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Survival in Amyotrophic Lateral Sclerosis

The Role of Psychological Factors

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Objective: Examining the relationship between psychological status and survival in amyotrophic lateral sclerosis. Our hypothesis is that psychological distress is associated with greater mortality and shorter survival time than psychological well-being.

Design: Cross-sectional, longitudinal. The baseline evaluations used were disease severity and 10 psychometric tests. A psychological status score was derived from these tests. Survival status was monitored for 3.5 years. Interviewers were blinded to other interviews and data analysis.

Setting: Patient's residence.

Patients: The criteria for eligibility were diagnosis of amyotrophic lateral sclerosis by a neurologist, dementia or alcoholism absent, communication in English, and any severity or length of disease. It was a volunteer sample consisting of 144 patients from amyotrophic lateral sclerosis clinics or community-based amyotrophic lateral sclerosis support groups. In this sample 66% were men, 94% were white, mean age at diagnosis was 55 years, 79% were married, 60% had some college education, and 61% died during the study.

Interventions: None.

Main Outcome Measures: End points: mortality during study, survival time from intake to last follow-up.

Results: Comparison between high and low psychological score groups: 32% of high and 82% of low died; survival curves were significantly different. Controlling for confounding factors (length of illness, disease severity, age), patients with psychological distress had a greater risk of mortality (relative risk, 6.76; 95% confidence limits, 1.69 to 27.12) and greater likelihood of dying in any given time period (relative risk, 2.24; 95% confidence limits, 1.08 to 4.64) than those with psychological well-being.

Conclusion: Adjusting for confounding factors, psychological status is strongly related to outcome in amyotrophic lateral sclerosis. Further studies on psychological status should be done to confirm its prognostic value.

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DURING 1993, an estimated 1 800 000 Americans will be diagnosed with various types of cancer, 80 000 with acquired immunodeficiency syndrome, and 6000 with amyotrophic lateral sclerosis (ALS). Many more will be diagnosed with other diseases of similarly poor prognoses. The devastating impact of these diseases and their seemingly unpredictable courses have prompted a search for the biological mechanisms of disease progression or, when these are elusive, at least the prognostic factors related to survival.

The value of these prognostic factors is evident in our daily evaluation and management of ill patients. Once a disease is diagnosed, we look at prognostic factors such as tumor nodal metastasis staging in head and neck or breast cancer, I through IV staging in Hodgkin's lymphoma, and Clark's levels in melanoma to help us predict the course and length of illness.

More recently, investigators have examined psychological variables as prognostic factors in disease progression and

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PATIENTS AND METHODS

GENERAL METHODS

The ALS Patient Profile Project was a cross-sectional and longitudinal analysis of 144 patients with ALS (see **Table 1** for demographic characteristics). To ensure adequate sample size and geographic representation, three field sites were selected: Seattle, Wash (n=44); San Francisco, Calif (n=56); and Philadelphia, Pa (n=44). Individuals were recruited on a voluntary basis through hospital-based ALS clinics and/or community-based ALS support groups. Accrual of patients took place from March 1987 through February 1988. Entry criteria consisted of a confirmed diagnosis of ALS made by a neurologist, the absence of diagnosed dementia or known alcoholism, and the ability to communicate in English. Patients with any degree of disease severity or length of illness were included. Ventilator-dependent patients were also eligible.

Participants were interviewed and evaluated at their residences by trained interviewers. All interviewers were trained in data collection techniques by experienced medical professionals. Each interviewer was blinded to the information obtained by other interviewers and to the ongoing data analysis. Protocol for this study was approved by the University of Washington Human Subjects Committee. Written consent was obtained from each participant.

Since there is no physiologic marker that can be used to monitor the progression of ALS, the physical status of every patient was evaluated according to the ALS Severity Scale.[27] This ordinal scale has an interrater reliability coefficient of 0.95. The degree of functional impairment in speech, swallowing, lower extremity function, and upper extremity function is measured to obtain a total score with a possible range from 3 (most functional impairment) to 40 (no functional impairment). This total score was used as our measure of disease severity.

