Turk J Dermatol 2019;13:1-7
DOI: 10.4274/tdd.galenos.2018.3699

Pınar İncel Uysal, Neslihan Akdoğan, Mesude Falay*, Buket Şahin, Gülsüm Özet*, Başak Yalçın

The Importance of Baseline Screening Investigations and Modified Severity Weighted Assessment Tool in Patients with Early Stage Mycosis Fungoides: A Four-year Retrospective Study

Erken Evre Mikozis Fungoidesli Hastalarda Başlangıç Tarama Testlerinin ve Modifiye Şiddet Ağırlıklı Değerlendirme Ölçeğinin Önemi: Dört Yıllık Bir Retrospektif Çalışma

Abstract

Objective: The present study aims to evaluate the prognosis and response to treatment relationship of baseline clinical and hematological parameters including eosinophil counts, neutrophil/lymphocyte ratio, levels of lactate dehydrogenase (LDH) and beta-2 microglobulin, flow cytometry and initial modified Severity Weighted Assessment Tool (mSWAT) scores in patients with mycosis fungoides (MF).

Methods: Medical records of 112 patients with the diagnosis of early-stage MF were examined retrospectively. Data of the patient and disease characteristics, and baseline laboratory tests were reviewed and evaluated in terms of stage and treatment response.

Results: In this study, patients were classified into two groups: responders and non-responders. Complete and partial responses were observed in 79 (70%) patients. Eight patients (7%) developed relapse in the follow-up period. In the staging groups (IA, IB, IIA), the frequency of elevated beta-2 microglobulin was different among all parameters. When the results were compared based on clinical responsiveness, until the time to diagnosis was significantly longer in non-responder patients than responders. High mSWAT scores, elevated beta-2 microglobulin and LDH levels, and plaque-type lesions were more frequent in non-responder patients.

Conclusion: Our study demonstrates that extensive screening tests may not be very meaningful in patients with early-stage MF. mSWAT scores, beta-2 microglobulin, and LDH tests should be evaluated as useful measurements in prediction the response to treatment.

Keywords: Early-stage mycosis fungoides, Modified Severity Weighted Assessment Tool, prognostic biomarkers, screening tests

Öz

Amaç: Bu çalışma mikozis fungoides (MF) hastalarında eozinofil sayısı, nötrofil/lenfosit oranı, laktat dehidrogenaz (LDH) ve beta-2 mikroglobulin seviyesi, akım sitometrisi ve başlangıç modifiye Şiddet Ağırlıklı Değerlendirme Ölçeği (mSWAT) skorunun dahil olduğu başlangıç klinik ve hematolojik parametrelerinin prognozla ve tedaviye cevapla ilişkisini değerlendirmeyi amaçlamaktadır.

Yöntemler: Erken evre MF tanılı 112 hastanın tıbbi kayıtları retrospektif olarak incelendi. Hasta ve hastalık karakteristikleri ile başlangıç laboratuvar testlerine ait veriler gözden geçirildi ve evre ve tedavi cevabı açısından değerlendirildi.

Bulgular: Bu çalışmada hastalar iki gruba ayrıldı: Tedaviye cevap verenler ve tedaviye cevapsız olanlar. Yetmiş dokuz hastada (%70) tam ve kısmi yanıt izlenmiştir. Sekiz hastada

Ankara Numune Training and Research Hospital, Clinic of Dermatology, Ankara, Turkey

*Ankara Numune Training and Research Hospital, Clinic of Hematology, Ankara, Turkey

Correspondence/ Yazışma Adresi:
Pınar İncel Uysal, Ankara Numune Training and Research Hospital, Clinic of Dermatology, Ankara, Turkey
E-mail: pinarincel@hotmail.com
ORCID-ID: orcid.org/0000-0002-4540-6560
Submitted/Geliş Tarihi: 15.05.2018
Accepted/Kabul Tarihi: 06.08.2018

Öz

(%7) relaps izlenmiştir. Evreleme gruplarında (IA, IB, IIA) tüm parametreler içerisinde yükselmiş beta-2 mikroglobulin sıklığı farklı idi. Klinik cevaplılığa göre sonuçlar kıyaslandığında teşhise dek geçen süre cevapsız hastalarda cevap verenlere göre belirgin derecede daha uzundu. Yüksek mSWAT skoru, yükselmiş beta-2 mikroglobulin ve LDH seviyeleri ve plak tip lezyonlar cevapsız hastalarda daha sıktı.

