

# Lactate Dehydrogenase, Beta-2 Microglobulin Levels and CD4/CD8 Lymphocyte Ratio in Patients with Mycosis Fungoides in Stage 1A

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## ABSTRACT

**Objective:** Mycosis fungoides is the most common type of primary cutaneous T-cell lymphomas. In this study, we aimed to investigate the biochemical parameters of beta-2 microglobulin, lactate dehydrogenase, CD4/CD8 lymphocyte ratio determined by flow cytometry, and T cell clonality in patients with MF and to correlate these parameters in stage 1A and other stages.

**Materials and Methods:** A hundred sixty-one (87 Male, 74 Female) patients followed-up between January 1995 and January 2019 were retrospectively evaluated. Patients' demographics, stage of the disease, peripheral lymph node and organ involvement, peripheral blood beta-2-microglobulin, lactate dehydrogenase levels, CD4/CD8 + lymphocyte ratio and presence of T cell clonality in biopsy samples were evaluated.

**Results:** Median beta-2 microglobulin levels were 1608.5 ng/ml for stage 1A and 1970.5 ng/ml for other stages. Peripheral blood median CD4/CD8 lymphocyte ratio was 1.60 for stage 1A and 1.85 for other stages. We found statistically significant difference between two groups in terms of beta-2 microglobulin levels and peripheral blood median CD4/CD8 lymphocyte ratio ( $p=0.001$ ,  $p=0.04$ ). No statistically significant difference was found between two groups in terms of lactate dehydrogenase levels and T-cell clonality ( $p=0.234$ ,  $p=0.525$ ).

**Conclusion:** Our study supports that high peripheral blood beta-2 microglobulin level and CD4/CD8 lymphocyte ratio at the time of diagnosis may imply advanced stage and poor prognosis in Mycosis Fungoides.

**Keywords:** Cutaneous T-cell lymphoma, Beta-2 microglobulin, CD4/CD8 lymphocyte ratio

## INTRODUCTION

Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma which composes approximately 50% of primary cutaneous lymphomas. It is characterized by

proliferation and occupation of malignant clonal T cell population in the skin [1]. The prognosis of patients with MF is related with the stage and the survival rates decrease in advanced stages. Plaque

lesions, involvement of more than 10% of the body surface, altered lactate dehydrogenase (LDH) and beta-2 microglobulin levels have been found to be associated with disease progression in patients with MF [2].

LDH is an enzyme which catalyzes the last step of the conversion of pyruvate to lactate during anaerobic glycolysis. Serum LDH is commonly increased in patients with hematopoietic malignancies and it is considered a strong predictor of survival in patients with aggressive lymphoid cancers [3].

Beta-2 microglobulin is a small polypeptide light chain that forms part of the major histocompatibility complex class I antigens. As white-blood-cell membrane turnover is the primary source of serum beta-2 microglobulin, elevated serum beta-2 microglobulin levels have been associated with lymphoid malignancies with significant tumour burden, high rates of cellular turnover and more invasive potential [4].

The pathophysiology of MF is thought to be due in part to dysregulated CD4+ T cells, with only approximately 20% of cases displaying a CD8+ phenotype. In MF, the pathologic CD4+T cell undergoes clonal expansion, potentially leading to abnormally elevated CD4:CD8 T-cell ratio in the peripheral blood [5]

MF is a mature T-cell lymphoma currently thought to develop primarily in the skin by a clonal expansion of a transformed, resident memory T cell (Skin colonization by circulating neoplastic clones in cutaneous T-cell lymphoma). Clonality has not been recorded in skin stage although the detection of a clonal T-cell population in the blood or lymph nodes has been associated with a poorer clinical outcome [6].

In this study, our aim was to investigate the biochemical parameters of beta-2 microglobulin, LDH, CD4/CD8 lymphocyte ratio determined by flow cytometry, and the presence of T cell clonality in skin biopsy samples in stage 1A and other stages of MF and to show if these parameters are also necessary for stage 1A disease. Also we hypothesized that the elevation in the biochemical parameters detected in our patient follow-up may be informative about the progression of the disease.

