Computation of Life Expectation in Chronic Glomerulonephritis

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A multiple regression equation for the life expectation of patients with chronic glomerulonephritis was derived by the least-squares method from the laboratory investigations on 13 patients admitted to our clinic during 1962-65. Components of the regression were blood urea nitrogen, maximum urinary specific gravity, and hemoglobin (per cent, Sahli) obtained at the first examination, which had apparently the closest correlation with the life length of the patients. First-order regression reduced the dispersion already more than any of a single component, and second-order regression did the same further.

This regression equation is useful in: 1) Estimation of the severity of the patients' condition; 2) classification of glomerulonephritis into slowly and quickly progressing types, if such exist, by comparing the difference between two estimations made at different time and the actual lapse of time between the estimations; and 3) evaluating therapeutic efficacy.

The same regression equation (first-order) seems to be applicable to a wide range of the severity of glomerulonephritis, since it permits to predict changes in the maximum urinary specific gravity over the age from 20 to 80 years in Japanese subjects.

It is an old desire of mankind to anticipate the date of death in sick as well as in healthy subjects, as seen, for example, in Pythagoras' calender in the medieval age.¹ In the day of scientific medicine, the prolongation of life is expected by means of adequate measures, and it seems still important to know the real expectation of life, when the efficacy of a new treatment or a remedy is to be evaluated.

In the case of chronic glomerulonephritis there is the unique difficulty in that the identification of the disease is not so simple, partly because of the historical transition in its concept. At first, morbus Brighti had only a vague boundary, and there were monistic and dualistic theories with regard to its etiology. Bartels² proposed his famous classification of parenchymatous and interstitial nephritis. But Senator³ included a component of Bartels' interstitium — namely, glomerulus — in parenchyma, and this resulted in a 'Babylonic' confusion of the terminology in literature.⁴ Then Volhard⁴ established his 'reasonable' system, and after him the controversies shifted in the field of etiology.

Volhard⁴ proposed originally 3 major factors in determining the prognosis of patients with chronic glomerulonephritis, *i.e.*, 1) urinary concentration and dilution as indicating renal functions, 2) hypertension and cardiac force as circulatory factors, and 3) predisposition to edema. But he observed that the most reliable index for the prognosis was NPN reported a little before him by Hohlweg.⁵ Strauss⁶ also appreciated highly the significance of NPN. Lichtwitz⁷ added retinal findings to the above three factors of Volhard. Until recently these factors were widely used as criteria in establishing the prognosis of the disease.

In the present study we selected 3 parameters, that is, blood urea nitrogen (BUN), maximum urinary concentration, and hemoglobin concentration as the factors most closely correlated to the life length of the patients, on the basis of clinical data of hospitalized patients in our clinic. It is interesting to notice that they are associated with renal cortical, medullary and general conditions of the patients, respectively.

Generally speaking, the correlation between a single factor and the life length of the patient is not very high. A clinician in practice, therefore, combines several bits of information of which weight depends on his own experiences. Apparently, if all information is favorable the expectation of life is also good, and an association of bad information will shorten the life expectation. In the midway, there might be a reasonable weighting of every bit of information predetermined in a given population of patients.

The progress of chronic glomerulonephritis is relatively monotonous. The estimation of severity function for this disease seems to be rather easy. Recently, however, artificial dialytic procedures have come to cause serious deviations in the natural course of chronic glomerulonephritis. It seems still worth-while, we think, to estimate a severity function in order to evaluate quantitatively the effectiveness of treatments on this disease.

MATERIALS AND METHODS

Materials for the present computation were obtained from protocols of 13 patients with chronic glomerulonephritis hospitalized in our clinic during 1962–65 as shown in Table 1. Among them two were admitted twice, and all deceased in the hospital except one. Patients with major complications were omitted. Before 1962, NPN and not BUN was measured. Therefore, patients admitted before 1962 were excluded from this study. The first measurements after admission were selected for the study so that the influence of treatments on the parameters was minimized. As for the maximum urinary specific gravity, the highest value was chosen from three sources; namely, values obtained with Fishberg's concentration tests, values of the earliest morning urine, and values from daily measurements in the ward; the last were adopted only when their values were available in repeated examinations. It is noteworthy that the values of Fishberg's test were not the highest in 5 of 8 cases. If only osmolar concentrations were known, they were

TABLE 1. *Clinical data of patients employed in this study*

Subject	Survival time (day)	BUN mg%	Urinary specific gravity (max.)	Hb (Sahli) %	Autopsy or biopsy
T.K. (2)	2	205	1,014	32	Autopsy
S.I.	3	165	1,010	32	
Y.S.	9	177	1,012	30	
H.S.	13	180	1,012	28	
J.T.	18	180	1,016	38	
K.Y.	25	175	1,014	24	Autopsy
M.I.	31	96	1,012	33	
K.I. (2)	34	92	1,011	73	
T.K.	38	111	1,014	30	
Y.M.	69	67	1,010	60	
T.K. (1)	402	76	1,017	62	Autopsy
A.Y.	463	35	1,019	80	
K.I. (1)	512	45	1,020	55	
Y.M.	999	23	1,026	70	
K.S.	1,042	28	1,021	81	

