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Unveiling malignancy patterns among rheumatology patients: Insights from a retrospective study

Romatoloji hastalarında malignite: Retrospektif bir çalışmadan değerlendirmeler

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Abstract

Objective: Malignancy is a significant comorbidity in patients with rheumatic diseases. This study investigates the incidence, prevalence, and risk factors of malignancies among patients with rheumatic diseases and non-inflammatory conditions in a rheumatology clinic.

Methods: A retrospective analysis was conducted on 2,600 patients between January 2021 and January 2024. Data collected included patient demographics, rheumatic disease types, non-inflammatory conditions, treatments, and cancer history. Statistical analyses included chi-square tests, Fisher's exact tests, Mann-Whitney U tests, logistic regression, and standard incidence ratio (SIR) calculations.

Results: Of the 2,600 patients, 100 had a cancer history, with a median age of 66 years, higher than those without cancer (p<0.001). Breast cancer was the most common malignancy (29%), followed by gynecologic and respiratory cancers. Cancer prevalence was higher among rheumatoid arthritis (RA) and osteoarthritis patients and lower in ankylosing spondylitis and fibromyalgia patients. Twenty-six patients received a cancer diagnosis after the onset of a rheumatic or non-inflammatory condition. In female patients, gynecologic cancers [SIR=3.76, 95% confidence interval (CI)=1.2-8.7, p=0.005] and lymphoma (SIR=8.14, CI=1.6-23.7, p=0.001) were more common. In male patients, the total number of cancers was significantly higher (SIR=381, CI=182.7-700.8, p<0.001). Moreover, two patients treated with nivolumab developed new-onset RA and psoriatic arthritis, while one patient treated with ribociclib developed systemic sclerosis. Logistic regression identified age [odds ratio (OR)=1.03], male gender (OR=2.16), the presence of inflammatory diseases (OR=4.52), and Charlson Comorbidity index score (OR=5.65) as significant predictors of cancer diagnosis.

Conclusion: This study highlights the need for vigilant cancer screening in rheumatic disease patients, especially the elderly. Future research should focus on prospective studies to develop targeted cancer prevention and management strategies for this population.

Keywords: Neoplasms, lymphoma, rheumatoid arthritis, autoimmune diseases

Öz

Amaç: Malignite romatizmal hastalıklarda önemli bir komorbiditedir. Bu çalışmada bir romatoloji kliniğinde takip edilen romatizmal ve non-enflamatuvar hastalıkları olan bireylerde maligniteleri insidansı, prevalansı ve risk faktörleri araştırılmaktadır.

Yöntem: Ocak 2021 ile Ocak 2024 arasında takip edilen 2.600 hasta üzerinde retrospektif bir analiz yapıldı. Toplanan veriler arasında hastaların demografik özellikleri, romatizmal hastalık türleri, enflamatuvar olmayan durumlar, tedaviler ve kanser geçmişine yer verildi. İstatistiksel analizlerden ki-kare, Fisher kesin olasılık ve Mann-Whitney U testleri, lojistik regresyon analizi ve standart insidans oranı (SIR) hesaplamaları kullanıldı.

Bulgular: 2.600 hastanın 100'ünde kanser öyküsü saptandı. Ortalama yaş 66 olup malignite öyküsü olanlarda olmayanlara göre daha yüksekti (p<0,001). Meme kanseri en sık görülen malignite (%29) olup, bunu jinekolojik ve solunum sistemi kanserleri takip etmekteydi. Kanser prevalansı romatoid artrit (RA) ve osteoartrit hastalarında daha yüksek, ankilozan spondilit ve fibromiyalji hastalarında ise daha düşüktü. Yirmi altı hastaya romatizmal veya enflamatuvar olmayan bir durumun başlangıcından sonra kanser tanısı konuldu. Kadın hastalarda jinekolojik kanserler [SIR=3,76, %95 güven aralığı (GA)=1,2-8,7, p=0,005] ve lenfoma (SIR=8,14, GA=1,6-23,7, p=0,001) daha sık görüldü. Erkek hastalarda toplam kanser sayısı anlamlı derecede yüksekti (SIR=381, GA=182,7-700,8, p<0,001). Ayrıca, nivolumab ile tedavi edilen iki hastada yeni başlayan RA ve psoriatik artrit gelişirken, ribosiklib ile tedavi edilen bir hastada sistemik skleroz gelişti. Lojistik regresyonda yaş [odds oranı (OR)=1,06], erkek cinsiyet (OR=2,16), enflamatuvar hastalık öyküsü (OR=4,52) ve Charlson komorbidite indeks skorunun (OR=5,65) kanser gelişiminde önemli belirleyiciler olduğunu saptandı.

Sonuç: Bu çalışma romatizmal hastalığı olan özellikle yaşlı bireylerde kanser taramasının gerekliliğini vurgulamaktadır. Bu hastalar için hedefe yönelik kanser önleme ve yönetim stratejileri geliştirme odaklı prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Neoplazmalar, lenfoma, romatoid artrit, otoimmün hastalıklar

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Introduction

Malignancies are a significant comorbidity in patients with rheumatic diseases, posing unique challenges in their management.[1] This increased risk arises from both the underlying autoimmune processes and potential side effects of treatments such as immunosuppressants. Shared environmental factors, like smoking, further amplify this risk.[2]

Chronic inflammation in rheumatic diseases fosters a pro-tumorigenic environment through cytokine-mediated DNA damage, angiogenesis, and immune dysregulation.[3,4] Notably, conditions like primary Sjögren's syndrome and systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) are associated with higher risks of lymphoma,[5-7] emphasizing the need for vigilance.

The impact of antirheumatic treatments on cancer risk remains debated.[8,9] While a 2019 systematic review found no increased cancer risk with biological disease-modifying antirheumatic drugs,[10] high doses of cyclophosphamide have been associated with lymphoproliferative and bladder cancers,[11] and prolonged azathioprine use may increase the risk of skin cancers and cervical atypia.[12]

Additionally, the relationship between autoimmunity and cancer is bidirectional.[13] Immune responses against tumors can target self-tissues, leading to paraneoplastic syndromes. Moreover, cancer therapies, including chemotherapy and immune-checkpoint inhibitors, can trigger immune-related adverse events.[14,15]

While existing studies often focus on individual rheumatic conditions, comprehensive analyses across multiple diseases are scarce, especially in Turkish cohorts.[16-18] This study aims to bridge this gap by examining the incidence, prevalence, and risk factors for malignancies in patients with rheumatic and non-inflammatory diseases over a three-year period.

Materials and Methods

The electronic medical records of all 2,600 consecutive patients who visited the two rheumatology clinics of a private hospital between January 2021 and January 2024 were retrospectively evaluated. This private hospital in Istanbul provides care to both Turkish and international patients, treating individuals aged 16 and above for rheumatic diseases and non-inflammatory conditions.

