Outcome after aneurysmal subarachnoid hemorrhage

R. LOCH MACDONALD, M.D., PH.D.

Division of Neurosurgery, St. Michael’s Hospital, Labatt Family Centre of Excellence in Brain Injury and Trauma Research, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael’s Hospital, Department of Surgery, University of Toronto, Ontario, Canada

Giraldo and colleagues have retrospectively assessed the relation of various clinical and radiological variables to clinical outcome on the Glasgow Outcome Scale (GOS) in 186 patients 6 months after aneurysmal subarachnoid hemorrhage (SAH) or at last clinical follow-up. They found that World Federation of Neurosurgical Societies (WFNS) grade determined after the patient was resuscitated was most strongly associated with clinical outcome as opposed to WFNS grade at presentation or the worst WFNS grade. This work is important for several reasons. It suggests that when the WFNS is assessed matters. Only one small study has investigated this previously. That study found that the worst WFNS grade before treatment correlated with outcome in 56 patients. Furthermore, the analysis of Giraldo et al. provides us with guidance as to the best time to assess the WFNS grade. This is a key point because of the importance of WFNS or clinical grade in the prediction of outcome after SAH.

Relatively few studies have investigated prognostic factors for outcome after SAH. Almost all studies of any size that used multivariable analysis found that age and clinical grade were among the most important prognostic factors. Other relatively consistently identified prognostic factors include the amount of subarachnoid, intraventricular, and intracerebral blood on the admission CT scan, location and size of the ruptured aneurysm, and history of hypertension. After admission, development of delayed cerebral ischemia or cerebral infarction is usually the most important and consistently identified negative prognostic factor. Most studies, including the current study of Giraldo et al., have quite substantial limitations when considered from a strict statistical modeling perspective. Only the studies with hundreds of patients, usually more than 1000, have an adequate events-per-variable ratio. Prognostic models need to be validated internally on the population on which they were developed and then externally, and this is seldom done.

These limitations apply to the current study. The sample size is small and the data collection is retrospective. Although the concept the authors raise is important, numerous other factors conspire to limit the interpretation of this study. The source of the patients matters, and is unknown here, although presumably most came from the local geographic area. If certain types of patients are admitted to other hospitals and treated and only a subtype with different features from the population as a whole are transferred to the Mayo Clinic, then bias may be introduced. The paper does not contain an abundance of data. The distributions of many of the baseline variables are not given, so one cannot tell how representative the sample is in relation to other studies. Examining Table 1 suggests the study sample is a relatively standard SAH population except that the number of patients with a history of alcohol abuse seems high. There are some means of categorical variables, but means are sometimes not a good way to represent categorical variables. We do not know about missing data. If a patient is intubated, the Glasgow Coma Scale (GCS) score has to be imputed. Another question is that patients with large intracerebral hematomas underwent emergency surgery and aneurysm clipping. Their WFNS grade could be better after surgery, although in my experience this is not usually the case. These patients take days to improve, but it was not clear to me when the WFNS was assessed in these patients. The definitions and assessment of some factors are vague, as one would expect from a retrospective analysis. New cerebral infarction is an important variable the authors assessed, and this may or may not include hypodensities due to focal effects of the SAH, the aneurysm securing procedure, delayed cerebral ischemia, and other and unknown factors. The cause of these hypodensities is sometimes difficult to determine, and the time when they develop is especially problematic to determine retrospectively. Multivariable regression was done, but I am not sure how the WFNS grade was handled in this analysis. It is difficult and perhaps unwarranted to try to internally validate the results of this study.

