Endoscopic Third Ventriculostomy in the Treatment of Childhood Hydrocephalus

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Objective To develop a model to predict the probability of endoscopic third ventriculostomy (ETV) success in the treatment for hydrocephalus on the basis of a child's individual characteristics.

Study design We analyzed 618 ETVs performed consecutively on children at 12 international institutions to identify predictors of ETV success at 6 months. A multivariable logistic regression model was developed on 70% of the dataset (training set) and validated on 30% of the dataset (validation set).

Results In the training set, 305/455 ETVs (67.0%) were successful. The regression model (containing patient age, cause of hydrocephalus, and previous cerebrospinal fluid shunt) demonstrated good fit (Hosmer-Lemeshow, $P = .78$) and discrimination (C statistic = 0.70). In the validation set, 105/163 ETVs (64.4%) were successful and the model maintained good fit (Hosmer-Lemeshow, $P = .45$), discrimination (C statistic = 0.68), and calibration (calibration slope = 0.88). A simplified ETV Success Score was devised that closely approximates the predicted probability of ETV success.

Conclusions Children most likely to succeed with ETV can now be accurately identified and spared the long-term complications of CSF shunting. *(J Pediatr 2009;155:254-9)*.

Hydrocephalus has many different causes and, although quite common in developed countries (0.7 per 1000 live births),[1] it is even more so in many developing countries.[2] Until recently, hydrocephalus could only be treated by insertion of a cerebrospinal fluid (CSF) shunt. This is, however, associated with long-term complications including infection, obstruction, and over-drainage of CSF, each requiring more surgery.[3] In the United States, CSF shunting and its complications account for 1.8% of all pediatric hospital days and 3.1% of all pediatric hospital charges (nearly $2 billion annually[4]). The use of endoscopy to create an internal CSF diversion through the floor of the third ventricle—an endoscopic third ventriculostomy (ETV)—has become an important alternative to CSF shunting for children with hydrocephalus.[5] This procedure allows the ventricular CSF to bypass anatomic obstructions and directly enter, and be absorbed through, the subarachnoid space via the hole created in the floor of the third ventricle, without the need for any implanted foreign device. This is the first major revolution in hydrocephalus treatment since the invention of the CSF shunt more than 50 years ago.[6] When successful, ETV provides a simple and durable treatment that avoids many of the long-term complications seen with CSF shunting. This is a particularly attractive option in developing countries, where the economic cost of the CSF shunt itself can be prohibitive for many families, and complications, such as shunt infection, are less likely to be managed in a timely fashion.[2,7,8] The problem, however, is that more than 30% of children will not respond to ETV and will then require a CSF shunt.[9] The early failure rate is even higher within many patient subgroups, exposing them to an unnecessarily high risk of repeat surgery. There remains uncertainty, however, over what combination of patient characteristics yields the highest chance of success with ETV. Our goal was to analyze ETV success in a large cohort of children, from a collaborative multicenter international network, and develop and validate a model to predict successful ETV. This would address the shortcomings of the current literature and provide a clinically useful scoring system that could be used to optimally select children for ETV, thus avoiding the long-term complications and healthcare costs associated with CSF shunting.

Methods

We collected data from all ETV procedures on patients 19 years or younger performed consecutively at each of 12 pediatric institutions in Canada, Israel, and the United Kingdom (**Appendix**; available at www.jpeds.com). The period of

CSF	Cerebrospinal fluid
ETV	Endoscopic third ventriculostomy

From the Hospital for Sick Children, Toronto, Ontario, Canada (A.K., J.D.) the Royal Liverpool Children's Hospital, Liverpool (C.M.), and the Birmingham Children's Hospital, Birmingham (S.S.) United Kingdom and the Dana Children's Hospital, Tel-Aviv Medical Center, Tel Aviv, Israel (J.R., S.C.)

