

UNIVARIATE & MULTIVARIATE ANALYSES ON MOCCA TREATED PATIENTS +

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Abstract

The biometric analysis of survival time (measured from the date of diagnosis until the failure or censure) of 130 MOCCA treated patients who were observed at homatologia hospital with certain generalized plasmacytoma is investigated. Several common risk factors, such as hemoglobin, urea and Beta2M seem to influence the survival time. Both univariate and multivariate analyses were used. For univariate case, we have used Logrank and Gehan tests. The analysis of multivariate is based upon proportional hazard model.

المستخلص

التحليل الحيوي الاحصائي لزمن النجاة لبيانات 130 مريض المستحصل عليهم من احدى المستشفيات والذين كانوا تحت فترة علاج يسمى موكا مقياس من زمن التشخيص الى حد الاخفاق او الفقدان للمرضه الذين يعانون من مرض سرطان الدم (بلاسيثوما خلايا مصل الدم) قد نوقشت احصائيا ، عدة عوامل خطرة مشتركة مثل الهيموكلوبين واليوريا و Beta2M يبدو لها تاثير في زمن النجاة . قمنا بعمل احصائيات وصفية كاملة مع التحليلين الاحادي والمتعدد ، في التحليل الاحادي استخدمنا اختبار Logrank و Gehan اما في التحليل المتعدد فقد استخدمنا تحليل الانحدار المبني على أنموذج الخطورة النسبي . Proportion hazard model.

Introduction

In this paper a more detailed analysis is given to the data on 130 MOCCA treated patients who where observed at homatologia hospital. A major problem is to select from clinical covariables [1] measured at the time of diagnosis, important risk factors for survival time [2], that is the time from the treatment until the failure time, and to quantify their influences.

The data on 130 patients displayed in table 1 are given in the appendix. Although explanation below, the table should generally suffice, some further explanation on method of measurements will be given. All intake covariables from ($x_3, \dots, x_{13}$) are measured just at time of diagnoses, the covariables are based on the median of 3 measurements.

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Aim Of Research

The aim of this research is to predict the outcome of the respond covariable for particular individual from the outcomes of a selection of predicting 13 covariables. From these predicting covariables, we could recognize which of these covariables are giving better survival time than others or whether they give a negative or positive relationship with the survival time of patients by using Breslow [3] and Cox and Oakes [4] tests for univariate analysis and proportional hazard model (regression) [5,6,7] for multivariate analysis. Both analyses have been carried out by using statistical software BMDP [8]. Descriptive statistics

(1) **Summary statistics:** In table 2^A a descriptive summary of data with respect to the most relevant covariables is given. It may be useful to have a look at it before attempting to select an appropriate set of predicting covariables [1]. From table 2^A one can see that BS and PP slightly are skewly distributed to the right. Almost all covariables have high and narrow peak and sharpest peak is at B2M, about 93 patient are greater than 60 years. The discrete covariables in table 2^B, shows that most patients i.e. (about 70%) are censored, while only smaller fraction i.e. (30%) dead. The situation in filtration (ID) is more patients fall in category A and only 6 patients fall in category LP. About 129 patients out of 135 have normal area and very few patient (6) have exceeded their normality.

Table 2. Descriptive statistics of patients with MOCCA treatments

A. Continuous covariables

Covariable	(min, M, max.)	SD	Skewness	Kurtosis
BS	(10, 80, 160)	40.67	0.09	1.89
HG	(12,115,152)	21.10	-1.08	5.76
TP	(63, 89, 140)	16.47	1.06	3.67
PP	(8, 33.5, 96)	18.55	0.77	3.06
ID	(3, 30, 96)	16.17	0.98	4.74
AGE	(35, 60, 90)	9.61	-0.31	3.43

B. Discrete covariables

<u>Covariables</u>	<u>percentage</u>	<u>category</u>
Infiltration	9%	BL
	33%	P
	5%	LP
	53%	A
Urea	4.4%	high
	95%	normal
Stage	6.6%	I
	48.1%	II
	39.33%	III
Censoring	5.9%	unknown
	70%	censored
	30%	dead

(2) **Dependencies among covariables:** There may exist various associations among covariables. In tables 3^A and 3^B, the sample correlation

coefficients are displayed. Under hypothesis of independence between two covariables, the standard error of the sample correlation coefficient is given by $1/(n-1)^{1/2} = 0.0864$, regardless of the fact whether the joint distribution of these two covariables is continuous, discrete or mixed. Sample correlation coefficients in which at least twice this standard error are typed in bold face.

