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Original Article

Analysis of prognostic factors in lymphoma patients with bone marrow involvement: a single center cohort study

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Abstract: The objective of this study was to explore prognostic factors in lymphoma patients with bone marrow involvement (Ann Arbor stage IV). To that end, we analyzed a cohort study of 68 stage IV lymphoma patients. We found that the most predictive thresholds for lymphocyte rate, monocyte rate, and lymphocyte to monocyte ratio (LMR) were 30%, 13%, and 3, respectively. A lymphocyte rate <30%, a monocyte rate >13%, and the presence of B symptoms were associated with shorter OS. LMR >3, Eastern Oncology Cooperative Group performance status ≤1, indolent lymphoma, and B cell (as opposed to T and NK cell) lymphoma predicted longer OS. Our study showed that these basic, easily acquired data can predict the outcome and overall survival in lymphoma patients with bone marrow involvement. These prognostic markers should be taken into consideration when devising new prognostic scoring systems for lymphomas.

Keywords: International prognostic index, lymphoma, bone marrow involvement, ann arbor stage IV, prognostic factor, overall survival

Introduction

Lymphoma is an obviously heterogeneous neoplasm, and the International Prognostic Index (IPI) is a well-established prognostication system for risk stratification of aggressive lymphoma [1, 2]. Although the IPI is considered the current standard prognostication system for lymphoma, it has been suggested that prognostic heterogeneity exists among patients within the same IPI risk group. In fact, many have inferred that the IPI may not fully predict the outcome of lymphoma [3-5]. As a result, promising prognostic markers such as novel molecular gene-expression profiling, genetic markers, immunohistochemistry-based detection of prognostic biomarkers, and positron emission tomography have been explored as potential predictive technologies that may identify high-risk patients [6-10]. However, most of these methods are costly, difficult to obtain and interpret, and in some cases, require further validation. Thus, the IPI has so far remained the standard use prognostication system. Consequently, there continues to be a need for inexpensive, widely available, and easily interpretable prognostic indicators for patients with lymphoma [11]. Cox et al. found that the low absolute lymphocyte count (ALC) at diagnosis of diffuse large B cell lymphoma (DLBCL) is a marker of negative prognosis; they thus incorporated the ALC into a revised international prognostic score and demonstrated that it is a more powerful predictor of overall survival (OS) [12, 13]. Conversely, Plonquet et al. prospectively analyzed the prognostic value of ALC in DLBCL patients and showed that the ALC did not correlate with disease outcome in their study [14]. Bari et al., Wilcox et al., and Tadmor et al. showed that monocytosis has adverse prognostic significance, negatively impacted survival in patients with T-cell lymphomas and diffuse large B-cell lymphoma [15-17].

The Ann Arbor staging system was originally devised in 1971 for staging Hodgkin disease,

and was gradually adopted into the non-Hodgkin lymphoma (NHL) staging system, even though this classification system is unreliable as a prognostic tool for NHL patients [1, 18]. A study by Prochazka et al. showed that unconventional prognostic factors for DLBCL may overshadow the standard factors in terms of reliability, as determined by multivariate Cox regression analysis [19]. To investigate the reliability of Ann Arbor staging and determine the factors that have significant correlation with prognosis and survival in lymphoma patients with bone marrow involvement (Ann Arbor stage IV), 68 patients with this disease were analyzed at initial diagnosis; lymphoma patients who have bone marrow involvement at initial diagnosis are encountered less frequently.

Materials and methods

Patients

We retrospectively studied 68 lymphoma patients with bone marrow involvement who presented at Tongji Hospital, Wuhan, Hubei, China between June 2004 and July 2013. Eligible patients presented with lymphoma with bone marrow involvement (Ann Arbor stage IV) at the initial diagnosis, and had no prior treatment. Lymphoma patients who had later progressed to bone marrow involvement and patients with HIV-related lymphoma were excluded. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Sixty-eight lymphoma patients were diagnosed by lymph node biopsy and the diagnoses were confirmed by bone marrow biopsy and immunohistochemistry. The diagnosis was established according to the World Health Organization 2008 classification [20]. The 68 lymphoma patients included cases of small lymphocytic lymphoma (n=9), plasmacytic lymphoma (n=10), follicular lymphoma (n=5), mantle cell lymphoma (n=4), diffuse large B-cell lymphoma (n=10), T-cell lymphoma (n=19), and NK cell lymphoma (n=11). The indolent lymphomas included small lymphocytic lymphoma, plasmacytic lymphoma, and follicular lymphoma. The aggressive lymphomas included mantle cell lymphoma, diffuse large B-cell lymphoma, T-cell lymphoma, and NK cell lymphoma. B cell lymphomas included small lymphocytic lymphoma, plasmacytic lymphoma, follicular lymphoma, mantle cell lymphoma, and diffuse large B-cell lymphoma. T-cell lymphoma included angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma.