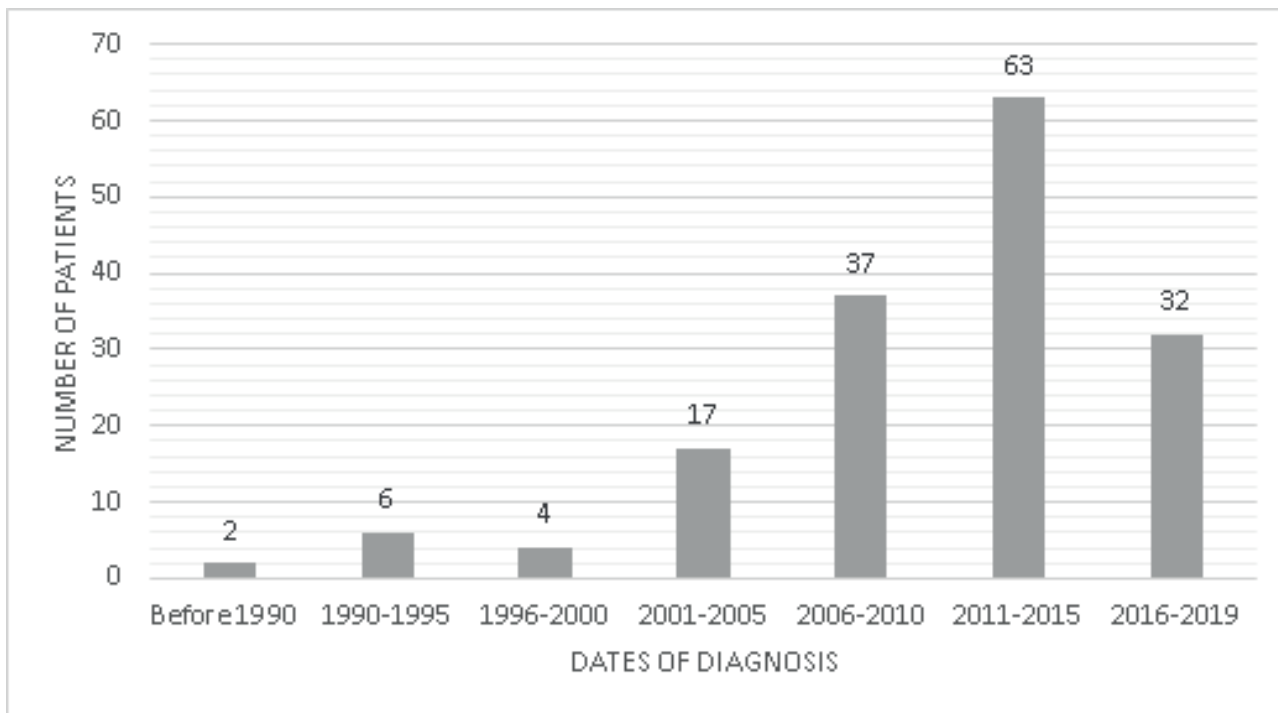
## MATERIALS and METHODS

After the study protocol was approved by the Hacettepe University School of Medicine ethics committee (2019/06-35), patients applied for the biopsy-proven MF at Hacettepe University School of Medicine, between January 1995 and January 2019 were retrospectively evaluated. Patients with inadequate data were excluded from the study. Patients' demographic data, disease stage at the diagnosis, baseline peripheral blood beta-2 microglobulin, LDH levels, CD4/CD8 lymphocyte ratio and the presence of T cell clonality in biopsy samples were retrospectively evaluated by using past medical records and electronic data base. Disease stage was determined according to International Society for Cutaneous Lymphomas/ European Organization of Research and Treatment of Cancer (ISCL/EORT) criteria which was proposed in 2007 and staging in patients with a diagnosis of previous years was updated according to the last staging system [7]. Peripheral blood CD4/CD8 lymphocyte ratio was analyzed by flow cytometry and T-cell clonality was evaluated by T-cell receptor (TCR) gene clonal rearrangement analysis in skin biopsy samples.