Patient Selection

All 2,600 patients who visited the outpatient clinics during the study period were included, regardless of their final diagnosis. While many patients had confirmed inflammatory rheumatic diseases based on established diagnostic criteria, some presented with non-inflammatory conditions or non-specific complaints.

Inclusion Criteria

Inflammatory Diseases

Patients were included if they met the diagnostic or classification criteria for inflammatory diseases, such as:

- RA[19]

- Spondyloarthritis (SpA),[20] comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA),[21] enteropathic arthritis, and reactive arthritis

- Connective tissue diseases (CTDs), such as SLE,[22] Sjögren's syndrome,[23] systemic sclerosis, myositis, and undifferentiated CTDs

- Polymyalgia rheumatica (PMR),[24] gout[25]

- Vasculitis, including Behçet's disease[26] and other systemic vasculitides.[27-29]

Non-inflammatory Conditions

Patients without a confirmed inflammatory diagnosis were included in the study for completeness, but their data were analyzed separately. Osteoarthritis,[30] and fibromyalgia[31] were diagnosed according to criteria. The remaining non-inflammatory conditions included cases such as isolated autoantibody positivity without clinical manifestations of autoimmune disease, elevated acute-phase reactants, non-specific musculoskeletal pain, or referrals for different complaints, such as headaches or mucocutaneous symptoms.

Data Collection

Data collected included age, gender, smoking status, type of rheumatic disease, and non-inflammatory conditions and treatments. Comorbidities were documented using the Charlson Comorbidity index (CCI) for each patient. Patients aged 65 and older at their last clinic visit were classified as geriatric patients. Survival information for Turkish citizens was obtained from the national registry, though specific times and causes of death were not available. This information was not available for international patients.

Malignancy Data

The type and onset of malignancies were recorded relative to the onset of rheumatic disease. Cancers were categorized as follows:

- Gastrointestinal cancers (C15-26): esophageal (C15), stomach (C16), colorectal (C18-20), pancreatic (C25) cancers

- Respiratory system cancers (C30-38): laryngeal (C32), lung (C34) cancers

- Skin cancers: melanoma (C43) and non-melanoma skin cancers (NMSC) (C44)

- Gynecologic cancers (C51-58): cervical (C53), endometrium (C54), ovarian (C56) cancers

- Male reproductive system cancers (C60-63): prostate (C61), testicular (C62) cancers

- Urinary tract cancers (C64-68): renal cell carcinoma (C64), bladder cancer (C67)

- Hematologic cancers (C81-96): lymphoma (C81-85), multiple myeloma (C90), chronic lymphocytic leukemia (C91.1)

- Sarcoma (C49), thyroid cancer (C73), carcinoma of unknown primary (C80.1).

Statistical Analysis

Data analysis was performed using SPSS version 26 and R version 4.2.2. Qualitative variables, such as the prevalences of rheumatic diseases and cancers, were presented as absolute and relative frequencies. Comparisons between groups for gender, smoking history, geriatric status, and prevalences of rheumatic diseases and cancers were conducted using the chi-square test. Fisher's exact test was utilized when expected frequencies were less than 5. Age differences among groups were assessed with the Mann-Whitney U test, and values were expressed as medians ± interquartile ranges (IQRs) due to the non-normal distribution of these variables. Logistic regression analysis was performed to determine the influence of variables on cancer history.

For newly diagnosed cancer cases during the study period, the standard incidence ratio (SIR), 95% confidence intervals (CIs), and p-values were calculated using the R program and the epiR package. The SIR was determined by dividing the number of observed cases by the expected cases. Observed cases refer to patients with a new cancer diagnosis during the follow-up period. Expected cases were calculated as person-years of follow-up multiplied by the incidence rate of each cancer in the general population. For patients without cancer, person-years of follow-up were calculated from their first to their last visit during the study period. For patients diagnosed with cancer after the onset of rheumatic disease, person-years of follow-up were calculated from the date of rheumatic disease diagnosis to the date of cancer diagnosis. The incidence rates of specific cancers in the Turkish population were obtained from 2018 public health records.[32]

Statistical significance was set at a p-value of less than 0.05.

The study was approved by the local ethics committee (Memorial Bahçelievler Hospital Ethics Committee – approval number: 133, date: 11.06.2024).

Results

General Demographics

The study included a total of 2,600 patients, with a median age of 49 years (IQR=26) and a female-to-male ratio of 7:3. Among all patients, 45.8% had inflammatory diseases, with RA (33.7%), SpA (31.2%), CTDs (11.5%), and crystalline arthropathies (11.1%) being the most common diagnoses. Osteoarthritis (18.1%) and fibromyalgia syndrome (14.8%) were among the most common non-inflammatory conditions leading to admission. Other musculoskeletal complaints (35.1%) and back pain (12.2%) accounted for the majority of the remaining cases (Table 1).

Cancer Prevalence and Demographics

Out of the 2,600 patients, 100 had a history of cancer. The female-to-male ratio was comparable between those with and without a history of cancer (p=0.13). However, the median age of patients with a history of cancer was 66 (IQR=16.5), while those without such a history were younger, with a median age of 48 (IQR=25) (Table 1).

In total, 41 patients (3.4%) with inflammatory diseases and 59 patients (4.2%) with non-inflammatory conditions had a history of cancer (Table 2). When comparing all patients with inflammatory diseases to those with non-inflammatory conditions (e.g., osteoarthritis, fibromyalgia, non-specific musculoskeletal pain), the prevalence of malignancy was not significantly different between the two groups in univariate analysis (p=0.32). However, when other parameters were taken into account in multivariate logistic regression, the difference became significant (p<0.001).

Further analysis of individual disease types revealed that patients with AS, SpA and fibromyalgia had a lower prevalence of cancer compared to other groups (p=0.005 for AS and SpA and p=0.01 for fibromyalgia). In contrast, osteoarthritis was associated with a higher prevalence of cancer (p=0.01) (Table 1).

By the end of the study, 39 patients were known to have died, accounting for 1.6% of known cases. Of these, 10 patients (10.1%) were from the cancer group, while 29 patients (1.2%) were from the non-cancer group (Table 1).

