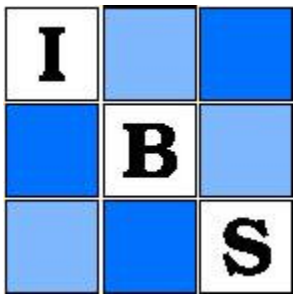

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COVARIANCE ANALYSIS OF CENSORED SURVIVAL DATA

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SUMMARY

The use of regression models for making covariance adjustments in the comparsion of survival curves is illustrated by application to a clinical trial of maintenance therapy for childhood leukemia. Three models are considered: the log linear exponential (Glasser [1967]); Cox's [1972] nonparametric generalization of this; and the linear exponential (Feigl and Zelen [1965]). Age and white blood count at diagnosis are both shown to be important for prognosis; adjustment for the latter variable has marked effects on the treatment comparisons. Both advantages and disadvantages with the regression approach are noted.

1. INTRODUCTION

The past few years have witnessed intense activity among statisticians in adapting the powerful methods of multiple regression and covariance analysis for use with censored survival data. Some of these efforts have been directed towards extending traditional least squares methods based on normal distribution theory (Sampford and Taylor [1959], Hartley and Hocking [1971]). However, researchers have found that working with distributions specifically proposed for life testing and survival problems, such as the exponential, Weibull, and Gompertz, often leads to methods which are mathematically more tractable and are conceptually and computationally somewhat simpler than is true for the normal. Regression models proposed for these distributions generally involve the assumption of proportional hazard functions which has long been used in the theory of competing risks (Chiang [1968], chapter 12). The present paper describes the application of three such models, two based on the exponential distribution and the other a closely related nonparametric model, to the analysis of clinical trial data.

2. THE CLINICAL TRIAL

Investigations reported here arose from a cooperative trial of acute lymphocytic leukemia begun in 1968 by members of Children's Cancer Study Group A. A complete account of the trial is given by Miller *et al.* [1973].

Children with newly diagnosed, previously untreated disease were entered on study after having successfully completed an induction course of chemotherapy. They were then randomized onto six maintenance regimens, of which five are considered here. Maintenance chemotherapy consisted of alternating eight week cycles of 6-mercaptopurine (6-MP) and methotrexate (MTX), to which actinomycin-D (ACT-D) or nitrogen mustard (HN2) were added according to regimen as outlined in Table 1. Regimen 5 was the control regimen.

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TABLE 1

ADDITIVE THERAPY AND SUMMARY STATISTICS FOR THE FIVE TREATMENT REGIMENS

Regimen	Additive Therapy 6-MP cycle	MTX cycle	Evaluable cases	Number in remission	WBC at dx (Geometric mean)	Age at dx (Mean years)	Median remission duration (Actuarial estimate)
1	ACT-D	HN2	46	20	9,000	4.61	510
2	ACT-D	ACT-D	52	18	12,308	5.25	409
3	HN2	HN2	64	18	15,014	5.70	307
4	HN2	ACT-D	54	14	9,124	4.30	416
5	none	none	52	17	13,421	5.02	420
1,2,4	-	-	152	52	10,067	4.74	435
3,5	-	-	116	35	14,280	5.40	340
ALL	-	-	268	87	11,711	5.02	412

Preliminary data are presented in Table 1 on 268 cases for whom complete and unambiguous information was available. White blood count (WBC) and age at diagnosis were considered as candidates for covariance adjustment. Although differences between regimens with respect to these variables were not significant by analysis of variance, the regimen with the lowest (highest) geometric mean WBC had the highest (lowest) median