The time from ictus to admission, and thus initial WFNS grading, is a key variable that is not mentioned here. This is likely to be of prognostic importance. Obviously, the longer one is from the SAH, then the closer one will be to the time of outcome assessment. Eventually the two meet and there will be a very good correlation between GCS and GOS scores. But short of that, time from SAH to admission has been shown to be an important prognostic factor. Patients die quickly after SAH so longer time to admission is associated with better outcome. Similarly, this will have an effect on the WFNS grade and to some extent, what Giraldo and colleagues found fits with experience and what one would logically expect. In a certain number of cases, patients present with SAH and then their condition deteriorates within hours from hydrocephalus,
rebleeding, and unidentified or other factors. If one took the WFNS grade at admission, then this early grade might be as good as the postresuscitation WFNS grade assuming the causes for deterioration were mostly reversible. If the cause of deterioration is not reversible (for example, rebleeding), then the WFNS grade after deterioration would most closely predict outcome. Logically, the WFNS grade used to predict outcome should be based on the patient’s best level of function soon after the hemorrhage. The caveat is that other catastrophes can occur after WFNS grading that will disrupt the correlation between WFNS grade and outcome. I have always assumed that the WFNS Grade IV or V patient who has a ventricular catheter placed and miraculously wakes up and becomes Grade II, should be assessed prognostically as a Grade II patient whereas a Grade I patient who experiences rebleeding 4 hours after admission and deteriorates to Grade V with no intracerebral hemorrhage to remove and no hydrocephalus is prognostically Grade V. This is similar to what the authors show here, although they don’t specifically dissect out the difference between the time from SAH to WFNS grading and the best/worst WFNS grade.

The authors raise another key point, which is that the patient who is always Grade I tends to have a better outcome than a patient who improves to Grade I or II after having been poor grade. They point out that the latter patient presumably has more secondary brain injury. This injury has received increasing attention recently and may represent one form of early brain injury, a term I attribute to Zhang and colleagues and that is given credence by this analysis. At the risk of offending others by omitting mention of them, I also want to mention Sehba and Bederson for their important contributions to the concept of early brain injury after SAH. This effect of early deterioration also may reflect the prognostic importance of delayed cerebral ischemia, which may be more common in such patients.

The authors discuss clipping and coiling rates as an explanation for why the one prior study of this issue found the opposite—that the patient’s worst WFNS grade was most strongly associated with outcome. On the other hand, the clip and coil rates should only affect the predictive value of the WFNS grade if clipping and coiling have different outcomes in relation to clinical grade. This may well be the case but it is not demonstrated by an interaction factor here.

The authors mention the use of the Hunt and Hess scale. While this is widely used in the US, it has outlasted its usefulness, and standardized scales like the GCS, upon which the WFNS grading system is based, have repeatedly been shown to have better interobserver variability. That said, I do not wish to diminish the contributions of Hunt and Hess. Along with Botterell and colleagues, they generated the concept that the clinical condition of the patient was important and that has been borne out repeatedly.

Outcome assessment in a complex disease like SAH is never going to be very precise. In addition to the factors mentioned above, numerous other factors have been associated with outcome in univariate analysis, including various biomarkers, fever, systemic inflammatory response syndrome, and serum glucose to name a few. Even models developed on thousands of patients only explain about a third of the variance in outcome. One explanation is that the included factors truly explain only a small proportion of the variance. Another is that the factors themselves are assessed variably or poorly. The clinical grade is certainly associated with outcome but that association will be weakened if the data used assess the WFNS grade at different times in different patients. Thus, a key message from Giraldo et al. is that the WFNS grade to use is probably the postresuscitation WFNS grade. The other problem is that if, for example, a patient with SAH has underlying coronary artery atherosclerosis and then suffers a myocardial infarction and dies, then at some point this is a prognostic factor for outcome. One would need a dataset of thousands of SAH patients for myocardial infarction to be detectable as a “significant” factor associated with outcome. Many other considerations affect outcome prediction. The patient population included as well as the distribution of the outcome variable affect the results of the multivariable analysis. For example, if all the good-grade patients with aneurysms that can be treated endovascularly are kept at local hospitals and only poor-grade patients and those with complex aneurysms are sent to the hospital where the study is done, then the prognostic factors for outcome and especially their relative importance may be very different from those in the overall population of patients with SAH.

In conclusion, Giraldo and colleagues raise an important issue in relation to clinical grading of patients with aneurysmal SAH. This small retrospective study suggests that collection of clinical grade at various times after SAH in a large number of patients from multiple centers may be warranted if one wants to gain understanding of the precise prognostic value of clinical grading.

Disclosure

Dr. Macdonald receives grant support from the Physicians Services Incorporated Foundation and the Heart and Stroke Foundation of Ontario. He is a consultant for Actelion Pharmaceuticals and chief scientific officer of Edge Therapeutics, Inc.

