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Abstract.

Objective: To evaluate the prognostic value of high-sensitivity troponin (hsT) in severe aneurysmal subarachnoid hemorrhage (aSAH).

Methods: This prospective non-interventional study was performed at a surgical intensive care unit (ICU) from 2012 to 2015. Consecutive patients who had severe aSAH were included. A modified Rankin Scale score ≥ 4 or death within 3 months defined a poor outcome. hsT levels were measured at ICU admission and 72 hours following symptom onset.

Results: A total of 137 patients were analyzed. The median hsT level was 29 ng/L (range: 7-4485). The best threshold level of hsT for predicting a poor outcome was 22 ng/L. At this threshold, the sensitivity was 71% (95% confidence interval [CI]: 58%-81%) and the specificity was 58% (95%CI: 46%-70%). The area under the ROC curve was 0.61 (95%CI: 0.52-0.71). Based on a multivariate analysis, the independent factors for a poor neurological prognosis were a World Federation of Neurologic Surgeons (WFNS) score ≥ 4 (odds ratio [OR]: 2.61; 95%CI: 1.04-6.56) and an hsT level > 22 ng/L (OR: 2.80; 95%CI: 1.18-6.64).

Conclusion: In patients with severe aSAH, with regard for the severity of disease (assessed by the WFNS score), an hsT level > 22 ng/L at ICU admission was associated with poor outcomes.

Key words: Aneurysmal subarachnoid hemorrhage, critical care, high-sensitivity troponin, outcome.

Introduction.

In the acute phase of aneurysmal subarachnoid hemorrhage (aSAH), cardiac involvement is frequent, but its manifestations vary from a simple electrocardiographic abnormality(ies) with no clinical consequence to cardiogenic shock with pulmonary edema [1]. The underlying mechanism is related to a sympathetic hyperactivation with a sudden increase in plasma catecholamines, notably norepinephrine, and in the most severe form, involves myocardial stunning with severe left ventricular dysfunction secondary to focal myocardial necrosis and an increase in cardiac enzymes [2].

The consequences of myocardial damage on the prognosis of aSAH warrant early detection by assessing cardiac enzymes and performing electrocardiogram(s) and/or echocardiography(s) and for patients presenting overt myocardial dysfunction or hemodynamic instability, by echocardiography and/or pulmonary artery catheterization [3-5]. In this context, the troponin assay is a biological reference test [1]. Elevation in cardiac troponin I or troponin T has been found to be associated with an increased risk of cardiopulmonary morbidity, delayed cerebral ischemia, and adverse functional outcome, although conflicting results have been reported [6-12]. Hence, due to their increased sensitivity and potential for enabling early diagnosis, high-sensitivity troponin T (hsT) assays, which are characterized by a coefficient of variation $\leq 10\%$ at the 99^{th} centile of a healthy reference population, have been developed and incorporated with other molecular assays for acute coronary disease [13]. In patients suffering from aSAH, hsT assays have a high sensitivity and specificity for detecting stress-induced cardiomyopathy; additionally, in one study, high levels of hsT detected shortly after symptom onset was independently associated with an adverse neurologic prognosis at one year [14,15]. Nevertheless, the intrinsic severity

of the disease may be relevant for limiting the accuracy of troponin ("standard" or "high sensitivity") to predict outcomes independent of the occurrence of myocardial damage.

In this context, the aim of this prospective study was to evaluate the accuracy of hsT in predicting functional outcomes and mortality in patients with severe aSAH under intensive care.

Methods.

Study design and setting

This prospective non-randomized observational study was conducted between October 2012 and August 2015 at the surgical intensive care unit (ICU) of a university hospital. The study was approved by the Institutional Review Board of University Hospital and written consent was not required according to the observational design of the study.

Patients

Severe aSAH was defined as aSAH requiring an ICU stay. All patients over 18 years of age who were admitted for aSAH at the surgical department were consecutively included. Patients with non-aSAH (due to arteriovenous malformation, head trauma or unknown etiology) or patients admitted to the ICU more than 48 hours after the onset of initial symptoms were excluded. Patients were followed up for a period of three months after inclusion.