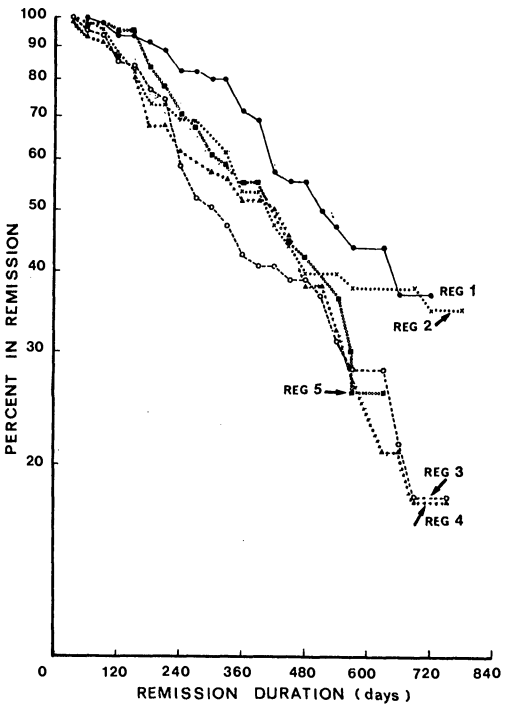

FIGURE 1

REMISSION DURATION BY TREATMENT REGIMEN

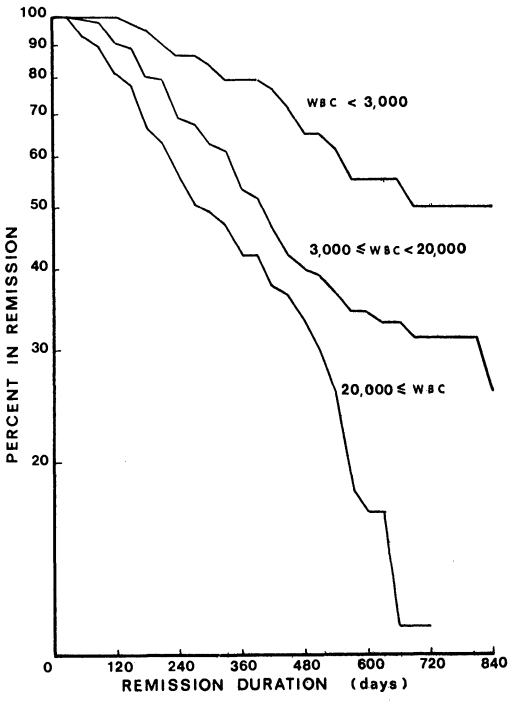

FIGURE 2

REMISSION DURATION BY WBC

remission duration. Many investigators had an *a priori* feeling that actinomycin-D was the active additive agent, so that the contrast between the pooled regimens 1, 2, and 4 vs. regimens 3 and 5 was of interest from the outset. Figure 1 shows the remission duration curves for the five treatments; Figure 2 shows similar curves for three groups defined by initial WBC. The variation in remission duration according to WBC appears sufficiently great as to bias the crude treatment effects, should there be inequalities in WBC among regimens. While the initial WBC is a well-known prognostic indicator for cases followed from diagnosis, it is perhaps not so widely recognized that this variable continues to be of importance for prognosis even after the patient has successfully achieved remission.

Eighty-seven cases were still in remission at the time the data were compiled, which means that the corresponding observations are censored. Of the 181 uncensored observations, 123 were distinct. Multiplicities ran from two (22 observations) to a high of eight (one observation).

In summary, two main questions are posed by the trial: (1) to what extent are differences between regimens, and especially between those employing ACT-D and those not, due to treatment as opposed to differences in baseline characteristics? and (2) what are the quantitative effects of treatment and baseline variables?

3. STATISTICAL METHODS: THE THREE REGRESSION MODELS

A common and useful approach to these questions is to divide the study population into strata on the basis of baseline characteristics and to estimate and compare remission duration curves for the different treatments separately within each one. Results of pa-

rametric or nonparametric tests may be pooled across strata if warranted, preferably by combination of summary statistics. With this approach few assumptions need be made about the relationships among variables. It encourages exploration of the data for interactions between treatment and baseline variables, which could invalidate more formal analyses, and gives a rough idea of the quantitative effects of the baseline characteristics for use in model selection. With increasing numbers of such variables, however, estimates in all the subgroups become unstable due to small numbers, and the overall results are difficult to interpret. Hence the need also for methods which take advantage of additional structure which may be present in the data. Regression methods can meet this need.