Each patient filled out a comprehensive data form containing questions about demographics, medical history, lifestyle, and attitudes and beliefs about themselves and their lives. In addition, a battery of 10 standardized tests designed to measure psychological status was administered (**Table 2**). This battery included constructs previously shown to be related to survival in patients with heart disease and cancer, since such information was lacking for patients with ALS.

Physical and psychological assessment was done seven times over 18 months at 3-month intervals. Survival status was monitored through September 1990. This article presents baseline physical and psychological measurements and their relationship to mortality and survival time.

STATISTICAL ANALYSIS

A total psychological status score was derived from the 10 psychological tests. Of these 10 tests, two, the UCLA Loneliness Scale and Sarason's Social Support Questionnaire, did not show substantial variability in our population and are not included in this score. A third test, Revised Ways of Coping Checklist, was also eliminated, since it is composed of five subscales with no summary score. The seven remaining scales were directionalized so that higher scores were associated with greater psychological well-being. To obtain a single standardized score for the psychological status of each patient, z-scores for these seven scales were calculated and summed. Higher scores of this summary variable thus reflect greater psychological well-being, while lower scores reflect greater psychological distress.

Our analysis was based on the measurement of psychological status at time of entry into the study. Five subjects had incomplete data for calculating psychological status, and one subject was unavailable for follow-up; this left 138 subjects, including three patients who died of causes

survival. These factors, which measure different aspects of psychological resiliency or well-being, have included both specific single variables, such as anxiety, depression, or hostility, and constellations of variables such as the type C personality. In some studies on patients with breast cancer, malignant melanoma, lung cancer, or coronary heart disease, researchers have found an association between psychological factors and survival time.[1-9] Other studies, however, have shown no such association.[10-13] This lack of agreement among studies regarding the role of psychological factors in mediating survival time may be related to (1) difficulty separating psychological effects from treatment effects, (2) insufficiently controlling for type or severity of disease, (3) failure to account for other factors related to survival such as date of diagnosis and complications of disease, and (4) use of nonstandardized psychological measures.[12,14]

We designed a prospective study with a twofold purpose: to explore the prognostic effect of psychological factors on mortality and survival time in a neuromuscular disease and to address the methodological issues listed above. Amyotrophic lateral sclerosis provided an excellent disease model to study because the rate of decline varies from case to case and there is no treatment to alter the course of the progressive paralysis of this disease. With this model, then, the effect of psychological factors on outcome is more easily assessed because there is no confounding effect of disease treatment. In this study we evaluated a constellation of psychological factors rather than a single factor.

Amyotrophic lateral sclerosis is a devastating neuromuscular disease with no known cause. Theories of causation include endogenous and exogenous toxins, slow viral infection, trauma, and immunologic abnormalities.[15] This disease involves degeneration of corticospinal and corticobulbar tracts, anterior horns of the spinal cord, and bulbar nuclei. Amyotrophic lateral sclerosis affects motor control of most voluntary muscles, includ-

other than ALS. For all analyses, $P \leq .05$ was regarded as significant.

STRATIFICATION BY THE PSYCHOLOGICAL STATUS VARIABLE

The population was initially divided into quartiles based on psychological status scores. Since the two middle quartiles did not vary in terms of mortality or survival time, they were collapsed into one group. The three groups used in this analysis represented high (top 25%), middle (middle 51%), and low (bottom 24%) psychological scores (**Table 3**). The high group represents psychological well-being, the middle group a more neutral psychological status, and the low group psychological distress (**Table 4**).

COVARIATE IDENTIFICATION

To accurately assess the effect of psychological status on survival, we first needed to identify covariates that might confound that relationship. For each of the three psychological score groups, means and frequencies for all conceptually relevant covariates measured at entry into the study were computed (see **Table 5** for selected results). Two key aspects of ALS, mode of onset and ventilator dependency, did not show significant variation among the three psychological score groups. However, severity of disease was significantly different among these three groups ($P=.03$). Of the demographic and lifestyle variables, mean age ($P=.03$) was found to differ among the three psychological score groups. Thus, we considered severity and age confounding factors. In addition, we evaluated whether either could be a major determinant of psychological status; however, the association between the continuous variables of severity ($r=.17$) or age ($r=-.23$) and psychological status was low, indicating a lack of dependence. Mean length of illness was not significantly different among the three groups ($P=.12$), but we still considered it a confounding variable because of the cross-sectional nature of our study. This allowed us to account for the different lengths of illness prior to entry into the study. Therefore, the covariates controlled for in the multivariate analyses of mortality and survival time were age (≤ 65 and >65 years), severity of disease (mild, moderate, severe), and length of illness (short, medium, long) (Table 3).

