of them assessed at the moment of a patient's admission to hospital – are the independent predictive factors after SAH. There is less coherence in various publications as far as other additional factors are concerned, such as cerebral vasospasm (CVS), size and location of the aneurysm, the method, according to which the ruptured blood vessel is managed, a history of arterial hypertension and some laboratory tests.[5] This is the first study, in which leukocytosis is described as an independent risk factor for the outcome among patients exposed to spontaneous SAH.

The state of consciousness is a well-documented and prevailing factor describing the later course of the disease.[12] The first universal tools for assessing the state of consciousness and clinical condition at the same time were Botterel's scale and, subsequently, its modification, the Hunt&Hess's scale.[13,14] However, these models are constructed on the basis of subjective perception and hence the repeatability of measurement when used. Consequently, the WFNS scale, a tool based on Glasgow Coma Scale,[15] was proposed to improve reliability and significance of grading the level of consciousness. Undoubtedly, the degree of brain tissue damage assessed by WFNS is the most valid predictor of poor outcome in SAH patients. However, selection of patients for management only on the basis of the neurological condition remains controversial.[12] Therefore, more complex evaluation of clinical state by adding other independent prognostic factors is crucial to improve SAH grading.

Undeniably, the risk of an unfavourable course of the disease increases in proportion to age. Elderly patients frequently experience massive subarachnoid haemorrhage and a dramatically serious clinical condition as early as at the onset of the disease.[16] However, the independent predictive value seems to depend on further cerebral and systemic complications. With age, as contrasted with younger patients, raised intracranial pressure is considered less significant for secondary damage of the central nerve system while the significance of arterial hypertension/hypotension and cerebral hypoxia increases.[17] What is more, chronic conditions that precede the onset of the disease and reduce the level of cardiovascular, respiratory and renal efficiency predispose the patient to serious systemic complications that will occur during his or her stay in hospital.[18,19,20] A combination of the factors discussed does manifestly contribute to an unfavourable course of the disease among elderly patients, which gives it special significance in the context of the analysed group of

patients.

The amount of blood assessed in particular CT scans proves to be related to the development of vascular spasm that leads to vasospasm and secondary ischemic brain damage, which is the most serious complication decisive for further course of the disease after the survival of primary cerebral haemorrhage.[10] However, the indirect pathophysiological mechanism which leads to this compilation remains unknown. The amount of SAH caused increased intracranial pressure, important mechanism of stopping the bleeding from the ruptured blood vessel and preventing the recurrence of haemorrhage but at the same time it caused decreased cerebral perfusion and secondary formation of brain oedema effects, thus increasing the intracranial pressure.[21,22] Several tools employed to determine the severity of SAH have been developed on the basis of CT imaging. They include the Fisher scale, which is a widely used tool in research studies. Our study has confirmed the predictive value of the mentioned scale and indicated Grade 4 as the worst predictive value. However, different studies suggest that Grade 4 incorrectly offers the highest predictive value.[23] This might have resulted from the analysed population[24,25] or the fact that the clot with a thickness of over 1 millimetre has become outdated nowadays.

We report in the first multivariate study that leucocytosis (WBC) is an independent risk factor for the poor outcome that applies to unoperated SAH patients. This is in agreement with previous studies indicating the predictive value of WBC in this disease population. However, the above mentioned studies did not adjust for confounding variables such as age, size of the haematoma, level of consciousness or other important predictors.[26,27]

The increased WBC during the acute phase of SAH is a component of systemic inflammatory response syndrome (SIRS). This process is commonly observed among those patients and depends on the severity of brain damage and the presence of blood breakdown

products in the subarachnoid space.[28] Despite this, the correlation between SIRS and prognosis seems independent from other prognostic factors.[29] It is also worth noting that surgical stress and anaesthesia may affect the components of the SIRS score, which may lead to overestimation.[30] Interestingly, in our study the connection between other individual SIRS criteria (tachypnea was not measured) and the course of the disease was ruled out. It seems that leucocytosis is a key component in the process responsible for adverse effects of systemic inflammatory reaction. Previous studies demonstrated the connection between leucocytosis and the development of CVS.[31] Furthermore, leucocytosis was reported to be associated with delayed cerebral ischemia (DCI).[32] WBC release a large number of cytokines, including in particular the tumour necrosis factor (TNF-α), interleukins (IL-1α, IL-1β, IL-6, IL-8) which activate and propagate the immune response. These proteins seem to play a key role in the development of CVS,[33,34] which of course can be symptomatic and lead to DCI. Furthermore, in experimental models, leukocytes and platelets adhere the microvasculature at the cerebral surface immediately after SAH. These early inflammatory and prothrombogenic responses may cause a whole-brain injury immediately after SAH.[35]

There is a lack of studies that compare elevated WBC count and recurrent bleeding from aneurysm. Existing research has not clearly indicated a relationship between leucocytosis and rebleeding.[36] However WBC count can play a certain role in this process. Leucocytes infiltration has been well documented in intracranial aneurysms and seems to be associated with aneurysmal wall destruction and rupture.[37]

Our study has confirmed the high morbidity and mortality rates in a non-operative treatment population. However, there is different subgroups of patients with different outcomes. New scale is a reliable tool that identify classes of patients with various outcome probabilities, which may contribute to more effective planning of therapeutic management

in patients with poor grade SAH. Another advantage is the fact that the created tool gives the opportunity for an earlier use. Nonetheless, further studies are needed to check its performance in a large, prospective analysis in patients suffering poor grade SAH.

