Predicting Outcome From Hypoxic-Ischemic Coma

David E. Levy, MD; John J. Caronna, MD; Burton H. Singer, PhD; Robert H. Lapinski, PhD; Halina Frydman, PhD; Fred Plum, MD

• Outcome from coma caused by cerebral hypoxia-ischemia (eg, cardiac arrest) was compared with serial neurological findings in 210 patients. Thirteen percent of patients regained independent function at some point during the first postarrest year. Computer application of new multivariate techniques to the prospectively observed findings generated easily utilized rules that classified patients by likely outcome. At the time of initial examination, 52 patients (one fourth of the total population) had absent pupillary light reflexes, and none of these patients ever regained independent daily function. By contrast, the initial presence of pupillary light reflexes, the development of spontaneous eye movements that were roving conjugate or better, and the findings of extensor, flexor, or withdrawal responses to pain identified a smaller group of 27 patients, 11 (41%) of whom regained independence in their daily lives. By 24 hours after onset, 93 poor-outcome patients were identified by motor responses that were absent, extensor, or flexor and by spontaneous eye movements that were neither orienting nor roving conjugate; only one regained independent function. This contrasts with recovery in 19 (63%) of 30 patients who at that time showed improvement in their eye-opening responses and obeyed commands or had motor responses that were withdrawal or localizing. Similarly simple rules distinguished between good- and poor-prognosis patients on postarrest days 3, 7, and 14.

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MOST patients sustaining cardiac arrest either undergo irreversible asystole or reawaken quickly and make a good physical and mental recovery. A few, however, experience sufficiently severe brain injury that they remain at least transiently in postarrest coma. Among this less fortunate group morbidity is high, but some retain the neurological capacity to do well. Others, however, are left with overwhelmingly severe brain damage. This study reports newly constructed, empirically derived guidelines to predict within the first few days which of these brain-injured patients will do well and which will do badly following cardiac arrest or similar global hypoxic-ischemic insults.

From the Department of Neurology and Research Center in Cerebrovascular Disease, New York Hospital-Cornell Medical Center (Drs Levy, Caronna, Lapinski, and Plum); Department of Statistics, Columbia University (Dr Singer); and the Graduate School of Business, New York University (Dr Frydman), New York.

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Reprint requests to Department of Neurology (A-569), Cornell Medical Center, 1300 York Ave, New York, NY 10021 (Dr Levy).

METHODS

Patient Evaluation

The analysis was performed on patients with cerebral hypoxia-ische drawn from a larger group of 500 subj with nontraumatic coma.[1,2] The op tional definition of coma was that pati failed to open their eyes either spont ously or in response to noise, that th expressed no comprehensible words, that they neither obeyed commands moved their extremities appropriately localize or resist painful stimuli. At pre termined intervals (the initial exami tion and 0 to 1, 2 to 3, 4 to 7, and 8 to days after the onset of coma), patie underwent focused neurological exami tions.[1,3] More than half (115, or 55%) w first examined by the investigators with six hours, 176 (84%) within 12 hours, 200 (95%) within the first day. Wh information was available from sev examinations, the best response in a g interval was used for analysis. To conc trate on patients in whom prognosis in doubt, we excluded those with an o ously good (eg, prolonged syncope delayed recovery from anesthesia) or p prognosis (eg, brain death) and requ that patients remain in coma for at le six hours. Patients, their families, health professionals were questioned re larly about a variety of neurological daily life functions; these included patient's housing, speech, return to prior level of function, and independ in ambulation, bathing, dressing, preparation, eating, and use of toilet f ities. Their functional state was cat rized at 1, 3, 6, and 12 months into on five grades[4]: (1) no recovery (contin coma until death), (2) the vegetative s (eyes-open wakefulness without evid of cognitive awareness), (3) severe dis

Table 1.—Factors Not Associated With Outcome*

Variable	No.	No. (%) Who Achieved Independent Function
Age, yr		
≤60	89	12 (13)
>60	121	14 (12)
Sex		
M	128	12 (9)
F	82	14 (17)
Site of onset		
Out-of-hospital	72	11 (15)
Intensive care	53	7 (13)
Operating suite	19	2 (11)
General ward	65	6 (9)
Cause of coma		
Cardiac arrest	150	15 (10)
Respiratory failure	22	4 (18)
Miscellaneous	38	7 (18)
Paroxysmal activity		
Convulsions	32	4 (13)
Isolated myoclonus	21	2 (10)
Neither	157	20 (13)

*None of these variables was significantly associated with outcome from coma by χ^2 testing with appropriate degrees of freedom.

