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Long-term vascular events after subarachnoid hemorrhage

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Abstract

Background

Spontaneous subarachnoid hemorrhage (SAH) long-term risk is not well known. Our aims are: describing long-term vascular event (VE) incidence rates in SAH survivors; describing VE: ischemic and/or hemorrhagic; identifying independent association of factors related to VE; and analyzing the usefulness of factors to increase predictive ability.

Methods

A prospective cohort study of consecutive patients admitted to Hospital del Mar with a diagnosis of SAH (n=566) between January 2007 and January 2020 was carried out. They were followed up until January 2021. The study endpoint was a new VE in the follow-up. We calculated both incidence rates and cumulative rates at five years. Cox regression survival models including vascular risk factors with and without specific data of SAH disease were developed. We analyzed ROC curves of all multivariate models.

Results

The cohort analyzed included 423 non-fatal SAH cases. Total patient-years were 2468.16 years. The average follow-up was 70.03±43.14;range:1-180 months. There were 49 VE, detected in 47 patients, 2 patients had more than one. The incidence rate was 0.020 events_per_patient/year, cumulative incidence at five years 11.11%. We found that the more frequent VE were cerebrovascular (28/49), mainly ischemic (21/28). Disability after SAH and the presence of multiple aneurysms were independently associated with a VE risk and improved the predictive capacity of multivariate models (AUC 0.679vs0.764;p=0.0062).

Conclusions

We reported a low vascular risk after SAH. We have shown the usefulness of SAH factors to identify patients with a higher risk of VE.

Keywords: Subarachnoid Hemorrhage, Vascular events, Risk Factors

Introduction

Spontaneous subarachnoid hemorrhage (SAH) represents approximately 3% of all strokes, and unlike other subtypes of stroke, it affects younger subjects.[1] In the last decades, mortality due to SAH had been decreasing thanks to advances in the treatment of aneurysms and the prevention of possible complications.[2,3] There are few studies[4–6] which describe the long-term vascular risk of SAH survivors, and they are focused on aneurysmal SAH (aSAH).[7] Moreover, during follow-up, it is usual for these patients to undergo endovascular or surgical procedures in order to treat or re-treat vascular anomalies, and these procedures are also associated with complications that could increase the vascular risk of these patients. Thus, we do not know what their real vascular risk is, and if it is similar to the risk of general population or to that of other vascular diseases, such as other stroke subtypes or coronary heart disease.

Our aims are:

1) Describing long-term vascular risk incidence rate in survivors of spontaneous SAH.
2) Describing vascular events (VE), ischemic and/or hemorrhagic, either spontaneous or related to endovascular or surgical procedures.
3) Identifying SAH-data related to VE.
4) Analyzing the usefulness of these data in order to increase the capacity of classical scores to predict vascular risk.

METHODS

Study design. We carried out a prospective observational study of consecutive patients admitted to Hospital del Mar (tertiary stroke center included in the Catalan SAH care system) between January 2007 and January 2020 with a diagnosis of first spontaneous SAH (n=566), who were followed up until January 2021. A structured questionnaire (SAH-BasicMar) was used to record the following variables: age, sex, hypertension, diabetes mellitus, hyperlipidemia, current smoking habit, atrial fibrillation, and previous vascular disease (documented stroke, coronary disease and/or diagnosis of peripheral arterial disease). Other variables recorded were: initial clinical severity (Hunt and Hess grade) and computed tomography (CT) findings (modified Fisher scale), perimesencephalic SAH, with vascular cause (including aneurism and/or other less frequents vascular alterations; arteriovenous malformations; and fistulas), multiple cerebral aneurysms, first treatment performed (endovascular or neurosurgical), complications: vasospasm, stroke (ischemic lesion of any cause and/or delayed cerebral ischemia) and cardiac (any acute myocardiopathy, heart failure and/or arrhythmia) within the first 90 days after SAH and disability after SAH (modified Rankin Scale >2 at three months). To simplify the analysis and understanding of the study, previous stroke, cardiac and peripheral disease were all considered as previous vascular disease. Follow-up consisted of a medical visit 3 months after the SAH and then, at the physician's discretion, a medical appointment or telephone contact every 6 months. In all cases, we have consulted electronic medical records, the primary care physician diagnostics, and hospital admissions records. At the study conclusion, we reviewed all patient events and death records.[8]

