doi:10.53446/actamednicomedia.1099663

Acta Medica Nicomedia

Cilt: 5 Sayı: 2 Haziran 2022 / Vol: 5 Issue: 2 June 2022
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

THE RELATIONSHIP BETWEEN MALIGNANCY AND PRIMARY SJOGREN'S SYNDROME; SINGLE CENTER RESULTS

MALİGNİTE VE PRİMER SJÖGREN SENDROMU ARASINDAKİ İLİŞKİ; TEK MERKEZ SONUÇLARI

Ozlem Ozdemir Isik[1], Ayten Yazici[1], Ayse Cefle[1]

[1]Kocaeli University, Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Kocaeli, Turkey.

ABSTRACT

Objective: In this study, we aimed to present malignancy data in patients who were followed up in our outpatient clinic with a diagnosis of primary Sjogren's syndrome (pSS).

Methods: Data of 151 patients diagnosed with pSS between 2004-2019 were retrospectively reviewed and clinical, demographic characteristics of 14 patients diagnosed with malignancy were examined. Standardized incidence ratios (SIRs) were calculated.

Results: All 14 patients with malignancy were female, their mean age was 55.9±12 years, and the disease duration was 10.5±5.3 years. Malignancy was detected in 9% of the patients who were followed up with the diagnosis of pSS. One patient was diagnosed with cervix cancer (CA), four patients with breast CA, three patients with thyroid papillary CA, one patient with MALT (mucosa-associated lymphoid tissue) lymphoma, one patient with diffuse large B-cell lymphoma (DLBCL), one patient with mycosis fungoides, one patient with vulvar epithelial carcinoma, and two patients with lung CA. Patients with malignancy and those without were compared in terms of clinical and laboratory findings. There was a significant difference between the presence of LAP and ILD and EULAR primary Sjogren's syndrome disease activity ındex (ESSDAI) activity scores of two groups.

Conclusion: In our study, an increased risk was observed for both hematological [SIR27.27 (95% CI 5.6-79.7)] and solid malignancies [SIR 7.75 (95% CI 3.9-13.9)] in Sjogren's Syndrom.

Keywords: Sjogren's syndrome, malignancy, lymphoma, solid cancer

ÖZ

Amaç: Bu çalışmada, polikliniğimizde primer Sjögren sendromu (pSS) tanısı ile takip edilen hastalarda malignite verilerini sunmayı amaçladık.

Yöntem: 2004-2019 yılları arasında pSS tanısı alan 151 hastanın verileri retrospektif olarak incelendi ve malignite tanısı alan 14 hastanın klinik, demografik özellikleri değerlendirildi. Standardize insidans oranları (SIR'ler) hesaplandı.

Bulgular: Malignite saptanan 14 hastanın tamamı kadın, yaş ortalaması 55.9±12 yıl ve hastalık süresi 10.5±5.3 yıl idi. pSS tanısı ile takip edilen hastaların %9'unda malignite saptandı. Bir hastaya serviks kanseri, dört hastaya meme kanseri, üç hastaya tiroid papiller karsinom, bir hastaya MALT (mukoza ile ilişkili lenfoid doku) lenfoma, bir hastaya diffüz büyük B hücreli lenfoma (DBBHL), bir hastaya mikozis fungoides, bir hastaya vulvar epitelyal karsinom ve iki hastaya akciğer kanseri tanısı konulmuştu. Malignitesi olan ve olmayan hastalar klinik ve laboratuvar bulguları açısından karşılaştırıldı. İki grupta lenfadenopati ve interstisyel akciğer hastalığı varlığı ile EULAR primer Sjögren sendromu hastalık aktivite indeksi (ESSDAI) aktivite skorları arasında anlamlı fark vardı.

Sonuç: Çalışmamızda Sjögren Sendromunda hem hematolojik [SIR27.27 (%95 CI 5.6-79.7)] hem de solid maligniteler [SIR 7.75 (%95 CI 3.9-13.9)] için risk artışı gözlendi.

Anahtar Kelimeler: Sjögren sendromu, malignite, lenfoma, solid kanser

***İletişim kurulacak yazar/Corresponding author:** Ozlem Ozdemir Isik; Kocaeli University, School of Medicine, Department of Rheumatology, Umuttepe, Kocaeli, Turkey, 41380
Telefon/Phone: +90 505 592 98 29 **e-posta/e-mail:** luska80@hotmail.com
Başvuru/Submitted: 06.04.2022 • **Kabul/Accepted:** 27.04.2022 • **Online Yayın/Published Online:** 27.06.2022

Introduction

Primary Sjogren's syndrome (pSS) is a systemic, autoimmune disease characterized by lymphoplasmcytic infiltration of exocrine glands.[1] It has been known since the study by Kassan et al. in 1978 that the risk of lymphoma in Sjogren's syndrome (SS) has increased.[2] In a meta-analysis published in 2005, it has been emphasized that the development risk of Non-Hodgkin Lymphoma (NHL) is high in SS.[3] Skin vasculitis, peripheral nerve involvement, low complement levels, swollen salivary gland, lymphadenopathy and cytotoxic drug use play a role in the etiology of lymphoma.[2,4] There are different study results about non-NHL and solid cancers.[5,6] In this study, we aimed to present the development of malignancy and its relationship with clinical and laboratory findings in pSS patients followed up in our outpatient clinic.