Table 2.—Clinical Signs That Predict Future Independent Function: Percent (No.) of Patients*

Neurological Response	No. of Days After Onset of Coma			
	0	1	3	7
Verbal response				
Oriented	. . .	. . .	100 (8/8)	100 (11/11)
Confused	. . .	71 (5/7)	80 (8/10)	75 (9/12)
Inappropriate	. . .	50 (1/2)	25 (1/4)	50 (1/2)
Incomprehensible	60 (3/5)	33 (3/9)	12 (1/8)	0 (0/5)
None	13 (11/82)	8 (5/59)	5 (2/37)	6 (1/17)
Eye opening				
Spontaneous	. . .	45 (14/31)	44 (22/50)	46 (23/50)
To noise	. . .	50 (5/10)	17 (1/6)	33 (1/3)
To pain	20 (5/25)	5 (1/21)	0 (0/11)	0 (0/6)
None	11 (20/185)	6 (6/104)	4 (2/57)	0 (0/17)
Pupillary light reflex				
Present	16 (25/157)	18 (25/138)	21 (24/112)	32 (23/71)
Absent	0 (0/52)	0 (0/29)	0 (0/11)	0 (0/4)
Corneal reflex				
Present	17 (22/130)	21 (25/119)	24 (24/101)	34 (23/68)
Absent	4 (3/71)	0 (0/37)	0 (0/14)	0 (0/2)
Spontaneous eye movements				
Orienting	. . .	70 (7/10)	77 (20/26)	74 (20/27)
Roving conjugate	36 (12/33)	29 (14/48)	11 (4/37)	10 (3/30)
Roving dysconjugate	17 (2/12)	14 (1/7)	0 (0/5)	0 (0/4)
Other movement	12 (3/25)	0 (0/21)	0 (0/9)	17 (1/6)
None	6 (8/140)	5 (4/80)	2 (1/46)	0 (0/9)
Oculocephalic response				
Normal	. . .	62 (10/16)	70 (19/27)	84 (21/25)
Full	17 (16/96)	13 (12/92)	6 (4/64)	5 (2/41)
Minimal	13 (4/31)	12 (2/16)	12 (1/8)	20 (1/5)
None	7 (6/83)	5 (2/42)	4 (1/24)	0 (0/3)
Oculovestibular response				
Normal	0 (0/2)	59 (10/17)	65 (13/20)	50 (10/20)
Full or tonic atypical	18 (21/115)	13 (12/89)	5 (3/58)	8 (2/25)
Minimal	5 (1/21)	0 (0/13)	17 (1/6)	50 (1/2)
None	5 (3/56)	6 (2/33)	6 (1/17)	0 (0/4)
Motor response (best limb)				
Obeying	. . .	64 (7/11)	86 (18/21)	78 (18/23)
Localizing	. . .	38 (3/8)	12 (1/8)	55 (5/9)
Withdrawal	29 (10/35)	38 (13/34)	24 (6/25)	8 (1/13)
Flexor	14 (5/35)	3 (1/30)	0 (0/18)	0 (0/12)
Extensor	18 (7/38)	0 (0/22)	0 (0/20)	0 (0/8)
None	4 (4/102)	3 (2/61)	0 (0/31)	0 (0/11)

*For each time period, the denominator in parentheses is the number of patients demonstrating each neurological response. The numerator indicates the number of these patients subsequently achieving a best one-year functional state of moderate disability or good recovery. Percentages represent the ratios in parentheses. Responses are arranged hierarchically, with the best in each group appearing first, and the poorest, last. With few exceptions, the relationship between different recovery patterns and the clinical responses was always significant by appropriate χ^2 tests with $P \leq .01$. Exceptional cases were eye opening and oculocephalic and oculovestibular responses at initial examination and pupillary light reflexes and corneal reflexes at three and seven days. The reliability of many of these clinical signs has been previously discussed.[8,9]

ity (conscious but dependent on others for aspects of daily function), (4) moderate disability (independent but unable to resume the prior level of activities), and (5) good recovery (able to resume the prior level of function). To avoid influencing patient outcomes, the investigators refrained from any involvement in their care.

