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Deriving Clinical Prediction Rules From Stroke Outcome Research

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Background and Purpose. **Our purpose was to determine whether clinical prediction rules could be derived from current stroke outcome research.**

Summary of Report. **We reviewed 92 articles on stroke outcome research to determine their suitability for implementation as a clinical prediction rule. Methodological problems in many of these studies made implementation of their results as a clinical prediction rule difficult.**

Conclusions. **Implementation of stroke outcome research as clinical prediction rules would be facilitated by description of patient population demographics; precise definitions of predictor and outcome measures; stratification of patients by stroke mechanism; use of adequate patient sample sizes; and description of the mathematical methods used, including coding schemes, cutpoints, beta coefficients, constant terms, and a priori probabilities. (*Stroke* 1991;22:1431–1436)**

Clinical prediction rules have emerged as tools to assist physicians in predicting outcomes for individual patients with specified diseases.[1] The wide dissemination of pocket, notebook, laptop, and desktop computers has given impetus to the implementation of these rules.

Clinical prediction rules use multivariate statistical methods to examine the predictive power of independent variables to predict disease outcomes.[2] The goal of these methods is to create a parsimonious statistical model using a restricted number of predictor variables to predict patient outcome. Prediction rules are based on a variety of statistical methods, including logistic regression, discriminant analysis, life-tables with proportional hazards, and multiple linear regression. In the case of stroke, predictor variables may be derived from demographics (age, gender, race), medical history (e.g., diabetes, hypertension, heart disease), neurological history (e.g., mode of onset, headache), neurological examination (e.g., aphasia, hemiparesis, hemianopia, level of consciousness), or laboratory examinations (e.g., computed tomography, magnetic resonance imaging, electroencephalography). Outcomes predicted include survival, stroke recurrence, and level of functional recovery.

A recent symposium on "Methodologic Issues in Stroke Outcome Research" has highlighted some problems with past and current stroke outcome research.[3] We examined studies of stroke outcome published between 1981 and 1991 to assess their applicability to the creation of a clinical prediction rule. Our purpose was to determine whether useful clinical prediction rules could be derived from the available published results.

Methods

We searched the Index Medicus between 1981 and 1991 for articles on stroke outcome or prognosis. Articles on transient ischemic attacks or articles not primarily designed to examine stroke outcome were excluded from the study. Ninety-two articles were reviewed; four examined outcome of cerebellar infarction or hemorrhage,[4–7] 38 examined outcome after either cerebral infarction or a heterogeneous stroke population,[8–45] 21 examined outcome of intracerebral hemorrhage,[46–66] and 29 examined outcome of subarachnoid hemorrhage.[67–95] Sixty-seven of the articles examined survival as a stroke outcome (Table 1). Each of these 67 articles was evaluated as to which of 31 predictor variables were either predictive or not predictive for survival after stroke (Table 1).

Twenty-seven of the studies used multivariate methods. These studies were subjected to an additional evaluation similar to that suggested by Wasson et al.[1] We applied the following criteria to each published report:

Gender. Was the composition of the patient sample by gender reported?

Race. Was the composition of the patient sample by race reported?

Socioeconomic status. Was some measure of the socioeconomic status of the sample reported?

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TABLE 1. Predictors of Survival After Stroke Based on 67 Published Articles

Adverse predictors	Infarctions or mixed stroke (n=21)	Intracerebral hemorrhage (n=21)	Subarachnoid hemorrhage (n=21)	Cerebellar strokes (n=21)
Demographic				
Older age				
Male sex	3/6	0/1	1/1	
No spouse	2/2			
Socioeconomic class	0/2			
Nonwhite race				
Medical				
Heart failure	5/5	0/1		
Diabetes mellitus	2/5	0/1		
Angina	1/2			
Hypertension	3/8			
Atrial fibrillation	0/2			
Prior myocardial infarction				
Abnormal electrocardiogram	2/2	1/2	1/1	
Obesity	1/2	0/1		
Pulmonary disease	1/1			
Prior stroke	3/3			
Smoking	0/2			
Renal disease	1/1			
Higher hematocrit	0/1			
Higher blood sugar	0/1			
Incontinence	1/1			
Neurologic				
Greater weakness	11/11	2/6	2/5	
Cognitive impairment	7/8	5/5		
Impaired consciousness	1/1	18/18	9/10	4/4
Greater stroke size		18/19	8/8	2/3
Stroke location	2/3	4/5	0/2	
Lower ADL score	0/2			
Stroke progresses	1/1	1/1		
Hydrocephalus		2/4	2/3	2/2
Mass effect		3/5	3/4	1/1
Ventricular extension		6/6	5/5	0/1
Headache				0/1

Data given as number of studies finding adverse predictor significant/number of studies examining predictor.
ADL, activities of daily living.