Methods

To further analyze the prognostic factors for stage IV lymphoma, the following dichotomous predictors were considered for each subject at the time of the diagnosis: sex, age (≤60 years vs. >60 years), A and B symptoms, presence of splenomegaly, Oncology Cooperative Group (ECOG) performance status (PS) (≤1, ≥2), lactate dehydrogenase (LDH) levels (normal vs. elevated), and beta-2-microglobulin (B2M) levels (normal vs. elevated). Data collected included white blood cells (WBC; $\leq 10\times10^9$/L vs. $>10\times10^9$/L), hemoglobin (HB; ≤120 g/L vs. >120 g/L), platelets (PLT; $\leq 100\times10^9$/L, $>100\times10^9$/L), lymphocyte rate, monocyte rate, LMR, tumor type (B-, T-, or NK cell lymphoma), and whether the lymphoma was indolent or aggressive. The data of extranodal involvement were excluded because there were too few data points.

The candidate prognostic factors, including the lymphocyte rate, monocyte rate, and lymphocyte to monocyte ratio (LMR), were analyzed as dichotomous variables with the cutoff values calculated according to the literature. OS was defined as the time from diagnosis of lymphoma to death from any cause or the last follow-up. B symptoms were defined as any signs of fever above 38°C for more than three consecutive days, night sweats, and weight loss of more than 10% in 6 months [21].

Statistical analysis

Univariate analysis was performed to determine significant independent factors for overall survival. Survival functions were estimated using the Kaplan-Meier method or the life-table method and compared by the log-rank test. The Cox proportional hazards model was used for the estimation of hazard ratio (HR) and its confidence interval (CI). All significant predictors were used in multivariate Cox regression analysis. We investigated the optimum cutoff value for diagnosis by maximizing the sum of sensitivity and specificity. Two-tailed $P<0.05$ was considered statistically significant. The date of

Table 1. Clinical characteristics of lymphoma patients with bone marrow involvement and their correlation with survival

Characteristic	Patients (n/Total)	Percentage (%)	Median OS (months)	HR	95% CI	*P*-value for OS
Age (years)						
≤60	47/68	69.12	15			
>60	21/68	30.88	32	0.667	0.324-1.370	0.270
Sex						
Male	42/68	61.76	18			
Female	26/68	38.24	17	1.11	0.588-2.093	0.747
ECOG PS						
0-1	34/68	0.5	80			
2-4	34/68	0.5	12	4.105	1.964-8.583	0.0001
B symptom						
No	39/68	57.35	58			
Yes	29/68	42.65	12	2.327	1.202-4.506	0.012
Ind/agg lymphoma						
Indolent	24/68	35.29	58			
Aggressive	44/68	64.71	12	3.047	1.388-6.689	0.005
B/T/NK cell lymphoma						
B cell	38/68	55.88	58			
T cell	19/68	27.94	14	0.143	0.059-0.346	0.0001
NK cell	11/68	16.18	6	0.457	0.196-1.064	0.069
LDH						
Normal	27/67	40.3	32			
Elevated	40/67	59.7	15	1.646	0.844-3.210	0.143
B2M						
Normal	26/63	41.27	15			
Elevated	37/63	58.73	17	0.839	0.443-1.592	0.586
Splenomegaly						
Yes	33/68	48.53	32			
No	35/68	51.47	13	1.483	0.786-2.799	0.224
WBC ($\times 10^9$/L)						
≤10	45/68	66.18	17			
>10	23/68	33.82	32	0.841	0.431-1.638	0.61
HB (g/L)						
≤120	45/68	66.18	32			
>120	23/68	33.82	15	1.203	0.631-2.296	0.574
PLT ($\times 10^9$/L)						
≤100	29/68	42.65	12			
>100	39/68	57.35	58	0.612	0.326-1.146	0.125
L% (30%)						
≤30%	24/68	35.29	11			
>30%	44/68	64.71	58	0.504	0.268-0.947	0.033
M% (13%)						
≤13%	54/68	79.41	32			
>13%	14/68	20.59	11	2.731	1.349-5.528	0.005
LMR (3)						
≤3	24/68	35.29	11			
>3	44/68	64.71	58	0.413	0.220-0.776	0.006

ECOG PS, Eastern Cooperative Oncology Group performance status; Ind, indolent; agg, aggressive; LDH, serum lactate dehydrogenase level; B2M, serum beta-2 microglobulin level; WBC, white blood cell; HB, hemoglobin; PLT, platelet count; L%(30%), lymphocyte rate (30%); M% (30%), monocyte rate (13%); LMR (3), lymphocyte to monocyte ratio (3); HR, hazard ratio; CI, confidence interval; OS, overall survival.