MORTALITY

Our analysis of mortality determined the extent to which psychological status was associated with risk of death during the study time. Patients in the low and middle psychological score groups were compared with the referent high group. Relative risk estimates for mortality were obtained by logistic regression. First, the unadjusted relative risk estimate for psychological status was computed. Next, the identified covariates were entered in the model and assessed for significance by likelihood ratio tests. Finally, the adjusted relative risk estimates for psychological status and all covariates in the model were calculated.

SURVIVAL TIME

Analysis of survival time was conducted with univariate and multivariate modeling strategies. Length of survival time was the cumulative number of days from entry into the study until death or last follow-up. First, Kaplan-Meier survival curves were constructed for the three psychological score groups.[37] The differences between the three curves were tested with Breslow's generalized Wilcoxon test. Next, Cox's proportional hazards regression model was used to derive unadjusted and adjusted hazard ratio estimates.[38] The overall goal of this analysis was to quantify the relationship between survival time and our set of covariates, thus determining the relative prognostic effect of psychological status and each covariate on the risk of death from ALS.

ing the muscles of respiration. The onset is usually insidious, beginning with either weakness in a limb or difficulty in speech or swallowing. Although death usually occurs within 3 to 5 years of diagnosis, some patients die within months of onset while others live many years.[16] Studies of survival in ALS report 5-year survival rates ranging from 18% to 42%.[17-21] An explanation for this wide variation is lacking.

Several studies have evaluated the psychological characteristics of ALS patients.[22-26] Results from these studies suggest that certain psychological tendencies may be inherent in the ALS population, but there is no consistent pattern among the studies. The sample sizes were relatively small (n=10 to 45), and none of these studies related their psychological findings to mortality or survival time.

In our investigation of patients with ALS we examined the relationship of psychological characteristics to mortality and survival time. We hypothesized that after accounting for physical state and other relevant prognostic factors, individuals who exhibited psychological distress would have significantly greater mortality and shorter survival time during the period of observation than individuals who exhibited psychological well-being. Psychological distress would be characterized by high levels of such factors as depression, hopelessness, and perceived stress, while psychological well-being would include low levels of these factors.

RESULTS

MORTALITY

Psychological status at the beginning of the study was significantly related to mortality; 32% of the high, 65% of the middle, and 82% of the low psychological score

Table 1. Characteristics of Total Sample*

Demographics	
Males	95 (66)
White	136 (94)
Age at diagnosis, y	55±13.1
Married	114 (79)
Education beyond high school	87 (60)
Income ≤$25 000 prior to ALS	72 (50)
Currently employed	24 (17)
Baseline medical status	
Length of illness†	27 (1-358)‡
Severity of disease (total ALSS)§	25±8.4
Onset mode	
Bulbar‖	22 (15)
Spinal¶	103 (72)
Ventilator dependent	18 (12)
Familial ALS	5 (4)
Survival status at end of study	
Alive	55 (38)
Died of ALS	84 (58)
Died of other cause	4 (3)
Lost to follow-up	1 (<1)
Survival time, days in study	646±111#

*Total sample, 144. Results as No. (%) or mean±SD.
†Months from diagnosis to entry into study.
‡Median (range).
§Amyotrophic Lateral Sclerosis (ALS) Severity Scale.
‖First symptom speech or swallowing.
¶First symptom in extremities.
#Median cumulative survival ±SE, derived from product-limit survival curve.