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data collection varied by center, ranging as far back as 1989 to as recently as 2006, although the vast majority of cases (95.4%) were performed since 1995. All patients had symptomatic, high-pressure hydrocephalus. Some had previous treatment with a CSF shunt and presented with a shunt malfunction for which ETV was performed. Only patients who had at least 6 months follow-up were included. In cases of multiple ETV procedures on the same patient, only data from the first procedure were included. Data from 5 centers (358 patients) were collected entirely prospectively; the remaining centers (260 patients) collected data retrospectively. Patients were identified through either prospectively-maintained dedicated databases or, in the case of retrospective data collection, from a review of both operative and admission databases maintained by the individual hospitals. Data from some of these patients have appeared in previous publications.[9-17] All data were anonymized, and data collection adhered to local research ethics protocols.

Successful ETV was defined as the absence of ETV failure within 6 months. Failure of ETV was defined as any subsequent surgical procedure for definitive CSF diversion or death related to hydrocephalus management within 6 months of the index procedure. Early ETV failure, within 6 months, is far more common than late failure and indicates that a patient's underlying CSF physiology was not favorable for ETV. In clinical practice, these are the patients who are most useful to identify. The status, at 6 months after treatment, of all patients in this cohort was known definitively on the basis of their direct contact with the treating center.

Statistical analysis

A survival curve was calculated by use of the Kaplan-Meier method. The length of follow-up after surgery was calculated on the basis of the last date at which the patient was seen at the treating center and known to be well.

We randomly divided the dataset into a training set (roughly 70% of the sample) for model development and a validation set (roughly 30% of the sample) for testing the model's fit, discrimination, and calibration. The variables considered for the model were factors that we believed beforehand would be the most important predictors of successful ETV on the basis of clinical reasoning and previous literature:[9,18-21] age at ETV, cause of hydrocephalus, presence of a previous CSF shunt, and center with high operative volume (>100 ETV cases performed). Age was categorized as <1 month, 1 to <6 months, 6 to <12 months, 1 to <10 years, and ≥10 years. These cut-offs were based on a preliminary analysis of ETV success within various age ranges. Cause of hydrocephalus was categorized as aqueductal stenosis, post-infectious, myelomeningocele, post-intraventricular hemorrhage, tectal tumor, other brain tumor (non-tectal), and other. Cause was defined by the treating surgeon on the basis of the patient's history and preoperative imaging. For the retrospective cases, these were re-reviewed to ensure accuracy.

We built a multivariable logistic regression model using a backward elimination process beginning with all 4 independent variables. Successful ETV at 6 months was the dependent variable. A variable was removed if its P value was >0.15. A more stringent cutoff was not used to avoid eliminating potentially important predictor variables. Multicollinearity was assessed with variance inflation factors, which is a measure of the degree to which a single predictor variable can be expressed as a linear combination of the remaining predictor variables; values greater than 10 are cause for concern.[22]

We tested the adequacy of the final model in several ways. We compared the predicted probability of ETV success between those who did and did not achieve a successful ETV with unpaired t test. Goodness-of-fit was tested with the Hosmer-Lemeshow statistic used with the cases divided by decile cut-points on the basis of predicted probability of successful ETV. This statistic compares the number of observed outcomes to the number predicted within each decile; a significant P value rejects the null hypothesis that the model fits the data well.[23] Model discrimination was assessed by determining the area under the receiver operating characteristic curve, which is equivalent to the C statistic.[24] This statistic can be interpreted as the probability that the model predicts a higher chance for ETV success in an actual successful case compared with a failed case; a value closer to 1.0 represents better model discrimination.[25]

To test the validity of the model, we recalculated these statistics using data from the validation set, with the parameters estimated in the training set. Optimism was defined as the difference in the C statistic between the training set and the validation set. A calibration slope was also calculated on the validation set (values closer to 1.0 represent better model calibration).[26] The calibration slope is, by definition, unity in the training set.[27]

We tested model performance in several subgroup analyses using C statistic. We compared cases from the earlier half of our series with the latter half, the first 30 cases done at a center with their more recent cases, different countries, high-volume centers (>100 cases) versus low-volume centers (≤100 cases), and prospectively- versus retrospectively-collected data. All analyses were done with SPSS Advanced Statistics 13.0 (SPSS Inc., Chicago, Illinois).