(1) and (2) signify the first and second admission, respectively.

rendered to values of specific gravity by the following formula:⁸

$$\text{Sp. gr. (max)} = 1000 + 0.03 \times (\text{mOsm}).$$

The statistical method was a multiple regression analysis.^{9,10} At first, the life length of the patients from the date of admission was changed into its logarithm. The first-order regression equation was:

$$\log t = \log t_0 + Zb + e$$

t : a 15-dimensional vector,

$$t_i = \text{life length of the } i\text{-th patient} \quad (i=1, \dots, 15)$$

t_0 : a constant

b : a 3-dimensional vector,

$$b_i = \frac{\partial \log t}{\partial z_i} \quad (i=1, 2, 3)$$

z : a 15×3 matrix (z_{ij}),

$$z_{i1} = 200 - \text{BUN}$$

$$z_{i2} = \text{Hb in \% (Sahli)} \quad (i=1, \dots, 15)$$

$$z_{i3} = \text{Sp.gr. (max)} - 1009$$

e : a 15-dimensional error vector,

$$e_i \quad (i=1, \dots, 15)$$

At practice of computation, a column $z_{i0} = 1$ ($i=1, \dots, 15$) was added to the matrix Z and $\log t_0$ was treated as 0-th component of b for convenience. The estimation of b and e was possible by the least-squares method, that is:

$$\hat{b} = (Z'Z)^{-1} Z' \log t$$

$$\hat{e} = \log t - Z\hat{b}.$$

The second-order regression equation was formulated as:

$$\log t_i = \log t_0 + z_i' b + 1/2 z_i' B z_i + e_i \quad (i=1, \dots, 15)$$

$Z = (z_1, \dots, z_{15})'$: a 15×3 matrix similar as above

B : a 3×3 matrix (b_{ij}),

$$b_{ij} = -\frac{\partial^2 \log t}{\partial z_i \partial z_j} \quad (i, j = 1, 2, 3)$$

B is mathematically a tensor of the second rank. This expression of regression equation facilitates to notice that a second-order regression equation is equivalent to the Taylor expansion up to the second derivatives in the differential calculus. In actual computations the same procedure was employed for $\log t_0$, and the tensor term is reduced in a quadratic form. The paucity in the number of cases rendered our second-order regression equation to one of little significance.

All computations were performed at the Data Processing Center of University of Tokyo with an OKITAC.

RESULTS

At first the relationships of three factors, BUN, maximum urinary specific gravity, and hemoglobin, to the life length are shown in Figs. 1, 2 and 3.

Fig. 1. Relationship between BUN and life length (survival). White circles indicate patients who underwent artificial dialysis.

Fig. 3. Relationship between hemoglobin (per cent, Sahli) and survival. White circles stand for the same as in Fig. 1.

the ratio of values. Only in one case of dialysis survival time is significantly lengthened.

Out of our 13 patients two were hospitalized twice, and their life expectations were evaluated at each time as shown in Fig. 5. One of the cases, whose slope seems to be less steep, deceased two days after the second admission. Although his life expectation was 5.8 days, it may not be regarded as a meaningful deviation from the original group. However, we can suspect from this result the existence of slowly and quickly progressing types of chronic glomerulonephritis. If such is the case with the estimations at two times of sufficiently long interval, one may find out the slopes of significantly different steepness than the standard one. Or, perhaps, there may be a continuous spectrum of such slopes.

From the clinical viewpoint, it is of cardinal importance to discriminate these types of patients in advance of their death. It may provide valuable information to compare the differences of the computed expectations at two distinct times and the actual lapse of time between these measurements. For this purpose, we can regard one variate and 3 variables in our regression equation as constituting a universe in a statistical meaning, and the equation as a conditional distribution of one component defined by the remaining three. Some day, it may be possible to find a key variable or variables which will yield a sufficient discriminant function before the death of the patients. Until then, one must have at least two measurements on each nephritic patient to decide the universe or the type of nephritis.

Fig. 4. Relationship between life length estimated by the first-order regression equation (survival function) and actual survival time. White circles indicate patients who underwent artificial dialysis.

Fig. 5. Relationship between estimated and actual survival time in two patients computed at two different times. Points for each patient are connected by solid line.

Fig. 6. Relationship between life length estimated by the second-order regression equation (survival function) and actual survival time.

Fig. 7. Expectation of life in Japanese at ages from 20 to 80 (at each decade) and estimated maximum urinary specific gravity at fixed BUN and Hb. σ is expressed also in specific gravity (see text).