Objectives

The main objective of the study was to evaluate the predictive value of hsT regarding neurological outcomes assessed by the modified Rankin Scale (MRS) at 3 months, with a poor prognosis being defined by an MRS score ≥ 4 or death [16]. The MRS score ranges from

0 to 6 (0 = no symptom, 1 = no significant disability despite symptoms, 2 = slight disability, unable to perform all activities but does not need assistance, 3 = moderate disability, 4 = moderately severe disability, unable to walk without assistance, 5 = severe disability, bedridden, incontinent and requires constant nursing care, and 6 = death) and is classified by rehabilitation physicians. The secondary objectives were to determine the impact of hemodynamic data (heart rate and mean arterial pressure [MAP] at admission and the use of catecholamines during the first 24 hours of ICU hospitalization), electrocardiogram abnormalities, cardiac dysfunction, and delayed cerebral ischemia on outcomes.

Diagnostic criteria and assessment of severity of aSAH

The diagnosis of SAH was made by cerebral computed tomography (CT), and the presence of an aneurysm was identified by cerebral computed angiography and/or cerebral angiography. Disease severity was assessed according to the World Federation of Neurologic Surgeons (WFNS) classification and the modified Fisher scale [17,18].

Data collection

The following data were collected: age, sex, body mass index (BMI), history of smoking, arterial hypertension, heart failure and/or ischemic heart disease, interval between symptom onset and ICU admission, disease severity assessed by the WFNS and Fisher scores, location of the aneurysm, presence or absence of initial hydrocephalus, and method of aneurysm control (coil *vs* clip). Creatinine levels and creatinine clearance (based on the Modification of the Diet in Renal Disease (MDRD) study equation) were reported.

A delayed cerebral ischemia was considered in the case of a new focal neurological deficit or deterioration in consciousness or in the Glasgow coma scale and the appearance of new

infarctions on cerebral CT or magnetic resonance imaging (MRI) in the absence of other explanations (e.g., neurosurgical or radiological intervention, perihematomal edema) during hospitalization and by MRI at 3 months in surviving patients [19]. In our institution, at 3 months, patients are systematically evaluated by MRI and evaluated for neurologic performance by a physician.

Heart rate and mean arterial pressure (MAP) at admission and the use and nature of catecholamines administered during the first 24 hours of ICU admission were recorded. A 12-lead electrocardiogram was performed at admission, and the following modifications were evaluated and notified: ST segment elevation or depression, negative T wave, atrial fibrillation, and/or left branch block (BBG). Additionally, echocardiography was performed during the first 24 hours of ICU admission, and left systolic ventricular function was calculated. Left ventricular dysfunction was defined as a left ventricular ejection fraction (LVEF) < 50%.

High-sensitivity troponin assay

Blood hsT levels were determined within 24 hours of admission (within 72 hours of symptom onset). Troponin levels and intervals between symptom onset and ICU admission were also recorded. Serum hsT was measured with an Elecsys Troponin T High-Sensitivity Immunoassay (Elecsys ® Troponin T – high-sensitive - Roche Diagnostics, Rotkreuz – Switzerland). The values were expressed in ng/L, and the lowest concentration with a coefficient of variation ≤ 10% (limit of quantification) was 13 ng/L.

Statistical analysis

SAS software version 9.4 (SAS Institute, Cary, NC) and R software V 3.3.1 (package pROC)

were used to perform statistical analyses. Quantitative and qualitative variables were expressed as the median (interquartile range) and numbers (percentage), respectively. The first step was to select the optimal level of hsT that differentiated patients with good and poor outcomes at 3 months based on receiver operating characteristic (ROC) curves and the Youden index. Therefore, from the defined threshold level of hsT, the risk factors of poor outcome were determined by logistic regressions and expressed by odds ratios (ORs) and 95% confidence intervals (CIs). Variables > 0.20 in univariate analysis were included in the multivariate model. For analyses, a $p < 0.05$ (two-sided) was considered significant.