Table 2. Psychological Assessment Scales*

	Mean±SD
Beck Hopelessness Scale[28]	6.9±5.2
Beck Depression Inventory[29]	12.9±7.5
UCLA Loneliness Scale[30]	7.7±2.1
Perceived Stress Scale[31]	24.7±8.1
Anger Expression Scale[32]	20.7±9.4
Purpose-in-Life Test[33]	106.2±17.3
Health Locus of Control Scale[34]	39.2±10.0
Life Rating Scale†	2.6±1.1
Social Support Questionnaire, Short Form[35]	
No. of people	3.8±2.3
Satisfaction	5.5±0.9
Revised Ways of Coping Checklist[36]	
Problem focused	24.8±7.0
Seeks social support	22.9±8.3
Blamed self	13.2±9.5
Wishful thinking	21.9±8.5
Avoidance	17.1±5.2

*Total sample, 144.
†Unpublished scale, the ALS (Amyotrophic Lateral Sclerosis) Patient Profile Project.

Table 3. Groupings for Psychological Status Variable and Covariates Used in Survival Analyses*

Variable, Grouping (Range)	No. (%)
Psychological score	
High (+3.11-+8.50)	34 (25)
Middle (−3.19-+3.10)	71 (51)
Low (−15.50-−3.20)	33 (24)
Length of illness, mo	
Short (1-18)	53 (38)
Medium (19-60)	42 (30)
Long (>60)	43 (31)
Severity of disease (total ALSS)†	
Mild (29-40)	57 (41)
Moderate (17-28)	56 (41)
Severe (3-16)	25 (18)
Age, y	
≤65 (25-65)	83 (60)
>65 (66-82)	55 (40)

*Sample, 138.
†Amyotrophic Lateral Sclerosis (ALS) Severity Scale.

group died during the study ($P<.001$). With mortality as the outcome, the unadjusted relative risk of dying sometime during the study for patients with psychological distress was 9.41 times that for patients with psychological well-being ($P<.001$). When the identified covariates of length of illness, severity of disease, and age were controlled, the adjusted relative risk of mortality for patients with psychological distress was 6.76 times that for patients with psychological well-being (95% confidence limits, 1.69 to 27.12, $P<.01$) (**Table 6**).

SURVIVAL TIME

Median survival time during the study period was significantly longer for the high (>1200 days) and middle-psychological score groups (609 days) than for the low group (333 days) ($P<.001$). A Kaplan-Meier survival plot of the three psychological score groups showed a significant difference between the survival curves ($P<.001$) (**Figure**). The probability of survival at any given point in time for the high psychological score group was greater than that for the middle or low groups.

The assumptions necessary to use Cox's proportional hazards regression analysis were met. Regression analysis with psychological status alone showed that the relative risk of death per unit time (the likelihood of dying in any given time interval within the study period) for a patient with psychological distress was 3.84 times that for a patient with psychological well-being ($P<.001$). When the covariates of length of illness, severity of disease, and age were controlled, the relative risk of death per unit time for a patient with psychological distress was 2.24 times that for a patient with psychological well-being (95% confidence limits, 1.08 to 4.64, $P=.02$) (Table 6).

Table 4. Characteristics of Psychological Well-Being and Distress*

Component Scales	Psychological Status: Well-being	Psychological Status: Distress
BHS	Less hopelessness	More hopelessness
BDI	Less depression	More depression
PSS	Less perceived stress	More perceived stress
AX/EX	Expressive of anger	Inexpressive of anger
PIL	Well-defined purpose	Poorly defined purpose
HLC	Greater perceived control over health care	Less perceived control over health care
LRS	High life satisfaction	Low life satisfaction

**BHS indicates Beck Hopelessness Scale; BDI, Beck Depression Inventory; PSS, Perceived Stress Scale; AX/EX, Anger Expression Scale; PIL, Purpose-in-Life Test; HLC, Health Locus of Control Scale, and LRS, Life Rating Scale.*

COMMENT

Our results show that patients with ALS who demonstrated psychological well-being had a lower risk of dying and a longer survival time than those with psychological distress. In fact, the risk of dying associated with psychological distress was greater than the risk associated with increased age and similar to that of disease severity. These results indicate that psychological status is an important prognostic factor in ALS, independent of length of time since diagnosis, disease severity, and age.