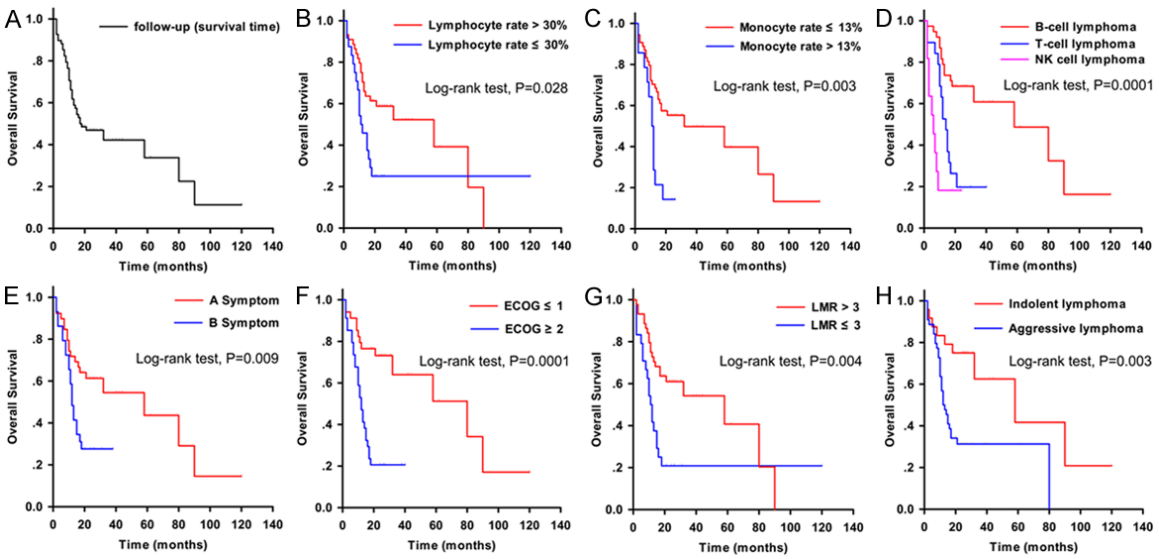

Figure 1. Outcome of lymphoma patients with bone marrow involvement (Ann Arbor stage IV) according to prognostic factors.

study was all performed with dichotomized values. All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

The median age of patients at diagnosis was 53 years (range 10-78 years), and 47 of the 68 patients (69.12%) were aged under 60 years. The male to female ratio was 1.6:1.

All lymphoma patients were with bone marrow involvement at Ann Arbor stage IV. As shown in **Table 1**, 34 (50%) of the patients presented with advanced ECOG PS (≥2) and 29 (42.65%) with B symptoms. Thirty-five (51.47%) patients were confirmed to have splenomegaly, and 24 (35.29%) and 44 (64.71%) patients were classified as having indolent and aggressive lymphoma, respectively. The number of patients identified with B-cell lymphoma, T-cell lymphoma, and NK cell lymphoma were 38 (55.88%), 19 (27.94%), and 11 (16.18%), respectively. According to laboratory data, serum LDH and B2M were elevated in 40 (59.7%) cases and 37 (58.73%) cases, respectively. Forty-five (66.18%) patients showed WBC counts under 10×10^9/L. There were 45 (66.18%) and 29 (42.65%) patients with HB <120 g/L and PLT $<100\times10^9$/L, respectively.

We analyzed different lymphocyte rates, monocyte rates, and LMRs, and found that the most predictive cutoff values of those were 30%, 13%, and 3, respectively.

General outcome

Median follow-up time of the surviving patients was 17.5 months (range 2-120 months). The median OS of all 68 patients was 17 months (95% CI, 2.910-31.090), with an estimated 12 months OS, 24 months OS, and 36 months OS of 61.8%, 46.95%, and 42.2%, respectively.