The primary outcome was the calculated sensitivity and specificity with corresponding 95% CIs. We specified a priori estimates of approximately 50% as no, approximately 75% as moderate and approximately 100% as excellent clinical test performance to interpret sensitivity and specificity (considered robust estimates) rather than positive or negative predictive values (which can be altered by disease prevalence). We estimated that a sample size of 140 patients would yield 80% power to detect 95% CIs no wider than 20% around sensitivity and specificity estimates provided these operating characteristics were approximately 75% using sample size calculations detailed by Flahault *et al.* [20].

Results.

A total of 160 patients were admitted for SAH to the surgical ICU during the study period, and 137 patients were finally included (Figure 1). The characteristics of the population are presented in Table 1. Sixty-five patients (47%) had a poor neurologic outcome at 3 months (MRS score ≥ 4). Twenty-two (16%) patients had MRS scores 4 to 5, and 43 (31%) patients died (40 in the ICU and 3 after discharge from the ICU). Of the 25 patients (18%) who died within 72 hours of ICU admission, 22 (88%) did not have their aneurysms secured because of

initial poor prognosis. The delays from hsT measurement and symptom onset to ICU admission are presented in Figure 2.

Prognostic value of high-sensitivity troponin

The median hsT level at admission was 29 ng/L (interquartile range 25-75: 10-212 ng/L). The best threshold level of hsT for predicting a poor outcome was 22 ng/L. At this threshold, the sensitivity was 71% (95% CI: 58%-81%), the specificity was 58% (95% CI: 46%-70%) and the positive and negative predictive values were 60% (95% CI: 49%-72%) and 69% (95% CI: 56%-80%), respectively. The area under the ROC curve was 0.61 (95% CI: 0.52-0.71) (Figure 3).

The results of the univariate analysis are provided in Table 1. The hsT level was significantly different between patients with favorable or unfavorable outcomes (Table 1). The multivariate analysis included the following variables: age, WFNS score, modified Fisher scale, aneurysm control (reference = no treatment *vs* clip or coil), creatinine clearance (MDRD) and hsT level (> 22 *vs* ≤ 22 ng/L). An hsT level > 22 ng/L measured early after admission and a WFNS score ≥ 4 were independent predictors of poor neurological prognoses. Securing of the aneurysm was a protective factor regardless of the method (clipping or coiling) (Table 2). The distribution of MRS scores according to the threshold of hsT > 22 *vs* ≤ 22 ng/L is shown in Figure 4.

Secondary criteria

Hemodynamic data, electrocardiogram findings, and echocardiographic LVEF are presented in Table 3. There was no significant difference in outcomes at 3 months regardless of the parameters studied.

Delayed cerebral ischemia was evaluated in 132 patients. At 3 months, among the 94 surviving patients, MRI was available in 89 (there was loss of follow up in 5 patients [MRS

score < 4, n = 4 and MRS score ≥ 4, n = 1]), and there was no significant difference between the two groups in the occurrence of delayed cerebral ischemia (MRS score ≥ 4, n = 29/64 (45%) *vs* MRS score < 4, n = 30/68 (44%), p = 0.890).

Discussion

In patients with severe aSAH requiring ICU admission at the acute phase, we found an association between admission hsT values > 22 ng/L and the prognosis at 3 months as assessed by the MRS score. This threshold was chosen based on the guidance of the Youden index to maximize misclassification by the ROC curve. Although the hsT level alone helped with achieving a prognosis for the 3-month outcome with a moderate sensitivity and specificity, these results may be better interpreted in a larger multivariate study including clinical variables. Severity assessed as an WFNS score ≥ 4 was also an independent risk factor of a poor outcome at 3 months.

Several groups have studied the relationship between troponin levels and cardiac complications, but few have examined long-term prognosis. Naidech *et al.* found that the peak level of troponin I was associated with death or severe disability at discharge but not at 3 months. In this prospective study including 253 patients, troponin level was measured only in patients who had abnormal electrocardiograms or symptoms of cardiac dysfunction, allowing for the selection of a certain population with SAH [7]. In a retrospective study, troponin levels were measured in 203/225 patients who had a non-traumatic SAH. A troponin level > 0.5 µg/L was not associated with in-hospital mortality in multivariate analysis, but age and severity assessed by the Hunt and Hess score were [11]. In 301 patients with aSAH, abnormalities in cardiac wall motion evaluated by echocardiography, but not troponin T, was found to be an independent factor of mortality and poor outcome (MRS score ≥ 4) [5]. In 163 patients who had non-traumatic aSAH, elevation in troponin T levels was found to be