Conclusions

The obtained results have allowed to draw the following conclusions. The natural course of the disease depends on: 1) the degree of consciousness (primary and specific brain damage during SAH); 2) the patient's age (brain plasticity, arteriosclerosis, chronic illness); 3) the size of intracranial bleeding (increasing intracranial pressure, decreased cerebral blood flow, cerebral vasospasm and early and delayed global cerebral edema). Finally, it also depends on leucocytosis as an indicator of systemic inflammatory activation in response to acute brain injury in the course of SAH. A new predictive scale built on above parameters seems to reliably predict the outcome in a 30-day observation period.

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Contributors

Conceived and designed the experiments: KR WZ TT. Performed the experiments: SS AM AK. Analyzed the data: SS. Contributed to the writing of the manuscript: KR SS. The content of the final manuscript was reviewed by all authors.

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Competing interests

None.

Ethics approval

The study was approved by the institutional review board of Medical University of Lublin. The institutional review board waived the need of written informed consent from the patients in this study.

Data sharing statement

No additional data available.

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Tables

Table 1. Factors influencing final outcome. Univariate logistic regression.

Variable	No. of Patients (%)		Overall P value
	Good outcome	Poor outcome	
Total group	21/101	80/101	-
Age, y			*0.005*
<=50	13	21	
51-65	6	30	
>65	2	29	
Male/Female	16/5	42/38	0.0573(NS)
Hypertension	8 (38)	44 (55)	0.172(NS)
Coronary artery disease	1 (5)	5 (6)	0.789(NS)
Cardiac arrhythmia	1 (5)	8 (10)	0.464(NS)
Diabetes mellitus	2 (10)	5 (7)	0.6017(NS)
Hyperglycemia (>=7.8mmol/l)	8 (52)	50 (68)	*0.0458*
Hyponatremia (<130mmol/l)	1 (5)	8 (10)	0.4406(NS)
Anemia (hemoglobin <9.0 g/l)	1 (5)	1 (1)	0.3527(NS)
Leukocytosis (WBC>15 × 10(9)/L)	5(24)	41(50)	*0.03*
Systolic blood pressure (median)	130-139	130-139	0.4491(NS)
Diastolic blood pressure (median)	<85	85-90	0.6057(NS)
Tachycardia (HR>100/min)	4 (21)	15 (22)	0.9882(NS)
Bradycardia (HR<60/min)	1 (6)	5 (7)	0.7908(NS)
Fever (>=38.0°C)	5 (24)	22 (29)	0.6425(NS)
Amount of blood (Fisher scale)			*0.0023*
I/II	4 (19)	2 (2,5)	
III	9 (43)	22 (27,5)	
IV	8 (38)	59 (74)	
WFNS grade			*<0.0001*
IV	15 (71)	11 (14)	
V	6 (29)	69 (86)	

Table 2. Results of multivariate logistic regression.

Variable included in model	Coef	StErr	OR	P
WFNS score	2.80454	0.73042	16.5195	0.0001
Age tertile	1.58949	0.5696	4.9013	0.0053
Fisher scale	1.43876	0.5135	4.2155	0.0051
Leukocytosis	1.81886	0.77252	6.1649	0.0186
Overall Model Fit				
Null model -2Log Likelihood				103.26
Full model -2Log Likelihood				55.89
Chi-square				47.371
DF				4
P value				<0.0001
Hosmer&Lemeshow test				
Chi-square				3.0342
DF				8
P value				0.9322

Table 3. Proposed scale characteristics.