Note that it is difficult to determine which population coefficient is larger than other ones. Besides it is difficult to give a clear interpretation of such assertion if these corresponding marginal distributions are of different type.

Table 3. Pearson correlation matrix
A. continuous covariables

	1	2	3	4	5	6	7
1. BS	1						
2. Hg	0.366	1					
3. TP	-0.366	0.013	1				
4. PP	-0.309	-0.271	-0.415	1			
5. ID	-0.103	0.416	0.091	-0.162	1		
6. Age	0.034	0.065	-0.233	0.021	-0.043	1	
7. B2M	-0.061	-0.244	0.000	0.055	-0.265	-0.157	1

“In sample correlation matrix that differs at least 2 standard error are typed in bold face”

B. Discrete covariables

	8	9	10
8. Urea	1		
9. Sex	-0.066	1	
10. Stage	-0.043	-0.006	1

C. Between continuous & discrete

	1	2	3	4	5	6	7
8. Urea	-0.133	0.005	0.112	0.081	-0.268	0.080	0.020
9. Sex	-0.011	0.126	0.136	-0.201	0.182	-0.077	0.067
10. Stage	0.016	0.116	-0.880	-0.106	-0.077	0.126	0.168

From table 3^A one can see that at least the following associations seem to be manifestly present in the population. PP is lower when Hg ($r = -0.271$) is higher, and TP ($r = -0.415$) is higher. Age and PP are negatively correlated with TP and BS respectively. If one takes a look at table 3^B for correlation among discrete covariables, one can see that there exists no single relation.

Again take a look at table 3^C for correlation between continuous and discrete covariables. Urea is negatively correlated with B2M ($r = 0.269$), where sex has two associations with continuous covariable. The result of table 3(A,B,C) is summarized in the following table:

Table 4.

Covariable	number	with	sign of r
1. BS	(3)	(2,3,4)	(+,-,-)
2. Hg	(3)	(4,5,6)	(-,+,-)
3. TP	(3)	(1,4,6)	(-,-,-)
4. PP	(3)	(1,2,3)	(-,-,-)
5. ID	(3)	(2,5,9)	(+,-,-)
6. Age	(2)	(3,5)	(-,-)
7. Urea	(1)	(7)	(-)
8. Sex	(2)	(2,5)	(-,+)
9. Stage	(0)	-----	-----
10. B2M	(2)	(2,5)	(-,-)

Theoretical Approach

- 1) Selecting a set of predicting covariables: the selection of an appropriate set of predicting covariables is an important step before entering the stage of making prediction. There is a course much similar to selecting variables in ordinary regression problem, for which wide literature exists. Main complications are the occurrence of censoring and infinite dimensional nuisance parameter $S(t/0)$ [9]. These complications are dealt with by considering asymptotic theory of the partial likelihood function[4,10]

$$L(B) = \prod_{j=1}^n (\exp(B^t z_j) / Q_j(B)^{\delta_j})$$

with

$$Q_j(B) = \sum_{h \in R(t_j)} \exp(B^t z_h)$$

Here, t_j is the observed life time (i.e. time to failure or censure) and $z_j = (z_{1j}, \dots, z_{kj})$ is the vector of covariate patient j , while d_j indicates whether ($d_j = 1$) or not ($d_j = 0$) Failure occurred before censoring. As usual $R(t_j)$ denotes the risk set of time t_j , i.e. the set of patients with life larger than or equal to t_j . The denominator $Q_j(B)$ will be called the partition function.

The dependence of $L(B)$ and $Q(B)$ on $z_1, \dots, z_n$ and $d_1, \dots, d_n$ is suppressed in the notation. Several investigators have argued or proven that this partial likelihood may be treated as ordinary likelihood [4,10].