References

10. Ibrahim GM, Weidauer S, Vatter H, Raabe A, Macdonald RL: A minimum of 10 patients per dependent variable is needed to use linear logistic regression modeling. Thus, the sample size was adequate. We used univariable logistic regression followed by multivariable logistic regression with the forward selection method using WFNS determined at postresuscitation as the primary predictor of interest. Then, ROC/AUC analysis was used to identify the best predictor of poor outcome. Missing data were minimal because we obtained the information from the Mayo Clinic Electronic Medical Data System, which had complete information about the variables included in our study.

In terms of the source of the patients studied, most of them came from the local geographical area through transfer from surrounding community hospitals. This might be a source of selection bias because only patients with SAH considered safe to be transferred were sent to our institution. In patients who required emergency hematoma evacuation and aneurysm clipping, GCS scores and WFNS grades were also obtained at presentation, nadir, and after initial aggressive resuscitation completed either in the emergency department or in the operating room immediately before surgery.

We agree with Dr. Macdonald that an ideal study should have hundreds or even thousands of patients to have a more adequate ratio of events per dependent variable, and that this study should be validated internally and externally. The ideal study should be prospective in order to have reliable information about time from ictus to admission and initial WFNS score. In the absence of such a study, our cohort shows that grading performed after stabilization and resuscitation (including correction of increased intracranial pressure) is the best predictor of outcome. Based on this observation, it is critical for future trials of aneurysmal SAH to provide precise specifications as to the timing of assessment of the patient’s neurological grade.

Reference

Response

ELIAS A. GIRALDO, M.D., M.S., 1 AND GIUSEPPE LANZINO, M.D. 2

1Department of Neurology, Drexel University College of Medicine, Philadelphia, Pennsylvania; and 2Department of Neurologic Surgery, Mayo Clinic, Rochester, Minnesota

We appreciate Dr. Macdonald’s thoughtful comments on our study. We evaluated the association of the GCS score and the WFNS grade assessed at different times, with poor outcome defined as a GOS score of 1–3 at 6 months, in 186 consecutive patients with aneurysmal SAH to find which time point for clinical grading is most predictive of poor outcome. Using logistic regression with receiver operating characteristic/area under the curve (ROC/AUC) analysis, we demonstrated that the WFNS grade determined after initial resuscitation was the best predictor of poor outcome, and the WFNS grade obtained at presentation was the worst predictor of poor outcome.

We acknowledge that our study has the limitations intrinsic to its retrospective design. However, we feel that the study methodology was appropriate to demonstrate the association between timing of clinical grading and poor outcome in our retrospective cohort. The study sample size was large enough to answer the research question. All statistical techniques including logistic regression used in our study were linear. A minimum of 10 patients per dependent variable is needed to use linear logistic regression modeling. Thus, the sample size was adequate. We used univariable logistic regression followed by multivariable logistic regression with the forward selection method using WFNS determined at postresuscitation as the primary predictor of interest. Then, ROC/AUC analysis was used to identify the best predictor of poor outcome. Missing data were minimal because we obtained the information from the Mayo Clinic Electronic Medical Data System, which had complete information about the variables included in our study.

In terms of the source of the patients studied, most of them came from the local geographical area through transfer from surrounding community hospitals. This might be a source of selection bias because only patients with SAH considered safe to be transferred were sent to our institution. In patients who required emergency hematoma evacuation and aneurysm clipping, GCS scores and WFNS grades were also obtained at presentation, nadir, and after initial aggressive resuscitation completed either in the emergency department or in the operating room immediately before surgery.

We agree with Dr. Macdonald that an ideal study should have hundreds or even thousands of patients to have a more adequate ratio of events per dependent variable, and that this study should be validated internally and externally. The ideal study should be prospective in order to have reliable information about time from ictus to admission and initial WFNS score. In the absence of such a study, our cohort shows that grading performed after stabilization and resuscitation (including correction of increased intracranial pressure) is the best predictor of outcome. Based on this observation, it is critical for future trials of aneurysmal SAH to provide precise specifications as to the timing of assessment of the patient’s neurological grade.

Reference

Please include this information when citing this paper: published online April 27, 2012; DOI: 10.3171/2012.3.JNS112105.