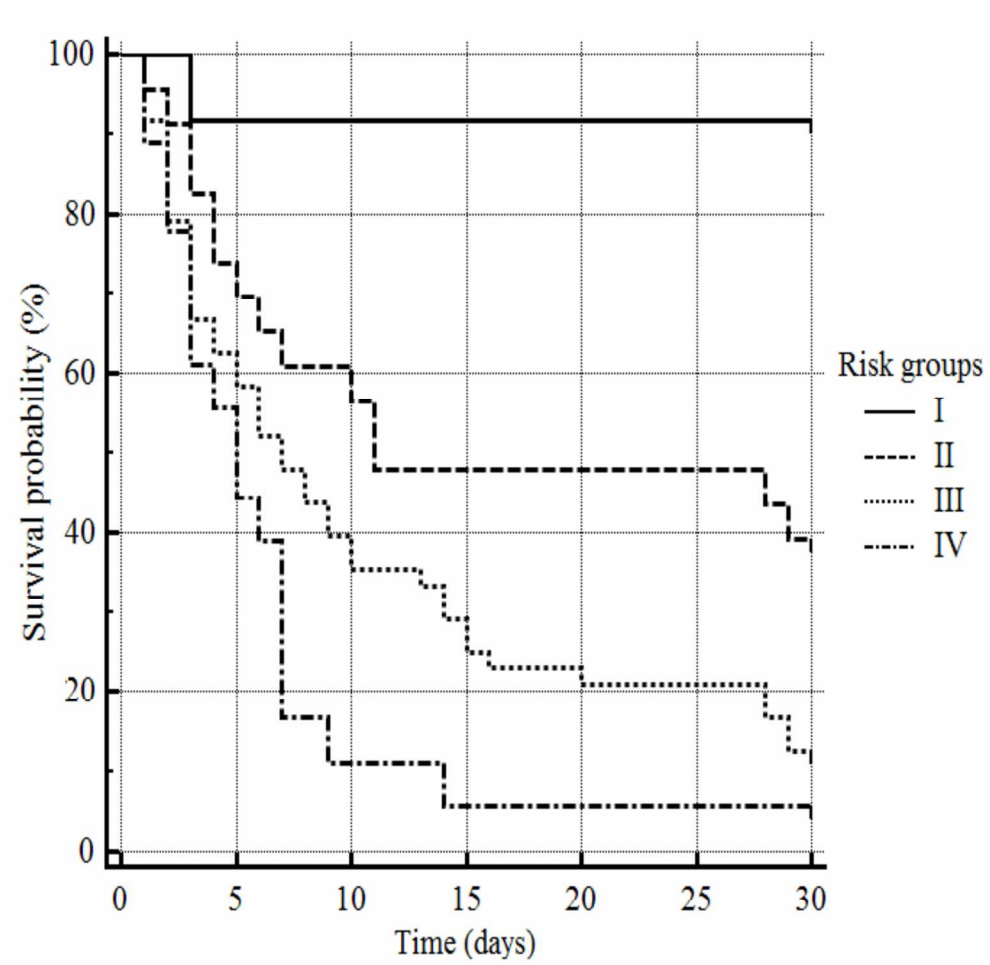
Component	Score point
WFNS grade	
IV	3
V	5
Age, y	
<=50	0
50-65	1
>65	2
Fisher grade	
I;II	0
III	1
IV	2
Leucocytosis	
WBC <15 × 10(9)/L	0
WBC >=15 × 10(9)/L	2
Total score	3 – 11

Table 4. Distribution of 101 patients with poor grade SAH, according to the new grading scale.

Score	Favorable outcome	Unfavorable outcome	Total
3	0	0 (0%)	0
4	3	1 (25%)	4
5	8	0 (0%)	7
6	4	6 (60%)	10
7	5	9 (64%)	14
8	1	25 (96%)	26
9	1	21 (95%)	22
10	0	8 (100%)	8
11	0	10 (100%)	10
3 -5	11	1 (9.1%)	11
6 -7	9	15 (62.5%)	24
8 - 9	2	46 (95.8%)	48
10 - 11	0	18 (100%)	18

Figure Legends

Figure 1. Kaplan-Meier survival curve.



68x68mm (600 x 600 DPI)

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

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[pages 1 - 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 4 - 5]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[pages 5 - 6]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[pages 5 - 6]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[page 5]** *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	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[page 6]**
Data sources/ measurement	8*	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 **[page 6]**
Bias	9	Describe any efforts to address potential sources of bias **[page 5]**
Study size	10	Explain how the study size was arrived at **[page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[page 6]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[pages 6 - 7]**
		(*b*) Describe any methods used to examine subgroups and interactions **[pages 6 - 7]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed**[N/A]** *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 **[N/A]**

Continued on next page

Results		
Participants	13*	(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 **[page 7]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 7; table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[page 8]**
		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	(*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 **[N/A]**
		(*b*) Report category boundaries when continuous variables were categorized **[N/A]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[pages 8 - 9; tables 1,2,3,4; figure 1]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[pages 8 - 9]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[page 13]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[pages 9 – 13]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[N/A]**
Other information		
Funding	22	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 [**page 14]**

*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.

BMJ Open

Predictive model for poor-grade subarachnoid haemorrhage patients in 30-day observation - a 9 year cohort study.

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Predictive model for poor grade subarachnoid haemorrhage patients in 30-day observation - a 9 year cohort study.

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Abstract

Objective: The purpose of this study was to identify prognostic factors and to create the predictive model based on poor-grade subarachnoid hemorrhage (SAH) population received only supportive symptomatic treatment.

Design: Prospective observational cohort study.

Setting: Intensive care unit at Clinical Department of Neurology.

Participants: A total of 101 spontaneous SAH patients disqualified from neurosurgical operative treatment due to poor clinical condition. Data were collected in nine years period.

Outcome measures: Unfavorable outcome was defined as a modified Rankin Score >=5 at 30 days of observation.