Due to the prognostic significance of psychological status, we examined additional factors that might have affected our results. One factor that might have influenced psychological status was rate of decline for the 6 months prior to entry into the study. Data to calculate this were not available, but we could estimate the rate of decline from date of first symptom to entry into the study. When we added this estimate of prior rate of decline as a covariate in our survival analysis model, it had no impact on the risk of dying or the risk of death per unit time associated with psychological distress.

We also looked at the possibility that our results merely reflected a natural progression of decreasing psychological well-being occurring from onset of disease to death. If that were true, a decreasing trend in psychological status scores would have been observed during the study period. While psychological scores of some individuals did decrease between their first and last psychological assessments, an equal number increased, and the majority of patients remained within the same psychological score group throughout the testing period.

We also looked at the possibility that the voluntary nature of patient recruitment gave us an atypical sample of the total ALS population, which could have skewed the results. However, in our study the mean age at diagnosis, male-to-female ratio, proportion with familial ALS, and proportion with bulbar vs spinal onset were similar to previous studies of ALS patients.[15,16,18,21] In addition, there was a wide range of disease severity, length of illness, and psychological assessment results, suggesting that we had a broad sample and had not selected a specific subset of the ALS population.

The prognostic significance of psychological status can be better understood by examining other studies on psychological factors and their relationship to disease. Numerous studies have linked many of the individual factors comprising our psychological status variable to a decrease in disease resistance or a shorter survival time. These factors include lack of anger expression,[39] depres-

Table 5. Characteristics of Sample by Psychological Score Groupings*

	Psychological Score: Low	Psychological Score: Middle	Psychological Score: High	P†
Sample, No. (%)	33 (24)	71 (51)	34 (25)	...
Possible covariates				
Age, y	64±12.5	59±11.7	57±12.0	.03
Length of illness, mo	49±71.1	48±54.9	72±70.3	.12
Severity of disease (total ALSS)‡	22±8.0	26±7.8	27±8.4	.03
Site				.57
San Francisco, Calif	12 (36)	26 (37)	16 (47)	...
Philadelphia, Pa	11 (33)	23 (32)	6 (18)	...
Seattle, Wash	10 (30)	22 (31)	12 (35)	...
Males	21 (64)	48 (68)	22 (65)	.91
Married	26 (79)	59 (83)	26 (77)	.70
Education beyond high school	20 (61)	39 (55)	25 (74)	.19
ALS support group attendance	12 (36)	31 (44)	13 (38)	.74
Onset mode				.39
Bulbar	5 (15)	13 (18)	3 (9)	...
Spinal	24 (73)	47 (66)	27 (79)	...
Ventilator dependent	2 (6)	9 (13)	5 (15)	.50
Income ≤$25 000 prior to ALS	17 (57)	38 (62)	14 (42)	.18
Received psychotherapy in past	6 (18)	12 (17)	5 (15)	.93
Currently receiving psychotherapy	0 (0)	5 (8)	1 (3)	.24
On experimental medication for ALS	2 (6)	5 (7)	2 (6)	.97
On symptomatic medication for ALS	24 (73)	42 (59)	17 (50)	.16
On medications for other conditions	13 (39)	36 (51)	19 (56)	.38
Survival data				
Dead at end of study	27 (82)	46 (65)	11 (32)	<.01
Survival time, days in study§	333±129	609±69	>1200‖	<.01

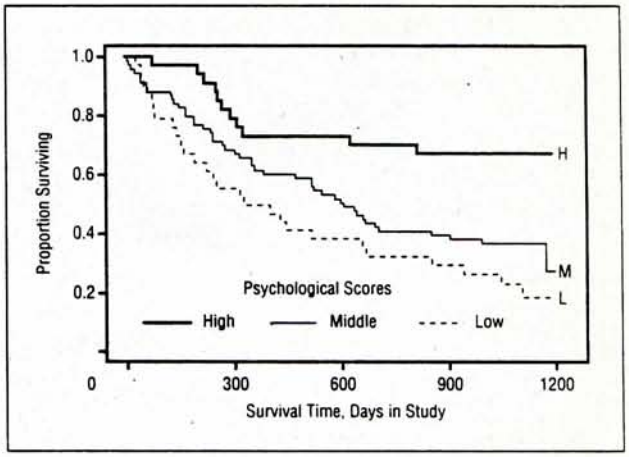
**Sample, 138. Results as No. (%) or mean± SD.*
†Based on Kruskal-Wallis one-way analysis of variance and χ^2 tests.
‡Amyotrophic Lateral Sclerosis (ALS) Severity Scale.
§Median cumulative survival ± SE, derived from product-limit survival curves.
‖Survival 68% at end of study.