The three regression models may all be defined via the equation

$$\lambda(t, \mathbf{Z}) = h(\boldsymbol{\beta}, \mathbf{Z})\lambda_0(t) \tag{1}$$

where $\lambda(t, \mathbf{Z})$ is the hazard function for a patient with regressor variables $\mathbf{Z}$, $h(\boldsymbol{\beta}, \mathbf{Z})$ expresses the relationship between $\mathbf{Z}$ and the regression parameters $\boldsymbol{\beta}$, and $\lambda_0(t)$ is the hazard function of the underlying remission duration distribution. $\mathbf{Z}$ is composed of 0–1 variables indicating treatment group (one fewer than number of treatments) as well as baseline variables. Feigl and Zelen [1965] treated the case $\lambda_0(t) \equiv \lambda$ constant, i.e. the underlying distribution exponential, and proposed several forms for h, notably

$$h(\boldsymbol{\beta}, \mathbf{Z}) = (1 + \boldsymbol{\beta}'\mathbf{Z})^{-1} \tag{2}$$

and

$$h(\boldsymbol{\beta}, \mathbf{Z}) = \exp(\boldsymbol{\beta}'\mathbf{Z}). \tag{3}$$

These two exponential models are henceforth designated Models I and II, respectively. Model I was extended to censored data by Zippin and Armitage [1966] and is considered also by Mantel and Myers [1971]. Model II is treated by Glasser [1967] and, from the viewpoint of Fraser's [1968] structural inference, by Prentice [1973]. Model III is a nonparametric generalization of Model II proposed by Cox [1972] in which (3) describes the effect of $\mathbf{Z}$ but $\lambda_0(t)$ is left arbitrary. Besides being more robust, an attractive feature of this model is the possibility of estimating the underlying distribution.

All the models were fit by maximum likelihood, using the inverse of the observed matrix of second partials of the log likelihood for Newton–Raphson iteration and ultimately to estimate covariances. Average values of $\mathbf{Z}$ over the entire study population were subtracted off from individual values to facilitate convergence and interpretation. Selection of relevant covariates and testing equality of treatments was accomplished by fitting submodels in which one or more covariates were eliminated or one or more treatment regimens pooled together, and comparing resulting ln-likelihoods.

Likelihood equations for Model I are given by Mantel and Myers [1971], whose method of "psuedo expectations" was needed to achieve convergence in some instances.

Likelihood equations for Model II have been given by Glasser [1967] for the case of a single covariate and are easily extended to multiple covariates. In this case it is possible to solve for treatment effects in terms of the regression parameters corresponding to baseline characteristics (covariates), thus reducing the dimension of the matrix needing inversion. No problems were encountered with the Newton–Raphson approach, here, starting from values of $\boldsymbol{\beta} = \mathbf{0}$.

The likelihood equations used for Model III differ from those presented in two other published versions of this model and consequently will be given explicitly along with a brief indication of how they were derived and how they compare with the others. Test

statistics for the K sample problem based on this model were previously proposed by Mantel [1966] and Peto and Peto [1972].

The original paper (Cox [1972]) setting forth Model III also sets forth a discrete time analogue to equation (1) which in fact is used for estimation of β and λ_0 . The underlying distribution is chosen to put conditional probability masses on each of k distinct, ordered, uncensored relapse times t_i , $i = 1, \cdots, k$. These are then related through the linear logistic equation

$$\text{logit } p_i(\mathbf{Z}) = \beta'\mathbf{Z} + \text{logit } p_i , \tag{4}$$

where $p_i(\mathbf{Z})$ is the conditional probability that a patient with covariables $\mathbf{Z}$ relapses at t_i , given that he was in remission at $t_i - 0$. A likelihood function for β is obtained using an intuitive argument whereby one conditions on the set of patients at risk of relapse at each t_i . The maximum likelihood (ML) estimator of β obtained therefrom is inserted into (4) to yield a likelihood function for the p_i .