There are at least two separate points of views to assess the relative importance of the various covariates in predicting the survival time.

View point 1

A covariate $z_j (i = 1, \dots, k)$ is considered to be statistically significant if the null hypothesis $H_0 : b_i = 0$ can not be rejected at 5% level in a model. No exact theory being available, one resorts to asymptotic methods for testing this hypothesis.

Let $\hat{B} = (\hat{b}_1, \dots, \hat{b}_i)$ and $\hat{B} = (\hat{b}_1, \dots, \hat{b}_{i-1})$ be the parameter vectors maximizing the partial likelihood function for model based on covariables $z_1, \dots, z_i$ and $z_1, \dots, z_{i-1}$ respectively. The information matrix

$$I(B) = - \left(\frac{\partial^2}{\partial B \partial B^t} \right) \ln L(B)$$

is assumed to be non-singular in a sufficiency large neighborhood of $\hat{B}$. The null hypothesis H_0 is rejected if

$$(i) \quad \hat{b} / SE(\hat{b}_i) > U_{\alpha/2}$$

or U_α if one-sided testing is allowed. The standard error being estimated by square root of $(I^{-1})_{ii}(\hat{B})$.

(ii) the score statistics

$$U_1(\hat{B}, 0) = \left(\frac{\partial}{\partial b_1} \right) \ln L(B) \Big|_{B = (\hat{B}, 0)}$$

is large with respect to its estimated standard error $\{(I^{-1})_{ii}(\hat{B}, 0)\}^{-1/2}$

$$(iii) \quad -2\{\ln L(\hat{B}, 0) - \ln L(\hat{B})\} > c_{1;\alpha}^2$$

Although under suitable regularity conditions, these three methods are asymptotically equivalent, for finite sample sizes they may lead to different result in a concrete situation, it is sometimes useful to apply more than one of them.

View point 2

Again considering the patients as a sample from large population, the covariate can be looked upon as a random variables and will be denoted by capitals. A covariate Z_i is considered to be more relevant for prediction than another covariate Z_h , if

$|\hat{b}_i| SD(Z_i) > |\hat{b}_h| SD(Z_h)$, where $SD(Z_i)$ denotes the estimated standard deviation of covariate Z_i . The motivation of this point of view is as follows: let us call patient for whom the i^{th} covariate differs one sample standard deviation from the estimated mean $\bar{Z}_i$ moderately deviant (with respect to the covariate Z_i). Then a moderately deviant patient will have a point estimated hazard rate which differs by a factor $\exp(\hat{b}_i SD(Z_i))$ from that of a typical patient with covariate Z_i and the same other covariates.

Note that for normally distributed covariates about 1/3 of the patients are at least moderately deviant. For dichotomous covariate ($Z_i = 0 \text{ or } 1$), it is convenient to look at relative risk associative with two possible values of covariate, which is $\exp(b_i')$. If this covariate is approximately symmetrically distributed (i.e. $E(Z_i) = 0.5$), then, to close approximation, $SD(Z_i) = 0.5$. Therefore, in practice, if some covariates are dichotomous with $E(Z)$ not close to (0 or 1) and other not, it is natural to compare quantities $\exp(b_i D_i)$, where $D_i = 0 \text{ or } 1$ for dichotomous covariate and $D = 2SD(Z)$ for other covariates, the two points of view, concentrate on different aspects.

View point 1 relates the estimated effects b_i' to their statistical uncertainty, which strongly depends on the effective sample size, whereas view point 2 roughly evaluate whether one risk factor is likely to be a more important predictor for survival time of new patient arriving at the hospital than some other factor. If for some covariate, adequacy of the proportional hazard model is considered dubious, the stratified model may be used. In that case $r = 1, \dots, s$ denoting the level of the stratifying variable:

$$L(B) = \sum_{r=1}^s L_r(B), \text{ where } L_r(B) \text{ is based on all observations in the stratum.}$$

Results:

The actual calculations were performed by using the Bio-Medical Data Processor Package [8].