Methods

The data of 151 patients who were diagnosed with pSS according to the classification criteria of the European-American Consensus Group[7] and admitted to our outpatient clinic between 2004 and 2019 were retrospectively reviewed. The clinical, demographic, and laboratory features and medications of 14 patients diagnosed with malignancy were examined. The study was performed according to the Declaration of Helsinki.

Statistics

Statistical evaluation was made with IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. Normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical variables were given as mean ± standard deviation and median+IR (min.-max.), and categorical variables as frequency (percentage). The difference between groups was determined with the independent sample t test for numerical variables with normal distribution, and with the Mann-Whitney U test for numerical variables that did not have a normal distribution. Relationships between categorical variables were evaluated by Chi square analysis. Binary logistic regression analysis was used to determine the factors affecting the variable of interest. Kaplan Meier test was used for survival analysis. In the test of two-sided hypotheses, $p<0.05$ was considered sufficient for statistical significance. The standardized incidence ratio (SIR) was computed as the ratio of observed to expected cancers. Expected cancers were determined by multiplying person-years by the corresponding sex- and age-specific incidence rates of cancer in the general Turkey population in 2018 (the most recent data available from the International Agency for Research on Cancer) provided by the GLOBOCAN project (https://gco.iarc.fr) and summing overall person-years. The 95% confidence intervals (CI) of the SIR were also calculated.

Results

The mean age of 151 pSS patients was 55.9±12 years, the disease duration was 126±64.7 months, and the follow-up period was 45.8±33.8 months. Of the patients, 3% were men and 97% were women. Fever was present in 5% of the patients, weight loss in 8%, and night sweats in 1%. 88% of the patients had dry mouth, 86% had dry eyes, 17% had parotitis, and 72% had decreased decreased uptake and excretion in salivary gland scintigraphy. Salivary gland biopsy confirmed the diagnosis in 76 % of the patients. The Schirmer test was positive in 82% of the patients, rheumatoid factor (RF) in 60%, antinuclear antibody (ANA) in 91%, SS-A in 62%, and SS-B in 50% (Table 1).

Table 1. Clinical and demographic data of all patients with primary Sjogren's syndrome and those with malignancy

n (%)		All Patients n=151	With Malignancy n=14
Gender	Female	147 (97)	14 (100)
	Male	4 (3)	
Dry mouth		133 (88)	13 (93)
Dry eyes		130 (86)	12 (86)
Arthritis		43 (29)	2 (14)
Parotitis		25 (17)	4 (29)
Raynaud Phenomenon		30 (20)	2 (14)
Lymphadenopathy		44 (29)	8 (57)
Interstitial Lung Disease		16 (11)	4 (29)
Smoking		31 (21)	6 (43)
Hypocomplementemia		18/120 (15) *	4 (29)
Malignancy		14 (9)	14 (100)
Nephrological involvement		5 (3)	-
Myositis		2 (1)	-
Vasculitis		6 (4)	-
Neuropathy		9 (6)	-
Leukopenia		35 (23)	5 (36)
Thrombocytopenia		4 (3)	-
Hypergammaglobulinemia		34 (23)	4 (29)

*Data are presented according to the number of patients with known complement levels

Malignancy was detected in 9% (14 patients) of the patients that followed up with diagnosis of pSS. A patient who has been followed up with pSS diagnosis for a long time was diagnosed with mixed connective tissue disease and the patient who was diagnosed with diffuse large B-cell lymphoma in the follow-up and treated by department of hematology was excluded from the study. A BIRADS-4 lesion was determined in the mammography report of a patient. During the evaluation period due to pre-diagnosis of breast cancer (CA), the patient died. One patient was diagnosed with lung CA originating from the region of previous pulmonary tuberculosis and died while receiving chemotherapy. The other patient died after diagnosis of lung CA at an advanced age. One patient had a gastric premalignant lesion and was being examined but lost during follow-up.