Results

The characteristics of the 618 patients are listed in **Table I**. There were no deaths at 6 months. The proportion of successful ETVs was similar for data that were collected prospectively versus retrospectively (0.66 for both, $P = 0.9$, χ^2) and for cases from the early half of the series versus those from the latter half (0.65 vs 0.68, $P = .5$, χ^2). The long-term survival curve for ETV success is shown in **Figure 1** (available at www.jpeds.com). For the 410 patients who had a successful ETV at 6 months, the 3-year and 5-year ETV success rate was 87% and 83%, respectively, with the Kaplan-Meier method.

Model development

With the training set (n = 455), the final logistic regression model contained 3 variables: age ($P < .001$), cause of

Table I. Patients' characteristics

Variable	Total Sample	Training Set	Validation Set
Number of patients	618	455	163
Calendar year in which ETV was performed			
1989 to 1994	28 (4.5%)	19 (4.2%)	9 (5.5%)
1995 to 1999	277 (44.8%)	200 (44.0%)	77 (47.2%)
2000 to 2006	313 (50.6%)	236 (51.9%)	77 (47.2%)
Age at ETV			
<1 month	39 (6.3%)	30 (6.6%)	9 (5.5%)
1 to <6 months	90 (14.6%)	69 (15.2%)	21 (12.9%)
6 to <12 months	49 (7.9%)	39 (8.6%)	10 (6.1%)
1 to <10 years	255 (41.3%)	181 (39.8%)	74 (45.4%)
≥10 years	185 (29.9%)	136 (29.9%)	49 (30.1%)
Cause of hydrocephalus			
Stenosis of cerebral aqueduct	194 (31.4%)	133 (29.2%)	61 (37.4%)
Other brain tumor (non-tectal)	120 (19.4%)	88 (19.3%)	32 (19.6%)
Post-intraventricular hemorrhage	80 (12.9%)	64 (14.1%)	16 (9.8%)
Tumor of the midbrain tectum	62 (10.0%)	45 (9.9%)	17 (10.4%)
Myelomeningocele	38 (6.1%)	28 (6.2%)	10 (6.1%)
Post-infectious	22 (3.6%)	15 (3.3%)	7 (4.3%)
Other	102 (16.5%)	82 (18.0%)	20 (12.3%)
Previous CSF shunt in place	156 (25.2%)	116 (25.5%)	40 (24.5%)
Patient treated at a high operative volume center (>100 ETV cases performed)	354 (57.3%)	260 (57.1%)	94 (57.7%)
Patients with prospectively-collected data	358 (57.9%)	266 (58.5%)	92 (56.4%)
Successful ETV at 6 months	410 (66.3%)	305 (67.0%)	105 (64.4%)

hydrocephalus ($P = .07$), and previous shunt ($P = .03$). High operative volume center was eliminated ($P = .44$). Variance inflation factors were all <2, suggesting that multicollinearity was not a concern. Parameter estimates (unstandardized regression coefficients) and odds ratios are shown in Table II.

This model performed well in the training set. The mean predicted probability of ETV success in those who were successful (n = 305) was significantly higher than in those who were not (n = 150) (mean [SD]: 0.71 [0.14] vs 0.59 [0.17], $P < .001$). The Hosmer-Lemeshow statistic was not significant ($P = .78$), suggesting adequate model fit. The C statistic was 0.70, suggesting good model discrimination.

Model validation

With the parameter estimates derived from the training set, the predicted probability of ETV success was calculated for each patient in the validation set (n = 163). The model maintained its predictive properties in the validation set. The mean predicted probability of ETV success in those who were successful (n = 105) was significantly higher than in those who were not (n = 58) (mean [SD]: 0.72 [0.14] vs. 0.62 [0.17], $P < .001$). The Hosmer-Lemeshow statistic was not significant ($P = .45$). The C statistic was 0.68, indicating minimal optimism (0.02) compared with the training set results. The calibration slope was 0.88, indicating good model calibration.

