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Higher Mortality Risk From Ovarian Carcinomas, Small Bowel Neoplasms, and B-Cell and Mucosa-Associated Lymphoid Tissue Lymphomas in Sjögren Syndrome Patients

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Objective: To evaluate the impact of the different types of neoplasms and lineages on Sjögren syndrome (SjS) patient mortality.

Methods: Medical records review study based on the Spanish Hospital Discharge Database and the *International Classification of Diseases, Tenth Revision, Clinical Modification* coding list. The neoplasm-related deaths in SjS patients with the general population during the period 2016–2019 were compared. A binary logistic regression analysis considering age, sex, tobacco use, and alcohol use was performed to determine the impact of SjS on the risk of dying from each neoplasm group and lineage.

Results: In the period studied, 705,557 in-hospital deaths were certified in Spain, 139,531 (19.8%) from neoplasms. Neoplasms surpassed SjS activity as a cause of mortality in primary SjS patients (11.3% vs. 1.6%, $p < 0.001$). SjS patients presented higher mortality rates from small bowel carcinoma (0.3% vs. 1.8%; odds ratio [OR], 5.41; 95% confidence interval [CI], 1.33–22) and gynecological neoplasms (6.4% vs. 3%; OR, 2.13; 95% CI, 1.01–4.58), related to ovarian carcinomas (4.6% vs. 1.3%; OR, 3.65; 95% CI, 1.48–8.97), than the general population. Hematological neoplasm–related deaths were more prevalent in SjS patients than in the non-SjS population (18.3% vs. 8.9%; OR, 2.04; 95% CI, 1.25–3.31), mostly attributable to the higher proportion of deaths from B-cell non-Hodgkin lymphoma (8.3% vs. 2.5%; OR, 3.04; 95% CI, 1.54–6.03) and mucosa-associated lymphoid tissue lymphoma (1.8% vs. 0.1%; OR, 70.17; 95% CI, 16.61–296.36).

Conclusion: SjS patients face an elevated risk of mortality from small bowel neoplasms, ovarian carcinomas, and B-cell and mucosa-associated lymphoid tissue lymphoma compared with the general Spanish population. Apart from developing approaches to mitigate their occurrence, it is crucial to explore thoroughly and consider the implementation of targeted early-detection programs for these specific conditions.

Key Words: Sjögren syndrome, mortality, neoplasm, ovarian neoplasm, small bowel carcinoma, B-cell lymphoma, MALT lymphoma

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Sjögren syndrome (SjS) is a systemic autoimmune disease predominantly affecting women between the fourth and sixth decades of life.[1] Exocrine gland involvement, principally in the mouth and eyes, leads to the sicca syndrome that distinguishes the disease. There is a subset of patients who develop extraglandular involvement with potentially severe interstitial lung disease, kidney disease, neurological involvement, vasculitis, and hematological complications, among others.[1,2] The increase in all-cause mortality compared with the general population, related to certain comorbidities such as cardiovascular disease, infections, and malignancy, is particularly noted in SjS patients with high activity and risk.[2,3]

Previous reports, including meta-analysis, have concluded that SjS disease has an established association with the development of lymphoproliferative malignancy, including lymphoma, mucosa-associated lymphoid tissue (MALT), and monoclonal immunoglobulin disorders.[4–6] However, to date, there is still contradictory evidence regarding overall survival of patients with these conditions.[2,3,7,8]

Other studies have suggested that the natural history of certain solid organ neoplasm (SON) might be different in SjS.[4,5,8,9] A higher incidence of lung, thyroid, and nonmelanoma cancer and a different progression from head and neck tumors have been described. Because this risk has been refuted in other studies, SON epidemiology, and especially its related mortality in patients with SjS, still presents a lot of uncertainties.[2,7,8]

In this nationwide analysis, we aimed to evaluate the impact of the different types of neoplasms and lineages on SjS patient mortality.

MATERIALS AND METHODS

An analysis on data extracted from the Spanish Hospital Discharge Database (SNHDD), a public access registry belonging to the Spanish Government, was performed. Demographic and epidemiological data and up to 20 discharge diagnoses carried out

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The authors declare no conflict of interest.