All the patients with malignancy were female, the mean age was 59±13 years and the disease duration were 9±5.8 (2-17) years. The Schirmer was below 5 mm in 86% of these patients whose clinical findings are given in Table-1, and decreased involvement in the parotid and

submandibular glands was found in 64% of the salivary gland scintigraphy. Salivary gland biopsy was compatible with the diagnosis of Sjogren's syndrome in 64% of the patients. RF, ANA, SS-A, and SS-B were positive in 64%, 93%, 71%, and 57% of the patients, respectively. While the C3 level was found to be low in 29% of the patients, the C4 level was normal in all patients. Hypergammaglobulinemia was observed in 29% of the patients (Table-1). The mean age of malignancy in these patients was 53±2 years, and the time from Sjogren's diagnosis to malignancy diagnosis was 59±33 months. In two patients, malignancy was diagnosed before SS diagnosis.

One patient was diagnosed with cervix CA, four patients breast CA, three patients with thyroid papillary CA, one patient with diffuse large B-cell lymphoma (DLBCL), one patient with MALT (mucosa-associated lymphoid tissue) lymphoma, one patient with mycosis fungoides, one patient with vulvar epithelial carcinoma, and two patients with lung CA (Table 2).

PSS patients with or without malignancy were compared in terms of clinical and laboratory findings. There was a significant difference between the presence of LAP and ILD and EULAR primary Sjogren's syndrome disease activity index (ESSDAI) activity scores of two groups (Table 3).

In the univariate logistic regression analysis performed to determine the factors affecting the development of malignancy, ILD [p=0.032 OR 4.17 (95% CI 1.13-15.3)] and LAP [p=0.022 OR 3.74 (95% CI 1.21-11.5)] were observed to increase the risk. In the evaluation performed with the ESDAI score [p=0.040 OR 1.08 (95% CI 1.00-1.17)], an increase in the development risk of malignancy with disease activity was observed. However, in the multivariate analysis, the relationship between the ESSDAI score and the risk of malignancy was not observed (Table 4).

Follow-up periods of patients with malignancies, age of disease and time to malignancy development were analyzed in different subgroups. When only the follow-up periods were considered, the time until the development of malignancy was found to be significantly shorter in patients with ILD compared to those without (p=0.044) (Figure 1).

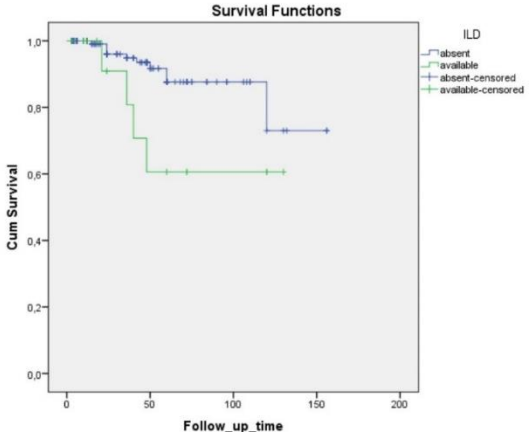

Figure 1. Malignancy development time in patients with or without Interstitial Lung Disease (ILD) according to follow-up time (month).

Although there was a difference between the duration of disease until development of malignancy in patients with hematological and solid malignancies, no statistical significance was found (p=0.115). According to GLOBOCAN data in 2018 for population over the age of 20, age-standardized cancer incidence rate in Turkey was reported as 363/100.000. While this rate was 262/100.000 for women and 460/100.000 for men. The average follow-up period of our patients was 3.81 years and the expected rate for all patients was calculated as 575 patients/year (560 patients/year for women, 15 patients/year for men). SIR was calculated with the expected and observed cancer rates according to GLOBOCAN data. Significantly increased rates were observed in hematological and solid malignancies. Since all the patients with malignancy were women in this present study, the expected cancer rates for male patients were not shared (Table 5).

Discussion

In our study, a significant increased risk was observed in both solid [SIR 7.75 (95% CI 3.9-13.9)] and hematological malignancies [27.27 (95% CI 5.6-79.7)] in pSS patients. Although the risk increase for malignancy (solid and hematological) in our data was higher than the results of meta-analysis[8] and previous studies[5,9], it was thought that the low number of our patients influenced this. In the Kassan et al.[2], a significant increased risk was found of non-Hodgkin lymphoma [SIR 44.4 (95%CI 16.7-118.4)]. Kauppi et al.[10] found an increased risk of all cancers [SIR 1.1 (95%CI 0.8-1.5)], non-hodgkin lymphomas [SIR 8.7 (95%CI 4.3-15.5)], Hodgkin's disease [SIR 13.1 (95%CI 1.6-47.4)]. Weng My et al.[11] found an increased risk of non-Hodgkin lymphoma [SIR 7.1 (95%CI 4.3-10.3)], multiple myeloma [SIR 6.1 (95%CI 2-14.2)] and thyroid CA [SIR 2.6 (95%CI 1.4-4.3)].