An alternative discrete version of Model III is obtained from equation (1) by Kalbfleisch and Prentice [1973] who consider the distributions arising from the partition of a continuous sample space. This leads to

$$\ln (1 - p_i(\mathbf{Z})) = \exp (\beta'\mathbf{Z}) \ln (1 - p_i) \tag{5}$$

in place of (4). A marginal likelihood function for β results from consideration of all possible orderings of the observations consistent with the observed pattern of ties and censorship. The ML estimator of β obtained therefrom is inserted in (5) to yield a likelihood function for λ_0 .

The numerical results presented below utilize a third approach (Breslow [1972]) to the simultaneous estimation of β and λ_0 , in which the underlying survival distribution is parameterized as a continuous one, having constant hazards $\lambda_i = \exp(\alpha_i)$ between each pair $t_{i-1} < t_i$ of distinct relapse times. If all withdrawals, or censored observations, which occur in the interval (t_i , t_{i+1}) are adjusted to have occurred at t_i , the ML estimator of λ_0 in terms of β is given at t_i by

$$\hat{\lambda}_i = \exp(\hat{\alpha}_i) = m_i/((t_i - t_{i-1}) \sum_{j \in R_i} \exp (\beta'\mathbf{Z}_j)) \tag{6}$$

where m_i is the number of relapses occurring at t_i while R_i denotes the set of patients "at risk", i.e. in remission and not withdrawn at $t_i - 0$. The underlying remission duration distribution is estimated by

$$\hat{F}(t_i) = \prod_{l=1}^{i} (1 - m_i/\sum_{j \in R_l} \exp (\beta'\mathbf{Z}_j)). \tag{7}$$

The regression parameters β and their covariances are estimated by differentiating the log-likelihood function

$$L(\beta) = \sum_{i=1}^{k} (\beta'\mathbf{s}_i - m_i \ln \sum_{j \in R_i} \exp (\beta'\mathbf{Z}_j)), \tag{8}$$

where $\mathbf{s}_i$ is the sum of $\mathbf{Z}_j$ over the m_i relapses occurring at t_i .

If there are no ties between observations ($m_i = 1$ for $i = 1, \cdots, k$), all three versions of Model III lead to the same likelihood function for β. Otherwise (8) can be regarded as an approximation to the considerably more complicated discrete likelihoods. The three versions do lead to distinct estimates of the remission duration distribution, with the discrete models requiring iteration at each t_i . However (7) can be obtained from both

discrete models by making linear approximations to the estimating equations. Numerical comparisons made below indicate that there may be little practical difference between these versions unless data are more heavily tied than here.

No problems were encountered with iteration based on (8) starting from $\beta = 0$.

4. RESULTS OF THE ANALYSIS

Table 2 summarizes the results of the regression analyses. Estimated coefficients for Models II and III are comparable, both being based on equation (3); those of Model I are not. The numbers of iterations required for convergence by Models II and III are shown, as are approximate standard errors for the estimated coefficients (Table 2, line 10). With the exception of the linear term for age, these standard errors did not vary by more than 0.01 from the indicated value over the nine lines of the table. The column of ln-likelihoods was used to test the improvement in fit by addition of indicated variables, with twice the difference of the values between different lines being referred to tables of chi-square with degrees of freedom (D.F.) equal to the difference in the number of parameters estimated.