Table 1. Demographics, rheumatic diseases, and non-inflammatory conditions in patients with and without cancer

	Total	Cancer present	Cancer absent	p	OR	CI
	n=2,600	n=100 (%)	n=2,500 (%)			
Age				**<0.001**		
Median (IQR)	49 (26)	66 (16.5)	48 (25)			
Min-max	16-88	28-88	16-88			
Gender				0.13		
Female	1862 (71.6)	65 (3.5)	1797 (96.5)			
Male	738 (28.4)	35 (4.7)	703 (95.3)			
Smoking ever	684 (26.3)	31 (31.0)	653 (26.1)	0.27		
No	1916 (73.7)	69 (69.0)	1847 (73.9)			
Yes	548 (21.1)	22 (22.0)	526 (21.0)			
Previous	136 (5.2)	9 (9.0)	127 (5.1)			
CCI (mean ± SD)	0.82±0.95	3.0±1.1	0.74±0.82	**<0.001**		
Mortality						
Yes	39 (1.6%)	10 (25.6%)	29 (74.4%)	**<0.001**	9.48	4.47-20.13
No	2282	80	2202			
Unknown	279	10	269			
Inflammatory diseases	1193 (45.8)	43 (3.6)	1150 (96.4)	0.55		
Rheumatoid arthritis	403 (15.5)	17 (4.2)	386 (95.8)	0.67		
Connective tissue diseases	138 (5.3)	9 (6.5)	129 (93.5)	0.09		
Systemic lupus erythematosus	52 (2.0)	1 (1.9)	51 (98.1)	0.72		
Sjögren's syndrome	37 (1.4)	3 (8.1)	34 (91.9)	0.16		
Others	49 (1.8)	5	44			
Spondyloarthropathies	373 (14.3)	5 (1.3)	368 (98.7)	**0.005**	0.30	0.12-0.76
Ankylosing spondylitis	255 (9.8)	2 (0.8)	253 (99.2)	**0.005**	0.18	0.04-0.74
Psoriatic arthritis	105 (4.0)	2 (1.9)	103 (98.1)	0.43		
Enteropatic and reactive arthritis	13	1 (7.6)	12 (92.3)			
Vasculitis	27 (1.0)	1 (3.7)	26 (96.3)	0.72		
Behcet's disease	30 (1.2)	0	30 (100)	0.62		
Polymyalgia rheumatica	30 (1.2)	1 (3.7)	29 (96.7)	0.67		
Familial Mediterranean fever	76 (2.9)	1 (1.3)	75 (98.7)	0.36		
Cryrstalline arthropathies	133 (5.1)	9 (6.8)	124 (93.2)	0.07		
Osteoarthritis	255 (9.8)	17 (6.7)	238 (93.3)	**0.01**	1.98	1.10-3.56
Fibromyalgia syndrome	209 (8.0)	2 (1.0)	207 (99.0)	**0.01**	0.20	0.04-0.83
Autoantibody positivity	85 (3.3)	2 (2.4)	83 (97.6)	0.57		
High acute phase reactants	46 (1.8)	3 (6.5)	43 (93.5)	0.42		
Other complaints	864 (33.2)	35	829			
Musculoskeletal	494 (19.0)	24	470			
Back pain	172 (6.6)	2	170			
Mucocutaneous	102 (3.9)	6	96			
Headache	3 (0.1)	1	2			
Pulmonary	13 (0.5)	1	12			
Thrombosis	9 (0.3)	1	8			

CCI: Charlson Comorbidity index, CI: Confidence interval, IQR: Interquartile range, Min-max: Minimum-maximum, OR: Odds ratio, SD: Standard deviation

Table 2. Comparison of cancer types and demographics in patients with inflammatory *vs.* non-inflammatory diseases

	All patients	Inflammatuary group	Non-inflammatuary group	p
	n=100	n=43 (%)	n=57 (%)	
Age				0.13
Median (IQR)	66 (16.5)	67.5 (13.5)	66 (18)	
Min-max	28-88	40-88	28-85	
Gender				0.65
Female	65	29 (67.4)	36 (63.2)	
Male	35	14 (32.6)	21 (36.8)	
Geriatric	57	28 (65.1)	29 (50.9)	0.15
Smoking ever	31	13 (30.2)	18 (31.6)	0.88
No	69	29 (69)	40 (69)	
Yes	22	7 (16.7)	15 (25.9)	
Previous	9	6 (14.3)	3 (5.2)	
Mortality				
Yes	10	6 (13.9)	4 (7.0)	0.30
No	80	31 (72.0)	49 (85.9)	
Unknown	10	5 (11.6)	5 (8.7)	
CCI (mean ± SD)	3.06±1.11	3.56±1.16	2.7±0.94	p<0.001
Breast cancer	29	12 (27.9)	17 (29.8)	0.83
Gynecologic cancers	10	5 (11.6)	5 (8.8)	0.63
Ovarian cancer	4	2 (4.7)	2 (3.5)	0.57
Endometrium cancer	3	2 (4.7)	1 (1.8)	0.57
Cervix cancer	3	1 (2.3)	2 (3.5)	0.60
Male reproductive cancers	10	5 (11.6)	5 (8.8)	0.63
Prostate cancer	9	5 (11.6)	4 (7.0)	0.49
Testicular cancer	1	0	1 (1.8)	0.57
Urological cancers	9	5 (11.6)	4 (7.0)	0.49
Renal cell carcinoma	4	2 (4.7)	2 (3.5)	0.57
Bladder cancer	5	3 (7.0)	2 (3.5)	0.64
Gastrointestinal cancers	12	7 (16.3)	5 (8.8)	0.25
Esophageal cancer	1	1 (2.3)	0	0.43
Stomach cancer	5	3 (7.0)	2 (3.5)	0.64
Colorectal cancer	5	2 (4.7)	3 (5.3)	0.63
Pancreatic cancer	2	1 (2.3)	1 (1.8)	0.67
Respiratory system cancers	10	4 (9.3)	6 (10.5)	0.55
Laryngeal cancer	3	2 (4.7)	1 (1.8)	0.57
Lung cancer	7	2 (4.7)	5 (8.8)	0.69
Thyroid cancer	10	4 (9.3)	6 (10.5)	0.55
Hematologic cancers	9	2 (4.7)	7 (12.3)	0.29
Lymphoma	4	2 (4.7)	2 (3.5)	0.57
Chronic lymphocytic leukemia	1	0	1 (1.8)	0.57
Multiple myeloma	4	0	4 (7.0)	0.13
Skin cancers	5	3 (7.0)	2 (3.5)	0.64
Non-melanoma skin cancer	2	0	2 (3.5)	0.50
Melanoma	3	3 (7.0)	0	0.07
Sarcoma	1	0	1 (1.8)	0.57
Carcinoma of unknown primary	1	0	1 (1.8)	0.57

CCI: Charlson Comorbidity index, IQR: Interquartile range, SD: Standard deviation

Analysis of Specific Cancers

Among the 100 cancer patients, the most prevalent cancer type was breast cancer, affecting 29 patients (Figure 1). Details of specific cancers are presented in Table 2. Five patients had multiple primary cancers: one patient had prostate and laryngeal cancer; one patient had prostate and lung cancer; one patient had prostate cancer and NMSC; one patient had stomach cancer and melanoma; and one patient had breast cancer, renal cell carcinoma, and melanoma. A smoking history was reported in 31 patients.