Sonuç: Çalışmamız erken evre MF hastalarında kapsamlı tarama testlerinin çok anlamlı olmayabileceğini ortaya koymaktadır. mSWAT skorları, beta-2 mikroglobulin ve LDH testleri tedaviye cevabın tahmin edilmesinde yararlı ölçümler olarak değerlendirilmelidir.

Anahtar kelimeler: Erken evre mikozis fungoides, Modifiye Şiddet Ağırlıklı Değerlendirme Ölçeği, prognostik biyobelirteçler, tarama testleri

Introduction

Cutaneous T cell lymphomas (CTCLs) which are characterized with clonal expansion of malignant T lymphocytes in the skin are a rare group of hematological malignancies. The most common subtype of CTCLs is mycosis fungoides (MF) (1). Clinical presentation may be highly variable but most patients present with stage I disease with indolent course. However, in some cases with early-stage MF the disease may progress to late stage or leukemic form of MF or may transform to high grade lymphoma (2,3). Thus, adverse prognostic markers should be considered as well as risk benefit ratio of the treatment modality, comorbidities of the patients and accessibility of the treatment.

The prognosis of patients with MF mainly depends on clinical stage. For today, MF is staged using revised tumor-node-metastasis-blood classification which was proposed by International Society for Cutaneous Lymphomas and European Organization for the Research and Treatment of Cancer (EORTC) (4). Early-stage MF disease (stage IA-IIA) has a favourable prognosis. However, stage IIA has a poorer prognosis than stage I (5). Owing to the prognostic heterogenity within these staging groups, there is still need for clarifying markers with prognostic significance. Because of low incidence of CTCLs, well described risk factors associated with aggressive course of early-stage MF are lacking in the literature. In this study, we conducted a chart review of demographical characteristics, baseline screening blood parameters including complete blood count, lactate dehydrogenase (LDH) and beta-2 microglobuline levels, flow cytometry findings, neutrophil/lymphocyte ratio (NLR), modified Severity Weighted Assessment Tool (mSWAT) scores and therapy responses of 112 patients with early-stage MF. We also investigated the link between these parameters and clinical responsiveness of the patients.

Methods

Study design

We retrospectively evaluated records of all MF/Sezary syndrome patients (187) who were diagnosed with MF in our clinic from 2014 to 2018. Patients with advanced stage MF and inadequate data were excluded from the analysis. We analysed the data of 112 patients who were diagnosed with early-stage MF in our department. Medical records of the patients who were followed for at least 1 year in our department were reviewed. Our study was performed to evaluate clinical and laboratory characteristics of the patients with stage IA, IB and IIA MF. The study protocol was approved with the code of E18-E1819 by the Ankara Numune Training and Research Hospital Local Ethics Committee of our hospital.

Patients

One hundred-twelve patients (50 female, 62 male) were included in this retrospective study. The patients were diagnosed with MF according to the clinicopathological criteria of world health organization/EORTC classification system (1). Demographical data, medical history, complete physical examination findings were reviewed. Also, following data were collected from the records: age at diagnosis, presence or absence of coexistent diseases, time to diagnosis (months), type of primary lesion (patch and/or plaque type lesions), clinical stage of the disease, mSWAT scores at baseline (6), treatment type and response to treatment. Response to treatment was identified based on the review of medical charts and defined as complete [complete resolution (CR) of lesions] and partial response (PR) (improvement in 50-99% of baseline lesions) in patients without new lesion (patch and/or plaque) development. Patients with stabile, progressive disease (PD) or relapsing lesions were classified as non-responders. Stabile disease (SD) was identified in patients with occurrence of a <25% or resolution of <50% of baseline lesions. Patients with increase of ≥25% in baseline lesions were grouped as having PD. Relapse was noted in patients who developed any recurrence after a CR (6).