Brito-Zerón P et al.[9] observed an increased risk of all cancers [SIR 1.9 (95%CI 1.59-2.27)], thyroid CA [SIR 5.05 (95%CI 1.89-13.45)], non-Hodgkin's [SIR 6.04 (95%CI 3.43-10.64)] and Hodgkin's lymphoma [SIR 19.41 (95%CI 7.29-51.72)]. Brom M et al.[12] observed, there was a significant increase in the risk of developing non-hodgkin lymphomas [SIR 41.4 (95%CI 10.1-102.1)], multiple myeloma [SIR 41.49 (95%CI 1.14-167.28)], breast [SIR 3.76 (95%CI 1.04-9.45)], lung [SIR 4.51 (95%CI 0.1-22.16)], tongue [SIR 44.4 (95%CI 1.23-177.3)] and overall cancer [SIR 4.17 (95%CI 2.3-6.87)]. Kang J et al.[13] found an increased risk of all cancers [SIR 1.30 (95%CI 1.16-1.43)], thyroid CA [SIR 1.19 (95%CI 0.87-1.52)], lung CA [SIR 1.59 (95%CI 1.08-2.09)] non-Hodgkin's [SIR 6.45 (95%CI 4.05-8.83)] and Hodgkin's lymphoma [SIR 6.03(95%CI 0-14.38)]. According to a meta-analysis published in 2014, patients with pSS had significantly increased risk for overall cancer [RR 1.53 (95% CI 1.17-1.88)]. According to this meta-analysis, an increased risk of NHL [RR 13.76 (95% CI 8.53-18.99)] and thyroid CA [RR 2.58 (95% CI 1.14-4.03)] was found in pSS patients, but no increased risk was reported in other malignancies.[8]

Table 2. Data of the malignancies of the patients

Case	Cancer Diagnosis Age	Sjogren Diagnosis Age	Time between Sjogren's Syndrome and CA diagnosis (months)	Pathology	Drugs used before cancer diagnosis	Survival
1	35	32	36	Thyroid papillary CA	HCQ+Nifedipine +ASA	36
2	60	58	15	Maltoma in tongue	HCQ+ MP	24*
3	46	41	55	Breast CA	HCQ	20
4	57	55	24	Thyroid papillary CA	HCQ+MP+ AZA+Pilocarpine	19
5	36	45	-	Breast CA	HCQ+MP+ AZA	36*
6	45	38	84	Cervix CA	MTX(Discontinued) MP+HCQ	48
7	51	44	85	Lung CA	HCQ+MP+AZA+ Pilocarpine	2(ex)
8	44	40	40	Breast CA	HCQ	20
9	68	72		Breast CA	HCQ+ MP	150
10	50	48	24	DLBCL	HCQ+ MP	80
11	52	41	125	Thyroid papillary CA	HCQ+MP	70
12	60	55	60	Mycosis Fungoides	6 cycle CyC+ HCQ+MP +AZA (Discontinued after MF diagnosis)	120
13	62	55	90	Vulva CA	HCQ+MP+RTX after AZA	10
14	80	75	58	Breast CA	HCQ+MP+AZA	2 (ex)

Followed for * month, then no follow-up (HCQ: Hydroxychloroquine, MP: Methylprednisolone, AZA: Azathioprine, RTX: Rituximab, CyC: Cyclophosphamide, MF: Mycosis Fungoides, ASA: Acetylsalicylic acid, MTX : Methotrexate)

Table 3. Comparison of clinical and laboratory findings in pSS patients according to the presence of malignancy

n (%)	PSS patients with malignancy n=14	PSS patients without malignancy n=137	p
Gender Female	14 (100)	133 (97)	
Male		4 (3)	1
Dry mouth	13 (93)	120 (88)	1
Dry eyes	12 (86)	118 (86)	1
ANA	13 (93)	124 (91)	1
SS-A	10 (71)	84 (61)	0.457
SS-B	8 (57)	68 (50)	0.593
Rheumatoid Factor	9 (64)	82 (60)	0.642
Raynaud Phenomenon	2 (14)	28 (20)	0.737
ILD	4 (29)	12 (9)	**0.044**
Hypocomplementemia	4 (29)	14 (10)	0.223
Hyperimmunoglobulinemia	4 (29)	30 (22)	0.519
Leukopenia	5 (36)	30 (22)	0.317
Lymphadenopathy	8 (57)	36 (26)	**0.027**
Parotitis	4 (29)	21 (15)	0.251
Smoking	6 (43)	25 (18)	0.085
ESSDAI≈	6.3±6.8	0.0±5 (0-28)ˆ	**0.039**
Clin-ESSDAI≈	6.4±7.4	0.0±6 (0-31)ˆ	0.087
Follow up time≈	3.2 ±2.4(1-10)ˆ	3.9 ±3.8(1-13)ˆ	0.905
Disease duration≈	9 ±5.8(2-17)ˆ	11 ±6.3(1-38)ˆ	0.354