Results: Multivariable logistic regression analysis indicated the World Federation of Neurosurgical Societies Scale score, increasing age, Fisher grade and admission leukocytosis as independent predictive factors. Proposed scale subdivides the study population into four prognostic groups with significantly different outcomes: grade I: probability of favorable outcome 89.9%; grade II: 47.5%; grade III: 4.2%; grade IV: 0%. The ROC curve for the prediction of outcome performed by the new scale had an AUC=0,910 (excellent accuracy).

Conclusions: Unfavorable outcome in non-operated poor-grade SAH patients is strongly predicted by traditional unmodifiable factors like age, amount of bleeding in CT, level of consciousness as well as leukocytosis. A new predictive scale created on above parameters seems to reliably predict the outcome and may contribute to more effective planning of therapeutic management in patients with poor-grade SAH.

Strengths and limitations of this study

- There is lack of studies analyzing population of the poor-grade SAH patients, which indeed represent a special cohort of patients, particularly due to different clinical course with extremely high mortality and morbidity rates as well as undefined clear treatment protocol.
- Proposed model provide an opportunity for easy use and early outcome prediction among poor clinical condition SAH patients which may contribute to more effective planning of therapeutic management.
- One potentially uncontrolled confounder that was not adjusted for is appropriate evaluation of morphological parameter of aneurysm.

Introduction

Bleeding into the subarachnoid space (SAH) is a serious medical condition with complex pathogenesis and variable clinical presentation. Surgery or endovascular treatment is a key component for the proper management of SAH patients. However, the implementation of definitive therapy for patients in poor grade SAH remains controversial due to its association with the high morbidity and mortality rates.[1,2] These patients are usually managed conservatively and those who survive and show clinical improvement are selected for definitive therapy. In recent years, there have been several studies indicating an improved outcome with the early treatment of the ruptured aneurysm in selected subgroup of patients with the poor-grade aneurysmal SAH.[1,2,3] Undoubtedly, early aneurysm occlusion prevents recurrent hemorrhage and vasospasm can be treated more effectively, yet nothing can be done about irreversible brain damage. Moreover, severe cerebral insult is not directly expressed in neurological condition at admission. Clinical presentation of poor grade SAH is a highly complex process caused by intracerebral hemorrhage, cerebral swelling, intraventricular hemorrhage, acute hydrocephalus, microcirculatory disturbances, decreased global cerebral perfusion, increased intracranial pressure and neurogenic cardiac or pulmonary dysfunction.[4] Therefore, more comprehensive evaluation of clinical condition is essential for the proper outcome prediction, especially in regard to this cohort. There has been an enormous effort to work out the prognostic models predicting an outcome in SAH patients over many years.[5] This was largely complicated by heterogeneity of study populations and treatment procedures as well as approaches having been used, which all influenced the outcome. Those studies included different subgroups of patients exposed to various treatment procedures with the majority of subjects in good-grade SAH who qualified for surgical treatment. Only few patients in these cohorts were not operated and they were

exposed only to supportive symptomatic treatment. Indeed, poor grade SAH patients received no surgical treatment, represent a special population, which deserves particular attention especially from the view of neurological wards.

In this study we focused on such non-operated, poor grade SAH population, treated in neurological intensive care unit (NICU) so as to identify predictive factors and build the prognostic model for such population.

Materials and methods

The study was conducted on a group of patients who had been admitted and treated with diagnosed spontaneous SAH (i.e., bleeding into subarachnoid space confirmed by a CT scan). The research protocol was planned for the prospective observational clinical study carried out in the period from January 2001 to December 2010. After completion of the data collection, the retrospective analysis was performed.

The study group only included patients disqualified from neurosurgical clipping or endovascular coiling due to poor clinical condition (i.e., World Federation of Neurological Surgeons Grades IV and V).

Exclusion criteria included: 1) patients aged <18 years; 2) admission criteria >24 h; 3) perimesencephalic patterns of hemorrhage on CT scans; 4) patients who were admitted in poor grades to NICU but after initial treatment were qualified to the operative treatment – only patients managed conservatively during the observation period were included in analysis; 5) posttraumatic hemorrhage, intoxication and the presence of any other serious medical conditions (active cancer, infectious, systemic, hematologic, cardiovascular diseases, etc.) that had existed prior to the occurrence of SAH and could otherwise have led to the significant disruption of the correct assessment of the clinical status and outcome among patients with SAH.

The study was approved by the hospital's institutional review board.