The study complies with the Declaration of Helsinki and was approved by the local research ethics committee (expedient number PI 80-21). The data were provided after all potential patient identifiers had been deleted, and data were given anonymously. Due to the design of the study, and according to Spanish law, informed consent was not required.

Data are available in a public, open-access repository. The data analyzed are extracted from the Spanish Hospital Discharge Database, a public access registry belonging to the Spanish Government.

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during admission and defined from January 1, 2016, by the *International Classification of Diseases, Tenth Revision* (*ICD-10*), are included in the SNHDD. The proportion and lineage of the neoplasm-related deaths of SjS patients and the general Spanish population were compared.

Study Population

Hospital admissions, from 2016 to 2019, for patients with a diagnosis within the *ICD-10 Clinical Modification* (*ICD-10-CM*) code M35.0 (SjS) at any position in the diagnostic list, were selected. Patients who presented secondary SjS, and therefore systemic lupus erythematosus (code M32), systemic sclerosis (code M34), or rheumatoid arthritis (codes M05 and M06), were excluded because these conditions might impact the neoplasm-related risk in the SjS population.[8,10,11] All the in-hospital deaths notified in Spain during 2016–2019 were retrieved from the SNHDD and were used as the control group to compare with the primary SjS patients.

Variables and Neoplasm-Related Deaths

According to the database structure and design, the main diagnosis was the defining reason for admission and the cause of death if that occurred. All main diagnoses of the deceased patients were decodified, analyzed, and clustered. Only those admissions and deaths attributable to neoplasms (from *ICD-10-CM* code C.00 to D.49), other than SjS itself (M.35), were analyzed.

Following the *ICD-10-CM* coding criteria, neoplasm-related deaths were classified as malignant neoplasms, which include solid organ malignant neoplasms (C00–C80), hematological malignant neoplasms (C81–C96), in situ neoplasms (D00–D09), benign SONs (D10–D36 and D3A), and unknown or nonspecified behavior neoplasms (D37–D49), in turn also including solid organ and hematological neoplasms (HNs). Myelodysplastic syndromes, based on their worse prognosis and mortality rate, were considered malignant HNs. Finally, the main solid organ and HN lineages and subsequent subclassifications, such as gastrointestinal, lung, breast, gynecological, and urological, together with lymphoma, leukemia, or myelodysplastic syndrome, among others, were considered and analyzed separately.

Statistical Analysis

The epidemiological and demographic data, as well as the proportion of deaths attributable to the distinct neoplasm types and lineages of the SjS patients, were compared with the general Spanish population. Categorical variables were reported as frequencies and percentages, whereas continuous variables were presented as mean and SD. The significance of differences between the 2 groups was determined by the χ^2 or Student *t* test, as appropriate. A binary logistic regression analysis for each neoplasm group and lineage was performed to determine the impact of SjS on the risk of dying from each of them. Age, female sex, tobacco, and alcohol consumption (according to *ICD-10-CM* codes F17 or Z72.0 and F10, K70 or I42.6, respectively) were adjusted for. For all the analyses, a significance level of 0.05 was set. Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, New York, USA).

Ethics

The study complies with the Declaration of Helsinki and was approved by the local research ethics committee (expedient number PI 80-21). The data were provided after all potential patient identifiers had been deleted and data were given anonymously. Due to the design of the study, and according to Spanish law, informed consent was not required.

RESULTS

Primary SjS Patient Characteristics

Between 2016 and 2019, 18,659 hospital admissions of patients with SjS were identified in the Spanish National Registry (Supplementary Table 1, http://links.lww.com/RHU/A730). Overall, 85.9% were female, 75.1% Caucasians, with a mean age of 68.3 years. A total of 979 SjS patients (5.2%) died during this period, and 826 (4.4%) were admitted to the intensive care unit. The mean length of admission was 5.3 days. Of the deceased patients, 16 (1.6%) died because of SjS-related activity per *ICD* code, and 109 (11.3%) from neoplasms ($p < 0.001$). The mean age of patients who died because of SjS activity was 57.5 years, and from neoplasms, 70.5 years ($p = 0.003$).

