Biochemical Response Evaluation on Lymphomas: Proposing a Scoring System

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ABSTRACT

Lymphomas encompass various lymphoid malignancies, although they are classified and evaluated in a similar manner. Prognostic stratification of lymphomas employs biochemical tests; however, these tests do not offer a viable means of assessing response. We included 108 patients with lymphoma who underwent treatment at the Department of Medical Oncology, Hacettepe University, between January 2015 and December 2017. Patients were grouped into good and poor responders, and changes in biochemical parameters were assessed for their utility in evaluating patient response. We evaluated the proposed scoring system's effect size using Cramer's V test. Fifty-seven patients were male, 51 patients were female, and the median age of the patients was 50 years. Twenty-seven patients had HL, 72 patients had B-cell NHL, and 9 patients had T-cell NHL. Fifty-three patients had stage IV, nine patients had stage III, 23 patients had stage II, and 22 patients had stage I disease. Levels of total protein (from 7.12 to 6.79 gr/dL, $p< 0.01$), ß2-microglobulin (from 2287 to 2039 ng/mL, $p= 0.07$), and lactate dehydrogenase (from 297.8 to 230.1 U/L, $p< 0.01$) decreased in patients with good response, whereas nothing significant was found in patients with poor response. After transforming the parameters, we proposed a 4-point ordinal system comprising total protein, ß2-microglobulin, and lactate dehydrogenase values. Subsequent analysis demonstrated a nearly high effect size (Cramer's V 0.461) and significance in logistic regression ($p< 0.01$). Our study presents the first scoring system for response assessment in lymphoma using biochemical tests. Further research is necessary to validate our scoring system.

Keywords: Lymphomas, Response evaluation, Biochemistry, Basic scoring

INTRODUCTION

Lymphomas are a diverse group of malignant lymphoid diseases arising from lymphoid precursors. In most cases, the neoplastic cells are arrested at some point in normal lymphocyte development, and these features are used in the classification of lymphomas and histologic diagnosis.[1] The classical classification of lymphomas includes Hodgkin's lymphoma and non-Hodgkin's lymphoma, as well as more than 80 subtypes recognized in the 5th edition of the World Health Organization's Classification of Lymphoid Neoplasms (WHO).[2] Regardless of pathologic diagnosis, the Ann Arbor staging system is used for all lymphomas, and follow-up is performed similarly for all lymphoma types.[3] Assessment of response to treatment is an essential step in deciding whether to continue, discontinue, or modify treatment.

In general, the response to lymphoma treatment is evaluated through a combination of PET-CT or CT scans, in addition to a comprehensive physical examination.[3-5] As most lymphomas are commonly treated with a combination of chemotherapy and radiotherapy, the main concerns are radiation exposure, radiation toxicity, the high cost of imaging studies, and radiation-related comorbidities.

Biochemical parameters have been widely utilized in routine clinical practice for risk stratification and prognosis prediction. However, there is not yet clear evidence to support the use of changes in biochemical parameters in the assessment of response to lymphoma therapy.[6,7] This is the first study to examine the association between changes in biochemical parameters and response to treatment.

PATIENTS AND METHODS

Study Design

Our study was a noninterventional, retrospective, single-center cohort study. All patients gave informed consent to participate in retrospective clinical trials at Hacettepe University Hospitals. The data of all patients were blinded during data collection to preserve identity.

The study was not sponsored, and data analyses were performed by the authors and the Department of Biostatistics, Hacettepe University (Ankara, Turkey). All authors reviewed and critiqued the following drafts and vouch for the accuracy and completeness of the data.

Study Population

All patients (18 years or older) admitted with a diagnosis of lymphoma between January 2015 and December 2017 were scanned for eligibility for the study. Patients diagnosed with lymphoma, regardless of pathologic subtype, who had received systemic chemotherapy for lymphoma are included. Patients with malignancies other than lymphoma, chronic kidney disease, and liver failure of any type, and patients who had previously received systemic chemotherapy for any other reason were excluded.

Selection of Biochemical Parameters and Data Preparation

The biochemical parameters evaluated include renal function tests, serum electrolytes, acute-phase reactants, and prognostic factors such as lactate dehydrogenase and ß2-microglobulin, as well as complete blood count. Liver enzymes are not included because their levels are influenced by many other factors.[8]

The response to treatment is assessed according to RECIL 2017[9] and Lugano[10] criteria. The response was classified into two main groups: complete response and partial response were assessed as a good response, while minor response, stable disease, and progressive disease were assessed as a poor response.