Collected data

After admission, the patients were managed in accordance with a standardized protocol used in our hospital. We considered all patient characteristics that could be collected reliably within the first hours after hospital admission. The clinical status of the patients was evaluated by World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage (WFNS).[6] At the same time blood samples were collected and basic laboratory tests were performed. Based on routinely collected data, potential predicting factors of unfavorable outcome were analyzed according to strict definitions. They included: 1) age (age tertiles were rounded to the nearest decade of age: <=50, 51-65, >65 years) and sex; 2) medical history (cardiac arrhythmia, hypertension, ischemic heart disease, diabetes); 3) admission laboratory findings; leukocytosis (white blood cells (WBC) >15 × 10(9)/L),[7,8] anemia (hemoglobin <9.0 g/l), hyperglycemia (blood glucose >=7.8 mmol/l),[9] hyponatremia (serum sodium <=130 mmol/l); 4) clinical factors; fever (body temperature >=38.0°C), tachycardia (heart rate >100/min.), bradycardia (heart rate <60/min.), systolic blood pressure (categories: <130, 130-139, 140-159, 160-179, 180-209, >=210 mm Hg) and diastolic blood pressure (categories:<85, 85-89, 90-99, 100-109, 110-119, >=120 mm Hg); 5) radiologic variables (Fisher scale).[10] The disease and its consequences were evaluated by means of a modified six-point Rankin scale (mRS) during a 30-day long hospital observation in the local clinic.

Statistical methods

The univariate logistic regression was conducted on the basis of 17 factors, depending on the dichotomous outcome division of the study group (favorable and unfavorable). In view of initial poor clinical condition, observation period and limited spread

of outcome seen in poor-grade patients, favorable outcome were defined as mRS score 0 to 4 and an unfavorable outcome as mRS score 5 and 6. Similar methods were followed in other studies in poor-grade SAH patients population.[11] Continuous variables were categorized to aid in a clinical application. The statistical analysis allowed to determine five factors that are correlated with the prognosis. Thereafter, a multivariate logistic regression analysis was carried out using backward elimination to identify independent predictors ($p < 0.05$). The relative weighting of each individual component was determined from the relative change of the odds ratio (OR) of the variables. On the basis of the collected data a 9 grades prognostic model was developed. Subsequently, the grading system was compressed to four grades for simplification of tool. New scale then was analyzed in terms of sensitivity and specificity, and the result has allowed to determine the reliability of the diagnostic test by ROC curve. In addition, to test prediction value of the new scale in relation to mortality, the Kaplan-Meier survival curves were performed. Statistical analyses were performed using MedCalc 12.2 (MedCalc Software, Ostend, Belgium) or Stata 11 (StataCorp, College Station, Texas).

Results

Baseline demographic and clinical data

A group of 101 patients out of 231 (114 women and 117 men) fulfilled the inclusion criteria for the study. Demographic and clinical features classified by the outcome are shown in Table 1. The age of the patients ranged from 21 to 87 years with a mean at the age of 57, which presented a linear relationship with the outcome. Male to female ratio was 1.4:1 (58 men and 43 women). According to medical history, hypertension was present in a half of the cases whereas other cardiovascular diseases were less frequent (cardiac arrhythmia 9%, coronary artery disease 6% and diabetes mellitus 7%). However, no chronic disease that was analyzed affected the outcome. Out of a total number of poor-grade patients, 27 (27%) were

in the WFNS Grade IV and 74 (73%) were in Grade V. Having assessed the CT scans on arrival of those patients, most patients (94 %) were in Fisher garde III (31%) and IV (63%). Angiogram (both digital subtraction angiography and/or computed tomographic angiogram) examination was attempted in all study subjects. In the total group of SAH patients, the intracranial aneurysms were precisely identified in 27 cases, and the arteriovenous malformation was found in 2 subjects, however were not excluded from the study because sample was too small to disrupt final results. Among the rest of the patients the direct source of bleeding was not exactly identified.

Out of those who were admitted to our department and subsequently analyzed, 21 individuals (21%) were found in an improved clinical condition after 30 days of the SAH treatment. Unfortunately, 80 patients (79%) had an unfavorable outcome, including in-hospital mortality that occurred in 74 cases (73%). Out of these deaths, 52 were due to the initial hemorrhage, 14 deaths were due to rebleeding documented by computer tomography, five deaths were due to vasospasm, two deaths were due to medical complication and there was one sudden death (unknown cause) .

Outcome predictors

The conducted multivariate analysis, which incorporates all five predictors that are relevant in simple models, has identified four independent predictors. The level of consciousness by WFNS score (OR=16.52; p<0.0001), increasing age (OR=4,9; p=0.0053), the amount of bleeding in CT estimated by the Fisher scale (OR=4.23; p=0.0051) and admission leukocytosis (OR=6,16; p=0.0186) achieved the strongest predictive value. Hosmer-Lemeshow test (chi-square goodness-of-fit=3.0342; p=0.9322) has indicated good calibration of multivariate logistic model (Table 2).

Proposed prognostic scale

On the basis of the analysis, a prognostic model was designed (Table 3). The total score is the sum of the points of the various characteristics. WFNS grade was strongest associated with the outcome, it was given the most weight on the scale. Other predictors were less important and adjudged to score each of them lower then WFNS IV. As the others predictors had relatively the same association with the outcome, there were weighted relatively similar. The proposed scale had 9 theoretical grades, and was collapsed to four grades (risk groups) for simplification. Grades were compressed when differences in poor outcomes were minimal or absent (Table 4). The ROC curve for the prediction of unfavorable outcome performed by the new scale had an AUC=0,910 (excellent accuracy). Figure 1 shows a survival curve during the period of observation – the patients classified in the four risk groups had different survival experience (log-rank chi-square = 25.11; p<0.0001), with a median survival of 5 days for group IV, 7 days for group III, and 11 days for group II.

