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VERIFICATION AND COMPARISON OF TWO DIFFERENT PREDICTIVE EQUATIONS IN HODGKIN'S DISEASE

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ABSTRACT

Background and Objective. In recent years, two predictive equations to estimate median expected survival at diagnosis for patients affected with Hodgkin's disease have developed at the University of Pavia Medical School. With this retrospective work we aimed to test correlation between mean survival estimated using the two equations and observed survival, and to compare the results of the two different equations.

Methods. Fifty-three deceased patients were considered from a series of 114 consecutive ones. All these patients had been treated in a conventional way according to therapeutic modalities similar to those used in the series from which the two equations were derived. Expected median survival values calculated with the older, linear equation and with the newer exponential one were compared with observed survival.

Results. Mean survival of the whole series was over 24 years, with survival probabilities of 85% after 5 years and 74% after 10 years. Using the first predictive equation on the 53 deceased patients resulted in a satisfactory correlation between estimated median survival and real survival: Pearson's R correlation coefficient value is 0.5996, with t value 5.35 and p<0.001. The more recent exponential predictive equation considered showed a better correlation between estimated median survival and observed survival: R=0.7338, t=7.71, p<0.001.

Interpretation and Conclusions. The new exponential equation, while apparently complex, is superior to the older one, and is a very reliable and straightforward tool for estimating median expected survival: its forecast reveals itself an important pretreatment parameter in every HD patient. These observations support widespread use of this tool in clinical practice, to evaluate Hodgkin patients' prognosis in a more accurate and flexible way.

Key words: Hodgkin's disease, prognosis, predictive equation

In 1988 Gobbi *et al*.[1] identified six factors [stage, histotype, patient age and sex, erythrocyte sedimentation rate (ESR) and serum albumin values] as having a significant prognostic impact in Hodgkin's disease (HD) and fitted them into a linear equation that could predict mean survival for patients affected with HD and treated according to conventional therapeutic schedules (Table 1).

Recently, the same hematological team from the University of Pavia[2] considered 5,023 patients diagnosed with HD and treated during the 1970's and 1980's: the series belonged to a larger one, the *International Database on Hodgkin's Disease* (IDHD), coming from 20 important institutions or cooperative groups in Western countries. Using multivariate regression analysis they identified seven prognostic factors at diagnosis: stage, age, histotype, systemic symptoms, serum albumin, sex, and involved area distribution (IAD). Unfavorable categories are: stage IV disease, advanced age, lymphocyte depletion histology, presence of systemic symptoms, hypoalbuminemia, male gender, more than three supradiaphragmatic lymph node areas, any subdiaphragmatic ones or any on both sides of the diaphragm. On these bases, they proposed a new, exponential predictive equation (Table 2).

With the represent retrospective work we wanted to test the correlation between mean survival estimated using the two equations and observed survival, and to compare the results of the two different equations.

Patients and Methods

We considered 53 deceased patients out of a series of 114 consecutive ones diagnosed with Hodgkin's disease in the Varese Hospital during the period 1973-1985. Before being treated, all patients were classified according to the Ann Arbor clinical staging system. Of the 114 cases, pathological stage was obtained by invasive procedures in 51 of them (laparotomy in 36 cases and laparoscopy in 15 cases). Early-stage (IA and IIA) patients underwent only radiation therapy; cases with stage III disease and/or systemic symptoms and/or unfavorable histology (mixed cellularity or lymphocyte depletion) underwent chemo- and radiotherapy, while patients with diffuse disease (stage IV) received polychemotherapy (MOPP and/or ABVD schemes). Follow-up was interrupted on December 31st, 1995. Median expected survival for each patient was estimated using the predictive equations proposed by Gobbi *et al.* in 1988[1] and 1994,[2] respectively, according to clinical and laboratory data at diagnosis.

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Table 1. Linear equation for estimating the mean survival (T) of Hodgkin patients developed by Gobbi *et al.* (1988).

T (months) = 329.5–64.6 × ESR – 70.6 × stage
– 60.2 × histotype – 40.4 × age – 20.9 × serum albumin
– 24.3 × sex

Values for the variables cited in the equation:
"1" if: ESR > 45 mm/1h; stage = III or IV; histotype = MC or LD; serum albumin ≤ 3.5 g/dL; sex = male.
"0" in other cases.