To evaluate the changes in biochemical parameters between chemotherapy cycles, biochemical parameters were assessed before each systemic chemotherapy cycle and at the time of treatment response assessment.

Normal values of biochemical parameters were assessed according to institutional biochemical reference ranges.

The study was approved by Hacettepe University Faculty of Medicine Ethical Committee (September 11, 2018, GO: 18/800-06).

Statistical Analysis

Statistical analysis of the study was performed with SPSS v. 25.0 (IBM, Armonk, NY, USA) and R 4.1 (R Foundation). The x2 test was used to compare categorical parameters. Normally distributed variables were analysed with the T-test and ANOVA, and nonnormally distributed variables were analysed with the Mann-Whitney U and Kruskal-Wallis tests. Dependent variable analysis was performed with Student's T-test, Wilcoxon test, and McNemar test. The ANOVA test was used for repeated measures, and regression tests were utilized to examine the relationship between variables. The effect size of the proposed scoring system was evaluated using Cramer's V test. Univariate and multivariate logistic regression was used to predict association with treatment response and proposed scoring system in subgroups. Results are reported in terms of odds ratio (OR) and 95% confidence interval (CI).

RESULTS

Demographics and Survival Statistics of Patients

A total of 108 patients were enrolled in the study, of whom 57 (52.8%) were male and 51 (47.2%) were female. The median age of all patients was 50

Table 1. Demographic characteristics of patients

Demographic Information	Male (n= 57)	Female (n= 51)	Total (n= 108)	p** value
Age, median (IQR)	45 (33-57)	58 (39-67)	50 (34-64)	< 0.01
Disease-related factors, n (%)				
Pathological diagnosis				0.28
Hodgkin's lymphoma	17 (29.8%)	10 (19.6%)	27 (25.0%)	
B-cell lymphoma	37 (64.9%)	35 (68.6%)	72 (66.7%)	
T-cell lymphoma	3 (5.3%)	6 (11.8%)	9 (8.3%)	
Stage				0.19
I	14 (24.6%)	8 (15.7%)	22 (20.4%)	
II	12 (21.0%)	12 (23.5%)	24 (22.2%)	
III	5 (8.8%)	4 (7.8%)	9 (8.3%)	
IV	26 (45.6%)	27 (52.9%)	53 (49.1%)	
ECOG performance status				0.08
0/1	44 (77.2%)	29 (56.9%)	73 (67.6%)	
2	8 (14.0%)	15 (29.4%)	23 (21.3%)	
3	4 (7.0%)	7 (13.7%)	11 (10.2%)	
4	1 (1.8%)	0 (0%)	1 (0.9%)	
Bone marrow involvement	14 (24.6%)	8 (15.7%)	22 (20.4%)	0.34
B symptoms†	36 (63.2%)	31 (60.8%)	67 (62.0%)	0.84
Extranodal involvement	22 (38.6%)	22 (43.1%)	44 (40.7%)	0.68

† B symptoms: fever, night sweats, unintentional weight loss
** Mann-Whitney U test for age, Chi-square for categorical data

(IQR 34-64) years. B-cell lymphoma was the most common pathological diagnosis in 72 (66.7%) patients, followed by Hodgkin's lymphoma in 27 (25.0%), regardless of gender; the least common pathological diagnoses were T-cell lymphomas in 9 patients (8.3%),. Ninety-eight (90.7%) patients had high-grade lymphoma, 53 (49.7%) patients were admitted with Ann Arbor stage IV, followed by stage II with 24 (22.2%) cases, stage I in 22 (20.4%) cases, and stage III in 9 (8.3%) cases. Seventy-three (67.7%) patients were admitted with an ECOG performance score of 0/1. Bone marrow was involved in 22 (20.4%) patients and adrenal glands in 44 (40.7%) patients. Sixty-seven patients (62.0%) had B symptoms at the time of diagnosis. Disease-related characteristics between genders were not significant ($p > 0.05$). Further details of patient demographics are provided in Table 1.

