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AN EVALUATION OF THE AST/ALT RATIO IN PATIENTS WITH MYCOSIS FUNGOIDES AND ITS ASSOCIATION WITH THE SEVERITY OF CUTANEOUS INVOLVEMENT

MİKOZİS FUNGOİDES HASTALARINDA AST/ALT ORANININ DEĞERLENDİRİLMESİ VE KUTANÖZ TUTULUMUN ŞİDDETİ İLE İLİŞKİSİ

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ABSTRACT

Objective: Mycosis fungoides (MF) is the most common T-cell skin lymphoma, and a simple and applicable parameter is needed to monitor the prognosis of the disease. We investigated the ratio of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in patients with MF.

Material and Methods: The research involved a retrospective, cross-sectional study. The records of MF patients were analysed. AST and ALT levels were recorded and the AST/ALT ratio was calculated and compared with the control group.

Results: Eighty-five MF patients and 85 healthy controls were included in the study. Males accounted for 56.5% (n=48) of MF patients and 57.6 % (n=49) of healthy group, with no significant difference (p>0.05) between them. AST levels were notably elevated in the MF group compared with the healthy group (p<0.001). Furthermore, there was a significant difference in the AST/ALT ratio between the two groups (p=0.005). The AST/ALT ratio cut-off value was 1.067. The AST value in the patients with abnormal lymphadenopathy (LAP) on ultrasonography (USG) was higher than in those with reactive LAP. The AST values of the patients with LAP with fluorodeoxyglucose (FDG) involvement on positron emission tomography (PET)/computed tomography (CT) were significantly higher than those of the patients without abnormal LAPs (p<0.05). The AST/ALT ratio was weakly positively correlated with the disease stage (p=0.018).

Conclusion: AST values and AST/ALT ratios of patients with MF were significantly higher than those of the control group. The

ÖZET

Amaç: Mikozis fungoides (MF), derinin en sık görülen T hücreli lenfoması olup hastalığın prognozunu takip etmede kullanışlı, basit parametrelere ihtiyaç duyulmaktadır. Çalışmamızda son zamanlarda birçok malignitede prognostik faktör olarak araştırılan aspartat aminotransaminaz (AST) ve alanin aminotransaminaz (ALT) oranının bir deri lenfoması olan MF'de değerlendirilmesini amaçladık.

Gereç ve Yöntem: Çalışmamız retrospektif kesitsel bir çalışmadır. Çalışmada MF tanısı alan hastaların dosya taraması yapıldı. AST, ALT değerleri kaydedilerek AST/ALT oranı hesaplanıp, kontrol grubu ile istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmaya 85 MF hastası ve 85 sağlıklı kontrol olmak üzere toplam 170 kişi dahil edildi. Buna göre, MF grubunun %56,5'i (n=48) ve sağlıklı kontrol grubunun %57.6 (n=49)'sı erkek idi ve gruplar arası anlamlı farklılık bulunmuyordu (p>0,05). MF grubunun AST değeri sağlıklı gruba göre daha yüksekti ve istatistiksel anlamlı farklılık saptandı (p<0,001). AST/ALT oranı her iki grup arasında istatistiksel olarak anlamlı farklılık saptandı (p=0,005). AST/ALT oranı cut-off değeri ise 1,067 bulunmuştur. USG'de anormal LAP saptanan hastalarda AST değeri reaktif LAP olanlara göre daha yüksek bulundu. PET CT'de ise, FDG tutulumu olan LAP'ları saptanan hastaların AST değeri, anormal LAP'ları olmayan hastalardan anlamlı yüksek olarak saptandı (p<0,05). AST/ALT oranı ise hastalık evresi ile zayıf pozitif korele bulundu (p=0,018).

Sonuç: Çalışmamızın sonucunda, MF'li hastaların AST değeri ve AST/ALT oranı sağlıklı kontrol grubuna göre istatistiksel olarak

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AST/ALT ratio can be used as an independent factor in monitoring the prognosis of patients with MF.

Keywords: Mycosis fungoides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST/ALT ratio, prognostic factor

anlamlı yüksek bulunmuştur. MF hastalarının prognozunun takibinde AST/ALT oranı bağımsız bir faktör olarak kullanılabilir.

