Life Expectancy and Median Survival Time in the Permanent Vegetative State

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The authors studied life expectancy and risk factors for mortality of persons in the vegetative state (VS). The study participants were 1,021 California patients in the VS during 1981-1996. Because of the large sample size, the authors were able to use multivariate methods to assess the effect of several risk factors on mortality. The authors found a strong secular trend in infant mortality, with rates in the mid-1990s being only one third of those in the early 1980s ($P < 0.01$). A smaller secular trend was observed for children aged 2-10 years and none for older patients. The mortality risk for older patients fell by approximately 8% for each year since the onset of the VS. The need for gastrostomy feeding was associated with a substantially higher risk, especially for infants and older patients ($P < 0.01$). Ventilator dependence also appeared to be a risk factor. On the basis of recent mortality rates, life expectancy in the VS is frequently higher than has generally been thought. For example, it is 10.5 additional years (± 2 years) for a 15-year-old patient who has been in the VS for 1 year, and 12.2 years for a 15-year-old patient who has been in the VS for 4 years.

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Introduction

The vegetative state (VS) has been described as a condition of complete unawareness accompanied by sleep-wake cycles and at least partial preservation of hypothalamic and brainstem functions [1]. If present for 1 month or more, the condition has been described as a persistent VS. Recovery of consciousness from a post-traumatic VS is rare after 12 months and is rare after 3 months in the case of a nontraumatic VS [1]. Such persons are considered to be in a permanent VS. The prevalence of persons in the VS in the United States has been estimated at 4,000-10,000 children and 20,000-35,000 adults [1].

The duration of survival in the VS has been extensively studied [1-15]. The issue is important for planning the resources needed to care for a given individual and is a factor in assessing the national overall cost of care of persons in the VS. It is well known that life expectancy in the VS is substantially reduced; what is much less clear is by how much and how the result is affected by factors such as the patient's age and need for special assistance or care.

The Multi-Society Task Force on the Persistent Vegetative State [1] summarized the duration of survival time thus: "... life expectancy ranges from 2 to 5 years; survival beyond 10 years is unusual." However, this statement needs considerable qualification and is overly pessimistic in many cases:

1. The statement reflects a widespread confusion over the terms *median survival time* and *life expectancy*. The former is the time at which half of a cohort will have died; the latter is the arithmetic mean of the survival times [16]. In high-risk groups, such as patients in the VS, the life expectancy is considerably longer than the median survival time [16]. In the great majority of studies of persons with disabilities the measure reported is actually the median survival time rather than life expectancy (the mean). The life expectancy is more difficult to compute because it is based on a life table and requires mortality rates at all ages [17]; it may also be less useful clinically, because it is sensitive to a few individuals with exceptionally long survival times.
2. Many of the commonly cited studies are 10-20 years old, and do not reflect the technologic advances that have been made in the care of the VS patient [6,7,13, 15]. The authors will return to this point.
3. Virtually all the studies demonstrate a very high mortality rate during the first year after the onset of the VS

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[1,8,9], but the mortality rate falls appreciably for patients who survive this initial period. In consequence, a patient who has been in the VS for 1 year or more has a greater median survival time than one who has just entered the VS. It is the latter that has generally been reported.
4. The populations studied in some of the reports consist of persons who are elderly or in infancy. The life expectancy of such persons cannot be assumed to apply to adolescents or young adults.
5. It is possible that life support has been withdrawn from some persons in the VS [2]. Data are difficult to obtain, but in one study of patients who had a locked-in syndrome [1] for more than 1 year, 81% survived at least 5 additional years [4,5]. This information is noteworthy because although locked-in syndrome resembles the VS in some respects, withdrawal of support would presumably never be considered.

In a study of 849 patients in the VS, Ashwal et al. [3] considered the effect of age and other factors on duration of survival. They reported median survival times of less than 5 years for infants less than 2 years of age but almost 10 years for patients older than 18 years of age. The median survival times reportedly decrease for more elderly patients with severe traumatic brain injury [14,18]. There do not appear to be other published studies of the effect of risk factors on survival in the VS, perhaps because this requires larger samples than have generally been available. As a result the wide disparities in published reports with respect to the populations studied and the survival rates reported are not well understood.

The present study is based on a large group of persons in the VS, which permitted the authors to take into account several important risk factors simultaneously. Factors considered included etiology, the need for special equipment (gastrostomy and ventilator dependence), the time since the onset of the VS, and the secular trend (systematic change with respect to year of onset). The authors focused on the period beginning 1 year after onset of the VS. By this time the condition can be considered permanent in almost all patients. The authors' purposes were to determine what effect these four risk factors, singly or in combination, have on the duration of survival in the VS and to develop a procedure for estimating the median survival time and life expectancy for a patient with a given profile of risk factors.