≈Mann-Whitney U test used, Relationships between categorical variables were evaluated using Chi-square analysis. ˆ Since the data are not normally distributed, Median±IR (min-max) values are given. (ANA: Anti-Nuclear Antibody, ILD: Interstitial Lung Disease, ESSDAI: EULAR primary Sjögren's syndrome disease activity ındex; clin ESSDAI: Clinical EULAR Sjögren's Syndrome Disease Activity Index)

Table 4. Factors affecting malignancy development according to the logistic regression model

	Univariate		Multivariate	
	p	OR (%95 CI)	p	OR (%95 CI)
Smoking	0.063	0.33 (0.107-1.05)		
Hypocomplementemia	0.142	2.62 (0.72-9.53)		
Hyperimmunoglobulinemia	0.847	1.13 (0.317-4.05)		
Parotitis	0.214	2.21 (0.63-7.70)		
LAP	**0.022**	3.74 (1.21-11.5)	**0.016**	4.21 (1.30-13.59)
ILD	**0.032**	4.17 (1.13-15.3)	**0.022**	4.98 (1.25-19.78)
ESSDAI	**0.040**	1.08 (1.00-1.17)		
Clin-ESSDAI	0.059	1.07 (0.99-1.15)		

LAP: Lymphadenopathy; ILD: Interstitial Lung Disease; ESSDAI: EULAR primary Sjögren's syndrome disease activity ındex; clin ESSDAI: Clinical EULAR Sjögren's Syndrome Disease Activity Index

Table 5. Standardized incidence ratios for cancer in PSS patients classified according to GLOBOCAN categories

Cancer Categories	Total (n = 151)				Women (n = 147)			
	Incidence rate in Turkey	Obs	Exp	SIR (%95CI)	Incidence rate in Turkey	Obs	Exp	SIR (%95CI)
All cancers	363.2	14	2.08	6.73 (3.7-11.3)	292.8	14	1.64	8.54 (4.7-14.3)
Solid Cancer	292.3	11	1.68	6.54 (3.3-11.7)	254.2	11	1.42	7.75 (3.9-13.9)
Breast Cancer	75.9	4	0.43	9.30 (2.5-23.8)	75.9	4	0.43	9.30 (2.5-23.8)
Thyroid Cancer	23	3	0.13	23.07 (4.8-67.4)	36	3	0.20	15 (3.1-43.8)
Lung Cancer	61.4	2	0.35	5.71 (0.7-20.6)	16.3	2	0.09	22.22 (2.7-80.2)
Servix Cancer	7.9	1	0.04	25 (0.6-139.3)	7.9	1	0.04	25 (0.6-139.3)
Vulva Cancer	0.8	1	0,004	250 (6.3-1393)	0.8	1	0.004	250 (6.3-1393)
Haematological Malignancy	24.1	3	0.14	21.42 (4.4-62.6)	20.2	3	0.11	27.27 (5.6-79.7)
NHL	9.6	3	0.06	50 (10.3-146.1)	8.2	3	0.05	60 (12.4-175.4)

NHL: Non-Hodgkin Lymphoma; Obs: observed; Exp:expected; SIR:standardized incidence ratios; CI:Confidence interval

According to 2014 unified data from Turkey[14], for women from all age groups diagnosed with cancer, 25% was breast CA, 12% thyroid CA, 2.4% cervix CA, 5% lung CA and 2.8% NHL. In our study, it was observed that 29% of women with malignancy had breast CA, 21% had thyroid papillary CA, 14% had lung CA and 21% had NHL.

In our study, a significant increase was found in the risk of developing all cancer, breast, thyroid, lung, cervix, vulva and non-hodgkin lymphoma. Malignancy was questioned in the family history of patients with breast and thyroid papillary CA. In the family history of a patient with breast CA, it was learned that her mother and aunts also had breast CA. Especially breast CA and thyroid CA malignancies are common in our country. There is a family history of malignancy in one of our breast CA patients. The risk of these common malignancies has increased in our patients as in other studies. Considering the prevalence in the community, these malignancies should not only be associated with sjogren's syndrome, but all the same time also the increased risk should not be ignored.