On the basis of the predicted probability of ETV success, we divided our sample into strata that would be meaningful in clinical decision-making. Table III (available at www.jpeds.com) shows the mean predicted probability of ETV success and the actual proportion of ETV success observed within these 3 strata.

ETV SUCCESS SCORE

= Age Score + Etiology Score + Previous Shunt Score
≈ percentage probability of ETV success

SCORE	AGE ↓	+ ETIOLOGY ↓	+ PREVIOUS SHUNT ↓
0	<1 MONTH	POST-INFECTIOUS	PREVIOUS SHUNT
10	1 MONTH TO <6 MONTHS		NO PREVIOUS SHUNT
20		MYELOMENINGOCELE INTRA-VENTRICULAR HEMORRHAGE NON-TECTAL BRAIN TUMOR	
30	6 MONTHS TO <1 YEAR	AQUEDUCTAL STENOSIS TECTAL TUMOR OTHER ETIOLOGY	
40	1 YEAR TO <10 YEARS		
50	≥10 YEARS		

Figure 2. The ETV Success Score is easily calculated and closely approximates the percentage probability of successful ETV.

Subgroup analyses

The model performed well across all subgroups (C statistic in parentheses): cases from the earlier half of our series (0.68) and the latter half (0.70); for the first 30 cases done at a center and their more recent cases (0.69 for both); for each of the 3 countries (Canada 0.68, Israel 0.74, United Kingdom 0.70); for patients from high-volume centers (0.70) and low-volume centers (0.69); and for prospectively-collected data (0.68) and retrospectively-collected data (0.72).

We developed a simplified scoring system (ETV success score) that can be used easily by clinicians in the field (Figure 2). The ETV Success Score very closely approximated the predicted probability of ETV success (Figure 3) and had a C statistic of 0.69 in the training set and 0.67 in the validation set.

Discussion

Our study has shown that age, cause, and presence of a previous CSF shunt are each important and independent factors in predicting success of ETV. Age was by far the strongest predictor, with infants, especially those younger than 6 months, having the lowest predicted ETV success,

Table II. Logistic regression model derived from the training set

Variable	Parameter estimate	Odds ratio for successful ETV (95% confidence interval)	Number of successful ETVs
Age at ETV			
<1 month	−2.275	0.10 (0.04 - 0.26)	13 (43.3%)
1 to <6 months	−1.960	0.14 (0.07 - 0.30)	31 (44.9%)
6 to <12 months	−1.012	0.36 (0.16 - 0.84)	25 (64.1%)
1 to <10 years	−0.750	0.47 (0.27 - 0.84)	125 (69.1%)
≥10 years	Reference	Reference	111 (81.6%)
Cause of hydrocephalus			
stenosis of cerebral aqueduct	0.283	1.33 (0.69 - 2.55)	92 (69.2%)
other brain tumor (non-tectal)	−0.558	0.57 (0.29 - 1.15)	59 (67.0%)
post-intraventricular hemorrhage	−0.426	0.65 (0.32 - 1.35)	35 (54.7%)
tumor of the midbrain tectum	0.177	1.19 (0.45 - 3.14)	37 (82.2%)
myelomeningocele	−0.104	0.90 (0.33-2.46)	18 (64.3%)
post-infectious	−1.092	0.34 (0.10 - 1.13)	6 (40.0%)
other	Reference	Reference	58 (70.7%)
Previous CSF shunt in place	−0.580	0.56 (0.33 - 0.95)	75 (64.7%)