All prognostic factors

Cox univariate analysis (**Table 1**) showed that the factors significantly associated with OS were ECOG PS (HR of 4.105 [95% CI 1.964-8.583, P=0.0001]), B symptoms (HR of 2.327 [95% CI 1.202--4.506, P=0.012]), lymphocyte rate (HR of 0.504 (95% CI 0.268-0.947, P=0.033]), monocyte rate (HR of 2.731 [95% CI 1.349-5.528, P=0.005]), LMR (HR of 0.413 [95% CI 0.220-0.776, P=0.006]), indolence vs. aggressiveness (HR of 3.047 [95% CI 1.388-6.689, P=0.005]), and type of lymphoma, i.e. B-cell, T-cell (HR of 0.143 [95% CI 0.059-0346, P=0.0001] compared to B-cell lymphoma), or NK cell lymphoma (HR of 0.457 [95% CI 0.196-1.064, P=0.069] compared to B cell lymphoma).

A lymphocyte rate >30% predicted longer OS (P=0.028). The 24-month estimated OS was

Table 2. Multivariate Cox regression analysis of the main prognostic factors

Variable	Overall survival N = 68 (40 events)		*P*-value
	HR	95% CI	
B symptoms	1.197	0.542-2.642	0.656
ECOG PS	1.997	0.834-4.781	0.121
L% (30%)	0.342	0.132-0.884	0.027
M% (13%)	2.877	1.017-8.140	0.046
LMR (3)	1.901	0.639-5.651	0.248
Ind/agg lymphoma	0.872	0.319-2.384	0.872
B/T/NK cell lymphoma			0.002
	0.153	0.052-0.444	0.001
	0.659	0.256-1.697	0.338

ECOG PS, Eastern Cooperative Oncology Group performance status; L% (30%), lymphocyte rate (30%); M% (30%), monocyte rate (13%); LMR (3), lymphocyte to monocyte ratio (3); HR, hazard ratio; CI, confidence interval; Ind, indolent; agg, aggressive.

58.8% in patients with a lymphocyte rate above 30%, and 25.0% in those with below 30%. A monocyte rate >13% predicted shorter OS (P=0.003). The 12-month estimated OS was 79.6% in patients with monocyte rate below 13%, and 14.3% in those above 13%. An LMR >3 predicted longer OS (P=0.004). The 24-month estimated OS was 61.0% in patients with an LMR above 3 and 20.8% in those with an LMR below 3. ECOG PS ≤1 predicted longer OS (P=0.0001). The 24-month estimated OS was 73.1% in patients with an ECOG PS ≤1 and 29.4% in those with an ECOG PS ≥2. The presence of B symptoms predicted shorter OS (P=0.009). The 24-month estimated OS was 61.3% in patients with a symptom and 27.6% in those with B symptoms. Indolent lymphoma predicted longer OS (P=0.003). The 24-month estimated OS was 45.5% in patients with indolent lymphoma and 20.8% in those with aggressive lymphoma. B-cell lymphoma patients achieved longer OS compared with T-cell lymphoma and NK cell lymphoma patients (P=0.0001). The 12-month estimated OS was 68.4% in patients with B-cell lymphoma, 36.8% in those with T-cell lymphoma, and 18.2% in those with NK cell lymphoma (**Figure 1**).

Sex, age, splenomegaly, LDH, B2M, WBC, HB, and PLT were not significant individual predictors for overall survival.

In the multivariate analysis, we included all the significant univariate predictors in the Cox regression model. Independent prognostic factors for OS included lymphocyte rates >30% (HR of 0.342 [95% CI 0.132-0.884, P=0.027]), monocyte rates >13% (HR of 2.877 [95% CI 1.017-8.140, P=0.046]), and type of lymphoma: B-cell, T-cell (HR of 0.153 [95% CI 0.052-0.444, P=0.001] compared to B-cell lymphoma), or NK cell (HR of 0.659 [95% CI 0.256-1.697, P=0.338] compared to B-cell lymphoma) (**Table 2**).