The subgroup analyzes performed in the meta-analysis revealed that RR 2.25; 95% CI 1.27-3.22 for malignancies was found higher in hospital-based studies compared to population-based studies. It is thought that the cause may be that hospitalized patients with pSS have more severe disease which suggests more severe pSS is more likely to develop into malignancy.[8] Therefore, ESSDAI and clin-ESSDAI scores were evaluated in terms of disease activity in our study. Activity scores were found to be higher in the group with malignancy than those without malignancy. However, the difference between the clin-ESSDAI scores of two groups was not significant, whereas the difference in ESSDAI scores was significant (p=0.039). Both groups had moderate disease activity according to their activity score (5< ESSDAI <14).

It was observed that ESSDAI and clin-ESSDAI scores were higher in patients with ILD compared to patients without ILD. Although it is thought that the higher malignancy development in ILD patients may be due to their higher disease activity, more comprehensive studies are required in this direction.

In the meta-analysis, it was also emphasized that the relationship between general malignancy risk and pSS might not be shown in patients with a mean follow-up less than 6.9 years. When our patient groups with or without malignancies were compared in terms of disease age and follow-up period, no significant difference were found between two groups. While two of our patients were diagnosed with malignancy before pSS diagnosis, it was observed that the remaining twelve patients were diagnosed with malignancy on an average 4.9±2.8 years after pSS diagnosis, which is not consistent with this meta-analysis.[8]

The underlying mechanisms of B-cell lymphoma development in pSS are apoptosis defect, continuous antigenic stimulation, mutagenicity of B cell and T-cell modulation (such as type 1 interferon or B cell activation factor of the TNF family).[15,16] Studies have also revealed that low peripheral CD4+ T lymphocyte or low CD4/CD8 ratio might be an important risk factor for lymphoma in SS.[17,18]

In addition, oligoclonal and monoclonal B cell proliferation was found in more than 14% of pSS patients, and it was emphasized that ectopic germinal centers developed in exocrine glands in 20-30% of the patients, monoclonal proliferated B cells were found mainly in ectopic germinal centers and these centers could be determinants of malignancy.[19]

In addition, in a Chinese cohort[6], 41% of pSS patients with malignancies (29/1320 patients), and 70% of pSS patients with hematological malignancies (eight patients with NHL and two patients with multiple myeloma) had high levels of monoclonal immunoglobulins in serum and these rates were found to be higher than the group without tumor. Although there is no known significant relationship between SS and multiple myeloma, it has been stated that the transformation of benign monoclonal gammaglobulin-producing plasma cells into malignant plasma cells may play a role in this process[19]. It is thought that monoclonal proliferation of B cells may predict the transformation into malignancy.[6] In our study, no relationship was found between hypergammaglobulinemia and development of malignancy. However, patients with hypergammaglobulinemia are closely followed for the development of monoclonality.

Although most cells that infiltrate the salivary glands of patients with pSS are T cells, most of the reported lymphomas are originated from B cells.[20] Different subtypes among B-cell lymphomas not only have different clinical presentations but also have different localization and prognosis. The most common types of lymphoma in pSS are MALT lymphoma (58%), diffuse large B-cell lymphoma (20%), and marginal zone lymphoma (13%).[9] The most common localization of lymphoma is the salivary glands, but extra nodal involvement is also seen. The other regions that might be involved are stomach, nasopharynx, skin, liver, kidney, lung, lymph nodes and bone marrow.[21] Studies have shown that the RR for lymphoma in pSS increases 16 times compared to the general population, and it increases and remains high even 15 years after the diagnosis of pSS.[22]

In a study, the time between the onset of SS symptoms and the development of lymphoma was determined as 65 months. In the same study, the estimated 10-year survival rates for patients with pSS were reported as 91% and 69% for patients with lymphoma.[23] Our patients diagnosed with diffuse large B-cell lymphoma and Mycosis Fungoides have been followed for approximately 6.6 and 10 years, respectively. Our patient diagnosed with MALT lymphoma was followed for about 2 years and was not followed up afterwards. The number of patients in our study and the follow-up times are not sufficient for survival analysis.

In our study, there were two patients who were followed up with the diagnosis of B-cell lymphoma and one of them was MALT lymphoma originated from the base of tongue and the other one was diffuse large B-cell