The second-order regression equation estimated was:

$$\begin{aligned}\log \hat{t} = & -0.581818 \\ & - 0.014535z_1 \\ & + 0.098616z_2 \\ & + 0.18327z_3 \\ & - 0.00028163z_1^2 \\ & - 0.0035496z_2^2 \\ & - 0.0080082z_3^2 \\ & + 0.0019985z_1z_2 \\ & - 0.0022513z_1z_3 \\ & + 0.0056090z_2z_3\end{aligned}$$

and the reduction in dispersion by the higher approximation is shown in Fig. 6. The estimated error was ± 0.12868 as compared with ± 0.283364 in the first-order regression. However, in the application of more accurate regression the degree of freedom decreased markedly, and the effective range is considered to be strictly confined within the space where the samples are distributed. This is easily seen by the inspection of the equation.

Finally, we tested the applicability of our equation outside the sample group by computing the expectation of life in a healthy population. The expectation of life at each age in common Japanese is assumed to depend on the reduction of renal concentrating capacity, since BUN and Hb may not deteriorate with advancing ages. In Fig. 7 the estimated maximum urinary specific gravity is shown in parentheses at every decade above the second. The estimated error in terms of specific gravity is also shown which is presumed to represent the whole deviation by this single factor. Although it must be admitted that not every Japanese will die of nephritis, the computed renal concentrating capacity yielded values more than satisfactory.

DISCUSSION

When Ellis¹¹ asserted that different types of chronic glomerulonephritis may have different causes, he challenged the theory of Volhard who assumed a continuous spectrum of nephritis. The controversy is not at all settled at the present time. We believe that any characteristic in nephritic patients will require mathematical evaluation in reference to its adequacy in discriminating nephritic types. In our study of small samples we could not make such an attempt. But if a sufficient number of cases are available for multiple estimations, we will be able to make a reliable prediction already with our simple method.

Another application of our survival function is an evaluation of the severity of the disease. Although the need for an estimation of life expectancy is recognized also in chronic glomerulonephritis since long time, it is considered practically impossible by experienced clinicians like Volhard,⁴ Lichtwitz,⁷ and Sassa.¹² They

were all aware of the difficulty in establishing such prognosis. However, every clinician has in fact his own severity function implicitly as White¹³ pointed out. When our equation will be used as a severity function, the computed expectation of life will mean that 50 per cent will die within the calculated date and 84 per cent until a period 1.92 times as long as the expectancy. The last figure is obtained by changing the estimated error of the first-order regression, 0.283364, from the logarithmic into the cartesian scale. Or, 68 per cent will die between the date 0.52 and 1.92 times as long as the computed life length.

Transformation of the variable is also applicable to the whole regression equation:

$$\hat{t} = \frac{10^{0.0642151 \text{Sp.gr.}} \cdot 10^{0.00262395 \text{Hb}}}{10^{62.5879} \cdot 10^{0.0090239 \text{BUN}}}$$

Here, one can observe easily how each factor influences the life expectancy. The relative weights of numerical values of measurements will be:

$$1 \text{ Sp. gr. (max)} \approx 7 \text{ BUN} \approx 24 \text{ Hb,}$$

that is, the change of a unit in the maximum urinary specific gravity is equivalent to that of 7 units of BUN or 24 units of Hb. It is noteworthy that, although anemia implies the last phase of the disease, this extrarenal factor has only a little to do with the expectation of life in the computation.

Recently, renal biopsy technique has come to afford new characterizations of clinical picture in chronic glomerulonephritis. However, our experience in this method is still too limited to allow any reliable evaluation of prognosis of the disease. In Japanese literatures, some attempts were made to correlate the pathological findings with the renal function tests.^{14,15} Other attempts were made to show a direct relationship between pathological categories and the progress of the disease.¹⁶⁻²⁰ It will be meaningful to remind here the words of Volhard⁴ in his early days that histological findings are nothing more than a symptom and that only after combined use with clinical data and the results of function tests they will be correctly interpreted.

Lastly, the improvement of precision in expecting the life length achieved by combining the measurements of the patient will be discussed briefly. Our regression equation eliminates the dispersion due to the non-parallel progress of symptoms of chronic glomerulonephritis. For example, Fishberg²¹ stated that at first the decline in renal concentrating capacity indicated the progress of the disease, but later, when this function was lost, BUN and urea clearance would be the best guide to the derangement of the kidney. This type of imprecision can be dismissed by our regression analysis.

Further improvement of precision may be attained by adding secondary factors beside the apparent correlative factors. For instance, albuminuria is said to be indicative only of the extent of 'nephrotic strike' and not correlative to the prognosis of the original disease.¹² However, it is also possible that such factors as

albuminuria, edema, and blood pressure will have some causative relationship with those primary factors taken up in this study. Evaluation of such factors deserves further investigation.

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