Twenty-two patients (20.4%) had bone marrow involvement, and 67 patients (62.0%) had B symptoms, regardless of pathologic lymphoma subgroups. More patients with B-cell and T-cell non-Hodgkin lymphomas had advanced stage; stage IV was present in 37 patients (52.1%) with B-cell and eight patients (88.9%) with T-cell lymphomas. Most patients had high-grade lymphoma regardless of pathologic subtypes; 98 patients (90.7%) had a high-grade disease, while only ten patients (9.3%) had a low-grade disease. The most common imaging modality for response assessment was PET-CT on 96 patients (88.9%), and 61 patients (56.5%) received radiotherapy. The most common systemic therapies administered were 48 (44.4%) R-CHOP for B-cell lymphomas and 26 (24.1%) Hodgkin's lymphomas, and ABVD for Hodgkin's lymphomas. Details of bone marrow involvement, presence of B symptoms, stage, and disease grade among pathologic subtypes are shown in Table 2.

Eleven cases with B-cell lymphoma and 5 cases with T-cell lymphoma died during the follow-up period. Median overall survival (OS) was not achieved for Hodgkin lymphoma and B-cell lymphoma. However, for T-cell lymphoma, the median OS was significantly lower at 19 months ($p < 0.01$).

Table 2. Disease and treatment properties among pathological subtypes

	Hodgkin's lymphoma n = 27, n (%)	B-cell NHL† n = 72, n (%)	T-cell NHL† n = 9, n (%)	Total n = 108 n (%)
Bone marrow involvement				p = 0.48
No	23 (85.2%)	57 (79.2%)	6 (66.7%)	86 (79.6%)
Yes	4 (14.8%)	15 (20.8%)	9 (33.3%)	22 (20.4%)
B symptoms				p = 0.07
No	15 (55.6%)	24 (33.3%)	2 (22.2%)	41 (38.0%)
Yes	12 (44.4%)	48 (66.7%)	7 (77.8%)	67 (62.0%)
Stage (Ann-Arbor)	p = 0.03			
I	6 (22.2%)	16 (22.2%)	0 (0%)	22 (20.4%)
II	11 (40.7%)	12 (16.7%)	1 (11.1%)	24 (22.2%)
III	2 (7.4%)	7 (9.7%)	0 (0%)	9 (8.3%)
IV	8 (29.6%)	37 (51.4%)	8 (88.9%)	53 (49.1%)
Grade	p = 0.16			
Low	0 (0%)	9 (5.6%)	1 (11.1%)	10 (9.3%)
High	27 (100%)	68 (94.4%)	8 (88.9%)	98 (90.7%)
Response assessment imaging modality				p = 0.40
PET-CT	26 (96.3%)	61 (84.7%)	9 (100%)	96 (88.9%)
CT	1 (3.7%)	8 (11.1%)	0 (0%)	9 (8.3%)
MRI/USG	0 (0%)	3 (4.2%)	0 (0%)	3 (2.8%)
Radiotherapy history				p < 0.01
Received	21 (77.8%)	38 (52.8%)	2 (22.2%)	61 (56.5%)

† Non-Hodgkin's lymphoma,
** p values are calculated with Chi-square test
PET-CT: Position emission tomography-computerized tomography, CT: Computerized tomography,
MRI: Magnetic resonance imaging, USG: Ultrasound

Changes in Biochemical Parameters among Good and Poor Response

There was a significant change in sodium [from 138.4 (± 3.07) to 139.3 (± 2.29) mEq/L; p=], potassium [from 4.29 (± 0.39) to 4.18 (± 0.38) mEq/L; p= 0.02], globulin [from 3.08 (± 0.59) to 2.58 (± 0.49) gr/dL; p< 0.01], total protein [from 7.17 (± 0.75) to 6.78 (± 0.58) gr/dL; p< 0.01], lactate dehydrogenase [from 297.8 (± 226.9) to 230.2 (± 84.5) U/L; p= 0.01], hemoglobin [from 12.57 (± 2.09) to 12.03 (± 1.85) gr/dL; p< 0.01], neutrophils [from 5447 (± 2868) to 3954 (± 2244) per microliter; p< 0.01], lymphocytes [from 1827 (± 1188) to 1368 (± 1443) per microliter; p= 0.04], platelets [from 303.454 (± 136.547) to 273.340 (± 108.594) per microliter; p= 0.03], erythrocyte sedimentation rate [from 27.65 (± 24.74) to 17.69 (± 15.31) mm/h; p< 0.01] and C-reactive protein level [from 6.75 (± 1.76) to 1.31 (± 1.17) mg/dL; p= 0.2] in good response before and after treatment, while no significant changes were observed in poor response. Although not significant, there was a decrease in ß2-microglobulin levels [from 2287 (±1543) to 2039 (±865) ng/mL; p= 0.07] with treatment. Details of the changes in biochemical parameters under treatment are provided in Table 3.