Gender-based and Age Stratified Differences in Cancer Prevalence

The detailed subgroup comparisons, including gender-based and age-stratified differences, are presented in Supplementary Tables. Smoking history was significantly higher in males (p=0.005). Among female patients (n=65), breast cancer (44.6%), gynecologic cancers (15.4%), and thyroid cancer (13.8%) were the most common. Among male patients (n=35), prostate cancer (25.7%) was the most prevalent, followed by respiratory system cancers (22.9%) and gastrointestinal cancers (17.1%). When comparing female and male patients, respiratory system cancers were more prevalent among males (p=0.003). Mortality was higher in the geriatric group (p=0.04), with nine patients known to have died compared to one patient in the non-geriatric group. In the non-geriatric group, the most common cancers were breast cancer (27.9%), thyroid cancer (20.9%), gynecologic cancers (11.6%), and hematologic cancers (11.6%). In the geriatric group, the most common cancers were breast cancer (29.8%), gastrointestinal cancers (17.5%), respiratory system cancers (15.8%), and prostate cancer (12.3%). Thyroid cancers were significantly more prevalent in the non-geriatric group (p=0.002).

Cancer Types Based on Rheumatic Diseases and Treatments

Among the 100 patients with a history of cancer, an analysis was conducted based on their rheumatic disease history. Of the 43 patients with an inflammatory diagnosis, the most prevalent rheumatic disease was RA, accounting for 17 cases (Figure 2). These patients represented 4.2% of all RA patients. The most common cancers among RA patients were breast cancer (23.5%), gastrointestinal cancers (23.5%), and gynecological cancers (17.6%). One-third of these patients had a history of smoking. Thirteen patients were treated with steroids. Methotrexate was used by 9 patients, hydroxychloroquine by 7 patients, and leflunomide by 2 patients. Adalimumab was the biological treatment used by only one patient. Nine patients with CTDs, nine patients with crystalline arthropathies, two patients with AS, and two patients with PsA had cancer. Detailed information on the rheumatic diseases and treatments received by the patients is presented in Table 3.

Non-inflammatory conditions accounted for 57 patients, with the most common reasons for admission being non-specific musculoskeletal complaints (24 patients) and primary osteoarthritis (17 patients). Additionally, 2 patients were referred to our clinics due to positive autoantibodies, and 3 patients were referred for elevated acute phase reactants.

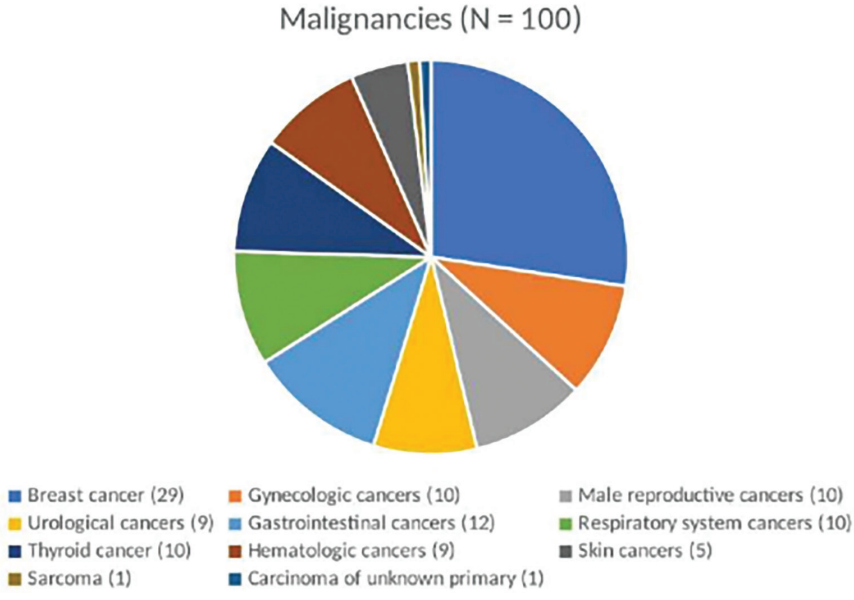

Figure 1. Types of malignancies

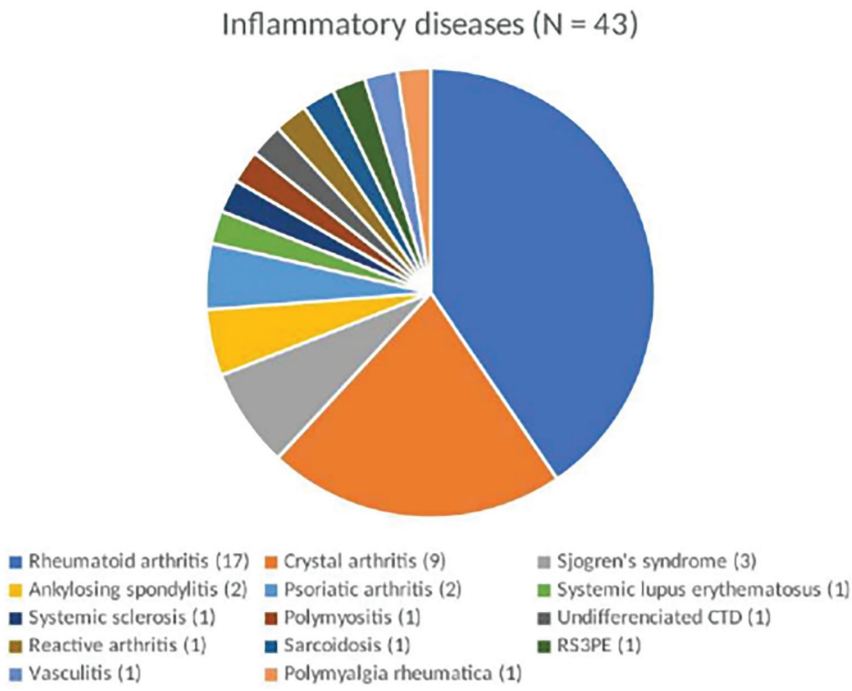

Figure 2. Inflammatory diseases with malignancy diagnosis

CTD: Connective tissue disease, RS3PE: Remitting seronegative symmetrical synovitis with pitting edema

Timing of Cancer Diagnosis Relative to Rheumatic Disease

Patients with cancer history were analyzed according to timing of the cancer history relative to the onset of rheumatic disease or non-inflammatory condition (Figure 3). Among 100 patients with cancer history, 74 patients had cancer diagnosis earlier than the rheumatic disease or non-inflammatory condition. Within these patients, 47 had non-inflammatory conditions and 27 had rheumatic diseases later on. In the latter group, 10 patients experienced the onset of rheumatic disease more than 10 years after their cancer diagnosis. Seven patients developed rheumatic disease between 5 and 10 years after their cancer diagnosis, six patients between 1 and 5 years, and four patients within the same year as their cancer diagnosis. Specific cases in the last group include: SLE onset following cervical cancer; systemic sclerosis onset after a breast cancer relapse; relapsing seronegative symmetrical synovitis with pitting edema following laryngeal cancer; and vasculitis following melanoma. The patient with a breast cancer relapse developed systemic sclerosis within three months of starting the kinase inhibitor ribociclib. In two patients treated with the immune checkpoint inhibitor nivolumab, one developed RA two years after an esophageal cancer diagnosis, and the other developed PsA three years after a melanoma diagnosis.