Analysis

Data were subjected to univariate and multivariate analyses in an effort to relate the early clinical picture to the ultimate functional state. Among the analytic methods applied was a computerized recursive partitioning algorithm[6] that constructed classification trees to predict the best functional state within the first year. Recursive partitioning first identifies the variable having greatest predictive power and, thereby, divides the population into two groups, each with relatively homogeneous outcomes. It then divides these subgroups on the basis of the most predictive variables for each; the process continues until a group either has uniform outcome or is too small to split further. The program utilizes categorical and ordered data rather than requiring interval scales (equal steps between the values) and thus avoids the artificiality of interpreting scores as strict numerical values. Recursive partitioning can be directed to maximize overall accuracy or, alternatively, to minimize particularly costly errors. Cost in this sense incorporates personal, social, humane, and economic considerations, and different assessments of cost will often result in different classification trees.[7] For the present study, we arbitrarily decided that the error of predicting a poor prognosis for someone who in fact does well should carry 20 times the cost of the converse error of predicting a good prognosis in someone who does badly; other misclassification errors were assigned intermediate costs. The program also allows the investigator to specify how complicated each classification tree could be. We permitted formation of three to five terminal branches because such a tree was most likely to be robust and easily used. Stability of recursive partitioning was assessed by developing rules on calibration subsamples containing 90% of the patients and testing on the other 10%, repeating the procedure on a total of ten separate 10% test subsamples, and inspecting the resulting rules and classifications for consistency.

RESULTS

Onset of Coma

Global cerebral hypoxia-ischemia was attributed to primary cardiac arrest (asystole or tachyarrhythmia) in 150 patients (71%), to primary respiratory failure in 22 (11%), and to other causes in the remaining 38 (18%), profound hypotension and an-

210 Patients at Initial Examination

Rule	Total No. of Patients	Best 1-yr Recovery (% of Total): No Recov Veg State	Sev Disab	Mod Disab Good Recov
Pupillary Reflex: Present? No	52	94 (84-99)	6 (1-16)	0 (0-7)
Pupillary Reflex: Present? Yes → Motor: Extensor or Better? No	62	89 (78-95)	5 (1-14)	6 (2-16)
Motor: Extensor or Better? Yes → Spont Eye Movt: Rov Conj or Better? No → Motor: Flexor or Better? No	47	77 (62-88)	13 (5-26)	11 (4-23)
Motor: Flexor or Better? Yes	22	59 (36-79)	14 (3-35)	27 (11-50)
Spont Eye Movt: Rov Conj or Better? Yes	27	41 (22-61)	19 (6-38)	41 (22-61)

168 Patients at 1 Day

Rule	Total No. of Patients	Best 1-yr Recovery (% of To…): No Recov Veg State	Sev Disab	Mod D… Good R…
1D Motor: Withdrawal or Better? No → 1D Spont Eye Movt: Rov Conj or Better? No	93	95 (88-98)	4 (1-11)	1 (0-6)
1D Spont Eye Movt: Rov Conj or Better? Yes	22	77 (55-92)	14 (3-35)	9 (1-2…)
1D Motor: Withdrawal or Better? Yes → 1D Eye Opening: Improved at Least 2 Grades? No	23	70 (47-87)	13 (3-34)	17 (5-3…)
1D Eye Opening: Improved at Least 2 Grades? Yes	30	7 (1-22)	3 (0-17)	63 (44-8…)

124 Patients at 3 Days

Rule	Total No. of Patients	Best 1-yr Recovery (% of Total): No Recov Veg State	Sev Disab	Mod Disab Good Recov
3D Motor: Withdrawal or Better? No	70	93 (84-98)	7 (2-16)	0 (0-5)
3D Motor: Withdrawal or Better? Yes → 3D Spont Eye Movt: Orienting? No	28	61 (41-79)	21 (8-41)	18 (6-37)
3D Spont Eye Movt: Orienting? Yes	26	8 (1-25)	15 (4-35)	77 (56-91)