Anahtar Kelimeler: Mikozis fungoides, aspartat aminotransferaz (AST), alanin aminoaminotransferaz (ALT), AST/ALT oranı, prognostik faktör

INTRODUCTION

Mycosis fungoides (MF) is the most common primary T-cell skin lymphoma. Its aetiology is uncertain although the emphasis is on genetic and environmental factors. The disease may progress with only cutaneous lesions. However, in patients with advanced disease, visceral involvement may occur. Skin lesions include patches, indurated plaques and tumours. Lesions of different morphologies may co-exist, and these lesions may also transform into each other. They tend to affect covered body areas (1). Survival in the early stages of the disease is 10-35 years, while around 25% of cases progress to the advanced stage with an average survival of 1-4 years (2). The tumour (T), lymph node (N), metastasis (M) and blood (B) (TNMB) system is the most important prognostic factor for MF. The early stage is defined as IA-IIA and the advanced stage as IIB-IV (3). Several independent prognostic factors in MF have been described in addition to TNMB staging. Increased lactate dehydrogenase levels, increased β2-microglobulin, eosinophilia, large cell transformation, older age, male sex and folliculotropic type MF have all been recognised as poor prognostic criteria (4). Aspartate aminotransferase (AST) is an enzyme that can be present in the cell, cytoplasm, and mitochondria. In addition to the liver, it can be found in several organs including the muscle, skeletal muscle, blood cells such as erythrocytes, the pancreas, and the brain. Alanine aminotransferase (ALT) is a cytoplasmic enzyme and is more specific to the liver. A more marked increase in ALT occurs in the event of liver damage (5). Aminotransferases like AST and ALT participate in cellular metabolism in healthy cells, and they also play a significant role in cancer cells and their turnover. ALT is crucial for the glucose-alanine cycle, whereas AST is necessary for aerobic glycolysis through adenine dinucleotide translocation within the mitochondria. These metabolic processes are particularly vital for cancer cells because of their heightened metabolic activity (6). The average reported AST/ALT ratio, also known as the "De Ritis ratio", in the cytoplasm of a normal hepatocyte cell is 0.6 (7). Recent research shows that the ratio of AST to ALT serves as an independent prognostic factor in many different types of cancer (8). The purpose of the present study was to investigate the relationship between the ratio of AST to ALT and the disease stage and extent of the affected body surface area in patients with MF. Our scan of the literature revealed no previous studies examining the "De Ritis ratio" in MF patients with T-cell lymphoma of the skin, and this study is thus the first on the subject.

MATERIAL AND METHODS

Study design

The research was conducted as a retrospective, single-centre, cross-sectional study.

Ethical approval

The study has ethical approval from the Atatürk University, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (Date: 29.03.2024, No: 192).

Setting

The study was conducted in a tertiary university hospital in a region in the east of Türkiye with approximately 4.5 million inhabitants, with a large patient population. The MF patient group participated from the chronic dermatological disease's clinic, while the control group consisted of individuals presenting to our hospital's occupation health and safety clinic for routine checks.

Participants

One hundred and seventy patients were included in the study. These consisted of 85 patients aged 18-85 presenting to our hospital's chronic dermatological diseases clinic between January 2018 and February 2024 with histopathologically confirmed MF. The healthy control group consisted of 85 individuals with demographic characteristics similar to those of the patient group and with no dermatological or systemic diseases. The data for healthy controls were obtained retrospectively from individuals presenting to our hospital's health and safety clinic for routine check-ups. Official permission for the use of these individuals' data was received from the chief physician's office. The patients and controls' demographic data and the patient group's duration of disease and clinical findings were recorded with retrospective screening of the files. Patients with a history of using dietary supplements or herbal products that may affect liver enzymes were not included in the study. The patient groups with existing symptoms as of the date of admission and their AST and ALT results for that time were screened and recorded. The AST/ALT ratio was calculated as the proportion of AST and ALT values. The patients' abdominal ultrasonography (USG) and positron emission tomography (PET)/computed tomography (CT) results were also recorded. The distribution and extent of the lesions and the stage of the disease-based lymph node involvement were determined. Lymph nodes whose USG findings revealed a loss of oval shape, larger than 1.5 cm in size, with

an indistinct hilus, a thick cortex, and hyperechoic necrotic areas were abnormal in structure. Our hospital's laboratory values were used for AST and ALT test result reference values. Accordingly, 0-40 U/L were evaluated as normal for AST and 0-50 U/L for ALT. The rule of nines was applied to calculate the body surface area. Accordingly, each leg was constituting 18% of the body area, each arm 9%, the front and rear trunk 19% each, and the head 9% (9). Patients without histologically confirmed diagnoses of MF, those aged under 18 or over 85 years, with other diseases affecting the liver, with histories of alcohol use, or with previously known malignancies were excluded from the study. Since the study was conducted retrospectively and it was designed as an archive scan of all patients' files, it was not necessary and not possible to obtain informed consent from the patients.