WBC was transformed by $\log_{10}$ prior to analysis. The effect of this variable is very pronounced: regression coefficients based on Models II and III are about 0.70 regardless

TABLE 2

RESULTS OF MULTIPLE REGRESSION ANALYSES

Line	N° of variables	Model	N° of iterations	ln-likelihood	Regression coefficients							
					Treatment contrasts					Baseline variables		
					1vs.5	2vs.5	3vs.5	4vs.5	1,2,4 vs.3,5	$\log_{10}$ WBC	Age	Age^2
		I		-1335.9								
1	0	II	1	-1335.946								
		III	1	- 900.839								
		I		-1321.2						-0.46		
2	1	II	4	-1319.377						0.71		
		III	5	- 881.570						0.78		
		I		-1332.9	0.47	0.26	-0.13	-0.02				
3	4	II	1	-1332.925	-0.38	-0.23	0.14	0.02				
		III	5	- 897.218	-0.43	-0.26	0.14	-0.02				
		I		-1334.5					0.30			
4	1	II	1	-1334.461					-0.26			
		III	4	- 898.867					-0.30			
		I		-1318.0	0.28	0.17	-0.04	-0.18		-0.46		
5	5	II	4	-1316.399	-0.27	-0.17	0.17	0.21		0.72		
		III	5	- 877.587	-0.31	-0.21	0.22	0.22		0.81		
		I		-1320.6					0.12	-0.47		
6	2	II	4	-1318.803					-0.16	0.70		
		III	5	- 880.593					-0.21	0.76		
7	6	II	4	-1316.111	-0.26	-0.18	0.17	0.22		0.73	0.02*	
		III	6	- 877.167	-0.31	-0.22	0.21	0.22		0.82	0.02*	
8	7	II	4	-1314.065	-0.32	-0.17	0.11	0.15		0.67	-0.14	0.011
		III	6	- 874.368	-0.38	-0.22	0.15	0.15		0.76	-0.17	0.014
9	6	II	4	-1327.920	-0.43	-0.20	0.08	-0.03			-0.24	0.018
		III	6	- 891.061	-0.49	-0.24	0.08	-0.07			-0.27	0.020
10		II	approximate standard errors of coefficients		0.26	0.24	0.23	0.23	0.15	0.13	0.08	0.005
		III			0.26	0.25	0.23	0.23	0.15	0.13	0.08	0.005

* S.E. = 0.02

of what other variables are accounted for, indicating that the relapse rate approximately doubles (exp (0.70) = 2.01) for every tenfold increase in WBC. The addition of a single linear term for age (Table 2, line 7) makes for little improvement in fit. However, children in the middle age ranges are known (Pierce *et al.* [1969]) to have a better prognosis than those older or younger. Hence when a quadratic term is included (line 8), a significant age effect emerges (χ_2^2 = 4.67 and 6.44 for Models II and III, respectively). Quantitatively, children of age two or ten years show only about a 25% increase in relapse rate compared to those of age six, so the magnitude of this effect is not great.

Adjusting for WBC, with or without simultaneous adjustment for age, makes for little difference in the overall test for equality of treatment regimens. The unadjusted vs. adjusted (WBC only) chi-squares, each with 4 D.F., are 6.04 vs. 6.40, 6.04 vs. 6.16, and 7.24 vs. 7.97 for Models I, II, and III. The unadjusted analyses based on Models I and II are identical. The effect of adjustment is to decrease the apparent superiority of Regimens 1 and 2 relative to the control. Under Models II and III, Regimens 3 and especially 4 are also moved to less favorable positions. With Model I, however, Regimen 3 is moved to a relatively more favorable position, a result which is in line with one's expectations from Table 1. Adjustment has a more profound effect on the single D.F. contrast for ACT-D. In this case the marginally significant unadjusted chi-squares (χ_1^2 = 2.97, 2.97, and 3.94 for Models I, II, and III) are changed to totally nonsignificant ones (χ_1^2 = 1.10, 1.15, and 1.95).

Table 3 examines the important question of parallelism of the regression on $\log_{10}$ (WBC) and indicates that the assumption of constant slope is reasonable for all models. Similar analyses validated the linearity of the regression. In spite of this, final analysis of the complete data set revealed important interactions between treatment and WBC (see discussion below).