Discussion

Owing to the advancement of diagnostics and the treatment of patients with SAH, the prognoses for these patients have significantly improved in recent decades. Notwithstanding, current epidemiological data still indicate a high percentage of disability (33%) and deaths (44%) among patients with SAH.[12] Patients who receive only conservative treatment due to a poor clinical condition are an important population that to a great extent predetermines the data.

Both current research conducted on the group of patients who receive only conservative treatment during a 30-day long monitoring and previously-published papers that analyse the patients who are surgically treated, indicate that level of consciousness, patient's age and the amount of bleeding in CT neuroimaging – all of them assessed at the moment of a patient's admission to hospital – are the independent predictive factors after

SAH. There is less coherence in various publications as far as other additional factors are concerned, such as cerebral vasospasm (CVS), size and location of the aneurysm, the method, according to which the ruptured blood vessel is managed, a history of arterial hypertension and some laboratory tests.[5] The relevance of leukocytosis on course of the disease after SAH has been reported in surgical cases. However, this studies mainly analyzed leukocytosis as a component of systemic inflammatory response syndrome (SIRS) and/or in aspect of vasospasm pathogenesis. Interestingly, the admission leukocytosis alone correlated independently and extraordinarily highly with outcome in non-surgical cases.

The state of consciousness is a well-documented and prevailing factor describing the later course of the disease.[13] The first universal tools for assessing the state of consciousness and clinical condition at the same time were Botterel's scale and, subsequently, its modification, the Hunt&Hess's scale.[14,15] However, these models are constructed on the basis of subjective perception and hence the repeatability of measurement when used. Consequently, the WFNS scale, a tool based on Glasgow Coma Scale,[16] was proposed to improve reliability and significance of grading the level of consciousness. Undoubtedly, the degree of brain tissue damage assessed by WFNS is the most valid predictor of poor outcome in SAH patients. However, selection of patients for management only on the basis of the neurological condition remains controversial.[13] Therefore, more complex evaluation of clinical state by adding other independent prognostic factors is crucial to improve SAH grading.

Undeniably, the risk of an unfavourable course of the disease increases in proportion to age. Elderly patients frequently experience massive subarachnoid haemorrhage and a dramatically serious clinical condition as early as at the onset of the disease.[17] However, the independent predictive value seems to depend on further cerebral and systemic

complications. With age, as contrasted with younger patients, raised intracranial pressure is considered less significant for secondary damage of the central nerve system while the significance of arterial hypertension/hypotension and cerebral hypoxia increases.[18] What is more, chronic conditions that precede the onset of the disease and reduce the level of cardiovascular, respiratory and renal efficiency predispose the patient to serious systemic complications that will occur during his or her stay in hospital.[19,20,21] A combination of the factors discussed does manifestly contribute to an unfavourable course of the disease among elderly patients, which gives it special significance in the context of the analysed group of patients.

The amount of blood assessed in particular CT scans proves to be related to the development of vascular spasm that leads to vasospasm and secondary ischemic brain damage, which is the most serious complication decisive for further course of the disease after the survival of primary cerebral haemorrhage.[10] However, the indirect pathophysiological mechanism which leads to this compilation remains unknown. The amount of SAH caused increased intracranial pressure, important mechanism of stopping the bleeding from the ruptured blood vessel and preventing the recurrence of haemorrhage but at the same time it caused decreased cerebral perfusion and secondary formation of brain oedema effects, thus increasing the intracranial pressure.[22,23] Several tools employed to determine the severity of SAH have been developed on the basis of CT imaging. They include the Fisher scale, which is a widely used tool in research studies. Our study has confirmed the predictive value of the mentioned scale and indicated Grade 4 as the worst predictive value. However, different studies suggest that Grade 4 incorrectly offers the highest predictive value.[24] This might have resulted from the analysed population[25,26] or the fact that the clot with a thickness of over 1 millimetre has become outdated nowadays.

As previously mentioned, the increased WBC during the acute phase of SAH is a component of SIRS. This process is commonly observed among those patients and depends on the severity of brain damage and the presence of blood breakdown products in the subarachnoid space.[27] Despite this, the correlation between SIRS and prognosis seems independent from other prognostic factors.[28] It is also worth noting that surgical stress and anaesthesia may affect the components of the SIRS score, which may lead to overestimation.[29] Interestingly, in our study the connection between other individual SIRS criteria (tachypnea was not measured) and the course of the disease was ruled out. It seems that leucocytosis is a key component in the process responsible for adverse effects of systemic inflammatory reaction. Previous studies demonstrated the connection between leucocytosis and the development of CVS.[30] Furthermore, leucocytosis was reported to be associated with delayed cerebral ischemia (DCI).[31] WBC release a large number of cytokines, including in particular the tumour necrosis factor (TNF-α), interleukins (IL-1α, IL-1β, IL-6, IL-8) which activate and propagate the immune response. These proteins seem to play a key role in the development of CVS,[32,33] which of course can be symptomatic and lead to DCI. Furthermore, in experimental models, leukocytes and platelets adhere the microvasculature at the cerebral surface immediately after SAH. These early inflammatory and prothrombogenic responses may cause a whole-brain injury immediately after SAH.[34]