- (1) **Univariate analysis:** The results of univariate analysis to sub-sample consist of 45 out of 135 randomly selected with 9 dead and the rest are censored as shown in table 5, where separate effects of various covariates are indicated by giving Approximately the two-sided P-values of the Gehan and Longrank tests with Wilcoxon and Savage score respectively. It is tested, for example, whether the patient with normal Hg has the same survival curve as a patient with lower Hg. The test of Gehan attaches gives more weight to early differences in the samples than Longrank test does.

The direction or the (significant) effects can be seen from the arrows in the fourth column, which refer to sub-samples indicated in the first column. The sample size of the smaller of the two sub-samples together with corresponding number of dead is displayed in the last column. We take the first line as an example: patient with higher Hg have significantly worse survival than patient with lower Hg. The smallest sub-sample consists of 7 patients with 0 dead, and consequently, the largest sub-sample of 38 patients with 9 dead. From the information about the sub-sample one can construct familiar 2 x 2 contingency tables which have to be considered with extreme caution of the censoring.

Table 5: Influence of single (dichotomous) factors on the survival of MOCCA treatment.

Covariant	P-values		Effect	Smallest sub-sample	
	Gehan	Longrank		Size	Dead
				Total	
Hg (normal=0, high=1)	**	**	↓	45	9
TP (normal=0, high=1)	***	***	↓	07	0
PP (lower=0, higher=1)	***	***	↓	15	3
				16	3
				02	0

Two sided P-values

*** : $P > 0.15$
** : $0.05 < P < 0.15$
* : $0.001 < P < 0.005$
. : $P < 0.0001$

Effect

↓ : Patients with this character have worse prognosis.
- : Test uninformative due to small sub-sample size.
↑ : Patients with this character have better prognosis.

(2) **Multivariate regression analysis:** For multiple regression analysis based on Cox's proportional hazard model, we decided to take separately the continuous and discrete covariables in order to avoid the multidimensionality and because the covariate B2M has missing values of 30 patients out of 130 cases. The results of the first round are presented in table 6. from view point 1, one can see that the Hg and B2M are highly significant, whereas the infiltration is just significant if one-sided test is allowed. The negative coefficient b' decreases the value of the hazard function and therefore indicates a positive relationship with survival whereas the positive b' has reverse interpretation.

Table 6: Multiple regression analysis based on PH model (round 1).

Covariable	b'	$b' / SE(b')$	$\exp(b'D)$
BS	-0.0121	-1.1183	0.3737
Hg	-0.0307	-3.6379	0.2737
TP	0.0161	1.4172	1.6997
PP	-0.0041	-0.3634	0.8589
Age	-0.0076	-0.4424	0.8641
ID	-0.0251	-1.9190	0.4441
B2M	0.0975	5.5791	4.9288

“D = $2SD$ if Z is continuous covariable”

The results of the second round for discrete covariables are summarized in table 7. One can see that the urea and the stage are just significant if one-sided test is allowed with positive coefficient which increases the value of the hazard function and therefore indicates negative relationship with survival.

Table 7: Multiple regression analysis based on PH model (round 2) [2].

Covariable	β	$\beta/SE(\beta)$	$\exp(\beta D)$
Urea	0.6953	1.6591	1.6383
Sex	-0.0900	-0.2628	0.9139
Stage	0.3814	1.6328	1.7148

D = 1 if Z is dichotomous covariable

Note that from view point 2, the TP and B2M in continuous case can be considered as relevant covariable for production, urea and stage in discrete case as well.

Conclusions & Suggestions

Conclusion

The results of univariate analysis to sub-sample of 45 out of 130 randomly selected with 9 dead and the rest are censored are shown in table 5. In this table the row of effect the patient with higher Hg ,TP, PP, B2M, Sex, and stage have worse prognosis, whereas Urea has better prognosis by using **Gehan** and **Logrank** tests [9],[11].

The results of multiple regression analysis based on Cox proportional hazard [7],[11] are shown in tables 6 and 7. for continuous case, the covariables TP and B2M (table 6) can be considered as relevant covariables for prediction, whereas for discrete case (table 7) the Urea and stage as well.