It is of interest to compare the estimates obtained using the simplified version of Model III, presented here in equation (8), to those obtained with the original version (Cox [1972]). Including effects for the four treatment contrasts and WBC (Table 2, line 5), the estimates

TABLE 3

ESTIMATED COEFFICIENTS (± STANDARD ERRORS) OF REGRESSION ON $\log_{10}$ WBC FOR EACH REGIMEN AND MODEL, WITH TEST FOR PARALLELISM

Regimen	Model I	Model II	Model III
1	- 0.48	.69 ± .33	.69 ± .33
2	- 0.41	.67 ± .26	.72 ± .26
3	- 0.46	.77 ± .22	.95 ± .23
4	- 0.58	.91 ± .29	1.05 ± .30
5	- 0.43	.50 ± .31	.41 ± .31
All (common coefficient)	- 0.46	.72 ± .12	.81 ± .13
χ_4^2 (test for parallelism)	1.06	1.05	2.88

of regression parameters for the present version are $\hat{\beta}' = (-0.31213, -0.20774, 0.21810, 0.21275, 0.80583)$ compared to $\hat{\beta}' = (-0.31346, -0.20857, 0.22098, 0.21554, 0.81390)$ for the original. Table 4 presents a similar comparison of the estimate of the underlying remission duration distribution, at times t_i corresponding to approximate deciles, for the original version of Model III (with original $\hat{\beta}$), the present version based on equation (7), and the unadjusted actuarial estimate (Kaplan and Meier [1958]) obtained by substituting $\beta = 0$ in (7). From a practical viewpoint, none of these estimates differ substantially for the first six or seven deciles. The actuarial estimate has a hazard function which is initially higher but drops below the other two as individuals with high WBC are gradually eliminated from the population at risk. The considerably different structure assumed by the linear logistic relationship (4) in the original version becomes apparent only towards the tail of the distribution, when the estimated conditional probabilities of relapse become large due to small numbers at risk.

A graph of the estimated underlying remission duration curve is presented in Figure 3 along with the best fitting exponential. Except for an initial shoulder, characteristic of populations of patients who have just achieved a remission, the estimated curve is well approximated by an exponential. The shoulder may explain to some extent the tendency of Models I and II to give more conservative values of test statistics than Model III, since it is known (Gehan and Thomas [1969]) that the parametric analysis is conservative when the hazard function is increasing with time.

TABLE 4

ESTIMATES OF THE UNDERLYING REMISSION DURATION FOR MODEL III

	Model III estimate					
	Original version		Present version		Actuarial estimate ($\beta = 0$)	
t_i*	P_i†	q_i†	P_i	q_i	P_i	q_i
122	.90362	.00 371	.90103	.00389	.89139	.00418
174 (2)	.80966	.00831	.80088	.00901	.78652	.00943
231 (3)	.71426	.01485	.70078	.01585	.68522	.01622
333	.62361	.00636	.60282	.00659	.59046	.00645
399 (2)	.51134	.01867	.50126	.01639	.49341	.01575
511	.39001	.01774	.40207	.01306	.39910	.01235
623	.26981	.02848	.30518	.02284	.31031	.02041
836	.15281	.14513	.20974	.09209	.23116	.06667

* Numbers in parentheses are multiplicites of uncensored observations.

† P_i is estimate of proportion remaining in remission, q_i of conditional probability of relapse, at t_i.