Sixteen patients with rheumatic diseases and 10 patients with non-inflammatory complaints had a later cancer diagnosis. This group comprised 17 females and 9 males, with a mean age of 66.4±9.7 years. Seven patients had a history of smoking. The detailed diagnoses of these patients are presented in Table 4A. These patients' specific cancer diagnoses, stratified by gender, number of observed and expected cases, and SIRs, are presented in Table 4B. In female patients, gynecologic cancers (p=0.005, CI=1.2-8.7), hematologic cancers (p=0.002, CI=1.4-13.5), and lymphoma (p=0.001, CI=1.6-23.7) were particularly more common.

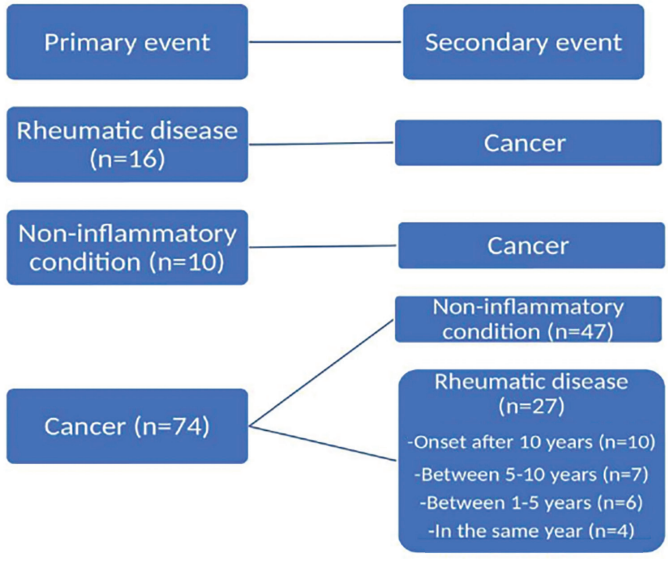

Figure 3. Temporal relationship between the onset of cancer and rheumatic or non-inflammatory diseases. The total number of patients with a history of both rheumatic diseases and cancer is 43

Table 3. Treatments administered and types of malignancies in patients with specific inflammatory diseases

Inflammatory diseases (n=43)	Treatments	Malignancies
Rheumatoid arthritis (n=17)	Steroid (n=13)	Breast (n=4)
	Methotrexate (n=9)	Stomach (n=2)
	Leflunomide (n=2)	Endometrial (n=2)
	Hydroxychloroquine (n=7)	Lung (n=2)
	Adalimumab (n=1)	Bladder (n=2)
		Prostate (n=2)
		Esophageal (n=1)
		Colorectal (n=1)
		Lymphoma (n=1)
Sjögren's syndrome (n=3)	Hydroxychloroquine (n=3)	Breast (n=3)
Systemic lupus erythematosus (n=1)	Steroid (n=1)	Cervix (n=1)
	Hydroxychloroquine (n=1)	
Systemic sclerosis (n=1)	Nifedipine (n=1)	Breast (n=1)
	Acetylsalicylic acid (n=1)	
Polymyositis (n=1)	Steroid (n=1)	Ovarian (n=1)
UCTD (n=1)	Nifedipine (n=1)	Lymphoma (n=1)
	Acetylsalicylic acid	
Ankylosing spondylitis (n=2)	NSAID (n=2)	Renal cell carcinoma (n=1)
	Etanercept (n=2)	Bladder (n=1)
Psoriatic arthritis (n=2)	Steroid (n=1)	Thyroid (n=1)
	Methotrexate (n=1)	Melanoma (n=1)
	Leflunomide (n=1)	
	Adalimumab (n=1)	
Reactive arthritis (n=1)	NSAID (n=1)	Thyroid (n=1)
Familial Mediterranean fever (n=1)	Colchicine (n=1)	Thyroid (n=1)
Sarcoidosis (n=1)	Steroid (n=1)	Thyroid (n=1)
RS3PE (n=1)	Steroid (n=1)	Larengeal (n=1)
Polymyalgia rheumatica (n=1)	Steroid (n=1)	Prostate (n=1)
	Leflunomide (n=1)	
Vasculitis (n=1)	Steroid (n=1)	Breast (n=1)
		Renal cell carcinoma (n=1)
		Melanoma (n=1)
Crystal arthritis (n=9)	Steroid (n=6)	Breast (n=3)
	Allopurinol (n=6)	Prostate (n=2)
	Colchicine (n=4)	Stomach (n=1)
		Colorectal (n=1)
		Pancreatic (n=1)
		Larengeal (n=1)
		Melanoma (n=1)

NSAID: Non-steroidal anti-inflammatory drug, RS3PE: Remitting seronegative symmetrical synovitis with pitting edema, UCTD: Undifferentiated connective tissue disease

In male patients, the total number of all cancers was significantly higher (p<0.001, CI=182.7-700.8), although no specific cancer type reached statistical significance.

Logistic regression analysis was performed to assess the effects of age, gender, smoking history, comorbidities, various rheumatic diseases, and treatments on the likelihood of cancer. The analysis identified significant associations between cancer diagnosis and age (p=0.002), male gender (p=0.02), the presence of inflammatory diseases (p<0.001), and CCI score (p<0.001) (Table 5). However, individual rheumatic diseases did not demonstrate statistical significance.