76 Patients at 1 wk

Rule	Total No. of Patients	Best 1-yr Recovery (% of Total): No Recov Veg State	Sev Disab	Mod D… Good Re…
1W Motor: Obeys Commands? No → Init Spont Eye Movt: Rov Conj or Better? No → 3D Eye Opening: Spontaneous? No	26	100 (87-100)	0 (0-13)	0 (0-13)
3D Eye Opening: Spontaneous? Yes	12	58 (27-85)	42 (15-72)	0 (0-26)
Init Spont Eye Movt: Rov Conj or Better? Yes	6	67 (22-96)	17 (0-64)	17 (0-64)
1W Motor: Obeys Commands? Yes	32	6 (1-21)	22 (9-40)	72 (53-8…)

61 Patients at 2 wk

Rule	Total No. of Patients	Best 1-yr Recovery (% of Total): No Recov Veg State	Sev Disab	Mod Dis… Good Rec…
2W Oculocephalic: Normal? No → Any? 3D Motor: Obeys Commands? 3D Eye Opening: Spontaneous? 2W Eye Opening: Improved at Least 2 Grades? No	17	100 (80-100)	0 (0-20)	0 (0-20)
Any? Yes	18	44 (22-69)	44 (22-69)	22 (6-48)
2W Oculocephalic: Normal? Yes	26	4 (0-20)	15 (4-35)	81 (61-9…)

Fig 1.—Rules based on neurological examination that classify patients in hypoxic-ischemic coma in accordance with their best functional state within first year. *Figures in parentheses represent the 95% confidence intervals for percentages given immediately above.* Abbreviations used in describing outcomes follow: recov indicates recovery; veg, vegetative; disab, disability; sev, severe; and mod, moderate. The following abbreviations are used in describing neurological signs: spont eye movt indicates spontaneous eye movements; and rov conj, *roving conjugate. Initial examination (top left) was obtained within six* hours of onset of coma in 55% of patients and within 12 hours in 84%. Modifiers INIT, 1D, 3D, 1W, and 2W refer to initial, 0- to 1-day, 2- to 3-day, 4- to 7-day, and 8- to 14-day examinations, respectively. If no data are available, response to relevant question is considered to be "no." Where changes in clinical signs are utilized (top right and bottom), difference is between best response of previous time interval and best response of current interval. Physicians applying these rules must exercise caution when residual anesthetics or depressant drugs (including anticonvulsants) are present, should wait until the end of each time interval to make certain that the best clinical response has been observed, and should not use any rules that require responses that are unavailable for a specific patient.

esthetic accidents being the most common. Roughly equal numbers of patients sustained their hypoxic-ischemic insults in an intensive care setting (53, or 26%), general hospital ward (66, or 31%), or out of hospital (72, or 34%). Nineteen ~~patients~~ (9%) failed to awaken after operative procedures. The population consisted of 108 men and 82 women. The median age was 61 years, with all but 16 older than 30 years of age.

Outcome

Most patients who were destined to awaken and do well did so within a short time. By three days after the onset of coma, 25 patients regained consciousness (with cognitive awareness); 19 of these went on to become independent. After two weeks, the number of conscious patients rose only to 28, of whom 21 recovered independence. Many patients reached a vegetative state rapidly; among such patients, within the first d… only 11 became independent su… quently, and among 33 patients ve… tative at one week, only th… regained independence. The num… of comatose patients dropped rapi… after the insult, with 106 still com… tose after one day, 57 at three day… and 17 at one week, of whom only o… ever regained consciousness.

Improvement after one month w…

ure. None of the 15 patients vegetative at one month ever regained independent function, and only three of 16 patients severely disabled at one month did so. None of these three patients had early clinical signs that would have placed them in the group with the poorest prognosis.

The death rate associated with hypoxic-ischemic coma of six or more hours was high: 42 (20%) died within the first 24 hours, 86 (41%) by the end of three days, and 134 (64%) by the end of the first week. Only 19 (10%) survived one year after the onset of coma. Of the 191 patients who died within a year, most (105, or 55%) succumbed to nonneurological problems; 67 (35%) died of neurological causes, and in 18 (10%), no exact determination of the cause of death was possible. Because of the frequency with which nonneurological factors interfered with full recovery, we analyzed our data to predict the best functional neurological state attained within the first year.

In terms of best outcome, over three fourths of the patients either died without opening their eyes (121, or 57%) or, although they opened their eyes, showed no evidence of cognitive function and were classified as vegetative (43, or 20%). Among the remaining patients who regained consciousness, 20 (10%) remained severely disabled and dependent on others for routine needs. Six patients (3%) achieved a moderate disability, and 20 (10%) achieved a good recovery; these 26 patients are grouped together as having recovered independent function. This is a useful distinction because Maas et al[7] found little interobserver variability in differentiating dependent from independent function.