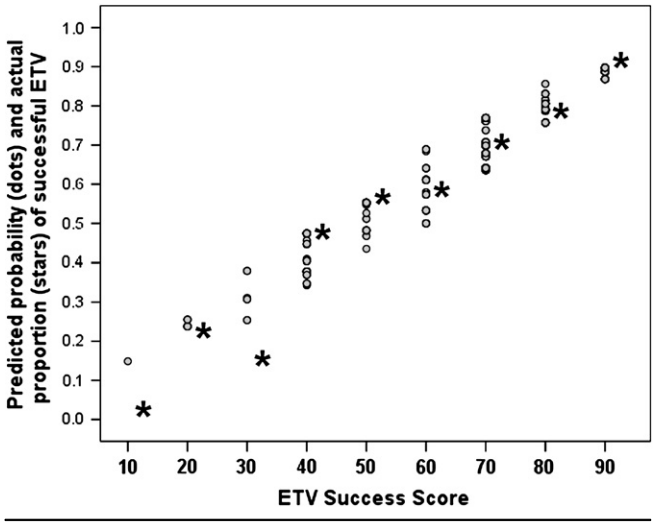

Figure 3. Graph shows the relationship of ETV Success Score (*horizontal axis*) with predicted probability of ETV success (*dots*) and actual proportion of ETV success (*stars*). The number of patients within each level of ETV Success Score was as follow: 10 (1 patient), 20 (10 patients), 30 (8 patients), 40 (67 patients), 50 (59 patients), 60 (50 patients), 70 (172 patients), 80 (177 patients), and 90 (74 patients). There were only a small number of patients in the lower ETV Success Score range, which explains some of the discrepancy between predicted probability of success and actual proportion of success.

with progressively higher success seen as a child ages. The effect of cause and presence of a previous CSF shunt appeared to be less in magnitude than age. On the basis of this, we developed a prediction model that displayed good fit, calibration and discrimination, on par with the performance of predictive models for other clinical conditions.[28] Using the simplified ETV Success Score, physicians can now predict success of ETV for a given patient, and, by weighing this against the option of CSF shunting, they can make a much more informed decision about hydrocephalus treatment.

Open third ventriculostomy, requiring a craniotomy, was first described by Dandy nearly 90 years ago but was associated with significant morbidity.[29] The advent of recent endoscopic techniques has now rendered this procedure safe, and it has the potential to revolutionize the management of thousands of children by eliminating the need for CSF shunting and its long-term complications. These complications are a major burden to the healthcare system[4] and can adversely impact the child's quality of life.[9,30-33] It has been very difficult, however, to predict which children will benefit from ETV, rather than fail and go on to need repeat surgery for CSF shunt insertion, thus exposing them to more surgical risk. The previous ETV literature has provided little help in making accurate predictions. Although some studies have proclaimed that patient age is the exclusive predictor of ETV success,[34,35] others have suggested that it is actually the cause of hydrocephalus that is the primary determinant, especially in infants.[19,36] Some researchers have used both preoperative and intraoperative factors to try to determine ETV success.[37] With few exceptions,[9,20] prior analyses have largely been single-center efforts with limited sample size.[38] They have occasionally provided relative risk estimates for certain patient factors, but without a simple and validated means of taking into account multiple factors to calculate the expected probability of success for a given child. Our analysis overcame these limitations by producing a predictive model on the basis of the largest sample size currently in the literature, collected from multiple international centers, and validated with rigorous statistical technique.

Although our model predicts the probability of early ETV success only, our data convincingly show that ETV is a very durable long-term treatment for hydrocephalus: early ETV success portends very good long-term success (83% at 5 years). This is in sharp contrast to CSF shunts, which experience an unabated fall-off in success year by year, because of delayed mechanical malfunctions. So, although the early failure rate for CSF shunting (about 30%-40%)[30] is similar to ETV, by 4 years of follow-up, the overall failure rate is about 59% for CSF shunts[39] compared with 43% for our ETV sample. Therefore selective use of ETV would greatly reduce the number of repeat surgeries over the long term compared with CSF shunting, as long as we can identify those patients with a high chance of early success. Our model now enables us to identify these patients.