Discussion

This study aimed to analyze the incidence, prevalence and characteristics of cancer among patients with rheumatic diseases and non-inflammatory conditions. The results

Table 4A. Comparison of patients diagnosed with cancer after inflammatory disease (n=16) onset or non-inflammatory conditions (n=10)

Inflammatory diseases (n=16)		Non-inflammatory conditions (n=10)	
Age (mean ± SD)	65.4±13.4	Age (mean ± SD)	65.4±9.5
Female/male	11:5	Female/male	6:4
Smoking ever	3	Smoking ever	4
Spesific diseases	**Malignancies**	**Spesific conditions**	**Malignancies**
Rheumatoid arthritis (n=9)	Breast (n=2)	Osteoarthritis (n=6)	Breast (n=1)
	Endometrial (n=2)		Ovarian (n=1)
	Stomach (n=1)		Prostate (n=2)
	Colorectal (n=1)		Pancreas (n=1)
	Lung (n=1)		Lymphoma (n=1)
	Bladder (n=1)		Multiple myeloma (n=1)
	Lymphoma (n=1)	Back pain (n=1)	Renal cell carcinoma (n=1)
Cryrstalline arthropathies (n=3)	Prostate (n=2)	Positive autoantibodies (n=1)	Lung (n=1)
	Stomach (n=1)*	Increased acute phase reactants (n=2)	Cervix (n=1)
	Melanoma (n=1)*		Multiple myeloma (n=1)
Ankylosing spondylitis (n=1)	Renal cell carcinoma (n=1)		
Sjogren syndrome (n=1)	Breast (n=1)		
Polymyositis (n=1)	Ovarian (n=1)		
UCTD (n=1)	Lymphoma (n=1)		

SD: Standard deviation, UCTD: Undifferentiated connective tissue disease

Table 4B. Specific diagnosis, observed and expected cases, and SIRs for malignancies, stratified by gender

	Female Observed	Expected	SIR	p	CI (95%)	Male Observed	Expected	SIR	p	CI (95%)
All cancers (C00-96)	17	10.5	1.62	0.044	0.9-2.5	10	0.03	381.10	**<0.001**	182.7-700.8
Breast cancer (C50)	4	2.7	1.47	0.279	0.4-3.7					
Gynecologic cancers (C51-58)	5	1.33	3.76	**0.005**	1.2-8.7					
Ovarian cancer (C56)	2	0.36	5.51	0.012	0.6-19.9					
Endometrium cancer (C54)	2	0.62	3.23	0.050	0.3-11.6					
Cervix cancer (C53)	1	0.23	4.26	0.047	0.1-23.7					
Male reproductive system cancers (C60-63)						3	1.04	2.88	0.043	0.5-8.4
Prostate cancer (C61)						3	0.94	3.20	0.031	0.6-9.3
Urinary tract cancers (C64-68)	2	0.36	5.51	0.012	0.6-19.9	1	0.65	1.53	0.280	0.04-8.5
Renal cell carcinoma (C64)	1	0.19	5.27	0.032	0.1-29.3	1	0.17	5.73	0.027	0.1-31.9
Bladder cancer (C67)	1	0.16	6.17	0.024	0.1-34.3	0				
Gastrointestinal cancers (C15-26)	1	1.64	0.61	0.977	0.02-3.3	3	1.25	2.39	0.077	0.4-6.9
Stomach cancer (C16)	1	0.36	2.75	0.104	0.07-15.3	1	0.33	3.05	0.087	0.08-16.9
Colorectal cancer (C18-20)						1	0.58	1.73	0.229	0.04-9.6
Pancreatic cancer (C25)						1	0.13	7.67	0.016	0.1-42.7
Respiratory system cancers (C30-38)	1	0.67	1.49	0.291	0.04-8.3	1	1.46	0.69	0.856	0.02-3.8
Lung cancer (C34)	1	0.61	1.64	0.250	0.04-9.1	1	1.29	0.77	0.741	0.02-4.3
Hematologic cancers (C81-96)	4	0.75	5.30	**0.002**	1.4-13.5	1	0.44	2.27	0.145	0.06-12.6
Lymphoma (C81-85)	3	0.37	8.14	**0.001**	1.6-23.7	0				
Multiple myeloma (C90)	1	0.12	8.52	0.013	0.2-47.5	1	0.07	14.32	0.005	0.3-79.7
Skin cancers (C43-44)	0					1	0.61	1.63	0.252	0.04-9.1
Melanoma (C43)	0					1	0.04	23.86	0.002	0.6-132.9

CI: Confidence interval, SD: Standard deviation

Table 5. Logistic regression analysis for malignancy

	p	Odds ratio	Confidence interval
Age	0.002	1.03	1.01-1.06
Male gender	0.026	2.16	1.09-4.28
Inflammatory disease history	<0.001	4.52	2.16-9.45
Charlson Comorbidity index	<0.001	5.65	2.87-11.13

revealed several noteworthy findings that align with and contribute to the current understanding of cancer risk in these patient populations.

Firstly, the overall prevalence of cancer in this cohort was 3.8%, with a higher median age among cancer patients compared to those without cancer. This aligns with existing literature suggesting that cancer incidence increases with age.[33] Interestingly, our study found a lower prevalence of cancer in patients with SpA, AS, and fibromyalgia, whereas those with osteoarthritis exhibited a higher prevalence. Studies have shown that the prevalence of cancer in patients with AS is not significantly elevated compared to the general population.[34]

In this study, although male sex (p<0.001) and a history of smoking-a known carcinogen- (p<0.001) were more common in AS patients, these patients were generally younger (p<0.001, mean: 38.8±10.6 years) and had lower CCI scores (p<0.001, 0.6±0.7), which may partly explain the reduced cancer prevalence observed in this group. On the other hand, fibromyalgia patients were predominantly female (p<0.001) and had lower CCI scores (p<0.001, 0.5±0.6), although age (p=0.33) and smoking history (p=0.49) did not differ between those with and without the condition.

In contrast, patients with osteoarthritis showed an increased risk of cancer, which may be linked to shared risk factors, particularly advanced age.[35] In our study, osteoarthritis patients were predominantly female (p<0.001), and smoking was less common among them (p<0.001). However, these patients were older (p<0.001, mean: 66.7±9.5 years) and had higher CCI scores (p=0.004, 0.97±1.1). These findings suggest that age and comorbidity status may have a greater influence on cancer risk in this cohort than factors such as sex or smoking history, particularly in patients with osteoarthritis.

The analysis of cancer prevalence with aging revealed that geriatric patients had a higher mortality rate, and a different distribution of cancer types compared to non-geriatric patients. Thyroid cancers were significantly more prevalent in the non-geriatric group, which might reflect differences in cancer biology and detection rates between age groups.[36] Although lung, gastrointestinal, and prostate cancers were more common in geriatric patients, these differences did not reach statistical significance. This suggests that while there are observable trends in cancer type distribution between age groups, the sample size or variability may limit the statistical power to detect significant differences.

In terms of rheumatic disease, RA was the most prevalent inflammatory disease in patients with cancer, with 17 RA patients in total. Most of the RA patients in this study were female (p<0.001), with a similar smoking history compared to those without RA (p=0.12). However, RA patients had higher CCI scores (p<0.001, 1.2±0.9) and were older (p<0.001, 57.4±15.1 years). Although the frequency of cancer did not reach statistical significance in this group, RA remained the most common inflammatory diagnosis among patients with a history of cancer, which may be attributed to the relatively small sample size. Consequently, it was not possible to draw definitive conclusions about the effects of different treatments on cancer incidence in this cohort.