The study endpoint was a new vascular event (VE) defined according to the REACH study criteria in the follow-up after 90 days since the SAH onset:[8] vascular death, non-fatal stroke, non-fatal coronary disease, or hospitalization for an atherothrombotic event, including any vascular interventions. We did not include as VE either those occurred within 90 days after the SAH onset or those cerebral endovascular/surgical procedures programmed as control or treatment of cerebral aneurysm/arterial malformation, unless they were associated with a further vascular complication. Our methodology of work, diagnosis, treatment, and follow-up in SAH and stroke patients has been previously well described.[3,8,9] Ischemic stroke was divided into lacunar/non-lacunar and into secondary to endovascular/surgical procedure or spontaneous; hemorrhagic stroke was divided into new SAH, lobar, deep, and intraventricular hemorrhage. For all cases of VE, we accessed the clinical record to determine all tests and procedures performed, and the events certified by a neurologist, a cardiologist, or a vascular surgeon. A member of the research team validated each event, and, when necessary, we contacted the attending physicians for confirmation.

Statistical analysis

We present data as means and SD for continuous variables, and as frequencies and percentages for categorical variables. Age was categorized based on quartiles to improve the interpretation of the results (q1=46 years, q3=65 years), although its inclusion as a continuous variable does not substantially modify the results. We calculated the incidence rate (events per patient-year) as the number of new events found during follow-up divided by the number of years of follow-up of patients at risk, and cumulative incidence at five years. Those variables with a p-value <0.1 in Kaplan-Meier bivariate analysis were selected to be included in the multivariate analysis. We used Cox regression survival analysis to estimate multivariate hazard ratio (HR) with a 95% confidence interval (CI) for VE (only model 2 is shown to simplify results). Reference subgroups in multivariate analysis were those with age under 46 years and sex female. We considered 2-sided p-values 0.05 as significant in regression models.

We performed four models: model 1 and 2 analyzed all events with only vascular risk factors and with all factors respectively, and models 3 and 4 analyzed only spontaneous events. Kaplan-Meier curves, Schoenfeld and deviance residuals were analyzed from a fitted Cox proportional hazards regression model in order to detect potential violations, discard outliers and confirm and test proportional hazard assumptions.[10] Areas Under the Curve (AUC) were calculated with ROC curves performed with pROC and ROCit libraries of R. The report of the analyses follows the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines. All analyses were conducted using R software (R version 4.12 (2021-11-01); ©2021The_R_Foundation_for_Statistical_Computing), and libraries used were detailed in supplementary tables already loaded to Figshare. Two biostatistician team reviewed all statistical analyses (JJ-B and EG-S).

Standard protocol approvals, registrations, and patient consent: The information used in this study was collected from the prospective SAH-BasicMar. Register with the approval of our local ethics committee (CEIC PSMAR 2008/3083/I). We obtained written informed consent from all patients or a designated representative, as appropriate.

RESULTS

Of a total of 566 consecutive SAH, we excluded from the study both fatal SAH (within hospital admission; n=115; 20.3%) and those occurred to patients living outside Catalonia, whose long-term follow-ups would have been impossible (n=28; 4.9%). The cohort analyzed included 423 cases; demographic, vascular risk factors, clinical and radiological data are described in Tables 1 and 2. Previous vascular diseases were: 12 cases with stroke, 11 with cardiac disease, and in 5 with arterial peripheral disease (6 of these cases had more than one event). 328 cases had an angiographic cause (311 aneurysms, 9 arteriovenous malformations, and 11 arteriovenous fistulas; 5 of these cases had more than one type of cause). 103 cases had neither endovascular nor surgical treatment (95 of them without angiographic cause, whereas the other 8 had cause but received no treatment).