lymphoma. One of our patients had a diagnosis of Mycosis Fungoides. Studies have shown that severe parotid involvement, purpura, leukopenia, anti-LA antibody, high BAFF and beta-2 microglobulin levels, cryoglobulins, monoclonal band and hypocomplementemia are risk factors for the development of B-cell lymphoma.[24-26] Although the number of B-cell lymphomas is quite low, no relation between malignancy and parotitis, vasculitis, presence of autoantibodies, leukopenia and hypocomplementemia was found in our study. There are different opinions regarding the relation of some of the drugs used in the treatment of SS with the development of malignancy. It has been observed that cyclophosphamide, among immunosuppressive drugs, is carcinogenic and increases the risk of hematological malignancy.[27] Methotrexate, azathioprine and other DMARD treatments have been presented as risk factors for lymphomas associated with RA and other rheumatic diseases.[28-30] However, other studies have not confirmed that these treatments, except azathioprine, lead to an increased risk of lymphoma.[31-33] Studies conducted with rituximab indicated that there was no increased risk for malignancy in long term follow up.[34,35] In our study, it was observed that one of the patients with malignancy used cyclophosphamide and six patients used azathioprine. The total number of patients using azathioprine was 36, and the relationship between azathioprine use and malignancy could not be demonstrated (p=0.323).
The limitations of our study are its retrospective design, loss of some patients during follow-up, a small number of patients and short follow-up time.

Conclusion

It is important to follow the patients with Sjogren's syndrome regularly due to the increased risk of lymphoma development and to be more careful in terms of malignancy development, especially in the presence of parotitis, vasculitis, hypocomplementemia, cryoglobulinemia, although it is not compatible with the results of our study. Monoclonal band presence is important in predicting the development of malignancy. Although the extended duration of disease increases the risk of malignancy, a malignancy may be diagnosed before the diagnosis, as in our data. As in our study, it should be kept in mind that there may be an increased risk not only for lymphoma but also for the other malignancies in this patient population.

Acknowledgements
None

Compliance with Ethical Standards
Kocaeli University ethical committee approved the study protocol (Date:23-Nov-2020, Approval Number:2020/289).

Conflict of Interest
None

Author contributions
OOI, AY and AC: Study idea, hypothesis, study design; OOI: Material preparation, data collection and analysis; OOI: Writing the first draft of the article; OOI, AY and AC: Critical review of the article finalization and publication process.

Financial Disclousure
None

References

1. Moutsopoulos HM. Sjogren's syndrome: autoimmune epithelitis. *Clin Immunol Immunopathol*. 1995;72(2):162-165. doi:10.1006/clin.1994.1123.
2. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. *Ann Intern Med*. 1978;89(6):888-892. doi:10.7326/0003-4819-89-6-888.
3. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005;165(20):2337-2344. doi:10.1001/archinte.165.20.2337.
4. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome. *Arthritis Rheum*. 2002;46(3):741-747. doi:10.1002/art.10221
5. Lazarus MN, Robinson D, Mak V, Møller H, Isenberg D A. Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. *Rheumatology.* 2006;45(8)1012-1015. doi:10.1093/rheumatology/kei281.
6. Zhang W, Feng S, Yan S, et al. Incidence of malignancy in primary Sjogren's syndrome in a Chinese cohort. *Rheumatology (Oxford)*. 2010;49(3):571-577. doi:10.1093/rheumatology/kep404.
7. Shiboski CH, Shiboski SC, Seror R, et al. American College of Rheumatology/European League Against Rheumatism Classification Criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheum*. 2017;69(1):35-45. doi:10.1002/art.39859.
8. Liang Y, Yang Z, Qin B, Zhong R. Primary Sjogren's syndrome and malignancy risk: a systematic review and meta-analysis. *Ann Rheum Dis.* 2014;73(6):1151-1156. doi: 10.1136/annrheumdis-2013-203305
9. Brito-Zerón P, Kostov B, Fraile G, et al. Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. *J Hematol Oncol.* 2017;10(1):90. doi:10.1186/s13045-017-0464-5.
10. Kauppi M, Pukkala E, Isomäki H. Elevated incidence of hematologic malignancies in patients with Sjögren's syndrome compared with patients with rheumatoid arthritis (Finland). *Cancer Causes Control*. 1997;8:201–4. doi:10.1023/a:1018472213872.
11. Weng MY, Huang YT, Liu MF, Lu TH. Incidence of cancer in a nationwide population cohort of 7852 patients with primary Sjogren's syndrome in Taiwan. *Ann Rheum Dis.* 2012;71(4):524-7. doi:10.1136/annrheumdis-2011-200402.
12. Brom M, Moyano S,Gandino IJ, Soriano ER, Scolnik M. Incidence of cancer in a cohort of patients with primary Sjögren syndrome in Argentina. *Rheumatol Int.* 2019;39(10):1697-1702. doi:10.1007/s00296-019-04433-2.
13. Kang J, Kim H, Kim J, et al. Risk of malignancy in Korean patients with primary Sjögren's syndrome. *Int J Rheum Dis*. 2020;23(9):1240-1247. doi:10.1111/1756-185X.13927.