Age. Was the composition of the patient sample by age reported?

Sample size. Was the sample size adequate for the multivariate method used and the number of predictor variables examined? As a rule of thumb, we considered sample size adequate if there were 10 patient cases for each predictor variable examined.

Adequate definitions. Were predictor variables and outcome variables precisely defined, including coding schemes for categorical (e.g., sex) or ordered (e.g., level of consciousness) variables? For continuous variables (e.g., blood pressure), was the unit of measurement specified? The method of measurement of both predictor and outcome variables should be reproducible by clinicians at other sites.

Stratification by stroke mechanism. As a minimum, studies should distinguish between subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic infarction. Preferably, infarction should be further separated into lacunar, embolic, or atherosclerotic mechanisms. Studies should be limited to those which look at a specific stroke mechanism, stratify patients according to stroke mechanism, or enter stroke mechanism into the multivariate model as an independent predictor variable.

Description of mathematical methods. The mathematical methods utilized should be adequately described.

Description of mathematical model. The mathematical prediction model should be adequately described and should include the coding scheme for the pre-

TABLE 2. Study Characteristics of Multivariate Studies of Stroke Outcome

First author	Publication year	Patients (*n*)	Predictors (*n*)	Patient type	Outcome assessed	Statistical method	Predictive model	Measure of predictive power
Adams	1985	1,778	11	SAH	Survival	Logistic regression	Yes	Relative risk ratio
Bonita	1988	635	16	MS	Survival	Proportional hazards	Yes	Survival curves
Chambers	1987	1,713	9	MS	Survival	Proportional hazards	Yes	Survival curves
Deverat	1991	166	11	ICH	Functional	Logistic regression	No	Odds ratio
Disney	1988	184	16	SAH	Survival	Discriminant analysis	Yes	Classification rate
Dove	1984	97	17	MS	Survival	Logistic regression	No	Odds ratio
Fullerton	1988	206	35	MS	Survival	Logistic regression	Yes	Classification rate
Henley	1985	172	44	MS	Functional	Discriminant analysis	Yes	Classification rate
Hertanu	1984	41	4	MS	Functional	Multiple regression	Yes	Multiple R
Hijdra	1988	176	6	SAH	Survival	Logistic regression	Yes	Class rate
Howard	1986	4,219	12	MS	Survival	Proportional hazards	Yes	Relative risk ratio
Howard	1985	379	16	INF	Functional	Logistic regression	Yes	Odds ratio
Kelly-Hayes	1988	213	13	MS	Survival	Logistic regression	Yes	None
Levine	1986	29	3	INF	Functional	Multiple regression	No	Multiple R
Loewen	1990	50	7	MS	Functional	Multiple regression	Yes	Multiple R
Niemi	1988	46	9	MS	Functional	Multiple regression	No	Multiple R
Portenoy	1987	112	8	ICH	Survival	Logistic regression	Yes	Classification rate
Sacco	1989	1,273	20	INF	Recurrence	Logistic regression	Yes	Relative risk ratio
Shah	1989	258	26	MS	Functional	Multiple regression	Yes	Multiple R
Sobel	1989	243	7	INF	Recurrence	Logistic regression	No	Relative risk ratio
Solzi	1983	1,369	6	INF	Survival	Proportional hazards	Yes	Median survival
Tuhrim	1988	94	85	ICH	Survival	Logistic regression	Yes	Classification rate
Ueda	1987	255	17	MS	Functional	Logistic regression	No	None
Viitanen	1987	428	13	MS	Survival	Proportional hazards	Yes	Relative risk ratio
Wade	1984	162	51	MS	Survival	Multiple regression	Yes	Multiple R
Wade	1985	99	14	MS	Functional	Multiple regression	Yes	Multiple R
Wade	1987	976	17	MS	Functional	Multiple regression	Yes	Multiple R

SAH, subarachnoid hemorrhage; MS, mixed stroke type; ICH, intracerebral hemorrhage; INF, infarction.

dictor and outcome variables, the beta coefficients, and the constant terms. For classification functions, discriminant functions, or logistic regression, cut-points should be described.

Base probabilities. Base probabilities should be specified. For discriminant analysis and logistic regression, the a priori class memberships should be reported (e.g., in a study of 100 cases of intracerebral hemorrhage, 70% survived at 30 days). For life-table studies using Cox regression methods, the base survival curve should be reported in either tabular or graphic format (e.g., after ischemic infarction, 80% of patients survived 1 year and 70% survived 2 years).