Laboratory Parameters

The following parameters were analysed in stage IA, IB and IIA MF patients in the light of clinical response to the treatment: eosinophil count, presence of eosinophilia, NLR, LDH levels, beta-2 microglobulin levels, flow cytometry findings (percentage of CD3+, CD3+4+, CD3+8+, CD5+, CD7+, CD26+ T cells, CD4/CD8 ratio). CD4/CD8 >5 was considered as elevated. We also assessed the clinical significance of presence of increased subsets of CD3+/CD4+ T cells with negativity of CD7 and/or CD26.

NLR was calculated based on complete blood count of patients and median value of NLR was identified as cut-off. For the

analyses of eosinophil count, LDH and beta-2 microglobulin, each value above upper limit was categorized as "elevated". The normal ranges of the laboratory parameters accepted in this study were as follows: eosinophil blood count (absolute) 0-0.4 10 3/µL, eosinophil count (%) 0.9-4, LDH 25-248 U/L, beta-2 microglobulin 1.09-2.53 mg/L.

Statistical Analysis

Statistical analyses were carried out using SPSS software (version 21.0 for Windows; SPSS Inc, Chicago, IL, USA). Parametric variables were presented as means and standart deviations and nonparametric variables were presented as medians and interquartile ranges. For categorical variables number of cases and percentages were used. Chi-square or Fischer's exact test were used for analyzing categorical variables. Kolmogorov-Smirnov and histogram analyses were used to determine whether continous variables were normally distributed. Normally distributed numeric variables were analysed using Student's t-test and ANOVA. Mann-Whitney U and Kruskal-Wallis tests were used for comparing nonnormally distributed numeric variables. Correlations of numeric variables were assessed by Spearman and Pearson tests.

Results

Demographical and Clinical Characteristics

Demographical and clinical characteristics are summarized in Table 1. Fifty female and 62 male patients included in the study. Among staging groups (stage IA, IB and IIA) and treatment response groups (responsive and unresponsive), male/female ratio was similar (p>0.05). Mean age at diagnosis was 46.3 in stage IA, 53.6 in stage IB, and 58.8 in stage IIA (p=0.015) (Table 2) . However, there was no difference regarding mean age at diagnosis in between responders (51.3 years) and non-responders (51.9 years) (p>0.05).

Primary lesion type (patch and/or plaque) was significantly different in responders and non-responders (p=0.035). Median value of time to diagnosis was similar in staging groups but significantly higher in patients without treatment response (60 months) than responsive patients (20 months) (p=0.005). Median mSWAT scores were as follows: 7.5 (stage IA), 13 (stage IB), 18 (stage IIA) (p<0.001). In non-responders median mSWAT score (mSWAT=13) was significantly higher than responders (mSWAT=9) (p=0.042). There was no statistically significant relationship between presence of coexistent disease and treatment response status. Patients were followed for a median of 21 [interquartile range (IQR): 14-29] months after initial presentation.

Treatment Responses

Eighty seven percent of patients (97/112) treated with first-line therapy. Of these 97 patients, 51 patients (45%) achieved CR. Six of these patients developed relapse at the time of

Table 1. Demographical and clinical characteristics of early-stage mycosis fungoides patients

	n=112
Gender	
Female [n (%)]	50(44%)
Male [n (%)]	62(56%)
Age at diagnosis [mean (standard deviation)] (years)	52 (16)
Stage IA	46.3
Stage IB	53.6
Stage IIA	58.8
Time to diagnosis [median (interquartile range)] (months)	36 (12-60)
Stage	
Stage IA [n (%)]	47 (41%)
Stage IB [n (%)]	35 (31%)
Stage IIA [n (%)]	30 (26%)
Skin involvement [n (%)]	
<10%	57 (51%)
>10%	55 (49%)
Primary lesion [n (%)]	
Patch	78 (69%)
Plaque	19 (17%)
Patch and plaque	15 (13%)
Nodal involvement	
Yes	30 (26%)
No	82 (74%)
Coexistent systemic diseases [n (%)]	
Yes	43 (38%)
No	69 (61%)
mSWAT scores at baseline [median (interquartile range)]	10 (4-18)
Treatment type [n]	
First line therapies	
Topical corticosteroids	45
Narrowband UVB	28
PUVA	24
Second line therapies [n]	
Oral retinoid	7
Retinoid + PUVA	7
Retinoid + IFN-α	5
IFN-α monotherapy	5
Retinoid + UVB	4
Low dose MTX	3
Median follow up time [median (interquartile range)] (months)	21 (14-29)
Treatment response [n (%)]	
CR	49 (43%)
PR	30 (38%)
SD	15 (13%)
PD	10 (8%)
Relapse	8 (7%)