Statistical analysis

The study data were analysed using SPSS version 27 software (IBM SPSS Corp., Armonk, NY, USA). Categorical data are presented as frequency and percentage and numeric data as mean, standard deviation, median, and interquartile range values. The Kolmogorov–Smirnov test was applied to assess the normality of the distribution of the continuous variables. The Mann–Whitney U test was used in the analysis of two independent non-normally distributed groups. Tukey's HSD test was employed in the post hoc analysis of variables with assumed equal variances. Spearman's correlation analysis was applied to non-normally distributed continuous variables. The area under the curve (AUC) was calculated using ROC analysis, and the cut-off values were determined using the Youden index. Categorical variables were analysed using Pearson's chi-square test. P values less than 0.05 were deemed statistically significant.

RESULTS

One hundred and seventy individuals were included in the study, 85 patients with MF and 85 healthy controls. A comparison of the participants' demographic characteristics and blood test values is shown in Table 1. Males represented 56.5% (n=48) of the MF group and 57.6% (n=49) of the healthy group, and the difference between the groups was not statistically significant ($p>0.05$). The median age was significantly higher, at 50 Interquartile Range (IQR) =31 in the MF group than in the healthy control group at 43 (IQR= 2) ($p<0.05$). The median AST value in the MF group was significantly higher than that in the healthy group [24.00 (IQR=15.00) vs. 18.50 (IQR=6.00), respectively] ($p<0.001$). However, there was no significant difference between the two groups' ALT values ($p>0.05$). The ratio of AST to ALT in the MF group, 1.2095 (IQR=0.56) was significantly higher than that in the healthy control group, at 1.0629 (IQR=0.54) ($p=0.005$).

AST and the ratio of AST to ALT ROC curves between the MF and healthy groups are shown in Figure 1. In the ROC analysis, the AUC value for AST was 0.729 (95 % CI: 0.653-0.806), and that for the AST/ALT ratio was 0.623 (95 %CI: 0.540-0.707) (Table 2). The cut-off values were 20.25 (with 75.3% sensitivity and 64.7% specificity) for AST and 1.067 (with 70.6% sensitivity and 51.8% specificity) for the AST/ALT ratio.

A comparison of the MF patients' AST, ALT, and AST/ALT ratio values in terms of their demographic characteristics and morphological and clinical disease findings is shown in Table 3. ALT was significantly higher in males and the AST/ALT ratio in women. AST values were higher in patients with abnormal LAP detected at USG than those with reactive LAP. At post-hoc analysis, AST values were similarly significantly higher in the presence of LAP and in the presence and absence of hepatosteatosis, in other words, in individuals with abnormal LAP, compared to those with reactive LAP. The ADT values of patients with LAP and FDG involvement at PET CT were significantly higher than those of the patients without abnormal LAP ($p<0.05$).

Analysis between continuous variables revealed a weak positive correlation between AT values and age, disease stage, the region of the body, and LAP circumference. ALT values exhibited no correlation with any parameters, whereas the AST/ALT ratio was weakly positively correlated with the disease stage (Table 4).

DISCUSSION

Mycosis fungoides (MF), the most common T-cell skin lymphoma, is capable of affecting the haematological system and the visceral organs in the advanced stage (1). More easily applied and inexpensive methods than expensive and time-consuming tests have recently become highly attractive for estimating the prognosis of several diseases. Several biomarkers have recently been investigated for monitoring the prognosis in malignant diseases. One such biomarker is the AST/ALT ratio. On that basis, we set out to add to the existing literature by investigating the AST/ALT ratios of patients with MF and a healthy control group and its relationship with the stage of the disease and spread of cutaneous involvement. The AST/ALT ratio is also known as the "De Ritis ratio", the concept first being employed in a study of the aetiology of hepatitis (10). ALT is more specific to the liver, while AST is an enzyme involved in aerobic glycolysis and capable of being synthesised in several types of tissue. AST may therefore rise more markedly than ALT in cases of widespread tissue damage and high tumour cell turnover. This makes the AST/ALT ratio a potential biomarker in malignancies (6). Aerobic glycolysis and pyruvate production are highly important for the increased metabolism of tumour cells. Increased nucleotide biosynthesis and the synthesis of non-essential amino acids in tumour cells contributes to the proliferation of cancer cells. Tumour cells should increase the synthesis of