14. Ed. Şencan İ, Keskinkılıç B (2017) Türkiye Kanser İstatistikleri. T.C. Sağlık Bakanlığı Türkiye Halk Sağlığı Kurumu.https://hsgm.saglik.gov.tr/depo/birimler/kanserdb/istatistik/2014
15. Masaki Y, Sugai S. Lymphoproliferative disorders in Sjogren's syndrome. *Autoimmun Rev*. 2004;3(3):175-82. doi:10.1016/S1568-9972(03)00102-2.
16. Groom J, Kalled SL, Cutler AH, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome. *The J Clin Invest.* 2002;109(1):59-68. doi:10.1172/JCI14121.
17. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT. Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis.* 2006;65(6):796-803. doi:10.1136/ard.2005.041186.
18. Pillemer SR. Lymphoma and other malignancies in primary Sjogren's syndrome. *Ann Rheum Dis.* 2006;65(6):704-706. doi:10.1136/ard.2005.044362.
19. Jonsson R, Nginamau E, Szyszko E, Brokstad KA. Role of B cells in Sjogren's syndrome from benign lymphoproliferation to overt malignancy. *Front Biosci*. 2007;12:2159-2170. doi:10.2741/2219.
20. Nocturne G, Mariette X. Sjogren syndrome associated lypmhomas: an update on pathogenesis and management. *Br J Haematol*. 2015;168(3):317-327. doi:10.1111/bjh.13192.
21. Voulgarelis M and Moutsopoulos HM. Malignant lymphoma in primary Sjogren's syndrome. *Isr Med Assoc J*. 2001;3(10): 761-766
22. Solans-Laque R, Lopez-Hernandez A, Bosch-Gil JA, Palacios A, Campillo M, Vilardell-Tarres M. Risk, predictors, and clinical characteristics of lymphoma development in primary Sjogren's syndrome. *Semin Arthritis Rheum*. 2011;41(3):415-423. doi:10.1016/j.semarthrit. 2011.04.006.
23. Suvajdzic N, Djurdjevic P, Todorovic M, et al. Clinical characteristics of patients with lymphoproliferative neoplasms in the setting of systemic autoimmune diseases. *Med Oncol*. 2012;29(3):2207-2211. doi:10.1007/s12032-011-0022-x.
24. Risselada AP, Kruize AA, Bijlsma JWJ. Clinical features distinguishing lymphoma development in primary Sjogren's syndrome—a retrospective cohort study. *Semin Arthritis Rheum*. 2013;43(2):171-177. doi:10.1016/j.semarthrit.2013.03.001.
25. Quartuccio L, Isola M, Baldini C, et al. Biomarkers of lymphoma in Sjogren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. *J Autoimmun*. 2014;51:75-80. doi:10.1016/j.jaut.2013.10.002.
26. Retamozo S, Gheitasi H, Quartuccio L, et al. Cryoglobulinaemic vasculitis at diagnosis predicts mortality in primary Sjogren syndrome: analysis of 515 patients. *Rheumatology (Oxford).* 2016;55:1443-1451. doi:10.1093/rheumatology/kew194.
27. Brodsky RA. High dose cyclophosphamide treatment for autoimmune disorders. *Scientific World Journal*.2002;2:1808-1815. doi:10.1100/tsw.2002.863.
28. Matteson EL, Hickey AR, Maguire L, Tilson HH, Urowitz MB. Occurrence of neoplasia in patients with rheumatoid arthritis enrolled in a DMARD Registry. Rheumatoid Arthritis Azathioprine Registry Steering Committee. *J Rheumatol*. 1991;18(6):809-814.
29. Jones M, Symmons D, Finn J, Wolfe F. Does exposure to immunosuppressive therapy increase the 10 year malignancy and mortality risks in rheumatoid arthritis? A matched cohort study. *Br J Rheumatol*. 1996;35(8): 738-745. doi:10.1093/rheumatology/35.8.738.
30. Asten P, Barrett J, Symmons D. Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. *J Rheumatol*. 1999;26(8)1705-1714.
31. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum*. 2006;54(3):692-701. doi:10.1002/art.21675.
32. Salliot C and van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis*. 2009;68(7): 1100-1104. doi:10.1136/ard.2008.093690.
33. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathiophrine and 6-mercaptopurine. A meta-analysis. *Clin. Gastroenterol Hepatol*. 2015;13(5):847-858.e4. doi:10.1016/j.cgh.2014.05.015.
34. Slimani S, Lukas C, Combe B, Morel J. Rituximab in rheumatoid arthritis and the risk of malignancies: report from a French cohort. *Joint Bone Spine*. 2011;78(8):484-487. doi:10.1016/j.jbspin.2010.11.012.
35. Van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm safety of Rituksimab: Final report of rheumatoid arthritis global cilinical trial program over 11 years. *J Rheumatol*. 2015;42(10)1761-1766. doi:10.3899/jrheum.150051.