Factors Not Related to Recovery

None of the following factors significantly ($P \geq .05$ by χ^2 testing with appropriate degrees of freedom) influenced the degree of recovery: patient age or sex, the site of the initial insult, the cause of coma, or the presence of postanoxic seizures (Table 1).

Individual Neurological Signs Related to Recovery

The absence of certain brainstem reflexes at the initial examination identified patients with little or no likelihood of meaningful recovery (Table 2). None of 52 patients lacking pupillary reflexes at the initial examination ever became independent, and only three regained consciousness. Three (4%) of 71 patients lacking corneal reflexes when first examined attained a good recovery within a year, but no patient who lacked corneal reflexes on or after the first day regained consciousness.

Table 3.—*Rules That Identify Patients With Poor or Good Prognosis**

Time After Cardiac Arrest	Clinical Sign
Patients With Virtually No Chance of Regaining Independence	
Initial examination	No pupillary light reflex
1 day	1-Day motor response no better than flexor and 1-day spontaneous eye movements neither orienting nor roving conjugate
3 days	3-Day motor response no better than flexor
1 wk	1-wk motor response not obeying commands and initial spontaneous eye movements neither orienting nor roving conjugate and 3-day eye opening not spontaneous
2 wk	2-wk oculocephalic response not normal and 3-day motor response not obeying commands and 3-day eye opening not spontaneous and 2-wk eye opening not improved at least two grades
Patients With Best Chance of Regaining Independence	
Initial examination	Pupillary light reflexes present and motor response flexor or extensor and spontaneous eye movements roving conjugate or orienting
1 day	1-Day motor response withdrawal or better and 1-day eye opening improved at least 2 grades
3 days	3-Day motor response withdrawal or better and 3-day spontaneous eye movements normal
1 wk	1-wk motor response obeying commands
2 wk	2-wk oculocephalic response normal

*This table summarizes the rules on the top and bottom lines of Fig 1.

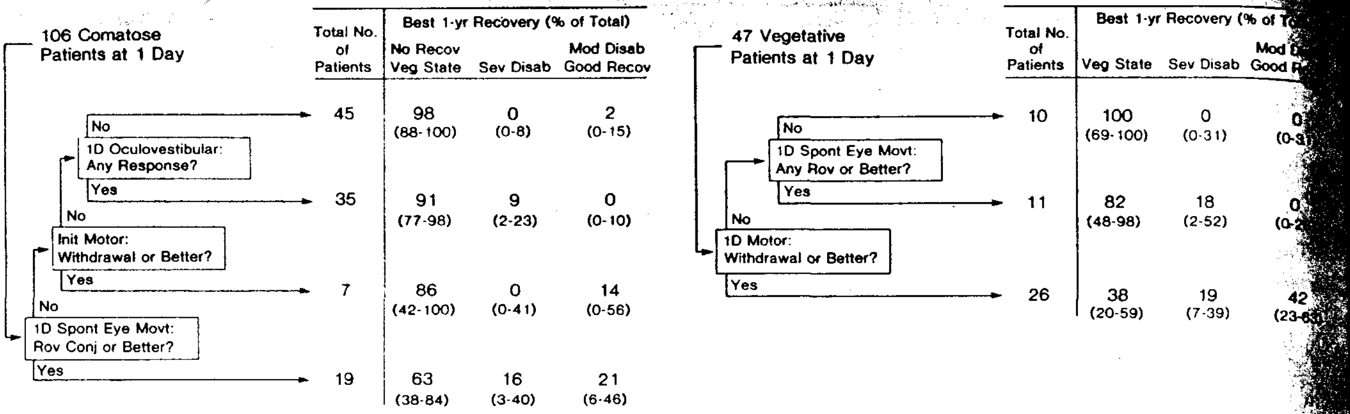
Although the pattern of motor responses eventually correlated with recovery, neither their initial absence nor the presence of extensor or flexor posturing ruled out recovery. After three days, however, absent or posturing motor responses were incompatible with future independence. Five patients who had motor responses poorer than withdrawal at three days and four patients at seven days regained consciousness, but all remained severely disabled.