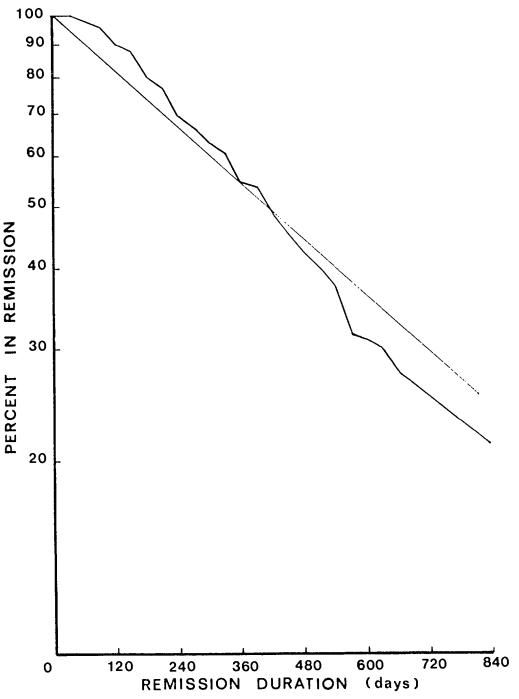

FIGURE 3

UNDERLYING REMISSION DURATION CURVE (MODELS II AND III)

5. DISCUSSION

The utility of the regression method in providing answers to the questions posed at the beginning of this inquiry has been amply demonstrated. There is good agreement in estimates of quantitative relationships for the two models based on equation (3) and good agreement in test statistics for the two parametric models. The method proved sensitive enough to detect the relatively weak quadratic age effect. This might easily go unnoticed in an approach based on broad stratification, especially if strata were not chosen optimally.

Little information is available from the analysis on which to base a choice between the two parametric models, i.e. between (2) and (3). Consequently patients were divided into 11 strata having increasing WBC and an estimate of the exponential parameter, λ, was made for each one. Plots of λ^{-1} and $\log \lambda$ against $\log_{10}$ WBC indicated the latter to be more linear, leading to an apparent preference for Model II. The ln-likelihoods for this model were also slightly higher, although this finding is difficult to interpret. Certainly Model II was the easiest of all three to work with. However, the slightly increased computational price paid for the related nonparametric model is definitely worth the return of greater robustness and, in this case, greater power.

The main disadvantages with the regression approach did not become evident until the complete set of data were assembled for final analysis more than a year later. Alerted to a possible interaction between treatment and WBC in the British Concord trial by the report of the Working Party on Leukaemia in Childhood [1971], a separate analysis (Miller *et al.* [1973]) was carried out using Model III on each of two groups of patients. For patients with lower WBC, several treatments were shown to be significantly superior to control.

For patients with higher WBC, none were superior and some appeared possibly harmful. Part, but not all, of the discrepancy can be attributed to the different sets of data which were employed in the two analyses: the final analysis included patients previously excluded due to problems with evaluation and used updated and corrected information on remission duration for the remainder. Nevertheless, when separate analyses were made splitting the 268 records analyzed here into the equivalent two groups, similar trends emerged and this in spite of the results of the formal test for parallelism (Table 3).

It is clear from the preceding that the question of parallelism is absolutely critical in using regression methods to adjust treatment comparisons for baseline differences. If the effects of baseline variables differ in the various treatment regimens, it is pointless to attempt an overall evaluation of treatment effectiveness. Rather, one wants to identify those subgroups within which treatments act differently. Treatment effects can then be estimated within each subgroup, using regression methods to make minor adjustments when necessary. In this regard the necessity of at least a preliminary look at the data in broad strata cannot be over stressed.

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ANALYSE DE COVARIANCE DE DONNEES TRONQUEES DE SURVIE

RESUME

L'emploi de modèles de régression pour effectuer des ajustements de covariance dans la comparaison de courbes de survie est illustré par leur application à un essai clinique de traitement d'entretien d'enfants leucémiques. Trois modèles sont examinés: le modèle exponentiel linéaire logarithmique (Glasser [1967]); la généralisation non paramétrique de Cox [1972] du dit modèle; et le modèle exponentiel linéaire (Feigl et Zelen [1965]). Il est montré que l'âge et le nombre de leucocytes au moment du diagnostic sont des facteurs importants pour le pronostic; l'adjustement par rapport à cette dernière variable a des effets sensibles sur les comparaisons thérapeutiques. Les avantages et inconvénients de la méthode de régression sont consignés.

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