Table 2. Exponential equation for estimating the mean survival (T) of Hodgkin patients developed by Gobbi *et al*. (1994).

T (months) = exp [3.75 + 1.25 × stage I + 0.77 × stage II
+ 0.46 × stage III – 0.00046 × (age^2) + 0.85 × histotype
+ 0.42 × symptoms + 0.24 × Ln (serum albumin)
+ 0.25 × sex + 0.25 × IAD]

Values for the variables cited in the equation:
stage I, stage II and stage III: "1" if present, otherwise "0"; age: patient age at diagnosis in years; histotype: "0" if lymphocyte depletion, otherwise "1"; symptoms: "0" if present (B category), "1" if absent (A); serum albumin: natural logarithm of percentile of the frequency distribution; sex: "0" if male, "1" if female; involved area distribution (IAD); "1" if no more than three involved lymph node areas above the diaphragm; "0" if all other conditions."0" in other cases.

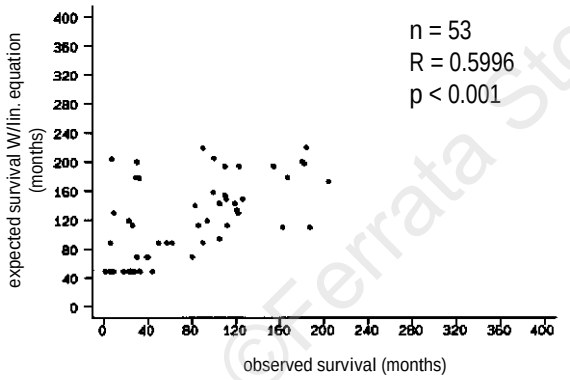

Figure 1. Relationship between observed survival and median expected survival estimated using the linear predictive equation developed by Gobbi *et al*. in 1988 on the 53 deceased patients of our series.

Results

Our whole series included 114 patients (62 males and 52 females); mean age at diagnosis was 40 years (range 10-84 years, standard deviation 16.9 years). Histology demonstrated 53 cases with nodular sclerosis (NS), 34 with mixed cellularity (MC), 20 with lymphocyte depletion (LD) and 7 with lymphocyte predominance (LP). Thirty-one patients were diagnosed with stage I disease, 30 with stage II, 27 with stage III and 26 with stage IV. At presentation 36 patients suffered from systemic symptoms and 45 showed no more than three involved lymphoid areas above the diaphragm. Serum albumin was under 3.5 g/dL (cut-off value) in 67 cases. ESR was higher than 45 mm/1 hour in 72 cases. At the end of the follow-up period, 53 patients had died. Mean survival of the whole series was over 24 years, with survival probabilities of 85% after 5 years and 74% after 10 years.

The first predictive equation proposed by Gobbi *et al*. in 1988[1] was applied to the 53 deceased patients and demonstrated a satisfactory correlation between estimated median survival and real survival: Pearson's R correlation coefficient value was 0.5996, with a *t* value of 5.35 and $p < 0.001$ (Figure 1). Table 3 shows the evolution of our patients according to the prognostic factors considered in the second predictive equation considered.[2] This new equation showed a better correlation between estimated median survival and observed survival: R = 0.7338, t = 7.71, $p < 0.001$ (Figure 2).

Table 3. Hodgkin patients' survival according to clinical and laboratory factors cited in Gobbi *et al*.'s exponential predictive equation (1994).

Prognostic factor	*Patient no.*	*Median survival (yrs)*	*% survival at 5 yrs*	*% survival at 10 yrs*	*p*
Stage					
I-II-III	88	>24	92	90	p < 0.001
IV	26	6	45	20	
Patient age					
< 45 years	69	>24	98	90	p < 0.001
≥ 45 years	45	10	68	50	
Histotype					
MC-NS-LP	94	>24	85	80	p < 0.001
LD	20	10	65	50	
Symptoms					
A (absence)	78	>24	90	90	p < 0.001
B (presence)	36	9	65	50	
Serum albumin					
> 3.5 g/dL	47	>24	92	90	p < 0.001
≤ 3.5 g/dL	67	8	60	48	
Sex					
female	52	>24	95	92	p < 0.001
male	62	14	75	60	
Involved area distribution					
= 1	45	>24	98	90	p < 0.001
= 0	69	11	75	55	