With the ETV Success Score, one would, for example, likely recommend ETV for a 15-year-old with newly diagnosed aqueductal stenosis (ETV Success Score = 90) over a 3-month-old with hydrocephalus caused by intraventricular hemorrhage (ETV Success Score = 40). In between these extremes are more equivocal situations like infants with

aqueductal stenosis (eg, for those 1 to 6 months old, the ETV Success Score = 50). This decision is more difficult, and, in fact, this particular group of infants is the subject of an on-going randomized trial (the International Infant Hydrocephalus Study).[40]

We recognize several limitations in our study. Our sample was collected over a lengthy period of time, from very diverse geographical areas, and from centers with varying operative volume. Although the ETV operative technique itself remained consistent throughout our series, there were some minor technological equipment changes and gained surgical experience since the earliest patients were treated. A high operative volume center was tested as a variable but was not significant. There may be some inherent differences in practice pattern within different countries, for example, varying standards for selection of patients for ETV, different thresholds for considering ETV failure, and different data collection (retrospective vs prospective). We did not include country as a variable in the model because we did not want to limit the use of this model to just the 3 countries involved. Within each of these different subgroups, however, the C statistic of the model proved satisfactory, suggesting that this model is robust, thus strengthening the generalizability of our results. We have not determined whether the predictive properties of this model are preserved for patients in other countries, that is, true external validation. Because a major role for ETV will likely be in the treatment of pediatric hydrocephalus in developing countries, it will be especially important to test external validity in such settings. Some causes within our sample were represented by only very few patients, especially children with myelomeningocele (the incidence of which greatly decreased during much of the period of this study)[41] and postinfectious hydrocephalus. Future work will help validate these results and, perhaps, result in adjustments to the model. ■

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Nutrition and Infection

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This lucid, seminal work triggered research that defined the interactions between infection, nutritional status, and host defenses. Observations in India, Africa, and Central America illustrated that when infected, children ate less, lost more nutrients via urine/stools, and stopped growing. The nutrition/infection relationship was conceptualized as a triangle in which diet and infection defined nutritional status, whereas nutrition affected case fatality from infection. The effects of retinol, ascorbate, tocopherol, iron, zinc, copper, and other essential nutrients on innate and acquired defense systems were soon recognized. The epidemiologic and laboratory work of Scrimshaw and Mata in Central America, Chandra in India, and Beisel and Good in the United States, among other researchers, established the critical role of protein-energy malnutrition in defining cellular and humoral immune function as well as nonspecific defenses. Methodological advances facilitated the study of cellular and molecular mechanisms underlying the initial observations in malnourished infants. Thus, the relationship between nutrition and infection expanded to include immunity and the myriad of effects mediated by tissue and circulating cytokines, setting the stage for new layers of complexity in this interaction. Traditional essential nutrients such as tocopherol, retinol, and zinc serve as key regulators of inflammation; arachidonic and eicosapentaenoic acids derived from essential fatty acids were found to mediate immunity, inflammation, and cell injury responses by generating eicosanoids and docosanoids.

The chain of interactive events presently includes nutrition, infection, immunity, inflammation, and cell injury. We now acknowledge that nutrient excess as well as deficit can interfere with normal host defense systems. When given in excess, α-tocopherol, a key antioxidant required for normal host defenses, interferes with superoxide production, compromising leukocyte-killing capacity and leading to increased mortality from necrotizing enterocolitis in neonates and pneumonia in older age groups. The role of nutrients in modifying pathogens such as viral agents is also recognized; for example, tocopherol and selenium deficiency in the host increases mutation rates of RNA viruses, leading to progressive increases in virulence of the virus and lethality of subjects further along the expansion of the infection.[1,2] More is yet to come in the next 50 years…

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References

1. Solomons NW. Malnutrition and infection: an update. Br J Nutr 2007;98:S5-10.
2. Katona R, Katona-Apte J. The interaction between nutrition and infection. Clin Infect Dis 2005;46:1582-8.