Differences in Neoplasm-Related Deaths in SjS Patients and the General Spanish Population

The mean Spanish population between 2016 and 2019 was 46,704,229 inhabitants (www.ine.es). In this period, the population life expectancy in Spain was 80.6 years for men and 86.3 years for women. A total of 705,557 in-hospital deaths were identified, 139,531 (19.8%) being from neoplasms. Overall, 127,153 (91.1%) of these deaths were related to SON and 12,378 (8.9%) to HN. The 109 patients with SjS who died of neoplasms were significantly older than the general Spanish population dying of the same cause (74.5 vs. 70.7 years, $p < 0.001$).

Tables 1 and 2 show the differences in neoplasm-related deaths between SjS patients and the general Spanish population. Overall, 81.7% of neoplasm-related deaths were attributable to SON versus 91.1% in the general Spanish population (Table 1) and 18.3% to HN (vs. 8.9% in the Spanish population; Table 2; $p = 0.002$). The mean age of patients deceased from SON was significantly higher in the SjS patients than that in the general population (74.7 vs. 70.6 years, $p < 0.001$). However, no age differences were found in the HN-related deaths (73.4 vs. 71.9 years, $p = 0.658$).

Because the rate of SON and HN deaths differed in SjS patients and the general Spanish population, a more detailed comparison considering the different neoplasm lineages was performed (Tables 1 and 2). A binary logistic regression analysis was carried out for each neoplasm lineage to determine the impact of SjS on the risk of death from certain neoplasms.

Solid Organ Neoplasms

The adjusted multivariate analysis confirmed that primary SjS patients presented a lower mortality frequency and risk of SON (81.7% vs. 91.1%; odds ratio [OR], 0.49; 95% confidence interval [CI], 0.30–0.80) than the general Spanish population (Table 1). Although these differences were probably secondary to the marginally lower risk of colorectal carcinoma (6.4% vs. 10.8%; OR, 0.51; 95% CI, 0.24–1.11), small bowel neoplasm mortality (1.8% vs. 0.3%; OR, 5.41; 95% CI, 1.33–22) was higher in patients with primary SjS. On the other hand, SjS patients presented a significantly higher gynecological mortality (6.4% vs. 3%; OR, 2.13; 95% CI, 1.01–4.58), resulting from the higher death rate from ovarian carcinomas (4.6% vs. 1.3%; OR, 3.65; 95% CI, 1.48–8.97). Finally, no significant differences between SjS patients and the general Spanish population were found for other SON lineage death rates or risk.

Hematological Neoplasms

Patients with primary SjS presented a higher mortality rate from HN (18.3% vs. 8.9%, $p = 0.002$; OR, 2.04; 95% CI, 1.25–

TABLE 1. Differences in Solid Organ Neoplasm–Related Deaths by Lineage Between SjS Patients and the General Spanish Population