Modelling and Proposing a Scoring System for Treatment Response Evaluation

When modeled, the cross-interaction between post-treatment ß2-microglobulin, lactate dehydrogenase, and total protein levels (p= 0.03) was significant between post-treatment ß2-microglobulin and lactate dehydrogenase levels and the difference between pre-and post-treatment total protein levels (p= 0.02). In the further evaluation of biochemical parameters, the changes in total protein, ß2-microglobulin, and lactate dehydrogenase were used to develop a 4-point scoring system to evaluate treatment success. For each biochemical parameter in the scoring system, 1 point was assigned. The components of the proposed scoring system are listed in Table 4.

Table 3. Changes in biochemical parameters among treatment

Biochemical parameter	Good Response			Poor Response		
	Before (Range; unit) mean (± SD)	After treatment mean (± SD)	p value treatment mean (± SD)	Before treatment mean (± SD)	After treatment mean (± SD)	p value treatment
Creatinine (Male: 0.67-1.17 Female: 0.51-0.95 mg/dL)	0.72 (± 0.18)	0.71 (± 0.18)	0.26	0.75 (± 0.30)	0.73 (± 0.28)	0.56
Sodium (136-146 mEq/L)	138.4 (± 3.07)	139.3 (± 2.29)	0.02	138.5 (± 2.2)	138.5 (± 2.3)	1.00
Potassium (3.5-5.1 mEq/L)	4.29 (± 0.39)	4.18 (± 0.38)	0.02	4.24 (± 0.28)	4.25 (± 0.36)	0.87
Phosphorus (inorganic) (2.5-4.5 mg/dL)	3.54 (± 0.60)	3.67 (± 0.63)	0.09	3.68 (± 0.62)	3.623 (± 0.67)	0.64
Calcium (total) (8.8-10.6 mg/dL)	9.48 (± 0.53)	9.43 (± 0.51)	0.44	9.35 (± 0.48)	9.26 (± 0.58)	0.31
Albumin (3.5-5.2 gr/dL)	4.12 (± 0.56)	4.19 (± 0.41)	0.14	4.03 (± 0.42)	3.98 (± 0.53)	0.61
Globulin (1.5-4.6 gr/dL)	3.08 (± 0.59)	2.58 (± 0.49)	< 0.01	2.87 (± 0.43)	2.79 (± 0.46)	0.24
Protein (total) (6.4-8.3 gr/dL)	7.17 (± 0.75)	6.78 (± 0.58)	< 0.01	6.90 (± 0.61)	6.78 (± 0.72)	0.26
ß2 microglobulin (609-2366 ng/mL)	2287 (± 1543)	2039 (± 865)	0.07	2593 (± 1524)	2321 (± 1001)	0.25
Lactate dehydrogenase (< 248 U/L)	297.8 (± 226.9)	230.2 (± 84.5)	0.01	294.8 (± 185.7)	287.8 (± 194.3)	0.83
Hemoglobin (Male: 13.6-17.2 gr/dL Female: 11.7-15.5 gr/dL)	12.57 (± 2.09)	12.03 (± 1.85)	< 0.01	11.67 (± 1.79)	11.21 (± 1.94)	0.07
Neutrophil (2100-6100/µL)	5447 (± 2868)	3954 (± 2244)	< 0.01	4774 (± 3390)	4400 (± 3069)	0.54
Lymphocyte (1300-3500/µL)	1827 (± 1188)	1468 (± 1443)	0.04	1527 (± 1940)	1183 (± 658)	0.14
Platelet (156.000-373.000/µL)	303,454 (± 136,547)	273,340 (± 108,594)	0.03	329,276 (± 126,396)	301,425 (± 177,071)	0.27
Erythrocyte sedimentation rate (0-20 mm/h)	27.65 (± 24.74)	17.69 (± 15.31)	< 0.01	31.19 (± 19.66)	31.00 (± 22.40)	0.97
C-reactive protein (< 0.8 mg/dL)	6.75 (± 1.76)	1.31 (± 1.17)	0.02	1.58 (± 1.75)	0.83 (± 0.10)	0.51