CR: Complete response, IFN: Interferon alfa, mSWAT: Modified Severity Weighted Assessment Tool, MTX: methotrexate, PD: Progressive disease, PR: Partial response, PUVA: Psoralen and ultraviolet A, SD: Stabile disease, UVB: Ultraviolet B

data analysis. Finally 45 patients achieved CR among patients who were given first-line therapies. CR rate was 40% (6/15) in patients who were treated with second-line treatments. Relapse rates in patients who achieved CR were as follows: 11% (6/51) in patients with first-line treatment, 33% (2/6) in patients with second-line treatment. Thus, totally 49 patients had achieved relapse free CR (Table 1). Switching to second line therapies because of SD, PD or relapse was noted in 16 (16%) of patients with first-line treatments. Treatment responses at the time of data analyses were summarized in the Table 1.

Peripheral Blood Flow Cytometry Findings

No significant difference was observed in presence of elevated CD4/CD8 ratio, median value of CD4/CD8 ratio and CD7 loss (CD4+/CD7-, 40% or more) among each stage group. Percentage of CD4+/CD26- cells were increasing in parallel with the stage of disease but this did not reach statistical significance (p>0.05) (Table 2). None of the baseline peripheral blood flow cytometry findings were predictive for response to treatment modalities.

Beta-2 Microglobulin Levels

Beta-2 microglobulin levels were significantly different among staging groups (p=0.001) (stage IA, 1.97, stage Ib 2.17, stage IIA 2.45). Stage of the disease and median beta-2 microglobulin levels were found to be positively correlated (p<0.001, r=0.433). Also, beta-2 microglobulin levels were significantly higher in non-responders (p<0.05) (median beta-2 microglobulin 2.45 (IQR: 2.07-3.18) in non-responders, median beta-2 microglobulin 2.01 (IQR: 1.85-2.18) in responder patients) (Table 3).

LDH Levels

In 38 (33%) patients high serum LDH levels (>248 U/L) were found. However there was not any association between disease stage and elevated LDH levels (p>0.05) (Table 2). Median serum LDH levels were similar but elevated levels of LDH (>248 U/L) were more frequent in patients without response (p=0.008) (Table 3).

NLR and Eosinophil Counts

The median NLR was 1.98 (range 1.53-2.53). In 55 patients (49%) NLR was >2. There was not any difference in NLR between staging groups (p>0.05). Also no correlation was detected between clinical responsiveness and NLR results (Table 3).

Median eosinophil counts are seen Table 2. Eosinophilia was observed in 22 (19%) patients. A comparison of eosinophil levels and presence of eosinophilia with respect to staging and clinical responsiveness did not reveal a significant difference.

Comparison of Clinical Characteristics and Baseline Biomarkers with Respect to Relapse

Among total of 57 patients who achieved CR, we found a relapse in 8 (14%) patients in the follow-up period. Regarding the disease characteristics of relapse factors there was no significant relation between relapse and gender, age at diagnosis, stage, primary lesion at initial presentation, mSWAT score (p>0.05). However; time to diagnosis was significantly higher in relapsed patients (66 months versus 12 months, p=0.044)

A comparison of baseline laboratory biomarkers with respect to relapse indicated that median value of baseline beta-2 microglobulin levels was higher in relapsed group (2.69 versus 2.17, p=0.045) while there was no difference between relapsed group and relapse-free patients in terms of baseline eosinophilia, NLR, serum LDH levels, CD4+/CD8+ ratio, presence of CD7 and CD26 loss.