Incidence rates

Total patient-years were 2468.16 years. Average follow-up was 70.03±43.14; range 1-180 months. All patients completed the follow-up until January 2021 except for 36 (8.51%) cases due to death to non-vascular causes, and 17 (4.02%) cases were censored due to loss of follow-up. There were 49 VE, detected in 47 patients (2 patients had more than one event), with an incidence rate of 0.020 events per patient/year (cumulative incidence 11.79% at five years). Survival curve is shown in Figure 1. The incidence rate of spontaneous VE was 0.013 events per patient/year (cumulative incidence 8.71% at five years), of fatal VE was 0.004 events per patient/year (cumulative incidence 4.10% at five years), and of coronary events was 0.002 events per patient/year (cumulative incidence 0.51% at five years).

Types of events

1) Spontaneous VE were 32 (65.3% of total events): **8 ischemic strokes**: 4 cases of lacunar stroke, 4 cases of embolic non-lacunar stroke; **7 hemorrhagic strokes**: 4 new SAH, 1 lobar hemorrhage, 1 deep hemorrhage, and 1 intraventricular hemorrhage; **7 cardiac events**: 6 coronary syndrome, and 1 valve intervention; **4 peripheral events**: 2 carotid interventions, 1 aortic intervention, and 1 bypass in the legs; and, finally, **6 sudden deaths**.

2) There were 17 events related to cerebrovascular procedures (34.7%) (2 surgical, 15 endovascular): 13 ischemic strokes, 1 new SAH, 1 lobar hemorrhage, and 2 femoral interventions. Only 2 out of 13 stroke cases related to cerebrovascular procedures were disabling compared with 6 out of 8 cases of spontaneous ischemic stroke (p= 0.026). 12 VE (24.48% of VE, and 2.83% of total cohort) were fatal events; 6 sudden deaths, 3 strokes, 2 hemorrhagic strokes and 1 cardiac event.

Associated factors to VE and predictive Cox models

We analyzed 47 events (two cases with two events were censored at the first event). Kaplan-Meier p-values of relationships between factors and VE are described in Tables 1 and 2.

1) For all events, Model 1 including age, sex, and vascular risk factors had an AUC of 0.679 (see Table 3). When adding factors associated with SAH (Model 2), disability after SAH and multiple aneurysms were independently associated with VE (hazard ratios are shown in Figure 2). Graphics of analysis of residuals are available in Supplement materials loaded to Figshare. In Model 2, the AUC increases to 0.764. The Delong´s test confirms a statistical difference of discrimination capacity between Models 2 and 1; p-value=0.0062 (Table 3).

2) In Models 3 and 4 we performed the same analysis but including only spontaneous VE, and we also found an independent association of disability and multiple aneurysms with VE. These models had a higher AUC (0.775 and 0.796, respectively), without statistically significant differences between them; p-value=0.217 (Table 3).

DISCUSSION

Incidence

The incidence of VE in our cohort was 0.020 events per patient/year, with a cumulative incidence at five years of 11.79%. Using the SCORE2 as reference, a score for 10-year cardiovascular disease risk for European population,[11] it would correspond to a high (>10%). Despite this, the risk of VE in SAH patients is lower than in those with other vascular diseases. Ois et al. described an incidence of long-term VE in ischemic stroke of 0.084 events per patient/year[8]. Two other studies described as well that a long-term risk of VE was lower in aSAH patients compared to TIA/minor stroke patients[4,5]. Regarding coronary heart disease, Jernberg described a VE risk of 18.3% in the first year and of 20% 1 to 4 years after a myocardial infarction.[12] This lower risk in our patients is probably due to the characteristics of SAH patients, usually younger and with less cardiovascular risk factors than patients with other subtypes of stroke or with coronary disease. Previous studies have described an increased risk of VE in SAH patients compared with the general population,[4,5,13] with incidences in the same range as ours. However, it is difficult to compare the results because of methodological differences between the studies: Wermer at al. described a cumulative incidence of VE at 8 years of 11.2% in clipped aSAH patients, not including recurrent aSAH as a VE;[4] Nieuwkamp et al. reported an cumulative incidence of VE of 23.9% in a cohort of SAH, with a wider definition of VE than ours, using International Classification of Diseases.[13,14] In another study with aSAH patients, Nieuwkamp et al. reported an incidence of VE (including recurrent aSAH) at 9 years of 14.3%.[5]