The analysis of specific cancer types revealed that breast cancer was the most common malignancy in this cohort, accounting for 29% of cancer cases. This finding is consistent with global cancer statistics, which identify breast cancer as the most prevalent cancer among women.[37] Additionally, this study identified sex-based disparities in cancer types, with thyroid cancers being more common in females and respiratory system and gastrointestinal cancers being more frequent in males. The higher prevalence of respiratory system cancers in males may be linked to the significantly higher smoking history observed in this group.[38]

An important aspect of this study was the timing of cancer diagnosis relative to the onset of rheumatic disease, which provided insights into potential causal relationships. In some cases, rheumatic diseases preceded the onset of cancer, while in others, rheumatic diseases developed after a cancer diagnosis. This bidirectional relationship suggests that chronic inflammation and immune dysregulation may play a role in the development of both conditions.[13] Among the 16 female patients with newly diagnosed cancers during follow-up, gynecologic cancers and lymphoma were significantly more common when SIRs were calculated based on the latest incidence rates in the Turkish population. In the 10 male patients with newly diagnosed cancers during follow-up, the total number of cancers was significantly higher. Moreover, the occurrence of rheumatic diseases following cancer treatment with immune checkpoint inhibitors and kinase inhibitors highlights the impact of these therapies on immune regulation, which was observed in three of our

patients.[39]

Rheumatologists may encounter malignancy in various contexts during routine clinical practice. Patients with rheumatic diseases might receive a new cancer diagnosis, requiring adjustments to their treatment plans. Additionally, patients presenting with symptoms commonly associated with rheumatic conditions, such as an elevated sedimentation rate, positive autoantibodies, or back pain, may have an underlying malignancy. In some cases, newly diagnosed seronegative arthritis may represent a paraneoplastic syndrome, though these diagnoses are often challenging to confirm. In this study, four patients were diagnosed with both rheumatic disease and cancer within the same year, suggesting a potential paraneoplastic relationship. The recognition of paraneoplastic syndromes is clinically significant, as they often mimic primary rheumatic diseases and can complicate the diagnosis and management of both conditions.

The results of the logistic regression analysis further elucidate the factors associated with cancer risk in this cohort. Age, male sex, the presence of inflammatory diseases, and higher CCI scores were all significantly associated with a higher likelihood of cancer. These findings align with the broader literature on cancer risk factors, emphasizing the role of age, comorbidity burden, and gender in determining cancer susceptibility. The lack of statistical significance for individual rheumatic diseases in the regression analysis may be attributed to the low number of cancer cases within each specific disease group. These results reinforce the need for comprehensive cancer risk assessments in patients with rheumatic diseases, especially those with multiple comorbidities or higher inflammatory disease activity.

In comparing our findings with previous Turkish studies on malignancy risk in rheumatic diseases, several similarities emerge. Similar to our study, research on patients with anti-neutrophil cytoplasmic autoantibody-associated vasculitis and primary Sjögren syndrome demonstrated an increased cancer risk compared to the general Turkish population. For instance, in the vasculitis cohort, the cancer risk was 2.1 times higher than in the general population, particularly for lung and head-neck cancers.[16] Likewise, the study on primary Sjögren syndrome reported an overall increased risk for both solid and hematologic malignancies (SIR=2.45), with ovarian and non-Hodgkin lymphoma cancers being notably more prevalent, underscoring the need for vigilant cancer monitoring across different rheumatic diseases.[17] Similarly, studies on systemic sclerosis also identified an elevated malignancy risk, particularly for breast and lung cancers.[18] In our study, RA was the most common rheumatic disease associated with a history of cancer, and breast cancer emerged as the most frequent malignancy.

Study Limitations

There is conflicting information regarding the incidence and prevalence of cancer in patients with rheumatic diseases, primarily due to methodological challenges in this research area.[40] Cancer risk is not constant or easily modeled over time.[41] Besides autoimmunity, other factors, such as genetics and smoking, also contribute to cancer risk. On the other hand, the risk of cancer development in patients with rheumatic disease is very low, estimated as 2-5 cases per 1000 patients treated annually.[42] Many studies are limited by short observation periods and small sample sizes, which hinder statistical significance.

This study has several limitations that may introduce bias and affect the interpretation of our findings. The retrospective design is a key limitation, as it relies on existing medical records, which are subject to missing data. This could lead to misclassification of both rheumatic diseases and cancer diagnoses, particularly in cases where detailed clinical histories or follow-up data were unavailable. Furthermore, the lack of detailed information on cancer staging, treatment responses, and disease progression limits our ability to assess cancer outcomes comprehensively.

Selection bias may also be present, as only patients followed at our center were included. This could result in the exclusion of patients with milder forms of disease who may not require frequent hospital visits, or those who sought care at other facilities. As a result, the patient population may not be fully representative of the broader rheumatic disease population, affecting the generalizability of our findings.

Additionally, survival bias is a potential issue, as patients with more severe cancer or advanced rheumatic diseases may have had limited follow-up, leading to an underestimation of cancer prevalence in our study. Patients who succumbed to cancer early in the disease course or those with poor health may have been less likely to be captured in the study, skewing the cancer incidence rates lower.

Finally, conducting the study at a single private hospital limits the external validity of our results, as patient demographics and healthcare practices may differ across other regions or healthcare systems. This could mean that our findings are not fully applicable to other populations, particularly in terms of cancer screening and treatment practices.

Conclusion

Despite these limitations, the large sample size and comprehensive analysis in this study provide valuable insights

into the prevalence and characteristics of cancer in patients with rheumatic diseases. The findings highlight the need for vigilant cancer screening and monitoring in this population, particularly considering the influence of age, gender, and specific rheumatic conditions. Future research should focus on well-designed, prospective, multicenter studies with longer follow-up periods and larger cohorts to further elucidate the complex relationship between rheumatic diseases and cancer and to develop targeted strategies for cancer prevention and management in these patients.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (Memorial Bahçelievler Hospital Ethics Committee - approval number: 133, date: 11.06.2024).

Informed Consent: Retrospective study.