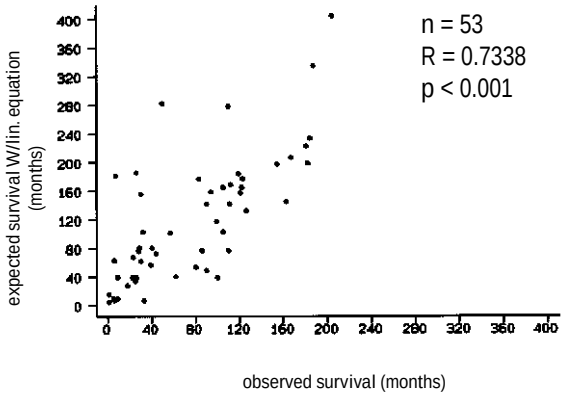

Figure 2. Relationship between observed survival and median expected survival estimated using the exponential predictive equation developed by Gobbi *et al*. in 1994 on the 53 deceased patients of our series.

Discussion

The correlation demonstrated between estimated median survival and observed survival is significant with both predictive equations and higher with the more recent one; this latter, which involves the use of an exponential and different coefficients, can better discriminate estimated survival, in particular in high-risk patients.

This new predictive equation enables us to consider teh significance of the clinical and laboratory features that show prognostic importance in HD. Stage is obviously of primary importance; our study confirms the unfavorable trend for stage IV patients, while survival differences were not clearly observed among earlier stages. As previously reported,[3,4] age is one of the most important prognostic parameters, with an unfavorable trend for patients diagnosed at an older age. HD in the elderly shows differences with respect to clinical presentation,[5] as demonstrated by the different distribution among histotypes versus younger patients.

We agree with other authors in saying that the unfavorable trend for older patients can only be imputed in part to biological disease differences.[6] In fact, comorbidity, a high incidence of toxic events with conventional chemotherapy and the unfairness of therapeutic decisions appear to be the main factors responsible for this trend.[7] Excellent results have been obtained in the treatment of pediatric Hodgkin's disease, both in terms of overall and relapse free survival, in spite of a high incidence of complications caused by the aggressive treatment used in this series.[8]

Another important factor is histotype; in our series the unfavorable trend for LD is clearly evident versus the other types. Systemic symptoms, serum albumin and sex could be considered of minor value, but their prognostic role is reinforced by their relationship with biological tumor features. The presence of body symptoms in fact reflects a cytokine-mediated interaction between host and tumor better than acute-phase protein or chronic disease laboratory indicators. According to Gobbi,[9,10] body symptoms should be re-evaluated, excluding night sweats and including severe pruritus, or better still, directly measured by the determination of some cytokines or their metabolites.

The importance of hypoalbuminemia, as shown in other studies,[11,12] does not reflect a clear understanding of its mechanism in neoplastic patients. Today, the more accepted reason is a dilution of the circulating albumin pool rather than reduced synthesis. Recently, a better prognosis for HD in female sex was confirmed.[13] The importance of involved area distribution in relation to tumor mass, in particular in early disease stages, has been pinpointed by recent studies;[14] this parameter integrates stage information (and probably albumin too) in the evaluation of HD tumor mass.

In conclusion, the new exponential equation, while apparently complex, is superior to the older one and is a very reliable and straightforward tool for estimating median expected survival. Its forecast proves to be an important pre-treatment parameter in every HD patient. So we agree with Gobbi *et al*.[2] in recommending the widespread use of this tool in clinical practice to evaluate the prognosis of Hodgkin patients in a more accurate and flexible way. For instance, median expected survival could be used to select high-risk patients who might be candidates for an aggressive therapy schedules,[15] including high dose sequential chemotherapy followed by autologous stem cell transplantation.[16]

For experimental purposes, median expected survival obtained with the new predictive equation could also be useful for a better stratification of patients undergoing clinical trials or for re-evaluating past therapeutic trials. Moreover, this equation summarizes the most important prognostic factors in HD in a parameter that can enter Cox's proportional hazards model (multivariate regression analysis) as an overall prognostic covariate.

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