Vascular death risk

In our cohort, cumulative incidence of vascular death was 4.1% at five years (0.004 events per patient/year), lower than in other studies that only include aSAH, with incidences around 8%,[6,13,14] which could be explained because we included non-aneurysmal hemorrhages, which have a better life expectancy.[5]

Subtypes of VE

Analyzing the types of VE registered in our cohort, the most frequent were ischemic strokes (44.7%), a fact which has been already reported in other works.[4,5] A possible explanation would be that most of SAH patients require more surgical or endovascular procedures after the event, as some of the stroke's cases in our cohort (13/21), who underwent these procedures. Other procedure-related vascular complications were one SAH, one lobar hemorrhage, and 2 femoral artery bleedings that required an intervention. In total, 17 VE (36.2%) occurred after cerebrovascular procedures, mainly endovascular (15/17). It is a relative high figure, but consistent reported complication rates.[15] Our incidence is probably higher than in previous SAH series that included more surgical treatments, and would reflect the growing trend towards treating aneurysms with endovascular procedures instead of surgical options.[4,13] Despite their incidence, most of these procedures related VE in our cohort were transitory or non-disabling. Regarding long term SAH recurrence, the incidence in our cohort was low (1.2%), like in previous studies,[4,13] which would be due to the advances in treatment in recent years.

Associated factors

Classical vascular risk factors were associated with a higher risk of VE, although in some cases statistical significance was not reached, mainly due to the small sample size. We think that the main relevance or focus of our study was the analysis of the relationship between specific factors related to SAH and the risk of long-term VE. As expected, we have not found an association between the initial punctuation in clinical and radiological scales of SAH and the increased risk of VE. Moreover, we have neither been able to confirm[7] that complications such as stroke or heart disease within 90 days since the SAH onset had a higher risk of VE. However, our definition of cardiac disease and methodology differs from previous studies that reported those associations.[7] SAH with cause and endovascular treatment only showed an association on the bivariate analysis. This would be explained by the low rebleeding risk (only 5 cases). Therefore, statistical association was lost after including the rest of the variables in the analyses.

However, the methodology of our work focused on the predictive value of analyzed factors rather than on the analysis of its independent associations. The factors that had a strong independent association with VE risk were multiple aneurysms and disability after SAH. Disability is a factor associated with a worse vascular risk prognosis, and it is explained by many cofactors that are deleterious in these patients compared to non-disability cases (less physical activity, greater obesity, bad control of CVDr factors).[16] In our study, the unexpected factor that was strongly related to vascular risk was the presence of multiple aneurysms. This association could be explained because of a higher risk of a new SAH in these patients and their need of undergoing more endovascular procedures, as these procedures are associated with VE.[15] However, the incidence rate of new SAH was extremely low, and this association was also found in spontaneous events. A previous study reported the association of this factor with an increased risk of death, although an increased VE risk was not found.[6] Our methodology of work included treatment of all detected aneurysms with a very experienced team, and reported low long-term mortality rates,[3] which can influence why we did not find an association with an increased risk of death. We do not have a clear explanation about the causes underlying the presence of multiple aneurysms in the same patient. There are genetic disorders, such as Marfan syndrome, neurofibromatosis type 1, Ehlers-Danlos syndrome type IV, or autosomal dominant polycystic kidney disease which entail a higher incidence of multiple cerebral aneurysms due to the associated congenital weakness of the vessel wall. On the other hand, prolonged exposure to comorbidities associated with the formation of intracranial aneurysms (arterial hypertension, smoking, atherosclerotic vessel degeneration), together with an advancing age may also contribute to a higher multiple aneurysms' prevalence in older adults.[18] Therefore, genetic, epigenetic, and other factors directly associated with the connective tissue could be involved in an added CVDr for these patients.

Predictive models

Our study analyzes, for the first time in the literature, predictive scores for calculating vascular risk in an unselected series of SAH. We confirm the usefulness of factors associated with SAH in improving the vascular risk predictive capacity of vascular risk factors. As expected, according to what we have previously discussed, a model with the classic factors predicts these spontaneous events better than the set of all of them, and although the AUC increases when adding the specific factors of the SAH, we have not been able to demonstrate a statistical difference, probably due to the fact of the sample's size.