Suggestion:

From the medical point of view, the MOCCA treatment gives longer survival time than any other treatments, especially for the cancer patients. So we advice the doctors who are working on cancer research take into account the covariables which are most relevant for prediction such as Urea, stage, TP, and B2M.

APPENDIX

TABLE 1. Survival data of 135 MOCCA treatmented patients.

X_0	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10} X_{12}	X_{11} X_{13}
1	042	0	040	120	090	45	40	1	5.20	0 2	3 60
2	024	0	083	105	074	23	14	0	3.30	0 1	3 60
3	033	0	095	090	072	26	20	2	4.50	0 2	4 76
4	045	0	059	096	078	15	50	2	2.60	0 2	1 70
5	036	0	033	141	007	18	10	1	6.00	0 2	2 60
6	096	0	095	120	088	25	35	1	5.30	0 1	2 59
7	072	0	115	130	078	25	28	4	2.30	0 2	2 61
8	176	0	100	120	080	35	15	1	2.80	1 2	2 59
9	012	1	032	120	083	33	18	1	22.1	0 1	3 73
10	020	1	135	110	123	50	35	1	16.8	0 1	3 77
11	026	0	120	110	100	40	38	1	2.60	0 2	2 67
12	061	0	155	115	087	36	30	2	2.40	0 2	2 56
13	045	0	022	140	080	12	08	2	4.00	0 1	2 70
14	048	1	043	138	088	22	15	2	3.40	0 2	2 69
15	024	0	150	087	105	62	20	1	3.00	0 1	4 60
16	033	0	088	092	072	64	25	1	3.90	0 1	4 69
17	029	0	021	122	068	15	53	1	5.70	0 2	3 54
18	072	0	140	087	077	90	55	2	2.30	0 2	3 56
19	048	1	126	114	088	27	17	1	8.30	0 1	1 77

[illegible]

45	084	1	039	129	089	35	30	1	2.30	0 2	3 77
46	036	1	135	108	118	65	30	1	6.00	0 2	2 67
47	028	1	100	097	090	35	40	2	3.70	0 2	3 36
48	060	1	064	115	077	26	35	1	6.70	0 2	2 70
49	060	1	078	085	078	10	43	2	5.20	0 1	3 69
50	066	1	070	119	090	40	35	2	2.70	0 1	4 60
51	097	1	097	130	139	82	38	2	4.30	0 1	3 69
52	018	1	014	131	070	16	04	3	3.70	0 1	3 54
53	082	0	080	080	078	10	80	1	1.70	0 1	2 56
54	042	0	066	141	093	25	10	1	13.8	0 1	2 77
55	072	0	130	110	117	26	37	2	0.50	0 1	3 55
56	024	0	100	139	095	30	15	2	5.80	0 2	2 55
57	016	1	080	109	080	40	20	2	18.5	0 2	2 40
58	042	0	050	110	072	35	20	1	2.90	0 2	3 79
59	048	1	059	116	080	29	06	1	5.20	0 1	2 63
60	037	0	143	135	090	70	49	1	1.70	0 1	3 50
61	047	0	044	148	087	27	12	1	3.90	0 1	2 58
62	048	1	043	083	072	15	35	2	13.9	0 2	2 74
63	036	0	060	110	076	20	35	1	13.9	0 2	3 49
64	073	0	070	125	090	45	30	1	2.90	0 2	3 64
65	036	1	055	103	087	25	18	1	8.70	0 1	2 64
66	055	0	101	115	100	50	40	1	2.50	0 2	3 73
67	077	0	063	128	078	20	20	2	2.40	0 2	2 60
68	034	0	033	130	078	25	15	2	1.80	0 2	2 47
69	043	0	028	138	080	28	20	1	11.7	0 1	2 64