Methods

Patients and Instrument. The authors reviewed data collected from the Client Development Evaluation report (CDER) [19] from January 1981 to December 1996. A CDER is filled out approximately annually for all 194,168 persons with neurologic deficits or other developmental disabilities who have received medical care or other assistance from the State of California. The CDER includes 261 items, including demographic information, etiology, associated medical conditions, level of motor functioning, self-care, and cognitive functioning. Because of the high cost of care for patients in the VS, it is believed that almost all such patients receive state assistance and are therefore included in the database. In addition, the database contains some cases in which the VS is a consequence of traumatic brain injury.

Mortality Data. Mortality information was obtained by matching annual computer tapes issued by the California Department of Health Services to the authors' CDER database. California law requires all deaths in the state to be reported to the department.

Vegetative State. The operational definition of the VS was the same as that used by Ashwal et al. [3] in their earlier study of the same population, namely that the patient's functioning is at the lowest level on 15 items of the CDER. The items included mobility (patient must be unable to lift head when lying on stomach, lack hand and arm use, and be unable to crawl, creep, or scoot); self-care (no self-care skills, fed entirely by others); and cognitive skill (no receptive or expressive language or communication). The reliability of these items has been investigated elsewhere and judged to be satisfactory [20-23].

Statistical Analysis. The authors began by identifying the starting and ending time of each patient's period of being in the VS. The starting date was the later of the date of the first VS CDER evaluation and 1 year after the time of onset of the VS. The ending date was the earliest date of the following: (1) December 31, 1996 (the end of the study period); (2) the date of death; (3) 15 months after the date of the last of the consecutive VS CDER evaluations if not followed by a non-VS CDER evaluation; and (4) the time of the last evaluation of being in the VS if this was followed by a non-VS evaluation. The purpose was to conservatively identify a period during which each patient could be considered to be in the VS.

The authors used the Pooled Repeated Observations approach to model the mortality rates in terms of risk factors [24-26]. In this method the units of analysis are the consecutive months each patient contributes between the starting and ending dates. The choice of months as the unit is arbitrary; any short interval would yield virtually identical results [27]. There were in all 25,960.9 months drawn from 1,021 patients, of whom 394 died during their time in the study, for an overall mortality rate of 182 deaths per 1,000 person-years. With each month, the authors associated the following risk factors: (1) a binary variable indicating whether the patient died or survived that month; (2) the patient's age that month; (3) the calendar year in which the month fell; (4) the time since the onset of the VS (because the onset of VS occurred at birth for many of the young children, the time since onset was highly correlated with age in that group; and, because current age was already factored into the model, the authors chose to work with the time since onset only for patients 10 years of age or older); (5) the patient's sex; (6) a binary variable for whether the patient was fed by gastrostomy tube that month; and (7) a similar variable for use of a ventilator.

Age, calendar year, and time since onset were all modeled both with linear and higher polynomial terms and with indicator variables for various intervals. To choose the most parsimonious model the authors used Wald and deviance statistics for nested models and the Akaike information criterion otherwise [28].

The authors also worked with a grouping of the etiology of the patient's condition; the categories were congenital abnormalities, traumatic injury, near drowning, and other/unspecified. The authors were, however, unable to find meaningful differences in survival between the groups, and the variable was excluded from further analysis.

In the primary analysis the authors used logistic regression [29] to analyze the effect of the risk factors on the mortality rates. The resulting mortality estimates are thus computed under the assumption that the patient remains in the VS throughout (i.e., that the patient is in a permanent VS). This approach is preferable to the more common cohort survival analysis, which would include patients who made some recovery.

Survival curves and life expectancies were computed by using the mortality rates from the logistic analysis to construct life tables [17]. Age-specific mortality rates for the tables were obtained using the logistic regression model for the first 15 years in the study and standard models for age-specific mortality thereafter [30]. Standard methods for

Table 1. Risk factors by percentage and crude mortality rates*

	Percentage	Mortality Rate per 1,000 Person-Years
Current age		
< 24 mo	14	452
2-5 yr	22	202
5-10 yr	21	131
10-20 yr	19	126
20-30 yr	13	93
30-50 yr	10	55
≥ 50 yr	2	277
Time since injury (yr)		
1-3	46	256
3-6	28	135
6-9	13	109
≥ 9	12	66
Sex		
Male	53	186
Female	47	172
Special aids		
Gastrostomy and ventilator	2	283
Gastrostomy, no ventilator	54	217
Neither	44	128
Calendar year†		
1981-1987	42	229
1988-1992	36	149
1993-1996	22	135

* Based on 25,961.9 person-months and 394 deaths.
† The current year, not the year of injury.