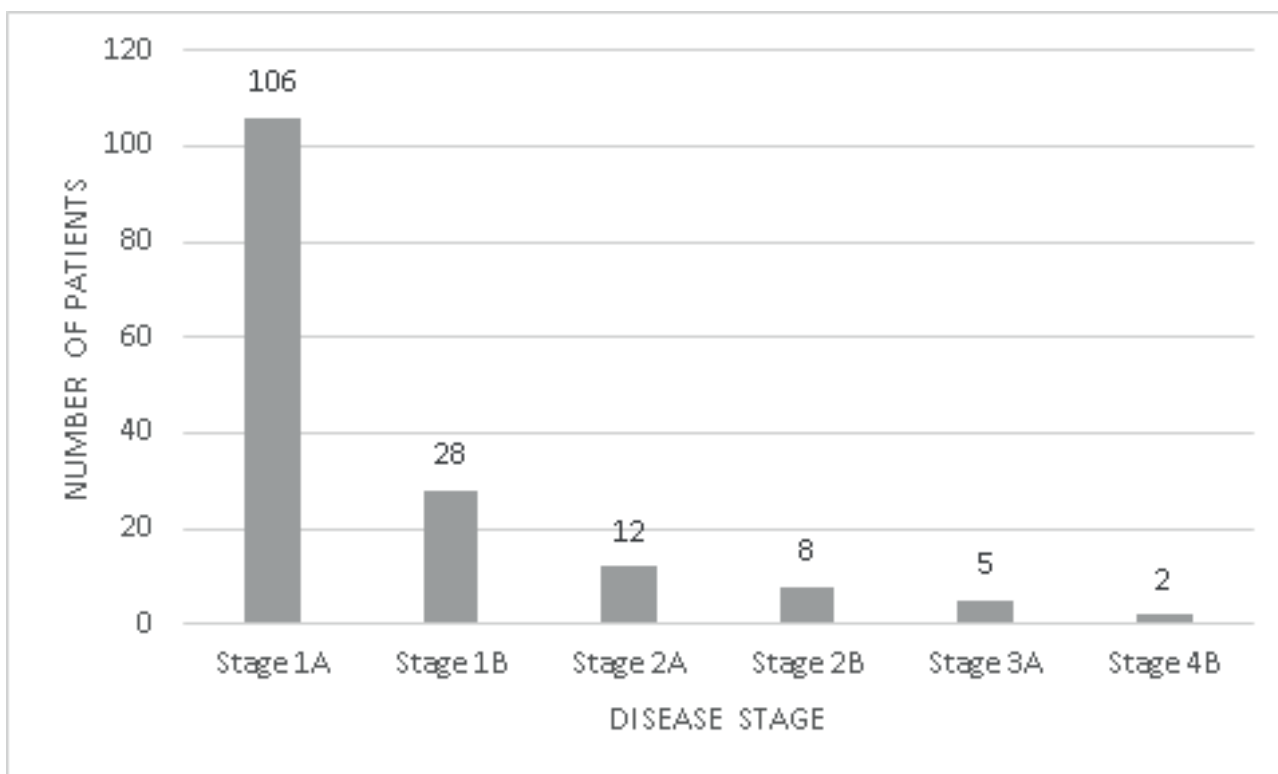
Statistical analyses were performed with the Statistical Package for the Social Sciences, software version 23.0. (SPSS Inc., Chicago, IL, USA). Numerical variables were summarized as mean  $\pm$  standard deviation or median (minimum-maximum). Numerical variables were compared by Mann-Whitney U test and categorical variables were given as frequencies and percentages. Categorical variables were compared by Chi-square test. A value of  $P < 0.05$  was considered statistically significant.

## RESULTS

Totally, 161 patients with the diagnosis of MF were included in the study. Seventy-four (46%) patients were female and 87 (54%) were male. The mean age was  $45.9 \pm 15.56$  years (range: 12-84 years). The distribution of the dates of diagnosis was given in Figure 1. The distribution of the disease stages was shown in Figure 2. Stage 1A disease was detected mostly and it was in 106 (65.8%) patients. Due to the lack of homogenous patient distribution according to disease stage, groups were categorized as stage 1A and other stages.



**Figure 1.** The distribution of the dates of diagnosis



**Figure 2.** The distribution of the disease stages

Lymph node involvement was found in 19 (11.8%) patients and internal organ involvement was only in 2 (1.2%) patients. Median LDH and beta-2 microglobulin levels for stage 1A were respectively 273.0 U/L (range: 123-548) and 1608.5 ng/ml (range: 941-4595). Median LDH and beta-2 microglobulin levels for other stages were respectively 318 U/L

(range:130-855) and 1970.5 ng/ml (range: 941-11021). We only found statistically significant difference in terms of beta-2 microglobulin levels between two groups ( $p=0.001$ ). Median CD4/CD8 lymphocyte ratio was 1.60 (range: 0.59-6.60) for stage 1A and 1.85 (0.70-17.40) for other stages (Table 1). There was statistically significant difference