70	033	0	074	087	076	40	30	1	2.50	0 2	3 62
71	054	0	100	100	074	80	40	2	2.00	0 1	2 63
72	024	1	090	110	074	20	30	1	42.0	0 1	2 61
73	060	1	068	119	077	15	40	1	3.90	0 2	3 65
74	027	1	079	120	115	18	45	3	5.50	0 1	3 58
75	042	0	070	115	095	30	70	1	7.50	0 1	3 50
76	048	0	150	084	130	70	45	1	3.60	0 1	2 62
77	060	0	131	122	115	56	38	1	2.10	0 1	3 61
78	018	0	102	134	101	72	42	1	2.50	0 1	2 62
79	180	1	090	124	090	50	35	1	6.80	0 2	2 70
80	033	0	070	105	078	10	30	1	1.30	0 2	3 78
81	141	0	080	112	090	35	25	2	6.10	0 2	2 66
82	054	1	025	126	078	20	10	1	2.50	0 1	2 55
83	033	0	078	120	095	54	38	1	21.0	0 2	3 53
84	040	1	043	115	112	50	39	1	26.0	0 2	3 71
85	074	0	136	108	128	41	35	1	9.60	0 1	3 85
86	056	0	130	110	112	50	42	2	4.60	0 1	3 65
87	055	0	070	125	090	40	45	2	3.00	0 1	2 65
88	109	0	100	129	071	15	15	1	30.0	0 1	2 56
89	064	0	025	135	078	35	28	1	3.70	0 2	2 63
90	048	1	092	103	114	73	25	3	0.00	0 1	3 61
91	072	1	080	105	105	40	30	1	0.00	0 2	3 69
92	036	1	150	082	140	41	26	2	0.00	0 2	3 90
93	047	0	108	126	078	42	20	3	0.00	0 2	2 81
94	049	0	100	095	107	40	38	2	0.00	0 2	2 64

95	057	0	120	092	134	90	14	1	0.00	0 2	2 73
96	021	0	103	112	099	40	30	1	0.00	0 1	2 77
97	045	0	126	122	090	55	32	1	0.00	0 1	2 63
98	047	0	082	152	067	16	15	1	0.00	0 1	3 71
99	041	0	122	129	109	55	18	2	0.00	0 1	2 60
100	033	0	039	130	086	08	15	2	3.50	0 2	1 70
111	021	0	060	089	066	18	30	2	0.00	0 1	3 80
112	039	0	088	106	077	30	40	2	0.00	0 2	2 67
113	033	0	111	151	102	20	03	1	2.50	0 1	1 36
114	033	0	101	121	086	46	35	2	0.00	0 1	2 65
115	177	0	130	110	072	60	50	2	2.50	0 1	3 80
116	043	0	108	126	078	30	28	1	0.00	0 1	2 72
117	030	1	100	120	080	30	30	2	2.10	0 2	2 65
118	024	1	080	012	090	10	45	1	0.00	0 1	3 66
119	021	0	136	120	092	55	18	1	0.00	0 1	3 55
120	079	0	063	123	080	15	12	1	0.00	0 2	2 71
121	069	0	100	125	100	40	38	1	21.0	0 1	2 59
122	104	0	100	130	090	45	35	1	0.00	0 1	1 68
123	021	0	037	130	089	25	15	1	0.00	0 2	2 60
124	021	0	048	135	088	40	30	2	0.00	0 1	2 59
125	021	0	040	130	080	13	20	2	0.00	1 2	1 50
126	037	0	059	094	080	25	50	4	0.00	0 2	2 58
127	045	0	146	085	093	40	17	3	0.00	0 2	3 35
128	090	0	151	073	106	50	52	3	0.00	0 2	2 64
129	031	0	070	092	075	43	25	1	0.00	0 2	2 58

130	042	1	097	077	094	57	25	1	0.00	0	2
										2	70

X_2 : Follow up (censored = 0, dead = 1), X_3 : Blood sedimentation (FW), X_4 = Hemoglobin (Hg), X_5 : Total protein (TP), X_6 : Para-protein (PP), X_7 : Plasma cell infiltration, X_8 : Infiltration quality {A=1 Asynchron, PL=4 Plasma blast P=2 Plasmocytic, LP=3 Lympho Plasmocytic}, X_9 : Beta 2 Microglobulli B2M (0: means the patient had not been undergone test), X_{10} : Urea U (Normal=0, high=1), X_{11} : Stage (stage 1=I, stage 2=II, stage 3=III), X_{12} : Gender (Male=1, Female=2), X_{13} : Age.

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