associated with a 30-day mortality, but this association did not reach statistical significance when controlling for the WFNS score or Glasgow coma scale, suggesting that the intrinsic severity of aSAH was more relevant than the troponin level in outcome prediction [12]. In contrast, in 68 patients who had aSAH, Schuiling *et al.* found that troponin I level ≥ 0.3 µg/L was an independent risk factor for poor outcomes at 3 months, although the addition of troponin to variables related to the severity of the aSAH only slightly improved the prognostic value [21]. More recently, poor outcomes evaluated by the Glasgow Outcome Scale score (1 to 3) and MRS score (4 to 6) at 3 months have been shown to be independently associated with troponin levels ≥ 0.3 µg/L [10]. The prospective study was conducted in 239 patients with aSAH, and only 84% of patients were effectively evaluated at 3 months. Finally, in a cohort of 368 patients, Degos *et al.* found that a Glasgow coma scale at admission < 13 and high levels of troponin and S100β (> 0.5 µg/L) were independently associated with mortality at 1 year, but only patients treated by coils were included in that study, excluding those treated by clip and those who were received neither clips nor coils [22].

In this context, hsT may provide good prognostic accuracy. Moreover, to the best of our knowledge, only one other study has evaluated the accuracy of hsT in predicting outcome. In a prospective study performed using the same kit to obtain hsT measurement that was used in our study, Oras *et al.* showed that in addition to age, the presence of cerebral infarction and WFNS scores 4-5, the peak hsT level (per 100 ng/L) was associated with poor neurological outcomes (Glasgow Outcome Scale score ≥ 4) at one year. The best threshold of hsT to predict poor outcome was 51 ng/L, with a specificity of 84%, a relatively low sensitivity (56%) and an area under the curve of 0.74 [14]. The study also showed higher heart rate and norepinephrine doses in patients with poor neurologic prognoses, suggesting that hemodynamic instability and an increase in cerebral metabolic demand may have favored brain ischemia. Our results are in accordance with these results, as we found an association

between hsT levels > 22 ng/L and outcome. Nevertheless, there was no difference in hemodynamic parameters, electrocardiograms or cardiac dysfunction assessed by echocardiography between patients with good and poor outcomes. Obviously, a small increase in the hsT level (the threshold of detection was 13 ng/L) can impact the prognosis. Nevertheless, it must be emphasized that while a threshold of 22 ng/L is potentially useful for physicians to identify patients at higher risk of poor outcomes, these data must be interpreted with caution. Indeed, the positive predictive value was relatively low (60%), and some patients achieved a good outcome despite having a high hsT level. The originality of our study is its focus on a selective population, as we recruited patients with more severe aSAH. In our study, more than 90% of patients had a Fisher score = 4 (compared to 31% in the Oras *et al.* study). Accordingly, contrary to the Oras *et al*. study, the mortality was higher (30% *vs* 14%), and patients who did not have their aneurysms secured were also included [14].

Nevertheless, our study has some limitations that must be noted. Some may argue that we have measured the level of troponin only at admission and early in the course of the disease. Nevertheless, it has been shown that troponin levels peak early in the course of disease, usually during the first hours of hospitalization (10,12) and decreases thereafter; therefore, we believe that based on a practical point of view and real-life situations, the level of troponin at admission is sufficient to categorize patients at risk of poor outcome. From this practical point of view, there is variability among troponin levels and symptom onset and the time of admission into the ICU, and we cannot rule out that a higher level of troponin may have been present. Moreover, we have not included a validation cohort to verify our cut off level of troponin in terms of risk prediction in our analysis. An external assessment and validation of the performance of biological-clinical scores would therefore be meaningful. In fact, it was difficult to perform such an analysis as it was necessary to prolong the study to nearly 3 years to include 137 patients. Furthermore, the threshold of 22 ng/L must be interpreted with regard

for its moderate sensitivity and specificity and the finding that it did not preclude a good outcome. Such a threshold must alert physicians about the higher risk of a poor outcome but should not be used to make decisions regarding the intensity of care. Finally, we analyzed the prognosis at 3 months and not at one year, as did Oras *et al.* [14]. Even if major neurological complications arise within 3 months, we cannot completely rule out that patients will functionally recover beyond this time, although most studies have evaluated the prognostic value of troponin at 3 months [7,10,21,22].