Table 6. Mortality and Survival Analyses

Prognostic Factor	RR*	CI†	P
Mortality: Logistic Regression			
Middle psychological score	3.06	1.08-8.66	.03
Low psychological score	6.76	1.69-27.12	<.01
Medium length	0.26	0.09-0.80	.02
Long length	0.03	0.01-0.11	<.01
Moderate severity	2.01	0.74-5.47	.16
Severe severity	6.48	1.55-27.12	.01
>65 age group	1.80	0.69-4.70	.23
Survival: Cox Regression			
Middle psychological score	1.60	0.81-3.16	.16
Low psychological score	2.24	1.08-4.64	.02
Medium length	0.51	0.31-0.83	.01
Long length	0.13	0.06-0.26	<.01
Moderate severity	1.81	1.09-2.98	.02
Severe severity	2.62	1.41-4.86	<.01
>65 age group	1.54	0.99-2.40	.06

**Relative risk; compared with relative risks of 1.00 for high psychological score, short length, mild severity, and ≤65 years; relative risks of greater than 1 are associated with higher mortality and relative risks of less than 1 are associated with lower mortality.*

†CI indicates 95% confidence interval.



Kaplan-Meier survival curves for three levels of psychological status in patients with amyotrophic lateral sclerosis. Probability of survival during a 1200-day period for 34 patients in the high, 71 in the middle, and 34 in the low psychological score groups.

sion,[40-42] external health locus of control,[5,43] hopelessness,[3,44,45] and stress.[45-47]

At the same time, however, results from other studies indicate that there is no relationship between psychological factors and disease resistance or survival time.[10,12,13,48] One possible explanation for this disparity could be that many of these studies investigated individual psychological factors as opposed to a constellation of factors. Just as a single blood test does not provide a comprehensive view of an individual's physical health, neither does an isolated psychological measurement necessarily represent an individual's psychological health. A variety of physical as well as psychological factors contribute to disease causation and progression. In this study the prognostic significance of psychological status is not only related to the individual factors that comprise this variable but also to the combined effect of these factors.

In this light, one might ask if our measurement of psychological status reflects an individual's true psychological status or simply reflects very high or low scores on one of the component tests. The fact that patients in the top quartile tended to score high on most tests while patients in the bottom quartile tended to score low suggests that we are measuring true psychological status, a constellation of factors, and not inadvertently measuring just one of the individual factors. It is important to realize that while most of the test scores for a patient with psychological well-being tended to be high, they were not necessarily in the upper quartile for each test; neither were all test scores for patients with psychological distress necessarily in the lower quartile for each test. Thus, selecting only one measure or examining several measures on an individual basis could have resulted in less accurate or even contradictory results.

While our results show psychological status to be a strong prognostic factor in ALS, it should not be applied as a psychological barometer to predict survival time for a single individual. We can only hypothesize that significant improvement in a patient's psychological status score and maintenance of that improvement would result in a longer survival time than previously expected. Spiegel et al[49] have shown the value of a related psychosocial intervention in a randomized group treatment for patients with breast cancer. To evaluate this possibility in ALS, an intervention study of patients from the lowest psychological score group would be needed. Psychological interventions could be applied to half of that group in an attempt to raise their psychological status scores to the middle or upper quartiles; survival time between these two populations could then be compared.

In summary, ALS provided a unique model because there were no confounding effects of treatment to obscure the relationship between psychological factors and mortality or survival time. Our results show that in ALS psychological status is a significant predictor of mortality and survival time, after adjusting for the covariates of length of illness, severity of disease, and age. This study provides evidence that psychological status is strongly related to outcome in ALS and suggests the need to broaden our view of illness beyond physical factors.

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