There is a lack of studies that compare elevated WBC count and recurrent bleeding from aneurysm. Existing researches has not clearly indicated a relationship between leucocytosis and rebleeding.[35] However WBC count can play a certain role in this process. Leucocytes infiltration has been well documented in intracranial aneurysms and seems to be associated with primarily aneurysmal wall destruction and rupture.[36] Thus leukocytes may induce damage directly to the unstable aneurysm and result in rebleeding.

Our study has confirmed the high morbidity and mortality rates in a non-operative treatment population. However, there is different subgroups of patients with different outcomes. New scale is a reliable tool that identify classes of patients with various outcome probabilities, which may contribute to more effective planning of therapeutic management in patients with poor grade SAH. Another advantage is the fact that the created tool gives the opportunity for an earlier use. Nonetheless, further studies are needed to check its performance in a large, prospective analysis in patients suffering poor grade SAH.

Conclusions

The obtained results have allowed to draw the following conclusions. The natural course of the disease depends on: 1) the degree of consciousness (primary and specific brain damage during SAH); 2) the patient's age (brain plasticity, arteriosclerosis, chronic illness); 3) the size of intracranial bleeding (increasing intracranial pressure, decreased cerebral blood flow, cerebral vasospasm and early and delayed global cerebral edema). Finally, it also depends on leucocytosis as an indicator of systemic inflammatory activation in response to acute brain injury in the course of SAH. A new predictive scale built on above parameters seems to reliably predict the outcome in a 30-day observation period.

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Contributors

Conceived and designed the experiments: KR WZ TT. Performed the experiments: SS AM AK. Analyzed the data: SS. Contributed to the writing of the manuscript: KR SS. The content of the final manuscript was reviewed by all authors.

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Competing interests

None.

Ethics approval

The study was approved by the institutional review board of Medical University of Lublin. The institutional review board waived the need of written informed consent from the patients in this study.

Data sharing statement

No additional data available.

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Tables

Table 1. Factors influencing final outcome. Univariate logistic regression.

Variable	No. of Patients (%)		Overall P value
	Good outcome	Poor outcome	
Total group	21/101	80/101	-
Age, y			*0.005*
<=50	13	21	
51-65	6	30	
>65	2	29	
Male/Female	16/5	42/38	0.0573(NS)
Hypertension	8 (38)	44 (55)	0.172(NS)
Coronary artery disease	1 (5)	5 (6)	0.789(NS)
Cardiac arrhythmia	1 (5)	8 (10)	0.464(NS)
Diabetes mellitus	2 (10)	5 (7)	0.6017(NS)
Hyperglycemia (>=7.8mmol/l)	8 (52)	50 (68)	*0.0458*
Hyponatremia (<130mmol/l)	1 (5)	8 (10)	0.4406(NS)
Anemia (hemoglobin <9.0 g/l)	1 (5)	1 (1)	0.3527(NS)
Leukocytosis (WBC>15 × 10(9)/L)	5(24)	41(50)	*0.03*
Systolic blood pressure (median)	130-139	130-139	0.4491(NS)
Diastolic blood pressure (median)	<85	85-90	0.6057(NS)
Tachycardia (HR>100/min)	4 (21)	15 (22)	0.9882(NS)
Bradycardia (HR<60/min)	1 (6)	5 (7)	0.7908(NS)
Fever (>=38.0°C)	5 (24)	22 (29)	0.6425(NS)
Amount of blood (Fisher scale)			*0.0023*
I/II	4 (19)	2 (2,5)	
III	9 (43)	22 (27,5)	
IV	8 (38)	59 (74)	
WFNS grade			*<0.0001*
IV	15 (71)	11 (14)	
V	6 (29)	69 (86)	

Table 2. Results of multivariate logistic regression.

Variable included in model	Coef	StErr	OR	P
WFNS score	2.80454	0.73042	16.5195	0.0001
Age tertile	1.58949	0.5696	4.9013	0.0053
Fisher scale	1.43876	0.5135	4.2155	0.0051
Leukocytosis	1.81886	0.77252	6.1649	0.0186
Overall Model Fit				
Null model -2Log Likelihood				103.26
Full model -2Log Likelihood				55.89
Chi-square				47.371
DF				4
P value				<0.0001
Hosmer&Lemeshow test				
Chi-square				3.0342
DF				8
P value				0.9322

Table 3. Proposed scale characteristics.