In conclusion, following the severity of aSAH, the plasma level of hsT at admission is significantly associated with the neurological outcome at three months in patients with aSAH admitted to the ICU.

Conflict of interest: The authors have no conflicts of interest to declare.

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outcomes in patients undergoing aneurysm coiling. Stroke. 2012;43(5):1253-9. doi:10.1161/STROKEAHA.111.638197. Cited in PubMed; PMID: 22363051

Figure legends.

Figure 1: Flow chart.

Figure 2: Delay between hsT measurement and symptom onset (A) and ICU admission (B).

Figure 3: Receiver operating characteristic curve.

Figure 4: Distribution of modified Rankin Scale scores according to the level of hsT: > or ≤ 22 ng/L. mRS: modified Rankin scale (see text for definition).

Fig1.

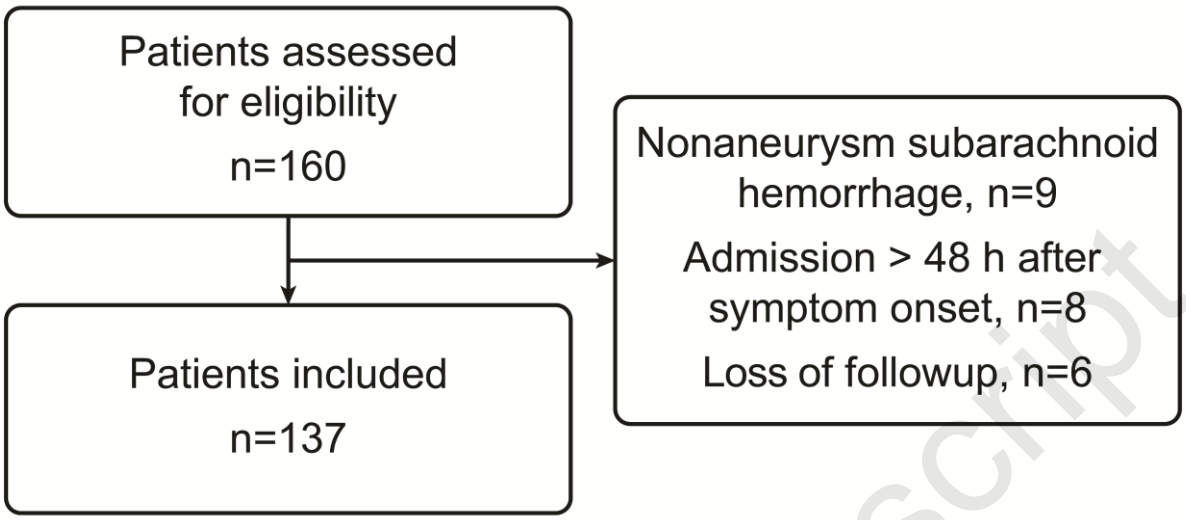

Fig. 2

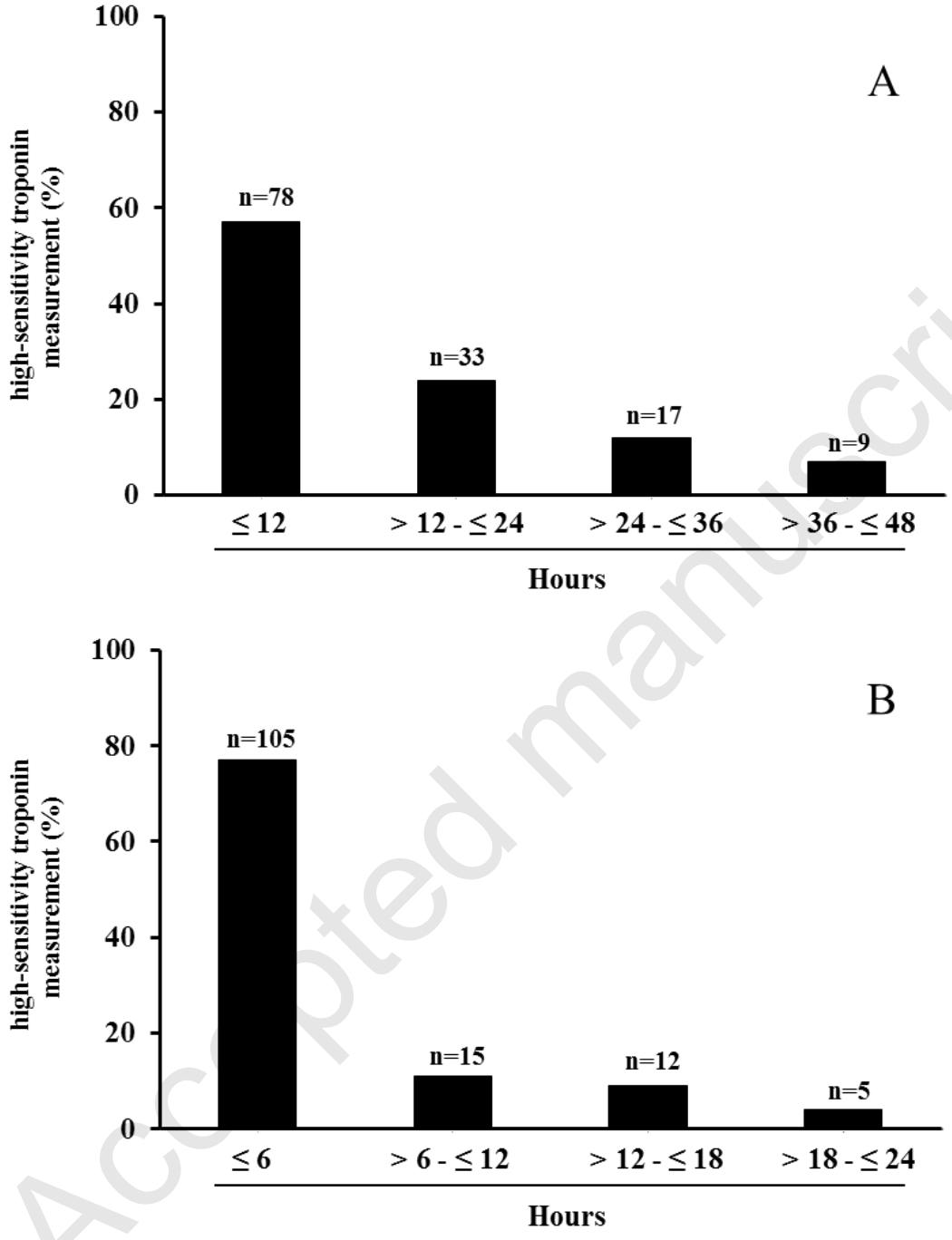

Fig. 3

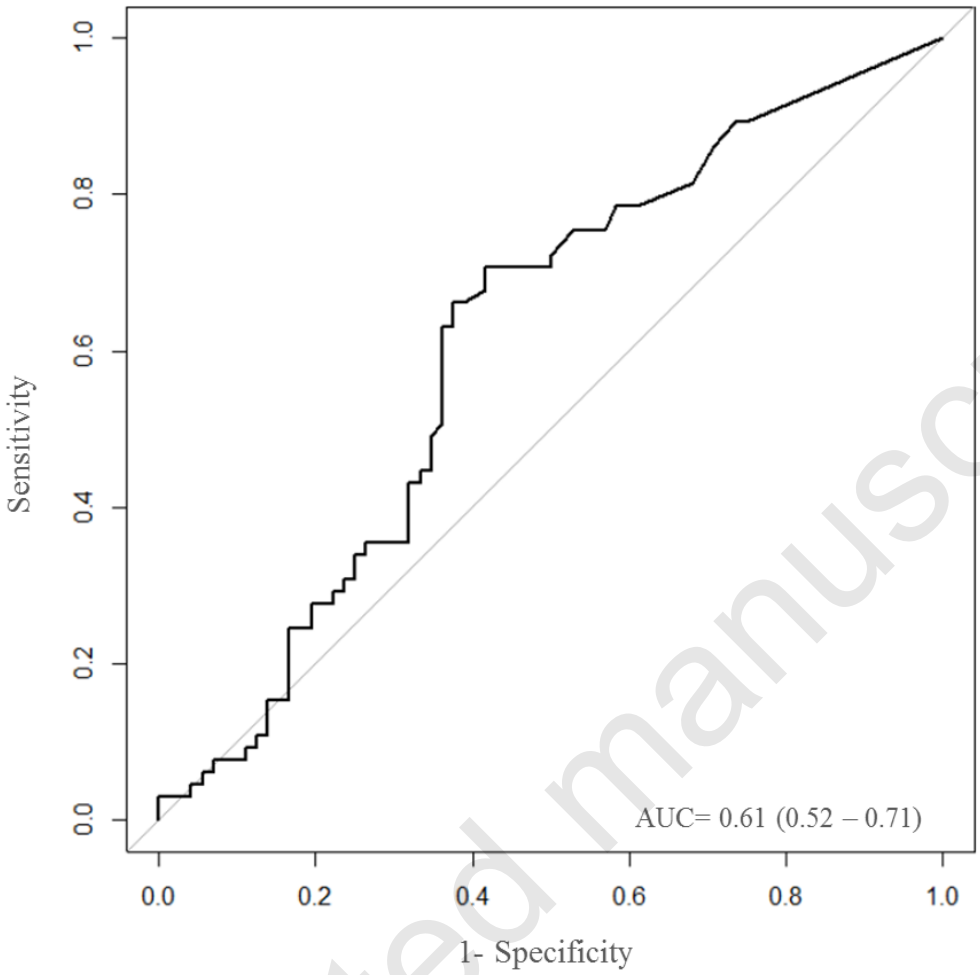

Fig. 4

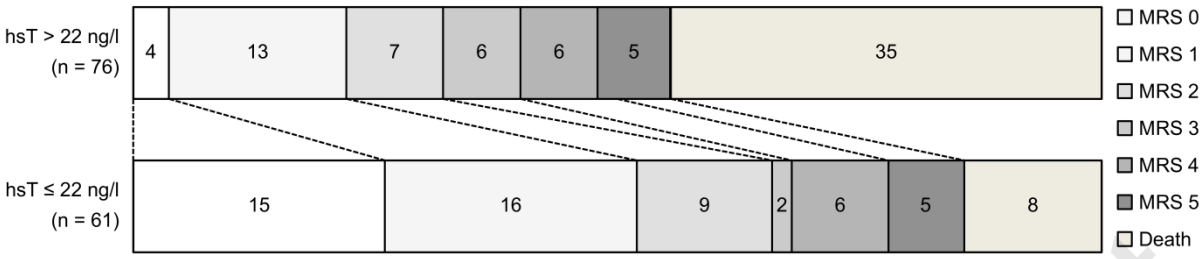

Table 1: Patients characteristics.

	Total (n=137)	**MRS* 0 to 3 (n=72)**	**MRS* 4 to 6 (n=65)**	**p**
Age, years	54 (46-63)	54 (46-60)	58 (46-65)	0.055
Sex, female	95 (69 %)	48 (67%)	47 (72%)	0.475
Body mass index, kg/m²	24 (21-28)	24 (21-28)	24 (20-28)	0.766
Medical history				
Smoking	59 (43%)	33 (46%)	26 (40%)	0.491
Arterial hypertension	39 (28%)	23 (32%)	16 (25%)	0.342
Coronary artery disease	2 (1%)	2 (3%)	0	0.498
Congestive heart failure	0	0	0	-
Delay between ICU admission and onset of symptoms, hours	7 (4-14)	7 (5-15)	6 (4-10)	0.332
WFNS[§] classification				<0.001
WFNS 1	15 (11%)	15 (21%)	0	
WFNS 2	21 (15%)	14 (19%)	7 (11%)	
WFNS 3	9 (7%)	5 (7%)	4 (6%)	
WFNS 4	36 (26%)	21 (29%)	15 (23%)	
WFNS 5	56 (41%)	17 (24%)	39 (60%)	
Modified Fisher scale				0.011
Fisher 1	0	0	0	
Fisher 2	3 (2%)	3 (4%)	0	
Fisher 3	9 (7%)	8 (11%)	1 (1%)	