Limitations

The main limitation of our study is the relatively small number of cases and the low incidence of VE for the robustness of the statistical analyses, but it does not invalidate our conclusions. Our data should be confirmed in larger and multicenter series including other populations. Despite this, our study has some important strengths. First, our data were prospectively collected from a cohort of consecutive patients with SAH, while previous studies focused only on aSAH. Second, we have a long follow up, during which patients have been exhaustively evaluated and followed up by a neurologist. Furthermore, we analyze associated factors that help understand the increased vascular risk in these patients, which, to the best of our knowledge, has not been described before.

Conclusion

SAH patients, inherent to their specific pathophysiology and treatments, have a higher CVDr than population, but lower than other vascular diseases. This fact makes more relevant to have specific vascular risk predictors for these patients in order to improve their long-term outcome. We have confirmed for the first time the usefulness of some of the factors related to SAH in order to increase the predictive capacity to identify patients with a higher risk. These results should be replicated in other cohorts in order to generalize its application.

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References:

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics - 2017 Update: A Report from the American Heart Association. Circulation.2017;135:e146–e603.
2. Lovelock CE, Rinkel FGJE, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage Population-based study and systematic review. Neurology.2010;74:1494–1501.
3. Roquer J, Cuadrado-Godia E, Guimaraens L, et al. Short- and long-term outcome of patients with aneurysmal subarachnoid hemorrhage. Neurology.2020;95:e1819–e1829.
4. Wermer MJH, Greebe P, Algra A, Rinkel GJE. Long-term mortality and vascular event risk after aneurysmal subarachnoid haemorrhage. Journal of neurology, neurosurgery, and psychiatry.2009;80:1399–1401.
5. Nieuwkamp DJ, Vaartjes I, Algra A, Rinkel GJE, Bots ML. Risk of cardiovascular events and death in the life after aneurysmal subarachnoid haemorrhage: a nationwide study. International journal of stroke : official journal of the International Stroke Society.2014;9:1090–1096.
6. Huhtakangas J, Lehto H, Seppä K, et al. Long-Term Excess Mortality After Aneurysmal Subarachnoid Hemorrhage. Stroke. American Heart Association;2015;46:1813–1818.
7. Norberg E, Odenstedt-Herges H, Rydenhag B, Oras J. Impact of Acute Cardiac Complications After Subarachnoid Hemorrhage on Long-Term Mortality and Cardiovascular Events. Neurocritical Care.2018;29:404–412.
8. Ois A, Cuadrado-Godia E, Rodríguez-Campello A, et al. Relevance of stroke subtype in vascular risk prediction. Neurology.2013;81:575–580.
9. Ois A, Cuadrado-Godia E, Giralt-Steinhauer E, et al. Long-Term Stroke Recurrence after Transient Ischemic Attack: Implications of Etiology. Journal of Stroke.2019;21:184–189.
10. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. Biometrika;1994;81:515–526.
11. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. European Heart Journal.2021;42:2439–2454.
12. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. European Heart Journal.2015;36:1163–1170.
13. Nieuwkamp DJ, Algra A, Blomqvist P, et al. Excess mortality and cardiovascular

events in patients surviving subarachnoid hemorrhage: a nationwide study in Sweden. Stroke.2011;42:902–907.

14. Nieuwkamp DJ, Vaartjes I, Algra A, Bots ML, Rinkel GJE. Age- and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in the Netherlands. International journal of stroke : official journal of the International Stroke Society.2013;8 Suppl A1:90–94.

15. Guimaraens L, Vivas E, Saldaña J, et al. Efficacy and safety of the dual-layer flow-diverting stent (FRED) for the treatment of intracranial aneurysms. Journal of NeuroInterventional Surgery.2020;12.

16. Gupta P, Sharma A, Singh J, et al. Sedentary Behavior, Exercise, and Cardiovascular Health. Circulation research.2019;61:1964–1972.

17. Jabbarli R, Dinger TF, Darkwah Oppong M, et al. Risk Factors for and Clinical Consequences of Multiple Intracranial Aneurysms: A Systematic Review and Meta-Analysis. Stroke.2018;49:848–855.

Data availability: Anonymized data not published within this article will be made available by request from any qualified investigator.