Predictive power of model. Some measure of the predictive power of the model and the predictor variables should be reported. For discriminant analysis and logistic regression, predictive power can be assessed by comparing the classification rate of the model with the base class memberships. For life-table models, predictive power can be estimated by reporting the relative risks associated with various values of the predictor variables.

Validation. Some method of validation of the prediction rule should be provided (e.g., replication of results in a new sample, split-half sample analysis, jack-knife).

Results

A large number of predictors were examined in the 67 studies examining survival after stroke (Table 1). The most frequently examined predictors were weakness, impaired level of consciousness, and stroke size. Age was the most commonly examined demographic factor, whereas race, gender, and education were not routinely examined. Only a few studies examined the effect of concurrent medical conditions on stroke outcome. Although most studies evaluated the effect of stroke size on stroke outcome, most studies did not examine the influence of mass effect, hydrocephalus, or stroke location on outcome.

The 27 multivariate studies were evaluated for their possible application as clinical prediction rules (Table 2). Twelve studies were deficient with regard to description of the patient sample by gender, 22 were deficient with regard to race, 12 were deficient with regard to age, and 23 were deficient with regard to socioeconomic status. Three of the studies lacked adequate definitions of or coding schemes for their predictor variables. Four studies lacked either adequate definitions for their outcome variables or had an outcome variable that was judged to be difficult to

implement by other investigators. Fifteen of the studies failed to stratify patients by stroke mechanism. In 10 of the studies, the sample size was judged inadequate for the number of predictor variables examined. All studies described the mathematical methods utilized; however, in seven studies an inadequate description of the mathematical model derived was given (i.e., missing beta coefficient or constant terms). Only one study failed to give the a priori or base probabilities for outcome. Two of the studies failed to give some measure of the predictive power of the model (e.g., R-squared, classification rate, odds ratio). None of the studies provided any form of validation of the predictive model presented (Table 1).

Discussion

Four forces are encouraging physicians to apply clinical prediction rules to stroke patients: 1) large stroke patient databases are available,[96] 2) sophisticated mathematical methods exist for the creation of prediction rules from these patient databases, 3) computers are increasingly available in the hospital and office environment to implement these prediction rules, and 4) expert systems are under development to assist physicians with stroke care.[97]

Although studies of stroke outcome are abundant, our understanding of the predictors of stroke outcome is still sketchy and incomplete. Only a few predictors, such as level of consciousness, stroke size, and weakness, have been studied in detail (Table 1). Although we found 27 multivariate studies of stroke outcome (Table 2), many of these studies would be difficult to implement as a clinical prediction rule. Many were flawed by a failure to describe patient demographics or to precisely define predictive and outcome measures. Seven of the studies lacked a sufficiently detailed description of the predictive model to allow its implementation as a prediction rule. None of the studies provided any validation of the predictive model presented. Taking the lead from Wasson et al,[1] we suggest that future multivariate studies of stroke outcome be designed so as to be potentially useful as clinical prediction rules. Future multivariate studies of stroke outcome should consider including the following elements:

1) Studies should report patient demographics including race, gender, age, and socioeconomic status. As indicated by Table 1, more information is needed about the influence of sex, age, race, and socioeconomic status on stroke outcome. Race has known effects on stroke type,[98] but its effects on stroke outcome are largely unstudied. The effects of gender on stroke outcome or stroke type have not been carefully scrutinized (Table 1). Age appears to be an adverse predictor of most but not all stroke outcomes (Table 1). Education and socioeconomic status may influence outcome in multi-infarct dementia,[99] but their influence on stroke outcome is largely unknown. Studies also need to identify any patient selection biases that might influence the generalizability of the prediction rule.

2) Studies should report precise definitions of both the predictor and outcome measures, including variable coding schemes.

3) Patients should be stratified by stroke mechanism. The growing availability of computed tomography and magnetic resonance imaging makes the distinction between cerebral infarction and cerebral hemorrhage routine. Predictor variables may vary according to stroke mechanism (Table 1).

4) Sample size should be adequate for the number of predictor measures evaluated.

5) Both the mathematical methods used and the mathematical model derived (including beta coefficients, cutpoints, and constant terms) should be described in sufficient detail to allow implementation by other investigators.

6) Base or a priori probabilities should be given for all outcomes.

7) The predictive power of the predictive model, including classification rates and odds ratios, should be reported.

8) Attempts to validate the predictive model should be reported. However, accurate description of the predictive model will allow other investigators to validate the predictive model externally.

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