Certain early signs were associated with relatively good chances of recovery. At the initial examination, the most favorable sign was incomprehensible speech (moaning), but this was rare. At one day, each of the following signs was associated with at least a 50% chance of regaining independence: confused or inappropriate speech, orienting spontaneous eye movements, normal oculocephalic or oculovestibular responses, and obedience to commands. Information on skeletal muscle tone and deep-tendon reflexes has been omitted because of concern about interobserver variability.

Multivariate Analysis of Prognostic Variables

Reliance on individual clinical signs can be potentially misleading. For example, the likely outcome of a patient with intact pupillary light reflexes but absent corneal reflexes cannot be deduced from inspection of Table 2. We applied several multivariate techniques to the data and found that recursive partitioning[8] was most useful in segregating patients into different groups on the basis of prognosis.

Figure 1 illustrates the classification rules generated by recursive partitioning for the 210 patients at different times after the onset of coma. Figure 1 (top left) shows, for example, that 52 patients at initial examination could be identified on the basis of absent pupillary light reflexes as being in the poorest prognosis group and that none of these ever achieved independent function; the 95% confidence interval for this result is 0% to 7%. By contrast, 27 patients had preserved pupillary light reflexes, motor responses that were extensor or better, and roving conjugate or orienting spontaneous eye movements. Eleven (41%) regained independent function; the confidence interval for this figure is 22% to 61%. Figure 1 (top right, center left, center right, and bottom) shows correspond-



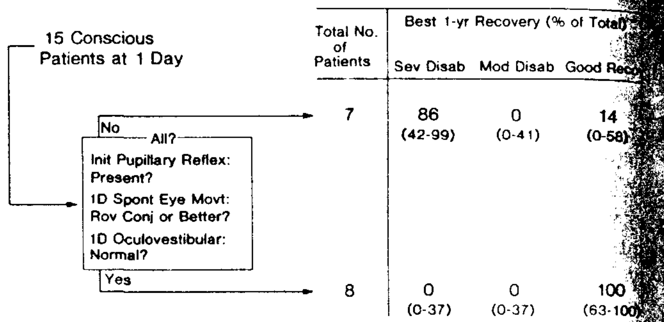


Fig 2.—Rules based on neurological examination that classify patients surviving one day after hypoxic-ischemic coma with different levels of consciousness in accordance with their best functional state within first year. Abbreviations are as described for Fig 1. Operational definitions of levels of consciousness follow: coma (top left)—no eye opening regardless of stimulus, no comprehensible words, and commands not obeyed; vegetative state (top right)—eye opening spontaneously, to noise, or to pain, but no comprehensible words, and commands not obeyed; and consciousness (bottom)—comprehensible words or commands obeyed. These definitions, which were adopted on detailed examination of vegetative patients,[11] were considered an improvement over those used at time study was begun and in previous publications[1,2] because they distinguish coma from vegetative state.

ing rules for patients who survived 1, 3, 7, and 14 days. Validity testing on split samples showed the rules to be stable. For example, at the initial examination, only one patient who did well was mistakenly classified in the group with poorest prognosis, an error rate well within the confidence interval of 0% to 7%.

The algorithms of Fig 1 permit several conclusions. Inspection of the clinical signs actually utilized in the classification rules shows that the most predictive variable at the initial examination was the pupillary light reflex, the sign shown by both Teasdale et al[8] and van den Berge et al[9] to have the least interobserver variability. Thereafter, the motor response became the variable having the greatest predictive power. Other powerful clinical observations that contributed empirically to useful rules were pupillary light reactions, spontaneous eye movements, eye opening, and oculocephalic response. The verbal response, a key component in the Glasgow Coma Scale,[10] never appeared as an important predictor of outcome.

Recursive partitioning identified at each time a portion of surviving patients as having very little chance of recovering independent function, and only one patient was incorrectly assigned to these groups with the poorest prognosis. That misclassification occurred at day 1 and concerned a young woman with underlying renal failure who suffered a cardiac arrest. Her early misclassification reflected poor clinical responses probably caused by renal failure. Although the clinician might weigh the mitigating influence of this metabolic insult, the computer program did not. Otherwise, the rules identified at each time a substantial proportion of survivors, none of whom ever recovered (25% at admission, 55% at one day, 56% at three days, 34% at seven days, and 28% at 14 days). These rules are summarized in Table 3.