Table 2. Laboratory findings of early-stage mycosis fungoides patients

		Stage IA (n=47)	Stage IB (n=35)	Stage IIA (n=30)
Laboratory findings				
Eosinophil absolute count (per μL)		150	200	100
Presence of eosinophilia [n (%)]		5 (10.7%)	9 (25.7%)	8 (26.6%)
NLR		1.96	2.2	2.1
Elevated beta-2 microglobulin level **[n (%)]		20 (42.5%)	24 (68.5%)	24 (80%)
LDH [median (interquartile range)]		208	197	234
Elevated LDH level (>248 U/L) [n (%)]		10 (21.2%)	12 (34.2%)	16 (53.3%)
Peripheral blood flow cytometry	CD26 loss [n (%)]	13 (28.9%)	10 (31.2%)	11 (36%)
	CD 7 loss [n (%)]	1	2	2
	CD4/CD8	1.45	1.52	1.9
	Increased ratio of CD4/CD8[ɣ] [n (%)]	-	2(5,7%)	1

CD: Clusters of differentiation, LDH: Lactate dehydrogenase, NLR: Neutrophil/lymphocyte ratio
**p<0.001, [ɣ]Cases with CD4/CD8 >5 were included

Table 3. Predictive analyses of baseline clinical and laboratory characteristics for treatment response in patients with early-stage mycosis fungoides

		Responders (n=79)	Non-responders (n=33)	p value
Clinical characteristics				
Sex Male Female		 48 31	 16 17	>0.05
Age at diagnosis [mean (SD)] (years)		52 (15)	51 (18)	>0.05
Time to diagnosis [median (interquartile range)] (months)		20 (11-54)	60 (24-120)	**0.005**
Stage Stage IA [n (%)] Stage IB [n (%)] Stage IIA [n (%)]		 40 (50.6%) 28 (35.4%) 11 (13.9%)	 8 (24.2%) 12 (36.3%) 13 (39.3%)	>0.05
Primary lesion Patch		 64 (81%)	 14 (42.4%)	**0.035**
Plaque		10 (12.6%)	9 (27.2%)	
Patch and plaque		5 (6.3%)	10 (30.3%)	
mSWAT score		9	13	**0.005**
Laboratory characteristics				
NLR		2,18	2.17	>0.05
Elevated beta-2 microglobulin level [n (%)]		17 (21 %)	15 (33%)	**0.019**
LDH level (U/L) [median (interquartile range)]		201 U/L (175-251 U/L)	218 (178-272 U/L)	>0.05
Elevated LDH level (>248 U/L) [n (%)]		31 (39%)	22 (66%)	**0.008**
Peripheral blood flow cytometry	CD26 loss [n (%)]	20 (25.3%)	14 (42.4%)	>0.05
	CD 7 loss [n (%)]	2 (2.5%)	3 (9%)	>0.05
	CD4/CD8	1.5	1.87	>0.05
	Increased ratio of CD4/CD8 [n (%)]	1 (1.2%)	1 (3%)	>0.05

CD: Clusters of differentiation, LDH: Lactate dehydrogenase, mSWAT: Modified Severity Weighted Assessment Tool, NLR: Neutrophil/lymphocyte ratio, SD: Standard deviation

Discussion

Owing to the rarity of MF, large long-term studies identifying high risk populations are still lacking. Indeed, prognostic models may help to improve outcomes of the patients with high risk disease. In addition extensive laboratory studies may be avoidable in patients with low-risk limited diseases. Early-stage MF consisting of stage IA, IB and IIA has prognostic heterogenity (5). Patients with stage I disease usually exhibit indolent course however the disease may progress approximately in %10 of patients with stage IB disease (7,8).

Many studies have been performed to establish prognostic factors for MF. Recently cutaneous lymphoma international prognostic index (CLIPi) has been proposed for early and late stage disease (9). Adverse prognostic factors at diagnosis are as follows: male sex, presence of plaques, age >60 years, folliculotropic variant and Nx/N1 node stage for early-stage disease. On the contrary some reports have suggested that CLIPi model failed to detect risk groups in their cohorts (8,10). We could not find any correlation between demographical characteristics including older age and male sex and poor prognosis in our study group. The presence of plaques in early stage disease has been reported to be associated with progression risk (5,7,11). In accordance with these findings, presence of plaques with or without patches was significantly different between responders and non-responders (19% in responders versus 57% in non-repsonders). Thereby, our findings confirm that absence of plaque lesions at presentation correlates with a favourable prognosis in patients with early-stage MF. In addition, in these patients time to diagnosis was considerably shorter than patients without response. However there was no difference in terms of clinical staging between treatment response groups.