Discussion

Lymphomas are malignant hematological diseases that have obvious prognostic heterogeneity. The IPI is a significant prognostication system for risk stratification of aggressive NHL. A modified version of the IPI is also used for indolent lymphoma. However, prognostic and biological heterogeneity suggest that the IPI may not be a completely reliable tool to predict the outcome of lymphoma [3, 4]. Many recent studies have focused on exploring inexpensive, widely available, and easily acquired prognostic factors that are more reliable than the IPI, as well as on constructing alternative prediction models. Wilcox et al. designed a prognostic model with multivariate analysis that encompassed IPI along with patient and tumor characteristics, and showed that IPI-related factors, ALCs, and absolute monocyte counts (AMCs) were independent predictors for OS in patients with diffuse B-cell lymphoma [16]. Hasenclever et al. and Siddiqui et al. showed low ALC at diagnosis is correlates with poor prognosis in patients with Hodgkin lymphoma and follicular lymphoma [22, 23]. Belotti et al. retrospectively analyzed 137 DLBCL and 132 FL patients, finding that an LMR value <2.4 was correlated with a worse 2-year progression-free survival but showed no difference in OS [24]. Tadmor et al. analyzed 1191 patients with DLBCL and showed that AMC in lymphoma patients may serve as an independent parameter correlated with poor prognosis and decreased OS [25]. Bari et al. showed that monocytosis has adverse prognostic significance and negatively impacts survival in patients with T-cell lymphoma [15].

Unfortunately, ALC, AMC, and LMR are not included as IPI parameters, and no large cohort

study has been performed with the aim of revising the IPI. The present study showed that the role of ALC, AMC, and LMR is overshadowed if more prognostic factors are included, as alluded to in previously studies [19].

To our knowledge, no study has investigated the prognostic factors for lymphoma patients with bone marrow involvement (Ann Arbor stage IV), nor has any study determined the lymphocyte and monocyte rates to be prognostic indicators. In our study of 68 cases of stage IV lymphoma patients, the optimum cutoff values for lymphocyte rate, monocyte rate, and LMR were 30%, 13%, and 3, respectively. Univariate Cox regression analysis showed that factors such as lymphocyte rate, monocyte rate, LMR, B symptoms, ECOG PS, and tumor indolence and type (B-cell, T-cell, or NK cell lymphoma) have significant impact in OS. Kaplan-Meier estimates and survival curves verified that lymphocyte rates <30%, monocyte rates >13%, and the presence of B symptoms were associated with shorter OS. LMR >3, ECOG PS ≤1, indolent lymphoma, and diagnosis with B-cell lymphoma and not T- or NK cell lymphoma predicted longer OS. The multivariate Cox regression model includes lymphocyte rate (30%), monocyte rate (13%), and type (B-cell, T-cell, or NK cell lymphoma), and the results using this model were similar to those attained by Wilcox et al., who showed that low ALC and high AMC predict poor OS and suggested combining the ALC and AMC to generate a prognostic score [16]. Lymphocytes play a significant role in immune surveillance in NHL, and several studies observed that low ALC is a negative prognostic indicator in NHL of various subtypes; the ALC is also universally regarded as a crucial marker of immunological reconstitution after stem cell transplantation in NHL [11]. High AMC could impair host-tumor immune-surveillance and the induction of angiogenesis and cell proliferation; monocytes may also directly promote the growth of malignant lymphocytes [26, 27]. Prochazka et al. speculated that high AMC could weaken the activity of antibody-dependent cellar cytotoxicity [19]. Separately, a study by Allavena and Mantovani showed that lymphoma cells cause the proliferation of monocytes and macrophages, promote tumor growth, and suppress the immune response [28].

LMR and the IPI-related factors ECOG PS and tumor aggressiveness were exclude in the multivariate Cox regressive analysis. While it is indisputable that ECOG PS and tumor aggressiveness are important predictors for the prognosis and survival of lymphoma patients, we considered whether the importance of some factors may be eclipsed by others in the final model.

Lymphocyte and monocyte rates at diagnosis, which were the data used in our study, are easily and inexpensively obtained parameters in clinical practice, and evidence suggests that they can be used to predict the outcome and survival time independently. ECOG PS and B symptoms can be easily determined by thorough examination of the patient. The type of lymphoma, as well as its aggressiveness, can be easily determined through lymph node biopsies and immunohistochemical analysis. In fact, these aforementioned attributes may constitute the main determining factors for treatment decisions and courses of action [29]. Our study of Ann Arbor stage IV lymphoma patients showed that lymphocyte and monocyte rates, tumor type and aggressiveness, LMR, manifestation of B symptoms, and ECOG PS could provide basic, easily acquired information to predict the outcome and OS. Such makers should be taken into consideration when devising new prognostic scoring systems for lymphomas.

Our retrospective study had some limitations: the number of patients was rather small and they received different regiments. There were no consensus cut-off values for lymphocyte or monocyte rates to be applied in the study because the optimum cut-off level of these values may differ in various populations. A large cohort study is needed to determine the optimal cut-off values for lymphocyte and monocyte rates.

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Disclosure of conflict of interest

None.

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