	Neoplasm-Related Deaths, n (%)			
	Non-SjS	SjS	*p* value	OR (95% CI)[a]
SON	127,064 (91.1)	89 (81.7)	0.002	**0.49 (0.30–0.80)**
Malign SON	124,819 (89.5)	87 (79.8)	0.002	**0.53 (0.33–0.86)**
Digestive system	41,559 (29.8)	32 (29.4)	0.994	0.93 (0.61–1.40)
Gastrointestinal tract	24,562 (17.6)	16 (14.7)	0.524	0.78 (0.46–1.33)
Esophagus	2320 (1.7)	1.000 (0.9)	1.000	0.91 (0.13–6.54)
Stomach	6423 (4.6)	6 (5.5)	0.643	1.19 (0.52–2.71)
Small bowel	457 (0.3)	2 (1.8)	0.050	**5.41 (1.33–22)**
Colorectal	15,056 (10.8)	7 (6.4)	0.164	0.51 (0.24–1.11)
Others	306 (0.2)	0	1.000	—
Hepatobiliary pancreatic	16.997 (12.2)	16 (14.7)	0.462	1.17 (0.68–1.98)
HCC and others	3.815 (2.7)	2 (1.8)	0.773	0.96 (0.23–3.96)
Pancreas	8.699 (6.2)	12 (11)	**0.047**	1.60 (0.88–2.92)
Cholangiocarcinoma	4.483 (3.2)	2 (1.8)	0.281	0.47 (0.12–1.90)
Lung	25.884 (18.6)	19 (17.4)	0.892	1.51 (0.91–2.51)
Mama	3.632 (2.6)	0	0.122	—
Gynecological	4.132 (3)	7 (6.4)	0.044	**2.13 (1.01–4.58)**
Vulva	280 (0.2)	1.000 (0.9)	0.197	3.90 (0.54–28.09)
Vagina	63 (0.1)	0	1.000	—
Cervical	651 (0.5)	0	1.000	—
Uterus	1.263 (0.9)	1.000 (0.9)	0.559	1.09 (0.15–7.80)
Ovary	1.744 (1.3)	5 (4.6)	0.012	**3.65 (1.48–8.97)**
Other	131 (0.1)	0	1.000	—
Otorhinolaryngological	4108 (2.9)	1.000 (0.9)	0.386	0.48 (0.07–3.47)
Endocrine	1782 (1.3)	0	0.653	—
Skin	1024 (0.7)	2 (1.8)	0.191	2.42 (0.60–9.84)
Central nervous system	4.029 (2.9)	2 (1.8)	0.774	0.72 (0.18–2.94)
Urological	11,067 (7.9)	7 (6.4)	0.722	1.22 (0.56–2.65)
Prostate	3289 (2.4)	1.000 (0.9)	0.526	0.99 (0.13–7.40)
Kidney	2136 (1.5)	2 (1.8)	0.685	1.29 (0.32–5.24)
Bladder	5145 (3.7)	4 (3.7)	1.000	1.38 (0.50–3.78)
Others	497 (0.4)	0	1.000	—
Others	4.210 (3)	5 (4.6)	0.389	1.52 (0.62–3.73)
MUUO	23,389 (16.8)	12 (11)	0.129	0.55 (0.30–1.01)
Benign SON	727 (0.5)	0	0.596	—
Unknown behavior SON	1326 (1)	1.000 (0.9)	1.000	0.82 (0.11–5.856)
Carcinoma in situ	186 (9.1)	1.000 (0.9)	0.136	6.58 (0.91–47.439)

Bold font highlights statistically significant differences.

[a] After adjustment for age, sex, alcohol, and tobacco consumption.

HCC, hepatocellular carcinoma; MUUO, metastasis from unknown/unspecified origin.

3.31), related to the higher proportion of deaths due to non-Hodgkin lymphoma (9.2% vs. 2.9%; OR, 3.09; 95% CI, 1.61–5.92), specifically of B-cell lineage (8.3% vs. 2.5%; OR, 3.04; 95% CI, 1.54–6.03) and MALT lymphomas (1.8.% vs. 0.1%; OR, 70.17; 95% CI, 16.61–296.36; Table 2). However, there were no differences in the mean age of the deceased from HN or of the risk related to leukemia, multiple myeloma, myelodysplastic syndrome, or myeloproliferative disorders, among others.

DISCUSSION

Other researchers have encountered challenges in confirming an overall cancer standardized mortality ratio in patients with SjS because of the heterogeneity of the disease, its association with other autoimmune conditions, and the premature deaths from the disease itself, along with other complications.[1,2,7,10–12] However, these investigations highlight that the general risk of neoplasms among SjS patients varies significantly according to the specific type or lineage of neoplasm.

In this nationwide epidemiological analysis focused on primary SjS, this population was shown to present an almost 10-fold higher rate of dying of neoplasms than from the disease itself, with B-cell and MALT lymphomas, small bowel neoplasms, and ovarian carcinomas being responsible. On the other hand, given the differences in age between deaths from SjS disease and neoplasms, the latter should be conceived as long-term complications of the disease, years after the characteristic onset age or the peak period of disease activity.[1,2]

TABLE 2. Differences in Hematological Neoplasm-Related Deaths by Lineage Between SjS Patients and the General Spanish Population