Fisher 4	125 (91%)	61 (85%)	64 (98%)	
Aneurysm location				0.342
Anterior communicating artery	54 (41%)	29 (41%)	25 (40%)	
Middle cerebral artery	43 (33%)	19 (27%)	24 (39%)	
Internal carotid artery	20 (15%)	11 (16%)	9 (14%)	
PICA[§§]	4 (3 %)	4 (6%)	0	
Posterior communicating artery	2 (1%)	1 (1%)	1 (2%)	
Others	9 (7%)	6 (9%)	3 (5%)	
Hydrocephalus	67 (49%)	32 (44%)	35 (54%)	0.272
Aneurysm treatment (ref= no treatment)				<0.001
None	22 (16%)	2 (3%)	20 (31%)	
Clipping	29 (21%)	11 (15%)	18 (28%)	
Coiling	86 (63%)	59 (82%)	27 (41%)	
hsT, ng/L	29 (10-212)	19 (7-187)	57 (17-255)	0.024
Delay between troponin measurement and onset of symptoms, hours	10 (6-22)	11 (6-23)	10 (5-21)	0.609
Delay between troponin measurement and ICU admission, hours	1 (1-5)	1 (1-4)	1 (1-6)	0.399
Creatinine, µmol/L	56 (46-67)	57 (46-68)	56 (46-66)	0.789
Clearance creatinine MDRD, ml/min[‡]	113 (94-138)	116 (95-144)	110 (93-137)	0.159

Values are expressed as median (interquartile range 25-75) or n (percentage). *MRS: Modified Rankin scale. [§]WFNS: World Federation of Neurosurgical Societies. [§§]PICA: Postero inferior cerebellar artery. [‡]MDRD: Modification of the Diet in Renal Disease.

Table 2: Independent risk factors of poor outcome at 3 months.

	OR [CI 95%]	**p**
Aneurysm treatment (ref=no treatment)		<0.001
-Clipping	0.21 [0.04 ; 1.15]	
-Coiling	0.05 [0.01 ; 0.25]	
WFNS* 4 and 5	2.61 [1.04 ; 6.56]	0.042
hsT[§] > 22ng/L	2.80 [1.18 ; 6.64]	0.020

*WFNS: World Federation of Neurosurgeries society. [§]high-sensitivity troponin

Table 3: Hemodynamic, electrocardiogram and echocardiographic data.

	Total (n=134)	**MRS* 0 to 3 (n=71)**	**MRS* 4 to 6 (n=63)**	**p**
Heart rate, rate/min	74 (63-88)	74 (62-85)	74 (65-95)	0.280
Mean arterial pressure, mmHg	90 (80-101)	90 (80-100)	91 (80-101)	0.483
Catecholamines use	53 (40%)	24 (34%)	29 (46%)	0.340
Norepinephrine	46 (34%)	22 (31%)	24 (38%)	
Dobutamine	6 (4%)	2 (3%)	4 (6%)	
Epinephrine	1 (1%)	0	1 (2%)	
Electrocardiogram (n=131)				
ST segment elevation or depression	14 (11%)	7 (10%)	7 (11%)	0.785
Negative T wave	23 (18%)	11 (16%)	12 (20%)	0.553
Atrial fibrillation	5 (4%)	2 (3%)	3 (5%)	0.663
Left block branch	6 (5%)	3 (4%)	3 (5%)	1.000
Echocardiography (n=98)				
LVEF[§] < 50%	16 (16%)	6 (11%)	10 (22%)	0.160

Values are expressed as median (interquartile range 25-75) or n (percentage). *MRS: modified Rankin Scale. [§]LVEF: Left ventricular ejection fraction.