Table 2. Logistic regression analysis* of the effect of risk factors on mortality rates

Variable	Risk Ratio†	95% Confidence Interval
Each year since onset of VS for persons ≥ 10 yr	0.92‡	0.87, 0.99
Age (yr) and feeding tube status§		
Age 0-2		
Tube fed	3.57	1.64, 7.76
Not tube fed	1.46	0.66, 3.25
Age 2-5		
Tube fed	1.55	0.72, 3.05
Not tube fed	1.48	0.78, 3.09
Age 5-10		
Tube fed	1.17	0.59, 2.32
Not tube fed	0.76	0.34, 1.70
Age 10-30		
Tube fed	2.46	1.50, 4.04
Not tube fed	1	—
Ventilator use	1.66	0.95, 2.90
Secular trend		
Age < 2 yr‖		
1981-1984	3.04	1.64, 5.65
1985-1992	1.75	0.95, 3.20
1993-1996	1	—
Age 2-10 yr¶		
1981-1984	2.21	1.36, 3.59
1985-1992	1.16	0.75, 1.81
1993-1996	1	—

* The "Pooled Repeated Measures" method [24]; unit of analysis is a person-month rather than a person. Thus the calendar years, ages, tube feeding status, etc. refer to the person-month in question, not to date of birth or onset.
† Mortality risk relative to the reference group.
‡ Indicates an 8% (1-0.92) reduction in risk for each year between the first and tenth years after onset of the VS.
§ Compared with the reference group, which consisted of persons 10-30 years of age who were not tube fed. The odds ratio for the latter is set at 1 by convention. The comparisons in this section of Table 2 apply to mortality in 1993-1996.
‖ Comparison of mortality rates for infants < 2 years of age across the study period, using the late period (1993-1996) as reference. Mortality rates in 1981-1984 were estimated to be 3.04 times higher than in 1993-1996, other factors being equal.
¶ Comparison of mortality rates for children 2-10 years of age across the study period.
Abbreviation:
VS = Vegetative state

computing confidence bounds on the survival functions and derived quantities are not available in this situation, but conservative confidence intervals (i.e., upper bounds for the confidence intervals) on the life expectancies were derived from the corresponding standard errors of the estimated hazard rates.

Results

Table 1 presents the data on the 25,961 person-months (drawn from 1,021 patients in the VS) for age, calendar year, and other factors. Table 1 also provides the death rates per 1,000 person-years for each item. These mortality comparisons are crude, or univariate, in that no adjustment was made for the effect of other factors.

Table 1 reveals that 14% of the data were derived from infants younger than 2 years of age and that the mortality rate during this time was a high 452 deaths per 1,000 person-years. The bulk of the remaining data was derived from children and young adolescents, and the crude mortality rate declined steadily with age until after 50 years of age. A feeding tube was used during 56% of the study intervals, and the mortality rate for tube-fed patients was almost double that of patients who were fed orally. Ventilator dependence was uncommon (2%), but it too was associated with higher mortality.

Table 2 presents the results of the logistic regression analysis that estimated the effects of the risk factors simultaneously. The first variable was the time since the onset of the VS, beginning 1 year after onset. A simple linear trend was the most parsimonious model. During the first 10 years after the onset of the VS, mortality declined by an estimated 8% (1-0.92) per year, other factors held constant ($P < 0.05$). Thus the chance of dying in the next year for a patient who has been in the VS for 7 years is only 60% ($= 0.92^6$) of its value for a patient in the VS for 1 year. The linearly declining trend during the first 10 years was statistically significant ($P < 0.05$). There were insufficient data to permit inferences about the trend after the first 10 years.

Mortality risk depended both on age and on the need for tube feeding rather than oral feeding. The risks in Table 2 are relative to the reference group (persons 10-30 years of age who were not tube fed) for whom the relative risk was