* p values are calculated with repeated measures ANOVA test

Table 4. Proposed coring system for lymphoma response evaluation

Biochemical parameter	Score parameters	Points
Protein (Total)	Levels before and after treatment ≥ 6,0 gr/dL and decline ≥ 0,50 gr/dL	1
ß2 microglobulin	Level after treatment ≤ 2500 ng/mL or decline of more than 10%	1
Lactate dehydrogenase	Level after treatment ≤ 275 U/L or decline ≥ 50 U/L	1
Total score range 0-3 (ordinal)		

Analysis of the scoring system revealed that all patients with a score of 0 had a poor response, while only 2 out of 26 patients (7.7%) with a score of 3 had a poor response. Logistic regression analysis showed significant results (p< 0.001), each one-point increase in score was associated with good response with OR 4.29 (95% CI: 2.07-8.91) in univariate analysis and OR 5.44 (95% CI: 2.07-14.24) in multivariate analysis, and the effect size was close to a high effect (Cramer's V test 0.461). Patient response analyses using the proposed scoring system are provided in Table 5. The area under the ROC curve (AUC) was 0.739, as shown in Figure 1.

In subgroup analyses, all 3 patients with B-cell lymphoma and 2 patients with T-cell lymphoma had a poor response with 0 points, whereas all 14 patients with B-cell lymphoma, all 8 patients with Hodgkin lymphoma, and 2 of 4 patients with T-cell lymphoma had a good response with 3 points. The response to each lymphoma subtype according to the proposed scoring system is shown in Table 6.

In univariate logistic regression analysis, bone marrow involvement at OR 0.42 (95% CI: 0.19-0.91; p= 0.03) and B symptoms at OR 0.14 (95% CI: 0.05-0.42, p< 0.01) were significantly associated with poor response, whereas in multivariate regression both were not significant (p= 0.72-0.82). Subgroups such as female vs. male sex, stage (II-III-IV vs. I), high grade vs. low grade were not associated with poor response (p= 0.12-0.99). Details of univariate and multivariate logistic regression was given in Table 7.

DISCUSSION

Lymphomas are the most common hematologic malignancies in industrialized countries, and response to treatment is usually satisfactory. Assessment of response in lymphoma is critical for the continuation of systemic treatment, modification, or discontinuation of treatment.[3,11] Assessment of response to treatment of lymphoma is usually performed by radiologic or nuclear medicine studies. Together with radiotherapy, the use of radiological or nuclear medicine examinations causes significant radiation exposure.[9,12,13] Considering the cost of radiological and nuclear medicine examinations and the risk of radiation-induced disease, studies have been conducted on less expensive and radiation-free examinations. However, because satisfactory results have not been obtained to date, no new response assessment method is available to guide clinical practice.[14] Although there are several prognostic scoring systems composed of biochemical parameters, and some biochemical parameters are used in the assessment of response to treatment in many diseases[6,7], there is no biochemical marker suitable for clinical use in all malignancies, including lymphoma. There are studies showing the response of different biochemical markers to treatment in various malignancies.[15-17]

Table 5. Analyses of response with proposed scoring system

Treatment response	Proposed Scoring System for Lymphoma Response Evaluation, n (%)			
	0	1	2	3
Good response	0 (0%)	7 (46.7%)	38 (70.4%)	24 (92.3%)
Poor response	5 (100%)	8 (53.3%)	16 (29.6%)	2 (7.7%)