Figure 1. Survival Curve

Figure 2. Hazard ratio of Cox regression Model 2

Table 1. Relationship of baseline age, sex, vascular risk factors, and previous vascular events.

Variable, No.(%)	Total n=423	VE n=47	No VE n=376	p
Age*(range:16-88 years)	54.76±14.17	60.15±13.4	54.09±14.13	0.02
Male*	168(39.7)	17(36.2)	151(40.2)	0.5
Hypertension*	174(41.1)	28(59.6)	146(38.8)	0.003
Diabetes mellitus*	29(6.9)	9(19.1)	20(5.3)	<0.001
Current smoking	150(35.5)	16(34)	134(35.6)	
Hyperlipidemia*	82(19.4)	16(34)	66(17.6)	0.004
Atrial Fibrillation	14(3.3)	3(6.4)	11(2.9)	
Previous Vascular disease*	20(4.7)	5(10.6)	15(4)	0.03

Age(mean± standard deviation);VE(vascular event).*Selected for Cox models.

Table 2. Relationship of baseline arterial, clinical, and radiological data related to SAH with vascular events(VE).

Variable, No.(%)	Total n=423	VE n=47	No VE n=376	Univariate p
Vascular cause*	328(77.3)	41(87.2)	287(76.3)	0.06
Multiple aneurysms*	87(20.6)	20(42.6)	67(17.8)	<0.001
Perimesencephalic	58(13.7)	7(14.9)	51(13.6)	
Vasospasm	181(42.8)	19(40.4)	162(43.1)	
Stroke_complications	140(33.1)	15(31.9)	125(33.2)	
Cardiac_complications	21(5)	1(2.1)	20(5.3)	
Endovascular treatment*	260(61.5)	34(72.3)	226(60.1)	0.08
Surgical	60(14.2)	5(10.6)	55(14.6)	
Disability*	94(22.2)	19(40.4)	75(19.9)	<0.001
Hunt and Hess				
1- 2	290(68.6)	33(70.3)	257(68.3)	
3	79(18.7)	8(17)	71(18.9)	
4	28(6.6)	3(6.4)	25(6.6)	
5	26(6.1)	3(6.4)	23(6.1)	
Fisher				
1	21(5)	2(4.3)	19(5.1)	
2	73(17.3)	8(17)	65(17.3)	
3	115(27.2)	11(23.4)	104(27.7)	
4	214(50.6)	26(55.3)	188(50)	

*Selected for Cox_models

Table 3. Cox Regression Models. (Models 1-2 all events; Models 3-4 spontaneous events).

HR (standard errors)

	Model_1	Model_2	Model_3	Model_4
Age46-65	1.600(0.446)	1.240(0.448)	2.117(0.649)	1.687(0.648)
Age>65	1.957(0.498)	1.918(0.502)	2.995(0.693)	2.513(0.694)
Male	0.928(0.310)	1.514(0.331)	1.386(0.365)	2.093(0.385)
Hypertension	1.461(0.226)	1.516(0.221)	1.998(0.294)*	2.198(0.289)*
Diabetes	1.374(0.235)	1.477(0.233)	1.482(0.272)	1.737(0.277)*
Hyperlipidemia	1.755(0.293)	2.050(0.312)*	2.273(0.307)*	2.054(0.325)*
Cardiovascular disease	1.170(0.367)	1.073(0.366)	1.014(0.416)	0.931(0.426)
Multiple Aneurysms		3.065(0.250)*		2.087(0.319)*
Disability		1.802(0.237)*		2.659(0.276)*
Vascular cause		1.323(0.297)		
Endovascular Treatment		0.954(0.436)		
AUC	**0.679**	**0.764**	**0.775**	**0.796**
p-value DeLong's test	ref.	**0.00627**	ref.	**0.21797**
P(>|Chi|)	ref.	2.717e-06	ref.	0.00123
AIC	524.773	501.590	344.258	330.541
R^2	0.047	0.115	0.072	0.110
Events	47	47	32	32
Observations.	423	423	423	423
PH_test	0.789	0.962	0.951	0.910

* p-value <0.05; DeLong's test(2vs.1&4vs.3); P(>|Chi|): Analysis of Deviance (2vs.1&4vs.3)