**Table 1.** Biochemical Parameters according to disease stages

PARAMETERS	TOTAL	STAGE 1A	STAGE 1B-4	P VALUE
<b>LDH (U/L)</b>				<b>0.234</b>
Available Count	155	101	54	
Mean	295.66	280.67	323.70	
Standard Deviation	126.25	100.78	160.99	
Median	278	273	318	
Range	123-855	123-548	130-855	
<b>BETA-2 MICROGLOBULIN (ng/mL)</b>				<b>0.001</b>
Available Count	152	100	52	
Mean	2017.95	1732.21	2567.44	
Standard Deviation	1198.01	537.72	1794.49	
Median	1676.50	1608.50	1970.50	
Range	941-11021	941-4595	1166-11021	
<b>Peripheral CD4/CD8 lymphocyte ratio</b>				<b>0.040</b>
Available Count	138	88	50	
Mean	2.01	1.76	2.43	
Standard Deviation	1.83	1.01	2.70	
Median	1.64	1.60	1.85	
Range	0.59-17.40	0.59-6.60	0.70-17.40	

between two groups in terms of peripheral blood CD4/CD8 lymphocyte ratio ( $p=0.04$ ). TCR gene rearrangement results were available only in 111 (68.9%) patients; 40 (5.6%) of 76 patients with stage 1A and 20 (57.1%) of 35 patients with other stages had proven T-cell clonality. No statistically significant difference was found between two groups in term of T-cell clonality ( $p=0.525$ ).

## DISCUSSION

In our study, we aimed to show the correlation between biochemical parameters that are frequently used for baseline screening of MF patients and disease stage. We wanted to show if detailed biochemical parameters are necessary for stage 1A disease. We only found statistically significant difference in beta-2 microglobulin and CD4/CD8 lymphocyte ratio between stage 1A and other stages.

Beta-2 microglobulin is a low molecular weight (17 kDa) protein found in all nucleated cells and body fluids such as serum, cerebrospinal fluid and urine [8]. Amorim et al [2] showed that altered LDH and beta-2 microglobulin levels were significantly associated with disease progression and higher frequency of deaths in MF patients. Similar to previous findings in the literature, our results

support that patients with other stages have higher beta-2 microglobulin levels than stage 1A patients who have better prognosis.

LDH is a routinely used biochemical marker in solid and hematological cancer patients to determine tumor burden, progression, prognosis and response to treatment. In order to proliferate efficiently and rapidly tumor cells mainly go through glycolysis to supply energy [9]. As shown in solid organ tumors and hematological cancers, prognostic significance of LDH is also demonstrated in MF patients. Serum LDH level is found to be positively correlated with advanced stage in MF patients and asserted to be used as an independent risk factor for disease progression [10]. In our study, we found higher LDH levels in patients with other stages but it was statistically non-significant. The low number of patients with other stages than 1A may be the reason for not being able to show this association.

Peripheral blood CD4/CD8 lymphocyte ratio which shows circulating lymphocyte subsets is found to be prognostically important parameter to predict the efficacy and clinical response to electron beam radiation therapy in patients with MF, higher levels of CD4/CD8 implying poor prognosis and response to therapy [11]. Like previous studies in the literature, our patients with other stages has higher peripheral blood CD4/CD8 lymphocyte ratio than stage 1A patients.

In our study, we analyzed the results of TCR gene clonal rearrangement analysis which are shown to be a useful tool to aid in the early diagnosis of MF [12]. Even though, detection of clonal T cells may be utilized to support the diagnosis of MF, however, the presence of non-clonal T-cells does not exclude the diagnosis of MF in the existence of other supportive, clinical, histopathological and immunochemical criteria [13]. In our study, we were not able to find any significant difference between stage 1A and other stages in terms of T-cell clonality in biopsy specimen. This data might suggest that T-cell clonality is a useful parameter for the diagnosis of MF but it cannot be an indicator of stage or prognosis.

The limitations of the study are the lack of homogenous patient distribution according to disease stage. This is a retrospective study and missing data cannot be analyzed. As the study covers a long period of 24 years, blood sampling time, sampling method, sample transport, and sample storage cannot be done under the same conditions.

In conclusion, our study supports that high peripheral blood beta-2 microglobulin level and CD4/CD8 lymphocyte ratio at the time of diagnosis may imply advanced stage and poor prognosis. The higher beta-2 microglobulin level and CD4/CD8 lymphocyte ratio we detected in advanced stage patients are also important data for the follow-up of the patients and these parameters can be informative about the progression of the disease. T-cell clonality might be needed to diagnose of MF but it is not an indicator of advanced stage.

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### **CONFLICT of INTEREST STATEMENT**

The authors declare that they have no conflict of interest.

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