The rules also identified early a sizable subpopulation of patients who did well after hypoxic-ischemic coma (Table 3). For example, the classification rules for all 168 survivors at one day placed 123 into either the poorest prognosis group (only one of 93 patients regaining independence) or the best prognosis group (with 21 of 30 patients regaining independent function). The overall proportion of survivors assigned the best prognosis rose gradually from 13% at admission, to 18% at one day, 21% at three days, 42% at seven days, and 43% at 14 days.

Likely Outcome Among Surviving Patients With Different Levels of Consciousness

The ease of applying recursive partitioning permitted us to examine specific subpopulations. For example, patients who survived various intervals after the onset of coma were subcategorized as comatose, vegetative, or conscious. Figure 2 illustrates the classification rules for patients who survived one day; other figures (not shown but available on request from the authors) were generated for patients with different levels of sensorium at later intervals after the onset of coma. Over one third of patients vegetative at one day could be classified as likely to remain vegetative on the basis of absent or posturing motor responses (Fig 2, top right). Among patients conscious at one day, recursive partitioning differentiated surprisingly well between those who were left with severe disability and those who regained independent function (Fig 2, bottom). The persistence of coma at seven days precluded recovery of independence. This was not true, however, for the vegetative state, where even after two weeks, two of 21 patients subsequently did well; these two patients were part of a subgroup of ten having motor responses that were withdrawal or better. Persistence of the vegetative state to one month ruled out recovery of independent function.

COMMENT

Coma describes only one dimension of severe hypoxic-ischemic brain dysfunction, and comatose patients will necessarily differ with respect to specific clinical variables and outcomes. This study shows that careful analysis of early clinical information in such patients distinguishes, in many instances, between a good and a poor prognosis. In general, specific evidence of brainstem dysfunction or of multifocal damage implies a grave prognosis.[2]

Comparison With Other Studies

Several groups[12-21] have attempted to predict early after cardiac arrest which patients will do well and which will be left with severe disabilities, but, to our knowledge, no comprehensive multivariate approach has yet been published. Bell and Hodgson[12] reported the unfavorable prognosis associated with prolonged postarrest coma and noted particularly the rarity of full recovery after coma lasting three days. Our data agree. Only two of 57 patients in whom eyes-closed coma lasted for three days regained independent function, and they could be identified by the presence of motor responses that were withdrawal or better; no patient who remained in coma at seven or 14 days ever became independent; and no patient vegetative at one month even regained consciousness. Willoughby and Leach[13] reported that nonpurposeful motor responses even one hour after a cardiac arrest were incompatible with intellectual recovery. Here our results contradict, because even after one day, three patients with motor responses poorer than withdrawal became independent.

Snyder et al[14-17] considered neurological factors associated with recovery after cardiopulmonary arrest in 63 consecutive patients. Only 41 patients with their lowest three levels of consciousness[14] at admission were comparable with our population of 210. As in the present study, they reported that recovery of independent function was associated with the pattern of the motor response[15] but not with seizures or myoclonus[16]; increased numbers of brainstem reflex abnormalities were associated with reduced chances for survival,[17] a finding with which we agree.

Earnest et al reported on early[18] and late[19] outcome from out-of-hospital cardiac arrest in 117 patients. Although they analyzed initial observations of only four neurological signs, they did observe that absence of pupillary light reactions, oculocephalic reflexes, or purposeful motor responses to pain each reduced chances of recovery.[18] They were unable to correlate admission neurological signs to late outcome (mean of 44 months)[19] but did record a failure to regain independence in all nine patients who were unconscious or required total care at discharge. In this regard, our early clinical criteria would not have assigned the poorest prognosis to either of two patients reported elsewhere as regaining consciousness after a prolonged vegetative state.[22,23]

Longstreth et al[20] utilized clinical information from patient charts collected over a ten-year period in a retrospective analysis of patients in coma after out-of-hospital cardiac arrest. Consequently, 40% to 55% of patients were missing one of the five clinical variables evaluated. They concentrated almost entirely on whether a patient awakened after coma rather than on the ultimate quality of life. Using their decision rule (their Table 4), 16 (16%) of their 98 patients predicted at one day as doing poorly actually did well (awakened). Four of them (4%; 95% confidence interval, 1% to 10%) regained independent function. If their "cutoff" is shifted from four to one, their rule still makes one error in 31 patients. The study thus suffers from several faults, especially a relatively high error rate in identifying poor-prognosis patients.