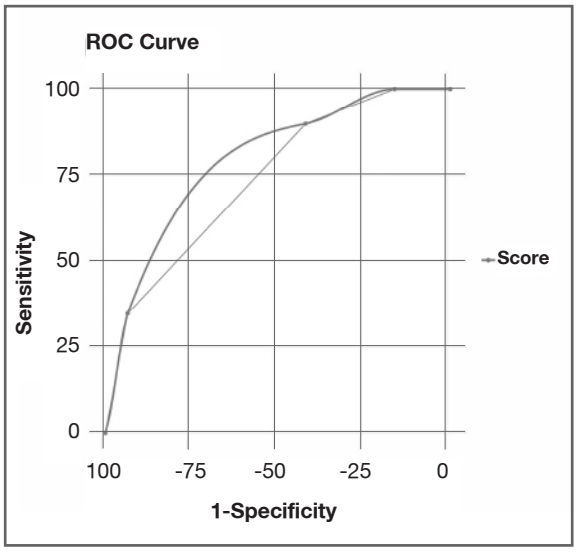

Figure 1. ROC curves of proposed scoring system

After excluding patients with concomitant diseases that could affect biochemical parameters, such as chronic kidney or liver disease, 108 patients diagnosed with lymphoma, regardless of pathological subtype, were enrolled in our study. fifty-seven patients (52.8%) were male and 51 (47.2%) were female. seventy-two patients (66.7%) had B-cell lymphoma, 27 patients (25.0%) had Hodgkin lymphoma, and 9 patients (8.3%) had T-cell lymphoma. The distribution of pathologic subtypes is consistent with population-based cancer statistics. In univariate regression analyses, patients with B symptoms or bone marrow involvement had a worse prognosis, consistent with known prognostic factors for lymphoma. The median OS was 19 months for T-cell lymphoma and was not reached for the other lymphomas, which may be due to the poor outcome of T-cell lymphomas.

The analyzes revealed a decrease in total protein, beta-2 microglobulin, and lactate dehydrogenase, so we developed a scoring system to evaluate the response to treatment based on the biochemical parameters. Higher scores indicate better response, so it seems useful for clinical practice. In subgroup analyses, the scoring system itself was shown to be the most significant indicator of treatment response without any confounders. We recommend that early treatment failure be scored as 0- or 1-point, routine intermediate control as 2 points, and end-of-treatment control as 3 points because a good response is usually observed.

The strengths of our study are that all biochemical and radiological/nuclear medicine examinations were performed at the same center, reducing the margin of error; response to treatment was assessed by standard criteria; and patients were followed up over a long period. Weaknesses are the small number of patients, and the follow-up of all patients in the same center, so the study may not be suitable for every lymphoma patient.

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Table 6. Analyses of proposed scoring system by histologic subgroups

Treatment response	Proposed Scoring System for Lymphoma Response Evaluation, n (%)			
Hodgkin's lymphoma	**0**	**1**	**2**	**3**
Good response	-	3 (42.9%)	12 (63.2%)	8 (100%)
Poor response	-	4 (57.1%)	7 (36.8%)	0 (0%)
B-cell lymphomas				
Good response	0 (0%)	3 (60%)	24 (75%)	14 (100%)
Poor response	3 (100%)	2 (40%)	8 (25%)	0 (0%)
T-cell lymphomas				
Good response	0 (0%)	1 (33.3%)	2 (66.7%)	2 (50%)
Poor response	2 (100%)	2 (66.7%)	1 (33.3%)	2 (50%)

Table 7. Univariate and multivariate logistic regression analyses of proposed scoring system by subgroups

Univariate logistic regression					Multivariate logistic regression				
Logistic regression coefficient	ß	SE	OR (95% CI)	p	Logistic regression coefficient	ß	SE	OR (95% CI)	p
Scoring (each 1 increase)	1.45	0.37 (2.07-8.92	4.30)	≤ 0.01	Scoring (each 1 increase)	1.69	0.58	5.44 (2.07-14.24)	< 0.01
Gender (female vs male)	0.07	0.34	1.08 (0.55-2.13)	0.82	Gender (female vs male)	0.20	0.58	1.22 (0.38-3.8)	0.73
Stage, (stage I as reference)	ß	SE	OR (95% CI)	p	Stage, (stage I as reference)	ß	SE	OR (95% CI)	p
II	-17.3	1391	-	0.99	II	-17.2	1615	-	0.99
III	-17.6	1391	-	0.99	III	-16.3	1615	-	0.99
IV	-18.2	1391	-	0.99	IV	-18.2	1615	-	0.99
Grade (high vs low	-1.62	1.06	0.19 (0.02-1.5)	0.12	Grade (high) vs low	-0.63	1.25	0.53 (0.04-6.16)	0.61
B symptoms	-1.05	0.56	0.14 (0.05-0.42)	< 0.01	B symptoms	-0.17	0.76	0.82 (0.18-3.74)	0.81
Bone marrow involvement	-0.87	0.40	0.42 (0.19-0.91)	0.03	Bone marrow involvement	-0.24	0.69	0.78 (0.20-3.05)	0.72

ß: beta value; SE: standard error; OR: odds ratio; CI: confidence interval

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