	Neoplasm-Related Deaths, n (%)			
	Non-SjS	SjS	*p*	OR (95% CI)[a]
Hematological	12,358 (8.9)	20 (18.3)	0.002	**2.04 (1.25–3.31)**
Malign hematological	11,987 (8.6)	20 (18.3)	0.002	**2.12 (1.30–3.44)**
Lymphoma	4237 (3)	11 (10.1)	0.001	**3.28 (1.76–6.13)**
Hodgkin lymphoma	260 (0.2)	1 (0.9)	0.185	6.18 (0.86–44.66)
Non-Hodgkin lymphoma	3977 (2.9)	10 (9.2)	0.001	**3.09 (1.61–5.92)**
B-cell lineage	3537 (2.5)	9 (8.3)	0.002	**3.04 (1.54–6.03)**
MALT	34 (0.1)	2 (1.8)	<0.001	**70.17 (16.61–296.36)**
T/NK cell lineage	441 (0.3)	1 (0.9)	0.292	3.22 (0.45–23.18)
Leukemia	4626 (3.3)	5 (4.6)	0.415	1.27 (0.52–3.13)
Myeloid lineage	3190 (2.3)	5 (4.6)	0.106	1.84 (0.75–4.51)
Lymphoid lineage	1006 (0.7)	0	1	—
Multiple myeloma	2161 (1.5)	4 (3.7)	0.09	2.04 (0.75–5.56)
Myelodysplastic syndrome	886 (0.6)	0	1	—
Others	77 (0.1)	0	1	—
Unknown behavior	371 (0.3)	0	1	—
Myeloproliferative disorders	243 (0.2)	0	1	—
Others	128 (0.1)	0	1	—

Bold font highlights statistically significant differences.

[a] After adjustment for age, sex, alcohol, and tobacco consumption.

In our study, HN accounted for 18% of deaths from neoplasms in patients with SjS, twice that of the general population, justifying in part the aforementioned increase in all-cause mortality in this population compared with matched controls.[2,3,12] Therefore, our study confirms that the higher incidence of lymphomas of B-cell lineage and MALT lymphomas identified in other reports indeed results in a greater mortality from these disorders.[1,4,5,7] It is of note that, in our study, SjS patients presented a 3- and 70-times higher risk of dying due to B-cell and MALT lymphoma, respectively. In parallel, small bowel neoplasms, strongly associated with lymphoid tissue and MALT lymphomas in this anatomic region, were seen as an important cause of death in this population.[13]

Our analysis identified a higher risk of death from ovarian carcinomas in patients with SjS. To our knowledge, only Aslan et al. have described a higher incidence of ovarian cancer in a Turkish population with primary SjS.[9] The complex relation of autoimmunity, hormonal factors, and immune response to tumors, including the association of certain autoimmune diseases with gynecological neoplasms, is already a known topic.[11] However, the increased mortality from ovarian neoplasms in SjS patients has not been noted previously. Interestingly, there is recent evidence correlating ovarian tumor biomarkers levels with primary SjS activity and a higher prevalence of anti-Ro52 antibodies in patients with ovarian cancer.[14,15] Although this association merits further research and confirmation in other studies, our nationwide analysis raises concern about ovarian cancer mortality in this population.

Several limitations of this study must be considered. Information regarding disease course and medication was not available and could have aided more solid conclusions. The exclusive inclusion of hospital admissions may have influenced statistical power and selection bias. Moreover, in a retrospective database chart review based on *ICD* diagnoses, definitive causes of death cannot be ascertained with certainty. In addition, the prevalence of SjS could not be properly assessed in the databases. Therefore, the rate, risk, or incidence of neoplasm could not be calculated, and only deaths could be compared. Despite these reservations, we believe that our study from a nationwide analysis of large sample size yields consistent results that confirm those seen in other studies and evaluates a robust outcome, namely, mortality.

In conclusion, individuals with primary SjS face a greater mortality from small bowel neoplasms, ovarian carcinomas, and B-cell and MALT lymphomas compared with the broader Spanish population. This results in a higher mortality from neoplasm than from the disease itself. Prior investigations have already pinpointed risk factors for cancer in SjS, linking elevated cancer risk to disease activity, systemic involvement, specific immunosuppressants such as cyclophosphamide, tobacco use, and age.[2,3,5] Our results emphasize the importance of identifying and developing strategies that might help to attenuate their occurrence and impact, such as decreasing the immunosuppressive burden. Additionally, there is a pressing need to explore and contemplate specialized early-detection and management initiatives for individuals with SjS, focused on HN and probably on ovarian carcinomas.

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