Advantages of Recursive Partitioning

Despite the general agreement of our findings with several earlier studies on cardiac arrest, to the best of our knowledge, the presentation of classification rules in our study is unique, as is their generation with a computerized recursive partitioning program.[5] The algorithm used to generate our rules can, if desired, maximize overall accuracy, but it can also be used to minimize certain costly errors of prediction. This capability enables the investigator to consider in humane terms the effect of acting on incorrect predictions. The program, moreover, does not require the variables to be restricted to interval scores; it can analyze variables recorded on categorical or ordinal scales as commonly encountered in a clinical setting. Most important, as opposed to techniques based on numerical scores, which often require a degree of mathematical manipulation, these rules can be easily integrated into the clinician's customary approach to management decisions because of their presentation in the form of decision trees.

Usefulness of Prognostic Information

The rules presented in this article should be applied with caution for several reasons. Although stability of recursive partitioning was tested on split samples of the data, the rules have not yet been tested prospectively. Depending on the relative costs assigned to misclassification errors, recursive partitioning can produce different rules.[5] One must also be careful in applying information obtained from one group of patients to another lest unrecognized bias be a factor in selection. Our patients had a high incidence of medical complications, with over half dying of nonneurological causes. Thus, our analysis concentrated on best outcome rather than on actual outcome. We have presented 95% confidence intervals assuming, as is customary, that our results were the best estimates of the "true" values. The ultimately conservative approach would assume that an observed ratio of zero in 100 patients represented not the true value but the lower extreme of a 95% confidence interval, with an upper limit as high as seven in 100. From an entirely different perspective, one should be cautious in interpreting absent brainstem responses in the first few hours after cardiac arrest. Despite the good correlation with outcome noted in our patients, the clinician must rule out the possible confounding effect of preexisting abnormalities or drugs (eg, anticholinergics on pupillary reactions, depressants on corneal reflexes, or paralytic agents on motor responses).

The ability to predict with assurance that even half of a population of patients in coma would have good or poor outcome and to act on these predictions can offer a major benefit to personal physicians, patients, patients' families, and health planners. One might ask why, if 134 of 210 patients died within a week, prediction even matters. Perhaps the best answer is that if one waits until patients either awaken or die, their medical condition will have stabilized. The result can be prolonged survival for vegetative patients who might otherwise have died. For most of us, this is an undesirable state. Many lay persons fear permanently incapacitating neurological disability: "Whatever you do, doctor, don't leave me a vegetable or a permanent burden on my family." Even for those who regain mental competence, being resuscitated seems to be a harrowing experience: 42% in one study[24] stated that they wished not to be similarly resuscitated in the future. The ability to predict outcome could also spare families the emotional and financial burden of prolonged care of patients with hopeless prognoses. The impact on allocation of scarce health resources can be appreciated from consideration of the potential effect of confidently identifying poor-prognosis patients. At one day, we identified as having a poor prognosis 93 patients (Fig 1, top right), all but one of whom failed to regain independence and 88 of whom failed even to recover consciousness. Continued support of these 88 patients involved a total of over 500 hospital days, frequently in intensive care units. Not only was this useless terminal care costly (over $250,000) but the intensive care beds could have been used to treat patients with greater chances of recovery. These results contrast, incidentally, with those of Liberthson et al[21] a decade ago, who concluded that 41% of patients who died did so within the first day, and 75% within the first week. Among our patients who died, only 23% did so within the first day, and half within the first week. Early identification of patients likely to remain vegetative after cardiac arrest could reduce the suffering of families and limit encroachment on the medical commons.

Even for patients who want every possible effort made, accurate prognosis can be valuable in choosing management. Recent evidence[25,26] suggests that neuropathological abnormalities can continue to evolve for hours or days after global brain ischemia. In such desperate cases, delayed treatment might still limit the eventual extent of ischemic brain damage. Identification of poor- and good-prognosis patients in the early hours or days after an arrest will facilitate the design and interpretation of appropriately stratified treatment trials.

The care of patients after cardiopulmonary arrest poses serious questions in terms of allocation of resources and humane care for both patients and their families. Implicit estimations of prognosis are involved in the management of all seriously ill patients, but in the absence of well-established facts, such predictions usually amount to little more than informed guess work. Judicious application of the present data may provide a more rational approach for managing patients who sustain hypoxic-ischemic coma.

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