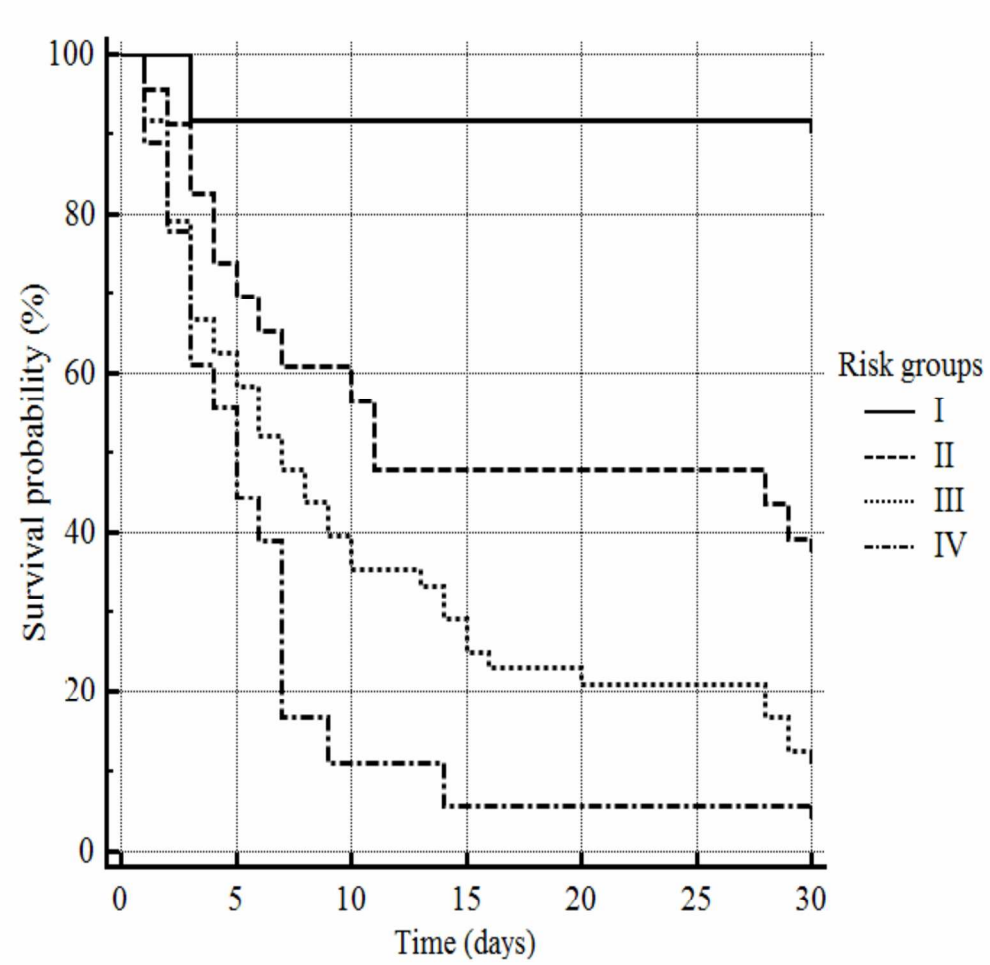
Component	Score point
WFNS grade	
IV	3
V	5
Age, y	
<=50	0
50-65	1
>65	2
Fisher grade	
I;II	0
III	1
IV	2
Leucocytosis	
WBC <15 × 10(9)/L	0
WBC >=15 × 10(9)/L	2
Total score	3 – 11

Table 4. Distribution of 101 patients with poor grade SAH, according to the new grading scale.

Score	Favorable outcome	Unfavorable outcome	Total
3	0	0 (0%)	0
4	3	1 (25%)	4
5	8	0 (0%)	7
6	4	6 (60%)	10
7	5	9 (64%)	14
8	1	25 (96%)	26
9	1	21 (95%)	22
10	0	8 (100%)	8
11	0	10 (100%)	10
3 -5	11	1 (9.1%)	11
6 -7	9	15 (62.5%)	24
8 – 9	2	46 (95.8%)	48
10 – 11	0	18 (100%)	18

Figure Legends

Figure 1. Kaplan-Meier survival curve.



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

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[pages 1 - 2]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[page 2]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 4 - 5]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[page 5]**
Methods		
Study design	4	Present key elements of study design early in the paper **[pages 5 - 6]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[pages 5 - 6]**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[page 5]** *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	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[page 6]**
Data sources/ measurement	8*	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 **[page 6]**
Bias	9	Describe any efforts to address potential sources of bias **[page 5]**
Study size	10	Explain how the study size was arrived at **[page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[page 6]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[pages 6 - 7]**
		(*b*) Describe any methods used to examine subgroups and interactions **[pages 6 - 7]**
		(*c*) Explain how missing data were addressed **[N/A]**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed**[N/A]** *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 **[N/A]**

Continued on next page

Results		
Participants	13*	(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 **[page 7]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[page 7; table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[N/A]**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **[page 8]**
		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	(*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 **[N/A]**
		(*b*) Report category boundaries when continuous variables were categorized **[N/A]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[pages 8 - 9; tables 1,2,3,4; figure 1]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[pages 8 - 9]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[page 13]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[pages 9 – 13]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[N/A]**
Other information		
Funding	22	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 [**page 14]**

*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.