Appendix

Participating centers (number of patients included, method of data collection) and individual participating surgeons and research team members:

Royal Liverpool Children's Hospital, Liverpool, United Kingdom (n = 135, prospective): C. L. Mallucci; Hospital for Sick Children, Toronto, Ontario, Canada (n = 118, prospective): P. B. Dirks, J. M. Drake, A. V. Kulkarni, J. T. Rutka, A. Van der Stoel, I. Veltman; Dana Children's Hospital, Tel Aviv, Israel (n = 101, retrospective): L. Beni-Adani, S. Constantini, J. Roth; Birmingham Children's Hospital, Birmingham, United Kingdom (n = 53, prospective): S. Sgouros; Children's & Women's Health Centre of British Columbia, Vancouver, British Columbia, Canada (n = 44, retrospective): D. D. Cochrane, P. Steinbok; Stollery Children's Hospital, Edmonton, Alberta, Canada (n = 42, prospective): K. Aronyk, V. Mehta; Montreal Children's Hospital, Montreal, Quebec, Canada (n = 39, retrospective): J. Atkinson, J. P. Farmer, J Montes; Alberta Children's Hospital, Calgary, Alberta, Canada (n = 36, retrospective): W. Hader; M. Hamilton; Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada (n = 18, retrospective): M. Vassilyadi, E. Ventureyra; London Health Sciences Centre, London, Ontario, Canada (n = 13, retrospective): A. Ranger; Winnipeg Children's Hospital, Winnipeg, Manitoba, Canada (n = 10, prospective): P. J. McDonald; IWK Health Centre, Halifax, Nova Scotia, Canada (n = 9, retrospective): W. Howes, P. D. McNeely, S. A. Walling.

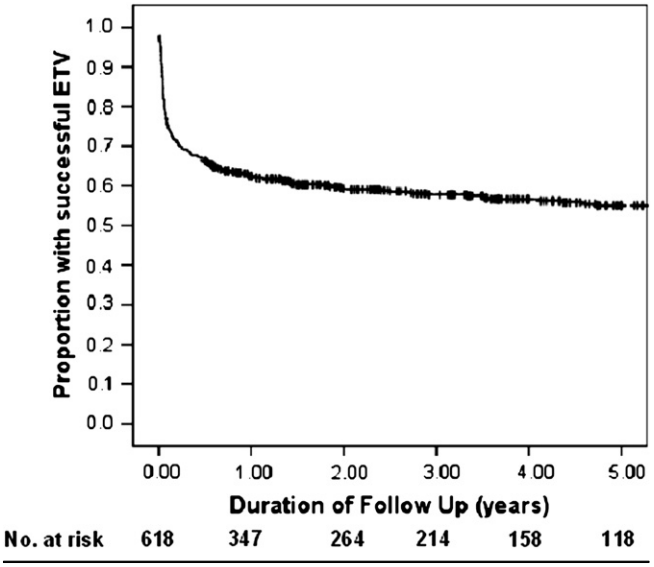

Figure 1. Survival curve showing the long-term success of endoscopic third ventriculostomy (ETV) for all 618 patients. Duration of follow-up is the number of years since surgery.

Table III. Comparison of predicted and actual ETV success stratified by predicted probability of successful ETV

Strata of predicted probability of successful ETV	Training set (n = 455)			Validation set (n = 163)		
	Number of cases	Actual proportion of successful ETV	Mean predicted probability of successful ETV (95% CI)	Number of cases	Actual proportion of successful ETV	Mean predicted probability of successful ETV (95% CI)
High chance of success (≥0.75)	205	0.80	0.81 (0.80-0.82)	77	0.77	0.82 (0.81-0.83)
Moderate chance of success (0.50 to <0.75)	174	0.63	0.62 (0.61-0.63)	65	0.57	0.63 (0.60-0.64)
Low chance of success (<0.50)	76	0.41	0.40 (0.38-0.42)	21	0.43	0.39 (0.35-0.43)