The mSWAT is a validated tool for identifying tumor burden in clinical studies (6,12). Despite the fact that this is a reliable tool which is used to assess clinical endpoints, it is not included in clinical staging (5). We analyzed relevance of baseline mSWAT scores which may be predictive for those patients with a poor prognosis. In fact in patients with a PR or CR, mSWAT scores were significantly lower than patients with PD, SD or relapse.

Recently, besides many other solid malignancies, elevated NLR was demonstrated in patients with lymphoma (13-15). Furthermore, it has been suggested that increased neutrophil count may serve as a marker

of inflammation and decreased lymphocyte may encourage immunosuppression which correlates with a worse outcome in these patients (16,17). Authors have demonstrated high NLR in correlation with poor prognosis in patients with MF (18). On the contrary, there was no link between progression status and NLR levels of early stage MF patients in another study evaluating data of 117 patients. Similarly, in our study we could not detect a difference between responders and non-responders regarding baseline NLR. Also, staging groups exhibited similar NLR at diagnosis. It is possible that high NLR at diagnosis may be predictive for only patients with advanced stage.

Tancrede-Bohin et al. (19) reported that blood eosinophilia at baseline is a prognostic marker in patients with CTCL. In addition blood eosinophilia has been associated with less responsiveness to treatment (20). However, in both our study and that by Cengiz et al. (18) there was no association between blood eosinophilia and unfavourable prognosis. Definitive explaining for this finding may be ethnical differences as it was proposed by Zampella et al. (20). Of note, since the present study included patients with early stage MF which has indolent course, these results seem to be expectable.

It has been shown that raised beta-2 microglobulin levels may correlate with disease progression and a poor prognosis (7,21). Consistently, we observed significant difference in frequency of elevated beta-2 microglobulin levels among staging groups (IA,IB, IIA) and treatment response groups (responders vs. non-responders). All other analyses regarding staging groups (IA, IB and IIA) revealed that there were no other differences. As it was reported in previous reports, in our study, baseline LDH levels were higher in non-responders (5,22). Moreover, in patients with relapse initial beta-2 microglobulin levels were higher than relapse free patients.

CD26 which is expressed in the majority of circulating lymphocytes in peripheral blood is a surface proteolytic enzyme (23). Detection of CD26-population in peripheral blood seems to be highly characteristics of MF/Sezary syndrome tumor cells (24). We observed loss of CD26 in 30.3% of our patients. These results were quietly similar to those reported by Kelemen et al. (25) who noted that CD26-T cell clone was seen in 33.3% of MF patients. However, the clinical relevance of low level peripheral blood involvement in patients with skin limited MF has not been studied so far. Notably, even so statistical significance could not be reached CD26 negativity exhibited gradually increase from stage IA to IIA in our study. On the other hand loss of CD7 expression was observed in 5 (4%) patients.

In our study we had low number of patients (8/112) with relapse. So, we were unable to detect a significant difference in many of the parameters between relapsed and relapse-free groups. Nevertheless, it is worth to consider that relapsed patients had remarkably longer time to diagnosis.

Study Limitations

Main limitations of this study were retrospective single-center study design and relatively small sample size because of rarity of the condition. Also the median follow-up period was short among study population.

The present study evaluates clinical characteristics and baseline hematological screening tests of patients with the diagnosis of early-stage MF at initial presentation.

Conclusion

In conclusion, in early stage MF patients, extensive routine work-up at diagnosis not appears to be of high yield. Currently, flow cytometric analyses are optional for stage IA disease (26). Any of the other immunophenotypic criteria, NLR, presence of eosinophilia don't seem to be useful to estimate clinical responsiveness of the patients. To date, the prognostic significance of mSWAT score has not been studied for early stage disease. In particular, we may speculate that mSWAT scores at diagnosis, presence of plaque lesions, initial beta-2 microglobuline and LDH levels may be informative in terms of prognosis and treatment responses of early-stage MF patients. Future large prospective studies are required to determine relevance of these clinical and laboratory parameters.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Numune Training and Research Hospital Clinical Research Ethics Committee Chair (approval number: E18-1819).