Table 1: A comparison of the two study groups

				MF group	Healthy group	P
Sex	Female		n	37	36	**0.877***
	%		43.5%	42.4%		
	Male		n	48	49	
	%		56.5%	57.6%		
Age	Mean			50.79	42.84	**0.007†**
	95% Confidence Interval for mean	Lower bound		46.92	42.66	
		Upper bound		54.66	43.01	
	Median			50.00	43.00	
	Std. deviation			17.93	0.80	
	Interquartile range			31.00	2.00	
AST	Mean			27.37	19.91	**<0.001†**
	95% Confidence Interval for mean	Lower bound		24.89	18.69	
		Upper bound		29.86	21.13	
	Median			24.00	18.50	
	Std. deviation			11.52	5.65	
	Interquartile range			15.00	6.00	
ALT	Mean			22.84	19.95	**0.131†**
	95% Confidence Interval for mean	Lower bound		20.44	18.01	
		Upper bound		25.25	21.89	
	Median			21.00	18.40	
	Std. deviation			11.14	8.98	
	Interquartile range			16.10	9.70	
AST/ALT ratio	Mean			1.3468	1.1336	**0.005†**
	95% Confidence Interval for mean	Lower bound		1.2188	1.0330	
		Upper bound		1.4748	1.2341	
	Median			1.2095	1.0629	
	Std. deviation			0.5934	0.4660	
	Interquartile range			0.56	0.54	

*: Pearson Chi–square test, †: Mann–Whitney U test, MF: Mycosis Fungoides, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.
Note: Bold p values indicate statistical significance between the groups.

Table 2: Area under the curve (AUC) values for AST and AST/ALT ratio levels were determined in the ROC curve analysis

Test result variable(s)	Area	Std. error[a]	Asymptotic sig.[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
AST	0.729	0.039	0.000	0.653	0.806
AST/ALT ratio	0.623	0.043	0.004	0.540	0.707

[a]: Under the non-parametric assumption, [b]: Null hypothesis: true area = 0.5, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

the non-essential amino acid glutamine to ensure this. In contrast, ALT catabolizes pyruvate and glutamine to α-ketoglutarate in order to reduce glutamine. One in vitro experiment showed lower ALT levels in invasive cancer cells than in non-invasive cancer cells. Cancer cells can cause this by increasing ALT consumption (11). In

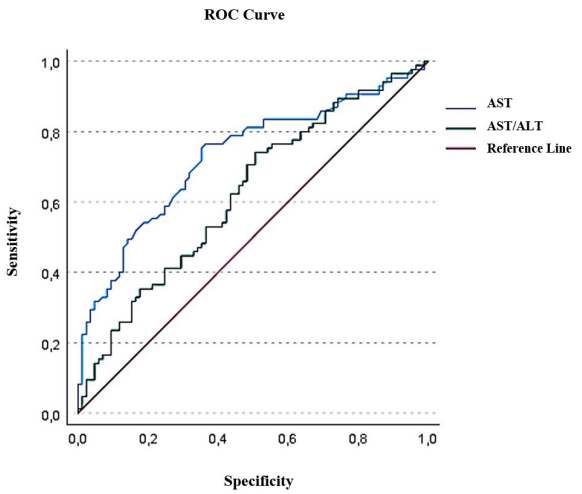

Figure 1: ROC curve analysis of AST and AST/ALT ratio between the study groups
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 3: Statistical comparisons of AST, ALT, and AST/ALT ratio values according to various morphologic features in the MF group

	AST	ALT	AST/ALT ratio
Sex	0.062*	**0.003***	**0.007***
Smoking	0.270†	0.741†	0.122†
Lesion type	0.377†	0.440†	0.681†
Subjective finding	0.343†	0.490†	0.840†
Symptom	0.372†	0.461†	0.561†
LAP present	0.052*	0.119*	0.972*
LAP morphology	**0.011†**	0.079†	0.926†
LAP location	0.491†	0.607†	0.528†
USG findings	**0.024†**	0.070†	0.716†
PET findings	**0.039***	0.073*	0.549*

*: Mann–Whitney U test, †: Kruskal–Wallis test, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LAP: Lymphadenopathy, PET: Positron Emission Tomography, USG: Ultrasonography.
Note: Bold p values indicate statistical significance between the groups.