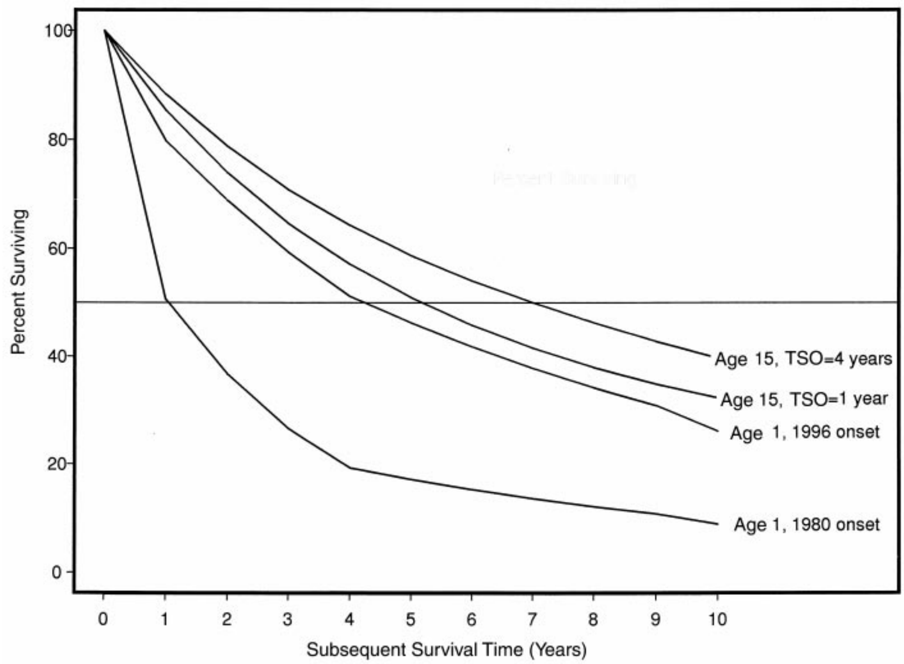

Figure 1. Survival curves (TSO: Time since onset). Also see Table 3 for median survival times and life expectancies.

taken to be 1 by convention. Tube-fed infants younger than 2 years of age were subject to the highest mortality. Mortality was lower for children 2-10 years of age, and need for tube feeding made little difference in this group. The disparity was much greater for young adults, with a relative risk of 2.46 ($P < 0.05$). Results for patients older than 30 years of age are not given here because the data for that range of ages were rather sparse. Ventilator dependence also appeared to be a risk factor. Almost all ventilator-dependent patients were fed by gastrostomy tube; among such patients, ventilator dependence was associated with a 66% increase in risk ($P < 0.05$, one-tailed test).

Secular trends were related to the age of the patient. For infants younger than 2 years of age, mortality rates fell steadily throughout the study period: in the mid-1990s, rates were only one third of their values at the beginning of the study period (early 1980s). For children 2-10 years of age, a smaller decline occurred from the early 1980s, and the rates appeared to level off thereafter. There was no indication of a secular trend for patients 10 years of age or older.

The authors were unable to detect significant differences in survival associated with the following factors: sex, etiology, ethnicity (coded as white/nonwhite), type or frequency of seizures, type of residence (e.g., family home, group home, state institution), number of associated severe medical conditions (as indicated by Internation Classification of Diseases, 9th revision codes with "severe" impact on the CDER).

Figure 1 presents four illustrative survival curves derived from this analysis. The results have been applied to 1-year-old infants born in 1980 and in the mid-1990s and to 15-year-old patients who had been in the VS for 1 year and for 4 years. It was not appropriate to stratify the analysis according to mode of feeding or ventilator dependence because many patients experienced a change in either or both of these factors during their time in the VS. The mortality rates were therefore derived from a reanalysis with these factors excluded. The graph illustrates the marked improvement in the survival of infants during the 1981-1996 study period.

Table 3 gives the median survival times and life expectancies for the survival curves of Figure 1. The estimated life expectancy doubled, from 3.6 to 7.2 years. Life expectancies for a 15-year-old patient were higher—10.5 years if the patient was in the VS for 1 year and 12 if for 4 years. As indicated the authors found no secular trend in survival for patients 10 years of age or older, so these results apply to both the 1980s and mid-1990s.

Table 3. Median survival times (years) and life expectancies (years) for data in Figure 1, with 95% confidence intervals

	Median Survival Time (Estimated 95% CI)	Life Expectancy (Estimated 95% CI)
Age 1		
1980 onset	1 (0.7, 1.6)	3.6 (2.5, 5.4)
1993-1996 mortality rates	4.2 (2.4, 8)	7.2 (4.7, 10.6)
Age 15		
1 yr after onset	5.2 (3.7, 7.3)	10.5 (7.2, 15.1)
4 yr after onset	7 (5.1, 10.2)	12.2 (8.6, 17.2)

Abbreviation:
CI = Confidence interval

Discussion

The results of the present study reveal that the life expectancy of patients who have been in the VS for 1 year or more is greater than has generally been thought. Although life expectancies in the range of 2-5 years have been previously cited [1], the authors obtained life expectancies of 10-12 years for patients 15 years of age. The life expectancy will be still higher if the patient is fed orally. There are several reasons for the common underestimation of life expectancies in children and young adults in the VS:

1. The confusion of life expectancy with median survival time, the latter being a shorter duration for persons in the VS.
2. The reliance on studies performed at a time when mortality rates in the VS were higher.
3. The choice of the onset of the VS as the starting time, rather than the first year after onset as in the present study. It has been estimated that 33-53% of adults in the VS die within the first year [2], although children in the VS may have better short-term survival prospects [31].
4. The lower mortality rates in the VS for children and young adults vs infants that had not been well documented.
5. Possible inclusion of patients whose death was the result of a decision to withdraw life support.

The mortality rates observed in the present study, although lower than those reported elsewhere, are conservative: if anything, they overestimate the true mortality rates and thus lead to underestimates of life expectancy. The reasons are as follows:

1. The authors' approach assumes that no patient will recover from the VS after 1 year, although in practice a small number may do so. In this respect the authors' analysis is more conservative than that of Ashwal et al. [3], who monitored all individuals with two consecutive evaluations meeting the VS criteria. The authors found that among such patients, approximately one third of those who survived several additional years had improved and no longer met the criteria. It may be that many of the patients demonstrating improvement had been in a minimally conscious state (in which the person demonstrates minimal but definite behavioral evidence of self or environmental awareness [32]) rather than a VS. In the present analysis, but not in the previous study, a patient is in effect censored [28] at the time of an evaluation demonstrating improvement.
2. The authors excluded intervals between evaluations in which the patient improved from the VS to a higher level. If the patient had been in the VS for a portion of that time, that portion would not be counted in the denominator of the deaths/exposure ratio.
3. Any deaths as a result of withdrawal of support in the authors' data would inflate mortality rates over their natural levels.

Because of the large sample size available for the present study, it was possible to assess the effect of a number of risk factors simultaneously. There was a clear reduction in the mortality risk when the time since the onset of the VS increased, other factors were held constant. This reduction is consistent with a healthy survivor effect.

Regarding age, mortality was greatest for infants younger than 2 years of age. For patients who could be fed orally, mortality declined with age thereafter, at least to 30 years of age. This pattern differs from those in some other reports. For example, in a large study of mortality after traumatic brain injury, mortality was elevated in children younger than 12 years of age but increased steadily thereafter [18]. Like most studies of mortality after traumatic brain injury, however, this was not specific to the VS and focused on short-term mortality rates. The decrease in risk for the orally fed patient as age increases may reflect an effect of etiology. The authors were unable to identify an association between etiology and risk. However, the etiology of the VS could not be determined for many patients, and the proportion of cases resulting from injury rather than congenital defects probably increases with age. Thus patients with injuries may tend to survive longer than those with congenital defects. Further investigation is needed.

A decline in infant mortality was clearly evident, with rates falling by approximately two thirds during the 16-year study period when other factors were held constant. This pattern was not observed for older patients in the VS and also contrasts with California studies of mortality in cerebral palsy [33,34] and traumatic brain injury [35], in which little or no secular trend was observed. The finding suggests an improvement in quality of care for infants in the VS, although it is not clear which aspects of care are responsible. It is unlikely to be related to the increased use of ventilators for patients in the VS because this practice was uncommon during the 1980s. It is the authors' impression, however, that heroic measures to sustain infants with severe neurologic deficits have become steadily more common in the past 20 years.

Patients with gastrostomies were subject to higher mortality than those fed orally, particularly for infants and older patients. Presumably, tube feeding is primarily a marker for increased risk of, or susceptibility to, recurrent aspiration, respiratory infections, gastroesophageal reflux, and other upper esophageal dysfunction rather than being a direct risk factor in its own right, although this has not been adequately investigated [27,36-39]. Similar remarks apply to the higher mortality of ventilator-dependent patients.

The VS differs importantly from the locked-in syndrome and the minimally conscious state. Most obviously, considerations of withdrawal of support do not arise in such conditions. A favorable functional outcome has been demonstrated to be more likely in a minimally conscious state than in the VS [40]. The prognosis for survival in the two conditions has not been compared, and the authors hope to report on this shortly. The authors have insufficient data on persons in a locked-in syndrome to estimate their survival rates or life expectancy.

Finally, when the life expectancy of a patient in the VS is required, it is appropriate and feasible to take into account age, time since onset, and other factors. Furthermore, adjustment to current conditions and mortality rates is preferable to reliance on historic rates. The method developed here and illustrated in Figure 1 can be applied to a patient with any profile of risk factors.

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