Informed Consent: Retrospective study

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: P.İ.U., B.Y., Design: P.İ.U., Data Collection or Processing: N.A., M.F., Analysis or Interpretation: B.Ş., G.Ö., Literature Search: N.A., Writing: P.İ.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-85.
2. van Doorn R, Van Haselen CW, van Voorst Vader PC, et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol 2000;136:504-10.
3. Hughes CF, Newland K, McCormack C, et al. Mycosis fungoides and Sezary syndrome: Current challenges in assessment, management and prognostic markers. Australas J Dermatol 2016;57:182-91.
4. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:1713-22.
5. Scarisbrick JJ, Kim YH, Whittaker SJ, et al. Prognostic factors, prognostic indices and staging in mycosis fungoides and Sezary syndrome: where are we now? Br J Dermatol 2014;170:1226-36.

6. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29:2598-607.
7. Scarisbrick JJ, Prince HM, Vermeer MH, et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J Clin Oncol 2015;33:3766-73.
8. Wernham AG, Shah F, Amel-Kashipaz R, et al. Stage I mycosis fungoides: frequent association with a favourable prognosis but disease progression and disease-specific mortality may occur. Br J Dermatol 2015;173:1295-7.
9. Benton EC, Crichton S, Talpur R, et al. A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome. Eur J Cancer 2013;49:2859-68.
10. Sanz-Bueno J, Lora D, Monsalvez V, et al. The new Cutaneous Lymphoma International Prognostic index (CLIPi) for early mycosis fungoides failed to identify prognostic groups in a cohort of Spanish patients. Br J Dermatol 2016;175:794-6.
11. Scarisbrick JJ. Prognostic factors in mycosis fungoides: international advances in the validation of prognostic indices. Br J Dermatol 2017;176:1129-30.
12. Schmid MH, Bird P, Dummer R, et al. Tumor burden index as a prognostic tool for cutaneous T-cell lymphoma: a new concept. Arch Dermatol 1999;135:1204-8.
13. Keam B, Ha H, Kim TM, et al. Neutrophil to lymphocyte ratio improves prognostic prediction of International Prognostic Index for patients with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. Leuk Lymphoma 2015;56:2032-8.
14. Koh YW, Kang HJ, Park C, et al. Prognostic significance of the ratio of absolute neutrophil count to absolute lymphocyte count in classic Hodgkin lymphoma. Am J Clin Pathol 2012;138:846-54.
15. Beltran BE, Castro D, De La Cruz-Vargas JA, et al. The neutrophil-lymphocyte ratio is prognostic in patients with early stage aggressive peripheral T cell lymphoma. Br J Haematol 2018.
16. Castillo JJ, Morales D, Quinones P, et al. Lymphopenia as a prognostic factor in patients with peripheral T-cell lymphoma, unspecified. Leuk Lymphoma 2010;51:1822-8.
17. Wei X, Wei Y, Huang F, et al. Lymphopenia predicts preclinical relapse in the routine follow-up of patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2015;56:1261-5.
18. Cengiz FP, Emiroglu N, Ozkaya DB, et al. Prognostic Evaluation of Neutrophil/Lymphocyte Ratio in Patients with Mycosis Fungoides. Ann Clin Lab Sci 2017;47:25-8.
19. Tancrede-Bohin E, Ionescu MA, de La Salmoniere P, et al. Prognostic value of blood eosinophilia in primary cutaneous T-cell lymphomas. Arch Dermatol 2004;140:1057-61.
20. Zampella JG, Hinds GA. Racial differences in mycosis fungoides: a retrospective study with a focus on eosinophilia. J Am Acad Dermatol 2013;68:967-71.
21. Diamandidou E, Colome M, Fayad L, et al. Prognostic factor analysis in mycosis fungoides/Sezary syndrome. J Am Acad Dermatol 1999;40:914-24.
22. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139:857-66.
23. Dang NH, Torimoto Y, Shimamura K, et al. 1F7 (CD26): a marker of thymic maturation involved in the differential regulation of the CD3 and CD2 pathways of human thymocyte activation. J Immunol 1991;147:2825-32.
24. Jones D, Dang NH, Duvic M, et al. Absence of CD26 expression is a useful marker for diagnosis of T-cell lymphoma in peripheral blood. Am J Clin Pathol 2001;115:885-92.
25. Kelemen K, Guitart J, Kuzel TM, et al. The usefulness of CD26 in flow cytometric analysis of peripheral blood in Sezary syndrome. Am J Clin Pathol 2008;129:146-56.
26. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Hodgkin's Lymphomas Version 4. 2014.