Table 4: Correlation analysis between AST, ALT and AST/ALT ratio values and demographic variables in the MF group

		AST	ALT	AST/ALT Ratio
Age	r	0.216*	0.092	0.061
	p	**0.047**	0.404	0.579
Disease Duration (months)	r	-0.032	-0.021	-0.033
	p	0.775	0.848	0.766
Disease Stage	r	0.388**	0.100	0.256*
	p	**<0.001**	0.363	0.018
Body Surface Area Involved	r	0.244*	0.146	0.074
	p	**0.025**	0.181	0.500
LAP Number	r	0.184	0.134	0.037
	p	0.093	0.221	0.734
LAP Circumference	r	0.359**	0.184	0.147
	p	**0.001**	0.092	0.180

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LAP: Lymphadenopathy
Note: Bold p values indicate statistical significance between the groups.

support of that finding, this study revealed no significant difference in ALT levels between the patients with MF and the healthy controls. In the previous literature, the AST/ALT ratio has been shown to be higher in several malignancies, such as renal cell carcinoma, bladder cancer, cholangiocarcinoma, pancreatic carcinoma, and breast carcinoma, compared to control groups, and be capable of use as a prognostic marker in patients with malignancies (12-16). However, we encountered no previous study investigating the AST/ALT ratio in haematological malignancies. This study is thus the first involving MF, a condition capable of causing dermatological, haematological, and visceral involvement. Significant differences in AST and AST/ALT ratio values were determined between the MF patients and the control group. The AST/ALT ratio was 1.2095 in the MF group and 1.0629 in the healthy control group. At the same time, a positive correlation was found between the extent of the skin surface and AST values in the MF patients. This may indicate that widespread cutaneous involvement may have raised AST values by increasing the tumour burden. Monitoring of liver enzymes may be particularly important in MF patients with diffuse skin involvement. Although several studies have reported that the AST/ALT ratio may be useful for determining prognosis in malignancies, a weak positive correlation was observed in the present study between the disease stage of MF patients and the AST/ALT ratio. The AST/ALT ratio may be a prognostic factor that becomes more important in aggressive malignancies with much faster metabolic activity. The statistically weak correlation between MF stage and AST/ALT ratio found in this study may be explained by the fact that MF is a slowly-progressive T-cell lymphoma. It can be posited that the lack of a significant correlation between the AST/ALT ratio and the disease stage may be attributable to the predominance of early stage MF patients within the study sample, potentially masking the potential relationship between these variables. In our opinion, the AST/

ALT ratio may be a more useful prognostic factor in the follow-up of patients with progressive MF. Therefore, we believe that our findings need to be supported by further prospective studies involving greater participation. MF is more common at the ages of 55-60 and in males (17). In agreement with the previous literature, the median age of the MF group in the present research was 50 (IQR=31) years, and 56.5% (n=48) of the MF patients were males. The ratio of AST to ALT showed a significant increase in female MF patients compared to males. Although a previous study reported that hepatic enzyme levels may vary by gender for genetic reasons, this is still unclear. There is a need for further research into this issue. (18).

ROC analysis between the MF patients and the healthy control group revealed AUC values of 0.729 for AST and 0.623 for the AST/ALT ratio. The cut-off values were 20.25 for AST (75.3% sensitivity and 64.7% specificity) and 1.067 for the AST/ALT ratio (70.6% sensitivity and 51.8% specificity). The patients' USG and PET results were examined, but no visceral organ involvement was observed in any case in the MF group. This may derive from the patients included in the study being in the early stage of MF. Hepatosteatosis and LAP were evaluated on the basis of USG and PET results, and the relationship between these findings and the AST/ALT ratio in the patient group was investigated. AST values were higher in the patients with abnormal LAP determined by both USG and PET compared with those with reactive LAP. However, no statistically significant association was observed with the AST/ALT ratio. We therefore think that hepatic enzymes should be measured during the disease in patients with MF with abnormal LAP detected both clinically and using tests such as USG and PET.

There are many limitations to this study. The first involves its retrospective nature. Another limitation is that some patients were evaluated while in receipt of treatment. A third limitation is that the single centre-nature of the research represents an obstacle to the generalisation of the results.

However, there are also some strengths to this study. The most powerful of these is that it is the first to evaluate the AST/ALT ratio in patients with MF. The relatively high numbers of both MF patients and healthy controls taking part constitutes another strength.

CONCLUSIONS

In conclusion, both AST and AST/ALT ratio values were higher in the MF group than in the healthy control group. Although the AST/ALT ratio exhibited a weak positive correlation with the stage of MF, we believe that this ratio, and particularly AST, can be used as a potential biomarker for monitoring the prognosis of the disease. To confirm and support the relationship between MF and the AST/ALT ratio, further multicenter prospective studies with larger numbers of participants are needed. We think that if this relationship is supported by further studies, it may contribute to the identification of patients who require close monitoring and to deciding whether to apply additional and more aggressive treatments in MF, a malignant disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the Atatürk University, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (Date: 29.03.2024, No: 192).

Informed Consent: Since the study was conducted retrospectively and it was designed as an archive scan of all patients' files, it was not necessary and not possible to obtain informed consent from the patients.

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