Footnotes

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

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Supplementary Table 1. Specific cancer types according to gender

	All patients	Female	Male	p	OR	CI
	n=100	n=65 (%)	n=35 (%)			
Age				0.22		
Median (IQR)	66 (16.5)	65 (15)	69 (13.5)			
Mean (SD)	63.7 (12.3)	62.6 (12.1)	65.8 (12.6)			
Min-max	28-88	28-88	33-85			
Gender						
Female	65					
Male	35					
Geriatric patients	57	32 (49.2)	25 (71.4)	**0.03**	2.5	1.06-6.2
Smoking	31	14 (21.5)	17 (48.6)	**0.005**	3.4	1.4-8.3
No	69	51 (78.5)	18 (51.4)			
Yes	22	11 (16.9)	11 (31.4)			
Previous	9	3 (4.6)	6 (17.1)			
Mortality				0.35		
Yes	10	5 (7.7)	5 (14.3)			
No	80	52 (80)	28 (80)			
Unknown	10	8 (12.3)	2 (5.7)			
Breast cancer (C50)	29	29 (44.6)	0			
Gynecologic cancers (C51-58)	10	10 (15.4)	0			
Ovarian cancer (C56)	4	4 (6.2)	0			
Endometrium cancer (C54)	3	3 (4.6)	0			
Cervix cancer (C53)	3	3 (4.6)	0			
Male reproductive system cancers (C60-63)	10	0	10 (28.6)			
Prostate cancer (C61)	9	0	9 (25.7)			
Testicular cancer (C62)	1	0	1 (2.9)			
Urinary tract cancers (C64-68)	9	4 (6.2)	5 (14.3)	0.27		
Renal cell carcinoma (C64)	4	2 (3.1)	2 (5.7)	0.61		
Bladder cancer (C67)	5	2 (3.1)	3 (8.6)	0.34		
Gastrointestinal cancers (C15-26)	12	6 (9.2)	6 (17.1)	0.24		
Esophageal cancer (C15)	1	1 (1.5)	0	0.65		
Stomach cancer (C16)	5	2 (3.1)	3 (8.6)	0.34		
Colorectal cancer (C18-20)	5	2 (3.1)	3 (8.6)	0.34		
Pancreatic cancer (C25)	2	1 (1.5)	1 (2.9)	0.58		
Respiratory system cancers (C30-38)	10	2 (3.1)	8 (22.9)	**0.003**	9.3	1.8-46.8
Laryngeal cancer (C32)	3	0	3 (8.6)	0.04	1.09	0.9-1.2
Lung cancer (C34)	7	2 (3.1)	5 (14.3)	0.04	5.2	0.9-28.6
Thyroid cancer (C73)	10	9 (13.8)	1 (2.9)	0.15		
Hematologic cancers (C81-96)	9	5 (7.7)	4 (11.4)	0.71		
Lymphoma (C81-85)	4	3 (4.6)	1 (2.9)	0.56		
Chronic lymphocytic leukemia (C91.1)	1	0	1 (2.9)	0.35		
Multiple myeloma (C90)	4	2 (3.1)	2 (5.7)	0.61		
Skin cancers (C43-44)	5	1 (1.5)	4 (11.4)	0.05		
Non-melanoma skin cancer (C44)	2	0	2 (5.7)	0.12		
Melanoma (C43)	3	1 (1.5)	2 (5.7)	0.28		
Sarcoma (C49)	1	0	1 (2.9)	0.35		
Carcinoma of unknown primary (C80.1)	1	1 (1.5)	0	0.65		

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio, SD: Standard deviation

Supplementary Table 2. Specific cancer types according to geriatric status

	All patients	Non-geriatric	Geriatric	p	OR	CI
	n=100	n=43 (%)	n=57 (%)			
Age				**<0.001**		
Median (IQR)	66 (16.5)	52 (13.5)	70 (9)			
Mean (SD)	63.7 (12.3)	52.5 (9.2)	72.2 (5.8)			
Min-max	28-88	28-64	65-88			
Gender				**0.03**	2.5	1.06-6.2
Female	65	33 (76.7)	32 (56.1)			
Male	35	10 (23.3)	25 (43.9)			
Geriatric patients	57					
Smoking	31	12 (27.9)	19 (33.3)	0.56		
No	69	31 (72.1)	38 (66.7)			
Yes	22	8 (18.6)	14 (24.6)			
Previous	9	4 (9.3)	5 (8.8)			
Mortality				**0.04**		
Yes	10	1 (2.3)	9 (15.8)			
No	80	37 (86)	43 (75.4)			
Unknown	10	5 (11.6)	5 (8.8)			
Breast cancer (C50)	29	12 (27.9)	17 (29.8)	0.83		
Gynecologic cancers (C51-58)	10	5 (11.6)	5 (8.8)	0.63		
Ovarian cancer (C56)	4	2 (4.7)	2 (3.5)	0.57		
Endometrium cancer (C54)	3	1 (2.3)	2 (3.5)	0.60		
Cervix cancer (C53)	3	2 (4.7)	1 (1.8)	0.57		
Male reproductive system cancers (C60-63)	10	3 (7.0)	7 (12.3)	0.50		
Prostate cancer (C61)	9	2 (4.7)	7 (12.3)	0.29		
Testicular cancer (C62)	1	1 (2.3)	0	0.43		
Urinary tract cancers (C64-68)	9	5 (11.6)	4 (7.0)	0.49		
Renal cell carcinoma (C64)	4	3 (7.0)	1 (1.8)	0.31		
Bladder cancer (C67)	5	2 (4.7)	3 (5.3)	0.63		
Gastrointestinal cancers (C15-26)	12	2 (4.7)	10 (17.5)	0.06		
Esophageal cancer (C15)	1	1 (2.3)	0	0.43		
Stomach cancer (C16)	5	0	5 (8.8)	0.06		
Colorectal cancer (C18-20)	5	1 (2.3)	4 (7.0)	0.38		
Pancreatic cancer (C25)	2	0	2 (3.5)	0.05		
Respiratory system cancers (C30-38)	10	1 (2.3)	9 (15.8)	0.04	7.8	0.9-64.7
Laryngeal cancer (C32)	3	0	3 (5.3)	0.25		
Lung cancer (C34)	7	1 (2.3)	6 (10.5)	0.23		
Thyroid cancer (C73)	10	9 (20.9)	1 (1.8)	**0.002**	0.06	0.008-0.5
Hematologic cancers (C81-96)	9	5 (11.6)	4 (7.0)	0.49		
Lymphoma (C81-85)	4	3 (7.0)	1 (1.8)	0.31		
Chronic lymphocytic leukemia (C91.1)	1	0	1 (1.8)	0.57		
Multiple myeloma (C90)	4	2 (4.7)	2 (3.5)	0.57		
Skin cancers (C43-44)	5	1 (2.3)	4 (7.0)	0.38		
Non-melanoma skin cancer (C44)	2	1 (2.3)	1 (1.8)	0.67		
Melanoma (C43)	3	0	3 (5.3)	0.25		
Sarcoma (C49)	1	0	1 (1.8)	0.57		
Carcinoma of unknown primary (C80.1)	1	1 (2.3)	0	0.43		

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio, SD: Standard deviation